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**INVESTIGATING THE GENETIC BASIS OF  
FEVER-ASSOCIATED EPILEPSIES USING  
COPY NUMBER VARIATION ANALYSIS AND  
TARGETED RESEQUENCING**

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## List of abbreviations

ADM-2	Aberration Detection Method 2
ADNFLE	autosomal dominant nocturnal frontal lobe epilepsy
ADTLE	autosomal dominant temporal lobe epilepsy
Array CGH	array comparative genomic hybridization
ASD	autism spectrum disorder
BFIS	benign familial infantile seizures
BWA	Burrows-Wheeler Aligner
CAE	childhood absence epilepsy
CCA	corpus callosum anomalies
CGA	congenital anomalies
CNV	copy number variant
DLRS	Derivative Log Ratio Spread
FIRES	febrile infection-related epilepsy syndrome
FS	febrile seizures
FS+	febrile seizures plus
GATK	Genome Analysis Toolkit
GEFS+	genetic epilepsy with febrile seizures plus
GGE	genetic generalized epilepsies
GTCS	generalized tonic-clonic seizure
ICE-GTC	intractable childhood epilepsy with generalized tonic-clonic seizures
ID	intellectual disability
IGV	Integrative Genomics Viewer
indel	small insertions and deletions
JME	juvenile myoclonic epilepsy
MAE	myoclonic-astatic epilepsy
MAQ	multiplex amplicon quantification
MIP	molecular inversion probe
MLPA	multiplex ligation-dependent probe amplification
MMPSI	malignant migrating partial seizures of infancy
NAHR	non-allelic homologous recombination
NTC	non-template control
PCR	polymerase chain reaction

PKD	paroxysmal kinesigenic dyskinesia
RFU	Relative Fluorescence Units
RT-PCR	real time polymerase chain reaction
SIGE1	severe idiopathic generalized epilepsy of infancy
SMEI	severe myoclonic epilepsy of infancy
SNV	single nucleotide variant
WGA	whole genome amplification

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# 1 Introduction

## 1.1 What is epilepsy?

Epilepsy is one of the most common disorders of the brain with around 50 million people affected world-wide (World Health Organization 2012). The term “epilepsy” comprises a heterogeneous spectrum of neurological conditions characterized by unprovoked, recurrent seizures due to abnormal, synchronized activity of central neurons. In addition to irregular neuronal firing, important elements to define a seizure are its transient occurrence and its clinical manifestation (Fisher et al. 2005) with the latter ranging from imperceptible absences to generalized tonic-clonic jerks and from relatively benign to severe and life-threatening. The burden of epilepsy, however, extends beyond the effects of seizures themselves: Many patients have to contend with associated cognitive, psychological, behavioral and social problems markedly impairing quality of life (Kerr 2012). Furthermore, affected individuals and their families may have to deal with the increased risk of accidental injury and even premature death (Fazel et al. 2013).

Different schemes have been developed to classify the epilepsies. The classification by etiology is one of the most commonly used concepts and roughly distinguishes three groups: epilepsy with a genetic basis often referred to as idiopathic or genetic epilepsy, epilepsy due to structural changes in the brain also called symptomatic or structural-metabolic epilepsy and simply epilepsy of unknown etiology (Berg et al. 2010). In reality, the boundaries between the different etiological groups are much more blurred than in this classification. It has become increasingly clear that many epilepsies follow a complex pattern of inheritance where both, genetic and acquired factors, contribute to the epilepsy phenotype (Berkovic et al. 2006). However, the different epilepsy syndromes tend toward one or the other end of the etiological spectrum between genetic and symptomatic.

In Europe, symptomatic epilepsies only account for about one third of all epilepsies while two thirds have a genetic basis or no obvious identifiable cause (Banerjee et al. 2009).

Epilepsies with a strong genetic background often have their onset in childhood or youth. Therefore, research in the field of epilepsy genetics mostly focuses on epilepsies of these age groups.

## **1.2 Febrile seizures and fever-associated epilepsies**

Febrile seizures (FS) are the most common convulsive event in childhood. They affect about 3% of all children (Nelson and Ellenberg 1978; Ross et al. 1980; Verity et al. 1985) and generally occur as a benign, self-limiting event between the age of 6 months and 6 years. FS are predominantly brief, generalized tonic-clonic seizures (GTCS) precipitated by fever as present during common childhood infections that do not affect the CNS (Baulac et al. 2004). Thus, FS have a clear provoking factor and are not traditionally diagnosed as epilepsy. However, FS might be a manifestation of less frequent fever-associated epilepsy syndromes like febrile seizures plus (FS+), genetic epilepsies with febrile seizures plus (GEFS+) and Dravet syndrome, first described as severe myoclonic epilepsy of infancy (SMEI).

The syndrome of FS+ includes different clinical presentations. One scenario involves FS lasting beyond the age of 6 years. A second type of presentation of FS+ is the occurrence of FS with additional afebrile seizures. The latter may coexist with FS during the typical time frame of 6 months to 6 years, but can also occur after remittance of FS (Scheffer and Berkovic 1997; Scheffer et al. 2005).

FS and FS+ represent the most common phenotypes of the familial epilepsy syndrome GEFS+. The term was introduced to describe families in which FS and epilepsy coexist (Scheffer and Berkovic 1997). Different FS-related phenotypes may segregate within one family, a diagnosis of GEFS+ requiring at least two affected family members (Scheffer et al. 2009). The phenotypic spectrum of GEFS+ shows a high degree of diversity as it ranges from classical FS and FS+ with or without additional afebrile tonic-clonic, myoclonic, atonic or absence seizures to the rare and severe Dravet syndrome.

Dravet syndrome is an epileptic encephalopathy, i.e. an epilepsy syndrome where seizures lead to impaired brain function and cognitive decline (Engel 2001). Dravet syndrome usually starts in healthy infants during the first year of life with FS often presenting as hemiclonic or generalized febrile status epilepticus (Dravet 2011). These seizures may recur during the following months with hemiclonic seizures changing to the alternate side. Later on, between one and four years, other seizure types develop including myoclonic seizures, focal (dyscognitive) seizures and atypical absence seizures (Scheffer et al. 2009). Another common feature of patients with Dravet syndrome is the temperature sensitivity with fever and warm baths triggering seizures. With advancing age, Dravet syndrome shows a devastating course with ongoing seizures, developmental slowing, cognitive regression and additional neurological symptoms, such as ataxia and pyramidal signs (Dravet 2011).

Some patients show a clinical picture similar to Dravet syndrome but with atypical features. One epilepsy syndrome very close to Dravet syndrome is severe idiopathic generalized epilepsy of infancy (SIGEI), where the major distinguishing feature is that GTCS represent the predominant seizure type while myoclonic seizures are absent or subtle (Doose et al. 1998). In literature, the syndrome of SIGEI also appears under the name of intractable childhood epilepsy with generalized tonic-clonic seizures (ICE-GTC) (Fujiwara et al. 2003).

### **1.3 Genetic contribution to the epilepsies**

#### **1.3.1 Genetic contribution to the epilepsies in general**

Since antiquity, genetics have been recognized as an important etiologic factor of epilepsy (Magiorkinis et al. 2010). Whereas the early idea of epilepsy as a genetic disorder was based on simple observations, in the mid-20<sup>th</sup> century, twin studies emerged as a first scientific approach to investigate the importance of genetic factors for epilepsy. Up to today, many twin studies provided evidence of a genetic contribution to the disease by showing that the concordance rates for disease occurrence in monozygotic twins considerably exceed those in dizygotic twins (Lennox 1951; Berkovic et al. 1998; Miller et al. 1999; Kjeldsen et al. 2001; Corey et al. 2011).

Family studies are another efficient tool to demonstrate the influence of genetics on the etiology of epilepsy. Comparing the prevalence of epilepsy in family members of affected individuals to the prevalence in the general population, family studies revealed that offspring of epileptic parents are at twice to fivefold the risk to develop epilepsy (Winawer and Shinnar 2005). Higher prevalence of epilepsy among first-degree relatives of probands with idiopathic than with symptomatic epilepsy (Bianchi et al. 2003; Wakamoto et al. 2004) supports the general view that genetic factors are particularly important for idiopathic epilepsies.

#### **1.3.2 Genetic contribution to febrile seizures and fever-associated epilepsies**

As well as for epilepsy in general, twin and family studies demonstrated a strong genetic contribution to FS and fever-associated epilepsies. Several studies investigated twins with FS revealing significantly higher probandwise concordance rates for monozygotic twins ranging from 0.36 to 0.42 than for dizygotic twins ranging from 0.12 to 0.14 (Miller et al. 1999; Kjeldsen et al. 2002; Corey et al. 2011). Family studies showed that relatives of affected have a higher risk of FS compared with the general population (Winawer and Shinnar 2005).

Furthermore, a recent twin study confirmed the genetic contribution to FS+ and FS with later epilepsy with casewise concordance rates for monozygotic to dizygotic twins of 0.83 to 0.22 and 0.25 to 0.0 respectively (Eckhaus et al. 2013).

## **1.4 Results of epilepsy research**

### **1.4.1 Genetics of epilepsy – an overview**

20 years ago, the first epilepsy gene *CHRNA4* was reported in a large Australian family with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (Steinlein et al. 1995). The identification of *CHRNA4* coding for the  $\alpha_4$  subunit of the nicotinic acetylcholine receptor, a ligand-gated ion channel, was soon followed by the discovery of further ion channel genes: Causative variants were identified in subunits of potassium channels (*KCNQ2* and *KCNQ3*) (Biervert et al. 1998; Charlier et al. 1998; Singh et al. 1998; Hirose et al. 2000), sodium channels (*SCN1B*, *SCN1A*, *SCN2A*) (Wallace et al. 1998; Escayg et al. 2000; Claes et al. 2001; Sugawara et al. 2001; Wallace et al. 2001b; Heron et al. 2002), gamma-aminobutyric acid receptors (*GABRG2*, *GABRA1*) (Baulac et al. 2001; Wallace et al. 2001a; Cossette et al. 2002; Maljevic et al. 2006) and additional subunits of nicotinic acetylcholine receptors (*CHRNA2*, *CHRNB2*) (De Fusco et al. 2000; Aridon et al. 2006) leading to the channelopathy concept for the pathogenesis of idiopathic epilepsies. However, in 2002, pedigrees of individuals with autosomal dominant temporal lobe epilepsy (ADTLE) revealed mutations in the first non-ion channel gene *LGII* (Kalachikov et al. 2002) involved in the regulation of synaptic transmission (Fukata et al. 2006).

So far, gene discovery has especially been successful in monogenic familial epilepsies and sporadic epileptic encephalopathies. Targeted approaches like linkage analysis in large families and subsequent candidate gene sequencing as performed in ADNFLE (Phillips et al. 1995; Steinlein et al. 1995) and ADTLE (Ottman et al. 1995; Kalachikov et al. 2002) led to the detection of causative genes. New massive parallel sequencing techniques enable the screening of multiple genes, the exome or even the whole genome in many patients at once and thus simplify the search for causative variants. Using these high-throughput sequencing methods, long-sought genes for familial epilepsies and causative mutations for sporadic epileptic encephalopathies have been identified. In 2012, *PRRT2* was reported as the major gene for benign familial infantile seizures (BFIS) (Heron et al. 2012a; Schubert et al. 2012) after exome sequencing had detected the gene in paroxysmal kinesigenic dyskinesia (PKD), a

movement disorder also occurring in BFIS families (Chen et al. 2011). Exome sequencing revealed *KCNT1* mutations in 6/12 patients with malignant migrating partial seizures of infancy (MMPSI) (Barcia et al. 2012) and causative *KCNT1* variants were also found in severe ADNFLE (Heron et al. 2012b).

*De novo* mutations in different genes have been discovered as a major cause of epileptic encephalopathies explaining at least 12% of cases (EuroEPINOMICS-RES Consortium et al. 2014). To only name some, *de novo* variants in *SCN1A*, *STXBP1* and *CDKL5* were reported in early infantile epileptic encephalopathies (Nicita et al. 2012). Recent studies extended the phenotypic spectrum of known epilepsy genes, but also discovered new genes for epileptic encephalopathies: Mutations in *GRIN2A* were detected in patients with severe rolandic epilepsy and epilepsy-aphasia syndromes (Carvill et al. 2013b; Lemke et al. 2013) and *CHD2* was found to cause a fever-sensitive myoclonic encephalopathy with similarities to Dravet syndrome (Suls et al. 2013b). As *LGII* and other epilepsy genes, *CHD2* and *PRRT2* are not encoding ion channel proteins further contesting the channelopathy concept.

Apart from sequence mutations, rare deletions and duplications contribute to the genetic basis of epileptic encephalopathies and were reported in 7.9% of patients (Mefford et al. 2011).

Regarding the overall burden of epilepsy monogenic familial epilepsies and epileptic encephalopathies are rare syndromes. In common epilepsies like the genetic generalized epilepsies (GGEs) accounting for 15-20% of all epilepsy syndromes (Jallon and Latour 2005), the discovery of underlying genetic variation has only just begun. GGEs are presumed to follow a complex inheritance pattern (Ottman 2005) and mutations with a strong pathogenic effect were only discovered in rare familial forms of these disorders (Lachance-Touchette et al. 2011). *CACNA1H* and *GABRD* were discussed as susceptibility genes contributing to the pathogenesis of GGE (Chen et al. 2003; Dibbens et al. 2004). Important progress in the identification of variants predisposing to GGE was made by investigating structural variation: Recurrent microdeletions at 15q13.3, 15q11.2 and 16p13.11 were identified as important risk factors for GGE occurring in three percent of patients (Helbig et al. 2009; de Kovel et al. 2010).

Another disorder that might present with a GGE phenotype is the GLUT1 deficiency syndrome encompassing a broad phenotypic spectrum with epileptic encephalopathies at the severe end (De Vivo et al. 1991; De Giorgis and Veggiotti 2013). In these patients, *SLC2A1* mutations lead to an impaired glucose transport over the blood-brain barrier (Seidner et al.

1998). Ketogenic diet is a treatment for GLUT1 deficiency and may improve seizure and cognitive outcome.

#### **1.4.2 Genetics of febrile seizures and fever-associated epilepsies**

Although the majority of FS is assumed to have polygenic inheritance (Rich et al. 1987), the examination of monogenic FS and fever-associated epilepsies has been the most successful approach towards gene discovery in these disorders. Investigating a large pedigree of family members with generalized epilepsies with a predominance of FS, Scheffer and Berkovic developed the concept of GEFS+ as a familial syndrome and diagnostic entity (Scheffer and Berkovic 1997). The use of this concept in subsequent genetic studies revealed the four genes *SCN1A*, *SCN1B*, *SCN2A* and *GABRG2* (table 1).

*SCN1B* was identified in a large GEFS+ pedigree (Wallace et al. 1998) and Escayg and colleagues discovered *SCN1A* mutations in two families with GEFS+ (Escayg et al. 2000). Later on, the combined frequency of *SCN1B* and *SCN1A* mutations in GEFS+ families was found to be 17% (Wallace et al. 2001b). Due to phenotypic overlaps and patients with Dravet syndrome and a family history of seizures, Dravet syndrome was added to the severe end of the GEFS+ spectrum (Singh et al. 2001). Claes and colleagues then sequenced *SCN1A* in Dravet syndrome and identified *de novo* mutations in all seven patients investigated (Claes et al. 2001). Subsequent studies confirmed *SCN1A* as the major causative gene of Dravet syndrome (Sugawara et al. 2002; Claes et al. 2003) with more than 70% of patients carrying a mutation (Marini et al. 2011). *SCN1A* mutations were also, but less frequently found in patients with SIGEI (Ebach et al. 2005). *SCN2A* has been implicated in a patient with FS+ and his father with FS (Sugawara et al. 2001). In addition, *SCN2A* plays a role in early infantile epileptic encephalopathies including Dravet syndrome (Shi et al. 2012). *GABRG2* was reported in GEFS+ pedigrees including a patient with Dravet syndrome (Baulac et al. 2001; Harkin et al. 2002), a family with childhood absence epilepsy (CAE) and FS (Wallace et al. 2001a) and in familial FS (Audenaert et al. 2006).

Only recently, *STX1B* mutations were identified in a family with fever-associated epilepsies consistent with the GEFS+ spectrum (Schubert et al. 2014) emphasizing the relevance of this concept.

The search for *de novo* mutations has been the most important approach for gene discovery in Dravet syndrome. It not only revealed the importance of *SCN1A*, but also identified variants

in *CHD2* (Suls et al. 2013b). Furthermore, mutations in *PCDH19* were reported in female individuals with a Dravet-like phenotype (Depienne et al. 2009).

Deletions and duplication of *SCN1A* in 2-3% of patients with Dravet syndrome (Marini et al. 2009) and 17q12 duplications in 0.45% (1/222) of individuals with familial FS and GEFS+ (Hardies et al. 2013) suggest that structural variation also contributes to the genetic background of fever-associated epilepsies.

Gene	Protein	Function
<i>SCN1A</i>	voltage-gated sodium channel type I, alpha subunit	ion channel subunit (Oliva et al. 2012)
<i>SCN1B</i>	voltage-gated sodium channel type I, beta subunit	ion channel subunit (Oliva et al. 2012)
<i>SCN2A</i>	voltage-gated sodium channel type II, alpha subunit	ion channel subunit (Oliva et al. 2012)
<i>GABRG2</i>	gamma-aminobutyric acid (GABA) A receptor, gamma 2 subunit	ion channel subunit (Macdonald et al. 2010)
<i>STX1B</i>	syntaxin 1B	involved in the release of presynaptic vesicles (Mishima et al. 2014)
<i>CHD2</i>	chromodomain helicase DNA binding protein 2	involved in modification of chromatin structure (Marfella and Imbalzano 2007)
<i>PCDH19</i>	protocadherin 19	involved in cell-adhesion (Emond et al. 2011)

**Table 1. Genes involved in fever-associated epilepsies.**

## 1.5 Targeted resequencing

DNA sequencing is used to detect single nucleotide variants (SNVs) and small insertions and deletions (indels). What began with non-automated Sanger sequencing has since advanced to today's high-throughput sequencing technologies also known as massive parallel sequencing or "next-generation" sequencing. The new techniques have revolutionized the field owing to their time-efficiency and cost-effectiveness, greatly accelerating disease gene discovery (see examples in chapter 1.4.1). Despite these advances, it is not yet broadly affordable to perform whole-exome or whole-genome sequencing for large numbers of patients. Instead, alternative approaches are taken to interrogate only certain intervals of the genome, for example several genes, a technique also known as targeted resequencing.

Different studies have shown that targeted resequencing can be a useful diagnostic tool in epilepsy. Lemke et al. performed gene panel sequencing in patients with various epilepsies and identified disease-causing variants in 16 of 33 individuals (Lemke et al. 2012). Another gene panel approach was applied to 500 patients with epileptic encephalopathies: Targeted resequencing of 65 genes revealed pathogenic mutations in 10% of patients (Carvill et al. 2013a).



As epileptic disorders are genetically heterogeneous it is difficult to choose only one candidate gene for sequencing. Gene panels strike a balance between single gene and whole-exome or whole-genome sequencing and are already commercially available for genetic testing in epilepsy.

## **1.6 Copy number variation analysis**

Copy number variants (CNVs) are deletions and duplications ranging from 1kb to a few Mb in size (Feuk et al. 2006). About one decade ago, these submicroscopic changes have been identified as a major source of genomic structural variation covering 12% of the human genome (Iafrate et al. 2004; Sebat et al. 2004; Redon et al. 2006). CNVs can be divided in two categories: recurrent and non-recurrent. Recurrent CNVs arise by non-allelic homologous recombination (NAHR). Regions of high sequence similarity lead to a misalignment of homologous chromosomes during meiosis so that subsequent rearrangements result in deletions and duplications (Watson et al. 2014). While recurrent CNVs occur at the same position in unrelated individuals, non-recurrent CNVs occur throughout the genome without consistent breakpoints.

CNVs may contribute to normal phenotypic variation, but have also been connected to disease. Charcot-Marie-Tooth type IA, Prader-Willi, Angelman and Williams-Beuren syndrome are neurological or neurodevelopmental disorders associated with recurrent CNVs (Butler et al. 1986; Magenis et al. 1987; Lupski et al. 1991; Perez Jurado et al. 1996). Patients with intellectual disability (ID), autism and schizophrenia constituted the first large disease cohorts systematically studied for CNVs (Sebat et al. 2007; International Schizophrenia Consortium 2008; Marshall et al. 2008; Sagoo et al. 2009). As the phenotypic spectrum of rare recurrent CNVs identified in these disorders were overlapping and also included seizures, epilepsy cohorts were subsequently investigated for copy number changes. Genome-wide CNV screening in GGE identified rare CNVs in 8.9% of patients including recurrent microdeletions at 15q11.2, 15q13.3 and 16p13.11 in 3% of individuals (Mefford et al. 2010). With an odds ratio of 68, the microdeletion 15q13.3 is the most important risk factor for GGE identified today (Dibbens et al. 2009). Heinzen and colleagues investigated more than 3000 patients with focal epilepsies and also found a significant enrichment of 16p13.11 deletions compared to controls. Interestingly, 15q13.3 deletions seem to represent a risk factor

specifically for generalized epilepsies as recurrent CNVs at this locus were not identified in focal forms (Heinzen et al. 2010).

7.9% of patients with epileptic encephalopathies carry rare CNVs. Microdeletions at 15q11.2, 15q13.3 and 16p13.11 were not identified in these individuals indicating a different genetic architecture for these severe epilepsies (Mefford et al. 2011).

CNVs may also highlight novel epilepsy genes. For example, a deletion encompassing *PCDH19* was identified in a patient with Dravet syndrome. Subsequent sequencing of *PCDH19* in additional individuals revealed sequence mutations and established *PCDH19* as an epilepsy gene (Depienne et al. 2009). Carvill et al. located *CHD2* in the smallest region of overlap of non-recurrent 15q26 deletions and identified *de novo* mutations of the gene in 1.2% of patients with epileptic encephalopathies using targeted resequencing (Carvill et al. 2013a).

## 1.7 Aims

FS and fever-associated epilepsy syndromes considerably contribute to the burden of epilepsy. Their etiology involves a strong genetic component and several genes for monogenic FS and fever-associated epilepsies have been identified. However, most patients do not carry mutations in these genes. Many cases remain unexplained and further genetic variants contributing to these genetically heterogeneous disorders need to be identified. Targeted resequencing was successfully performed in different epilepsies. Most pathogenic mutations found in FS and fever-associated epilepsies were SNVs, but the identification of CNVs in GGE and epileptic encephalopathies suggests that deletions and duplications might also be involved in the pathogenesis of these epilepsies.

We performed targeted resequencing and a genome-wide CNV screening in patients with recurrent FS and fever-associated epilepsies to

- 1) evaluate the impact of 19 candidate epilepsy genes in recurrent FS and fever-associated epilepsies and define the phenotypic spectrum of 13 known epilepsy genes.

- 2) assess the importance of rare CNVs in fever-associated epilepsies.

## 2 Patients and Methods

### 2.1 Patient cohort selection

The ethics committee of the Christian-Albrechts-University Kiel, the Antwerp University Hospital and the University of Washington, Seattle approved this study.

86 patients with fever-associated epilepsies were selected from the biobanks of the Department of Neuropediatrics at the Christian-Albrechts-University Kiel and the Vlaams Instituut voor Biotechnologie (VIB) Department of Molecular Genetics at the University of Antwerp.

DNA was obtained from blood lymphocytes or derived from whole genome amplification (WGA) following standard protocols.

Two cohorts of patients were investigated. In cohort 1 targeted resequencing of candidate and known epilepsy genes was performed to detect novel causative mutations within these genes. In cohort 2 genome-wide array comparative genomic hybridization (array CGH) was performed to detect pathogenic CNVs.

#### 2.1.1 Cohort 1: Targeted resequencing

Cohort 1 consisted of 84 patients with fever-related seizures or status epilepticus in the first years of life as the most prominent clinical features (table 2). Two additional individuals carrying *SCN1A* mutations were included as positive controls. 35/43 individuals with typical or atypical Dravet syndrome previously tested negative for *SCN1A* sequence mutations.

Epilepsy phenotype	Number of patients (% of total cohort)
<b>Dravet syndrome</b>	<b>43 (51%)</b>
typical Dravet syndrome	22
atypical Dravet syndrome/SIGEI	21
<b>GEFS+/FS+</b>	<b>27 (32%)</b>
FS+ afebrile	15
FS+ prolonged	7
FS+ absence	2
FS+ other	3
<b>recurrent FS (<math>\geq 4</math>)</b>	<b>11 (13%)</b>
<b>unclassified fever-associated epilepsy</b>	<b>3 (4%)</b>
<b>Total</b>	<b>84</b>

**Table 2. Patient phenotypes for cohort 1.** FS, febrile seizures; FS+, febrile seizures plus; GEFS+, genetic epilepsy with febrile seizures plus; SIGEI, severe idiopathic generalized epilepsy of infancy.

Classification was performed similarly as described in Hartmann et al. 2015: Most patients with atypical Dravet syndrome were classified as having severe idiopathic generalized epilepsy of infancy (SIGEI) (Doose et al. 1998) with predominant GTCS and without or with only subtle myoclonic seizures. Furthermore, patients with SIGEI were lacking the alternating hemiclonic seizures of typical Dravet syndrome.

All patients with GEFS+/FS+ presented with simple FS with additional seizure types or FS persisting beyond the usual age of remission. Patients with additional afebrile GTCS were classified as “FS+ afebrile”. Individuals with FS persisting beyond the age of six years were categorized as “FS+ prolonged”. If additional absence seizures occurred, the phenotype was referred to as “FS+ absence”. Three patients had additional myoclonic, astatic, atonic and tonic seizures and constituted the group of “FS+ other”.

Patients with recurrent FS were included if they had at least four FS.

Subjects with unclassified fever-associated epilepsy had prominent fever-associated seizures and additional syndromic features including profound ID, autism, short stature, dysmorphic features, macrocephaly and muscular hypotonia. In these patients, a diagnosis of FS+, Dravet syndrome or SIGEI would be justifiable if only regarding their epilepsy.

### **2.1.2 Cohort 2: Copy number variation analysis**

Cohort 2 constituted a subgroup of cohort 1 and consisted of 36 patients with typical and atypical Dravet syndrome (SIGEI), GEFS+/FS+ and unclassified fever-associated epilepsy (table 3).

All individuals tested negative for *SCN1A* sequence mutations as part of the investigations in cohort 1 and 18/36 patients had a negative screening for *SCN1A* deletions and duplications using multiplex ligation-dependent probe amplification (MLPA) or multiplex amplicon quantification (MAQ). The remaining patients were not previously investigated for copy number changes of *SCN1A*.

Among all patients, a diagnosis of ID was present in 26/36 (72%) patients, autism was diagnosed in 5/36 (14%) individuals and 6/36 (17%) patients had congenital anomalies (CGA). 18/26 (69%) of the patients with ID had normal development before seizure onset and cognitive impairment started with epileptic activity in terms of an epileptic encephalopathy (Hartmann et al. 2015).

Epilepsy phenotype	Number of patients	Number of patients with				
		ID with onset			autism	CGA
		prior to epilepsy	after epilepsy	unknown		
<b>SCN1A-negative Dravet syndrome</b>	<b>23 (64%)</b>					
typical Dravet syndrome	13	2	18	3	4	4
atypical Dravet syndrome/SIGEI	10					
<b>GEFS+/FS+</b>	<b>11 (31%)</b>					
FS+ afebrile	4	1 <sup>a</sup>	0	0	0	0
FS+ prolonged	4					
FS+ absence	1					
FS+ other	2					
<b>unclassified fever-associated epilepsy</b>	<b>2 (6%)</b>	2	0	0	1	2
<b>Total</b>	<b>36</b>	<b>5 (14%)</b>	<b>18 (50%)</b>	<b>3 (8%)</b>	<b>5 (14%)</b>	<b>6 (17%)</b>

**Table 3. Patient phenotypes for cohort 2.**

CGA, congenital anomalies; FS+, febrile seizures plus; GEFS+, genetic epilepsy with febrile seizures plus; ID, intellectual disability; SIGEI, severe idiopathic generalized epilepsy of infancy.

<sup>a</sup> patient with borderline ID (full scale intelligence quotient of 75 in the Hamburg Wechsler Intelligenztest für Kinder IV as the German adaptation of Wechsler Intelligence Scale for Children IV) (Daseking et al. 2007); (table as published in Hartmann et al 2015, license agreement with John Wiley and Sons available)

## 2.2 Targeted resequencing

Targeted resequencing was performed in 19 candidate and 13 known epilepsy genes in order to identify mutations in cohort 1 (table 4).

### 2.2.1 Selecting genes for targeted resequencing

Dr. Gemma Carvill (Postdoctoral fellow, Department of Pediatrics, Division of Genetic Medicine, University of Washington, Seattle) selected 32 candidate and known epilepsy genes for targeted resequencing.

13 known epilepsy genes were selected based on the presence of mutations in more than one individual and are generally associated with more severe presentations.

Candidate epilepsy genes were selected from within epilepsy-associated CNVs from published studies

Candidate genes	Known genes
<i>ADAM22</i>	<i>ARX</i>
<i>ADAM23</i>	<i>CDKL5</i>
<i>CACNA2D1</i>	<i>GABRA1</i>
<i>CPLX1</i>	<i>GABRG2</i>
<i>DLGAP1</i>	<i>GRIN2A</i>
<i>DLGAP2</i>	<i>KCNQ2</i>
<i>DLGAP3</i>	<i>PCDH19</i>
<i>EPHA6</i>	<i>SCN1A</i>
<i>GNAI1</i>	<i>SCN1B</i>
<i>MAPK8</i>	<i>SCN2A</i>
<i>OTX1</i>	<i>SLC2A1</i>
<i>SEMA3A</i>	<i>SPTAN1</i>
<i>SH3GL2</i>	<i>STXBP1</i>
<i>SLC1A1</i>	
<i>SLC1A3</i>	
<i>SMARCA2</i>	
<i>SV2A</i>	
<i>SV2B</i>	
<i>SYT2</i>	

**Table 4. Candidate and known epilepsy genes.**

(Heinzen et al. 2010; Mefford et al. 2010; Mefford et al. 2011) and unpublished data as described in Carvill et al. 2013 (Supplementary Note and Supplementary Table 2).

### **2.2.2 Capture methods for targeted resequencing: molecular inversion probes**

Targeted resequencing allows the selective interrogation of specific regions of the genome. To capture all regions of interest several methods have been developed including multiplex polymerase chain reaction (PCR), capture-by-circularization and capture-by-hybridization methods (Turner et al. 2009b). In this study, we used molecular inversion probes (MIPs), that fall into the category of capture-by-circularization, to capture and amplify all exons and intron-exon-boundaries of the 32 candidate and known epilepsy genes (table 4) for subsequent next-generation sequencing in all individuals of cohort 1. Advantages of MIP capture methods are the high specificity, good scalability and the compatibility with a high level of multiplexing.

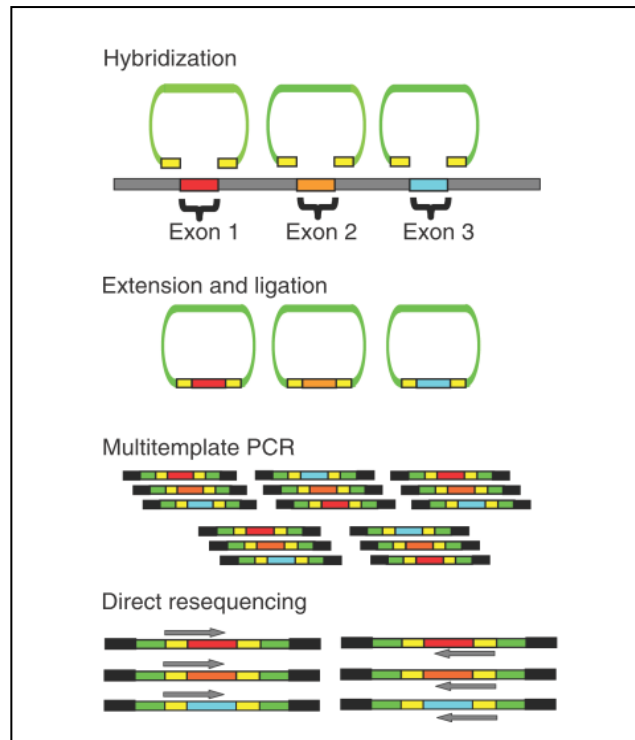
MIPs are single stranded DNA molecules consisting of two target-specific arms connected by a common backbone. The name “molecular inversion probe” is derived from the configurational inversion of the whole molecule upon target binding.

MIPs originate from padlock probes that were initially used to specifically detect single nucleotide changes (Nilsson et al. 1994; Hardenbol et al. 2003).

In contrast to padlock probes, the targeting arms of MIPs are 112bp apart when hybridized to their target, and by performing a “gap fill” step the target sequence of the patient can be captured for future sequencing. The process of MIP capture is shown in figure 1. Briefly, patient DNA was denatured and MIPs were allowed to hybridize to target DNA. DNA polymerase was then used to fill the gap with target-complementary sequence and enzymatic ligation created a single circular MIP molecule. Exonuclease treatment removed remaining linear DNA molecules from the reaction mix. The MIP regions containing the target’s complement were amplified in a multitemplate PCR using universal primers that bound in the common backbone. The primers were connected to unique 8bp barcodes and universal sequencing adaptors that were hence introduced into each PCR product so that these could be pooled together. Subsequent bead purification of PCR products resulted in a target-enriched library that was then subject to next generation sequencing.

### Figure 1. Target capture using MIPs.

MIPs consist of target-specific arms (yellow) and a common backbone (green) containing universal binding sites for PCR primers. MIPs hybridize to their target DNA and undergo configurational inversion. An extension and ligation step results in circularized MIPs carrying a copy of the target. Captured sequences are amplified in a multitemplate PCR incorporating sequencing adaptors (black) and unique 8bp barcodes. Purified PCR products are directly sequenced producing paired-end reads. (figure as published in Turner et al. 2009a, license agreement with Nature Publishing Group available)



In order to capture the 32 candidate and known epilepsy genes, a total target size of 90,071bp, 1325 MIPs with a length of 70bp and a gap-size of 112bp were designed as previously described (O'Roak et al. 2012, Supplementary Material, p. 4) (for MIP sequences see annex, table S1). Integrated DNA Technologies (Coralville, IA) performed column synthesis of MIPs.

#### 2.2.3 Pooling of MIPs

In order to multiplex capture reactions, all 1325 MIPs with a concentration of 100 $\mu$ mol/l were pooled together. In previous experiments using the same probes, uniformity calculations revealed 147 MIPs with a coverage below 100X. These poorly capturing MIPs were therefore added at a 50 times higher amount than the remaining MIPs to the final pool.

#### 2.2.4 Phosphorylation of MIPs

MIPs have to be 5'-phosphorylated so that the DNA sequence in the gap fill can be ligated to the ligation arm allowing the molecule to circularize. This kinase reaction was performed in the following 50 $\mu$ l reaction:

Reagent	Amount in $\mu\text{l}$	Company
pooled MIPs	37.5	Integrated DNA Technologies (Coralville, IA)
10X T4 DNA Ligase Reaction Buffer	5	New England BioLabs (Ipswich, MA)
T4 Polynucleotide Kinase (3' phosphatase minus)	2.5	New England BioLabs (Ipswich, MA)
Molecular Biology Grade Water	5	Mediatech (Manassas, VA)

**Table 5. Reagents for phosphorylation.**

Reaction conditions were set on the GeneAmp PCR System 9700 (Applied Biosystems, Carlsbad, CA) as follows:

incubation: 37°C for 45 min  
kinase heat inactivation: 65°C for 20 min  
cooling: 4°C until program was stopped

### 2.2.5 Target capture

For target capture the MIPs' ligation and extension arms were hybridized to the denatured proband DNA. The gap was filled by DNA polymerase using free nucleotides. Finally, ligase connected the gap-fill with the ligation arm resulting in a circularized molecule. The reaction was also performed for a non-template control (NTC) where DNA was replaced by water. Table 6 shows all reagents of the reaction mix.

Reagent	Amount in $\mu\text{l}$	Company
Ampligase 10X Reaction Buffer	2.5	Epicentre (Madison, WI)
pooled, phosphorylated MIPs, diluted 1:250	0.3113	Integrated DNA Technologies (Coralville, IA)
dNTP mix, 25mM each, diluted 1:100	0.0640	Fermentas (Waltham, MA)
AmpliTaq DNA Polymerase, Stoffel Fragment 10U/ $\mu\text{l}$	0.04	Applied Biosystems (Carlsbad, CA)
Ampligase DNA Ligase 100U/ $\mu\text{l}$	0.01	Epicentre (Madison, WI)
Molecular Biology Grade Water	17.0747	Mediatech (Manassas, VA)

**Table 6. Reagents for target capture.**

For each sample 5 $\mu\text{l}$  of DNA with  $c = 20\text{ng}/\mu\text{l}$  were added to 20 $\mu\text{l}$  of reaction mix.

Reaction conditions were set on the GeneAmp PCR System 9700 (Applied Biosystems, Carlsbad, CA) as follows:



denaturation: 95°C for 10min  
 capture: 65°C for 24h  
 cooling: 4°C until program was stopped

### 2.2.6 Exonuclease treatment

The capture product was treated with exonucleases I and III to remove uncircularized molecules and any remaining linear DNA. 2µl of the following reaction mix (table 7) were added to 25µl of each target capture product.

Reagent	Amount in µl	Company
Exonuclease 1 (E. coli), 20000U/ml	0.5	New England Bio Labs (Ipswich, MA)
Exonuclease 3 (E. coli), 100000U/ml	0.5	New England Bio Labs (Ipswich, MA)
Ampligase 10X Reaction Buffer	0.2	Epicentre (Madison, WI)
Molecular Biology Grade Water	0.8	Mediatech (Manassas, VA)

**Table 7. Reagents for exonuclease treatment.**

Reaction conditions were set on the GeneAmp PCR System 9700 (Applied Biosystems, Carlsbad, CA) as follows:

incubation: 37°C for 30min  
 enzyme inactivation: 95°C for 5min  
 cooling: 4°C until program was stopped

### 2.2.7 Real time PCR

Real time PCR (RT-PCR) was performed for a subset of 17 exonuclease-treated capture reactions in order to qualitatively validate capture efficiency. Additionally, the number of PCR cycles required for effective target amplification of all samples was estimated. The investigated reactions included products from eight DNA samples, eight WGA samples and the NTC.

SYBR green (Invitrogen, Carlsbad, CA), a fluorescent dye that intercalates into double-stranded DNA, was used to track target amplification, as the accumulation of RT-PCR products correlates with the increase in fluorescence intensity at the end of every cycle. The fluorescence intensity was measured for each single reaction by a laser-detector-system. To

visualize the data, Relative Fluorescence Units (RFU) were plotted against cycle number (figure 2).

Reagent	Amount in $\mu\text{l}$	Company
2x iProof HF Master Mix	12.5	Bio-Rad (Hercules, CA)
Forward primer, 100 $\mu\text{M}$	0.25	Eurofins MWG Operon (Huntsville, AL)
SYBR Green I Nucleic Acid Gel Stain	0.125	Invitrogen (Carlsbad, CA)
Molecular Biology Grade Water	4.625	Mediatech (Manassas, VA)

**Table 8. Reagents for RT-PCR.**

5 $\mu\text{l}$  of exonuclease treatment product and 2.5 $\mu\text{l}$  of different barcoded reverse primer for each sample (10 $\mu\text{M}$ , Integrated DNA Technologies, Coralville, IA) were added to 17.5 $\mu\text{l}$  of reaction mix (table 8). For primer sequences see annex, table S2.

Reaction conditions and fluorescence measurement on the Bio-Rad C1000 Thermal Cycler with CFX96 Real-Time System module (Bio-Rad, Hercules, CA) were set as follows:

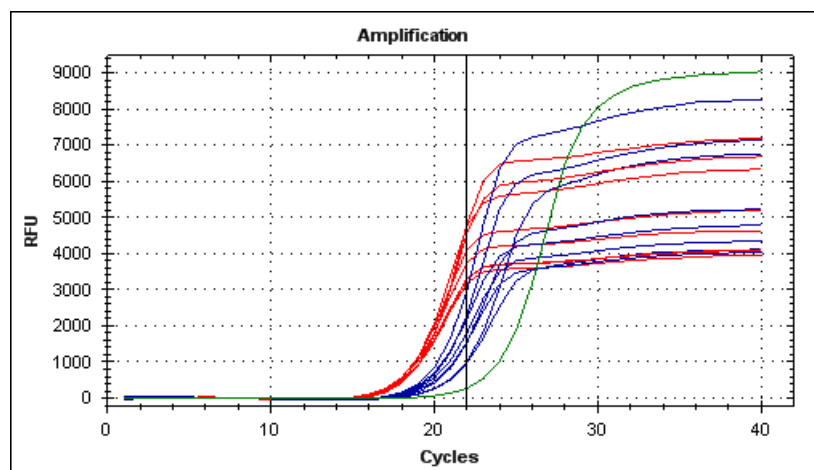
initial DNA denaturation:	98°C for 30sec	
DNA denaturation:	98°C for 10sec	} 40 cycles
primer annealing:	60°C for 30sec	
product elongation:	72°C for 20sec	
fluorescence measurement:	for every cycle	
product elongation:	72°C for 10sec	
cooling:	4°C until program was stopped	

**Figure 2. RFU-cycle-diagram.**

Graphs show the amplification of exonuclease-treated capture products of DNA samples (red), WGA samples (blue) and the NTC (green). The black line marks the 21<sup>st</sup> cycle before the first reaction plateaus.

Red graphs are detectable above background in earlier cycles than blue graphs indicating that amplification in DNA reactions started with a higher amount of starting material than WGA reactions. Thus, capture worked more efficiently for DNA samples than WGA samples.

The green graph increases later than all other graphs, which was expected as the NTC did not include any target DNA for capture. The amplification detected was assumed to result from MIPs that circularized without the insertion of a target.



The cycle number required in PCR was determined graphically as the cycle before the first graph reaches the plateau and amplification slows down dramatically. This was the case for the 21<sup>st</sup> cycle marked by the black line in figure 2.

### 2.2.8 PCR amplification

Exonuclease-treated capture products were added to PCR to amplify the parts of the MIPs containing the target copy. Unique 8bp barcodes and universal sequencing adaptors were incorporated during the reaction as they were appended to the universal primers.

Reagent	Amount in $\mu$ l	Company
2x iProof HF Master Mix	12.5	Bio-Rad (Hercules, CA)
Forward primer, 100 $\mu$ M	0.25	Eurofins MWG Operon (Huntsville, AL)
Molecular Biology Grade Water	4.75	Mediatech (Manassas, VA)

**Table 9. Reagents for PCR master mix.**

5 $\mu$ l of exonuclease-treated capture products and 2.5 $\mu$ l of different barcoded reverse primer for each sample (10 $\mu$ M, Integrated DNA Technologies, Coralville, IA) were added to 17.5 $\mu$ l of reaction mix (table 9). For primer sequences see annex, table S2.

Reaction conditions were set on the GeneAmp PCR System 9700 (Applied Biosystems, Carlsbad, CA) as follows:

initial DNA denaturation:	98°C for 30sec	
DNA denaturation:	98°C for 10sec	} 21 cycles
primer annealing:	60°C for 30sec	
product elongation:	72°C for 30sec	
final product elongation:	72°C for 2min	
cooling:	4°C until program was stopped	

### 2.2.9 Bead purification

5 $\mu$ l of all PCR reactions were pooled together as every sample could now be identified by its unique barcode. Purification was performed using magnetic beads (table 10).

0.9 $\mu$ l of beads per sample were added to the pooled PCR products, mixed and incubated for 5min at room temperature. The tube was then placed onto a magnet for 2 min separating the PCR products bound to the beads from the solution containing the unincorporated primers and

dNTPs. The solution was removed and the beads were rinsed with 70% ethanol allowing to incubate for 30sec. Used ethanol was removed and ethanol washing was repeated before beads were allowed to dry for 5min. Subsequently, beads were reconstituted in 100µl of Elution Buffer, mixed and again placed on the magnet for 1min. The solution containing the final library was removed, placed into a new tube and analyzed in gel electrophoresis as described in chapter 2.3.2.

<b>Reagent</b>	<b>Company</b>
Agencourt AMPURE XP	Beckman Coulter (Brea, CA)
DynaMag-2 Magnet	Invitrogen (Carlsbad, CA)
Pure Ethanol 200 Proof	Decon Laboratories (King of Prussia, PA)
Buffer EB	Qiagen (Venlo, Netherlands)

**Table 10. Materials and reagents for bead purification.**

Additionally, the library concentration was measured on the Gemini XPS Fluorescence Microplate Reader (Molecular Devices, Sunnyvale, CA) using the Quant-iT dsDNA Assay Kit (Invitrogen, Carlsbad, CA) following the manufacturer's instructions.

### **2.2.10 Sequencing**

Libraries from this work and another project were combined to create a final pool of 162 individual capture reactions. This final pool was applied to next generation sequencing on one lane of the Illumina HiSeq (San Diego, CA) according to the manufacturer's instructions.

The sequencing protocol consisted of two paired-end sequencing reads with a length of 101bp and a third read of 8bp to sequence the barcode. For primer sequences see annex, table S3.

### **2.2.11 Sequence analysis and variant calling**

Sequence analysis and variant calling was performed similarly as described in O'Roak et al. 2012 and Carvill et al. 2013: Each FASTQ file contained sequence information for approximately 150 million reads. Sequences of the 101bp runs were trimmed to 76bp which resulted in paired-end reads without overlap avoiding double counting of overlapping sequence and analysis of lower quality data from the end of the reads. The barcode reads correlate to their corresponding 76bp sequences according to their flow cell coordinates. The Burrows-Wheeler Aligner (BWA, version 0.5.6) (Li and Durbin 2009; BWA 2010) was then used to align the trimmed and barcoded reads to the human genome (hg19/NCBI build 37) and to generate a SAM file containing alignment information for the paired-end reads.

Subsequently the aligned reads were filtered for the correct target length of 150-154bp and for being properly paired and mapped using the SAM flags 83, 99, 147 and 163 (Li et al. 2009a). In this step, 4.2% of reads were excluded from further analysis as they did not meet these quality criteria. The extension and ligation arm sequences were removed from the sequence reads. SAM files were converted to indexed BAM files and applied to SNV and indel calling and variant filtration using the Genome Analysis Toolkit (GATK, version 2.1) (McKenna et al. 2010; GATK 2012). Clustered variants (window size 10) and variants with an allele balance  $> 0.70$  (for heterozygous calls),  $QD < 5$ ,  $QUAL < 30$  or coverage  $< 25X$  were excluded. Variants were visually inspected using the Integrative Genomics Viewer (IGV, version 2.1.24) (Robinson et al. 2011; IGV 2012) and annotated with Seattle Seq (version 134) (SeattleSeq 2011). Following a dominant or *de novo* model, only variants not present in the ESP6500 data set (Exome Variant Server 2012) as our control population were assessed further. For recessive candidates we considered variants with a frequency of  $< 1\%$  in controls. We only considered nonsynonymous, splice-site and frameshift variants.

### **2.2.12 Quality control**

Sequencing coverage calculations of target DNA regions were performed using the GATK DepthOfCoverage tool (GATK 2012). Across all samples, on average 93% of bases of each target gene were sequenced with a coverage above 25X (annex, figure S1 and S2).

Former studies applying a similar MIP capture protocol for subsequent sequencing achieved a sensitivity of 91-99% for single nucleotide variants (O'Roak et al. 2012; Carvill et al. 2013a). In our study, both known control variants, a missense and a frameshift mutation in *SCN1A*, were identified.

## 2.3 Validation and segregation analysis of rare SNVs

Sanger sequencing was performed to confirm all rare variants not present in the ESP6500 data set (Exome Variant Server 2012) that were discovered by targeted resequencing and to investigate the available samples of probands' relatives for these sequence mutations. The process from genomic DNA to sequencing data included the following steps:

1. PCR
2. Gel electrophoresis
3. PCR product purification
4. Sequencing reaction
5. Sequencing product purification
6. Basecalling and sequence analysis

### 2.3.1 PCR

PCR was performed to specifically amplify the genomic regions encompassing the identified variants. Primers were designed according to the NCBI Reference Sequence (National Center for Biotechnology Information 2002) for each gene involved (annex, table S4). Each run included one NTC per each different amplicon where DNA was replaced by water.

PCR amplification was implemented in a 25 $\mu$ l reaction containing the following reagents:

Reagent	Amount in $\mu$ l	Company
PCR Master Mix, 2X	12.5	Promega (Fitchburg, WI)
Forward primer, 10 $\mu$ M	1.0	Integrated DNA Technologies, Coralville, IA
Reverse primer, 10 $\mu$ M	1.0	Integrated DNA Technologies, Coralville, IA
Molecular Biology Grade Water	8.5	Mediatech (Manassas, VA)

**Table 11. PCR reagents.**

For each sample 2 $\mu$ l of DNA with c = 25ng/ $\mu$ l were added to 23 $\mu$ l of reaction mix.

Reaction conditions were set on the GeneAmp PCR System 9700 (Applied Biosystems, Carlsbad, CA) as follows:

initial DNA denaturation: 95°C for 3min  
 DNA denaturation: 95°C for 30sec  
 primer annealing: 55°C for 30sec  
 product elongation: 72°C for 30sec  
 final product elongation: 72°C for 5min  
 cooling: 4°C until program was stopped

} 30 cycles

### 2.3.2 Gel electrophoresis

During electrophoresis, an electrical field is applied so that negatively charged DNA molecules migrate to the positive anode. The speed at which a DNA fragment moves through the gel depends on its size so that DNA molecules are separated by base pair amounts. DNA fragments of known size (DNA Ladder) are used as markers allowing an estimate of PCR product length.

Gel electrophoresis was performed for PCR products and NTCs to evaluate the yield, product length accuracy, reaction specificity and contamination of the PCR. Reagents are listed in table 12.

A 1.5% agarose gel was produced by adding 0.75g Agarose to 50ml Tris-Acetate-EDTA (TAE) Buffer 1X and briefly heating this mixture in a microwave. After adding 1µl Ethidium Bromide Solution (10mg/ml), the mixture was poured into a gel tray using a gel comb to form wells. 5µl of each PCR product, NTC and 100bp DNA Ladder (100µg/µl) were mixed with 1µl Blue/Orange Loading Dye 6X respectively and loaded into the wells of the gel stored in TAE Buffer 1X on the Model H5 horizontal gel electrophoresis system (Life Technologies, Carlsbad, CA). Electrophoresis was performed at 100V for 30-60 min depending on PCR product length. The gel was visualized using the Gel Doc 2000 system (Bio-Rad, Hercules, CA) and Quantity One software (version 4.6.5, Bio-Rad, Hercules, CA).

Reagent	Company
Agarose HS, Molecular Biology Grade	Denville Scientific (South Plainfield, NJ)
TAE Buffer 40X (1.6M Tris-Acetate, 40mM EDTA)	Promega (Fitchburg, WI)
Ethidium Bromide Solution (10mg/ml)	Promega (Fitchburg, WI)
100bp DNA Ladder (500µg/ml)	New England Bio Labs (Ipswich, MA)
Blue/Orange Loading Dye, 6X	Promega (Fitchburg, WI)

**Table 12. Reagents for gel electrophoresis.**

### 2.3.3 PCR product purification

To remove unincorporated primers and nucleotides, the enzymes Exonuclease I and Thermosensitive Alkaline Phosphatase were added to 5 $\mu$ l of PCR product as part of the following reaction mix:

Reagent	Amount in $\mu$ l	Company
Exonuclease 1, E. coli (20U/ $\mu$ l)	0.5	Epicentre (Madison, WI)
FastAP Thermosensitive Alkaline Phosphatase (1U/ $\mu$ l)	1.0	Thermo Fisher Scientific (Waltham, MA)
Molecular Biology Grade Water	2.5	Mediatech (Manassas, VA)

**Table 13. Reagents for PCR product purification.**

Reaction conditions for the purification reaction were set on the GeneAmp PCR System 9700 (Applied Biosystems, Carlsbad, CA) as follows:

temperature of enzyme activity: 37°C for 15min  
inactivation of enzymes: 80°C for 15min  
cooling: 4°C until program was stopped

### 2.3.4. Sanger sequencing reaction

The purified PCR products were sequenced by fluorescence-based cycle sequencing that is based on the chain termination sequencing method described by Sanger et al. (Sanger et al. 1977). In contrast to the original technique using radioactively labeled dideoxynucleotides in four different reaction mixes, today's method uses fluorescently labeled dideoxynucleotides and only needs one reaction.

2 $\mu$ l of purified PCR product were added to 8 $\mu$ l of the following reaction mix (for primer sequences see annex, table S4):

Reagent	Amount in $\mu$ l	Company
Big Dye Terminator v3.1 Ready RR-100	2.0	Applied Biosystems (Carlsbad, CA)
BigDye Terminator v1.1/v3.1 Sequencing Buffer (5X)	2.0	Applied Biosystems (Carlsbad, CA)
Molecular Biology Grade Water	0.8	Mediatech (Manassas, VA)
Forward or reverse primer, 1 $\mu$ M	3.2	Integrated DNA Technologies (Coralville, IA)

**Table 14. Reagents for sequencing reaction.**



Reaction conditions for the sequencing reaction were set on the GeneAmp PCR System 9700 (Applied Biosystems, Carlsbad, CA) as follows:

initial DNA denaturation:	96°C for 1min	
DNA denaturation:	96°C for 10sec	} 25 cycles
primer annealing:	50°C for 5sec	
product elongation:	60°C for 4min	
cooling:	4°C until program was stopped	

### 2.3.5. Sequencing product purification

Reagent	Company
MultiScreen-HV plate, pore size 0.45µm	Millipore (Billerica, MA)
Sephadex G-50 Fine	GE Healthcare (Little Chalfont, United Kingdom)
MultiScreen Column Loader, 45µl	Millipore (Billerica, MA)
Molecular Biology Grade Water	Mediatech (Manassas, VA)
PCR Plate	Bioexpress (Kaysville, UT)
MicroAmp 96-Well Tray/Retainer Set	Applied Biosystems (Carlsbad, CA)
MicroAmp 96-Well Base	Applied Biosystems (Carlsbad, CA)
Formamide	Amresco (Solon, OH)
Mineral oil	Hoefer (Holliston, MA)
Round Bottom 96-Well Plate	Fisher Scientific (Waltham, MA)
MultiScreen Centrifuge Alignment Frame	Millipore (Billerica, MA)
96-Well Plate Septa	Applied Biosystems (Carlsbad, CA)

**Table 15. Reagents and materials for sequencing product purification.**

To remove unincorporated dye and nucleotides, sequencing products were purified using filter plates filled with a gel-filtration medium (for materials and reagents see table 15): Each well of a MultiScreen-HV plate was filled with Sephadex G-50 Fine using a MultiScreen Column Loader and hydrated with 300µl of Molecular Biology Grade Water. The plate was stored for two hours at room temperature. A PCR plate was placed into a MicroAmp 96-Well Tray/Retainer Set and onto a MicroAmp 96-Well Base. Each well of the PCR plate was filled with 10µl of formamide and 10µl of mineral oil. To remove excess water, the hydrated MultiScreen-HV plate was centrifuged at 910 x g for 6 min while connected to a Round Bottom 96-Well Plate and subsequently placed on top of the PCR plate using a MultiScreen Centrifuge Alignment Frame. 10µl of sequencing reaction product were transferred to each well of the MultiScreen-HV plate. By centrifuging the attached plates at 910 x g for 6 min, the sequencing product ran through the filtration medium and filter of the MultiScreen-HV

plate into the formamide of the PCR plate. This plate was sealed with a 96-Well Plate Septa and subsequently applied to basecalling.

### **2.3.6. Basecalling and sequence analysis**

Basecalling is an automated process utilizing a combination of capillary electrophoresis and fluorescence detection.

Basecalling was performed on the Applied Biosystems 3130xl Genetic Analyzer with 36cm capillary array length and POP-7 polymer (Applied Biosystems, Carlsbad, CA) using the KB basecaller software (Applied Biosystems, Carlsbad, CA).

Sequencing data was analyzed with the CLC Main Workbench software (version 6.6.1, CLC bio, Aarhus, Denmark). Once sequences were assembled to the corresponding NCBI Reference Sequences (National Center for Biotechnology Information 2002), conflicts were identified using the software's secondary peak calling. Additionally to software analysis, all electropherograms were visually inspected for the rare variants identified in targeted resequencing.

## 2.4 Copy number variation analysis

Array CGH detects copy number differences between a sample and a reference DNA. The reference DNA is gained from a healthy individual and assumed to not contain pathogenic variants. Sample and reference DNA are differentially labeled with cyanine fluorescent dyes (Cy3 and Cy5) and then simultaneously hybridized to an oligonucleotide slide. Every oligonucleotide probe represents a locus along the human genome. If sample and reference DNA differ in copy number at a certain locus, this will be reflected in fluorescent intensity differences of Cy3 and Cy5 for the corresponding probe. The fluorescence is excited and measured by a laser scanner. To visualize the data the  $\log_2$  of fluorescence intensity ratios is plotted against the loci of probes.

Genome-wide array CGH was applied to the identification of rare CNVs in all patients from cohort 2. Arrays with rare non-recurrent CNVs were replicated for validation. Where available, parental DNA was investigated to determine whether the CNV had arisen *de novo* or was inherited.

Array platforms used had a median probe spacing of 13kb for 4x180K arrays (Agilent Technologies, Santa Clara, CA) and 2.1kb for 1M arrays (Agilent Technologies, Santa Clara, CA) with a slightly higher probe coverage within RefSeq genes (National Center for Biotechnology Information 2002).

### 2.4.1 Labeling

Labeling was performed using the Dual-Color DNA Labeling Kit (NimbleGen, Madison, WI, table 16). Reference DNA originated from a male Caucasian and was extracted from an EBV-transformed B-lymphocyte cell line.

The labeling process as well as isopropanol precipitation and ethanol washing were carried out following the manufacturer's instructions (Roche NimbleGen 2011, chapter 3) with minor modifications: The initial sample and reference DNA amounts were changed from 500ng to 250ng. Accordingly, the amounts of all labeling reagents, isopropanol and ethanol were halved.

The dried pellets were gradually rehydrated with 15-35  $\mu$ l of water per 250ng starting material to reach a DNA concentration around 2000ng/ $\mu$ l measured on the NanoDrop 2000 Spectrophotometer (Thermo Fisher Scientific, Waltham, MA).

Reagent	Company
Dual-Color DNA Labeling Kit - PCR Grade Water - Random Primer Buffer - Cy3 Random Nonamers - Cy5 Random Nonamers - Klenow Fragment (3'->5' exo-), 50 U/μl - dNTP Mix (10mM each dNTP) - Stop Solution	NimbleGen (Madison, WI)
2-Mercaptoethanol	Bio-Rad (Hercules, CA)
2-Propanol (Isopropanol)	Sigma Aldrich (St. Louis, MO)
Pure Ethanol 200 Proof	Decon Laboratories (King of Prussia, PA)

**Table 16. Reagents for labeling, isopropanol precipitation and ethanol washing.**

## 2.4.2 Hybridization

Equal amounts of labeled sample and reference DNA were added together as specified in table 17 and prepared for hybridization with the Agilent Oligo aCGH/ChIP-on-Chip Hybridization Kit (table 18) following the manufacturer's instructions (Agilent Technologies 2011, chapter 4, step 3). Cot-1 DNA was not used and its volume replaced by water.

Labeled DNA	4x180K array	1M array
Sample DNA	10μg	25μg
Reference DNA	10μg	25μg

**Table 17. Amounts of labeled DNA prepared for hybridization.**

Reagent	Company
Oligo aCGH/ChIP-on-Chip Hybridization Kit - 2X Hi-RPM Hybridization Buffer - 10X Oligo aCGH/ChIP-on-Chip Blocking Agent	Agilent Technologies (Santa Clara, CA)

**Table 18. Reagents for hybridization preparation.**

Microarray loading was conducted as specified by Agilent Technologies (Agilent Technologies 2011, chapter 5, step 1) using the following materials:

Material	Company
Gasket slide, 4 microarrays/slide format	Agilent Technologies (Santa Clara, CA)
Gasket slide, 1 microarray/slide format	Agilent Technologies (Santa Clara, CA)
SurePrint G3 Human CGH Microarray Kit, 4x180K	Agilent Technologies (Santa Clara, CA)
SurePrint G3 Human CGH Microarray Kit, 1x1M	Agilent Technologies (Santa Clara, CA)
Microarray Hybridization Chamber Kit	Agilent Technologies (Santa Clara, CA)

**Table 19. Hybridization materials.**

Loaded 4x180K arrays were incubated at 65°C for 40 hours, 1x1M arrays at 65°C for 48 hours in the G2545A Hybridization Oven (Agilent Technologies, Santa Clara, CA) with rotary motion (16rpm).

### 2.4.3 Washing

After hybridization, the microarray slides were washed to remove excess hybridization solution. Washing was performed as described in the Agilent protocol (Agilent Technologies 2011, chapter 5, step 2 and 3, washing procedure A) using the materials and reagents listed in table 20. Subsequently, slides were placed in a slide holder and covered with an ozone-barrier slide to avoid ozone-induced degradation of Cyanine dyes.

Reagent/material	Company
Oligo aCGH/ChIP-on-Chip WB1	Agilent Technologies (Santa Clara, CA)
Oligo aCGH/ChIP-on-Chip WB2	Agilent Technologies (Santa Clara, CA)
Slide holder	Agilent Technologies (Santa Clara, CA)
Ozone-Barrier Slide Cover Kit	Agilent Technologies (Santa Clara, CA)

**Table 20. Washing materials and reagents.**

### 2.4.4 Scanning and Feature Extraction

Microarray slides were scanned on a G2505C DNA Microarray Scanner (Agilent Technologies, Santa Clara, CA) using the Agilent Scan Control software (version A.8.4.1) with the preset Agilent G3 CGH/CNV/ChIP scan profile (resolution 3 $\mu$ m).

The output image file was further processed by the Agilent Feature Extraction software (version 10.7.3.1) using the default CGH\_107\_Sep09 protocol.

### 2.4.5 Data processing and CNV calling

Further data processing and analysis were performed using the Agilent Genomic Workbench software (standard edition, version 5.0.14). Log<sub>2</sub> ratios for each array were normalized applying the centralization algorithm with bin size 10 and centralization threshold 6.0. Intra-array replicates were combined using the corresponding Genomic Workbench function. Saturated and non-uniform features were excluded from further analysis.

The Derivative Log Ratio Spread (DLRS) is an estimate of signal noise and was used for quality control. It describes the standard deviation of the probe-to-probe log<sub>2</sub> ratio difference, averaged across the genome and divided by  $\sqrt{2}$ . All arrays had a DLRS  $\leq 0.3$  and 26 of 36 arrays had a DLRS  $< 0.2$  defined as excellent by Agilent Technologies.

CNVs were called applying the Aberration Detection Method 2 (ADM-2) algorithm provided by Genomic Workbench with a threshold of 6.0. Additionally, all arrays were visually inspected for CNVs.

#### **2.4.6 Filtering CNV calls**

Aberration filters in Genomic Workbench were set so that only CNVs containing at least 5 probes with a minimum average absolute log ratio of 0.5 were reported.

Subsequently, variants were filtered as previously described (Mefford et al. 2011) to eliminate CNVs that did not overlap any RefSeq genes (National Center for Biotechnology Information 2002), lay entirely within segmental duplications or had a >50% overlap with a CNV detected in 4,519 published controls (Itsara et al. 2009; Shaikh et al. 2009). The last criterion was not applied to established hotspot CNVs known to rarely occur in healthy controls.

All filtered CNVs were assessed by visual analysis in Genomic Workbench.

### **2.5 Deletion breakpoint mapping**

To evaluate if *HNRNPU*, a candidate gene for epilepsy and ID (Caliebe et al. 2010; Ballif et al. 2012; Thierry et al. 2012), was included in the 1q44 deletion of patient #2, deletion breakpoints were refined using the Takara LA PCR Kit (version 2.1, Takara Bio, Otsu, Japan) according to the manufacturer's instructions. Primers were designed to amplify the genomic region encompassing the deletion breakpoints (annex, table S5). Length estimation of PCR fragments in gel electrophoresis allowed to refine the breakpoint regions. Gel electrophoresis was performed as described in chapter 2.3.2 using a 0.6% agarose gel and 1kbp DNA ladder (New England Bio Labs, Ipswich, MA).

### **2.6 Microsatellite analysis**

Microsatellite analysis was used to confirm maternity and paternity for parents of individuals with *de novo* variants in CNV analysis or targeted resequencing. Patient #2 did not undergo microsatellite analysis as she carried further CNVs that were either maternally or paternally inherited. Microsatellite analysis was performed using the PowerPlex S5 System (Promega, Fitchburg, WI) as recommended by the manufacturer.

## 2.7 Evaluation of pathogenicity

### 2.7.1 Pathogenicity of rare SNVs

Only nonsynonymous, splice-site or frameshift variants not present in 6500 controls were analyzed (Exome Variant Server 2012). Variants were assumed to be pathogenic if they had arisen *de novo* or segregated with the disorder. *SCN1A* mutations were also evaluated as pathogenic if the *SCN1A* variant database included mutations at the same cDNA position in affected individuals (*SCN1A* variant database 2009). Additionally, we used the freely available online tools PolyPhen-2 (Adzhubei et al. 2010; PolyPhen-2 2010) and SIFT (Ng and Henikoff 2001; SIFT 2001) to assess the pathogenicity of missense mutations.

Rare variants, where parental DNA was unavailable for analysis, would have been interpreted as likely pathogenic if they led to protein truncation (splice-site, frameshift and nonsense changes). However, such variants were not identified in this study.

All remaining variants were interpreted as of unknown significance.

### 2.7.2 Pathogenicity of rare CNVs

Based on previous CNV studies (Mefford et al. 2011) and on guidelines for the interpretation of clinical array CGH results in patients with autism, ID or CGA (Miller et al. 2010), we established the criteria in table 21 to evaluate the pathogenicity of rare CNVs identified in our study.

Classification	Criteria
pathogenic	- known pathogenic CNVs - CNVs including known epilepsy genes - de novo deletions
likely pathogenic	- de novo duplications - CNVs > 1 Mb (inherited or of unknown inheritance)
of unknown significance	- all remaining CNVs

**Table 21. Evaluation of pathogenicity for rare CNVs.**

## 2.8. Detailed phenotyping

Clinical documentation was reviewed for epilepsy, developmental and general medical history for all patients with rare SNVs, pathogenic or likely pathogenic CNVs. Furthermore, phenotyping included review of imaging and EEG data where available.

## 3 Results

### 3.1 Targeted resequencing

23 (27%) of 84 individuals with recurrent FS or fever-associated epilepsies carried a rare possibly damaging SNV, hence a nonsynonymous, splice-site or frameshift mutation not present in 6500 controls (Exome Variant Server 2012). Five variants occurred *de novo* and nine variants were inherited of which three segregated with the disorder. Nine variants were of unknown inheritance. We did not identify any deleterious recessive mutations.

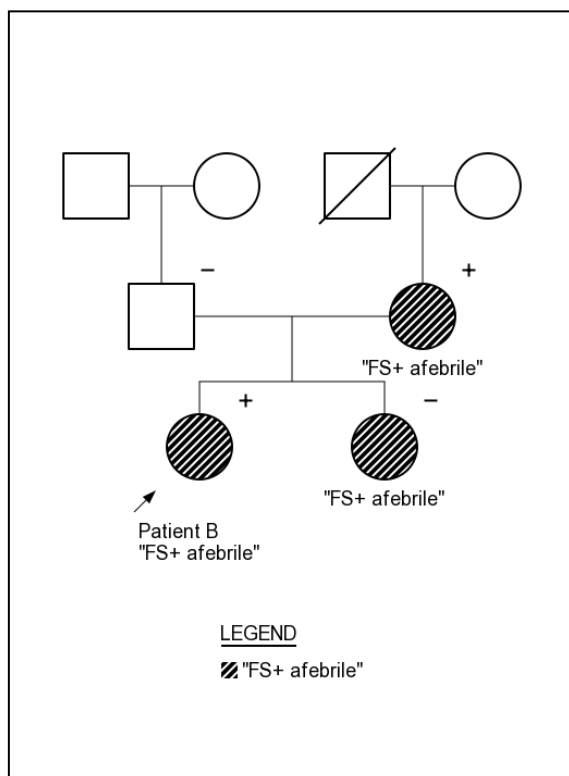
All variants were validated using Sanger sequencing. Microsatellite analysis confirmed maternity and paternity for the parents of individuals with *de novo* mutations.

#### 3.1.1 Pathogenic rare SNVs

We detected 10 pathogenic variants all occurring in known epilepsy genes (table 22).

Eight pathogenic variants occurred in *SCN1A*. Surprisingly, five of eight patients with newly identified *SCN1A* variants were previously tested negative for mutations in this gene using Sanger sequencing.

Three mutation carriers presented with FS+ or SIGEI in the context of GEFS+:

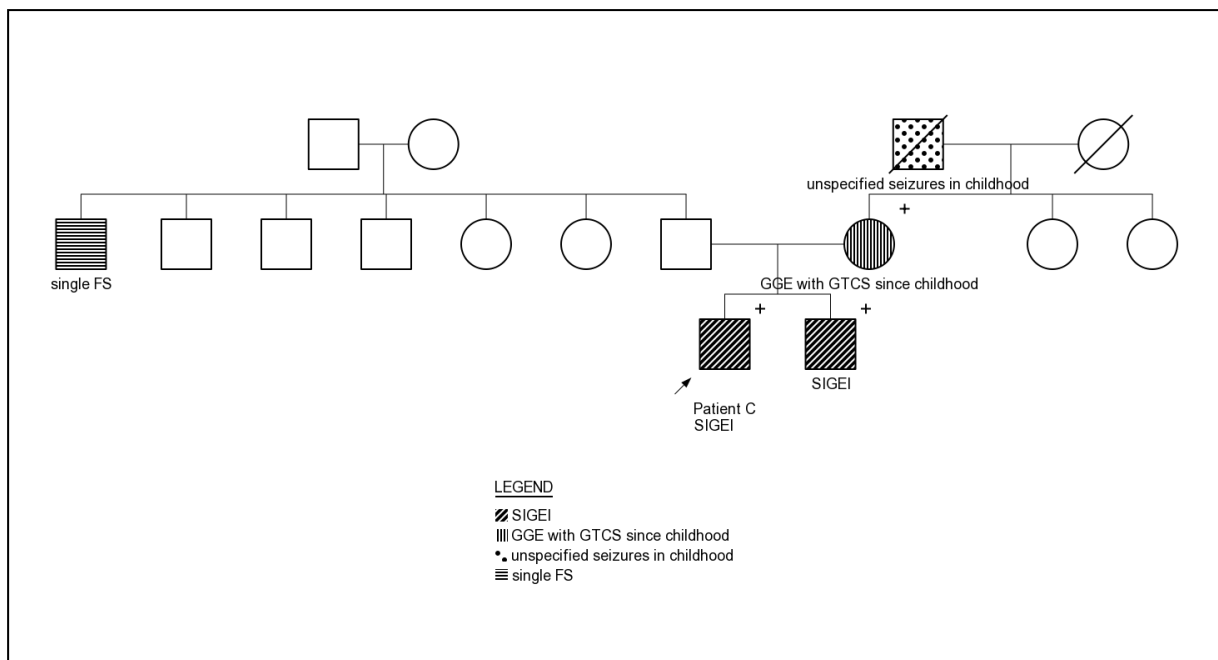


**Figure 3. Pedigree of family 1 with GEFS+ and *SCN1A* mutation.**

FS+ = febrile seizures plus. The arrow indicates the proband. + carries the mutation; - does not carry the mutation; not marked: not investigated for variants in *SCN1A*



Family 1 (patient B) involved the proband, mother and sister with „FS+ afebrile“ and the unaffected father and grandparents (figure 3). The *SCN1A* mutation was maternally inherited. The also affected sister with recurrent FS in childhood and afebrile GTCS in youth did not carry the variant. We nevertheless evaluated the variant as pathogenic considering the sister’s clinical presentation a phenocopy. Epilepsy and especially FS are relatively frequent in the population and might occur in GEFS+ pedigrees but be due to different genetic risk factors than the one segregating in the family (Helbig 2014). The grandparents were not tested for *SCN1A* mutations.



**Figure 4. Pedigree of family 2 with GEFS+ and *SCN1A* mutation.**

FS = febrile seizures; GGE = genetic generalized epilepsy; GTCS = generalized tonic-clonic seizures; SIGEI = severe idiopathic generalized epilepsy of infancy. The arrow indicates the proband. + carries the mutation; - does not carry the mutation; not marked: not investigated for variants in *SCN1A*

Family 2 (patient C) comprised the proband and his brother with SIGEI, the mother with GGE and the unaffected father (figure 4). The maternally inherited *SCN1A* mutation also occurred in the affected brother strongly suggesting pathogenicity of the variant. The maternal grandfather had unspecified seizures in childhood. A paternal uncle had FS in early childhood. The father, aunts, uncles and grandparents were not tested for *SCN1A* variants.

Patient D of family 3 presented with FS+ and additional myoclonic and atonic seizures in accordance with myoclonic-astatic epilepsy (MAE). The *SCN1A* mutation was paternally inherited and segregated with recurrent FS in brother and sister and with FS+ in the proband

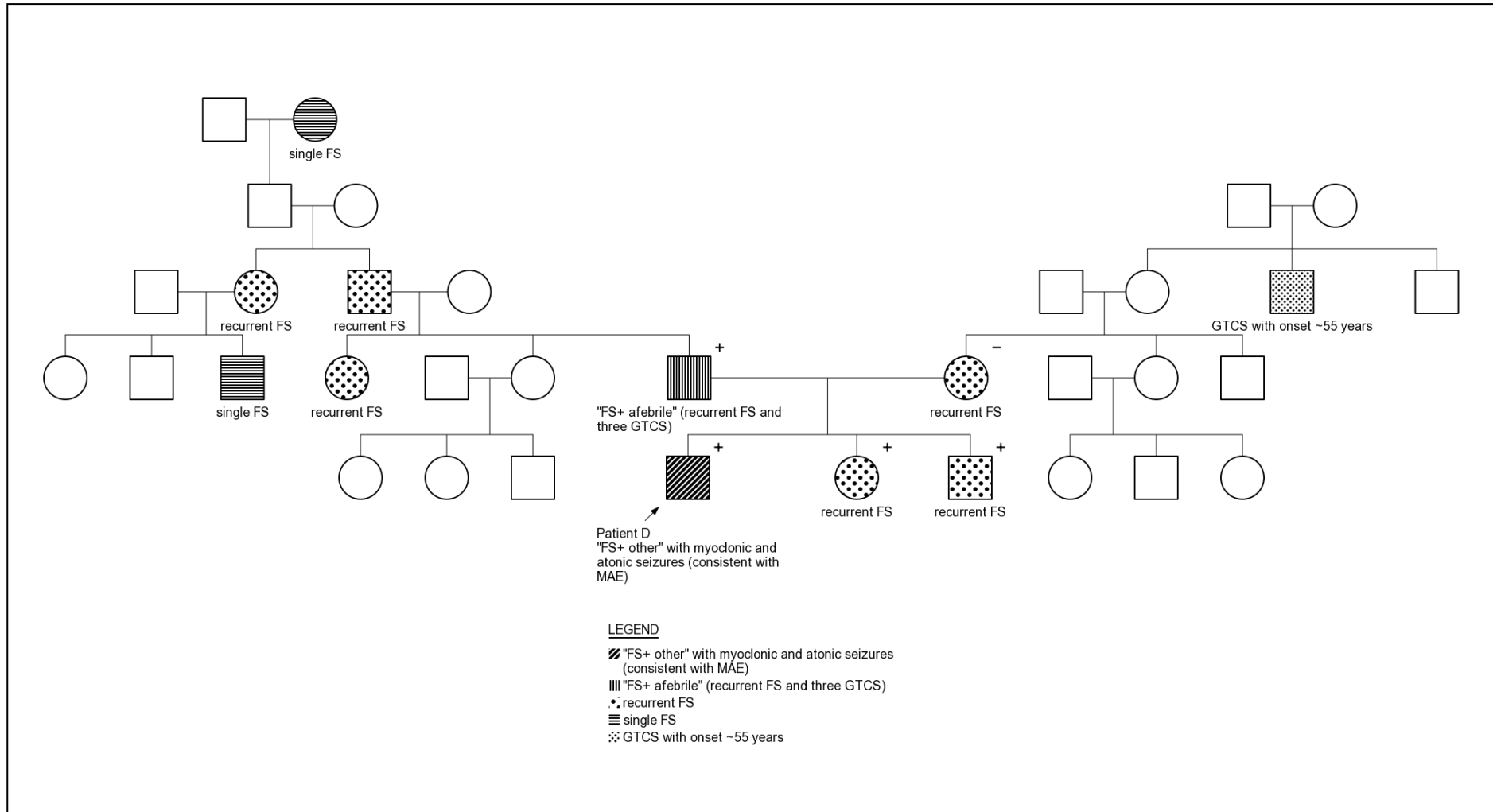
and his father (figure 5). The also affected mother (recurrent FS) did not carry the mutation, but was interpreted as a phenocopy. Moreover, five additional paternal relatives presented with a single or recurrent FS indicating that the variant segregated from the paternal side of the family. However, we did not investigate these individuals for mutations in *SCN1A*.

We identified *de novo* *SCN1A* mutations in three patients and *SCN1A* variants of unknown inheritance in two patients with typical or atypical Dravet syndrome. For the latter, the *SCN1A* variant database included mutations at the same cDNA position in patients with Dravet syndrome supporting the assumption of pathogenicity for these variants (*SCN1A* variant database 2009).

One pathogenic *de novo* mutation was identified in *GABRA1* and *SCN2A* respectively. Both variants were missense mutations and predicted to be damaging by PolyPhen-2 and SIFT.

The *GABRA1* mutation was identified in a patient with hemiclonic status epilepticus while bathing and one generalized seizure during febrile illness in the first year of life. In infancy, the patient's phenotype was consistent with Dravet syndrome. However, later on, frequent absence seizures, mild ID, long periods of seizure-freedom as well as 3/s-spike waves and photosensitivity in the EEG suggested a diagnosis in favor of GGE.

The *SCN2A* mutation occurred in an individual with a diagnosis of *SCN1A*-negative Dravet syndrome, but a febrile infection-related epilepsy syndrome (FIRES) was also taken into consideration. The first seizures occurred at the age of three years during a febrile illness without an identifiable focus of infection. Two weeks after seizure onset, the child developed catastrophic epilepsy with several therapy-resistant convulsive seizures per hour. This biphasic clinical course with a short interval between initial seizures in the context of febrile illness and acute period of high seizure activity would be typical of FIRES. However, the patient's outcome was better than in most individuals with FIRES that frequently present with therapy-refractory focal epilepsy and a vegetative or minimally conscious state (van Baalen et al. 2010): The development before seizure onset was unremarkable. The child experienced regression at seizure onset and presented with moderate ID over time. The patient predominantly had generalized seizures including myoclonic seizures that are common in Dravet syndrome. At the age of 21 years, the patient had a few epileptic seizures per year.



**Figure 5. Pedigree of family 3 with GEFS+ and SCN1A mutation.**

FS = febrile seizures; FS+ = febrile seizures plus; GTCS = generalized tonic-clonic seizures; MAE = myoclonic-astatic epilepsy. The arrow indicates the proband. + carries the mutation; - does not carry the mutation; not marked: not investigated for variants in *SCN1A*

Patient (sex)	Gene with variant	Inheritance	Family history	gDNA change (hg19)	cDNA change	Amino acid change	Function	Poly Phen-2 (HumVar) <sup>a</sup>	SIFT <sup>b</sup>	Evaluation of pathogenicity
Patient A (♂)	<i>GABRA1</i>	<i>de novo</i>	no epilepsy in family	chr5:161322732A>C	c.917A>C (NM_001127644)	p.Lys306Thr (NP_001121116)	missense	prob. damaging (0.932)	damaging (0)	pathogenic
Patient B (♀)	<i>SCN1A</i>	maternal, S does not carry the mutation	M and S: FS+ afebrile (recurrent FS in childhood, afebrile GTCS in youth); F: unaffected (figure 3)	chr2:166870327C>T	c.3632G>A (NM_001165963)	p.Cys1211Tyr (NP_001159435)	missense	prob. damaging (1.000)	damaging (0)	pathogenic
Patient C (♂)	<i>SCN1A</i>	maternal, B also carries the mutation	M: GGE with GTCS; F: unaffected; B: SIGEI (figure 4)	chr2:166870299A>C	c.3660T>G (NM_001165963)	p.Phe1220Leu (NP_001159435)	missense	prob. damaging (0.999)	damaging (0)	pathogenic
Patient D (♂)	<i>SCN1A</i>	paternal, B and S also carry the mutation	F: FS+ afebrile (recurrent FS, three afebrile GTCS); M, B, S: recurrent FS (figure 5)	chr2:166848659G>T	c.5126C>A (NM_001165963)	p.Thr1709Asn (NP_001159435)	missense	prob. damaging (1.000)	damaging (0)	pathogenic ( <i>SCN1A</i> database)
Patient E (♀)	<i>SCN1A</i>	unknown	maternal grandmother: two FS, apart from that no epilepsy in family	chr2:166904174A>G	c.1133T>C (NM_001165963)	p.Leu378Pro (NP_001159435)	missense	prob. damaging (0.999)	damaging (0)	pathogenic ( <i>SCN1A</i> database)
Patient F (♀)	<i>SCN1A</i>	<i>de novo</i>	paternal aunt: seizures after vaccination, apart from that no epilepsy in family	chr2:166904279C>T	c.1029-1G>A (NM_001165963)	unknown	splice-site	NA	NA	pathogenic ( <i>SCN1A</i> database)
Patient G (♀)	<i>SCN1A</i>	not in M	no epilepsy in family	chr2:166904178G>A	c.1129C>T (NM_001165963)	p.Arg377* (NP_001159435)	stop-gained	NA	NA	pathogenic ( <i>SCN1A</i> database)
Patient H (♀)	<i>SCN1A</i>	<i>de novo</i>	no epilepsy in family	chr2:166848852G>A	c.4933C>T (NM_001165963)	p.Arg1645* (NP_001159435)	stop-gained	NA	NA	pathogenic ( <i>SCN1A</i> database)
Patient I (♂)	<i>SCN1A</i>	<i>de novo</i>	no epilepsy in family	chr2:166872228C>A	c.3439G>T (NM_001165963)	p.Glu1147* (NP_001159435)	stop-gained	NA	NA	pathogenic
Patient J (♀)	<i>SCN2A</i>	<i>de novo</i>	no epilepsy in family	chr2:166223873G>C	c.3776G>C (NM_021007)	p.Gly1223Arg (NP_066287)	missense	prob. damaging (0.987)	damaging (0.01)	pathogenic

**Table 22. Pathogenic SNVs identified in targeted resequencing of 84 patients.**

B: brother; F: father; FS = febrile seizures; FS+ = febrile seizures plus; GGE = genetic generalized epilepsy; GTCS = generalized tonic-clonic seizures; M: mother; S: sister; SIGEI = severe idiopathic generalized epilepsy of infancy, *SCN1A* database = entry in the *SCN1A* variant database included affected individuals with mutations at the same cDNA position; <sup>a</sup>(Adzhubei et al. 2010; PolyPhen-2 2010); <sup>b</sup>(Ng and Henikoff 2001; SIFT 2001)

### 3.1.2 Rare SNVs of unknown significance

We identified 13 rare variants of unknown significance (table 23). All variants were missense mutations not segregating with the disorder or of unknown inheritance.

Six variants occurred in known epilepsy genes. An individual with FS+ carried a *GABRG2* mutation predicted as damaging by PolyPhen-2 and SIFT, but of unknown inheritance. A *SCN1B* mutation predicted as probably damaging was detected in a patient with *SCN1A*-negative Dravet syndrome. Unfortunately, parental DNA was unavailable for this individual. We identified two *SLC2A1* variants. One mutation occurred in a patient with SIGEI and was evaluated as benign by both online tools. The other *SLC2A1* variant was detected in a patient with FS+ and inherited from an unaffected mother. The father and sister with recurrent FS did not carry the mutation suggesting that other genetic risk factors might contribute to the epilepsy phenotypes in this family. Mutations in *SPTAN1* were found in a patient with *SCN1A*-negative Dravet syndrome (inherited from an unaffected mother) and an individual with recurrent FS (of unknown inheritance). PolyPhen-2 and SIFT gave contradictory predictions for these variants.

Seven variants of unknown significance occurred in candidate epilepsy genes. An *EPHA6* variant of unknown inheritance was identified in a patient with mild FS+ and predicted as benign by both online tools. *ADAM22* mutations occurred in a patient with FS+ and in an individual with *SCN1A*-negative Dravet syndrome and had contradictory predictions for pathogenicity by PolyPhen-2 and SIFT. The variants were inherited from an unaffected father and a mother with unknown medical history respectively. A mildly affected individual with FS+ and a patient with *SCN1A*-negative Dravet syndrome each carried a *DLGAP2* variant predicted as benign. The mutation of the FS+ patient was inherited from an unaffected mother and also occurred in both unaffected sisters arguing against pathogenicity of the variant. The other *DLGAP2* mutation was of unknown inheritance. Mutations with contradictory pathogenicity predictions were identified in *DLGAP1* in a patient with FS+ and in *ADAM23* in a patient with *SCN1A*-negative Dravet syndrome. The *DLGAP1* variant was inherited from an unaffected mother. The *ADAM23* mutation was of unknown inheritance.

### 3.1.3 Phenotypes of patients with rare SNVs

Table 24 gives detailed information on the phenotypes of all patients with rare variants.

Patient (sex)	Gene with variant	Inheritance	Family history	gDNA change (hg19)	cDNA change	Amino acid change	Function	Poly Phen-2 (HumVar) <sup>a</sup>	SIFT <sup>b</sup>	Evaluation of pathogenicity
Patient K (♂)	<i>GABRG2</i>	unknown	no epilepsy in family	chr5:161580306C>T	c.1480C>T (NM_198903)	p.Arg494Trp (NP_944493)	missense	prob. damaging (1.000)	damaging (0)	unknown
Patient L (♀)	<i>SCN1B</i>	unknown	M: unspecified epilepsy in infancy, apart from that no epilepsy in family	chr19:35523453G>A	c.62G>A (NM_001037)	p.Cys21Tyr (NP_001028)	missense	prob. damaging (0.979)	damaging (0; low conf.)	unknown
Patient M (♂)	<i>SLC2A1</i>	maternal, S does not carry the mutation	M: unaffected; F and S: recurrent FS	chr1:43394886C>T	c.967G>A (NM_006516)	p.Val323Met (NP_006507)	missense	prob. damaging (0.964)	damaging (0)	unknown
Patient N (♀)	<i>SLC2A1</i>	unknown	no neurological disorders in family	chr1:43394653C>T	c.1024G>A (NM_006516)	p.Ala342Thr (NP_006507)	missense	benign (0.027)	tolerated (0.2)	unknown
Patient O (♂)	<i>SPTAN1</i>	unknown	no epilepsy in family; F: speech delay	chr9:131395569G>A	c.7390G>A (NM_001130438)	p.Ala2464Thr (NP_001123910)	missense	prob. damaging (0.982)	tolerated (0.71; low conf.)	unknown
Patient P (♀)	<i>SPTAN1</i>	maternal	no epilepsy in family	chr9:131367651G>A	c.3941G>A (NM_001130438)	p.Cys1314Tyr (NP_001123910)	missense	prob. damaging (0.979)	tolerated (0.11)	unknown
Patient Q (♂)	<i>ADAM22</i>	paternal	no epilepsy in family	chr7:87778355T>C	c.1549T>C (NM_021723)	p.Ser517Pro (NP_068369)	missense	benign (0.004)	damaging (0.04)	unknown
Patient R (♂)	<i>ADAM22</i>	maternal	unknown	chr7:87760671C>G	c.913C>G (NM_021723)	p.Pro305Ala (NP_068369)	missense	possib. damaging (0.511)	tolerated (0.41)	unknown
Patient S (♀)	<i>ADAM23</i>	unknown	no epilepsy in family	chr2:207460812C>T	c.2285C>T (NM_003812)	p.Thr762Ile (NP_003803)	missense	benign (0.317)	damaging (0.04)	unknown
Patient T (♂)	<i>DLGAP1</i>	maternal	no epilepsy in family	chr18:3880037T>C	c.32A>G (NM_004746)	p.His11Arg (NP_004737)	missense	prob. damaging (0.999)	tolerated (0.08)	unknown
Patient U (♂)	<i>DLGAP2</i>	maternal, S1 and S2 also carry the mutation	M, S1 and S2: unaffected; F: one FS	chr8:1514057A>T	c.1199A>T (NM_004745)	p.Gln400Leu (NP_004736)	missense	benign (0.075)	tolerated (0.1)	unknown
Patient V (♂)	<i>DLGAP2</i>	unknown	no epilepsy in family	chr8:1616750G>C	c.1826G>C (NM_004745)	p.Ser609Thr (NP_004736)	missense	benign (0.002)	tolerated (0.72)	unknown
Patient W (♂)	<i>EPHA6</i>	not in M	no epilepsy in family	chr3:96945251A>G	c.1258A>G (NM_001080448)	p.Met420Val (NP_001073917)	missense	benign (0.004)	tolerated (0.46)	unknown

**Table 23. Rare SNVs of unknown significance identified in targeted resequencing of 84 patients.**

B: brother; F: father; FS = febrile seizures; low conf. = low confidence; M: mother; S: sister; <sup>a</sup>(Adzhubei et al. 2010; PolyPhen-2 2010); <sup>b</sup>(Ng and Henikoff 2001; SIFT 2001)

Patient (sex)	age at last clinical assessment	Diagnosis at clinical assessment	Seizure onset, seizure type	Other seizure types	Seizure outcome at last clinical assessment	Development: before, after seizure onset (regression)	EEG	MRI	Additional features/information	Gene with variant
Patient A (♂)	20 y	atypical DS, no previous <i>SCN1A</i> sequencing	8 mo, hemiclonic SE while bathing	Abs, Ast, GTCS, FDS, M	seizure-free for 3 y	normal, mild ID (no)	8 mo: right centro-parietal foci and hypersynchronous activity; 2 y: 3/s-SW and theta activity; 19 y: borderline background slowing and photosensitivity °II	12 y: normal	temperature-sensitive seizures; behavioral problems with strong aggressive tendencies	<i>GABRA1</i>
Patient B (♀)	17 y	<i>SCN1A</i> -negative FS+ afebrile	18 mo, recurrent convulsive FS	febrile and afebrile seizures, GTCS	single GTCS, longer periods of seizure freedom (months to several years)	normal, normal (no)	at onset: NA; 2 y: theta activity, irregular generalized SW; 17 y: normal	NA	Wolff-Parkinson-White syndrome	<i>SCN1A</i>
Patient C (♂)	15 y	<i>SCN1A</i> -negative atypical DS/SIGE1	22 mo, recurrent febrile GTCS	febrile and afebrile GTCS	seizure-free for 5 y	normal, moderate ID (unknown)	2 y: normal; 3 y: irregular SW; 15 y: normal under VPA and potassium bromide	NA	behavioral problems with strong aggressive tendencies	<i>SCN1A</i>
Patient D (♂)	8 y	FS+ other (consistent with MAE), no previous <i>SCN1A</i> sequencing	4 mo, FS	febrile GTCS, At, M, Abs	seizure-free for several months	unknown, ID (no)	3 y: generalized SW, polySW; 8 y: pronounced central $\mu$ -rhythm, single sharp waves with left occipital emphasis under hyperventilation	bifrontal, nonspecific subcortical gliosis	Pierre Robin sequence	<i>SCN1A</i>
Patient E (♀)	5 y	DS, previous negative HRMCA of <i>SCN1A</i>	6mo, M	M, febrile and afebrile GCTS, febrile and afebrile SE	seizure reduction with single seizures during fever, then febrile SE	normal, severe ID (yes); dependent on nursing care	8 mo: normal	NA	-	<i>SCN1A</i>
Patient F (♀)	23 y	<i>SCN1A</i> -negative atypical DS/SIGE1	8 mo, GTCS	febrile and afebrile GTCS, SE, myoclonic Abs, Ast, T	1-2 seizures per week	normal, moderate ID (no)	at onset: normal; 2 y: theta activity, 3/s and irregular SW; 23 y: theta activity, irregular SW and SSW	NA	-	<i>SCN1A</i>

**Table 24. Clinical features of patients with rare SNVs.**

Patient (sex)	age at last clinical assessment	Diagnosis at clinical assessment	Seizure onset, seizure type	Other seizure types	Seizure outcome at last clinical assessment	Development: before, after seizure onset (regression)	EEG	MRI	Additional features/information	Gene with variant
Patient G (♀)	5y	<i>SCN1A</i> -negative atypical DS/SIGE1	6 mo, prolonged GTCS	febrile FC evolving to BC, Abs, GTCS, M	~2 GTCS per month	normal, global developmental delay (no)	6 mo: normal; 3 y: background slowing; 5 y: generalized slowing and left centro-temporo-parietal hypersynchronous activity	16 mo: slightly asymmetric occipital lobes (left > right)	-	<i>SCN1A</i>
Patient H (♀)	4 y	<i>SCN1A</i> -negative atypical DS/SIGE1	6 mo, FS	febrile and afebrile GTCS, SE, Abs, M, FDS	single (prolonged) seizures with seizure-free periods of one to a few months	unknown, moderate ID (unknown)	3 y: background slowing, diffuse theta-delta-activity; 4 y: sharp waves, SSW and spikes with right fronto-parietal emphasis, 4/s-activity	3 y: normal	-	<i>SCN1A</i>
Patient I (♂)	19 y	DS, no previous <i>SCN1A</i> sequencing	6 mo, afebrile convulsive seizure	hemiclonic seizure, convulsive FS, focal motor seizures, GTCS	up to 11 GTCS per month	anamnestically normal, moderate ID (unknown)	6 mo: normal; 8 mo: theta and intermittent delta activity, several generalized spikes; 19 y: diffuse theta activity, irregular generalized SW under hyperventilation	18 y: normal	15 y: VNS implantation	<i>SCN1A</i>
Patient J (♀)	21 y	<i>SCN1A</i> -negative DS (FIRES-like phenotype)	3 y, convulsive seizure during fever episode, M	GTCS, M, At, nonconvulsive SE, atypical Abs	few epileptic seizures per year	normal, moderate ID (yes)	diffuse background slowing, generalized spikes, polyspikes and (poly)SW	normal	mild ataxia	<i>SCN2A</i>
Patient K (♂)	13 y	FS+ prolonged and afebrile	2 y, uncomplicated FS	febrile and afebrile GTCS	seizure-free for 3 y	normal; motor delay, then normal (no)	at onset: NA; 2y: normal; 10 y: small centroparietal and left temporal sharp waves; 13 y: normal	NA	-	<i>GABRG2</i>
Patient L (♀)	11 y	<i>SCN1A</i> -negative DS	23 mo, tonic FS	FS, SE, hemiconvulsive seizures, FDS, GTCS	ongoing seizures, predominantly during fever	normal, mild ID (unknown)	generalized polyspikes and SW	normal	microcephaly, axial hypotonia, ataxia	<i>SCN1B</i>

**Table 24 (continued). Clinical features of patients with rare SNVs.**



Patient (sex)	age at last clinical assessment	Diagnosis at clinical assessment	Seizure onset, seizure type	Other seizure types	Seizure outcome at last clinical assessment	Development: before, after seizure onset (regression)	EEG	MRI	Additional features/information	Gene with variant
Patient M (♂)	6 y	FS+ absences	10 mo, convulsive FS	febrile FDS, Abs	ongoing Abs	normal, speech delay (no)	at onset: not done; 4 y: generalized SW, left and single right frontal sharp waves; 6 y: generalized polySW and 3/s SW, right fronto-temporo-parietal sharp and polysharp waves	5 y: three locations of peritrigonal white matter gliosis evaluated as probably not connected to epilepsy	-	<i>SLC2A1</i>
Patient N (♀)	15 y	<i>SCN1A</i> -negative atypical DS/SIGE1	13 mo, febrile GTCS	febrile and afebrile GTCS, T, FDS	ongoing GTCS, single FDS	normal, moderate ID (yes)	at onset: not done; 2 y: theta-delta-activity, stretches of right- or left-hemispheric slow waves; 15 y: theta-delta-activity, single multiregional sharp waves under hyperventilation	2 y: normal	ataxia	<i>SLC2A1</i>
Patient O (♂)	5 y	recurrent FS	unknown, recurrent FS	FS (last one with 2 y)	seizure-free for 3 y	unknown, speech delay (unknown)	at onset: NA; 22 mo: theta activity; 5 y: background slowing (3/s-activity) under hyperventilation	NA	-	<i>SPTAN1</i>
Patient P (♀)	11 y	<i>SCN1A</i> -negative DS	5 mo, hemiconvulsive FS	FS, hemiconvulsive seizures, GTCS, M	ongoing seizures	normal, severe ID (unknown)	slow generalized SW, multifocal epileptic activity	cerebral atrophy, vermis hypoplasia	muscular hypotonia	<i>SPTAN1</i>
Patient Q (♂)	7 y	FS+ afebrile	2 y, febrile GTCS	recurrent febrile and afebrile GTCS, FDS	single FDS (seizure-free periods of several months)	normal; speech and motor delay, then normal (no)	first EEGs: normal; 7 y: irregular generalized SW and polySW, photosensitivity °IV; 7y: normal (under VPA)	6 y: normal	-	<i>ADAM22</i>
Patient R (♂)	unknown	<i>SCN1A</i> -negative DS	unknown	unknown	unknown	unknown	unknown	unknown	unknown	<i>ADAM22</i>
Patient S (♀)	21 y	<i>SCN1A</i> -negative DS	4 mo, M	myoclonic Abs, Abs	ongoing seizures, predominantly at sleep onset	normal, mild to moderate ID (unknown)	generalized SW	periventricular leukomalacia	dysmorphic features	<i>ADAM23</i>
Patient T (♂)	8 y	FS+ afebrile	10 mo, febrile GTS	one FS, three afebrile GTCS	seizure-free for several years	normal, normal (no)	at onset: NA; 13 mo: normal; 8 y: normal	13 mo: slightly delayed myelination	-	<i>DLGAP1</i>

**Table 24 (continued). Clinical features of patients with rare SNVs.**

Patient (sex)	age at last clinical assessment	Diagnosis at clinical assessment	Seizure onset, seizure type	Other seizure types	Seizure outcome at last clinical assessment	Development: before, after seizure onset (regression)	EEG	MRI	Additional features/information	Gene with variant
Patient U (♂)	13 y	FS+ prolonged	3 y, uncomplicated FS	8 y: one FS	seizure-free for several years	normal; speech delay, then normal (no)	at onset: NA; 8 y: normal; 13 y: photosensitivity °I	NA	legasthenia	<i>DLGAP2</i>
Patient V (♂)	24 y	<i>SCN1A</i> -negative DS	8 mo, convulsive FS	FS, GTCS, Abs, myoclonic Abs	ongoing seizures	normal, moderate ID (unknown)	at onset: normal; 2y: generalized SW, diffuse slowing	normal	ataxia	<i>DLGAP2</i>
Patient W (♂)	15 y	FS+ afebrile	first year of life, two FS	one afebrile GTCS	seizure-free for 2 mo	normal, normal (no)	at onset: NA; 14 y: single SW complexes under hyperventilation, photosensitivity °IV; 15 y: photosensitivity °IV	NA	-	<i>EPHA6</i>

**Table 24 (continued). Clinical features of patients with rare SNVs.**

Abs = absence seizures; Ast = astatic seizures; At = atonic seizures; BC = bilateral convulsive seizure; DS = Dravet syndrome; FC = focal clonic seizures; FDS = focal dyscognitive seizures; FIRES = febrile infection-related epilepsy syndrome; FS = febrile seizures; FS+ = febrile seizures plus; GTCS = generalized tonic-clonic seizures; GTS = generalized tonic seizure; HRMCA = high resolution melting curve analysis; ID = intellectual disability; M = myoclonic seizures; mo = months; NA = not available; polySW = polyspike waves; SE = status epilepticus; SIGEI = severe idiopathic generalized epilepsy of infancy; SSW = sharp slow waves; SW = spike waves; T = tonic seizures; VPA = valproic acid; y = years

## 3.2 Copy number variation analysis

### 3.2.1 Rare CNVs

We identified 13 rare CNVs in eight (22%) of 36 patients (table 25) including four individuals with a single, three patients with two and one patient with three CNVs. Three CNVs occurred *de novo*, four variants were inherited and six CNVs were of unknown inheritance.

Microsatellite and CNV segregation analysis confirmed maternity and paternity for the parents of individuals with *de novo* mutations.

Four patients carried pathogenic CNVs previously described in neurodevelopmental disorders (figure 6). Pathogenic variants included two recurrent CNVs, namely a 1q21.1 duplication in patient #8 with *SCN1A*-negative Dravet syndrome and a distal 16p11.2 deletion in patient #3 with unclassified fever-associated epilepsy, ID, autism, generalized muscular hypotonia and macrocephaly. Patient #2 with unclassified fever-associated epilepsy, ID, dysmorphic features, and short stature carried a 1q44 deletion. This individual presented with two additional rare inherited CNVs of unknown significance including a duplication at 6q23.3 and a deletion at 7p22.1. Furthermore, we identified a maternally inherited pathogenic 14q23.3 deletion interrupting *GPHN* and a 4q28.3 deletion of unknown significance in patient #1 with FS+.

Three likely pathogenic CNVs were discovered in two individuals (figure 7). Patient #4 with FS+ presented with a 1.6Mb duplication at 3q13.11 including *ALCAM* and *CBLB*. Two likely pathogenic *de novo* CNVs were identified in patient #5 with atypical Dravet syndrome, a 191kb duplication at 7p14.2 including *ELMO1* and a 217kb duplication at 18q12.2 comprising five zinc finger genes.

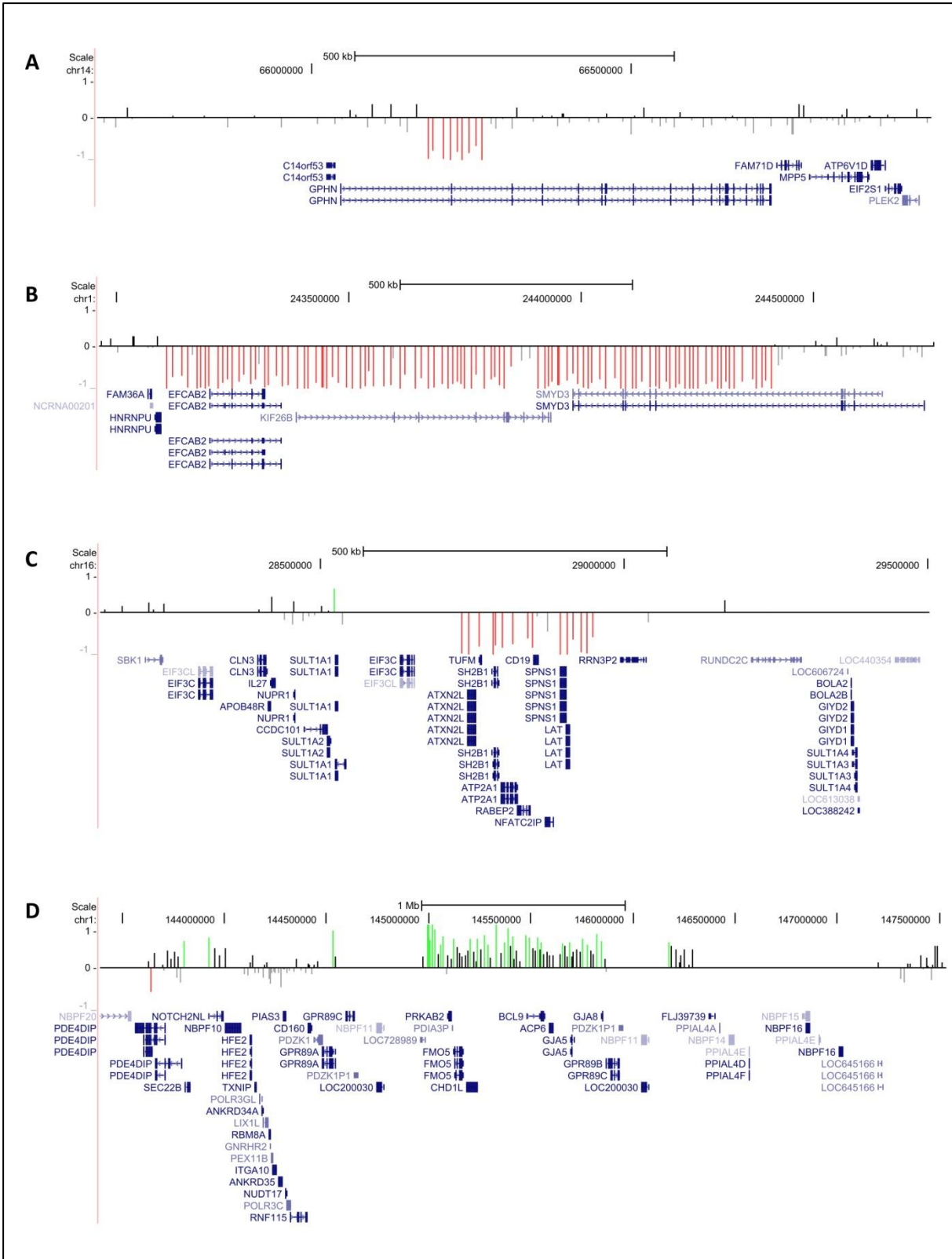
We discovered three additional duplications at 11p15.1, 1p22.3 and 4p15.31 in two patients. These were of unknown significance.

The breakpoints of the 1q44 deletion in patient #2 were narrowed down to chr1: 243090300-243093300 and chr1: 244408023-244411023 (NCBI Build 36), interrupting *HNRNPU* by deleting the first exon of the gene.

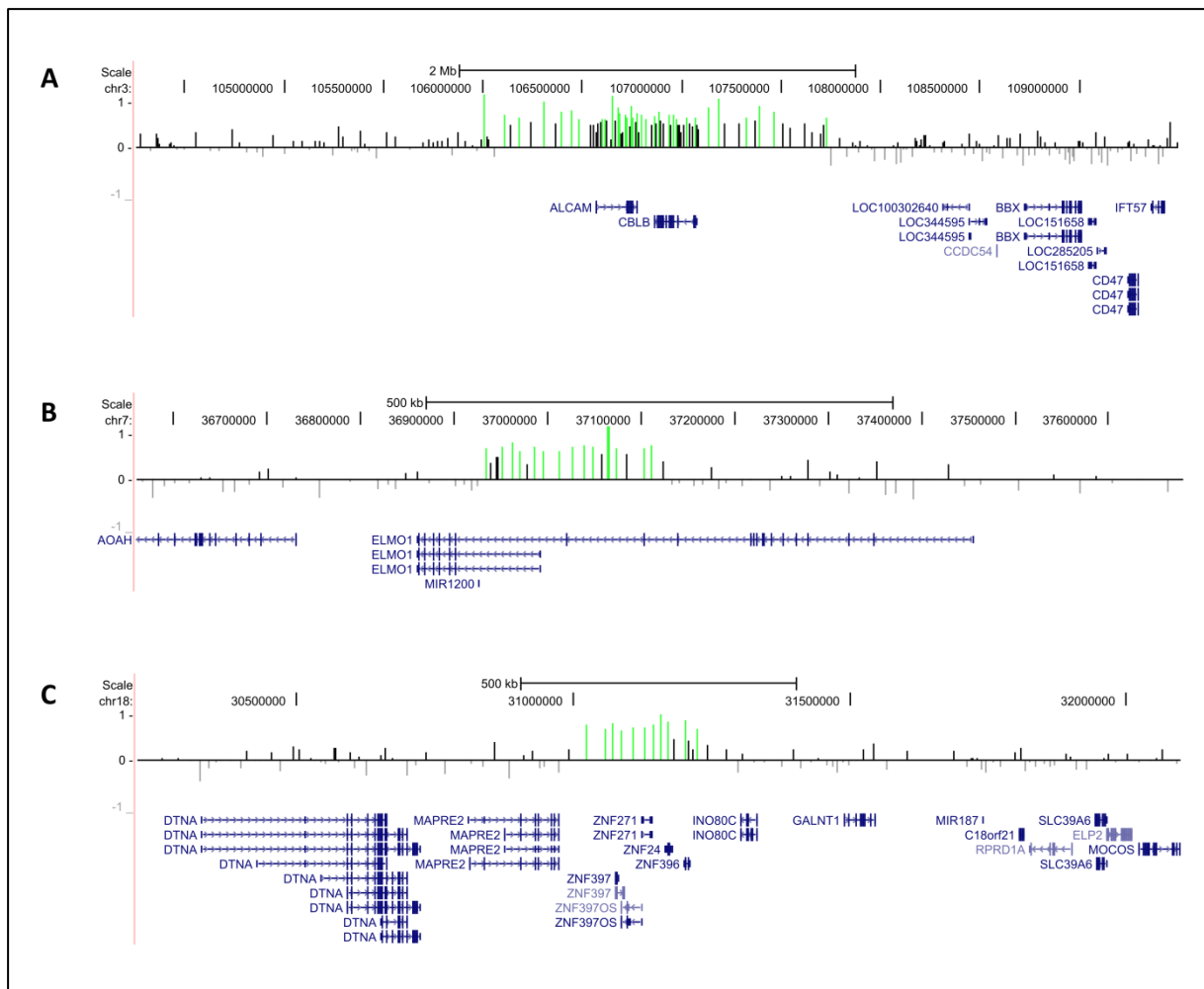
Pat.	Epilepsy phenotype	ID, autism, CGA	CNV, chr location	Coordinates (Build 36, Mb)	Size (kb)	RefSeq genes <sup>c</sup> included	Inheritance	Evaluation of pathogenicity
#1	FS+ afebrile	-	del, 4q28.3	139.29-139.49	197	<i>SLC7A11</i>	not in mother	of unknown significance
			del, 14q23.3	66.18-66.27	85	<i>GPHN</i>	M	pathogenic
#2	unclassified fever-associated epilepsy	ID, short stature, dysmorphic features	del, 1q44	243.11-244.41 <sup>a</sup>	1301 <sup>a</sup>	<i>HNRNPU<sup>a</sup>, EFCAB2, KIF26B, SMYD3</i>	<i>de novo</i>	pathogenic
			dup, 6q23.3	135.89-136.07	184	<i>MIR548H4, C6orf217</i>	M	of unknown significance
			del, 7p22.1	4.88-4.97	85	<i>RADIL, MMD2</i>	F	of unknown significance
#3	unclassified fever-associated epilepsy	ID, autism, generalized muscular hypotonia, macrocephaly	del, 16p11.2	28.73-28.95	218	<i>ATXN2L, TUFM, SH2B1, ATP2A1, RABEP2, CD19, NFATC2IP, SPNS1, LAT</i>	unknown	pathogenic
#4	FS+ prolonged	borderline ID <sup>b</sup>	dup, 3q13.11	106.11-107.73	1623	<i>ALCAM, CBLB</i>	not in mother	likely pathogenic
#5	<i>SCN1A</i> -negative atypical Dravet syndrome	ID	dup, 7p14.2	36.93-37.12	191	<i>ELMO1</i>	<i>de novo</i>	likely pathogenic
			dup, 18q12.2	31.02-31.24	217	<i>ZNF397, ZNF397OS, ZNF271, ZNF24, ZNF396</i>	<i>de novo</i>	likely pathogenic
#6	<i>SCN1A</i> -negative Dravet syndrome	ID, autism	dup, 11p15.1	21.30-21.39	92	<i>NELLI1</i>	M	of unknown significance
#7	<i>SCN1A</i> -negative Dravet syndrome	ID, microcephaly	dup, 1p22.3	87.17-87.28	115	<i>HS2ST1</i>	unknown	of unknown significance
			dup, 4p15.31	21.87-22.73	855	<i>GPR125, GBA3</i>	unknown	of unknown significance
#8	<i>SCN1A</i> -negative Dravet syndrome	ID	dup, 1q21.1	144.53-146.27	1744	<i>GPR89A, GPR89C, PDZK1P1, LOC200030, NBPFI1, LOC728989, PRKAB2, PDIA3P, FMO5, CHD1L, BCL9, ACP6, GJA5, GJA8, GPR89B</i>	unknown	pathogenic

**Table 25. Rare CNVs identified in 36 patients with *SCN1A*-negative fever-associated epilepsies.**

CGA, congenital anomalies; F, inherited from father; FS+, febrile seizures plus; ID, intellectual disability; M, inherited from mother; <sup>a</sup> *HNRNPU* was shown to be interrupted by the deletion by refining the breakpoints with long-range PCR and gel electrophoresis to chr1: 243090300-243093300 and chr1: 244408023-244411023 (NCBI Build 36); <sup>b</sup> full scale intelligence quotient of 75 in the Hamburg Wechsler Intelligenztest für Kinder IV as the German adaption of Wechsler Intelligence Scale for Children IV (Daseking et al. 2007); <sup>c</sup> (National Center for Biotechnology Information 2002); (table as published in Hartmann et al 2015, license agreement with John Wiley and Sons available)



**Figure 6. Array CGH results for all pathogenic CNVs detected in 36 patients.** patient #1, del 14q23.3 (A); patient #2, del 1q44 (B); patient #3, distal del 16p11.2 (C); patient #8, dup 1q21.1 (D). Probe log<sub>2</sub> ratios are plotted against the loci of probes and depicted by vertical lines: between -0.5 and 0 colored gray, between 0 and 0.5 colored black, < -0.5 colored red, > 0.5 colored green. RefSeq genes (National Center for Biotechnology Information 2002) are shown in blue. (figure as published in Hartmann et al 2015, license agreement with John Wiley and Sons available)



**Figure 7. Array CGH results for all likely pathogenic CNVs detected in 36 patients.** patient #4, dup 3q13.11 (A); patient #5, dup 7p14.2 (B); patient #5, dup18q12.2 (C). Probe log<sub>2</sub> ratios are plotted against the loci of probes and depicted by vertical lines: between -0.5 and 0 colored gray, between 0 and 0.5 colored black, < -0.5 colored red, > 0.5 colored green. RefSeq genes (National Center for Biotechnology Information 2002) are shown in blue. (figure as published in Hartmann et al 2015, license agreement with John Wiley and Sons available)

### 3.2.2 Phenotypes of patients with pathogenic CNVs

Phenotype descriptions were published in Hartmann et al. 2015 (agreement with John Wiley and Sons available):

“Patient #1 (FS+ afebrile)

At the age of 17 months, the patient experienced a febrile GTCS in the course of gastroenteritis. A first afebrile generalized tonic seizure occurred in the fourth year of life. Five months later, the patient presented with a second afebrile GTCS. Long-term medication was not started. A first EEG at three and a half years was unremarkable, while a postictal follow-up EEG after the second afebrile seizure revealed intermittent slowing in the right

occipital region. A subsequent follow-up EEG was unremarkable. MRI was not performed. Psychomotor development was unremarkable. Family history was negative with the exception of a maternal aunt with unclassified epilepsy. Array CGH identified a maternally inherited 14q23.3 deletion interrupting *GPHN* and a 4q28.3 deletion of unclear inheritance. Paternal DNA was not available.

*Patient #2 (unclassified fever-associated epilepsy)*

From the age of nine months, the patient experienced recurrent GTCS with fever. Brief absence-like events with extension of the neck occurred up to three times a day starting at the age of 18 months, reminiscent of eyelid myoclonias with absences. In addition, myoclonic seizures were suspected, but could not be recorded. Frequency of GTCS decreased under pharmacotherapy with valproic acid and ethosuximide and the patient was seizure-free from the age of three to five. One break-through seizure resulted in an increase of valproic acid. At the last consultation at the age of seven, the patient had been seizure-free for about two years. Multiple EEGs during the first year of life showed generalized spike-wave discharges. EEGs from the age of two onwards showed no epileptiform activity, but mild to severe background slowing. An MRI performed at the age of two years showed bilateral hippocampal malrotation and a pineal cyst. The findings were not interpreted as causal. Developmental delay was first noted at four months. Unaided sitting was achieved at 14 months, supported walking and single words were present at two years. At the last consultation at the age of seven years, the patient had moderate to severe ID. The patient also had short stature (below the third percentile), head circumference was between the third and tenth percentile. Furthermore, the patient had mild dysmorphic features including a thin upper lip, smooth philtrum, wrinkled skin on the hands and cutaneous syndactyly of second and third toe. Family history was negative for epilepsy. Array CGH revealed a *de novo* 1q44 deletion as well as a 6q23.3 duplication inherited from the mother and a 7p22.1 deletion inherited from the father.

*Patient #3 (unclassified fever-associated epilepsy)*

Between the ages of one to two years, the patient experienced recurrent generalized seizures during fever. The first afebrile GTCS occurred at the age of three. Carbamazepine was initiated at the age of five, resulting in temporary seizure control until the age of seven, when recurring afebrile seizures were refractory to carbamazepine and oxcarbazepine. Seizures were finally controlled by valproic acid in combination with levetiracetam. During the last

consultation at the age of nine years, the patient had been seizure free for four months. Based on clinical grounds, a diagnosis of FS+ could be considered given the prominence of fever-related attacks. However, given the additional syndromic features, we refrained from making this diagnosis. An EEG at the age of one was unremarkable, follow-up EEGs showed severe background slowing and multiregional sharp-waves. MRIs in infancy and at the age of eight were unremarkable. The patient had a diagnosis of autism, severe ID and generalized muscular hypotonia present from birth. Independent walking and single words were present at the age of four. The patient had macrocephaly (>97th percentile), but no dysmorphic features. Family history for epilepsy was negative except for a maternal aunt with unclassified epilepsy in childhood. The patient had previous negative testing for Fragile X, Angelman syndrome and spinal muscular atrophy (*SMNI*). Array CGH detected a distal 16p11.2 deletion of unknown inheritance.

*Patient #8 (SCN1A-negative Dravet syndrome)*

The patient presented with a convulsive febrile status epilepticus at the age of ten months. On valproic acid, the patient experienced four simple FS from twelve months to the age of two and a half years. Subsequently, a second febrile convulsive status epilepticus lateralized to the right side occurred. Lamotrigine was added to valproic acid, resulting in afebrile and febrile GTCS every three months. At the age of six, Lamotrigine was replaced by topiramate, resulting in a reduced seizure frequency of two afebrile and one febrile GTCS between the age of seven and twelve at the last consultation. First EEGs were unremarkable. From the age of six onwards, EEGs showed diffuse slowing but no epileptiform discharges. An MRI performed at the age of seven was unremarkable. Development before seizure onset was reported as normal. Later on, the patient presented with ID; non-verbal IQ (Leiter scale) [(Leiter 1982)] at the age of six was 56. Independent walking was achieved with two and a half years. The patient did not have dysmorphic features, macrocephaly or autism. Family history was negative for epilepsy and other neurological disorders. Array CGH showed a pathogenic 1q21.1 duplication of unknown inheritance.”

### **3.2.3 Phenotypes of patients with likely pathogenic CNVs**

Phenotype descriptions were published in Hartmann et al. 2015 (agreement with John Wiley and Sons available):



*“Patient #4 (FS+ prolonged)*

The patient presented with several febrile seizures per year starting in the second year of life, which lasted until year eight. Seizures were intermittently treated with Primidone, which was eventually discontinued due to side effects. From year three onwards, the patient did not take antiepileptic medication. An EEG at the age of five years was unremarkable. An EEG at age 15 showed photosensitivity grade I-II. A subsequent EEG was unremarkable. An MRI at age 14 did not show any pathologic findings. The patient underwent physiotherapy, occupational therapy and speech therapy as development was slightly delayed. Speech delay persisted during childhood and the patient was diagnosed with dysgrammatism and dyslalia. The patient attended a regular school. In adolescence, psychological testing showed below-average intelligence (HAWIK-IV full scale IQ: 75, CFT20 full scale IQ: 82) [(Cattell and Weiß 1978; Daseking et al. 2007)]. At the age of 14, the patient developed an undifferentiated somatoform disorder that presented with paresthesias of the legs, transient vertigo, headaches, exertional dyspnea and abdominal pain and was treated with psychotherapy. Family history was positive for childhood epilepsy in the mother. Array CGH identified a 1.6 Mb 3q13.11 duplication of unknown inheritance comprising the *ALCAM* and *CBLB* genes. The mother did not carry the CNV. Paternal DNA was not available.

*“Patient #5 (SCN1A-negative atypical Dravet syndrome)*

This patient presented with GTCS at the age of 11 months. Soon, she developed a therapy-resistant epilepsy including afebrile and occasional febrile GTCS, multiple myoclonic seizures a day, absence seizures, and frequent status epilepticus. She had severe intellectual disability and was initially diagnosed with Dravet syndrome. However, fever sensitivity was not as pronounced as would be expected in this syndrome. An EEG at the age of 14 years was unremarkable, earlier EEGs were unavailable for review. Family history was negative for febrile seizures and epilepsy. Array CGH identified two *de novo* duplications at 7p14.2 including *ELMO1* and at 18q12.2 comprising five zinc finger genes.”

## 4 Discussion

### 4.1 Diagnostic yield of targeted resequencing and CNV analysis

We performed targeted resequencing and genome-wide CNV analysis in individuals with recurrent FS and fever-associated epilepsies. We identified rare SNVs in 23 (27%) of 84 patients and rare CNVs in 8 (22%) of 36 individuals. In 10 (12%) of 84 patients and 4 (11%) of 36 individuals, SNVs and CNVs were evaluated as pathogenic.

The diagnostic yield of 12% in targeted resequencing is consistent with the results of a previous study: Carvill et al. identified pathogenic variants in 10% of patients performing gene panel sequencing of 65 genes in 500 individuals with epileptic encephalopathies (Carvill et al. 2013a). However, the comparability of targeted resequencing studies is limited as findings depend on the genes, number of genes and phenotypes investigated. For example, Lemke et al. detected disease-causing variants in 16 (48%) of 33 individuals with various epilepsies sequencing 265 genes (Lemke et al. 2012).

The frequency of pathogenic CNVs in array studies of individuals with epilepsy with or without comorbidities ranges from approximately 5% to 30% (Spreiz et al. 2014). The diagnostic yield of 11% in our CNV analysis lies within this range. Variation in diagnostic yields might be due to differences in array platforms, criteria of pathogenicity and investigated phenotypes. Besides in epilepsy, CNVs have also been established as an important source of mutation in ID, autism and CGA (Miller et al. 2010). Given the comorbidity of these disorders (Pellock 2004; Berg et al. 2011), the diagnostic yield of CNV studies in epilepsy might be upwardly biased due to overlapping phenotypes. Indeed, Mullen et al. identified significantly more individuals carrying rare recurrent CNVs in a cohort with GGE and ID (6/60; 10%) compared to a cohort with GGE alone (11/359; 3%) (Mullen et al. 2013). Our study cohort included several individuals with ID, autism and CGA in addition to fever-associated epilepsy, with ID being the most frequent additional phenotype (table 3). However, in most of the patients with ID (18/26; 69%) cognitive impairment emerged in terms of an epileptic encephalopathy and development was unremarkable before seizure onset. Previous studies suggest that pathogenic CNVs are less frequent in patients with epileptic encephalopathies than in patients with GGE and ID (8/315; 2.5% vs. 11/60; 18%) (Mefford et al. 2011; Mullen et al. 2013). In addition, the frequency of pathogenic CNVs in epileptic encephalopathies does not exceed the one in GGE alone (8/315; 2.5% vs. up to 46/517; 9% depending on criteria of pathogenicity) (Mefford et al. 2010; Mefford et al. 2011).

This indicates that ID linked to epileptic encephalopathies does not relevantly increase the amount of pathogenic CNVs. We compared patients with fever-associated epilepsy and ID present before epilepsy onset or with unknown starting point, autism or CGA to patients with fever-associated epilepsy without these additional features and did not find a significant difference in the amount of pathogenic CNVs (2/14 and 2/22,  $p=0.63$ , Fisher's exact test). However, replication of our investigations in a larger cohort is needed to provide a more accurate estimate of diagnostic yields in fever-associated epilepsies with and without additional neurodevelopmental phenotypes.

## **4.2 The impact of 19 candidate genes in recurrent FS and fever-associated epilepsies**

All pathogenic variants were identified in known epilepsy genes. In addition, we detected 13 variants of unknown significance. Seven of these were found in five of 19 candidate genes. Variants of unknown significance were evaluated as such due to missense mutation type and unknown inheritance or missing segregation with the disorder. In several cases, pathogenicity scores pointed towards a benign variant.

Our results do not give evidence of the investigated candidate genes having an impact in recurrent FS and fever-associated epilepsies. However, variants of unknown significance might still be disease-causing or contribute to the corresponding phenotype. All criteria of pathogenicity can only serve as guidelines, but not as general rules. For example, a variant might just seem to not segregate with the disorder due to reduced penetrance or phenocopies. The latter phenomenon is especially found with disorders having a high frequency in the general population as is the case for FS. In addition, several variants were of unknown significance due to the unavailability of parental DNA or family history, but might have occurred *de novo* or segregate with the disorder.

In our study, we did not identify any pathogenic variants in 19 candidate epilepsy genes. The identification of new epilepsy genes remains difficult. Epilepsy is a genetically heterogeneous disorder and a certain gene might cause disease in only a small percentage of patients requiring large cohorts for gene identification.

## **4.3 Extending the phenotypic spectrum of known epilepsy genes**

We identified eight pathogenic *SCN1A* mutations. This would usually not be surprising for a cohort with fever-associated epilepsies as *SCN1A* mutations are a known cause of Dravet

syndrome and FS+/GEFS+. However, five of eight patients previously had a negative mutation screening for *SCN1A* using Sanger sequencing.

The phenomenon of *SCN1A* mutations in “*SCN1A*-negative” individuals has recently been discovered in different next generation sequencing projects (Suls et al. 2013a; Carvill et al. 2014). An error in PCR resulting in the exclusive replication of the wildtype allele is a possible scenario leading to these false-negative findings. A bias towards one allele during PCR might occur through an impaired primer binding. If a patient carried a single nucleotide polymorphism (SNP) in the primer binding site of the mutated allele the primer might not be able to anneal. Only the wild type allele would be replicated and undergo sequencing. Errors might also occur during analysis of the electropherograms. Heterozygous mutations are sometimes missed by software algorithms and might also escape visual analysis. Capture and replication techniques preceding next generation sequencing are increasingly optimized in terms of allelic bias (Turner et al. 2009b) and as high-throughput sequencing produces many reads of the same sequence, mutations are less likely to escape analysis.

The finding of missed *SCN1A* variants shows that *SCN1A* mutations can be detected in even more than the generally reported 70-80% in Dravet syndrome (Marini et al. 2011) and 10% in GEFS+ (Wallace et al. 2001b; Marini et al. 2007). Sanger sequencing might not be as sensitive as assumed and it might be worth retesting “*SCN1A*-negative” individuals with a next generation sequencing technique.

We detected two additional pathogenic mutations in *GABRA1* and *SCN2A*. The clinical presentation of the affected individuals has not yet been associated with mutations in these known epilepsy genes.

A *de novo* *GABRA1* mutation was identified in an individual showing a clinical picture of Dravet syndrome in the first years of life, but developing symptoms and signs of GGE over time.

*GABRA1* encodes the  $\alpha_1$  subunit of the GABA<sub>A</sub> receptor that mediates inhibition of neuronal activity (Badawy et al. 2009). *GABRA1* mutations have previously been described in two families with GGE and FS (Lachance-Touchette et al. 2011), a proband with sporadic CAE (Maljevic et al. 2006) and in autosomal dominant JME (Cossette et al. 2002). Our patient was also included in a study searching for genes that underlie *SCN1A*-negative Dravet syndrome (Carvill et al. 2014). In total, this study identified four *GABRA1* mutations in 77 individuals with Dravet syndrome. A third study identified a *de novo* *GABRA1* mutation in an individual

with infantile spasms out of 264 patients with infantile spasms and Lennox-Gastaut syndrome (Epi4K Consortium and Epilepsy Phenome/Genome Project 2013).

Our work and the study by Carvill et al. extend the phenotypic spectrum of *GABRA1* mutations to Dravet syndrome. Mutations in the *GABRA1* gene have a broad phenotypic spectrum with GGE and FS at the mild end up to severe epileptic encephalopathies as Dravet syndrome and infantile spasms. This phenotypic diversity might occur inter-, but also intraindividually as in our study patient who was first diagnosed with Dravet syndrome, but presented with GGE at a later point in development.

We identified a *de novo* *SCN2A* mutation in a patient with a diagnosis of Dravet syndrome. However, considering the biphasic and disastrous seizure onset, FIRES was taken into account as a differential diagnosis.

*SCN2A* encodes the  $\alpha_2$  subunit of the neuronal sodium channel. Inherited *SCN2A* mutations have previously been identified in a patient with FS+ (Sugawara et al. 2001) and in families with benign familial neonatal-infantile seizures (BFNIS) (Heron et al. 2002). *De novo* mutations of *SCN2A* were implicated in early infantile epileptic encephalopathies including Dravet syndrome (Shi et al. 2012; Carvill et al. 2013a; Epi4K Consortium and Epilepsy Phenome/Genome Project 2013) and in autism spectrum disorders (Sanders et al. 2012).

Our patient showed clinical features of Dravet syndrome and FIRES. Patients with FIRES have previously been investigated for mutations in *SCN1A*, *POLG* and *PCDH19*, but no pathogenic variants were found (Appenzeller et al. 2012). With our study patient, clinical features of FIRES have now been associated with a *de novo* *SCN2A* mutation. Sequencing of *SCN2A* in patients with FIRES might reveal additional mutations.

## **4.4 The importance of rare CNVs in fever-associated epilepsies**

We detected 13 rare CNVs in eight of 36 individuals with *SCN1A*-negative fever-associated epilepsies. We identified pathogenic CNVs in four and likely pathogenic CNVs in two patients. All pathogenic CNVs were known to occur in patients with different neurodevelopmental disorders and were hence not specific for fever-associated epilepsies.

Our findings extend the phenotypic spectrum of several known microdeletion syndromes to fever-associated epilepsy.

### **4.4.1 Discussion of pathogenic CNVs**

Pathogenic CNVs were discussed in Hartmann et al. 2015:

We detected a pathogenic distal 1q21.1 duplication of unknown inheritance in a patient with *SCN1A*-negative Dravet syndrome. Autism, ID, dysmorphic features and macrocephaly have been described as the main phenotypes in duplication carriers. However, the high frequency of these clinical presentations might be due to an ascertainment bias as these features are common indications for array CGH testing. Several individuals with unspecified seizures and GGE have been reported in the literature (Brunetti-Pierri et al. 2008; Mefford et al. 2008; Rosenfeld et al. 2012). Our study patient did not have autism, dysmorphic features or macrocephaly, but presented with Dravet syndrome associated with ID. Our study adds features of Dravet syndrome to the phenotypic spectrum of 1q21.1 duplications.

A patient with recurrent febrile and afebrile GTCS, profound ID, autism and macrocephaly carried a distal 16p11.2 deletion. This recurrent CNV has previously been identified in individuals with developmental delay, behavioral problems, unusual facial morphology and obesity. Epileptic seizures have only rarely been described in 16p11.2 deletion carriers. Focal dyscognitive seizures occurred in an individual with abnormal configuration of both hippocampi (Barge-Schaapveld et al. 2011). In addition, recurrent febrile and afebrile seizures (Bachmann-Gagescu et al. 2010), SIGEI (Mefford et al. 2010) and unclassified epileptic encephalopathy with febrile and predominant absence seizures (Mefford et al. 2011) have been reported. Our study patient and previously described individuals with distal 16p11.2 deletion presented with fever-associated epilepsy syndromes. Fever-associated epilepsy may represent a recurring feature of 16p11.2 deletion carriers.

The main phenotypes of individuals with 1q44 deletion comprise developmental delay, ID, microcephaly, short stature, corpus callosum anomalies (CCA) and seizures (Caliebe et al. 2010; Ballif et al. 2012; Thierry et al. 2012). We identified a 1q44 deletion in a patient with all of these features besides microcephaly and CCA. In early infancy, the girl was diagnosed with Dravet syndrome as she presented with recurrent febrile GTCS and was suspected of having myoclonic seizures. However, throughout development, additional syndromic features were noted and the epilepsy showed a relatively benign course with seizure-free periods of several years. These findings were not in accordance with the diagnosis of Dravet syndrome and the patient's seizure disorder was therefore reported as "unclassified fever-associated epilepsy".

Breakpoint mapping of the 1q44 deletion in our study patient indicated the disruption of the *HNRNPU* gene, suggesting *HNRNPU* as the causative gene. The identification of *de novo* and truncating mutations in patients with epileptic encephalopathies (Carvill et al. 2013a; Epi4K Consortium and Epilepsy Phenome/Genome Project 2013) suggested *HNRNPU* as the gene responsible for the epilepsy phenotype. Additional *de novo HNRNPU* mutations were identified in an individual with a complex phenotype including epilepsy, ID and CGA (Need et al. 2012) and a patient with epilepsy, ID and autism spectrum disorder (ASD) (Hamdan et al. 2014).

Our findings and previously reported cases suggest that epilepsy may be a main phenotype of 1q44 deletions spanning the *HNRNPU* gene.

We also detected a 14q23.3 deletion disrupting *GPHN* in a patient with FS+. Homozygous mutations are a known cause of Molybdenum cofactor deficiency (Reiss et al. 2001; Reiss et al. 2011) as Gephyrin, the protein encoded by *GPHN*, is required for the biosynthesis of molybdenum cofactors (Stallmeyer et al. 1999). In addition, Gephyrin is essential for glycine and GABA<sub>A</sub> receptor clustering at postsynaptic sites (Feng et al. 1998; Kneussel et al. 1999). The involvement in synaptic accumulation of neurotransmitter receptors might be a link of *GPHN* to epilepsy. Hemizygous deletions have been identified in patients with autism, schizophrenia and GGE (Lionel et al. 2013; Dejanovic et al. 2014; Hu et al. 2015). Our patient presented with febrile and afebrile GTCS, supporting a causative role of hemizygous *GPHN* deletions in epilepsy and extending the associated phenotypic spectrum to mild fever-associated epilepsies.

Variable expressivity and reduced penetrance as observed in other pathogenic microdeletions may explain that our patient's deletion was inherited from the unaffected mother.

#### 4.4.2 Discussion of likely pathogenic CNVs

Likely pathogenic CNVs were discussed in Hartmann et al. 2015:

We identified a 1.6 Mb duplication of unknown inheritance at 3q13.11 in a patient with FS+ and borderline ID. This CNV included *ALCAM*, encoding a cell adhesion molecule, and *CBLB*, encoding a E3 ubiquitin ligase. *ALCAM* is increasingly expressed during neuroinflammation and mediates the recruitment of leukocytes across the blood-brain barrier (Cayrol et al. 2008). In addition, *ALCAM* is required for cell migration during chick diencephalic development (Heffron and Golden 2000).

*CBLB* was described to promote T cell tolerance by negatively regulating T cell activation (Venuprasad 2010; Wallner et al. 2012). *Cblb* null mice show an enhancement of long-term memory retention (Tan et al. 2006) and another study suggested that proteins from the Cbl family suppress cell death in healthy neurons (Sproul et al. 2009).

*ALCAM* and *CBLB* were the only genes included in a 2.5 Mb *de novo* deletion identified in a patient with multiple dysmorphic features and a congenital heart defect (Simovich et al. 2008). However, ID and seizures as present in our study patient were not reported in this individual.

*ALCAM* and *CBLB* were found to play a role in various processes in the brain. Both genes might contribute to our patient's phenotype, but further studies are required to confirm their relevance in epilepsy.

We detected two *de novo* duplications at 7p14.2 and 18q12.2 in a patient with *SCN1A*-negative atypical Dravet syndrome. *ELMO1*, encoding a cytoplasmic protein promoting phagocytosis and cell migration (Gumienny et al. 2001), was the only gene partially included in the 7p14.2 duplication. The gene is highly expressed in brain (GNF Gene Expression Atlas 2) (Su et al. 2004) and involved in dendritic spine morphogenesis in rat hippocampal neurons (Kim et al. 2011). Defective phagocytic clearance in *Elmo1* null mice leads to accumulation of apoptotic nuclei resulting in impaired adult neurogenesis (Lu et al. 2011).

Five zinc finger genes *ZNF397*, *ZNF397OS*, *ZNF271*, *ZNF24* and *ZNF396* were included in the 18q12.2 duplication. All genes code for transcription factors whose target genes and specific functions are largely unknown. The mouse homologue of *ZNF24* was shown to have a vital role in early mouse development and cell proliferation (Li et al. 2006; Khalfallah et al.



2009) and Li et al. presumed that the transcription factor might be involved in brain development (Li et al. 2009b).

Both duplications might contribute to our patient's phenotype. Its high expression in the brain and relevance in neuronal morphogenesis make *ELMO1* a promising candidate gene for epilepsy in this patient.

In this study, duplications at 3q13.11, 7p14.2 and 18q12.2 were evaluated as likely pathogenic due to CNV size or *de novo* occurrence. The duplications comprized several genes that are involved in different brain processes and might have an impact on the epilepsy phenotype. However, the identified CNVs have not been associated with epilepsy so far and additional cases with overlapping CNVs or mutations in the discussed genes are needed to elucidate their role in epilepsy.

## 5 Summary and Conclusions

Simple febrile seizures are frequent in the population and have a strong genetic contribution. However, genetic studies have not revealed any causative variants for simple febrile seizures yet, but have mainly been successful in fever-associated epilepsies like genetic epilepsy with febrile seizures plus and Dravet syndrome. Despite the discovery of several genes, most individuals with fever-associated epilepsies do not carry variants in these genes and further causative genetic variants need to be identified. Targeted resequencing and copy number variation analysis were successfully applied for the identification of pathogenic variants in different epilepsies including genetic generalized epilepsies and epileptic encephalopathies. In this study, we performed targeted resequencing and genome-wide array comparative genomic hybridization in patients with recurrent febrile seizures and fever-associated epilepsies. We aimed to evaluate the impact of 19 candidate epilepsy genes, define the phenotypic spectrum of 13 known epilepsy genes and to assess the importance of rare copy number variants in fever-associated epilepsies.

We identified pathogenic single nucleotide variants in 10 (12%) of 84 patients with recurrent febrile seizures and fever-associated epilepsies. This cohort included 43 individuals with typical or atypical Dravet syndrome of which 35 previously tested negative for *SCN1A* sequence mutations. The diagnostic yield of targeted resequencing was consistent with a previous gene panel study. However, it has to be taken into account that mutation identification depends on the genes, number of genes and phenotypes studied.

We detected pathogenic copy number variants in 4 (11%) of 36 *SCN1A*-negative individuals, as a subgroup of the first cohort. The diagnostic yield in our cohort was in accordance with previous array studies. Additional clinical features like intellectual disability, autism spectrum disorders and congenital anomalies might upwardly bias the diagnostic yield of copy number variant analysis in patients with epilepsy. Intellectual disability was the most frequent additional neurodevelopmental phenotype in our cohort. However, in most of our study patients, intellectual disability occurred in terms of an epileptic encephalopathy and previous studies suggest that intellectual disability linked to epileptic encephalopathies does not relevantly increase the amount of pathogenic copy number variants.

Targeted resequencing did not identify any pathogenic mutations in candidate epilepsy genes. Seven rare variants in five of 19 candidate genes were classified as variants of unknown

significance. The investigation of larger cohorts might reveal pathogenic variants in some of the candidate genes.

We extended the phenotypic spectrum of the known epilepsy genes *GABRA1* and *SCN2A*. We identified a *GABRA1 de novo* mutation in a patient first diagnosed with Dravet syndrome, but with clinical features of genetic generalized epilepsy at a later point in development. Our finding supports *GABRA1* as a new gene for patients with clinical features of Dravet syndrome in early childhood. We detected a *de novo SCN2A* mutation in a patient with features of Dravet syndrome and febrile infection-related epilepsy syndrome. While Dravet syndrome has already been associated with *SCN2A* mutations, our study suggests *SCN2A* as a new candidate gene for febrile infection-related epilepsy syndrome.

*SCN1A* mutations were identified in patients previously tested negative for variants in this gene using Sanger sequencing. Next-generation sequencing techniques seem to be more sensitive in the identification of *SCN1A* mutations so that it might be worth retesting individuals that have been investigated with Sanger sequencing.

All pathogenic copy number variants identified were not specific for fever-associated epilepsies, but extended the phenotypic spectrum of several known microdeletion syndromes to these epilepsies. Our study adds features of Dravet syndrome to the phenotypic presentations of 1q21.1 duplications. 16p11.2 deletion carriers may present with fever-associated epilepsy as a recurring feature. In addition, our study and previous findings suggest epilepsy as a main phenotype of 1q44 deletions spanning the *HNRNPU* gene. Our results support a causative role of hemizygous *GPHN* deletions in epilepsy and extend the associated phenotypic spectrum to mild fever-associated epilepsies.

Our study suggests that copy number variant analysis may be a useful step in the diagnostic work-up of fever-associated epilepsies with or without additional neurodevelopmental features once variants in major candidate genes such as *SCN1A* have been excluded. Targeted resequencing proved to be a powerful diagnostic tool in patients with fever-associated epilepsies solving 12% of cases and detecting *SCN1A* mutations in patients with previous negative Sanger sequencing for this gene. Our study identified pathogenic variants known to play a role in epilepsy and extended their phenotypic spectrum. Further efforts are required to discover new causative variants for fever-associated epilepsies.

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# 7 Annex

## 7.1 Supporting tables

MIP name	MIP sequence
ADAM22_MIP_1	gtaagttagccgtcctctgtgctCTTCAGCTTCCCGATATCCGACGGTAGTGTgaggagctgagcgtct
ADAM22_MIP_2	caggtccccaggacacagagcagCTTCAGCTTCCCGATATCCGACGGTAGTGTgcgcactcgggaaatgg
ADAM22_MIP_3	cctcatctaccgctcggcgCTTCAGCTTCCCGATATCCGACGGTAGTGTggtcattatctcctttt
ADAM22_MIP_4	gaagcggtttccctcctctctCTTCAGCTTCCCGATATCCGACGGTAGTGTgaccgagcctcctacct
ADAM22_MIP_5	agttgggtcccgatcgagtcagCTTCAGCTTCCCGATATCCGACGGTAGTGTggcgacctcgtgagcc
ADAM22_MIP_6	gtgttgagttgcaactgcttCTTCAGCTTCCCGATATCCGACGGTAGTGTgattagatggtgagtaa
ADAM22_MIP_7	aaggtatttattactcagccatCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgacaaaaagcaagtg
ADAM22_MIP_8	atcttctactgtgggaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTcgtgtttacattttggg
ADAM22_MIP_9	atccccaaaaatgtaaacacgaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtccccacaagttaggaaa
ADAM22_MIP_10	acttcagtaagtgtcaaaaagtCTTCAGCTTCCCGATATCCGACGGTAGTGTagctgattcctctgtg
ADAM22_MIP_11	ggcatgttgacaatgcaacaCTTCAGCTTCCCGATATCCGACGGTAGTGTtccatcaccaatgaaatgc
ADAM22_MIP_12	aaatgtttatgctgagagcttCTTCAGCTTCCCGATATCCGACGGTAGTGTggccatgcctaatatctt
ADAM22_MIP_13	aaaaaataatgagcatggcaCTTCAGCTTCCCGATATCCGACGGTAGTGTgagctctcagcataaaca
ADAM22_MIP_14	catctggtatgatctcatatagCTTCAGCTTCCCGATATCCGACGGTAGTGTtttgactaggctgga
ADAM22_MIP_15	caaacagctggatttgtaaacCTTCAGCTTCCCGATATCCGACGGTAGTGTcagatgtggctaatgat
ADAM22_MIP_16	cagtgggtgtcgtgttattCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaaatctgacaaatgcac
ADAM22_MIP_17	gtgcattgtcagatttctcaatCTTCAGCTTCCCGATATCCGACGGTAGTGTacacgacacaccactg
ADAM22_MIP_18	cctagggtaaaactgtgagctCTTCAGCTTCCCGATATCCGACGGTAGTGTtgttcttctcgtgttta
ADAM22_MIP_19	acacaggaaggaacagcaccctCTTCAGCTTCCCGATATCCGACGGTAGTGTcagttttaccctaggca
ADAM22_MIP_20	gcctagaagattctatttccCTTCAGCTTCCCGATATCCGACGGTAGTGTgcaagaccctcactgtt
ADAM22_MIP_21	aacaagtgaaggtctgcaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaataagaatctctagggc
ADAM22_MIP_22	accctacgtgagttatgaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTtacagctgatgtgtcat
ADAM22_MIP_23	gtcggccaggttccatagcCTTCAGCTTCCCGATATCCGACGGTAGTGTtcatcattacagaagttac
ADAM22_MIP_24	agtaggtgtgaacatctgtacaCTTCAGCTTCCCGATATCCGACGGTAGTGTtttgactgtgaacagt
ADAM22_MIP_25	cattcacgcctcctcttctCTTCAGCTTCCCGATATCCGACGGTAGTGTcaccatactgatttgtaata
ADAM22_MIP_26	gaaagttagcaagtgtaagtCTTCAGCTTCCCGATATCCGACGGTAGTGTttgctagtgacaatttg
ADAM22_MIP_27	gggctaatgactgggcaagtCTTCAGCTTCCCGATATCCGACGGTAGTGTaagcaactaaatcaaaaaat
ADAM22_MIP_28	gctgtgctgttctctcttagCTTCAGCTTCCCGATATCCGACGGTAGTGTctttataacaaggcatgtg
ADAM22_MIP_29	cacatgcctgttataaagtgaCTTCAGCTTCCCGATATCCGACGGTAGTGTagaagacaacagcacagc
ADAM22_MIP_30	acctctaaggttaataagtggtCTTCAGCTTCCCGATATCCGACGGTAGTGTtgagttgaccagctca
ADAM22_MIP_31	gttgaagagcagcaccacCTTCAGCTTCCCGATATCCGACGGTAGTGTtatgtacatacaggccaagt
ADAM22_MIP_32	gtaattcagggtcattccaggCTTCAGCTTCCCGATATCCGACGGTAGTGTgtcacttttggttttcc
ADAM22_MIP_33	gaggaaaacaaaaagtgaactCTTCAGCTTCCCGATATCCGACGGTAGTGTctggaatgacctgaatt
ADAM22_MIP_34	gctgtaaaaagtgcaggtaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtttgcaaggtgacacc
ADAM22_MIP_35	caacactctgctcctcaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTcccagcctaatgatttaa
ADAM22_MIP_36	acttatgggaaaaagtggggCTTCAGCTTCCCGATATCCGACGGTAGTGTcacgttgattttgttcat
ADAM22_MIP_37	aatgaacaaaaatcaactgtgCTTCAGCTTCCCGATATCCGACGGTAGTGTcccacttttcccataag
ADAM22_MIP_38	cagcatgaaggaactgaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtgcactgcatttcttc
ADAM22_MIP_39	aaatgcagtgcaaaatataaggcCTTCAGCTTCCCGATATCCGACGGTAGTGTcctttcatgctgtgaca
ADAM22_MIP_40	gtcagcggacttctcaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTtcaatgggtatttgcctttc
ADAM22_MIP_41	ggaaaaagcaaataccattagcgaCTTCAGCTTCCCGATATCCGACGGTAGTGTgagaagtcggcctga
ADAM22_MIP_42	aggtggagacgtcagcccagCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaaaatttttctgct
ADAM22_MIP_43	ggcagaaaaaaatctctatcagCTTCAGCTTCCCGATATCCGACGGTAGTGTgctgacgtctccacctc
ADAM22_MIP_44	gtcagcaaggaagaacatiCTTCAGCTTCCCGATATCCGACGGTAGTGTtatatttggaaaaagaagta
ADAM22_MIP_45	caccatcgagttctcaagcCTTCAGCTTCCCGATATCCGACGGTAGTGTtaattgaaaacggaaaggaa
ADAM22_MIP_46	cctgtgcttcttcaactttCTTCAGCTTCCCGATATCCGACGGTAGTGTgattcatttttctctca
ADAM22_MIP_47	agacacctgtttcaagcacaCTTCAGCTTCCCGATATCCGACGGTAGTGTggctctctatttctgt
ADAM22_MIP_48	ggtatcactctgtctgcaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgagagttgacatttactcta
ADAM22_MIP_49	atcagaacctatccagtgctgCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagtttcagagagcag
ADAM22_MIP_50	ggataaactcgtgggtaCTTCAGCTTCCCGATATCCGACGGTAGTGTacaataaagttctgaaagg
ADAM22_MIP_51	ccagcaactaaaatggtgccaCTTCAGCTTCCCGATATCCGACGGTAGTGTtattcaaccaatgatacaaa
ADAM22_MIP_52	gactcatattagcattgtgaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcttgatgctctcc
ADAM22_MIP_53	ggaaggacatcaagaggggagCTTCAGCTTCCCGATATCCGACGGTAGTGTcaacaatgctaatatgagtc
ADAM22_MIP_54	gtctgctttctgtcgcattCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgaaatgtttattatgcc
ADAM22_MIP_55	aactagatgctgagttgtgcCTTCAGCTTCCCGATATCCGACGGTAGTGTtaacattcaagaaagaagg

Table S1. MIP sequences.

MIP name	MIP sequence
ADAM22_MIP_56	actcttggcaaggtagaggcCTTCAGCTTCCCGATATCCGACGGTAGTGTtggttacattttgaaaca
ADAM22_MIP_57	cgaggctgcccattttcacagCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgtgggagagagcta
ADAM22_MIP_58	cctgtgcaaatagtgtaaaagCTTCAGCTTCCCGATATCCGACGGTAGTGTctagcttaaacgctctt
ADAM22_MIP_59	aaaagacggttagagctagaCTTCAGCTTCCCGATATCCGACGGTAGTGTttttgacactatttgaca
ADAM22_MIP_60	aaactggaaggaccatacttCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgctgtgattttcag
ADAM22_MIP_61	gtctctttgaacatgggtttCTTCAGCTTCCCGATATCCGACGGTAGTGTccagtacactacagtat
ADAM22_MIP_62	cgacaaagtgccagggtatgCTTCAGCTTCCCGATATCCGACGGTAGTGTaattcatgttctcaacatct
ADAM22_MIP_63	gtcctcatcaggaaagtgaggcCTTCAGCTTCCCGATATCCGACGGTAGTGTtaggaacaaggaggaa
ADAM22_MIP_64	gctcttcagacaatacgaagacCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcttttctgtgtg
ADAM22_MIP_65	cacaacagaaaagagcaaaattCTTCAGCTTCCCGATATCCGACGGTAGTGTtctattgtctgaagagc
ADAM23_MIP_1	ccccggcccgcacggccctCTTCAGCTTCCCGATATCCGACGGTAGTGTcggcgccgggagctatga
ADAM23_MIP_2	gctggcaggcaccgagccggCTTCAGCTTCCCGATATCCGACGGTAGTGTcgaaaggcaccggggccat
ADAM23_MIP_3	gaaagaaatcacactgccttaagCTTCAGCTTCCCGATATCCGACGGTAGTGTacccccctacctcac
ADAM23_MIP_4	caatgtattgtctcatctgccCTTCAGCTTCCCGATATCCGACGGTAGTGTtgcctttgtctaaagaa
ADAM23_MIP_5	gaatctgagttcacaattttaciCTTCAGCTTCCCGATATCCGACGGTAGTGTcgaaagcccttatca
ADAM23_MIP_6	caggtgcaataaagcttcttCTTCAGCTTCCCGATATCCGACGGTAGTGTtctctgtcttttgaatcc
ADAM23_MIP_7	gattcaaaaagacagaagaacctCTTCAGCTTCCCGATATCCGACGGTAGTGTatttctgtcttctgactgc
ADAM23_MIP_8	gttaccggcgtcgcaagtaCTTCAGCTTCCCGATATCCGACGGTAGTGTgattgttttaaacctccaa
ADAM23_MIP_9	gacactggaggttaaaaacaatCTTCAGCTTCCCGATATCCGACGGTAGTGTgacttccgagcgcg
ADAM23_MIP_10	gtggctctgtaacctgcaatCTTCAGCTTCCCGATATCCGACGGTAGTGTttttgtcttatgaaagca
ADAM23_MIP_11	cgctctgatgcttccatggtCTTCAGCTTCCCGATATCCGACGGTAGTGTgcacggaagagctactaaa
ADAM23_MIP_12	gcaactttgtctttgagaagaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtgtgtggttctttgtg
ADAM23_MIP_13	gcacaaaagaaaccacacaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctctcaagacaaaagttg
ADAM23_MIP_14	gcaaatgaagaatctcagtaagCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagtccaactgttt
ADAM23_MIP_15	aggtttctggtattatgtgtCTTCAGCTTCCCGATATCCGACGGTAGTGTtccactccaacaagcc
ADAM23_MIP_16	cctattttactcaatgaagtcCTTCAGCTTCCCGATATCCGACGGTAGTGTatttctgactaatttttc
ADAM23_MIP_17	cagaaaggaaaaattagatcCTTCAGCTTCCCGATATCCGACGGTAGTGTcaatcactcattgagta
ADAM23_MIP_18	gtaagaatataagtcagtggtCTTCAGCTTCCCGATATCCGACGGTAGTGTagtgcactagagaga
ADAM23_MIP_19	gtttgtgatcattaacaatCTTCAGCTTCCCGATATCCGACGGTAGTGTaaatcaagtcaatataatg
ADAM23_MIP_20	gtgcaagatggaatgtttaCTTCAGCTTCCCGATATCCGACGGTAGTGTggcagtgactggtatgta
ADAM23_MIP_21	aatacataccagtcactgccaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaccattccatctggc
ADAM23_MIP_22	gttctcaaaataccggcagcgCTTCAGCTTCCCGATATCCGACGGTAGTGTacctgctctgtgtataacc
ADAM23_MIP_23	gagcatctgcacagggttggCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaccacaaaaggataaa
ADAM23_MIP_24	atctttgcatctgttcttttCTTCAGCTTCCCGATATCCGACGGTAGTGTatagcactgcttttctt
ADAM23_MIP_25	gaaaaagcagtgctatcagaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgaacagatgcaaatgta
ADAM23_MIP_26	actgaccttctactcatttcaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcccacacatttcaa
ADAM23_MIP_27	agagttgaaagtgtgaggagCTTCAGCTTCCCGATATCCGACGGTAGTGTtgaaaatgtaagaaggt
ADAM23_MIP_28	cctttgtcaaaattgctgtCTTCAGCTTCCCGATATCCGACGGTAGTGTtctttgttcttttctt
ADAM23_MIP_29	agaagaaaaaggaacaaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTacacagcaattttgcaaaa
ADAM23_MIP_30	ccttttcaacaggccaacaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTctgatgattgcttttgta
ADAM23_MIP_31	ggctccactctctctgtaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTacaagaaactgctttcc
ADAM23_MIP_32	atcttactgtgcaaacaggCTTCAGCTTCCCGATATCCGACGGTAGTGTtctctctgctcctaactct
ADAM23_MIP_33	gagattaggacagaaaggaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgtttcaccaagtaagat
ADAM23_MIP_34	gtttctgacagtttcatcttCTTCAGCTTCCCGATATCCGACGGTAGTGTgctcttcgcttactcac
ADAM23_MIP_35	acacttcagtgagtaagcgCTTCAGCTTCCCGATATCCGACGGTAGTGTttaaagaagatgaaactg
ADAM23_MIP_36	cattttactgtacaggtgagtCTTCAGCTTCCCGATATCCGACGGTAGTGTatattgattttgattt
ADAM23_MIP_37	caaatcaaaattcaatattaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTacctgtacaagtataat
ADAM23_MIP_38	gtaatttaaaaaggattcatCTTCAGCTTCCCGATATCCGACGGTAGTGTattatctgaaggtacctagc
ADAM23_MIP_39	cagcatgctaggtacctcaCTTCAGCTTCCCGATATCCGACGGTAGTGTtttccaatgaatcctttta
ADAM23_MIP_40	cattttcttaatagtgttcttCTTCAGCTTCCCGATATCCGACGGTAGTGTgctctcacatgtgtgc
ADAM23_MIP_41	gggacaggagcacacatgtgCTTCAGCTTCCCGATATCCGACGGTAGTGTgacagagaacactattaa
ADAM23_MIP_42	agtgtcagctctaaggccaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttctgcttactccaa
ADAM23_MIP_43	ggagataggcaagagaagaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTttagagctgaccactca
ADAM23_MIP_44	gggtgattgactcaggttaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgtttgtttctttacac
ADAM23_MIP_45	gccttgatgtagaaggagtCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttctctgttaaaaact
ADAM23_MIP_46	gcctaaatatgacagctgtCTTCAGCTTCCCGATATCCGACGGTAGTGTatgggatctttctgttt
ADAM23_MIP_47	gaattgtaggcacttccgatCTTCAGCTTCCCGATATCCGACGGTAGTGTtataaagtcacagcactgt
ADAM23_MIP_48	cccaagggtttgtgattttCTTCAGCTTCCCGATATCCGACGGTAGTGTccaatctgttcttttt
ADAM23_MIP_49	gggtgaaaggttcttaactCTTCAGCTTCCCGATATCCGACGGTAGTGTcagatattcttatgtgtctc
ADAM23_MIP_50	gcegatgttcttctcagCTTCAGCTTCCCGATATCCGACGGTAGTGTtatgactcttctccatgat
ADAM23_MIP_51	gatcatgggaagagatcatatgCTTCAGCTTCCCGATATCCGACGGTAGTGTgagaagaagacatcggg
ADAM23_MIP_52	cagcagtgactggaactattCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttttactcactctg

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
ADAM23_MIP_53	ccagagtgagtcaaaagaagatCTTCAGCTTCCCGATATCCGACGGTAGTGTagtccagtaaacactgct
ARX_MIP_1	ctttggccttgagcctcagcgCTTCAGCTTCCCGATATCCGACGGTAGTGTgagtggtgctgagtgaggt
ARX_MIP_2	gcacgcggcgcagctcacgcagctCTTCAGCTTCCCGATATCCGACGGTAGTGTgcgctcctgagacagc
ARX_MIP_3	cgctcggggcagcgtctcccggcCTTCAGCTTCCCGATATCCGACGGTAGTGTctccacggcgggtgtg
ARX_MIP_4	gcggagtaggctcgggaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTgacttccgaggtcgcgt
ARX_MIP_5	cggcagcctgcccccagcgCTTCAGCTTCCCGATATCCGACGGTAGTGTcaccaccgctcagcccc
ARX_MIP_6	ggttctggaaccagacctgcaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTcggagggaaggggctg
ARX_MIP_7	cggccaagtggcgcaagcgggaCTTCAGCTTCCCGATATCCGACGGTAGTGTcgggtggaaaggaagg
ARX_MIP_8	ctatttctctctatggcaggcCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttctctgtttgtgc
ARX_MIP_9	gctgcacaacagagggaagagCTTCAGCTTCCCGATATCCGACGGTAGTGTcctgcatagaggagaaa
ARX_MIP_10	ccctctccgagtcgctgcccgcCTTCAGCTTCCCGATATCCGACGGTAGTGTgaccaccctacgcgc
ARX_MIP_11	cagttaccagctaccagctggCTTCAGCTTCCCGATATCCGACGGTAGTGTaccacagaggagctgc
ARX_MIP_12	gcgcgcgggcgtgctctccagcCTTCAGCTTCCCGATATCCGACGGTAGTGTcgttctccgggtgcagc
ARX_MIP_13	cagcagctgccgctcagtgCTTCAGCTTCCCGATATCCGACGGTAGTGTaggacaagaagatgaggac
ARX_MIP_14	cgggtcgtagcggggggCTTCAGCTTCCCGATATCCGACGGTAGTGTccagcagttcttctct
ARX_MIP_15	aggagcgcctcggcgtggccCTTCAGCTTCCCGATATCCGACGGTAGTGTcgctcaagatcagccagcg
ARX_MIP_16	cggaggggcctccccgctgCTTCAGCTTCCCGATATCCGACGGTAGTGTcggcgtgatgctcactgctg
ARX_MIP_17	cgccaccgcaaccgcgcggCTTCAGCTTCCCGATATCCGACGGTAGTGTagtgcggcgcctgtacggc
ARX_MIP_18	cggggagtcccagcagggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTggaggcggccccggccc
ARX_MIP_19	gatgcagtaggaggagagcaagCTTCAGCTTCCCGATATCCGACGGTAGTGTcctgacgggagcatct
ARX_MIP_20	cccgtgcaaaatgcggttctgCTTCAGCTTCCCGATATCCGACGGTAGTGTcctggaaaaagccccag
CACNA2D1_MIP_1	aacaccaccacagtcagtataCTTCAGCTTCCCGATATCCGACGGTAGTGTgggtcggagttaacta
CACNA2D1_MIP_2	ccctgtgtatatactgaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgattactctgaaagatgt
CACNA2D1_MIP_3	cgtagctaaaagagactgtCTTCAGCTTCCCGATATCCGACGGTAGTGTeggacagtgaccattaatt
CACNA2D1_MIP_4	ccaaatcctgtgacatggttCTTCAGCTTCCCGATATCCGACGGTAGTGTtggatgagatgaatgatg
CACNA2D1_MIP_5	gctttctccatgaaagattctCTTCAGCTTCCCGATATCCGACGGTAGTGTatgcttttcttccaga
CACNA2D1_MIP_6	agcaaaaggacatgctcatgCTTCAGCTTCCCGATATCCGACGGTAGTGTatgtaagaatcttgaaga
CACNA2D1_MIP_7	gtcatcctcctcatctcaacCTTCAGCTTCCCGATATCCGACGGTAGTGTctcctgaaataaataatt
CACNA2D1_MIP_8	ggcctcctgtccaagcagaCTTCAGCTTCCCGATATCCGACGGTAGTGTcttatacgtttatttctc
CACNA2D1_MIP_9	gtttttacatgtaccatacacaCTTCAGCTTCCCGATATCCGACGGTAGTGTatgacaaggtctgagca
CACNA2D1_MIP_10	gtaaatgctcagacctgtcaCTTCAGCTTCCCGATATCCGACGGTAGTGTatgtatgggtacatgta
CACNA2D1_MIP_11	gtcaaaattttagtttattCTTCAGCTTCCCGATATCCGACGGTAGTGTcaattctcaagggttactca
CACNA2D1_MIP_12	ataagattgttaaaagcatCTTCAGCTTCCCGATATCCGACGGTAGTGTtactgtactgagagacact
CACNA2D1_MIP_13	cagttagttagttagccggctCTTCAGCTTCCCGATATCCGACGGTAGTGTattttaagtcacgttct
CACNA2D1_MIP_14	caaaataaagtgaacagttaacCTTCAGCTTCCCGATATCCGACGGTAGTGTtccgggaaacacactt
CACNA2D1_MIP_15	gctttcaaaagtgtttcccCTTCAGCTTCCCGATATCCGACGGTAGTGTaatgttattgatttctt
CACNA2D1_MIP_16	gttataattgaaatctgaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTatgtaatttaaatagt
CACNA2D1_MIP_17	gaaactatttaaatcacttCTTCAGCTTCCCGATATCCGACGGTAGTGTttcagaatttctaattat
CACNA2D1_MIP_18	gtataattagatgtaatacaacCTTCAGCTTCCCGATATCCGACGGTAGTGTacatagcataagaat
CACNA2D1_MIP_19	gatatttttaaaaattctatgCTTCAGCTTCCCGATATCCGACGGTAGTGTgcaaaaggtgtattaca
CACNA2D1_MIP_20	ggcaccaggtccactttctaCTTCAGCTTCCCGATATCCGACGGTAGTGTaataataatgccaagtaaca
CACNA2D1_MIP_21	atcgggcattatgtaagcaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgctagaattttaagcaa
CACNA2D1_MIP_22	gcctaagggagaaatgctCTTCAGCTTCCCGATATCCGACGGTAGTGTgagaaaagctgaattccaaa
CACNA2D1_MIP_23	ggcaagaaaaccagagacatCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttcttagacatacctga
CACNA2D1_MIP_24	cagaagacaaaacaagaaatgCTTCAGCTTCCCGATATCCGACGGTAGTGTacaatccttggcgcagt
CACNA2D1_MIP_25	aagactgcgcaaggtttgCTTCAGCTTCCCGATATCCGACGGTAGTGTcaatttctgttttctt
CACNA2D1_MIP_26	cgcgttaccaaacagaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTactaaatgaaatgcagaat
CACNA2D1_MIP_27	gcaggctttacaatgaacttCTTCAGCTTCCCGATATCCGACGGTAGTGTctactctaattgcttttg
CACNA2D1_MIP_28	gcagtaactctggaaaaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaccacactcaagcaat
CACNA2D1_MIP_29	gcagtaactctggaaaaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaccacactcaagcaat
CACNA2D1_MIP_30	atttcaacgagtttattgatagaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgttttactactctt
CACNA2D1_MIP_31	ggattagatagtaattcagagtCTTCAGCTTCCCGATATCCGACGGTAGTGTaaggcctagctactgat
CACNA2D1_MIP_32	cagttagtagccttcaacaCTTCAGCTTCCCGATATCCGACGGTAGTGTgaattacatctaatctg
CACNA2D1_MIP_33	gcaaaaggggtcataaacaCTTCAGCTTCCCGATATCCGACGGTAGTGTggaatgtcaaggttact
CACNA2D1_MIP_34	gtacactgacatttccactgaCTTCAGCTTCCCGATATCCGACGGTAGTGTttatgaccccccttctg
CACNA2D1_MIP_35	agcataaacacaaaacaacaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaatgacacctgaagtca
CACNA2D1_MIP_36	gtgacttcagggtcctttgtCTTCAGCTTCCCGATATCCGACGGTAGTGTgtttgtttgtttatgc
CACNA2D1_MIP_37	atatatacgaaaaagtaagcggCTTCAGCTTCCCGATATCCGACGGTAGTGTacataaaaacagtaaat
CACNA2D1_MIP_38	actgtattttatgtattgtgCTTCAGCTTCCCGATATCCGACGGTAGTGTtttctgtatattcat
CACNA2D1_MIP_39	caaaagctgacctgcaaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTgaataagctagaatcaattc
CACNA2D1_MIP_40	gaattgattctagcttattctaaCTTCAGCTTCCCGATATCCGACGGTAGTGTggcaggtcagctttg
CACNA2D1_MIP_41	gggtctacacagaaaacaataCTTCAGCTTCCCGATATCCGACGGTAGTGTgtagaatgagtcatacc

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
CACNA2D1_MIP_42	acattggattccttgatgcaCTTCAGCTTCCCGATATCCGACGGTAGTGTatcctagtgaaatgttga
CACNA2D1_MIP_43	ccattggggcacagctggaaCTTCAGCTTCCCGATATCCGACGGTAGTGTacaatcctattaagaacatt
CACNA2D1_MIP_44	atcctaattggtatgttttataCTTCAGCTTCCCGATATCCGACGGTAGTGTatataaatgttatfta
CACNA2D1_MIP_45	caagaatcagctggttctataaCTTCAGCTTCCCGATATCCGACGGTAGTGTctaagtgccaagtaagt
CACNA2D1_MIP_46	gatgggagtagatgtcttttgaCTTCAGCTTCCCGATATCCGACGGTAGTGTctaagtggaataata
CACNA2D1_MIP_47	ccagttcctaaaaatagattcagCTTCAGCTTCCCGATATCCGACGGTAGTGTtagcttcaacgtcacagt
CACNA2D1_MIP_48	cattactggaactcttccggCTTCAGCTTCCCGATATCCGACGGTAGTGTtttggctctttataaagt
CACNA2D1_MIP_49	ccattgcttcccaaaacaCTTCAGCTTCCCGATATCCGACGGTAGTGTatctagaagaagtagaagt
CACNA2D1_MIP_50	gtgtacctggatcattggtaaCTTCAGCTTCCCGATATCCGACGGTAGTGTatttcaacacagcattcc
CACNA2D1_MIP_51	attattttatttataataCTTCAGCTTCCCGATATCCGACGGTAGTGTaacaagttttaataatca
CACNA2D1_MIP_52	gattattttaaactgtttaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtttataaataaaataatt
CACNA2D1_MIP_53	ctggaatacacgtacctggaCTTCAGCTTCCCGATATCCGACGGTAGTGTtagtacactaataacaacta
CACNA2D1_MIP_54	gttcaacacaattatgacagagCTTCAGCTTCCCGATATCCGACGGTAGTGTattcaactgaaagcact
CACNA2D1_MIP_55	gcagtttgcctggaacatCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaccacctagatcattat
CACNA2D1_MIP_56	gctattcacggatggaggagaagCTTCAGCTTCCCGATATCCGACGGTAGTGTgcaactgcatatgctc
CACNA2D1_MIP_57	aacactttttatttctacatCTTCAGCTTCCCGATATCCGACGGTAGTGTacaattgacaacaaca
CACNA2D1_MIP_58	gaaggccttagtttcttttCTTCAGCTTCCCGATATCCGACGGTAGTGTttttgagtttaacagca
CACNA2D1_MIP_59	gcttactcttcaaatggaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaacagttacatcctga
CACNA2D1_MIP_60	gacaaatggccatacatgtCTTCAGCTTCCCGATATCCGACGGTAGTGTaatgcagtcattctatact
CACNA2D1_MIP_61	cctgaattaattgcaatttctCTTCAGCTTCCCGATATCCGACGGTAGTGTtctaggagtgaagtgt
CACNA2D1_MIP_62	gttgaattgataattactgactctCTTCAGCTTCCCGATATCCGACGGTAGTGTtagtatttaaacact
CACNA2D1_MIP_63	gggagattgtagataacagtCTTCAGCTTCCCGATATCCGACGGTAGTGTtttggagagaanaagcat
CACNA2D1_MIP_64	atattagatatgcttaaaaaataCTTCAGCTTCCCGATATCCGACGGTAGTGTcatggctagtaaaaat
CACNA2D1_MIP_65	gaatttttagctagccatgaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtttttagcatalctaat
CACNA2D1_MIP_66	cactgtccagttgagttcatCTTCAGCTTCCCGATATCCGACGGTAGTGTggaacttgacaatgattga
CACNA2D1_MIP_67	gcgaggaagaccctcattaCTTCAGCTTCCCGATATCCGACGGTAGTGTaataaatgaaacattcagt
CACNA2D1_MIP_68	gcctggctcactgtcatttCTTCAGCTTCCCGATATCCGACGGTAGTGTccaacagatgtaacattct
CACNA2D1_MIP_69	gaagatgctaattttggcagacCTTCAGCTTCCCGATATCCGACGGTAGTGTgcaagtaaaagaagtgc
CACNA2D1_MIP_70	attttaataaaaacaactCTTCAGCTTCCCGATATCCGACGGTAGTGTatataagccaatcatttta
CACNA2D1_MIP_71	gtaaaatgattgacctatctCTTCAGCTTCCCGATATCCGACGGTAGTGTtagtattttttatataaaa
CACNA2D1_MIP_72	atcttagaattcaaatgaacacCTTCAGCTTCCCGATATCCGACGGTAGTGTcatacacaatatgcaag
CACNA2D1_MIP_73	aacccttttaactacttgattCTTCAGCTTCCCGATATCCGACGGTAGTGTttttatataacaattcc
CACNA2D1_MIP_74	ctggcgtcattattggttCTTCAGCTTCCCGATATCCGACGGTAGTGTtagacatgaaaataaataa
CACNA2D1_MIP_75	ggtagaattgcagccaggCTTCAGCTTCCCGATATCCGACGGTAGTGTaaatacattccaatgggaa
CACNA2D1_MIP_76	ccatgattgatactgcagaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgtagaactgcattcgaa
CACNA2D1_MIP_77	gcaagaagaccctgtcacacCTTCAGCTTCCCGATATCCGACGGTAGTGTatttaaggcatttaataga
CACNA2D1_MIP_78	gtgtcagagtaagggcagcaggCTTCAGCTTCCCGATATCCGACGGTAGTGTggaaccgacccccacc
CACNA2D1_MIP_79	ccaactttgtctatcggccccCTTCAGCTTCCCGATATCCGACGGTAGTGTcgtgtgctctcttccctc
CDKL5_MIP_1	cgttccttgagtttgagcaatCTTCAGCTTCCCGATATCCGACGGTAGTGTcttttggcgccatgtttt
CDKL5_MIP_2	actcctctttgatgcaagcCTTCAGCTTCCCGATATCCGACGGTAGTGTgtaggaaactaactggtt
CDKL5_MIP_3	gtcttgcgtgggcatgtaCTTCAGCTTCCCGATATCCGACGGTAGTGTgcccttgattgttacttc
CDKL5_MIP_4	aaagaagtaaacatcaagggcCTTCAGCTTCCCGATATCCGACGGTAGTGTtacatgccacacgcaaa
CDKL5_MIP_5	gtttttatacatagagtggCTTCAGCTTCCCGATATCCGACGGTAGTGTtctctctgctcttttcc
CDKL5_MIP_6	agggaaaagaagcagaaggaCTTCAGCTTCCCGATATCCGACGGTAGTGTccacactctatgataaaa
CDKL5_MIP_7	ggggaagtgtacttggtgtCTTCAGCTTCCCGATATCCGACGGTAGTGTttttgctcttaccatt
CDKL5_MIP_8	gttttctgcttgagagtcggCTTCAGCTTCCCGATATCCGACGGTAGTGTgcagaaacagccttaaat
CDKL5_MIP_9	actggtgccataagaatgatctCTTCAGCTTCCCGATATCCGACGGTAGTGTgcctactaatttgggaa
CDKL5_MIP_10	aggtggaactcatttggcaCTTCAGCTTCCCGATATCCGACGGTAGTGTactttaaactttatttgatg
CDKL5_MIP_11	gtaacacatagtagcttttCTTCAGCTTCCCGATATCCGACGGTAGTGTtttttttatcttgacact
CDKL5_MIP_12	gagtgtcaagataaaaaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaagctacatgtgtta
CDKL5_MIP_13	ggtgagttaccgtcccaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttttcaaaagtacaac
CDKL5_MIP_14	gcattattgccttctgacagaCTTCAGCTTCCCGATATCCGACGGTAGTGTtagatgaactcaaacaaat
CDKL5_MIP_15	cttagcagtgacagcctttCTTCAGCTTCCCGATATCCGACGGTAGTGTgttcacaataattggaaa
CDKL5_MIP_16	ccaagaatacacgccaccgacCTTCAGCTTCCCGATATCCGACGGTAGTGTcatggaagcaggattac
CDKL5_MIP_17	ggaatgctaaactatctttgaaCTTCAGCTTCCCGATATCCGACGGTAGTGTcacttccatctgagcag
CDKL5_MIP_18	ggtaaaggcaattgatattatctCTTCAGCTTCCCGATATCCGACGGTAGTGTcactatgcttcccaaa
CDKL5_MIP_19	ggtatcttcttccaaggactgCTTCAGCTTCCCGATATCCGACGGTAGTGTtcatcattataaagcagggc
CDKL5_MIP_20	gttctccttcaaggtcagcaCTTCAGCTTCCCGATATCCGACGGTAGTGTgactttgtaagtgtttaa
CDKL5_MIP_21	atccagaagtctctgggtttaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaccctctccactact
CDKL5_MIP_22	gtctcctgccaatgaaagcCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaactgatatacttctt
CDKL5_MIP_23	gggcaggcctacactcaggttCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgagatctttgctgtag
CDKL5_MIP_24	cagggacaaagtacctcaagtcaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaagcagccagcctggg

**Table S1 (continued). MIP sequences.**



MIP name	MIP sequence
CDKL5_MIP_25	gccttctgaaggctttgggtCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgtcaatatagctatgcc
CDKL5_MIP_26	gtctgtgagcaaccttctgaagCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaaagctgggacactgc
CDKL5_MIP_27	ccttgctctgtagagggactCTTCAGCTTCCCGATATCCGACGGTAGTGTctgggtgggagaattcaag
CDKL5_MIP_28	cacaaccagacattctaagacgCTTCAGCTTCCCGATATCCGACGGTAGTGTtccatctagctgcttag
CDKL5_MIP_29	ccagcgttccctcatttcggtCTTCAGCTTCCCGATATCCGACGGTAGTGTggtgtagcccagtcataa
CDKL5_MIP_30	catagggcaaggatggcagcCTTCAGCTTCCCGATATCCGACGGTAGTGTgcacctcacgaatctttt
CDKL5_MIP_31	caagcttccatccaagcccttgCTTCAGCTTCCCGATATCCGACGGTAGTGTggacctcatcacatccc
CDKL5_MIP_32	cagaagtctgaggtatgtcacCTTCAGCTTCCCGATATCCGACGGTAGTGTaacagatgctcttataaa
CDKL5_MIP_33	cgtgtatggaaggagaggtCTTCAGCTTCCCGATATCCGACGGTAGTGTtactacttcttataagccac
CDKL5_MIP_34	gtccaaggagaggtgtagCTTCAGCTTCCCGATATCCGACGGTAGTGTtagcaatattgcatcaatg
CDKL5_MIP_35	ggtgtctattttcttgggggctCTTCAGCTTCCCGATATCCGACGGTAGTGTggcctgagtcggtgaa
CDKL5_MIP_36	aaaagacaaccagcattcgatCTTCAGCTTCCCGATATCCGACGGTAGTGTtagtccatcagtgacttact
CDKL5_MIP_37	gagtgtgtggtccagaactgcCTTCAGCTTCCCGATATCCGACGGTAGTGTgacctgagggaaagga
CDKL5_MIP_38	ggtcaatgaaaaaagaaagaaagCTTCAGCTTCCCGATATCCGACGGTAGTGTttgtcacacaatggca
CDKL5_MIP_39	aaactctgcttctttttccCTTCAGCTTCCCGATATCCGACGGTAGTGTatcaacttggattgcaaa
CDKL5_MIP_40	agatctcagatctgcagaccCTTCAGCTTCCCGATATCCGACGGTAGTGTgtcttattgaatgctgtc
CDKL5_MIP_41	cctttgctgctgcttggagCTTCAGCTTCCCGATATCCGACGGTAGTGTgagagcctaagtttctct
CDKL5_MIP_42	attcctctcagaattcgggaCTTCAGCTTCCCGATATCCGACGGTAGTGTgcaattcatccttcttt
CDKL5_MIP_43	atttgaggccgaagagagatgtaCTTCAGCTTCCCGATATCCGACGGTAGTGTgggttctgccgatgt
CDKL5_MIP_44	ccttctactctgaacagctgggtCTTCAGCTTCCCGATATCCGACGGTAGTGTaggcctctgcccggag
CDKL5_MIP_45	caagctgccataacgacctCTTCAGCTTCCCGATATCCGACGGTAGTGTttttgttctcccactaac
CDKL5_MIP_46	gttagtggggagaacaaaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTggcgttatgagcacttg
CDKL5_MIP_47	ccgaggcacttccatgtgccCTTCAGCTTCCCGATATCCGACGGTAGTGTactgcctctgaatatttct
CDKL5_MIP_48	cctggagtactggataggagcCTTCAGCTTCCCGATATCCGACGGTAGTGTgcaattccgaggtacagc
CDKL5_MIP_49	gctgcctctgacataccatgCTTCAGCTTCCCGATATCCGACGGTAGTGTtagagctcactgctagc
CDKL5_MIP_50	ggtttacctggccctgtgaCTTCAGCTTCCCGATATCCGACGGTAGTGTatggttattcattggtggtt
CPLX1_MIP_1	caggatctctctgctcctctctCTTCAGCTTCCCGATATCCGACGGTAGTGTgtccctcagggcctcc
CPLX1_MIP_2	caggacatgctcaagaagtagccCTTCAGCTTCCCGATATCCGACGGTAGTGTatggaggccaactccga
CPLX1_MIP_3	ccgggcccggcgcagcctctCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttctggccggctcaagc
CPLX1_MIP_4	ccttcttggcggcgtctgggtCTTCAGCTTCCCGATATCCGACGGTAGTGTtagcggggccggcccggcg
CPLX1_MIP_5	aggagcgcaagccaagtacCTTCAGCTTCCCGATATCCGACGGTAGTGTggtctgaatcacaacttct
CPLX1_MIP_6	cagaactcacacgaagtatggCTTCAGCTTCCCGATATCCGACGGTAGTGTctgctgtggtgctctct
CPLX1_MIP_7	acatfgagagaccaccacagcaCTTCAGCTTCCCGATATCCGACGGTAGTGTgccatacttgcgtgtgag
DLGAP1_MIP_1	ggcgttccgggctcctgctgcCTTCAGCTTCCCGATATCCGACGGTAGTGTtctggcggcggcggcggg
DLGAP1_MIP_2	atggccccaagcgcgcgcgtCTTCAGCTTCCCGATATCCGACGGTAGTGTaacctctgctttgatca
DLGAP1_MIP_3	gttctgatctgcacactgatatCTTCAGCTTCCCGATATCCGACGGTAGTGTgagagggccctctc
DLGAP1_MIP_4	ccccaaaccccgcaaatccCTTCAGCTTCCCGATATCCGACGGTAGTGTaatgaaccatacaaaatcta
DLGAP1_MIP_5	catgctgcagttgtccatagCTTCAGCTTCCCGATATCCGACGGTAGTGTtattgaaaatgctttttg
DLGAP1_MIP_6	cctagaactgaaagagcaaaacaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcatggcactagcaggg
DLGAP1_MIP_7	cagtggcagtgcccaacttcCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgtgccattttccctaat
DLGAP1_MIP_8	ccaccctccatgctgctctCTTCAGCTTCCCGATATCCGACGGTAGTGTcagagaagaaaacaaggg
DLGAP1_MIP_9	ggagaacgggaaacaaccCTTCAGCTTCCCGATATCCGACGGTAGTGTgattgactctatcactgaag
DLGAP1_MIP_10	gtttcctgagccctgaatgctgCTTCAGCTTCCCGATATCCGACGGTAGTGTggcacactgaccttgc
DLGAP1_MIP_11	cctgtgcccgatgatgacCTTCAGCTTCCCGATATCCGACGGTAGTGTtccatgataatctgaaaaat
DLGAP1_MIP_12	cttgggagaatagaaaaaagaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTgtctggccatggggcc
DLGAP1_MIP_13	ccacctggagaatcatcaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcaaaacatcaagcaaaaa
DLGAP1_MIP_14	caaaaacaggggagaataaagcCTTCAGCTTCCCGATATCCGACGGTAGTGTacaaaacattccagtcata
DLGAP1_MIP_15	gcagtgatttggccatgtgCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttattcaaaaggataga
DLGAP1_MIP_16	gtcaccaccgactaccatagCTTCAGCTTCCCGATATCCGACGGTAGTGTtagccagcttgactcag
DLGAP1_MIP_17	gtttcgtgtagttctgggtggCTTCAGCTTCCCGATATCCGACGGTAGTGTatactgtccagctctcg
DLGAP1_MIP_18	cacagcccagtagcacagaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaattaaaaccacgcaga
DLGAP1_MIP_19	ggagcagcctttcaatggcccCTTCAGCTTCCCGATATCCGACGGTAGTGTccatagccagcacaggg
DLGAP1_MIP_20	acgagtgctgtccctgaggtcCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgtcggagctcgtctc
DLGAP1_MIP_21	ccttccaagcatctgcgaacttcCTTCAGCTTCCCGATATCCGACGGTAGTGTggcctgcgactccagc
DLGAP1_MIP_22	ggttgatggagactcactcactgCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgaccaccgctgcc
DLGAP1_MIP_23	gagcctggacagcctggaccCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgactttggaatgtga
DLGAP1_MIP_24	agtctccactgtcttcatcccCTTCAGCTTCCCGATATCCGACGGTAGTGTgactatcgaaggtcagg
DLGAP1_MIP_25	agtccaagccttccaataCTTCAGCTTCCCGATATCCGACGGTAGTGTaataggttccaagaatga
DLGAP1_MIP_26	gatttaacattctatttttCTTCAGCTTCCCGATATCCGACGGTAGTGTatggaatttcatctttt
DLGAP1_MIP_27	gatttaacattcttttttCTTCAGCTTCCCGATATCCGACGGTAGTGTatggaatttcatctttt
DLGAP1_MIP_28	cttctctatgatttccgaCTTCAGCTTCCCGATATCCGACGGTAGTGTctttccatagcccagaat
DLGAP1_MIP_29	gcaattctgggctatgaaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTtcggcaatcatagagag

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
DLGAP1_MIP_30	ccatggcctggccatgtttacCTTCAGCTTCCCGATATCCGACGGTAGTGTgccaagactagaaccag
DLGAP1_MIP_31	gccagctactgcaggtaccatttCTTCAGCTTCCCGATATCCGACGGTAGTGTcgctgctgaagaagagc
DLGAP1_MIP_32	gtaggcctccaggaagtactgtgaCTTCAGCTTCCCGATATCCGACGGTAGTGTgagcgtggaggaccagg
DLGAP1_MIP_33	ggagcaacaacgacgtcaagtCTTCAGCTTCCCGATATCCGACGGTAGTGTggatgggtgacatgtgcatc
DLGAP1_MIP_34	gcgcgcgcctgcgcctcgtcaggCTTCAGCTTCCCGATATCCGACGGTAGTGTcccggggggcgtgggt
DLGAP1_MIP_35	ggcaaacgcagcaagagcaagCTTCAGCTTCCCGATATCCGACGGTAGTGTcccggcccatccgccacct
DLGAP1_MIP_36	gaactggctccagcaggtggcCTTCAGCTTCCCGATATCCGACGGTAGTGTtgggtaagagcttctgga
DLGAP1_MIP_37	gatggctatcacacctgcagtaCTTCAGCTTCCCGATATCCGACGGTAGTGTtaggcactcacctcgca
DLGAP1_MIP_38	gggtggtgctcactgggtcaCTTCAGCTTCCCGATATCCGACGGTAGTGTctctgctcctcagctcttg
DLGAP1_MIP_39	caccagcggaaactcctccagCTTCAGCTTCCCGATATCCGACGGTAGTGTtatcaggcagccgcagcc
DLGAP1_MIP_40	aagaaaaaggcaaaagtcgtaacCTTCAGCTTCCCGATATCCGACGGTAGTGTtagtgaccccgtggtga
DLGAP2_MIP_1	cgacgcgcggcccccctacctgctCTTCAGCTTCCCGATATCCGACGGTAGTGTgagcgtactcgcggc
DLGAP2_MIP_2	gcccgtggtgcaggtgctcgcagCTTCAGCTTCCCGATATCCGACGGTAGTGTacacgtggtcggccagc
DLGAP2_MIP_3	cccggccaacctgctggaccCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgcgtgatgatccgggtgg
DLGAP2_MIP_4	gcgtgctgtagtgcgagctgtaCTTCAGCTTCCCGATATCCGACGGTAGTGTgacgtcctctgctactgc
DLGAP2_MIP_5	gctttcacaagtcgactcgcCTTCAGCTTCCCGATATCCGACGGTAGTGTtagttggagagcagctgc
DLGAP2_MIP_6	cacggagtgtaccaggtggcggCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgtctccttctgctgt
DLGAP2_MIP_7	cgcccagcgtgctcaaccggCTTCAGCTTCCCGATATCCGACGGTAGTGTaccacgcccaccacgccaag
DLGAP2_MIP_8	gataggtgctgctgctcagcCTTCAGCTTCCCGATATCCGACGGTAGTGTccgagcactgacgtcg
DLGAP2_MIP_9	caagagctcgtgaacctggaCTTCAGCTTCCCGATATCCGACGGTAGTGTaagacctcaagagcaaca
DLGAP2_MIP_10	accaggagctgccttcagctaCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgagcctgcttacctgg
DLGAP2_MIP_11	actgcatacacatttaggtgtgctCTTCAGCTTCCCGATATCCGACGGTAGTGTaccaggacgccaagcc
DLGAP2_MIP_12	gagttacattaagccatgggggCTTCAGCTTCCCGATATCCGACGGTAGTGTtgcgcttctcagtgaca
DLGAP2_MIP_13	acttctcattctctgcaggaaCTTCAGCTTCCCGATATCCGACGGTAGTGTctctccaagcggtctct
DLGAP2_MIP_14	cactcctcgcgagctcctctCTTCAGCTTCCCGATATCCGACGGTAGTGTactccagcccgaagacatc
DLGAP2_MIP_15	atccgctcccgaaccagaCTTCAGCTTCCCGATATCCGACGGTAGTGTtccctcgaagcgggtgctca
DLGAP2_MIP_16	ggggtccagcgtgtgtccacaCTTCAGCTTCCCGATATCCGACGGTAGTGTactggaccgggggagaa
DLGAP2_MIP_17	gatgtttccgaacaaggagtcacaCTTCAGCTTCCCGATATCCGACGGTAGTGTggggcatcagctgtgc
DLGAP2_MIP_18	agggcatecatggcctgagatCTTCAGCTTCCCGATATCCGACGGTAGTGTctgttgacctgatggtgga
DLGAP2_MIP_19	cagtacaatgtactctctgacCTTCAGCTTCCCGATATCCGACGGTAGTGTgacacctctgacatcac
DLGAP2_MIP_20	accaggacgcctaccaggaCTTCAGCTTCCCGATATCCGACGGTAGTGTcctgttgacttggacttcc
DLGAP2_MIP_21	gagatcagaggcctggaggtggCTTCAGCTTCCCGATATCCGACGGTAGTGTcttgttctgtccaggct
DLGAP2_MIP_22	cctggtgtccaagcggaggagCTTCAGCTTCCCGATATCCGACGGTAGTGTcggccctctacaactcca
DLGAP2_MIP_23	ggccttctcgtgctcggcaCTTCAGCTTCCCGATATCCGACGGTAGTGTgttttgcttattctaggct
DLGAP2_MIP_24	cttttttggatgttcagcgcCTTCAGCTTCCCGATATCCGACGGTAGTGTgtctccacctgtggct
DLGAP2_MIP_25	atgaagccacagctgtgagaccCTTCAGCTTCCCGATATCCGACGGTAGTGTtgcgatgaacatccaaaa
DLGAP2_MIP_26	actcagcccctcctgacacgCTTCAGCTTCCCGATATCCGACGGTAGTGTcccagtttctcagttcaaaa
DLGAP2_MIP_27	gcttctcatttccactgacccCTTCAGCTTCCCGATATCCGACGGTAGTGTaaactatgcccctgtt
DLGAP2_MIP_28	ccttcagttcggctcactcttcCTTCAGCTTCCCGATATCCGACGGTAGTGTtaccatctgtctctctc
DLGAP2_MIP_29	gtggtgatgtggcctgggaacCTTCAGCTTCCCGATATCCGACGGTAGTGTgggtccgatagcttctct
DLGAP2_MIP_30	gatggctcgtggttttgaagctgCTTCAGCTTCCCGATATCCGACGGTAGTGTtagggctcttcagcta
DLGAP2_MIP_31	acggagacatcctccagctctCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaagcctgagcttactt
DLGAP2_MIP_32	ctccctttgtattcaagtgaCTTCAGCTTCCCGATATCCGACGGTAGTGTtagatggagagagagggc
DLGAP2_MIP_33	gttttattggctttccaacaCTTCAGCTTCCCGATATCCGACGGTAGTGTctgcttttgttaattgac
DLGAP2_MIP_34	gctggaattctgggacatgagCTTCAGCTTCCCGATATCCGACGGTAGTGTcagtggaactctttgac
DLGAP2_MIP_35	gtcagcatgaagttcagagctCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgcccgcaggagact
DLGAP2_MIP_36	caatggagagctgcagcatgctCTTCAGCTTCCCGATATCCGACGGTAGTGTcagtgagaagggggttt
DLGAP2_MIP_37	agagaaaaatccctggacctgcccCTTCAGCTTCCCGATATCCGACGGTAGTGTgagctcgcagctgct
DLGAP2_MIP_38	ggtattggagcgggaccttctCTTCAGCTTCCCGATATCCGACGGTAGTGTggaattctccggaagga
DLGAP2_MIP_39	ccctcgtccttccgcttctCTTCAGCTTCCCGATATCCGACGGTAGTGTcggagcgcctcatggccg
DLGAP3_MIP_1	gccgcttgcgcttctctgctCTTCAGCTTCCCGATATCCGACGGTAGTGTggcccggccgggctggggc
DLGAP3_MIP_2	cctggcggccaagcgcgccgttCTTCAGCTTCCCGATATCCGACGGTAGTGTgccccgcaggaggaga
DLGAP3_MIP_3	cgaacgcgatggcgtcagaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtatcggcggagggaccttc
DLGAP3_MIP_4	gtaggaggtcccagaaccggCTTCAGCTTCCCGATATCCGACGGTAGTGTgaatttcccagagctggc
DLGAP3_MIP_5	aggatgtaccctcaagttctgCTTCAGCTTCCCGATATCCGACGGTAGTGTgctgggctcagacctc
DLGAP3_MIP_6	actagaaaagcagaaggaaattcCTTCAGCTTCCCGATATCCGACGGTAGTGTtcatgtatctgttagga
DLGAP3_MIP_7	gtcgttgggcagcacacaacCTTCAGCTTCCCGATATCCGACGGTAGTGTtggatcacacagtgccaag
DLGAP3_MIP_8	catcttgatgaacctcggcctcCTTCAGCTTCCCGATATCCGACGGTAGTGTgaggccatgttccccca
DLGAP3_MIP_9	gcagatggagcgtgagcgggaCTTCAGCTTCCCGATATCCGACGGTAGTGTcgtgactcctgtagagc
DLGAP3_MIP_10	ggtaggcccactggccctgctCTTCAGCTTCCCGATATCCGACGGTAGTGTgggagctcagtgaaacc
DLGAP3_MIP_11	cgagggctaccactgcccgtCTTCAGCTTCCCGATATCCGACGGTAGTGTggccacagaagacaaggccc
DLGAP3_MIP_12	cctggggagaggggtgctgctCTTCAGCTTCCCGATATCCGACGGTAGTGTtctggaaggagctgcaa

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
DLGAP3_MIP_13	gagcaaggttaacgcctccCTTCAGCTTCCCGATATCCGACGGTAGTGTaagtgcataaggttaaatgtcc
DLGAP3_MIP_14	atctgagatcgtctccactggCTTCAGCTTCCCGATATCCGACGGTAGTGTctatgcagccctctctcc
DLGAP3_MIP_15	ccggaggagggttccactctattggCTTCAGCTTCCCGATATCCGACGGTAGTGTcttggggcgcagccat
DLGAP3_MIP_16	gtcttgatgatgagtggtggggcCTTCAGCTTCCCGATATCCGACGGTAGTGTcaccaccgccccgacc
DLGAP3_MIP_17	ccattgggtgcaggtatggaacgCTTCAGCTTCCCGATATCCGACGGTAGTGTgcgcgcacactggag
DLGAP3_MIP_18	gctctggcggtgatggagatgCTTCAGCTTCCCGATATCCGACGGTAGTGTcccggggcggcaccggcg
DLGAP3_MIP_19	gcaccgactccgcgcacgagCTTCAGCTTCCCGATATCCGACGGTAGTGTaggcaggggccgcagcctca
DLGAP3_MIP_20	gtccgcacgcggaacagccCTTCAGCTTCCCGATATCCGACGGTAGTGTggccggggcaggggcagga
DLGAP3_MIP_21	ccatccaggccggtgctctcCTTCAGCTTCCCGATATCCGACGGTAGTGTgctcagcgtatgattgaac
DLGAP3_MIP_22	aagacctctatctgcagaggCTTCAGCTTCCCGATATCCGACGGTAGTGTacaccgaccgcacac
DLGAP3_MIP_23	aacagtggactgtaggaggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTtctccaggcactatggg
DLGAP3_MIP_24	cccagtatgcctggaggaaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctagcagctccactggt
DLGAP3_MIP_25	actgctttggagatgcttctCTTCAGCTTCCCGATATCCGACGGTAGTGTccactctacacacatctcc
DLGAP3_MIP_26	gateaagtaaggacagggaggcCTTCAGCTTCCCGATATCCGACGGTAGTGTgagcggcagctatca
DLGAP3_MIP_27	gtctctcagacatgacctagtCTTCAGCTTCCCGATATCCGACGGTAGTGTctctctcatccccatg
DLGAP3_MIP_28	ggtatccatcccggcctgCTTCAGCTTCCCGATATCCGACGGTAGTGTagtgcacaagactggtgaag
DLGAP3_MIP_29	ccaaggccaagccagacttaCTTCAGCTTCCCGATATCCGACGGTAGTGTgcactggcagtgccatg
DLGAP3_MIP_30	aaggaccaccaggtccccagCTTCAGCTTCCCGATATCCGACGGTAGTGTactcctgaccgactg
DLGAP3_MIP_31	cctggagggtccagatggctctCTTCAGCTTCCCGATATCCGACGGTAGTGTggaccgcaagggggatg
DLGAP3_MIP_32	ggtggtgatggaggtggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTactgtccaagttgcatcg
DLGAP3_MIP_33	accagtcccggcaccgcaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTggggaagcggactataat
DLGAP3_MIP_34	ggcagtcccctccctggcgtggCTTCAGCTTCCCGATATCCGACGGTAGTGTcctcagcctggggcc
DLGAP3_MIP_35	geatccggcactggttcattCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaaaagcagttgccatt
DLGAP3_MIP_36	cagggtacatcctgggaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgtggaagccatctgt
DLGAP3_MIP_37	gacacctgtgaagactgtgtgCTTCAGCTTCCCGATATCCGACGGTAGTGTcatttctctgaaggcc
DLGAP3_MIP_38	ggcctctgcagcaggggcccCTTCAGCTTCCCGATATCCGACGGTAGTGTctcctcagggcctaccgac
DLGAP3_MIP_39	aggccttctccaccagcccCTTCAGCTTCCCGATATCCGACGGTAGTGTgagccttgcagcagcag
DLGAP3_MIP_40	catctttattagcactctgtaCTTCAGCTTCCCGATATCCGACGGTAGTGTggtcgcagtgtaacc
EPHA6_MIP_1	cctggaccctcgtgcctgttcCTTCAGCTTCCCGATATCCGACGGTAGTGTccaagtgaatagctctcg
EPHA6_MIP_2	gcaggtgcagctgctcggagCTTCAGCTTCCCGATATCCGACGGTAGTGTgatggggctctgtccac
EPHA6_MIP_3	ggcctcgaagtcgggaatttCTTCAGCTTCCCGATATCCGACGGTAGTGTgggtggaggaggaagagg
EPHA6_MIP_4	ggctcttttctctcccttaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTcggcccgtccctacc
EPHA6_MIP_5	actggttgcctctcagctCTTCAGCTTCCCGATATCCGACGGTAGTGTaattgtttctcttgcct
EPHA6_MIP_6	gtctttttagattttaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTagaanaatcaggaatttt
EPHA6_MIP_7	aattaaatagaaaataaaattcCTTCAGCTTCCCGATATCCGACGGTAGTGTactattaggagatctta
EPHA6_MIP_8	cccgtgatgcagctcagaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtactacttttcccttttg
EPHA6_MIP_9	atccagttgtacgaagccagCTTCAGCTTCCCGATATCCGACGGTAGTGTgactcactgattccat
EPHA6_MIP_10	atcgcatcctcaaaccaacCTTCAGCTTCCCGATATCCGACGGTAGTGTcttgcaagaacatttaaat
EPHA6_MIP_11	cccaaatcactctggtaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTatttctgtagaaaacagc
EPHA6_MIP_12	cctctttggtgaagtacggCTTCAGCTTCCCGATATCCGACGGTAGTGTgattttatctgctttcaa
EPHA6_MIP_13	ggaatcaaccctggaatgtaCTTCAGCTTCCCGATATCCGACGGTAGTGTcatatcctgactgcaga
EPHA6_MIP_14	aaaagttttatttttaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTggagcgtgatgagattggc
EPHA6_MIP_15	aagggttatttccgagctgaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagtgtttttctctttt
EPHA6_MIP_16	ccatgatgttaactgtgtgCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaagaccaaaagggttg
EPHA6_MIP_17	gacacaggaggagaaaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTgcataattcattgtcctat
EPHA6_MIP_18	ggtggctccattccaaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTtgtttgatcagccctgtatg
EPHA6_MIP_19	agtttttcccaagccattcacCTTCAGCTTCCCGATATCCGACGGTAGTGTtgggtggaggactccg
EPHA6_MIP_20	aagggtgaattcacgtgagacCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagaattatggctctgt
EPHA6_MIP_21	cattctggactacgagatcaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctctgccaaltaattctt
EPHA6_MIP_22	caggtcctgcatgataggCTTCAGCTTCCCGATATCCGACGGTAGTGTaatatagataacgacatgc
EPHA6_MIP_23	cacatccagtgagaactgcCTTCAGCTTCCCGATATCCGACGGTAGTGTaactctgttcttctctt
EPHA6_MIP_24	gctttggacctgtggaagagCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaactactttcatccc
EPHA6_MIP_25	gtgtcccaagttttatagctgCTTCAGCTTCCCGATATCCGACGGTAGTGTacagatacagtggt
EPHA6_MIP_26	caggcttccaatgatgtctCTTCAGCTTCCCGATATCCGACGGTAGTGTctcttggctcattatattcc
EPHA6_MIP_27	gaaccaagagaaaataatgactCTTCAGCTTCCCGATATCCGACGGTAGTGTgacctgatttggccc
EPHA6_MIP_28	actttattcttctgactcctgCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaatgtcaccagg
EPHA6_MIP_29	aggatgacgaggagaggtgaatccCTTCAGCTTCCCGATATCCGACGGTAGTGTcctcaggtgtgctttgt
EPHA6_MIP_30	cgagggactttcttctcattCTTCAGCTTCCCGATATCCGACGGTAGTGTtggatgcatcactctt
EPHA6_MIP_31	gaagtatgatcatacaatgcaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTagaagtcctcgcct
EPHA6_MIP_32	cctcaagaattcgtattgagagagCTTCAGCTTCCCGATATCCGACGGTAGTGTctcaactaaatcaat
EPHA6_MIP_33	cctttgcaattcagtgactgCTTCAGCTTCCCGATATCCGACGGTAGTGTgccaagatttaagatagt
EPHA6_MIP_34	actttgaaaggtggccacatgCTTCAGCTTCCCGATATCCGACGGTAGTGTactcttctgaaatgtaagt

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
EPHA6_MIP_35	gatctcttttccctgggtgcCTTCAGCTTCCCGATATCCGACGGTAGTGTtttggtgacaaccctt
EPHA6_MIP_36	attaaggaataacttagttagcCTTCAGCTTCCCGATATCCGACGGTAGTGTccaacatcattgcct
EPHA6_MIP_37	catccagtgccagggggaggCTTCAGCTTCCCGATATCCGACGGTAGTGTgcttttccataaagaagac
EPHA6_MIP_38	ggggcctggatgctattttaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcatttgtattggggcc
EPHA6_MIP_39	gttctatatttaaacatttatcaCTTCAGCTTCCCGATATCCGACGGTAGTGTtattctcttgcct
EPHA6_MIP_40	gttaagagataccagctgtggCTTCAGCTTCCCGATATCCGACGGTAGTGTaacacctcaccgcaaaa
EPHA6_MIP_41	gatatgggttatgttcatcgagCTTCAGCTTCCCGATATCCGACGGTAGTGTgcacacctgcattaaaa
EPHA6_MIP_42	gaaagatacttcatgcctgatgCTTCAGCTTCCCGATATCCGACGGTAGTGTtgggtataagcagcttc
EPHA6_MIP_43	ccttctaattttctgcttgaCTTCAGCTTCCCGATATCCGACGGTAGTGTtggctctccagagtgct
EPHA6_MIP_44	aagacatagcctacaccaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgcataattacagttctgtta
EPHA6_MIP_45	gttaacagaactgtaattatgcaCTTCAGCTTCCCGATATCCGACGGTAGTGTgggtgtagctatgct
EPHA6_MIP_46	gtcatgctctatggagagagaCTTCAGCTTCCCGATATCCGACGGTAGTGTtagtcaagaatctccaatt
EPHA6_MIP_47	cccacatgacaatgccatagcCTTCAGCTTCCCGATATCCGACGGTAGTGTgaggacaaaaggcataat
EPHA6_MIP_48	gaaggagagaatcacagaccCTTCAGCTTCCCGATATCCGACGGTAGTGTgcctaaaaataagagagt
EPHA6_MIP_49	gccagcagtgagcatcagCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaaactcaacattatgcc
EPHA6_MIP_50	cgtggcagcaggggttacaCTTCAGCTTCCCGATATCCGACGGTAGTGTtccatgttttggttt
EPHA6_MIP_51	agtattctgtattgccccatCTTCAGCTTCCCGATATCCGACGGTAGTGTgggttcttgatacagca
EPHA6_MIP_52	gtatgaaagtaccacaagcaccCTTCAGCTTCCCGATATCCGACGGTAGTGTtggctctctcttctt
EPHA6_MIP_53	gaaatcccttctctgtatgCTTCAGCTTCCCGATATCCGACGGTAGTGTagtgtaacagaagactg
GABRA1_MIP_1	gactggaagaaggtggggacCTTCAGCTTCCCGATATCCGACGGTAGTGTataacctgatgttcttgc
GABRA1_MIP_2	cctcatcgccggctggagcaCTTCAGCTTCCCGATATCCGACGGTAGTGTccccgataaaataaatgaaa
GABRA1_MIP_3	gattgggagtaggtgcatCTTCAGCTTCCCGATATCCGACGGTAGTGTtattgcttctttagttt
GABRA1_MIP_4	gtccaaaatcctggtgaagacCTTCAGCTTCCCGATATCCGACGGTAGTGTttgaccatttagaggtaa
GABRA1_MIP_5	catgatatgtaagtggacactCTTCAGCTTCCCGATATCCGACGGTAGTGTcagtatgtggtggtgaga
GABRA1_MIP_6	gaaacgggtccgaaactgtgCTTCAGCTTCCCGATATCCGACGGTAGTGTcaciaaaatagccaaga
GABRA1_MIP_7	ggactccggacacatttttCTTCAGCTTCCCGATATCCGACGGTAGTGTcgtcattttcaaaattacc
GABRA1_MIP_8	gattttactgcccattaggtattCTTCAGCTTCCCGATATCCGACGGTAGTGTgcagccatcttacc
GABRA1_MIP_9	cctgttttcaaccttaacaatCTTCAGCTTCCCGATATCCGACGGTAGTGTaggatggcaccttctg
GABRA1_MIP_10	acttttctgtattgtaagtcattaCTTCAGCTTCCCGATATCCGACGGTAGTGTtggttgtattctatg
GABRA1_MIP_11	gggaaacatagaatacaacaCTTCAGCTTCCCGATATCCGACGGTAGTGTtaatgacttacaatcaag
GABRA1_MIP_12	acgtctaaaccagatgacctCTTCAGCTTCCCGATATCCGACGGTAGTGTtagaagaatgaagtgtaaa
GABRA1_MIP_13	cgtgctggctctctgtccaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttctctccataactga
GABRA1_MIP_14	gtgattctctacaagtctccCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagtcaaatgctcatct
GABRA1_MIP_15	gaataacaaagtacccatcttCTTCAGCTTCCCGATATCCGACGGTAGTGTatacccttcttgcgt
GABRA1_MIP_16	ggtttattgccgtgtgctatCTTCAGCTTCCCGATATCCGACGGTAGTGTcacagatgaactgcatca
GABRA1_MIP_17	ccatagctgttcataagccCTTCAGCTTCCCGATATCCGACGGTAGTGTtaaacgatttaccctttct
GABRA1_MIP_18	gtttgacctgtgtattgCTTCAGCTTCCCGATATCCGACGGTAGTGTtgcacagtaaaccttca
GABRA1_MIP_19	accctaattggccagggCTTCAGCTTCCCGATATCCGACGGTAGTGTtcagcaacttataatttgc
GABRA1_MIP_20	gctggtgctgttggagcgtCTTCAGCTTCCCGATATCCGACGGTAGTGTtttctgacactgttaaagg
GABRA1_MIP_21	ctaaaagccccacaccacateCTTCAGCTTCCCGATATCCGACGGTAGTGTaccaccagacccaagaa
GABRA1_MIP_22	gaggctctgtttaaatacCTTCAGCTTCCCGATATCCGACGGTAGTGTtctttaaagacagagcaa
GABRG2_MIP_1	gacggtgtgattctgctcctCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaggggaggtattctt
GABRG2_MIP_2	actgagttctgtgctccatctCTTCAGCTTCCCGATATCCGACGGTAGTGTtccccacacctcccc
GABRG2_MIP_3	cctgagggtgatgactgctCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaagtcaactgtgtgta
GABRG2_MIP_4	caagggaagatttaattatacttCTTCAGCTTCCCGATATCCGACGGTAGTGTctggaaggatagaca
GABRG2_MIP_5	catcatcagattctgctagtCTTCAGCTTCCCGATATCCGACGGTAGTGTaaacctctatcagcgc
GABRG2_MIP_6	gtttgagagaaaatgtgatgCTTCAGCTTCCCGATATCCGACGGTAGTGTcaattctatgtttctttaa
GABRG2_MIP_7	gtgtgcacatagagaggtgcCTTCAGCTTCCCGATATCCGACGGTAGTGTcatgctaataaacagacaa
GABRG2_MIP_8	catggtgggaaaatctggaCTTCAGCTTCCCGATATCCGACGGTAGTGTactgtgtacaaaattctgt
GABRG2_MIP_9	gtaggaagaaaacaaacaCTTCAGCTTCCCGATATCCGACGGTAGTGTcactttctcagaattcca
GABRG2_MIP_10	ggtgctgttaaattcaaacgtCTTCAGCTTCCCGATATCCGACGGTAGTGTcattccaaattctcagca
GABRG2_MIP_11	actcctgccccctggagttcCTTCAGCTTCCCGATATCCGACGGTAGTGTcattttaaattgtgcaaat
GABRG2_MIP_12	gtgcaattgtaattggcactcagCTTCAGCTTCCCGATATCCGACGGTAGTGTtatgcttcttcaatta
GABRG2_MIP_13	ccttggcctccagtagctgCTTCAGCTTCCCGATATCCGACGGTAGTGTggttggttggttggttt
GABRG2_MIP_14	cagaagcgaagctgtatgCTTCAGCTTCCCGATATCCGACGGTAGTGTgataaatccagcttgggc
GABRG2_MIP_15	ataccaccgaagtgtgagacCTTCAGCTTCCCGATATCCGACGGTAGTGTgagcttctctatcagc
GABRG2_MIP_16	gtgtgcccaactcaacagaCTTCAGCTTCCCGATATCCGACGGTAGTGTataccaaaattcaactct
GABRG2_MIP_17	cctatcctgggtgcttcttggCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaggggtgatggtgtt
GABRG2_MIP_18	caatgagtgtcaggggataCTTCAGCTTCCCGATATCCGACGGTAGTGTatggacataaaaattactg
GABRG2_MIP_19	gtctctatgtcacagcagctgCTTCAGCTTCCCGATATCCGACGGTAGTGTcacgagtactcagttac
GABRG2_MIP_20	caggctaaggctcagcagtttCTTCAGCTTCCCGATATCCGACGGTAGTGTtattttgcaacaccgga
GABRG2_MIP_21	gggagcgattccggcaatCTTCAGCTTCCCGATATCCGACGGTAGTGTtattcttctctgcttgg

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
GABRG2_MIP_22	gtttatgagtagacatttaagcCTTCAGCTTCCCGATATCCGACGGTAGTGTtctctttctgctaca
GABRG2_MIP_23	gggttttagacagaaaagagCTTCAGCTTCCCGATATCCGACGGTAGTGTgcttaaatgctactcat
GABRG2_MIP_24	actgtgccagtttttctgctgCTTCAGCTTCCCGATATCCGACGGTAGTGTcttccctaccctcgtcc
GABRG2_MIP_25	gagagatgtctgttaagccacCTTCAGCTTCCCGATATCCGACGGTAGTGTgactcctatgctcgga
GABRG2_MIP_26	ccagacactcatagccgtactCTTCAGCTTCCCGATATCCGACGGTAGTGTaaggcagtggggaaagaag
GNAI1_MIP_1	caacctccgtgaggacggcgaCTTCAGCTTCCCGATATCCGACGGTAGTGTgattccccctgcttgagg
GNAI1_MIP_2	ggtcgatcatcttactccgctccCTTCAGCTTCCCGATATCCGACGGTAGTGTaaacgccaggggccg
GNAI1_MIP_3	caccaaaattgctgttaagtaCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgtgtgggagttgaa
GNAI1_MIP_4	caactcccaacacacaaacCTTCAGCTTCCCGATATCCGACGGTAGTGTaaacagcaaattggtgtt
GNAI1_MIP_5	gttgagatagactttggtgacCTTCAGCTTCCCGATATCCGACGGTAGTGTttttccctttgctca
GNAI1_MIP_6	ccactgctttgtattgtttacaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctttttaccatcaggt
GNAI1_MIP_7	gtggaagatagtggtgtacaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgacgtatcccttttac
GNAI1_MIP_8	ccagctagcacaagagttgCTTCAGCTTCCCGATATCCGACGGTAGTGTacttactatgctcagaatc
GNAI1_MIP_9	acattcttgacaacttaggataCTTCAGCTTCCCGATATCCGACGGTAGTGTcccagagatccagct
GNAI1_MIP_10	gagtgaaaactacaggaattgCTTCAGCTTCCCGATATCCGACGGTAGTGTggatgactttattgct
GNAI1_MIP_11	gttctgagaacatcttggagCTTCAGCTTCCCGATATCCGACGGTAGTGTtacactttttattctaa
GNAI1_MIP_12	ggttctagctgaagatgaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTtgaactcattctctc
GNAI1_MIP_13	gtcactcagtgctacacagaCTTCAGCTTCCCGATATCCGACGGTAGTGTcctgactttcaaatgta
GNAI1_MIP_14	gaaaaaatcaaaaagagcccCTTCAGCTTCCCGATATCCGACGGTAGTGTgattggtttatttttct
GNAI1_MIP_15	ccactgtgttcatatgctgCTTCAGCTTCCCGATATCCGACGGTAGTGTgacaagttattccaga
GNAI1_MIP_16	acttcacatgctccacagatCTTCAGCTTCCCGATATCCGACGGTAGTGTtaacttttgcattatgt
GNAI1_MIP_17	gggtatattcctttgtgctCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaatgcatttaccatga
GRIN2A_MIP_1	attcatgaatattcttgcataCTTCAGCTTCCCGATATCCGACGGTAGTGTgtagctatgcttaatg
GRIN2A_MIP_2	cgttaaaagctgtgtaagtCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaacacctggtttgtt
GRIN2A_MIP_3	gtgtccatgacctcagcactCTTCAGCTTCCCGATATCCGACGGTAGTGTtctctatagacatttaaat
GRIN2A_MIP_4	gtgaaaacaaatgcaaccagCTTCAGCTTCCCGATATCCGACGGTAGTGTtgtatgctactggtagtc
GRIN2A_MIP_5	acatacattgtatgcccagCTTCAGCTTCCCGATATCCGACGGTAGTGTttcacatattttttta
GRIN2A_MIP_6	cagagtgcagctaccaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaatgagttctgtcaaca
GRIN2A_MIP_7	gtgccccccattcctctacCTTCAGCTTCCCGATATCCGACGGTAGTGTacaaattctctgtctata
GRIN2A_MIP_8	ccagataaaactgtgaaaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTgagaagaagaaatgcagaa
GRIN2A_MIP_9	gcaatatctggaatgttgcacCTTCAGCTTCCCGATATCCGACGGTAGTGTaagggataaaactggc
GRIN2A_MIP_10	gattcacaagttgcccaggCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagactaagaggtttatct
GRIN2A_MIP_11	ccaccactgcagcaaaaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaaaaacgaaaagatgct
GRIN2A_MIP_12	aaattaaagaataaacagaCTTCAGCTTCCCGATATCCGACGGTAGTGTattaagattctctctct
GRIN2A_MIP_13	caaggaaagaaatctaatCTTCAGCTTCCCGATATCCGACGGTAGTGTctgtttattcttttaaat
GRIN2A_MIP_14	atctgtgggaggggtggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgactgagctccat
GRIN2A_MIP_15	gaccaagtggggaagatactggCTTCAGCTTCCCGATATCCGACGGTAGTGTgagcagggcgggtga
GRIN2A_MIP_16	ggatgaccttcgggacatgtttaCTTCAGCTTCCCGATATCCGACGGTAGTGTggttggggcagctgg
GRIN2A_MIP_17	ataaagtctgaaacgtgacggaCTTCAGCTTCCCGATATCCGACGGTAGTGTtaccagatggtctacc
GRIN2A_MIP_18	gctctgagggcaggcggggCTTCAGCTTCCCGATATCCGACGGTAGTGTctgctcacttcccacaggt
GRIN2A_MIP_19	aagtgagcagctgaggtcagaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcagagccagctgcc
GRIN2A_MIP_20	atggctggaatggcagaggactCTTCAGCTTCCCGATATCCGACGGTAGTGTgagggggtggccaggt
GRIN2A_MIP_21	accatcggcggcctggcttacCTTCAGCTTCCCGATATCCGACGGTAGTGTgacagtagccattccctg
GRIN2A_MIP_22	cacataaggctgcatctctgctCTTCAGCTTCCCGATATCCGACGGTAGTGTaaccacacctcagaagg
GRIN2A_MIP_23	gatggtctcaacaacctggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTcagctctagttggaact
GRIN2A_MIP_24	atgaactctgggtcaggttggCTTCAGCTTCCCGATATCCGACGGTAGTGTgacagagctaggtccc
GRIN2A_MIP_25	ccactgggccattggtgaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTctgactagctctcag
GRIN2A_MIP_26	actgccttgccttaaccatCTTCAGCTTCCCGATATCCGACGGTAGTGTgagcctagccactgat
GRIN2A_MIP_27	gtaagatcagtggtgtaggctCTTCAGCTTCCCGATATCCGACGGTAGTGTcatgggttagggacaagg
GRIN2A_MIP_28	cctgggtggtcagctggagcagCTTCAGCTTCCCGATATCCGACGGTAGTGTctgctcacttaccctg
GRIN2A_MIP_29	gatcatgaagctctgctgggagCTTCAGCTTCCCGATATCCGACGGTAGTGTtactgtccagggctcc
GRIN2A_MIP_30	actggcaggagggaaggcaggtCTTCAGCTTCCCGATATCCGACGGTAGTGTgagcggcctagggtg
GRIN2A_MIP_31	gtcatcggtgccaccgcccCTTCAGCTTCCCGATATCCGACGGTAGTGTatgagctcaaggacgaaga
GRIN2A_MIP_32	caaggaccttctcccctgctCTTCAGCTTCCCGATATCCGACGGTAGTGTgcaacaggtacctgagtc
GRIN2A_MIP_33	cttctggatgtattctgagaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgagaactcaggcagggtg
GRIN2A_MIP_34	ggtatttccaaaggcaagacaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgatgccagggggcacg
GRIN2A_MIP_35	cacaagaacctgctacctctctCTTCAGCTTCCCGATATCCGACGGTAGTGTgagccccgcttcat
GRIN2A_MIP_36	cagggccttgaggtgcatctCTTCAGCTTCCCGATATCCGACGGTAGTGTggtgtcacaacttccag
GRIN2A_MIP_37	gcatcctggatggcaacaagCTTCAGCTTCCCGATATCCGACGGTAGTGTcagtgctctcggataag
GRIN2A_MIP_38	cctacaaggaaagggaaccaagCTTCAGCTTCCCGATATCCGACGGTAGTGTgaccaccagtgggcata
GRIN2A_MIP_39	gcagggcatggtgcctaccCTTCAGCTTCCCGATATCCGACGGTAGTGTggccagtgattaaactta
GRIN2A_MIP_40	cctttgagtagtggagtaggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTtaatgtggccagccct

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
GRIN2A_MIP_41	accccagtggtgggtcaaggagCTTCAGCTTCCCGATATCCGACGGTAGTGTccctgagcctcccatt
GRIN2A_MIP_42	gtgaccgtgctgacttggaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaggcctgccaccccac
GRIN2A_MIP_43	ggcctgatggctccgaggacCTTCAGCTTCCCGATATCCGACGGTAGTGTccaaagtacttaacagtctg
GRIN2A_MIP_44	cacagagagggactgtttatggCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttggggaccacagcc
GRIN2A_MIP_45	atccccatcttggatgggaCTTCAGCTTCCCGATATCCGACGGTAGTGTctgctctgtggctgattg
GRIN2A_MIP_46	gagcagcccatctgcaaggaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgcaggggaccaccccc
GRIN2A_MIP_47	caacgttctcatcatggtcctgCTTCAGCTTCCCGATATCCGACGGTAGTGTatagcaagggtcgaagc
GRIN2A_MIP_48	ccagggcaaatagtgctgcaggCTTCAGCTTCCCGATATCCGACGGTAGTGTggctggccttgaccatg
GRIN2A_MIP_49	gtggggagagataaaatccagcatCTTCAGCTTCCCGATATCCGACGGTAGTGTaagacctgcagcagct
GRIN2A_MIP_50	gtggggagagacaaaatccagcatCTTCAGCTTCCCGATATCCGACGGTAGTGTaagacctgcagcagct
GRIN2A_MIP_51	gtcacgtctggctgtgaccagCTTCAGCTTCCCGATATCCGACGGTAGTGTatgagctgcacacgtg
GRIN2A_MIP_52	gtcacgtctggctgtgaccagCTTCAGCTTCCCGATATCCGACGGTAGTGTatgagctgcacacttg
GRIN2A_MIP_53	gagcgcgaactcgaactgtCTTCAGCTTCCCGATATCCGACGGTAGTGTggctattggacctgct
GRIN2A_MIP_54	gagcgcgaactcgaactgtCTTCAGCTTCCCGATATCCGACGGTAGTGTggctattggacctgct
GRIN2A_MIP_55	aaaggattaccaactggcttccCTTCAGCTTCCCGATATCCGACGGTAGTGTcgcagaccagaag
GRIN2A_MIP_56	aaaggattaccaactggcttccCTTCAGCTTCCCGATATCCGACGGTAGTGTcgcagaccagaag
KCNQ2_MIP_1	acagaggtcggagtcggtctgCTTCAGCTTCCCGATATCCGACGGTAGTGTaccgtgctgaggagg
KCNQ2_MIP_2	ggcggagggtcccttggtagcCTTCAGCTTCCCGATATCCGACGGTAGTGTggatgctctcaacagctg
KCNQ2_MIP_3	gatggagatggactgtctctCTTCAGCTTCCCGATATCCGACGGTAGTGTatgtagggcctgactttgg
KCNQ2_MIP_4	ggcttcagcatctcccagtcctCTTCAGCTTCCCGATATCCGACGGTAGTGTgccagatggagtctct
KCNQ2_MIP_5	ccgtggccctggcggggtgctCTTCAGCTTCCCGATATCCGACGGTAGTGTgggtgctctctgccc
KCNQ2_MIP_6	acctccccgtggggaccacggcCTTCAGCTTCCCGATATCCGACGGTAGTGTcaagatcgtgctctc
KCNQ2_MIP_7	caaagtagcctcgtctctCTTCAGCTTCCCGATATCCGACGGTAGTGTgccgagagttctctgg
KCNQ2_MIP_8	gcccggagccggcggccgtaccCTTCAGCTTCCCGATATCCGACGGTAGTGTcacccagcccagcagc
KCNQ2_MIP_9	cgcccacgatctgtccacCTTCAGCTTCCCGATATCCGACGGTAGTGTcgcaccctcccgccagc
KCNQ2_MIP_10	gatcacggacaaggaccgaccaCTTCAGCTTCCCGATATCCGACGGTAGTGTgcctagaccaggggca
KCNQ2_MIP_11	ggacaccaggaaccgcatgCTTCAGCTTCCCGATATCCGACGGTAGTGTgacaggcaggcgggctctt
KCNQ2_MIP_12	gtgatggactcatcgagcagtCTTCAGCTTCCCGATATCCGACGGTAGTGTctaggaaggtcgtgctg
KCNQ2_MIP_13	geagctctgtatccacaatgctCTTCAGCTTCCCGATATCCGACGGTAGTGTggcaggaccaccgagc
KCNQ2_MIP_14	ccccggcctcaaaatcagcatCTTCAGCTTCCCGATATCCGACGGTAGTGTcccgggaatagctctccc
KCNQ2_MIP_15	gcacctgctgggctgtctctCTTCAGCTTCCCGATATCCGACGGTAGTGTccatccccgagagatg
KCNQ2_MIP_16	caagagctggagcttggggCTTCAGCTTCCCGATATCCGACGGTAGTGTcaagttgaaagatcgtgtct
KCNQ2_MIP_17	ggagagaagtcactctcaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTcctcacagctgggct
KCNQ2_MIP_18	gaggagagcacagttagctctCTTCAGCTTCCCGATATCCGACGGTAGTGTctagtaagcaggagggg
KCNQ2_MIP_19	gcccctcctgcttactagagCTTCAGCTTCCCGATATCCGACGGTAGTGTggactaactgtgctctct
KCNQ2_MIP_20	ccccccacagtccatgggtcaCTTCAGCTTCCCGATATCCGACGGTAGTGTacaccaggtagcagcag
KCNQ2_MIP_21	ccccctgctctaccctgctgCTTCAGCTTCCCGATATCCGACGGTAGTGTgaccatgggactgtgg
KCNQ2_MIP_22	aaggagagggagtgagcgtctCTTCAGCTTCCCGATATCCGACGGTAGTGTaggaggactgagacgcc
KCNQ2_MIP_23	gggtggcgtctcagctctctCTTCAGCTTCCCGATATCCGACGGTAGTGTgagacgctcactcccctc
KCNQ2_MIP_24	atgaacaaatagtgaggaaagtCTTCAGCTTCCCGATATCCGACGGTAGTGTggcctctgtccatgc
KCNQ2_MIP_25	gaaatgcatggacagaagccCTTCAGCTTCCCGATATCCGACGGTAGTGTtacttctcaactattgt
KCNQ2_MIP_26	gtacatgggacggtagcctCTTCAGCTTCCCGATATCCGACGGTAGTGTcctttgtaaaaatcattt
KCNQ2_MIP_27	gccaccaagcaactgtttcatttCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttcccctccgagtc
KCNQ2_MIP_28	gccaggcactcaggactctggCTTCAGCTTCCCGATATCCGACGGTAGTGTgggtggctagaatccca
KCNQ2_MIP_29	caagatgcccgtcaatcatcagCTTCAGCTTCCCGATATCCGACGGTAGTGTggacaagggtgtgctg
KCNQ2_MIP_30	gtctgggttggcctgaaggttCTTCAGCTTCCCGATATCCGACGGTAGTGTggagtgctgtgacct
KCNQ2_MIP_31	gtgtcagcgtgatctgtgggacCTTCAGCTTCCCGATATCCGACGGTAGTGTcctccaaaggcagcag
KCNQ2_MIP_32	gcaacctcaccctcatcgtgCTTCAGCTTCCCGATATCCGACGGTAGTGTgtccagctgcccctag
KCNQ2_MIP_33	caggcagtgaaccgctctgCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaccacaatgaccacaact
KCNQ2_MIP_34	gtacttggcagagaagggggagCTTCAGCTTCCCGATATCCGACGGTAGTGTtgggttgggtggtgga
KCNQ2_MIP_35	atctcaggaagcgcagcctCTTCAGCTTCCCGATATCCGACGGTAGTGTgccaggactctcgtgctg
KCNQ2_MIP_36	ggggaggcactggaagctgCTTCAGCTTCCCGATATCCGACGGTAGTGTtttagacatcatggtgctc
KCNQ2_MIP_37	gtgcagagggggcggaaaggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTcggcgccagcaccgcaa
KCNQ2_MIP_38	aacaccacgatagtcagatttCTTCAGCTTCCCGATATCCGACGGTAGTGTgcaataccaccccacca
KCNQ2_MIP_39	ggcgtggactctgtcgggaCTTCAGCTTCCCGATATCCGACGGTAGTGTcctctgtgcttggctct
KCNQ2_MIP_40	aggaaactggggcagggaaagCTTCAGCTTCCCGATATCCGACGGTAGTGTctctctctgggcacttc
KCNQ2_MIP_41	gtctgtgtgtttccaccatcaaCTTCAGCTTCCCGATATCCGACGGTAGTGTctgctgctggctggtg
KCNQ2_MIP_42	cgcgcccccgcgcgaggttCTTCAGCTTCCCGATATCCGACGGTAGTGTggggccccgccggcactc
KCNQ2_MIP_43	gaagcccccaagcgaacgcttCTTCAGCTTCCCGATATCCGACGGTAGTGTggctctggtggctgg
KCNQ2_MIP_44	gtcagagctcagggggcggCTTCAGCTTCCCGATATCCGACGGTAGTGTggagtcggcgccggggg
MAPK8_MIP_1	gtcagagctcaaggaaataCTTCAGCTTCCCGATATCCGACGGTAGTGTtttggatgaagccattaaat
MAPK8_MIP_2	atatgttctcagactgtgaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaatatttccaaggtatc

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
MAPK8_MIP_3	gcctacagagagctagttctCTTCAGCTTCCCGATATCCGACGGTAGTGTattttgcttgaagttttt
MAPK8_MIP_4	cgcttggcatgagctgatiCTTCAGCTTCCCGATATCCGACGGTAGTGTcctaataatttagctttga
MAPK8_MIP_5	aagtcgagagacagaaaaatagCTTCAGCTTCCCGATATCCGACGGTAGTGTgtccagcagcaatcta
MAPK8_MIP_6	ctagatcatgaaagaatgtctacCTTCAGCTTCCCGATATCCGACGGTAGTGTttttgtaagttagta
MAPK8_MIP_7	ccatctgaatcacttggcaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTcaatgagaaaaaaga
MAPK8_MIP_8	atgacgccttatgtagtactCTTCAGCTTCCCGATATCCGACGGTAGTGTatcatggcagcattttt
MAPK8_MIP_9	gttctgcagtcctggccagCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaaaaaagcctaatacagaa
MAPK8_MIP_10	gcgatgaactctttatgttctcCTTCAGCTTCCCGATATCCGACGGTAGTGTtetttgtgctgcaaa
MAPK8_MIP_11	gtttgcagcacaagaaggaCTTCAGCTTCCCGATATCCGACGGTAGTGTcataaagaagttcatcgcc
MAPK8_MIP_12	gtagtttctaaaggtcaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTatctttatgtaatgcat
MAPK8_MIP_13	caatgacattaacataaagatttCTTCAGCTTCCCGATATCCGACGGTAGTGTttgaccttagaaact
MAPK8_MIP_14	atatgctggatagctttgaCTTCAGCTTCCCGATATCCGACGGTAGTGTatttttctagctactga
MAPK8_MIP_15	caacgtaagtcttactgttggCTTCAGCTTCCCGATATCCGACGGTAGTGTaccctaaatgggattaaa
MAPK8_MIP_16	atcctctgaagcagaagctCTTCAGCTTCCCGATATCCGACGGTAGTGTgtacattaacaccattatg
MAPK8_MIP_17	ggagagcttcatctacagagaCTTCAGCTTCCCGATATCCGACGGTAGTGTaattaaaggtctcctcca
MAPK8_MIP_18	cttctggttttatatggtgaCTTCAGCTTCCCGATATCCGACGGTAGTGTggttatttgccttgtg
MAPK8_MIP_19	aggcaataaacaagtcagtCTTCAGCTTCCCGATATCCGACGGTAGTGTataaaaccagaagctcc
MAPK8_MIP_20	cctctcctttagttggttacaCTTCAGCTTCCCGATATCCGACGGTAGTGTatcatgcttggagatt
MAPK8_MIP_21	gccccgtataactcattctCTTCAGCTTCCCGATATCCGACGGTAGTGTaagcctggaataaatga
MAPK8_MIP_22	cagctagaagcagcagctgCTTCAGCTTCCCGATATCCGACGGTAGTGTgatttctgtttgttctc
MAPK8_MIP_23	gtctgtatcagaggccaagtCTTCAGCTTCCCGATATCCGACGGTAGTGTaataagaccactgaattgt
OTX1_MIP_1	caccagccctccgacctgccCTTCAGCTTCCCGATATCCGACGGTAGTGTgctggggcgccctcacc
OTX1_MIP_2	gggtggaggcgccccgacggCTTCAGCTTCCCGATATCCGACGGTAGTGTcagggtcgggaggctggtg
OTX1_MIP_3	gacatcttcatcgggaggaggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTaccaatgaccccgccg
OTX1_MIP_4	ggtagcagagcttggcgaagCTTCAGCTTCCCGATATCCGACGGTAGTGTgacctctagacctccc
OTX1_MIP_5	caagaagaagtcctctccagtcCTTCAGCTTCCCGATATCCGACGGTAGTGTcaacaagctcccctagc
OTX1_MIP_6	ggcgcgctcttggctccgctcCTTCAGCTTCCCGATATCCGACGGTAGTGTccggtgggtggcgaaga
OTX1_MIP_7	atctatctggagccccgectccCTTCAGCTTCCCGATATCCGACGGTAGTGTctgttccagctctgct
OTX1_MIP_8	ccaccgggttcccactagtcCTTCAGCTTCCCGATATCCGACGGTAGTGTcacaacagaggtgtgcta
OTX1_MIP_9	gacctctctctactttgCTTCAGCTTCCCGATATCCGACGGTAGTGTgccggaccattggccgctc
OTX1_MIP_10	gtagccttgcccagctgctcCTTCAGCTTCCCGATATCCGACGGTAGTGTgtggtgatgatggtgccc
OTX1_MIP_11	accaccaccaccaaggctacgCTTCAGCTTCCCGATATCCGACGGTAGTGTcatgcaactcacatccac
OTX1_MIP_12	gtggtggtgctgagactgCTTCAGCTTCCCGATATCCGACGGTAGTGTggggagttgaagttagtt
OTX1_MIP_13	ggagaagaacgcaactacctgCTTCAGCTTCCCGATATCCGACGGTAGTGTgattacaaggacctg
PCDH19_MIP_1	gggctcagctcagaggagacCTTCAGCTTCCCGATATCCGACGGTAGTGTtttctcttctctgagag
PCDH19_MIP_2	ggagctgatagcgaagaagtcatCTTCAGCTTCCCGATATCCGACGGTAGTGTaagagctctctcccac
PCDH19_MIP_3	catgacagctcttgccttCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgaagacgggaagc
PCDH19_MIP_4	gagcgcattagccctgtcaccCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaccttgggaaagatgt
PCDH19_MIP_5	cacatgctcagggacttggaaacCTTCAGCTTCCCGATATCCGACGGTAGTGTcctctcctcagccgggt
PCDH19_MIP_6	ggaacatcatcgctgtctCTTCAGCTTCCCGATATCCGACGGTAGTGTttctttttccaacagat
PCDH19_MIP_7	ccttgtggaaatggcacttttagCTTCAGCTTCCCGATATCCGACGGTAGTGTggcatttcccggca
PCDH19_MIP_8	gtcaactctctcatgtccactaCTTCAGCTTCCCGATATCCGACGGTAGTGTtatcatcaaccagctct
PCDH19_MIP_9	catgatgtccagcggacctCTTCAGCTTCCCGATATCCGACGGTAGTGTttttaaaacagatctgca
PCDH19_MIP_10	gatttgaactgcctacttagaCTTCAGCTTCCCGATATCCGACGGTAGTGTaagcaagcaaaccaaca
PCDH19_MIP_11	gttggttctgcttattgctCTTCAGCTTCCCGATATCCGACGGTAGTGTtagggcagttcgaatct
PCDH19_MIP_12	gttctccacattcagaaagtgcCTTCAGCTTCCCGATATCCGACGGTAGTGTacagagccacttagctg
PCDH19_MIP_13	gaatacccgaacaccagctgctCTTCAGCTTCCCGATATCCGACGGTAGTGTgacagacaagatgaacg
PCDH19_MIP_14	attctatgtgacagaaaagcagCTTCAGCTTCCCGATATCCGACGGTAGTGTagggaagagcaactgac
PCDH19_MIP_15	gctgagtactcctatgggcaCTTCAGCTTCCCGATATCCGACGGTAGTGTatgtaatgcaccagaataag
PCDH19_MIP_16	agccgaggagacaagtatggCTTCAGCTTCCCGATATCCGACGGTAGTGTatgagggaaatgctttt
PCDH19_MIP_17	aaggacaaaacagcaagtgtctCTTCAGCTTCCCGATATCCGACGGTAGTGTctttatgttccagttgca
PCDH19_MIP_18	atcaaggacaagttcacagagcCTTCAGCTTCCCGATATCCGACGGTAGTGTaagaagaanaactggct
PCDH19_MIP_19	cattattgccctgggctccattCTTCAGCTTCCCGATATCCGACGGTAGTGTatgaccttatctggtgg
PCDH19_MIP_20	ggctcatgctaggtgactcggCTTCAGCTTCCCGATATCCGACGGTAGTGTgagatgcttccctggt
PCDH19_MIP_21	gaccgcgcttcttgaatagCTTCAGCTTCCCGATATCCGACGGTAGTGTctgattaacggcactgc
PCDH19_MIP_22	ccttggccagcacttgaattcCTTCAGCTTCCCGATATCCGACGGTAGTGTtgcgggtatgtagacc
PCDH19_MIP_23	gctacggtgctgctcatctCTTCAGCTTCCCGATATCCGACGGTAGTGTtcacctatgtctccatcaa
PCDH19_MIP_24	cagatagcgcaccagcgtgtCTTCAGCTTCCCGATATCCGACGGTAGTGTtagatgctcctgagttgg
PCDH19_MIP_25	gacctgggtctcaacggcagctCTTCAGCTTCCCGATATCCGACGGTAGTGTagtctttaccgtgctcat
PCDH19_MIP_26	cagaatagtggagaagctctcCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgttcttttctgtag
PCDH19_MIP_27	gcacgaccaatacaacctcaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgtctgatcgcgact
PCDH19_MIP_28	attgtcattgtgtccagcagcCTTCAGCTTCCCGATATCCGACGGTAGTGTactgcacagctcattga

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
PCDH19_MIP_29	cggatcatcaacctgctgtcagcCTTCAGCTTCCCGATATCCGACGGTAGTGTactggcgcttttagactac
PCDH19_MIP_30	catagaaggagtagaccacctggCTTCAGCTTCCCGATATCCGACGGTAGTGTccaagctcttagcctgc
PCDH19_MIP_31	gtcttttcagatcgaccgcacaCTTCAGCTTCCCGATATCCGACGGTAGTGTggtgagcgtgccagaaa
PCDH19_MIP_32	ccaccgtctagcgcagtgatcCTTCAGCTTCCCGATATCCGACGGTAGTGTgacgggtgtgtggagg
PCDH19_MIP_33	gactccaatgacaacaaccggCTTCAGCTTCCCGATATCCGACGGTAGTGTttgccgaactcgtggt
PCDH19_MIP_34	cgccaaagcttctgagctgCTTCAGCTTCCCGATATCCGACGGTAGTGTaagctgtagtcgactgc
PCDH19_MIP_35	gcagacttacgagctcagccCTTCAGCTTCCCGATATCCGACGGTAGTGTaaggacctgaacgacaatg
PCDH19_MIP_36	ggtcaatcttctgcttgggtgaccCTTCAGCTTCCCGATATCCGACGGTAGTGTctccgggaaactgggc
PCDH19_MIP_37	gaggtcatgtccagctcaatggaCTTCAGCTTCCCGATATCCGACGGTAGTGTtttcgctggtgtccaa
PCDH19_MIP_38	gcgctgctccttctaccgaCTTCAGCTTCCCGATATCCGACGGTAGTGTgagctgggattgatgtcca
PCDH19_MIP_39	ggtgattgccaacgtgccaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTgcagagccccgtcag
SCN1A_MIP_1	gaccccgaggtcgggaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTcgtgattggacaatattgac
SCN1A_MIP_2	cctgctggaaccagtcatcatCTTCAGCTTCCCGATATCCGACGGTAGTGTcctgagcttccaagca
SCN1A_MIP_3	gatggcgtgggacctggggCTTCAGCTTCCCGATATCCGACGGTAGTGTgaacagggcagttgtagg
SCN1A_MIP_4	agagcttctggacagtgacgccCTTCAGCTTCCCGATATCCGACGGTAGTGTcaagaagccatggatggc
SCN1A_MIP_5	atagcttccacagatcttctgaCTTCAGCTTCCCGATATCCGACGGTAGTGTggctccctggaagccc
SCN1A_MIP_6	caagggtgagctgcagatgCTTCAGCTTCCCGATATCCGACGGTAGTGTatgggctagggaaacagaaa
SCN1A_MIP_7	atggtggtgatgagaatgctgCTTCAGCTTCCCGATATCCGACGGTAGTGTccccagactcgtct
SCN1A_MIP_8	acctccatagaatcttggtagCTTCAGCTTCCCGATATCCGACGGTAGTGTgtccaaggtattagcagc
SCN1A_MIP_9	gtggcagactcatcaaacaggaCTTCAGCTTCCCGATATCCGACGGTAGTGTggacctgtttctccc
SCN1A_MIP_10	gtgtgcttcacgtgttctgaCTTCAGCTTCCCGATATCCGACGGTAGTGTgtctctcagagccaac
SCN1A_MIP_11	gttaagggacttggagacagagCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaagcagggctccgat
SCN1A_MIP_12	ggccccctgaacctcagcctCTTCAGCTTCCCGATATCCGACGGTAGTGTggcagaactcaaaact
SCN1A_MIP_13	gcaggatgatctctctctctctCTTCAGCTTCCCGATATCCGACGGTAGTGTgacccccgccctacc
SCN1A_MIP_14	gacctgctgcagccctgctcCTTCAGCTTCCCGATATCCGACGGTAGTGTttctctctgctcttgg
SCN1A_MIP_15	aagaagaaaacgaaaagaagaacCTTCAGCTTCCCGATATCCGACGGTAGTGTcccctcccagaag
SCN1A_MIP_16	caacatacttcaatttctcagCTTCAGCTTCCCGATATCCGACGGTAGTGTggcctacacatgaga
SCN1A_MIP_17	caccaagttgtctgcttcttCTTCAGCTTCCCGATATCCGACGGTAGTGTtagagctgctttgtctg
SCN1A_MIP_18	caagacaaaagcagctctcaCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaagcagacaaaactggtg
SCN1A_MIP_19	gtatagttcttccaggaactcCTTCAGCTTCCCGATATCCGACGGTAGTGTctacctaccactacca
SCN1A_MIP_20	gatgatctgaccattaagctgtgCTTCAGCTTCCCGATATCCGACGGTAGTGTcctggtgtcatgcc
SCN1A_MIP_21	atgaggcagagatgccaacCTTCAGCTTCCCGATATCCGACGGTAGTGTcaccctcaagcctttt
SCN1A_MIP_22	gtgggtttgactttgatggCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgtatcttactaagtacg
SCN1A_MIP_23	gggtgagtgccagagccacCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgtggaaggttaagtct
SCN1A_MIP_24	gttgatgactatcttgcacggCTTCAGCTTCCCGATATCCGACGGTAGTGTgcccagaggtgagcatg
SCN1A_MIP_25	cagtcggaagatctgtcttCTTCAGCTTCCCGATATCCGACGGTAGTGTctcaccacagcactata
SCN1A_MIP_26	ccaccaagaacaacaatgCTTCAGCTTCCCGATATCCGACGGTAGTGTctgagactagagatgaa
SCN1A_MIP_27	gggggggctcgcggggCTTCAGCTTCCCGATATCCGACGGTAGTGTggcgggaaggccccggcgc
SCN1A_MIP_28	ggggccggctcttccgcccCTTCAGCTTCCCGATATCCGACGGTAGTGTcggcagggccccggcgc
SCN1A_MIP_29	atgctgcacggcgaagcggCTTCAGCTTCCCGATATCCGACGGTAGTGTgggtcgcggcggggcgc
SCN1A_MIP_30	gtggcctaggcctcatcaagaacCTTCAGCTTCCCGATATCCGACGGTAGTGTtcccagcgggttgc
SCN1A_MIP_31	gtgtcctccagcttcttccagaCTTCAGCTTCCCGATATCCGACGGTAGTGTgggggctgcaactccc
SCN1A_MIP_32	caagtccctgaagtctggagagCTTCAGCTTCCCGATATCCGACGGTAGTGTcaccggggcgagatta
SCN1A_MIP_33	cagtcaccggcggcctgcagcCTTCAGCTTCCCGATATCCGACGGTAGTGTgaccggggagtagccggc
SCN1A_MIP_34	caccgacaggttcttcaattgaCTTCAGCTTCCCGATATCCGACGGTAGTGTctgctgcttcagcag
SCN1A_MIP_35	gggagggggtgtgaggggaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTtagcctcgtgtgcatctc
SCN1A_MIP_36	gtgtgtgggacagcaagtctgCTTCAGCTTCCCGATATCCGACGGTAGTGTgccagtgaaatcaccac
SCN1A_MIP_37	ggcaggatggtgctcaggcctCTTCAGCTTCCCGATATCCGACGGTAGTGTtagggccctggtctag
SCN1A_MIP_38	gtgtacaagattggcgtgagcCTTCAGCTTCCCGATATCCGACGGTAGTGTgtggtcaaggcgtgaa
SCN1A_MIP_39	gtgcttcaggagactgctCTTCAGCTTCCCGATATCCGACGGTAGTGTtagggacacggccttgcgtt
SCN1A_MIP_40	gtttagccgatcttctgatgtaCTTCAGCTTCCCGATATCCGACGGTAGTGTctctggccaggggt
SCN1A_MIP_41	atcagcactgcagctcgcCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgtgagctcatttgtt
SCN1A_MIP_42	ccaccgtgcccttgtgcccctCTTCAGCTTCCCGATATCCGACGGTAGTGTctgggtgtgaaagcagctc
SCN1A_MIP_43	ggcatctccaagaatggcgagacCTTCAGCTTCCCGATATCCGACGGTAGTGTgaagtgaggtggggcca
SCN1A_MIP_44	ggacatccaacatacaatttctCTTCAGCTTCCCGATATCCGACGGTAGTGTgtaaccaaggcaatca
SCN1A_MIP_45	atgtagtacttgggtctcgaacCTTCAGCTTCCCGATATCCGACGGTAGTGTccccagctgtccttga
SCN1A_MIP_46	gggaccagggagtcctggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTttccagagggagatgctc
SCN1A_MIP_47	actcatcaagaacatgatcagCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaggtatgctggtg
SCN1A_MIP_48	caaatgaggaggtattgacaaaagCTTCAGCTTCCCGATATCCGACGGTAGTGTtagagcaccgggttcc
SCN1A_MIP_49	caagtctatcatcctgatggCTTCAGCTTCCCGATATCCGACGGTAGTGTattccccactaactg
SCN1A_MIP_50	atgaccacgatgttggctggCTTCAGCTTCCCGATATCCGACGGTAGTGTaagaccatagcctgggga
SCN1A_MIP_51	gttagtgggggaattgtagaCTTCAGCTTCCCGATATCCGACGGTAGTGTggatgatagactttaa

**Table S1 (continued). MIP sequences.**



MIP name	MIP sequence
SCN1A_MIP_52	gtacagtgaccctgccagcCTTCAGCTTCCCGATATCCGACGGTAGTGTttaaacctcaactatcttc
SCN1A_MIP_53	cagccatctgaagccagcaCTTCAGCTTCCCGATATCCGACGGTAGTGTgatactccatgaacttacc
SCN1A_MIP_54	ccagtctctggcggggattgCTTCAGCTTCCCGATATCCGACGGTAGTGTgttgacacaaaactctgt
SCN1A_MIP_55	cgtgggattatgattgggaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgacaaccttaactaac
SCN1A_MIP_56	catgggattatgattgggaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgacaaccttaactaac
SCN1A_MIP_57	cacggaaggtttgggcatcCTTCAGCTTCCCGATATCCGACGGTAGTGTgtcacactttttctcaat
SCN1A_MIP_58	catacaagcatattaatgaggCTTCAGCTTCCCGATATCCGACGGTAGTGTttaaagtgcagtcttttc
SCN1A_MIP_59	gaatcgtctccctggccctgtCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaaggaacctttgcctat
SCN1A_MIP_60	cggaaaggtttacaatgatggtaCTTCAGCTTCCCGATATCCGACGGTAGTGTtaatgccctctcaca
SCN1A_MIP_61	gaatcgtctccccggccctgtCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaaggaacctttgcctat
SCN1A_MIP_62	cagccctcctcaagagtctaCTTCAGCTTCCCGATATCCGACGGTAGTGTacggagaaaagtggatgga
SCN1A_MIP_63	accattcttgcctcacacgatCTTCAGCTTCCCGATATCCGACGGTAGTGTctgtttgcctgtttgtt
SCN1A_MIP_64	accattcttgcctcacacgatCTTCAGCTTCCCGATATCCGACGGTAGTGTctgtttgcctgtttgtt
SCN1A_MIP_65	caagcacagatagaagtgcgCTTCAGCTTCCCGATATCCGACGGTAGTGTatttgaaattttgaatt
SCN1A_MIP_66	attttatttaagtgctgattCTTCAGCTTCCCGATATCCGACGGTAGTGTttagcctcatgaacaaa
SCN1A_MIP_67	actaaacagaggtggttcgaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctggagtcgcaaggaa
SCN1A_MIP_68	gtgcaaaagctcctggaatcagCTTCAGCTTCCCGATATCCGACGGTAGTGTgatagagaaggtcccca
SCN1A_MIP_69	actaaacagagatggttcgaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctggagtcgcaaggaa
SCN1A_MIP_70	gggtctctttgaaactaacaCTTCAGCTTCCCGATATCCGACGGTAGTGTaatttaaaatgaaactgtt
SCN1A_MIP_71	gcgtttggggttacaagaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTgccaacctaatcctac
SCN1A_MIP_72	actttggcagttctgtcagttCTTCAGCTTCCCGATATCCGACGGTAGTGTaagtttgcgaacagatg
SCN1A_MIP_73	cctcgggtgattttggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTgcagtttaagcaattgaag
SCN1A_MIP_74	accacatatcaatggcaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTtaactgtcacagatgaaa
SCN1A_MIP_75	ccagatggcaacttgaacttCTTCAGCTTCCCGATATCCGACGGTAGTGTaaattacaggtttgtgtt
SCN1A_MIP_76	aagaacttctgtctttgtCTTCAGCTTCCCGATATCCGACGGTAGTGTgcaaaatgactataaaaa
SCN1A_MIP_77	actactgaagttcaagacctCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaagccttcatctct
SCN1A_MIP_78	ggaccgtatgacctgactCTTCAGCTTCCCGATATCCGACGGTAGTGTtactgttattgtaccttc
SCN1A_MIP_79	gttagattagctgggaatgtCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttcaagaaaacagct
SCN1A_MIP_80	gagacacacagtcccaggctCTTCAGCTTCCCGATATCCGACGGTAGTGTattgtttgtgtgatgat
SCN1A_MIP_81	cacggcagctggaagtgccCTTCAGCTTCCCGATATCCGACGGTAGTGTgggtaaatgatacggctatt
SCN1A_MIP_82	ggctaacactattggggcataCTTCAGCTTCCCGATATCCGACGGTAGTGTgatgccaggtgctttta
SCN1A_MIP_83	aaggtgttttctgaacaggatgaCTTCAGCTTCCCGATATCCGACGGTAGTGTcccttggcctgtccg
SCN1A_MIP_84	catgtagcccctcaacagaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctctgaaaaatccttttaa
SCN1A_MIP_85	gccacagtccactccatgaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcccatcaccateaccac
SCN1A_MIP_86	caatgaaaaaattattcttCTTCAGCTTCCCGATATCCGACGGTAGTGTaataacaagtaaagataca
SCN1A_MIP_87	caatagataaaattattcttCTTCAGCTTCCCGATATCCGACGGTAGTGTaataacaagtaaagataca
SCN1A_MIP_88	atcctttgaatgtgcctatCTTCAGCTTCCCGATATCCGACGGTAGTGTtagaatcatttctgtgc
SCN1A_MIP_89	atcctttaaatgtgcctatCTTCAGCTTCCCGATATCCGACGGTAGTGTtagaatcatttctgtgc
SCN1A_MIP_90	aatgtatgcagcagttgatiCTTCAGCTTCCCGATATCCGACGGTAGTGTtcaaaaatattccctttg
SCN1A_MIP_91	aatgtatgcagcagttgatiCTTCAGCTTCCCGATATCCGACGGTAGTGTtcaaaaatattccctttg
SCN1B_MIP_1	gtggcgtcgggacacggggCTTCAGCTTCCCGATATCCGACGGTAGTGTgagggggcgagcagcgc
SCN1B_MIP_2	ggcgtgctgcgccccctcCTTCAGCTTCCCGATATCCGACGGTAGTGTccccgttcccggagccac
SCN1B_MIP_3	gatgacctcaaaattcttgcCTTCAGCTTCCCGATATCCGACGGTAGTGTggtttgtaggggctctgg
SCN1B_MIP_4	cggtctcagctccactccacCTTCAGCTTCCCGATATCCGACGGTAGTGTcggcacacctgacaaac
SCN1B_MIP_5	gtttaataatgctgtgattgctCTTCAGCTTCCCGATATCCGACGGTAGTGTagtggacctccgcca
SCN1B_MIP_6	ggcagccggggcaccaaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTgttcaggttaaggagagag
SCN1B_MIP_7	gtcactcctccagctgcaacCTTCAGCTTCCCGATATCCGACGGTAGTGTtagagcagggttagacg
SCN1B_MIP_8	gtgcctgcccccttaccgtCTTCAGCTTCCCGATATCCGACGGTAGTGTaatgtcacctacaaccactc
SCN1B_MIP_9	gtggtgtgtgctcgtagttttCTTCAGCTTCCCGATATCCGACGGTAGTGTgagccagcctgctctgt
SCN1B_MIP_10	gcctctgtttccctccagcccaCTTCAGCTTCCCGATATCCGACGGTAGTGTggagagccagatggaggg
SCN1B_MIP_11	gcctctgtttctctccagcccaCTTCAGCTTCCCGATATCCGACGGTAGTGTggagagccagatggaggg
SCN1B_MIP_12	ctggagtgggcaggaggggctCTTCAGCTTCCCGATATCCGACGGTAGTGTctcagagacagaagccacc
SCN1B_MIP_13	atgaggattgagcagctgcagCTTCAGCTTCCCGATATCCGACGGTAGTGTcactgtcctgtatgacct
SCN1B_MIP_14	atttactgctacaagaatcgctCTTCAGCTTCCCGATATCCGACGGTAGTGTtcagcctgggctacc
SCN1B_MIP_15	agccatattgtcaacaccacCTTCAGCTTCCCGATATCCGACGGTAGTGTtctctctgcaagtgtga
SCN1B_MIP_16	gatggctggcagaggggaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTtgggtcgtctgatgat
SCN1B_MIP_17	catcatcagaccgaccaaccctcCTTCAGCTTCCCGATATCCGACGGTAGTGTtcccttgcagccctac
SCN2A_MIP_1	ccaaacaggaacgcaaggatgaCTTCAGCTTCCCGATATCCGACGGTAGTGTtaaagagcaggatgaa
SCN2A_MIP_2	caatgcgtgttcaatagcagCTTCAGCTTCCCGATATCCGACGGTAGTGTcatctctggaggaatgct
SCN2A_MIP_3	actgcctattactaattggttcCTTCAGCTTCCCGATATCCGACGGTAGTGTacttgaagcaggaaaa
SCN2A_MIP_4	cctattagaaaattagctattCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttaatatattctaatg
SCN2A_MIP_5	aatgtaaaggcagggggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTtagatatttggaaaatgtg

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
SCN2A_MIP_6	actggacaagaatgtggagtCTTCAGCTTCCCGATATCCGACGGTAGTGTtgtagtgcataaaagtaa
SCN2A_MIP_7	cacagttgtaagaatcgtgcCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagaaattgaggaggtc
SCN2A_MIP_8	gttgatttcacagtcattactCTTCAGCTTCCCGATATCCGACGGTAGTGTtaatgtgagcttggctat
SCN2A_MIP_9	atcccgtaaaaatgtgaaatcttcCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgtcaaggcaagcc
SCN2A_MIP_10	gtcttgagagctttgaaactCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaaaggtcttgatgaaa
SCN2A_MIP_11	gaaagttcgaagagctgaaacatCTTCAGCTTCCCGATATCCGACGGTAGTGTtaggggttcacacaca
SCN2A_MIP_12	caccgagctgacttttagctaCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgtgtgaacccttatta
SCN2A_MIP_13	gttcatgggcaacctacgaaCTTCAGCTTCCCGATATCCGACGGTAGTGTcccccttctgatttgtttg
SCN2A_MIP_14	actgcaatcctattagcgcaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcactgtctattgaaa
SCN2A_MIP_15	gttctctaaatattaatattatCTTCAGCTTCCCGATATCCGACGGTAGTGTcacttcttcttaaca
SCN2A_MIP_16	gtgtcaataacctgccacctCTTCAGCTTCCCGATATCCGACGGTAGTGTtctattcttcttcttaaa
SCN2A_MIP_17	aatcctgtaaaacacttcagccCTTCAGCTTCCCGATATCCGACGGTAGTGTggactgaaactcagtagg
SCN2A_MIP_18	gtccttattctgtctcatgactCTTCAGCTTCCCGATATCCGACGGTAGTGTccgttattgacttcttt
SCN2A_MIP_19	ggggttctaccagcttcaCTTCAGCTTCCCGATATCCGACGGTAGTGTtatgattctcagaaaaatga
SCN2A_MIP_20	aggacagaatcagccacatCTTCAGCTTCCCGATATCCGACGGTAGTGTaaatctcttccattttg
SCN2A_MIP_21	ataggccatggccaccacagcCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaacaaaggccgatgc
SCN2A_MIP_22	gaaaaagagctgaaaaacagaagCTTCAGCTTCCCGATATCCGACGGTAGTGTacatacttgcgccctt
SCN2A_MIP_23	ggagctcaacttagatgctactCTTCAGCTTCCCGATATCCGACGGTAGTGTaacggaacctttcttc
SCN2A_MIP_24	ccacaccaggtaaaaatataaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgaacagcttggagaaga
SCN2A_MIP_25	atctctttcatatgctagcctCTTCAGCTTCCCGATATCCGACGGTAGTGTactctgaaagcattgtgc
SCN2A_MIP_26	ggctctgagaatgactttgcCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcttcatctcattttg
SCN2A_MIP_27	gtcttgagagaaaaaggagccCTTCAGCTTCCCGATATCCGACGGTAGTGTggcacgaacagagagct
SCN2A_MIP_28	atgcatagcgtgtggactgCTTCAGCTTCCCGATATCCGACGGTAGTGTacctttgaggacaatgacag
SCN2A_MIP_29	cccattcatgggcaggatggCTTCAGCTTCCCGATATCCGACGGTAGTGTcacaactctctcatcag
SCN2A_MIP_30	gtattttaccacaccatggCTTCAGCTTCCCGATATCCGACGGTAGTGTtcatctgaaattctacttc
SCN2A_MIP_31	aacatgataagaactggaccgCTTCAGCTTCCCGATATCCGACGGTAGTGTtttcatcattaccaaaagca
SCN2A_MIP_32	acctgttgaatggaccgaCTTCAGCTTCCCGATATCCGACGGTAGTGTgagttcaacttttttctt
SCN2A_MIP_33	gtttacccttaaccatggttaCTTCAGCTTCCCGATATCCGACGGTAGTGTcagacagctactgctg
SCN2A_MIP_34	gagttataattgccttagtgaaCTTCAGCTTCCCGATATCCGACGGTAGTGTcaccatctgacttctct
SCN2A_MIP_35	ccttagtttaattggaactgCTTCAGCTTCCCGATATCCGACGGTAGTGTataatgactacacttctca
SCN2A_MIP_36	atccatggcaattatcttgagaCTTCAGCTTCCCGATATCCGACGGTAGTGTttaaattaccagccgga
SCN2A_MIP_37	catcattataatattgaatCTTCAGCTTCCCGATATCCGACGGTAGTGTtttgcaaatgtggaag
SCN2A_MIP_38	catcgtcttcttttctgctCTTCAGCTTCCCGATATCCGACGGTAGTGTcactgttctgcttttatt
SCN2A_MIP_39	ggccaataccaaggtgaggtCTTCAGCTTCCCGATATCCGACGGTAGTGTcaggaaagagtgaaaaagt
SCN2A_MIP_40	atgatgtcatggtgattgaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTtcaactgtgacatgca
SCN2A_MIP_41	gtttggccagcgacctccatCTTCAGCTTCCCGATATCCGACGGTAGTGTacaaaatattctcagttga
SCN2A_MIP_42	atcgaaaaggaatcgttttCTTCAGCTTCCCGATATCCGACGGTAGTGTgtttttctgctgtgtt
SCN2A_MIP_43	cccacagaactctggagattCTTCAGCTTCCCGATATCCGACGGTAGTGTcagctgtctttttattatt
SCN2A_MIP_44	gaaaaatagctggtgaaagCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaccgttgaagatct
SCN2A_MIP_45	gtgcctatgccactagtagtCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgctgaattctcagat
SCN2A_MIP_46	caggtgttttaaatgctgctCTTCAGCTTCCCGATATCCGACGGTAGTGTgagaactgactttgaaaa
SCN2A_MIP_47	cctgttttacagaagtaagcCTTCAGCTTCCCGATATCCGACGGTAGTGTgttttttggggattgat
SCN2A_MIP_48	ggagctccaatatcaaccgCTTCAGCTTCCCGATATCCGACGGTAGTGTataaatgaaaaaatgggt
SCN2A_MIP_49	aactctgtggaattgaggaCTTCAGCTTCCCGATATCCGACGGTAGTGTaatgaatctcccacaaca
SCN2A_MIP_50	gcttactgacaacactgaaactCTTCAGCTTCCCGATATCCGACGGTAGTGTatcacctaccagagccc
SCN2A_MIP_51	atgagaagaatatgtgtgactCTTCAGCTTCCCGATATCCGACGGTAGTGTtgaactctgctgagcag
SCN2A_MIP_52	gttgcataatgtttcaagtgtCTTCAGCTTCCCGATATCCGACGGTAGTGTaatgaatttttgactt
SCN2A_MIP_53	gtgaaaacctgtcagcatattCTTCAGCTTCCCGATATCCGACGGTAGTGTgaataaagcagcaagtg
SCN2A_MIP_54	cggtttgaaggaaatgaggtaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaattgtgttcttttc
SCN2A_MIP_55	gacaaagctctcagtgccctCTTCAGCTTCCCGATATCCGACGGTAGTGTtcaatgaaatgtaagac
SCN2A_MIP_56	gctggcaagtttaccattgtCTTCAGCTTCCCGATATCCGACGGTAGTGTtatttttcttctcatct
SCN2A_MIP_57	gagattcactccatgatactCTTCAGCTTCCCGATATCCGACGGTAGTGTtcaattttccacctgg
SCN2A_MIP_58	gagtctaaagttttctctctCTTCAGCTTCCCGATATCCGACGGTAGTGTattgagagcaataaact
SCN2A_MIP_59	atattgtaatttagtgatatCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaatgatgactttct
SCN2A_MIP_60	gaaaagtcatacttttttctCTTCAGCTTCCCGATATCCGACGGTAGTGTactaattacaatatt
SCN2A_MIP_61	catagataactcaaccaacagCTTCAGCTTCCCGATATCCGACGGTAGTGTtacaacttctcatattc
SCN2A_MIP_62	gattcaaggtaaagaatgaaccaCTTCAGCTTCCCGATATCCGACGGTAGTGTattgattttggagcct
SCN2A_MIP_63	catacctgacctgtgtaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgcaaaagacacaatttaac
SCN2A_MIP_64	gtatttcttctgttctctgcaCTTCAGCTTCCCGATATCCGACGGTAGTGTtagaaattcgggctgtg
SCN2A_MIP_65	ggaaccgatgaccagagtcCTTCAGCTTCCCGATATCCGACGGTAGTGTtctaatggaactttatcat
SCN2A_MIP_66	ggtgacctgtaagcgagaCTTCAGCTTCCCGATATCCGACGGTAGTGTagtgaatagtagtaacgaa
SCN2A_MIP_67	gtaagaagaggtgctttattCTTCAGCTTCCCGATATCCGACGGTAGTGTctgtaaatctgtgtt

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
SCN2A_MIP_68	caccacaaaatcaaaaatattccCTTCAGCTTCCCGATATCCGACGGTAGTGTttgggagtttgggatg
SCN2A_MIP_69	caggattggccgaatctctacCTTCAGCTTCCCGATATCCGACGGTAGTGTaaactttcattgctacta
SCN2A_MIP_70	gatcactcggaaacagggttagcCTTCAGCTTCCCGATATCCGACGGTAGTGTaatgaccaggaaaagaa
SCN2A_MIP_71	cccttggcaacagcatgatctgCTTCAGCTTCCCGATATCCGACGGTAGTGTccctctctgctgtt
SCN2A_MIP_72	atcccaacttccctcttaacatCTTCAGCTTCCCGATATCCGACGGTAGTGTgctagggtcacagctgg
SCN2A_MIP_73	cctgggtgtggtgaacatgtCTTCAGCTTCCCGATATCCGACGGTAGTGTgacacattcttaaatg
SCN2A_MIP_74	aagaaaatcccaacagatgggCTTCAGCTTCCCGATATCCGACGGTAGTGTagaacatctcaaaagtcac
SCN2A_MIP_75	cccttctcatagcaaaaccaCTTCAGCTTCCCGATATCCGACGGTAGTGTagaagtgacagcctct
SCN2A_MIP_76	atccagggcatctgcaaaatcaCTTCAGCTTCCCGATATCCGACGGTAGTGTcactctcaccacaaacac
SCN2A_MIP_77	caaagtctctatgagccattacCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgagtggtgaccgga
SCN2A_MIP_78	gaatcgtcttccatctgtaCTTCAGCTTCCCGATATCCGACGGTAGTGTcttttaacttttcttca
SCN2A_MIP_79	caactccagagaaaaccgatCTTCAGCTTCCCGATATCCGACGGTAGTGTgcttacagagctacctc
SCN2A_MIP_80	attctcattcagttatcaatCTTCAGCTTCCCGATATCCGACGGTAGTGTctgatatttcccttgt
SCN2A_MIP_81	actcccacagagggtctatgcCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagacaaatcagaaaagg
SEMA3A_MIP_1	cccttggcagctgtttctgCTTCAGCTTCCCGATATCCGACGGTAGTGTgagtttctagaggtaatg
SEMA3A_MIP_2	caggacatacccagggaaacagCTTCAGCTTCCCGATATCCGACGGTAGTGTgatcatcacactgaccag
SEMA3A_MIP_3	gggttaccttaagaagagtttgCTTCAGCTTCCCGATATCCGACGGTAGTGTgcatgacacactgctgac
SEMA3A_MIP_4	ggaagtcattgacacagagcaCTTCAGCTTCCCGATATCCGACGGTAGTGTgagtgatgatcatatca
SEMA3A_MIP_5	attatgtttaggcacattttaCTTCAGCTTCCCGATATCCGACGGTAGTGTagaagcctgatctgt
SEMA3A_MIP_6	attctcttcagggtctgctgCTTCAGCTTCCCGATATCCGACGGTAGTGTcagtcagttcattctg
SEMA3A_MIP_7	ggtgtagaagaatagtagcacatCTTCAGCTTCCCGATATCCGACGGTAGTGTctgtctctgaatttc
SEMA3A_MIP_8	ccatttttcccttctaggaCTTCAGCTTCCCGATATCCGACGGTAGTGTgacaggttgaagatgaa
SEMA3A_MIP_9	atcttcaacctgctaagaccCTTCAGCTTCCCGATATCCGACGGTAGTGTgaagggaaaaataaggata
SEMA3A_MIP_10	ccgtaaatatcacaccggctCTTCAGCTTCCCGATATCCGACGGTAGTGTataactagcaaacattcat
SEMA3A_MIP_11	aaagcgtgtgctgagtgctgCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagaacaagagatttaa
SEMA3A_MIP_12	ggtcaattagaacagccagcCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaacaccagaattaaaca
SEMA3A_MIP_13	caattatgtattaccattgaatCTTCAGCTTCCCGATATCCGACGGTAGTGTatggcagtgctgagtta
SEMA3A_MIP_14	gtcccaacatcttgaagaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaagacgtacaactgaact
SEMA3A_MIP_15	gttcttaaagtagttcaattctCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaaggaagaccgat
SEMA3A_MIP_16	cactattggcgattgtcaCTTCAGCTTCCCGATATCCGACGGTAGTGTtccgaaaaagtttacage
SEMA3A_MIP_17	gaccgagtgatgcagaagatCTTCAGCTTCCCGATATCCGACGGTAGTGTgacacttctgatgatg
SEMA3A_MIP_18	cataattataaattataataaacCTTCAGCTTCCCGATATCCGACGGTAGTGTctggatgacttctg
SEMA3A_MIP_19	gtatacatcacacggctgCTTCAGCTTCCCGATATCCGACGGTAGTGTattttaaaccacctaagctac
SEMA3A_MIP_20	gtgagaagggtttcctgCTTCAGCTTCCCGATATCCGACGGTAGTGTtctaaatgtaagaactcag
SEMA3A_MIP_21	gaatggcaagctgaacaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTggtagttaaaaagttact
SEMA3A_MIP_22	gtaacttttaactacctaCTTCAGCTTCCCGATATCCGACGGTAGTGTgttctacatttgccattcc
SEMA3A_MIP_23	gtcattctgaaagaagggaacCTTCAGCTTCCCGATATCCGACGGTAGTGTacataaacactagctctt
SEMA3A_MIP_24	ggagggcacagaagctgctgCTTCAGCTTCCCGATATCCGACGGTAGTGTtaggaactttaaacatg
SEMA3A_MIP_25	gtatactttgtcatctcagCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaaagctttatggaaaat
SEMA3A_MIP_26	ccgtgaaaatgcaatagatggagCTTCAGCTTCCCGATATCCGACGGTAGTGTaatgattatttatta
SEMA3A_MIP_27	cagctgcagttccagatgatCTTCAGCTTCCCGATATCCGACGGTAGTGTtacacatgttacatgcta
SEMA3A_MIP_28	ggggcgagactttgctatctCTTCAGCTTCCCGATATCCGACGGTAGTGTcataaacatgaaacttgc
SEMA3A_MIP_29	gtgagttctccagcttaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaagaacataaacctgttt
SEMA3A_MIP_30	gaaaacggcctgggaaagagCTTCAGCTTCCCGATATCCGACGGTAGTGTacatgaatacttgacatctc
SEMA3A_MIP_31	gcacattcttctgtaagacaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTttttaaagccagcgt
SEMA3A_MIP_32	cagactcactgtacgcctgtCTTCAGCTTCCCGATATCCGACGGTAGTGTacaactctgtccagcatg
SEMA3A_MIP_33	cacacaatctaaggacagagaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaacactttgtccca
SEMA3A_MIP_34	ccagaagagatgaatgcaagtCTTCAGCTTCCCGATATCCGACGGTAGTGTtggaaacttcttacttca
SEMA3A_MIP_35	cgttctcatcctcaaaaggaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtactataactgagatgc
SEMA3A_MIP_36	gctgtatgttgagcaaaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTcttcacattaataaccaatg
SEMA3A_MIP_37	ccatgctgcagacgctgtagCTTCAGCTTCCCGATATCCGACGGTAGTGTaataaaaagaaaataagat
SEMA3A_MIP_38	ggattgtctgtctttctgggCTTCAGCTTCCCGATATCCGACGGTAGTGTatgaaactgacataatca
SH3GL2_MIP_1	gctggccgtccggcggcagcCTTCAGCTTCCCGATATCCGACGGTAGTGTcccggcggcggcctctgc
SH3GL2_MIP_2	gcaggagccgcctggcggcCTTCAGCTTCCCGATATCCGACGGTAGTGTctgccggcggcggcggcagc
SH3GL2_MIP_3	gagatgaaaaggtaagcctCTTCAGCTTCCCGATATCCGACGGTAGTGTaatgctttaaatttctaac
SH3GL2_MIP_4	agtcacatctagcttggctcCTTCAGCTTCCCGATATCCGACGGTAGTGTgatttctcagagaccag
SH3GL2_MIP_5	catcttatatgtttaaaggaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctaaagctcatatttgg
SH3GL2_MIP_6	gttttggtagtctgtatacaCTTCAGCTTCCCGATATCCGACGGTAGTGTctggattgggtgaaagg
SH3GL2_MIP_7	atttggaagagactggagatCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttctcttccactt
SH3GL2_MIP_8	gcgcctctgctgagatagCTTCAGCTTCCCGATATCCGACGGTAGTGTctacagaatttctaccagc
SH3GL2_MIP_9	cagaactcattgacctcttCTTCAGCTTCCCGATATCCGACGGTAGTGTgcgagtgacttcatctt
SH3GL2_MIP_10	gtccaaagacttctgactcCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaagcactctcatctgt

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
SH3GL2_MIP_11	agtctaaggaatgctgagtcactTCAGCTTCCCGATATCCGACGGTAGTGTcctgcacctgactttg
SH3GL2_MIP_12	caaatctctagagcttgacgCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagggatagccttta
SH3GL2_MIP_13	gtattctacagttccctgcattCTTCAGCTTCCCGATATCCGACGGTAGTGTggcatgatttcccatca
SH3GL2_MIP_14	gatctggactgctgcttgctTCCTCAGCTTCCCGATATCCGACGGTAGTGTtagacgtttgtctcaaatg
SH3GL2_MIP_15	acaggcaactcccaaaccttcaCTTCAGCTTCCCGATATCCGACGGTAGTGTaccactttcttttactg
SH3GL2_MIP_16	gggctgagtagtcttccagttCTTCAGCTTCCCGATATCCGACGGTAGTGTtagccagattggactattc
SH3GL2_MIP_17	attgatgagaactggtatgaggCTTCAGCTTCCCGATATCCGACGGTAGTGTtctctcctgctcttact
SH3GL2_MIP_18	ggttagtgagtgatgatcctTCCTCAGCTTCCCGATATCCGACGGTAGTGTggtaagaggaggcgag
SLC1A1_MIP_1	ggcgatgagcggcaccctcaagCTTCAGCTTCCCGATATCCGACGGTAGTGTgcacaatagcggcgaca
SLC1A1_MIP_2	gtcggcctattgtcgcctggCTTCAGCTTCCCGATATCCGACGGTAGTGTagggtgcgcgatcgcca
SLC1A1_MIP_3	aaattctaagcggatgctgaCTTCAGCTTCCCGATATCCGACGGTAGTGTaggagaactcaataatgtt
SLC1A1_MIP_4	agtgagaggttctgctgttCTTCAGCTTCCCGATATCCGACGGTAGTGTatggactaatatagagaaca
SLC1A1_MIP_5	gtattattctgtaccactctcaCTTCAGCTTCCCGATATCCGACGGTAGTGTctgaggataaatcgg
SLC1A1_MIP_6	gtgcagcaacactgaagggCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaaaaatcaccattacat
SLC1A1_MIP_7	catcagtgagtgctttgccacaCTTCAGCTTCCCGATATCCGACGGTAGTGTgacgctgttcttgcca
SLC1A1_MIP_8	cagggtgctgctgctctcCTTCAGCTTCCCGATATCCGACGGTAGTGTatttcaatcacgtaacgca
SLC1A1_MIP_9	actgtaccctcttcccatCTTCAGCTTCCCGATATCCGACGGTAGTGTattagatgacaaaacaa
SLC1A1_MIP_10	aaggcagtattatgtagggcCTTCAGCTTCCCGATATCCGACGGTAGTGTcagcagaaaaaacattt
SLC1A1_MIP_11	acagetgcatgacaactgcCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcaaaagcttaaaaaaa
SLC1A1_MIP_12	aaggactcttctgcatgttcatCTTCAGCTTCCCGATATCCGACGGTAGTGTtgcgattctgtaatga
SLC1A1_MIP_13	attgaaaaatgggagaaaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTcgtgcatcaatattgtt
SLC1A1_MIP_14	acaagtccaagacaaggcaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtaggggaagcaaatgaca
SLC1A1_MIP_15	ctttacatggccacagtcctCTTCAGCTTCCCGATATCCGACGGTAGTGTgagaagcacttgatgacg
SLC1A1_MIP_16	gatcttcccagaatcaggaacaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcagcggccatcc
SLC1A1_MIP_17	atttccatgggaatggccaCTTCAGCTTCCCGATATCCGACGGTAGTGTtaggattaagtgtggggagg
SLC1A1_MIP_18	ggaaaagggttcttctgacgCTTCAGCTTCCCGATATCCGACGGTAGTGTgctgtttttaaagtgag
SLC1A1_MIP_19	caacaatcaacatggatgggaCTTCAGCTTCCCGATATCCGACGGTAGTGTtagcattctagacataagt
SLC1A1_MIP_20	atccttctgacactggttctCTTCAGCTTCCCGATATCCGACGGTAGTGTgatggtgatgctgccc
SLC1A1_MIP_21	gtgatgaattctttttgatctCTTCAGCTTCCCGATATCCGACGGTAGTGTgacctggacttgggca
SLC1A1_MIP_22	gaggatgacacctgatcattCTTCAGCTTCCCGATATCCGACGGTAGTGTtctaactcttctctgct
SLC1A1_MIP_23	cccacggcactcagcacaatCTTCAGCTTCCCGATATCCGACGGTAGTGTagaatgatcagactcgag
SLC1A1_MIP_24	aacatttgaaatcccttgccttgCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcccctctctccc
SLC1A1_MIP_25	actcagatgaaacatccatctgCTTCAGCTTCCCGATATCCGACGGTAGTGTgaggctggtgaaatga
SLC1A1_MIP_26	actaatgccaagtgtacattCTTCAGCTTCCCGATATCCGACGGTAGTGTtagacaagtctgacacca
SLC1A3_MIP_1	gaacattacaaggaggtatgtaCTTCAGCTTCCCGATATCCGACGGTAGTGTagaagagacctctag
SLC1A3_MIP_2	gactccctgctggaatctctccCTTCAGCTTCCCGATATCCGACGGTAGTGTaatcaaatgactcacca
SLC1A3_MIP_3	cctaggcttctctgaaactgaCTTCAGCTTCCCGATATCCGACGGTAGTGTcagtcaccctgctcatt
SLC1A3_MIP_4	gggaacttctgatgaggatgCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttctgtttcaaaaaag
SLC1A3_MIP_5	ggagaagtactgactcccgCTTCAGCTTCCCGATATCCGACGGTAGTGTtctttgcaataaacacac
SLC1A3_MIP_6	catcatccatcctgggaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTatcttctgttgcctccac
SLC1A3_MIP_7	gacaatgattatgcaatcaccacCTTCAGCTTCCCGATATCCGACGGTAGTGTacccaaaaggacgggc
SLC1A3_MIP_8	ccctcttccctgctcattCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagtactattacttttt
SLC1A3_MIP_9	caagaaaagtaatagtcactgCTTCAGCTTCCCGATATCCGACGGTAGTGTtagcagggaaaaagagg
SLC1A3_MIP_10	gaatcacagaggagctgctcCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgtgctttttttttt
SLC1A3_MIP_11	agacacattgtttatcacagcaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttcatgtttccaatca
SLC1A3_MIP_12	ggtagcagtaataatgtggtatgCTTCAGCTTCCCGATATCCGACGGTAGTGTgaatggagtaaatgccc
SLC1A3_MIP_13	gtctcatgatgcttctgtaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgagaaactgcaattggcc
SLC1A3_MIP_14	ggcttactcattcacgcagtcctCTTCAGCTTCCCGATATCCGACGGTAGTGTctggtgttcttctccc
SLC1A3_MIP_15	cccccaatcacaccatgtcttcCTTCAGCTTCCCGATATCCGACGGTAGTGTgcttgcagcaaacctcc
SLC1A3_MIP_16	gggtgtaggagaagccatttCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaaaaaccttgggtttt
SLC1A3_MIP_17	actgcctctatgaggctttgCTTCAGCTTCCCGATATCCGACGGTAGTGTtgcctatttctactgtct
SLC1A3_MIP_18	cggggagcacgaatctggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTatagaactcttctctgtac
SLC1A3_MIP_19	cctgagccaggagttcaagCTTCAGCTTCCCGATATCCGACGGTAGTGTtccgacaaattattacaat
SLC1A3_MIP_20	gtcatcategctggactCTTCAGCTTCCCGATATCCGACGGTAGTGTctgttctgacttctctgta
SLC1A3_MIP_21	gatgtctcagtgaggcaggeCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcagagttcttctgta
SLC1A3_MIP_22	ggtaactcagtgattgaagagCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttctctctcccacc
SLC1A3_MIP_23	cagttcatgtgacaagtgCTTCAGCTTCCCGATATCCGACGGTAGTGTattgtagctctacacttgg
SLC1A3_MIP_24	atcttcccttctcctctctgaCTTCAGCTTCCCGATATCCGACGGTAGTGTagaaacctcagcagct
SLC2A1_MIP_1	agcgatctcatgaaagtccCTTCAGCTTCCCGATATCCGACGGTAGTGTccttagggctgctgggagca
SLC2A1_MIP_2	catcctggctgtaggacttggactTCCTCAGCTTCCCGATATCCGACGGTAGTGTagtctcaggaacttga
SLC2A1_MIP_3	ccatccctggggctgattcCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcctgttctgttcttca
SLC2A1_MIP_4	atgaacatgggatgggcccaggCTTCAGCTTCCCGATATCCGACGGTAGTGTgagacagtgagggttct

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
SLC2A1_MIP_5	atgaacatgggatagggccaggCTTCAGCTTCCCGATATCCGACGGTAGTGTgagacagtggggttct
SLC2A1_MIP_6	gagatatgcgagaaggcaggaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagatggccacgatgct
SLC2A1_MIP_7	gagctatgcgagaaggcaggaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagatggccacgatgct
SLC2A1_MIP_8	gcegttgacgcttctccaaCTTCAGCTTCCCGATATCCGACGGTAGTGTctaccctggatgctctatct
SLC2A1_MIP_9	cagagacagcgtcagtgccaccCTTCAGCTTCCCGATATCCGACGGTAGTGTctccagaacctagcaact
SLC2A1_MIP_10	cagagacagtgctcagtgccaccCTTCAGCTTCCCGATATCCGACGGTAGTGTctccagaacctagcaact
SLC2A1_MIP_11	gagttgctaggttctggagagtCTTCAGCTTCCCGATATCCGACGGTAGTGTggcactgacgctgctct
SLC2A1_MIP_12	gagttgctaggttctggagagtCTTCAGCTTCCCGATATCCGACGGTAGTGTggcactgacgctgctct
SLC2A1_MIP_13	cagacaagagaaactgttggggcCTTCAGCTTCCCGATATCCGACGGTAGTGTgccagtaagcaagact
SLC2A1_MIP_14	gagcttttctactgccccCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaacgttctctgtct
SLC2A1_MIP_15	gcatcatctgccgactgcttctCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgggtggggcactc
SLC2A1_MIP_16	gcatcatctgccgacttctctCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgggtggggcactc
SLC2A1_MIP_17	actttggcccgttctctctCTTCAGCTTCCCGATATCCGACGGTAGTGTgggtcagctcagctgct
SLC2A1_MIP_18	ccagccatctcatcgctgtgtCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgctaaagaagctgc
SLC2A1_MIP_19	aacacctgggggaagcaggggcCTTCAGCTTCCCGATATCCGACGGTAGTGTgttgatgagcaggaagcg
SLC2A1_MIP_20	cctgccctctcccactcccCTTCAGCTTCCCGATATCCGACGGTAGTGTtctagactggggcccttc
SLC2A1_MIP_21	ggactccatcatgggcaacaagCTTCAGCTTCCCGATATCCGACGGTAGTGTtctagactggggcccttc
SLC2A1_MIP_22	acgaagcctgtgtcagggccCTTCAGCTTCCCGATATCCGACGGTAGTGTgccgtgccagcaggtagat
SLC2A1_MIP_23	cattccttggctcaggggctCTTCAGCTTCCCGATATCCGACGGTAGTGTgatcagcatcctaaag
SLC2A1_MIP_24	cctgggaccctgcaccagctCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcgaactgggcaagt
SLC2A1_MIP_25	cagaaaagatgccactgagaggCTTCAGCTTCCCGATATCCGACGGTAGTGTccaccctctgggact
SLC2A1_MIP_26	cagtctctttcttctctctCTTCAGCTTCCCGATATCCGACGGTAGTGTccagagcgtggtagc
SLC2A1_MIP_27	gtggcctttctgtaaccgCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgatcagggattctcaa
SLC2A1_MIP_28	aacaaaccactgttataggctCTTCAGCTTCCCGATATCCGACGGTAGTGTgccaacgatggcacag
SLC2A1_MIP_29	gtgccatcgttgcttatggaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaacagtgtgtttttc
SLC2A1_MIP_30	gtccgggactcccactgagctCTTCAGCTTCCCGATATCCGACGGTAGTGTcccgggcccggcact
SLC2A1_MIP_31	gagtcgcgcccgcggcctctCTTCAGCTTCCCGATATCCGACGGTAGTGTagtggggagccccgga
SMARCA2_MIP_1	catccccagttccgtccacaCTTCAGCTTCCCGATATCCGACGGTAGTGTtactgactggcagagacag
SMARCA2_MIP_2	cctgttctgactaggcccCTTCAGCTTCCCGATATCCGACGGTAGTGTacttactcattatgcaattg
SMARCA2_MIP_3	atcatgcaagatcttcttctaCTTCAGCTTCCCGATATCCGACGGTAGTGTccacaggaagcagctgc
SMARCA2_MIP_4	cctcccagagtcctaatggaCTTCAGCTTCCCGATATCCGACGGTAGTGTtagaggtgctactaatgt
SMARCA2_MIP_5	ccatcgcctgggtgaggtggCTTCAGCTTCCCGATATCCGACGGTAGTGTtagacacattcttggaaatt
SMARCA2_MIP_6	cacctcagatgccaccaagccCTTCAGCTTCCCGATATCCGACGGTAGTGTtctttcaggggtgtaggg
SMARCA2_MIP_7	agttggcctctccagacataCTTCAGCTTCCCGATATCCGACGGTAGTGTctaaaactgagctcga
SMARCA2_MIP_8	aaggacgttgctggttgcagCTTCAGCTTCCCGATATCCGACGGTAGTGTgcccacagaggtcct
SMARCA2_MIP_9	ggactgcaagctgcagcgttctCTTCAGCTTCCCGATATCCGACGGTAGTGTcgtgctgtggttgc
SMARCA2_MIP_10	caactggataacaagactgctcCTTCAGCTTCCCGATATCCGACGGTAGTGTtagcagcaacagcagcc
SMARCA2_MIP_11	cgcagtgcggggcctcagctCTTCAGCTTCCCGATATCCGACGGTAGTGTccatgctgcttctgccc
SMARCA2_MIP_12	ccggggcggctcggcggctcggCTTCAGCTTCCCGATATCCGACGGTAGTGTaattccacggggctc
SMARCA2_MIP_13	cctgctcttgggtggccaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTatccagaaccgcaagc
SMARCA2_MIP_14	cgttactcaattccagcgCTTCAGCTTCCCGATATCCGACGGTAGTGTctctttcccattttatgt
SMARCA2_MIP_15	cgggtgcttgggttctaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTattgaatgactaaaggca
SMARCA2_MIP_16	catgaccgagaagctggagaagCTTCAGCTTCCCGATATCCGACGGTAGTGTtctaactgctcttctt
SMARCA2_MIP_17	gagcttctctcagagtctggCTTCAGCTTCCCGATATCCGACGGTAGTGTatttgatgaattcattggac
SMARCA2_MIP_18	catgccaactgaaagagagCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttttctccctttttg
SMARCA2_MIP_19	cggccacagaccgatgatctCTTCAGCTTCCCGATATCCGACGGTAGTGTtctctcaggagttcctt
SMARCA2_MIP_20	gtttgggagcacaagcaagcCTTCAGCTTCCCGATATCCGACGGTAGTGTatcctgctcttcttctta
SMARCA2_MIP_21	cagattggctacatactcatcgCTTCAGCTTCCCGATATCCGACGGTAGTGTtaaaaacttatccctgcc
SMARCA2_MIP_22	gtctgtccatacctggcagCTTCAGCTTCCCGATATCCGACGGTAGTGTtggttactataacattcga
SMARCA2_MIP_23	acaatgctcaatgttataagtaacCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgctccaggtatggc
SMARCA2_MIP_24	aagcaagtgcagctggaccccCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttaacatgaacctgtgac
SMARCA2_MIP_25	ggtccgaacagaacctggcCTTCAGCTTCCCGATATCCGACGGTAGTGTagttttagtttcgagatcgt
SMARCA2_MIP_26	aggaaagaattctctgaatgCTTCAGCTTCCCGATATCCGACGGTAGTGTctcttctcactctttt
SMARCA2_MIP_27	ggaaaaagagtggagagagCTTCAGCTTCCCGATATCCGACGGTAGTGTcattcaggaagaatttctt
SMARCA2_MIP_28	ccaaatagcgaagaagttctCTTCAGCTTCCCGATATCCGACGGTAGTGTgtcttttcagaaaatgtca
SMARCA2_MIP_29	cgtttctgctactggacCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaagaaaattcattaagca
SMARCA2_MIP_30	gtctgccctcctaattaatgCTTCAGCTTCCCGATATCCGACGGTAGTGTtctccacttttctcttc
SMARCA2_MIP_31	gttttcccctctccgagaCTTCAGCTTCCCGATATCCGACGGTAGTGTgccccttagtcaacatgtg
SMARCA2_MIP_32	atggggcttgaaagaccatCTTCAGCTTCCCGATATCCGACGGTAGTGTgggtgtattaggattaatt
SMARCA2_MIP_33	catcggctaaattccgttcCTTCAGCTTCCCGATATCCGACGGTAGTGTacgatgactgtggaataaat
SMARCA2_MIP_34	aaaagcaaaaaatagacctCTTCAGCTTCCCGATATCCGACGGTAGTGTtttttctgtgttttttt
SMARCA2_MIP_35	aaaaaaaacaacagaaaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTagggtctatttttgccttt

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
SMARCA2_MIP_36	cattcttgcaaaagtattgttttCTTCAGCTTCCCGATATCCGACGGTAGTGTgatcatgcatgattttt
SMARCA2_MIP_37	caagaggacattgaattgccCTTCAGCTTCCCGATATCCGACGGTAGTGTtccaattacactactgact
SMARCA2_MIP_38	actatgtggccccagaaggaCTTCAGCTTCCCGATATCCGACGGTAGTGTgtattttcccttgcttac
SMARCA2_MIP_39	agtgttcaagacctgagtcageCTTCAGCTTCCCGATATCCGACGGTAGTGTaccattgttcaaatgtgc
SMARCA2_MIP_40	gcctaaagctgagaacattaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttccaacaatttttaa
SMARCA2_MIP_41	cccgaaaaagtattgtgcacCTTCAGCTTCCCGATATCCGACGGTAGTGTcaattcataataagcctct
SMARCA2_MIP_42	ggtcttaacaccttatgtagacgCTTCAGCTTCCCGATATCCGACGGTAGTGTcaatttcagaggcagggt
SMARCA2_MIP_43	gaaagataagaaggtacgttgcCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgcttgcctacttac
SMARCA2_MIP_44	atcccccttgcttgcataatggcCTTCAGCTTCCCGATATCCGACGGTAGTGTcagcattagcagggatgc
SMARCA2_MIP_45	gttttgagcctgattgtgctaaCTTCAGCTTCCCGATATCCGACGGTAGTGTatttttcccttccactg
SMARCA2_MIP_46	cagtggaagggaataatagaaCTTCAGCTTCCCGATATCCGACGGTAGTGTcacaatcaggtcaaaac
SMARCA2_MIP_47	gttgtggccttacataaacCTTCAGCTTCCCGATATCCGACGGTAGTGTtaataattacatttttaaa
SMARCA2_MIP_48	gatttataaaaatgtaattatCTTCAGCTTCCCGATATCCGACGGTAGTGTgagttatgtaagccaac
SMARCA2_MIP_49	catctctcatgaccatcatggCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttctgttttgcatttt
SMARCA2_MIP_50	catctggcagaaaagcagcaCTTCAGCTTCCCGATATCCGACGGTAGTGTtaagtgcceattacccttc
SMARCA2_MIP_51	gcttaaatcttcagcagctCTTCAGCTTCCCGATATCCGACGGTAGTGTtggcaaaataattttctc
SMARCA2_MIP_52	caggccaccagctctgtgcCTTCAGCTTCCCGATATCCGACGGTAGTGTtaatgaactgatcatcttt
SMARCA2_MIP_53	caaaatacaagctgaactggaCTTCAGCTTCCCGATATCCGACGGTAGTGTatagcatattgaccccc
SMARCA2_MIP_54	gttcacggtacagagcctcagtaCTTCAGCTTCCCGATATCCGACGGTAGTGTcaagatggcctgcagga
SMARCA2_MIP_55	ccctttgttaaaaaactctcggCTTCAGCTTCCCGATATCCGACGGTAGTGTcaagccagagcggag
SMARCA2_MIP_56	gctttatactctgcccttCTTCAGCTTCCCGATATCCGACGGTAGTGTaaatcactctgttttaacc
SMARCA2_MIP_57	gattttaaccagtgagacgtCTTCAGCTTCCCGATATCCGACGGTAGTGTaagcattgtgttcatgat
SMARCA2_MIP_58	gtagaaggtcactctggaCTTCAGCTTCCCGATATCCGACGGTAGTGTgaccctcttattaatgtct
SMARCA2_MIP_59	cctctccttaaacgggcttCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgaggcgtcactgtag
SMARCA2_MIP_60	gagaaaccaggggcctagagcCTTCAGCTTCCCGATATCCGACGGTAGTGTaatatttggagggggtcc
SMARCA2_MIP_61	ctaagaagagaaagagccgctCTTCAGCTTCCCGATATCCGACGGTAGTGTctccttgtttccaacgaa
SMARCA2_MIP_62	caatttctctgtcttttctgCTTCAGCTTCCCGATATCCGACGGTAGTGTtatacagatcatgatga
SMARCA2_MIP_63	gttaagtgtgcaacttagtttCTTCAGCTTCCCGATATCCGACGGTAGTGTaaactgacaaagcagatg
SMARCA2_MIP_64	ccctctcttaataacagctatccCTTCAGCTTCCCGATATCCGACGGTAGTGTggggacgagaaccag
SMARCA2_MIP_65	ccctctcttaataacaggtatccCTTCAGCTTCCCGATATCCGACGGTAGTGTggggacgagaaccag
SMARCA2_MIP_66	cggtagagtagaaagaactagcCTTCAGCTTCCCGATATCCGACGGTAGTGTatgattcaactgtttc
SMARCA2_MIP_67	ggaagcctgagattcaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtccctcagtaattgtttgat
SMARCA2_MIP_68	catagattctgtaattcttctcCTTCAGCTTCCCGATATCCGACGGTAGTGTtggcgtcagctccaa
SMARCA2_MIP_69	cagacgttcaacctggagggaCTTCAGCTTCCCGATATCCGACGGTAGTGTtgcgtgaatttctctctcc
SMARCA2_MIP_70	acatctctccaggtcgcetaCTTCAGCTTCCCGATATCCGACGGTAGTGTtagaaaatgaaatattct
SMARCA2_MIP_71	aaagtgaagaaagtcagagtcCTTCAGCTTCCCGATATCCGACGGTAGTGTacagatgccctttgacc
SMARCA2_MIP_72	attgcttctcctcactctcCTTCAGCTTCCCGATATCCGACGGTAGTGTtctaaagcttctctgtga
SMARCA2_MIP_73	gccaaacctgtagtgcgaCTTCAGCTTCCCGATATCCGACGGTAGTGTgattactcactgtgtctat
SMARCA2_MIP_74	cctcgatttggccttttctgcCTTCAGCTTCCCGATATCCGACGGTAGTGTgggcatgaaatgcaaga
SMARCA2_MIP_75	gtctcatttctaccagtgcCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttgcattgattgact
SMARCA2_MIP_76	atgaagtaacatcacatgcaagCTTCAGCTTCCCGATATCCGACGGTAGTGTactcactggtagaaatg
SPTAN1_MIP_1	gtcagaagctggaagattctCTTCAGCTTCCCGATATCCGACGGTAGTGTgcccattttgctttcag
SPTAN1_MIP_2	gttgagagttccttgaagcggCTTCAGCTTCCCGATATCCGACGGTAGTGTagtgttgggtctttata
SPTAN1_MIP_3	aatcagacgagaaaagtactCTTCAGCTTCCCGATATCCGACGGTAGTGTggagaatgatacagga
SPTAN1_MIP_4	catctgaaccatacgggtgagtCTTCAGCTTCCCGATATCCGACGGTAGTGTacttcaaggtccgcaa
SPTAN1_MIP_5	aaatgcccttctgagatcatCTTCAGCTTCCCGATATCCGACGGTAGTGTttaaagcctggaaaagtc
SPTAN1_MIP_6	gtgaggacgtgaggtgactggCTTCAGCTTCCCGATATCCGACGGTAGTGTaaactctgatttgaacttt
SPTAN1_MIP_7	cgtaagtactgcaccaactctgCTTCAGCTTCCCGATATCCGACGGTAGTGTtgtgtaaacactgggtc
SPTAN1_MIP_8	gagttaatgaagtgaaccagtttCTTCAGCTTCCCGATATCCGACGGTAGTGTgctctcttatgttccct
SPTAN1_MIP_9	catgagcagccatatctgttCTTCAGCTTCCCGATATCCGACGGTAGTGTgaccaatcataaaatttta
SPTAN1_MIP_10	ctctttgggcagcagaagttCTTCAGCTTCCCGATATCCGACGGTAGTGTtacaatccagctctctct
SPTAN1_MIP_11	gccaggctgattgactctatCTTCAGCTTCCCGATATCCGACGGTAGTGTtcacaactccccctcag
SPTAN1_MIP_12	ggtctggagagagattctgctCTTCAGCTTCCCGATATCCGACGGTAGTGTactggtgcctttgtctg
SPTAN1_MIP_13	ccgaagcagagcctgaacacCTTCAGCTTCCCGATATCCGACGGTAGTGTggccttgacctaataatgaa
SPTAN1_MIP_14	gattacaactgggagcagatCTTCAGCTTCCCGATATCCGACGGTAGTGTgttaccagggtcaggaga
SPTAN1_MIP_15	gttctctcgttctcactgaCTTCAGCTTCCCGATATCCGACGGTAGTGTtattctcttccaaaaaag
SPTAN1_MIP_16	cctgctagatagacaccaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttcttcttcttctcc
SPTAN1_MIP_17	cacatcactggcaagctcatctCTTCAGCTTCCCGATATCCGACGGTAGTGTgccgactataggcctcac
SPTAN1_MIP_18	agaagagaaatggagctttgaCTTCAGCTTCCCGATATCCGACGGTAGTGTggccttgtttttctcc
SPTAN1_MIP_19	caggagaaaaaacaagccaCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaaagctccatttctctt
SPTAN1_MIP_20	caggtggacaactgatgagcaCTTCAGCTTCCCGATATCCGACGGTAGTGTtccatgtctctatgcccc
SPTAN1_MIP_21	caggtgtcccgtagaagagcCTTCAGCTTCCCGATATCCGACGGTAGTGTatgtactgatgtctctaaaa

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
SPTAN1_MIP_22	cagtaagacccttctgtcaCTTCAGCTTCCCGATATCCGACGGTAGTGTacactttgttctcttggc
SPTAN1_MIP_23	ctctctggcactaaggatttCTTCAGCTTCCCGATATCCGACGGTAGTGTaccacaggagactctg
SPTAN1_MIP_24	atgctcctcttttggtaacaCTTCAGCTTCCCGATATCCGACGGTAGTGTtaccacatgaagaactct
SPTAN1_MIP_25	gagttctcattgtaagcacacCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaaaaggaggagcatg
SPTAN1_MIP_26	atgagctcaagagttgggtcaatCTTCAGCTTCCCGATATCCGACGGTAGTGTctagagactcacagggg
SPTAN1_MIP_27	agaatcacgaaaaactgctgCTTCAGCTTCCCGATATCCGACGGTAGTGTacaatttattgtgagagc
SPTAN1_MIP_28	ctgattgatgtaaccactatgCTTCAGCTTCCCGATATCCGACGGTAGTGTaagaacccctcttcta
SPTAN1_MIP_29	ggccagcttctccaaggcaCTTCAGCTTCCCGATATCCGACGGTAGTGTgcacaattcaatgaaacat
SPTAN1_MIP_30	cggatgattacggcaagatCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagcagtaaaaataaac
SPTAN1_MIP_31	agccaagtgaccttacttcaCTTCAGCTTCCCGATATCCGACGGTAGTGTttctgacttacttggcc
SPTAN1_MIP_32	cgctatgaggcactcaaggagCTTCAGCTTCCCGATATCCGACGGTAGTGTgtaaagctgctctgtcct
SPTAN1_MIP_33	cacgagggcttctgtttctcCTTCAGCTTCCCGATATCCGACGGTAGTGTcaatggcctcttctctc
SPTAN1_MIP_34	ggatggcagggtcgaaatataCTTCAGCTTCCCGATATCCGACGGTAGTGTatgaggagacgtggatt
SPTAN1_MIP_35	catggtggaggaaggtgagtCTTCAGCTTCCCGATATCCGACGGTAGTGTggactggtctgtctt
SPTAN1_MIP_36	cattccctctgtgtaactgcCTTCAGCTTCCCGATATCCGACGGTAGTGTggatggtattcagcccc
SPTAN1_MIP_37	gcagggccagcagcttctgCTTCAGCTTCCCGATATCCGACGGTAGTGTtctttccctaccactctc
SPTAN1_MIP_38	gggaagcttggcttctcagtgCTTCAGCTTCCCGATATCCGACGGTAGTGTgactcttctccttggca
SPTAN1_MIP_39	gcttgactgagaaggaagtagCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagcagctgaaacct
SPTAN1_MIP_40	gtttatgggtactggaggagCTTCAGCTTCCCGATATCCGACGGTAGTGTccatgtgtgttttgg
SPTAN1_MIP_41	aaacaaaaccacacatggagCTTCAGCTTCCCGATATCCGACGGTAGTGTccctcagtaaccataa
SPTAN1_MIP_42	ccttacctactcaacagcacCTTCAGCTTCCCGATATCCGACGGTAGTGTtttgccttcttggatt
SPTAN1_MIP_43	cccttctcatggtgacctCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcattcaggagacat
SPTAN1_MIP_44	caaggcagcatagcactcggCTTCAGCTTCCCGATATCCGACGGTAGTGTcagttctcctctttttcc
SPTAN1_MIP_45	gactgggggggtccaatttcCTTCAGCTTCCCGATATCCGACGGTAGTGTcatgtggaacagagatagc
SPTAN1_MIP_46	gctaccctatccattctcctctCTTCAGCTTCCCGATATCCGACGGTAGTGTcatgttttctgtgccc
SPTAN1_MIP_47	gaggggacacagcaaaagcatCTTCAGCTTCCCGATATCCGACGGTAGTGTcagagggaaatggatagg
SPTAN1_MIP_48	gagaaggaaagccgctctgacCTTCAGCTTCCCGATATCCGACGGTAGTGTgaccctcttgaatccat
SPTAN1_MIP_49	gcttcacggaacaacataaactCTTCAGCTTCCCGATATCCGACGGTAGTGTgaagactgccatacctt
SPTAN1_MIP_50	gtcagtggtatgactcggcCTTCAGCTTCCCGATATCCGACGGTAGTGTagaagttgatgactcca
SPTAN1_MIP_51	caacaggtaggtgtctccateCTTCAGCTTCCCGATATCCGACGGTAGTGTgggttttagttattggc
SPTAN1_MIP_52	agacctcagactccaggtctCTTCAGCTTCCCGATATCCGACGGTAGTGTgtatgaaacactgctgt
SPTAN1_MIP_53	gggaagaatatcaagccaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTgagagatggtatttctt
SPTAN1_MIP_54	agagagaaccagttttattataCTTCAGCTTCCCGATATCCGACGGTAGTGTtagcaattctgatgaag
SPTAN1_MIP_55	gtgtgcttctctgaaatattcCTTCAGCTTCCCGATATCCGACGGTAGTGTgacctaaatcctcttc
SPTAN1_MIP_56	gaaagaggaaatttagcagccaaCTTCAGCTTCCCGATATCCGACGGTAGTGTttagcagaagagccacac
SPTAN1_MIP_57	gtctacagcagagcttcttCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgttctcctccac
SPTAN1_MIP_58	ggtaggaggaaagcagaagcCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagcctctgcttagac
SPTAN1_MIP_59	ggctgggagaggagaaacagCTTCAGCTTCCCGATATCCGACGGTAGTGTctgatgtttctgtctctg
SPTAN1_MIP_60	cctgtcatgccccagtcagCTTCAGCTTCCCGATATCCGACGGTAGTGTctgtgaaacctctgacttc
SPTAN1_MIP_61	gagggtctcagagggacctCTTCAGCTTCCCGATATCCGACGGTAGTGTaaacctgaaatgtctcgc
SPTAN1_MIP_62	ggacactggcagatcatgtccCTTCAGCTTCCCGATATCCGACGGTAGTGTctgcagaacagaagactc
SPTAN1_MIP_63	ggaacgtgcagatcagcgcCTTCAGCTTCCCGATATCCGACGGTAGTGTcattcaccactttctccca
SPTAN1_MIP_64	gtccaggcctggttaactcCTTCAGCTTCCCGATATCCGACGGTAGTGTtacaagaaggctctatg
SPTAN1_MIP_65	gtggacctgctctgagtagCTTCAGCTTCCCGATATCCGACGGTAGTGTtctttttctggggctg
SPTAN1_MIP_66	gaaaccagcaccagaaaaatagCTTCAGCTTCCCGATATCCGACGGTAGTGTtactcagcaggcagg
SPTAN1_MIP_67	aactgatattctgaccaggagCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttccctcttttgg
SPTAN1_MIP_68	gcttgatctcagggtggcatCTTCAGCTTCCCGATATCCGACGGTAGTGTgcaaggaaacctctgtca
SPTAN1_MIP_69	caaaaaacatgaagactttgacaCTTCAGCTTCCCGATATCCGACGGTAGTGTacctgccctctgcctc
SPTAN1_MIP_70	cagagcctctacgctgtccaCTTCAGCTTCCCGATATCCGACGGTAGTGTcttgagatataacagtgac
SPTAN1_MIP_71	gtgtctgtggactgacatCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcatgctttgtttctg
SPTAN1_MIP_72	cagaaaacaaaggcatgagatcaCTTCAGCTTCCCGATATCCGACGGTAGTGTicagtgccacaggacac
SPTAN1_MIP_73	gaaaaaftgcaaacagcagctCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcatggttactcttt
SPTAN1_MIP_74	ccacatcccgtgaactgtCTTCAGCTTCCCGATATCCGACGGTAGTGTtactcaataacataaggc
SPTAN1_MIP_75	ggtttgctgtgtctctcaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgtctttaaactctgtt
SPTAN1_MIP_76	aacagatataaagaacaagagttcCTTCAGCTTCCCGATATCCGACGGTAGTGTtagaccagcaaacg
SPTAN1_MIP_77	attgaactgagcctgtgccCTTCAGCTTCCCGATATCCGACGGTAGTGTtagcaggactggtttggaa
SPTAN1_MIP_78	agggagttgccatgtctgatCTTCAGCTTCCCGATATCCGACGGTAGTGTtctaaagactgtatgccaag
SPTAN1_MIP_79	gcagaactcaacacagggaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcatagattcaictctt
SPTAN1_MIP_80	gctgtgtgcttcttctcagttCTTCAGCTTCCCGATATCCGACGGTAGTGTggttttggcactgatgg
SPTAN1_MIP_81	gtaagcaaggaggcggcCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttcttttgttttca
SPTAN1_MIP_82	catggcagatatactcttCTTCAGCTTCCCGATATCCGACGGTAGTGTacaaccttgagaatgct
SPTAN1_MIP_83	cagaagatcaagagcatggcCTTCAGCTTCCCGATATCCGACGGTAGTGTgacctcttatgtccct

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
SPTAN1_MIP_84	gcccgttgatggtgctccctctCTTCAGCTTCCCGATATCCGACGGTAGTGTctagagggctgagaagaca
SPTAN1_MIP_85	ccggctattcagtaaggaggCTTCAGCTTCCCGATATCCGACGGTAGTGTctgttcccactctcatt
SPTAN1_MIP_86	gctcttctcaggttctgcacgCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaataagcgcaagggg
SPTAN1_MIP_87	aaagagctgaagcagctggcaCTTCAGCTTCCCGATATCCGACGGTAGTGTgactacctgctttaacct
SPTAN1_MIP_88	gtgtgtcatcggacagcttctCTTCAGCTTCCCGATATCCGACGGTAGTGTgctggccttccactg
SPTAN1_MIP_89	attatggcgacactctgcccCTTCAGCTTCCCGATATCCGACGGTAGTGTgattttctctgtctctct
SPTAN1_MIP_90	ggccaccagggtcattttctcatCTTCAGCTTCCCGATATCCGACGGTAGTGTgagcaggggcctctaacc
SPTAN1_MIP_91	cccattggaagacctccatcgCTTCAGCTTCCCGATATCCGACGGTAGTGTccttggctgcttctactc
SPTAN1_MIP_92	gagtagaagcagccaaggcaCTTCAGCTTCCCGATATCCGACGGTAGTGTggagggttaccatggg
SPTAN1_MIP_93	actcggccttctcagttcaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgtgctctctccatg
SPTAN1_MIP_94	gctttctccaggctgacactttCTTCAGCTTCCCGATATCCGACGGTAGTGTcagctctgggaaggctc
SPTAN1_MIP_95	gtatgcagatagcatctgtgagCTTCAGCTTCCCGATATCCGACGGTAGTGTattttccacacttggtt
SPTAN1_MIP_96	gtggaatatactgcccctcCTTCAGCTTCCCGATATCCGACGGTAGTGTatctgcatacatttcaacc
SPTAN1_MIP_97	gttcagtcacaagggcctcagCTTCAGCTTCCCGATATCCGACGGTAGTGTctgtggagtcaccacaat
SPTAN1_MIP_98	gagaagctgatcttggaggcaCTTCAGCTTCCCGATATCCGACGGTAGTGTgcccagctgactctgag
SPTAN1_MIP_99	ggagagctgtgagctcagtgcaCTTCAGCTTCCCGATATCCGACGGTAGTGTcaagaagaagctctggag
SPTAN1_MIP_100	aaatacaagcttggcggaggCTTCAGCTTCCCGATATCCGACGGTAGTGTactcagctctctctgcttc
SPTAN1_MIP_101	cgggctgtgtaagtctctctcCTTCAGCTTCCCGATATCCGACGGTAGTGTcggaaagctctgactg
SPTAN1_MIP_102	aaaatcatcaaggtacacctcccCTTCAGCTTCCCGATATCCGACGGTAGTGTgctctgccagctgga
SPTAN1_MIP_103	gggctccatggtaaccaggCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgtcgtgactcagtta
SPTAN1_MIP_104	cgccaggagttggccagcacCTTCAGCTTCCCGATATCCGACGGTAGTGTgagccatctgtgaaggag
SPTAN1_MIP_105	ccgctgttcctctgagctCTTCAGCTTCCCGATATCCGACGGTAGTGTcttaagtacagcaggacat
SPTAN1_MIP_106	gtggcctgcttgggaggaCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgtccggacaccactt
SPTAN1_MIP_107	gagacaaggtggtgctccggacaacCTTCAGCTTCCCGATATCCGACGGTAGTGTatctcccacaagccag
SPTAN1_MIP_108	gtgggctctgcccagcagagaCTTCAGCTTCCCGATATCCGACGGTAGTGTgttcatctgagctctc
SPTAN1_MIP_109	acgtggaagcagctgaggaaagCTTCAGCTTCCCGATATCCGACGGTAGTGTgaggaaggggtaccctg
SPTAN1_MIP_110	acatggaaggacagtgaggaaagCTTCAGCTTCCCGATATCCGACGGTAGTGTagggaaggggtaccctg
SPTAN1_MIP_111	ctctactctggacaacaagatcacCTTCAGCTTCCCGATATCCGACGGTAGTGTgactgagctgagggc
SPTAN1_MIP_112	caggctctgatctttttagctCTTCAGCTTCCCGATATCCGACGGTAGTGTctgctgctccaggtt
SPTAN1_MIP_113	ccctaatttctgttttctccagCTTCAGCTTCCCGATATCCGACGGTAGTGTgggcatgcatgag
SPTAN1_MIP_114	gaacagacctccacacagcagctCTTCAGCTTCCCGATATCCGACGGTAGTGTctgctgccgaacacc
SPTAN1_MIP_115	gagttcagggaatcctggacacCTTCAGCTTCCCGATATCCGACGGTAGTGTccctcggcttctgctg
SPTAN1_MIP_116	caggcaagatttgaactcctgatCTTCAGCTTCCCGATATCCGACGGTAGTGTcggcagagggctcaca
SPTAN1_MIP_117	gagggaaagccttacgtgaccaagCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttcccccgctcc
SPTAN1_MIP_118	gctctcaatctctcgtggaCTTCAGCTTCCCGATATCCGACGGTAGTGTctcagctctgcccacaatt
SPTAN1_MIP_119	cgctttctgtaactgagccaCTTCAGCTTCCCGATATCCGACGGTAGTGTggtccactcttaccacca
SPTAN1_MIP_120	gggtgaaactccagtagtgaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaagctaaagccttaag
STXBP1_MIP_1	cagcggcagggcctccgagcggCTTCAGCTTCCCGATATCCGACGGTAGTGTccggagactcggcagc
STXBP1_MIP_2	gctgcgagctctcccggctcCTTCAGCTTCCCGATATCCGACGGTAGTGTctcggaggcctggcgctg
STXBP1_MIP_3	gaaaaatcagaaggggatggaCTTCAGCTTCCCGATATCCGACGGTAGTGTaatttctctctctctct
STXBP1_MIP_4	aaagagagagagagaggaatCTTCAGCTTCCCGATATCCGACGGTAGTGTactccatcccctctga
STXBP1_MIP_5	cacttgagcagctgctggagcctCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaagccatcagctgtt
STXBP1_MIP_6	cgatggcttcatgcatctgCTTCAGCTTCCCGATATCCGACGGTAGTGTcactgctcaagtgcagag
STXBP1_MIP_7	ccagagaggactctggctaCTTCAGCTTCCCGATATCCGACGGTAGTGTccatcatgttttctattca
STXBP1_MIP_8	acagtgaataagaaacatgatggCTTCAGCTTCCCGATATCCGACGGTAGTGTtagccagagctctct
STXBP1_MIP_9	ctgtcccagctccatcagcCTTCAGCTTCCCGATATCCGACGGTAGTGTgattcaggtctccctttt
STXBP1_MIP_10	aaaaagggagcctgaaatcaatCTTCAGCTTCCCGATATCCGACGGTAGTGTgagggactggggacag
STXBP1_MIP_11	cctgagtaggggtgcaaaagCTTCAGCTTCCCGATATCCGACGGTAGTGTactgtctttgtcatactg
STXBP1_MIP_12	caagtagacaaaagacagttggcCTTCAGCTTCCCGATATCCGACGGTAGTGTgacccctactcagg
STXBP1_MIP_13	gtgccacctgaaggagtaeCTTCAGCTTCCCGATATCCGACGGTAGTGTttaaacttttctctccc
STXBP1_MIP_14	ggcgctccagtagattctcCTTCAGCTTCCCGATATCCGACGGTAGTGTcaggccagctctcact
STXBP1_MIP_15	gttctcttaccaggaccgagCTTCAGCTTCCCGATATCCGACGGTAGTGTctgtcaccctcttctg
STXBP1_MIP_16	acaagggaggggtgacagagcaCTTCAGCTTCCCGATATCCGACGGTAGTGTggtccttggtaagagaa
STXBP1_MIP_17	gcctatcgaatgatgtatacaCTTCAGCTTCCCGATATCCGACGGTAGTGTgcatctccctgtttcc
STXBP1_MIP_18	gcctgaaaagtaattcatggCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaacaaaaaacccgttc
STXBP1_MIP_19	cagaggtgtcccagtaagagccCTTCAGCTTCCCGATATCCGACGGTAGTGTcagctcactccactgag
STXBP1_MIP_20	gtcttggcgcagtgctaCTTCAGCTTCCCGATATCCGACGGTAGTGTcaagaagaaacgaattcacac
STXBP1_MIP_21	gctttctcttaagagcaggCTTCAGCTTCCCGATATCCGACGGTAGTGTacttagctgctctcttta
STXBP1_MIP_22	gaagataaaaggagcagctaaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcccctgctcttagagag
STXBP1_MIP_23	cagctgaaaaagactctcaaCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgcttcttccctta
STXBP1_MIP_24	cactctaaggcctgatgtCTTCAGCTTCCCGATATCCGACGGTAGTGTactcaattattcaaacagat
STXBP1_MIP_25	gttttggcagcctattacCTTCAGCTTCCCGATATCCGACGGTAGTGTacaaactgtgtgctttt

**Table S1 (continued). MIP sequences.**



MIP name	MIP sequence
STXBP1_MIP_26	ggaaaaagcacacaacagtttgaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaataggcctggcaaaa
STXBP1_MIP_27	gcatcatccttctacatcttCTTCAGCTTCCCGATATCCGACGGTAGTGTgccaatgaggtgtgtttt
STXBP1_MIP_28	gacattggcatccagcagaatCTTCAGCTTCCCGATATCCGACGGTAGTGTtctttgttctcttcttct
STXBP1_MIP_29	atgtaagaggccagctcagcttCTTCAGCTTCCCGATATCCGACGGTAGTGTatcgggtgtcttgtgccc
STXBP1_MIP_30	cgaggtgagccatgttgatCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttggactacgaggtgt
STXBP1_MIP_31	gttagtctggggcacaggggaCTTCAGCTTCCCGATATCCGACGGTAGTGTgttctaacctgggtgtgtgt
STXBP1_MIP_32	ccatgatgtccttgataatcggCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaatcctcaagtggagg
STXBP1_MIP_33	gacagaggggagccagctctCTTCAGCTTCCCGATATCCGACGGTAGTGTatatctgtctctttctctc
STXBP1_MIP_34	ggaaaaagacagatattagcttCTTCAGCTTCCCGATATCCGACGGTAGTGTggctcccctctgtcctt
STXBP1_MIP_35	atgagatgcgctgcctacCTTCAGCTTCCCGATATCCGACGGTAGTGTaactgactgacattctctt
STXBP1_MIP_36	gtcacacccccaaagatgaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaaagcgtggaatggag
STXBP1_MIP_37	agagccaaagaacaagaatgaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTggcctctgtctccca
STXBP1_MIP_38	gataccctagaggactccctCTTCAGCTTCCCGATATCCGACGGTAGTGTagaataaagaaaaagagtgt
STXBP1_MIP_39	caaaacacgccccatcccaCTTCAGCTTCCCGATATCCGACGGTAGTGTcaagctcactgttctctct
STXBP1_MIP_40	gagcttccagttctgtttccCTTCAGCTTCCCGATATCCGACGGTAGTGTgttttggagggcgactt
SV2A_MIP_1	gagatgggtgcagccttggCTTCAGCTTCCCGATATCCGACGGTAGTGTggagtgttggctccacag
SV2A_MIP_2	cccttgccttggcagctctctCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcctgagcagaccaca
SV2A_MIP_3	caagaggagagagaaggtgtCTTCAGCTTCCCGATATCCGACGGTAGTGTggcattcaggaagcaaaa
SV2A_MIP_4	ggcggactcactgttccaaaaCTTCAGCTTCCCGATATCCGACGGTAGTGTaatcactgcctgcctc
SV2A_MIP_5	ggcgtgttactgttgaacttaCTTCAGCTTCCCGATATCCGACGGTAGTGTgctccagctggctcca
SV2A_MIP_6	gcccagatgagacttctccCTTCAGCTTCCCGATATCCGACGGTAGTGTcaggaagaagcaggagaca
SV2A_MIP_7	catgtaggcacttgcctcCTTCAGCTTCCCGATATCCGACGGTAGTGTtactatcagatctgactca
SV2A_MIP_8	gggacactggcagtgcttccCTTCAGCTTCCCGATATCCGACGGTAGTGTgacctgtcaggtacaagt
SV2A_MIP_9	gttagtaggagggctctcaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTtcagacggctgttca
SV2A_MIP_10	gaatctcaaaggacactgacCTTCAGCTTCCCGATATCCGACGGTAGTGTaacctttgtctgacacc
SV2A_MIP_11	gttatttggagatgacacatccCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcctaaagagtgagt
SV2A_MIP_12	gtccactgcctggagatggcCTTCAGCTTCCCGATATCCGACGGTAGTGTtgaagttaaaagtcacca
SV2A_MIP_13	cgcacccgcacaaaagtgtCTTCAGCTTCCCGATATCCGACGGTAGTGTtctcctgattctaactc
SV2A_MIP_14	ggaccagacaaagtcagacttCTTCAGCTTCCCGATATCCGACGGTAGTGTcaccacacatcaaccagc
SV2A_MIP_15	gtggctgggtgatgtgtgtCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaggtctgactttgtctg
SV2A_MIP_16	gttacctgggtcaagagaaggCTTCAGCTTCCCGATATCCGACGGTAGTGTtctaccacccgtccac
SV2A_MIP_17	gacgattcatcaggagatgaaCTTCAGCTTCCCGATATCCGACGGTAGTGTagggtatcatatccacct
SV2A_MIP_18	gacacaatccccacatccaagtcCTTCAGCTTCCCGATATCCGACGGTAGTGTgctctgagtcggagggg
SV2A_MIP_19	cctcccactcagactcccaCTTCAGCTTCCCGATATCCGACGGTAGTGTggatgtgggattgtgtct
SV2A_MIP_20	gcagaacctctgaaactccaCTTCAGCTTCCCGATATCCGACGGTAGTGTatgcagctcagccccat
SV2A_MIP_21	agctggagggctctctctcCTTCAGCTTCCCGATATCCGACGGTAGTGTttttgacctcctcctct
SV2A_MIP_22	ggccagaaactggagaatagCTTCAGCTTCCCGATATCCGACGGTAGTGTAcctgggtgatttcc
SV2A_MIP_23	ctggctctcatgttttgatgaCTTCAGCTTCCCGATATCCGACGGTAGTGTgatcaggactatggcca
SV2A_MIP_24	gttgactgagagcagatgagcCTTCAGCTTCCCGATATCCGACGGTAGTGTcagtaccagacacagt
SV2A_MIP_25	cgtttcgccttctctctctCTTCAGCTTCCCGATATCCGACGGTAGTGTtgcctgttttctctctc
SV2A_MIP_26	cacaaaatacagtgctcactggaCTTCAGCTTCCCGATATCCGACGGTAGTGTtggacccccatgtct
SV2A_MIP_27	gacggtgtgaggtcttgggtgCTTCAGCTTCCCGATATCCGACGGTAGTGTggggggaggcacaacg
SV2A_MIP_28	gcccggggaatgcctgataCTTCAGCTTCCCGATATCCGACGGTAGTGTgttctctctgttcttccg
SV2A_MIP_29	agtctggggcaaaaggcagCTTCAGCTTCCCGATATCCGACGGTAGTGTccagtgatgattaccga
SV2A_MIP_30	atattctctgactctctctCTTCAGCTTCCCGATATCCGACGGTAGTGTtcaagtagcactgagtg
SV2A_MIP_31	gaagatctactccccttctCTTCAGCTTCCCGATATCCGACGGTAGTGTcatcatggaagaggcttc
SV2A_MIP_32	gtcaaggactttagagtaCTTCAGCTTCCCGATATCCGACGGTAGTGTttttgacctccttagca
SV2B_MIP_1	agaagatgcacagagtgtctCTTCAGCTTCCCGATATCCGACGGTAGTGTcagggatataagctcaag
SV2B_MIP_2	ggtaatagccatcactgggagcaCTTCAGCTTCCCGATATCCGACGGTAGTGTcctgcttggccttgaca
SV2B_MIP_3	cgagaccatcatggatgaggtCTTCAGCTTCCCGATATCCGACGGTAGTGTgtatecctcaccagatg
SV2B_MIP_4	catcttcagcctctcagccaCTTCAGCTTCCCGATATCCGACGGTAGTGTaaaactcaccacgaact
SV2B_MIP_5	aagggaaggagaagtaaaattatCTTCAGCTTCCCGATATCCGACGGTAGTGTgatggccgatgggtg
SV2B_MIP_6	cagcatgtcttggccgcaCTTCAGCTTCCCGATATCCGACGGTAGTGTaatctttgtcttctctc
SV2B_MIP_7	gettcttcccagttatcagcCTTCAGCTTCCCGATATCCGACGGTAGTGTagtccacctccctaaga
SV2B_MIP_8	catcttctggatgactggggCTTCAGCTTCCCGATATCCGACGGTAGTGTtagtgtatgactgattct
SV2B_MIP_9	cccagacaagaattcagaaaaatCTTCAGCTTCCCGATATCCGACGGTAGTGTggccccctagctgtt
SV2B_MIP_10	cagagagcccaaggtttctgcCTTCAGCTTCCCGATATCCGACGGTAGTGTttgactctcctctt
SV2B_MIP_11	catgaactcaggccaccatgCTTCAGCTTCCCGATATCCGACGGTAGTGTaaagcagcagagatgtg
SV2B_MIP_12	ccaataagaagggttctccCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttctctgttctac
SV2B_MIP_13	gtgaaaccaaggaaagacacagCTTCAGCTTCCCGATATCCGACGGTAGTGTgaaccccccttattgg
SV2B_MIP_14	caagaccatttcaagcaggtCTTCAGCTTCCCGATATCCGACGGTAGTGTgggggtcaaatctctat
SV2B_MIP_15	accaggtcctgttgaacttggCTTCAGCTTCCCGATATCCGACGGTAGTGTggatgttcaggagctgc

**Table S1 (continued). MIP sequences.**

MIP name	MIP sequence
SV2B_MIP_16	atttcgtaattccctgtgcctcCTTCAGCTTCCCGATATCCGACGGTAGTGTcttctctggtatgggttg
SV2B_MIP_17	caaccataccagagaagattCTTCAGCTTCCCGATATCCGACGGTAGTGTcacagggaattacgaaat
SV2B_MIP_18	atcaactcaccgatgaaaatcaCTTCAGCTTCCCGATATCCGACGGTAGTGTtctgctctccactc
SV2B_MIP_19	cttctatttagactgtattctCTTCAGCTTCCCGATATCCGACGGTAGTGTgtcacacctgatgtgag
SV2B_MIP_20	gaatcaaccatctttacaacacCTTCAGCTTCCCGATATCCGACGGTAGTGTgggtcaacctcttcca
SV2B_MIP_21	caaaatagcactcgtcaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTtcttgacaacacaagtgg
SV2B_MIP_22	atttacctcgtcagcttctctggCTTCAGCTTCCCGATATCCGACGGTAGTGTaaccgaagtttcttct
SV2B_MIP_23	aggaaagtcattatcttctccaCTTCAGCTTCCCGATATCCGACGGTAGTGTggaaccaggaatgacce
SV2B_MIP_24	cctgttctgtgggacaagcattCTTCAGCTTCCCGATATCCGACGGTAGTGTcaagacacaggcctcatg
SV2B_MIP_25	attgcagactcactgttccaCTTCAGCTTCCCGATATCCGACGGTAGTGTcaaaacagtcctctgaggaa
SV2B_MIP_26	gctgctgcttctctggttggCTTCAGCTTCCCGATATCCGACGGTAGTGTtatttccattcctcttta
SV2B_MIP_27	gaaggatggggaccactttggttCTTCAGCTTCCCGATATCCGACGGTAGTGTttcagtgctctggaca
SYT2_MIP_1	gaccagtgccgagctctgtgCTTCAGCTTCCCGATATCCGACGGTAGTGTgtgtccgtgaaagtgtgg
SYT2_MIP_2	caagcctgaggaggaggtggaCTTCAGCTTCCCGATATCCGACGGTAGTGTtatgacaagctggcaaga
SYT2_MIP_3	aatttatcctccatcaacctctaCTTCAGCTTCCCGATATCCGACGGTAGTGTcgaagatctgcctatg
SYT2_MIP_4	gttcttcttcttctgagccCTTCAGCTTCCCGATATCCGACGGTAGTGTatacatgtttgcctcccc
SYT2_MIP_5	gtgaagaagaagaccctgaaccCTTCAGCTTCCCGATATCCGACGGTAGTGTggtacattcgaggaa
SYT2_MIP_6	cagatgtcgeccagcttctcCTTCAGCTTCCCGATATCCGACGGTAGTGTggtgccaccaatgacagcc
SYT2_MIP_7	gcegggaagctcactgtctgCTTCAGCTTCCCGATATCCGACGGTAGTGTctaatttggcaagaaagag
SYT2_MIP_8	cggtcaaaatcatagatgcatCTTCAGCTTCCCGATATCCGACGGTAGTGTggcctcatctctctct
SYT2_MIP_9	ccaaacatgacatcattggagagCTTCAGCTTCCCGATATCCGACGGTAGTGTcccatagaccctgga
SYT2_MIP_10	gacataaagggtctgaggtgcctcCTTCAGCTTCCCGATATCCGACGGTAGTGTgggagctggagtcacce
SYT2_MIP_11	aggtcttctcctctctgacaagCTTCAGCTTCCCGATATCCGACGGTAGTGTtgtgtattggagcagt
SYT2_MIP_12	gettttctctctctcctctcCTTCAGCTTCCCGATATCCGACGGTAGTGTgttctatccccctccac
SYT2_MIP_13	gcagtttccctggactatgattCTTCAGCTTCCCGATATCCGACGGTAGTGTggtctctctctttaa
SYT2_MIP_14	gttcttcttctctgagcagcCTTCAGCTTCCCGATATCCGACGGTAGTGTcctttcagcatcaggaa
SYT2_MIP_15	gagaaggcaagcgaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTatcttctctgtgtggc
SYT2_MIP_16	actctcagtgaggtgtccacgCTTCAGCTTCCCGATATCCGACGGTAGTGTtctccagactctagcct
SYT2_MIP_17	caggaggacatgtttgcaaacCTTCAGCTTCCCGATATCCGACGGTAGTGTtctctgcccacatgag
SYT2_MIP_18	agaagctctttatagatcaagaCTTCAGCTTCCCGATATCCGACGGTAGTGTggctctgttctctt

**Table S1 (continued). MIP sequences.**

Primer name	Primer sequence
Universal forward primer	AATGATACGGCGACCACCGAGATCTACACATACGAGATCCGTAATCGGGAAGCTGAAG
Reverse primer 1	CAAGCAGAAGACGGCATAACGAGATTATCAGCGACACGCACGATCCGACGGTAGTGT
Reverse primer 2	CAAGCAGAAGACGGCATAACGAGATTGCGTGTAACACGCACGATCCGACGGTAGTGT
Reverse primer 3	CAAGCAGAAGACGGCATAACGAGATCGTTATCCACACGCACGATCCGACGGTAGTGT
Reverse primer 4	CAAGCAGAAGACGGCATAACGAGATTACGATACACACGCACGATCCGACGGTAGTGT
Reverse primer 5	CAAGCAGAAGACGGCATAACGAGATTAGCCGATACACGCACGATCCGACGGTAGTGT
Reverse primer 6	CAAGCAGAAGACGGCATAACGAGATATCCGAATACACGCACGATCCGACGGTAGTGT
Reverse primer 7	CAAGCAGAAGACGGCATAACGAGATTGCTATGAACACGCACGATCCGACGGTAGTGT
Reverse primer 8	CAAGCAGAAGACGGCATAACGAGATGAACTACCACACGCACGATCCGACGGTAGTGT
Reverse primer 9	CAAGCAGAAGACGGCATAACGAGATGGTATTCCGACACGCACGATCCGACGGTAGTGT
Reverse primer 10	CAAGCAGAAGACGGCATAACGAGATTACGAGTTACACGCACGATCCGACGGTAGTGT
Reverse primer 11	CAAGCAGAAGACGGCATAACGAGATGCACATAGACACGCACGATCCGACGGTAGTGT
Reverse primer 12	CAAGCAGAAGACGGCATAACGAGATGAGCGATAACACGCACGATCCGACGGTAGTGT
Reverse primer 13	CAAGCAGAAGACGGCATAACGAGATACGTGTTAACACGCACGATCCGACGGTAGTGT
Reverse primer 14	CAAGCAGAAGACGGCATAACGAGATTATCCAGCACACGCACGATCCGACGGTAGTGT
Reverse primer 15	CAAGCAGAAGACGGCATAACGAGATTATCGGTTACACGCACGATCCGACGGTAGTGT
Reverse primer 16	CAAGCAGAAGACGGCATAACGAGATCTTGCGTAACACGCACGATCCGACGGTAGTGT
Reverse primer 17	CAAGCAGAAGACGGCATAACGAGATCTATTGTCACACGCACGATCCGACGGTAGTGT
Reverse primer 18	CAAGCAGAAGACGGCATAACGAGATTGCGATCTACACGCACGATCCGACGGTAGTGT
Reverse primer 19	CAAGCAGAAGACGGCATAACGAGATTGACGAAGACACGCACGATCCGACGGTAGTGT
Reverse primer 20	CAAGCAGAAGACGGCATAACGAGATATTGGACGACACGCACGATCCGACGGTAGTGT
Reverse primer 21	CAAGCAGAAGACGGCATAACGAGATACATTGCCACACGCACGATCCGACGGTAGTGT
Reverse primer 22	CAAGCAGAAGACGGCATAACGAGATTCACTTGACACGCACGATCCGACGGTAGTGT
Reverse primer 23	CAAGCAGAAGACGGCATAACGAGATTTACCGACACACGCACGATCCGACGGTAGTGT
Reverse primer 24	CAAGCAGAAGACGGCATAACGAGATCATGTACCACACGCACGATCCGACGGTAGTGT
Reverse primer 25	CAAGCAGAAGACGGCATAACGAGATTTGTTCCAACACGCACGATCCGACGGTAGTGT
Reverse primer 26	CAAGCAGAAGACGGCATAACGAGATTGATTATCACACGCACGATCCGACGGTAGTGT
Reverse primer 27	CAAGCAGAAGACGGCATAACGAGATCTCTGATACACGCACGATCCGACGGTAGTGT
Reverse primer 28	CAAGCAGAAGACGGCATAACGAGATTCCTCTAGACACGCACGATCCGACGGTAGTGT
Reverse primer 29	CAAGCAGAAGACGGCATAACGAGATGTACTCAGACACGCACGATCCGACGGTAGTGT
Reverse primer 30	CAAGCAGAAGACGGCATAACGAGATCAATGAGGACACGCACGATCCGACGGTAGTGT
Reverse primer 31	CAAGCAGAAGACGGCATAACGAGATCACGCATAACACGCACGATCCGACGGTAGTGT
Reverse primer 32	CAAGCAGAAGACGGCATAACGAGATCAATAGCCACACGCACGATCCGACGGTAGTGT
Reverse primer 33	CAAGCAGAAGACGGCATAACGAGATCTCAGAGAACACGCACGATCCGACGGTAGTGT
Reverse primer 34	CAAGCAGAAGACGGCATAACGAGATCACAGTAGACACGCACGATCCGACGGTAGTGT
Reverse primer 35	CAAGCAGAAGACGGCATAACGAGATTAACGAGAACACGCACGATCCGACGGTAGTGT
Reverse primer 36	CAAGCAGAAGACGGCATAACGAGATTCTGCTTAACACGCACGATCCGACGGTAGTGT
Reverse primer 37	CAAGCAGAAGACGGCATAACGAGATTGTATAACACACGCACGATCCGACGGTAGTGT
Reverse primer 38	CAAGCAGAAGACGGCATAACGAGATGTATACATACACGCACGATCCGACGGTAGTGT
Reverse primer 39	CAAGCAGAAGACGGCATAACGAGATATGGCACAACACGCACGATCCGACGGTAGTGT
Reverse primer 40	CAAGCAGAAGACGGCATAACGAGATAACTCGAAACACGCACGATCCGACGGTAGTGT
Reverse primer 41	CAAGCAGAAGACGGCATAACGAGATGATCTGGTACACGCACGATCCGACGGTAGTGT
Reverse primer 42	CAAGCAGAAGACGGCATAACGAGATAAAGTCAACACGCACGATCCGACGGTAGTGT
Reverse primer 43	CAAGCAGAAGACGGCATAACGAGATACGAGACTACACGCACGATCCGACGGTAGTGT
Reverse primer 44	CAAGCAGAAGACGGCATAACGAGATATGAGTACACACGCACGATCCGACGGTAGTGT
Reverse primer 45	CAAGCAGAAGACGGCATAACGAGATATCAAGCACACGCACGATCCGACGGTAGTGT
Reverse primer 46	CAAGCAGAAGACGGCATAACGAGATCGGAATTGACACGCACGATCCGACGGTAGTGT
Reverse primer 47	CAAGCAGAAGACGGCATAACGAGATCTGGAGTTACACGCACGATCCGACGGTAGTGT
Reverse primer 48	CAAGCAGAAGACGGCATAACGAGATGTCCATCAACACGCACGATCCGACGGTAGTGT
Reverse primer 49	CAAGCAGAAGACGGCATAACGAGATTAACAGTCACACGCACGATCCGACGGTAGTGT
Reverse primer 50	CAAGCAGAAGACGGCATAACGAGATCATTGTGCACACGCACGATCCGACGGTAGTGT
Reverse primer 51	CAAGCAGAAGACGGCATAACGAGATACTTGATTACACGCACGATCCGACGGTAGTGT
Reverse primer 52	CAAGCAGAAGACGGCATAACGAGATTTGACCGTACACGCACGATCCGACGGTAGTGT
Reverse primer 53	CAAGCAGAAGACGGCATAACGAGATAACAATGTGACACGCACGATCCGACGGTAGTGT
Reverse primer 54	CAAGCAGAAGACGGCATAACGAGATAAAGTTCCTACACGCACGATCCGACGGTAGTGT
Reverse primer 55	CAAGCAGAAGACGGCATAACGAGATCGCCATAAACACGCACGATCCGACGGTAGTGT
Reverse primer 56	CAAGCAGAAGACGGCATAACGAGATAGACGAGTACACGCACGATCCGACGGTAGTGT
Reverse primer 57	CAAGCAGAAGACGGCATAACGAGATACCGTATTACACGCACGATCCGACGGTAGTGT
Reverse primer 58	CAAGCAGAAGACGGCATAACGAGATGCTAACAGACACGCACGATCCGACGGTAGTGT
Reverse primer 59	CAAGCAGAAGACGGCATAACGAGATCTATGCTGACACGCACGATCCGACGGTAGTGT
Reverse primer 60	CAAGCAGAAGACGGCATAACGAGATTAACCTCGACACGCACGATCCGACGGTAGTGT

**Table S2. Primers for RT-PCR and PCR of MIP capture products.**

Primer name	Primer sequence
Reverse primer 61	CAAGCAGAAGACGGCATAACGAGATTTCAAGAAACACGCACGATCCGACGGTAGTGT
Reverse primer 62	CAAGCAGAAGACGGCATAACGAGATACGGTGTAAACACGCACGATCCGACGGTAGTGT
Reverse primer 63	CAAGCAGAAGACGGCATAACGAGATACAGTATACACGCACGATCCGACGGTAGTGT
Reverse primer 64	CAAGCAGAAGACGGCATAACGAGATCCATGTACACACGCACGATCCGACGGTAGTGT
Reverse primer 65	CAAGCAGAAGACGGCATAACGAGATTACGCAATACACGCACGATCCGACGGTAGTGT
Reverse primer 66	CAAGCAGAAGACGGCATAACGAGATTCTATAGTACACGCACGATCCGACGGTAGTGT
Reverse primer 67	CAAGCAGAAGACGGCATAACGAGATTTTCAGAGTACACGCACGATCCGACGGTAGTGT
Reverse primer 68	CAAGCAGAAGACGGCATAACGAGATATCCTGTACACGCACGATCCGACGGTAGTGT
Reverse primer 69	CAAGCAGAAGACGGCATAACGAGATTTCCACGTACACGCACGATCCGACGGTAGTGT
Reverse primer 70	CAAGCAGAAGACGGCATAACGAGATTAACCTTAGACACGCACGATCCGACGGTAGTGT
Reverse primer 71	CAAGCAGAAGACGGCATAACGAGATATCTTAGAACACGCACGATCCGACGGTAGTGT
Reverse primer 72	CAAGCAGAAGACGGCATAACGAGATCATACTGACACGCACGATCCGACGGTAGTGT
Reverse primer 73	CAAGCAGAAGACGGCATAACGAGATTAGAGTCTACACGCACGATCCGACGGTAGTGT
Reverse primer 74	CAAGCAGAAGACGGCATAACGAGATATGACCAACACGCACGATCCGACGGTAGTGT
Reverse primer 75	CAAGCAGAAGACGGCATAACGAGATTATACGGTACACGCACGATCCGACGGTAGTGT
Reverse primer 76	CAAGCAGAAGACGGCATAACGAGATCGTTCTATACACGCACGATCCGACGGTAGTGT
Reverse primer 77	CAAGCAGAAGACGGCATAACGAGATGGAATAGCACACGCACGATCCGACGGTAGTGT
Reverse primer 78	CAAGCAGAAGACGGCATAACGAGATTCAGACCAACACGCACGATCCGACGGTAGTGT
Reverse primer 79	CAAGCAGAAGACGGCATAACGAGATCCTCGTAAACACGCACGATCCGACGGTAGTGT
Reverse primer 80	CAAGCAGAAGACGGCATAACGAGATCATTGGAACACGCACGATCCGACGGTAGTGT
Reverse primer 81	CAAGCAGAAGACGGCATAACGAGATACGGCAATACACGCACGATCCGACGGTAGTGT
Reverse primer 82	CAAGCAGAAGACGGCATAACGAGATTAACCATGACACGCACGATCCGACGGTAGTGT
Reverse primer 83	CAAGCAGAAGACGGCATAACGAGATTTGTCAACACACGCACGATCCGACGGTAGTGT
Reverse primer 84	CAAGCAGAAGACGGCATAACGAGATCAGTTGAAACACGCACGATCCGACGGTAGTGT
Reverse primer 85	CAAGCAGAAGACGGCATAACGAGATAGAAGCTAACACGCACGATCCGACGGTAGTGT
Reverse primer 86	CAAGCAGAAGACGGCATAACGAGATTGCTATCCTACACGCACGATCCGACGGTAGTGT
Reverse primer 87	CAAGCAGAAGACGGCATAACGAGATACTGGAGAACACGCACGATCCGACGGTAGTGT
Reverse primer 88	CAAGCAGAAGACGGCATAACGAGATCCATAGTTACACGCACGATCCGACGGTAGTGT
Reverse primer 89	CAAGCAGAAGACGGCATAACGAGATCTAAGTTAACACGCACGATCCGACGGTAGTGT
Reverse primer 90	CAAGCAGAAGACGGCATAACGAGATGTTAGCCTACACGCACGATCCGACGGTAGTGT
Reverse primer 91	CAAGCAGAAGACGGCATAACGAGATTTCTGTGAGACACGCACGATCCGACGGTAGTGT
Reverse primer 92	CAAGCAGAAGACGGCATAACGAGATAGTCTCTTACACGCACGATCCGACGGTAGTGT
Reverse primer 93	CAAGCAGAAGACGGCATAACGAGATGGATATACACACGCACGATCCGACGGTAGTGT
Reverse primer 94	CAAGCAGAAGACGGCATAACGAGATAAGACGCTACACGCACGATCCGACGGTAGTGT
Reverse primer 95	CAAGCAGAAGACGGCATAACGAGATGTGTCTGAACACGCACGATCCGACGGTAGTGT
Reverse primer 96	CAAGCAGAAGACGGCATAACGAGATAGAGTGCAACACGCACGATCCGACGGTAGTGT

**Table S2 (continued). Primers for RT-PCR and PCR of MIP capture products.**

Primer name	Primer sequence
Forward primer	CATACGAGATCCGTAATCGGGAAGCTGAAG
Reverse primer	ACACGCACGATCCGACGGTAGTGT
Barcode primer	ACACTACCGTCCGATCGTGCGTGT

**Table S3. Primers for next generation sequencing.**

Patient	Mutation	Forward primer	Reverse primer
Patient A	<i>GABRA1</i> , chr5:161322732A>C (hg19), c.917A>C (NM_001127644), p.Lys306Thr (NP_001121116)	GTTC AAGTAGGCTGTCCCATCA	ACTGTGGCAA ACTCAATCAGAGC
Patient B	<i>SCN1A</i> , chr2:166870327C>T (hg19), c.3632G>A (NM_001165963), p.Cys1211Tyr (NP_001159435)	CCCATCCCAGGGCTTCCAATAACT	CTACTCTAGGCTTAGAGAGCTATGCT
Patient C	<i>SCN1A</i> , chr2:166870299A>C (hg19), c.3660T>G (NM_001165963), p.Phe1220Leu (NP_001159435)	CCCATCCCAGGGCTTCCAATAACT	CTACTCTAGGCTTAGAGAGCTATGCT
Patient D	<i>SCN1A</i> , chr2:166848659G>T (hg19), c.5126C>A (NM_001165963), p.Thr1709Asn (NP_001159435)	CCCACAGTCTCCCTTAACTGAGC	CATAGGTATGTTTCTTGCCGAGCT
Patient E	<i>SCN1A</i> , chr2:166904174A>G (hg19), c.1133T>C (NM_001165963), p.Leu378Pro (NP_001159435)	GCAATCCTTGGCATCACTCTGC	TGAAATGGAGGTGTTGAAAATGC
Patient F	<i>SCN1A</i> , chr2:166904279C>T (hg19), c.1029-1G>A (NM_001165963)	GCAATCCTTGGCATCACTCTGC	TGAAATGGAGGTGTTGAAAATGC
Patient G	<i>SCN1A</i> , chr2:166904178G>A (hg19), c.1129C>T (NM_001165963), p.Arg377* (NP_001159435)	GCAATCCTTGGCATCACTCTGC	TGAAATGGAGGTGTTGAAAATGC
Patient H	<i>SCN1A</i> , chr2:166848852G>A (hg19), c.4933C>T (NM_001165963), p.Arg1645* (NP_001159435)	CCCACAGTCTCCCTTAACTGAGC	CATAGGTATGTTTCTTGCCGAGCT
Patient I	<i>SCN1A</i> , chr2:166872228C>A (hg19), c.3439G>T (NM_001165963), p.Glu1147* (NP_001159435)	TGGGCAGATATAATCAAAGCATGACA	CCTTTCTTGGCAGGCAACTTATTACC
Patient J	<i>SCN2A</i> , chr2:166223873G>C (hg19), c.3776G>C (NM_021007), p.Gly1223Arg (NP_066287)	AGCATAGAAGAAGGCAAAGGGAAAC	AGTGGGTAATATGAGTTGATTGAAGGG
Patient K	<i>GABRG2</i> , chr5:161580306C>T (hg19), c.1480C>T (NM_198903), p.Arg494Trp (NP_944493)	GGTGACATTGTGGA AAAACAGCC	AAAACCCATACCTCCTCACAGG
Patient L	<i>SCN1B</i> , chr19:35523453G>A (hg19), c.62G>A (NM_001037), p.Cys21Tyr (NP_001028)	TGCTTGGGTTCTCCAGCAA	CTTCTGGCGGAAGGTCCACT
Patient M	<i>SLC2A1</i> , chr1:43394886C>T (hg19), c.967G>A (NM_006516), p.Val323Met (NP_006507)	CCGCATCCCTCACTCTCCAG	GCAGTGCCCTTCTGCCTGA

**Table S4. PCR and Sanger sequencing primers for validation of findings in targeted resequencing and segregation analysis.**

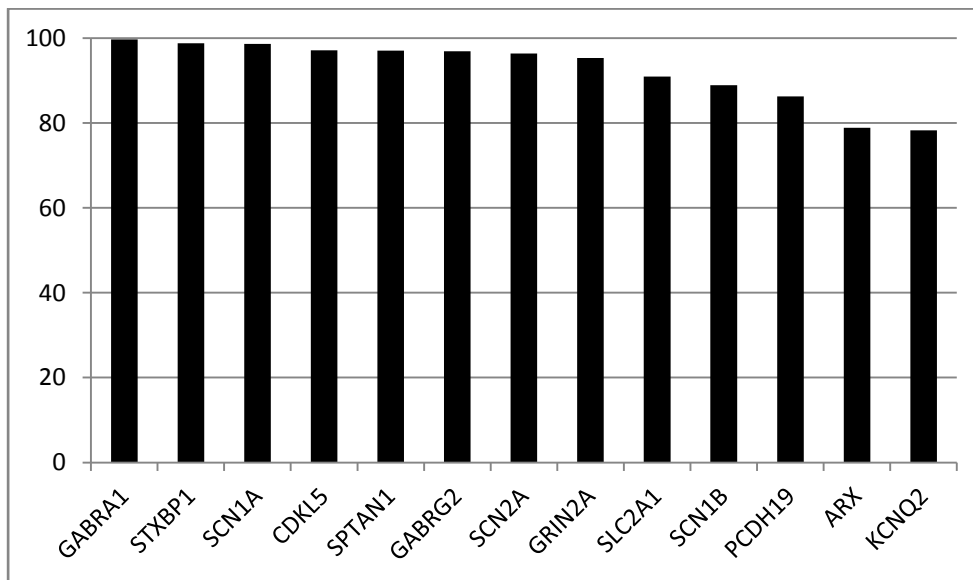
Patient	Mutation	Forward primer	Reverse primer
Patient N	<i>SLC2A1</i> , chr1:43394653C>T (hg19), c.1024G>A (NM_006516), p.Ala342Thr (NP_006507)	CCGCATCCCTCACTCTCCAG	GCAGTGCCCTTCTGCCTGA
Patient O	<i>SPTAN1</i> , chr9:131395569G>A (hg19), c.7390G>A (NM_001130438), p.Ala2464Thr (NP_001123910)	TGTAGAAGCAGCTCCGAGCC	GGAGGGTGGGAGAGAGAACAAG
Patient P	<i>SPTAN1</i> , chr9:131367651G>A (hg19), c.3941G>A (NM_001130438), p.Cys1314Tyr (NP_001123910)	TCAAGGCAGTTGTACTTGGCA	CTGAGTGAACATGGCTCCGT
Patient Q	<i>ADAM22</i> , chr7:87778355T>C (hg19), c.1549T>C (NM_021723), p.Ser517Pro (NP_068369)	TCAGTAACTGTGGTTTTGACAGA	TGAAAAGAAAATGCCTTGTACTACCT
Patient R	<i>ADAM22</i> , chr7:87760671C>G (hg19), c.913C>G (NM_021723), p.Pro305Ala (NP_068369)	GTTTCCAAAAAGTGCTCTGTTCTTTG	CAAATCTATCTGCCATCTGCCATG
Patient S	<i>ADAM23</i> , chr2:207460812C>T (hg19), c.2285C>T (NM_003812), p.Thr762Ile (NP_003803)	TGCATTATTACCTTGTGTCTAGTGA	TTCTTCCCAATCTCAGTTCTAGACT
Patient T	<i>DLGAP1</i> , chr18:3880037T>C (hg19), c.32A>G (NM_004746), p.His11Arg (NP_004737)	AGCAGGTTGGCGGGGATG	ACGACTTTGCCCTTTTCTTCA
Patient U	<i>DLGAP2</i> , chr8:1514057A>T (hg19), c.1199A>T (NM_004745), p.Gln400Leu (NP_004736)	CATGTCTGTCTGCTCCAGG	GAAAGATACGATGGCTCATGTTGG
Patient V	<i>DLGAP2</i> , chr8:1616750G>C (hg19), c.1826G>C (NM_004745), p.Ser609Thr (NP_004736)	GAACACGCCTGTTGACTTGG	CCTGCTGGGGTTACAGTCAG
Patient W	<i>EPHA6</i> , chr3:96945251A>G (hg19), c.1258A>G (NM_001080448), p.Met420Val (NP_001073917)	ACACTGTACTCTGAGATCCAATGT	TGTAGGGCCTCAAACCAGTG

**Table S4 (continued). PCR and Sanger sequencing primers for validation of findings in targeted resequencing and segregation analysis.**

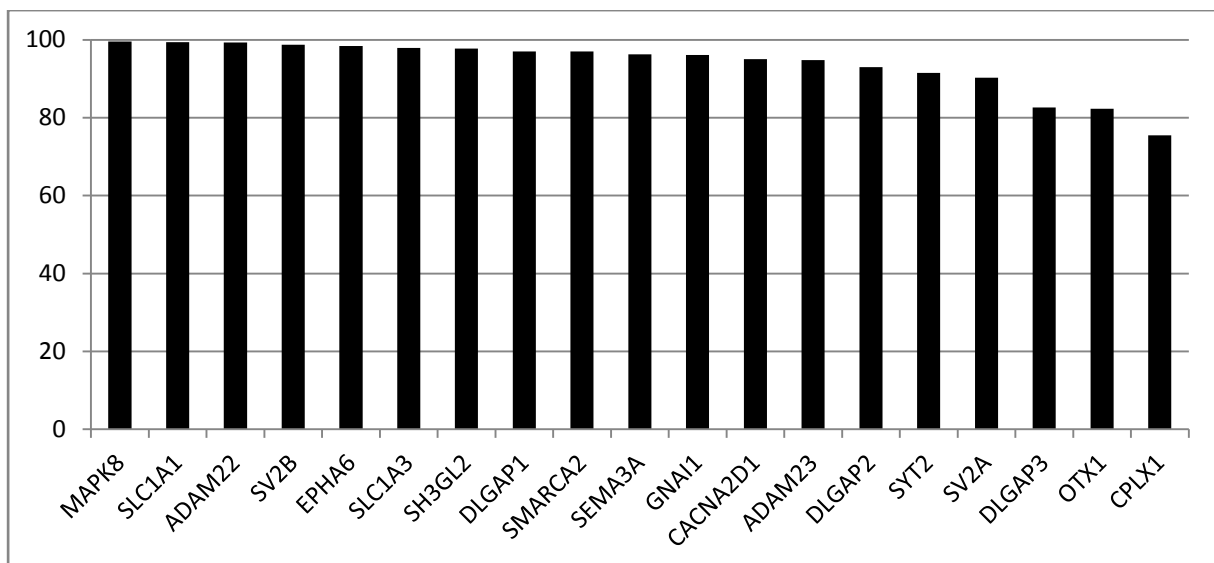
Primer pair	Forward primer: sequence, start, end (Build 36)	Reverse primer: sequence, start, end (Build 36)	Length of PCR fragment in bp <sup>a</sup>
1	CGCCTAGCTCTGCATGGCAAGTTCTAAC, 243089690, 243089717	CCTTTTCCTCTTTGGCTGCTACTCTGATA, 244409887, 244409916	no fragment
2	CGCCTAGCTCTGCATGGCAAGTTCTAAC, 243089690, 243089717	CATGGTTCCTACCACTTCTCAAGGATGGGA, 244410994, 244411023	2000-3000
3	GATGCTCTTCCTCCAGCCAAAGAAAAGC, 243090300, 243090328	TGCTTGGCACACGGGTTGTAGAAGTACT, 244411682, 244411709	2000-3000
4	TCCTCTTTACCCAGGACTGCCTGTTCAA, 243090962, 243090989	TGCTTGGCACACGGGTTGTAGAAGTACT, 244411682, 244411709	no fragment

**Table S5. Deletion breakpoint mapping: Primer pairs and length of PCR fragments.** <sup>a</sup> as estimated from gel electrophoresis; (table as published in Hartmann et al 2015, license agreement with John Wiley and Sons available)

## 7.2 Supporting figures



**Figure S1. Known genes: mean percentage of bases covered above 25x across 84 samples.**



**Figure S2. Candidate genes: mean percentage of bases covered above 25x across 84 samples.**

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## 9 Curriculum Vitae

**Name:** Corinna Hartmann  
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**Place of birth:** Nordhorn, Germany

### Education

**since 2015** Residency at the Institute of Neurogenetics, University of Lübeck and Department of Neurology, University Medical Center Schleswig-Holstein, Lübeck

**2011-2016** Doctoral thesis in the Pediatric Epilepsy Genetics Research Group, Department of Neuropediatrics, University Medical Center Schleswig-Holstein, Kiel (supervisor: Prof. Dr. Ulrich Stephani): „Investigating the genetic basis of fever-associated epilepsies using copy number variation analysis and targeted resequencing“

**2014** Second Medical Examination and license to practice medicine

**2011-2012** Research year in the laboratory of Heather Mefford, MD, PhD at the University of Washington, Department of Pediatrics, Seattle, Washington, USA

**2009** First Medical Examination

**2007-2014** Medical studies at the Christian-Albrechts-University, Kiel

**2007** High school diploma (Abitur), Gymnasium Nordhorn

## 10 Publications

1. **Hartmann, C.** (2012). "Abstract: Targeted next-generation sequencing in patients with fever-related seizures and epilepsies." *Young Researchers in Pediatric Epileptology: From Gene to Disease*. Kiel, Germany. August 23-25, 2012.
2. **Hartmann, C.**, von Spiczak, S., Suls, A., Weckhuysen, S., Buyse, G., Vilain, C., Van Bogaert, P., De Jonghe, P., Muhle, H., Stephani, U., Helbig, I. and Mefford, H. C. (2012). "Abstract 3.317: Copy number variation analysis in patients with SCN1A-related epilepsies." *American Epilepsy Society Annual Meeting*. San Diego, California, USA. November 30-December 4, 2012.
3. Carvill, G. L., Weckhuysen, S., McMahon, J. M., **Hartmann, C.**, Moller, R. S., Hjalgrim, H., Cook, J., Geraghty, E., O'Roak, B. J., Petrou, S., Clarke, A., Gill, D., Sadleir, L. G., Muhle, H., von Spiczak, S., Nikanorova, M., Hodgson, B. L., Gazina, E. V., Suls, A., Shendure, J., Dibbens, L. M., De Jonghe, P., Helbig, I., Berkovic, S. F., Scheffer, I. E. and Mefford, H. C. (2014). "GABRA1 and STXBP1: novel genetic causes of Dravet syndrome." *Neurology* **82**(14): 1245-1253.
4. **Hartmann, C.**, von Spiczak, S., Suls, A., Weckhuysen, S., Buyse, G., Vilain, C., Van Bogaert, P., De Jonghe, P., Cook, J., Muhle, H., Stephani, U., Helbig, I. and Mefford, H. C. (2015). "Investigating the genetic basis of fever-associated syndromic epilepsies using copy number variation analysis." *Epilepsia* **56**(3): e26-32.