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Diagnostic yield from 339 epilepsy patients screened on a clinical gene panel

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Abstract

Background—The contribution of genetic factors to epilepsy has long been recognized and has been estimated to play a role in 70–80% of cases. Identification of a pathogenic variant can help families to better cope with the disorder, allow for genetic counseling to determine recurrence risk, and in some cases, can directly influence treatment options. In this study, we determined the diagnostic yield of a clinical gene panel applied to an unselected cohort of epilepsy patients.

Methods—Variant reports from 339 clinically-referred epilepsy patients screened using a 110-gene panel were retrospectively reviewed. Variants were classified using ACMG guidelines.

Results—Pathogenic or likely pathogenic variants were identified in 62 individuals (18%) and potentially causative variants were identified in an additional 21 individuals (6%). Causative and potentially causative variants were most frequently identified in *SCN1A* (n = 15) and *KCNQ2* (n = 10). Other genes in which disease-causing variants were identified in multiple individuals included *CDKL5*, *SCN2A*, *SCN8A*, *SCN1B*, *STXBPI*, *TPP1*, *PCDH19*, *CACNA1A*, *GABRA1*, *GRIN2A*, *SLC2A1*, and *TSC2*. Sixteen additional genes had variants identified in single individuals.

Conclusions—We identified 87 variants in 30 different genes that could explain disease, of which 54% were not previously reported. This study confirms the utility of targeted gene panel analysis in epilepsy and highlights several factors to improve the yield of diagnostic genetic testing, including the critical need for clinical phenotype information and parental samples, microarray analysis for whole exon deletions and duplications, and frequent update of panels to incorporate new disease genes.

Keywords

diagnostic yield; epilepsy; epileptic encephalopathy; genetic testing

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CONFLICTS OF INTERESTS

CdS and JJA are employed by and receive a salary from EGL Genetics. The Epilepsy and Seizure Disorders panel is among EGL Genetics' commercially available tests. MH is a former employee of EGL Genetics. KMB and AE have no conflicts of interest.

SUPPLEMENTAL MATERIAL

S1. Genes of the Epilepsy and Seizure Disorders panel

INTRODUCTION

Epilepsy comprises a group of disorders that are characterized by recurrent, unprovoked seizures that collectively affect about 1% of the population. Although epilepsy can develop following insults such as head trauma, stroke, and infection, it is now believed that genetic factors may contribute to 70–80% of epilepsy cases.¹

Advances in next generation sequencing have allowed for the identification of new causal genes in both familial and sporadic forms of epilepsy.^{2,3} To date, pathogenic variants in over one hundred different genes have been reported to cause epilepsy and seizures.⁴ Many of these research findings have been used to develop clinical gene panels, which are available to physicians to aid in diagnosis. These panels can range in size from dozens to hundreds of genes and may be specific to epilepsy subtype, such as early-infantile epileptic encephalopathy, or more broadly encompass many known epilepsy genes.

In this study, we investigated the diagnostic yield of one such gene panel, known as the Epilepsy and Seizure Disorders (ESD) panel, in an unselected cohort of 339 clinically-referred patients. The ESD panel uses a targeted sequencing library of 110 genes that are associated with a spectrum of epilepsies, as well as genes associated with metabolic and structural disorders that include epilepsy as a prominent symptom. Identification of a causative variant can help families to better cope with the disorder, allow for genetic counseling to determine recurrence risk, and in some cases, can directly influence treatment options.^{5–7} Additionally, it can end the often long and expensive diagnostic odyssey that families experience when searching for answers.

MATERIALS AND METHODS

Patients

Variant reports from 339 consecutive, clinically-referred patients screened between 2013 and 2016 were retrospectively reviewed for this study. All molecular diagnostic testing was performed at EGL Genetics, a Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathologists (CAP) accredited laboratory. This study was approved by the institutional review board of Emory University.

Targeted gene panel testing

A custom-designed in-solution hybridization probe library (IDT or SureSelect, Agilent Technologies, Santa Clara, CA) was used to capture the coding exons of the 110 genes on the Epilepsy and Seizure Disorders (ESD) panel. Direct sequencing of the amplified captured regions was performed using next-generation sequencing (2×100bp, paired-end reads) on an Illumina HiSeq 2500 (Illumina, San Diego, CA) in rapid run mode. The individual DNA sequence reads were aligned to the published human genome reference (hg19 build) and variants were called using NextGENe® (SoftGenetics, State College, PA). Further analysis was performed using the EGL bioinformatics pipeline, which annotates identified variants utilizing a variety of external and internal sources. Variants are called within the coding exons and +/- 10bp of flanking intronic sequence. Relevant regions of epilepsy genes not amenable to NGS were filled in using the Sanger sequencing method. A

list of the 110 genes examined as part of the ESD panel can be found in the supplemental information for this article (Supplemental materials).

Variant Evaluation

Variants were evaluated and classified by board certified clinical molecular geneticists using the ACMG guidelines for variant classification.⁸ Briefly, variants were classified as (1) pathogenic, (2) likely pathogenic, (3) of unknown significance, (4) likely benign, or (5) benign. For research purposes, we considered certain variants of unknown significance to be “potentially causative” if specific conditions were met, such as the variant was absent from the population, *in silico* analyses predicted the variant to be damaging, and/or the variant was located in a critical or evolutionarily conserved region of the protein.⁸ Classified variants were submitted to ClinVar database (<https://www.ncbi.nlm.nih.gov/clinvar/>) as well as EGL Genetics’ publicly-available database EmVClass (www.egl-eurofins.com/emvclass/emvclass.php).

RESULTS

Patient demographics

Demographic information was available for approximately 80% of the 339 individuals. The age range of individuals referred for genetic testing was 2.5 months to 74 years; however, most of the referrals were children and more than half were below the age of 5 years. There were equal numbers of males and females. The amount of clinical information that accompanied each referral varied widely, with nearly 22% of the referrals lacking any clinical information about the patient. For the referrals that did include clinical information, 75% of cases reported two or more phenotypes. Aside from seizures, developmental delay was the next most common phenotype reported, followed by hypotonia, epileptic encephalopathy, intellectual disability, autism, and developmental regression. Additional phenotypes frequently encountered included ataxia, microcephaly, and spasticity. A positive family history of seizures or other neurological disorders was noted for 4% of cases.

Yield from the ESD Panel

Pathogenic or likely pathogenic variants were identified in 62 (18%) of the 339 individuals screened (Table 1). Twenty-one additional patients (6%) had potentially causative variants. Pathogenic, likely pathogenic, and potentially causative variants were identified in 30 different genes, accounting for 27% of the 110 genes on the ESD panel. Approximately 75% of the variants were in genes associated with autosomal dominant inheritance, while 17% and 8% of the variants affected X-linked and autosomal recessive genes, respectively. Pathogenic, likely pathogenic, and potentially causative variants were most frequently identified in *SCN1A* (n = 15) and *KCNQ2* (n = 10). Other genes in which variants were identified in multiple individuals included *CDKL5* (n = 6), *SCN2A* (n = 6), *SCN8A* (n = 5), *SCN1B* (n = 4), *STXBPI* (n = 4), *TPP1* (n = 3), *PCDH19* (n = 3), *CACNA1A* (n = 3), *GABRA1* (n = 2), *GRIN2A* (n = 2), *SLC2A1* (n = 2), and *TSC2* (n = 2). Sixteen additional genes had variants identified in single individuals (Figure 1, Table 1).

DISCUSSION

In this study, we determined the diagnostic yield of a clinical gene panel in an unselected cohort of 339 physician-referred epilepsy patients. This is one of the largest unselected epilepsy cohorts to be examined in this manner. We detected pathogenic or likely pathogenic variants in 18% of screened individuals, consistent with two recent studies that used gene panels to screen selected cohorts of individuals with severe, early-onset seizures, developmental delay, and intellectual disability.^{9,10}

We also observed potentially causative variants in an additional 6% of screened cases (21 individuals). These variants occurred in many of the same genes as the pathogenic and likely pathogenic variants (Figure 1), but were generally novel missense changes, which are more difficult to interpret clinically and will require additional functional evidence to be classified as pathogenic/likely pathogenic. Classification of these variants was often made more challenging due to a lack accompanying clinical information and parental samples to assist with the determination of variant inheritance.

The majority of the disease-causing variants identified in our study were detected in a small number of genes. *SCN1A* had the largest number of variants, followed by *KCNQ2*, together accounting for nearly 30% of the cases with a pathogenic, likely pathogenic, or potentially causative variant. Furthermore, multiple individuals had variants in *CDKL5*, *SCN2A*, *SCN8A*, *STXBPI*, and *PCDH19*, genes which are associated with epileptic encephalopathies, and in which pathogenic variants are consistently identified using gene panels and whole exome sequencing in different epilepsy studies.^{2,3,9} We also observed two or more variants each in *CACNA1A*, *GABRA1*, *GRIN2A*, *SCN1B*, *SLC2A1*, *TPP1*, and *TSC2*. Pathogenic variants in these genes can cause severe seizures and epileptic encephalopathy, but each gene has also been associated with other clinical phenotypes, for instance movement disorders, migraine, and milder forms of epilepsy. Although we were limited in the amount of clinical information provided with each case, the identified genes would suggest that the individuals with pathogenic or potentially causative variants are most likely affected with severe forms of childhood epilepsy. This highlights the benefit of genetic testing in children with severe epilepsy.

Sixteen additional genes had variants that were seen in only one patient. This low frequency may be explained for some genes, such as *ZEB2* (Mowat-Wilson syndrome) and *MECP2* (Rett syndrome), which typically present with very distinctive phenotypes that may prompt gene-specific testing rather than broader screening on an epilepsy gene panel. In other instances, affected individuals may be less likely to be referred for an epilepsy-specific gene panel. For example, individuals with pathogenic variants in *FLNA* and *RELN*, which are associated with periventricular nodular heterotopia and lissencephaly, respectively, may be referred for testing on a brain malformations panel rather than an epilepsy panel. On the other hand, the individuals with variants in these genes that were referred for screening on an epilepsy-specific panel may represent cases with atypical presentation. For example, we identified the compound heterozygous *RELN* variants, Thr606Ile and Val734Asp, in an individual with epilepsy, cerebral palsy, and developmental delay, but without any significant magnetic resonance imaging (MRI) findings (Table 1). These individual cases emphasize the

utility of referring individuals with unexplained epilepsy for a gene panel rather than testing single genes.

The epilepsy panel used in this study contained 110 genes curated for association with epilepsy and seizures (Supplemental materials). Because of their known role in epilepsy, the majority of these genes are present on other commercially-available epilepsy panels. Therefore, it is likely that a similar diagnostic yield would be obtained if the cohort examined in this study was tested using another epilepsy panel, especially since most of the pathogenic variants were identified in a small number of genes (Figure 1).

Whole exome sequencing (WES), which examines all known coding regions in the genome, has the potential to result in a higher diagnostic yield compared to gene panels; however, clinical laboratories are currently only able to assign pathogenicity to variants in known epilepsy genes. Furthermore, WES is more expensive and time-consuming, and is most efficient when both parents are also screened (trio format).

Based on this study, we identified several factors that could improve the diagnostic yield of gene panel testing for epilepsy. First, although parental samples are not routinely included when performing gene panel analysis, follow up testing on parental samples is critical for the reclassification of variants of unknown significance identified in the proband. It would be beneficial to collect parent samples at the same time as the proband sample when sending for testing in order to avoid delays in follow up of variants that require further analysis. Greater availability of parental samples might have increased the yield in our cohort by allowing for the identification of *de novo* variants and phasing of recessive variants. Second, the diagnostic yield would also likely have been higher if more samples were accompanied by clinical information since such knowledge can facilitate variant interpretation by allowing for comparisons with previously reported cases. This information is also helpful for identifying individuals with atypical clinical presentations that may expand the phenotypic spectrum of a given gene. The expansion of clinical spectrum has already been demonstrated for many epilepsy genes, including *SCN2A* and *CACNA1A*.^{11,12} Third, although recent publications have demonstrated the ability of next-generation sequencing (NGS) to detect intragenic copy number variation, these algorithms are still in the development stage and need confirmatory testing.¹³ Therefore, exon level copy number analysis for single and multiple exon deletions and duplications is still beneficial for identifying variants that may be missed by NGS. For instance, there were three individuals in our cohort that had concurrent deletion/duplication testing that detected copy number variants that could explain their epilepsy. Finally, it is important to frequently update gene panels to incorporate newly identified epilepsy genes. Many laboratories now perform sequencing on large sets of known disease genes (referred to as a Mendeliome) but only analyze a subset of those genes according to the test ordered. In negative cases, with appropriate consent, the expanded gene set could be evaluated to identify variants in genes not previously associated with epilepsy. Even as whole exome and genome sequencing approaches become more commonly used for genetic testing, it will remain important to have up-to-date epilepsy gene lists to aid in variant prioritization and phenotype definition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Genes with pathogenic/likely pathogenic (black) and potentially causative (grey) variants detected in 339 clinically-referred epilepsy patients.

Table 1.

Diagnostic yield from 339 epilepsy patients screened on the Epilepsy and Seizure disorders panel.

Pathogenic and Likely Pathogenic variants					
Case No.	Gene	Nucleotide	Protein	Classification	Phenotype (if provided)
1	<i>ALDH7A1</i>	c.1093+1G>A, c.1279G>C	p.Glu427Gln	Pathogenic	Seizures, epileptic encephalopathy, macrocephaly, hypotonia, muscle weakness, and developmental delay
2	<i>ARX</i>	c.30C>A	p.Cys10Ter	Pathogenic	Infantile spasms, dysphagia, and poor weight gain
3	<i>CDKL5</i>	c.1891_1916delATAGGGCAAGGGATGGCAGCTAGAGC	p.Ile631Glnfs *43	Pathogenic	Unspecified Epilepsy
4	<i>CDKL5</i>	c.1152C>G	p.Tyr384Ter	Pathogenic	Epileptic encephalopathy, myotonic and tonic-clonic seizures, and a coarse gyral pattern on brain imaging
5	<i>CDKL5</i>	c.1553delC	p.Pro518Hisfs *5	Pathogenic	Seizures and spasticity
6	<i>CDKL5</i>	c.212delA	p.Asn71Thrfs *5	Pathogenic	Infantile/epileptic spasms and hypotonia
7	<i>CDKL5</i>	c.1108_1109dupAA	p.Asn370Lysfs *124	Pathogenic	N/A
8	<i>FOXG1</i>	c.648_655delTTACTACC	p.Tyr217Argfs *235	Pathogenic	Unspecified Epilepsy
9	<i>GABRA1</i>	c.335G>A	p.Arg112Gln	Likely Pathogenic	N/A
10	<i>GABRA1</i>	c.640C>A	p.Arg214Ser	Likely pathogenic	Generalized convulsive epilepsy with intractable epilepsy
11	<i>GRIN2A</i>	c.2890delC	p.Gln964Lysfs *37	Pathogenic	Generalized seizures and speech disturbance
12	<i>GRIN2A</i>	c.3813G>A	p.Trp1271Ter	Pathogenic	N/A
13	<i>KCNA1</i>	c.1222G>A	p.Val408Met	Likely Pathogenic	Seizures, developmental delay, and multiple joint contractures
14	<i>KCNQ2</i>	c.793G>A	p.Ala265Thr	Likely pathogenic	Neonatal seizure disorder
15	<i>KCNQ2</i>	c.637C>T	p.Arg213Trp	Pathogenic	Neonatal seizure disorder

16	<i>KCNQ2</i>	c.640C>T	p.Arg214Trp	Likely pathogenic	Autism, seizures, hydrocephaly, a brother with autism and epilepsy, and a father with a history of epilepsy in childhood
17	<i>KCNQ2</i>	c.1118+2T>C		Pathogenic	Infantile/epileptic spasms
18	<i>KCNQ2</i>	c.701C>T	p.Thr234Ile	Likely pathogenic	Seizures and developmental delay
19	<i>KCNQ2</i>	c.821C>T	p.Thr274Met	Likely pathogenic	N/A
20	<i>KCNQ2</i>	c.841G>A	p.Gly281Arg	Likely pathogenic	N/A
21	<i>KCNQ2</i>	c.1088A>G	p.Tyr363Cys	Likely pathogenic	Neonatal seizure disorder and epileptic encephalopathy
22	<i>KCNT1</i>	c.2849G>A	p.Arg950Gln	Likely Pathogenic	N/A
23	<i>MECP2</i>	c.880C>T	p.Arg294Ter	Pathogenic	Delayed milestones and intractable epilepsy
24	<i>PCDH19</i>	c.814C>T	p.Gln272Ter	Pathogenic	Seizure disorder
25	<i>PCDH19</i>	c.1091dupC	p.Tyr366Leufs *10	Pathogenic	Intellectual disability, autism, and seizures
26	<i>PCDH19</i>	c.1265_1266delCA	p.Thr422Asnfs *23	Pathogenic	N/A
27	<i>SCN1A</i>	c.2584C>T	p.Arg862Ter	Pathogenic	Psychomotor epilepsy, intellectual disability, phenotype consistent with Dravet syndrome
28	<i>SCN1A</i>	c.4907G>A	p.Arg1636Gln	Likely pathogenic	Epileptic encephalopathy, myoclonic seizures, dystonia, and spasticity
29	<i>SCN1A</i>	c.602+1G>A		Pathogenic	Seizures and developmental delay
30	<i>SCN1A</i>	c.269T>C	p.Phe90Ser	Likely pathogenic	Prolonged seizures, possible myoclonus, and a clinical suspicion for Dravet syndrome
31	<i>SCN1A</i>	c.1264G>A	p.Val422Met	Likely pathogenic	Infantile spasms, focal seizures, hypotonia, bilateral

					polydactyly, lack of coordination, and grand mal status
32	<i>SCN1A</i>	c.1259C>A	p.Ala420Asp	Likely pathogenic	N/A
33	<i>SCN1A</i>	c.302G>A	p.Arg101Gln	Pathogenic	N/A
34	<i>SCN1A</i>	c.5389G>C	p.Ala1797Pro	Likely Pathogenic	Tonic-clonic and focal seizures
35	<i>SCN1A</i>	c.5348C>T	p.Ala1783Val	Pathogenic	N/A
36	<i>SCN1A</i>	c.4812delG	p.Trp1604Ter	Pathogenic	N/A
37	<i>SCN1A</i>	c.5563C>T	p.Pro1855Ser	Likely Pathogenic	N/A
38	<i>SCN1A</i>	c.1076A>G	p.Asn359Ser	Likely Pathogenic	N/A
39	<i>SCN1B</i>	c.347delC	p.Ser116Trpfs *31	Pathogenic	Hypotonia and seizures
40	<i>SCN1B</i>	c.653delG	p.Ser218Thrfs *21	Likely Pathogenic	Developmental delay, seizures with an abnormal EEG, and high myopia
41	<i>SCN1B</i>	c.363C>G	p.Cys121Trp	Pathogenic	N/A
42	<i>SCN1B</i>	c.363C>G	p.Cys121Trp	Pathogenic	N/A
43	<i>SCN2A</i>	c.5387_5390dup AGAT	p.Met1797Ilefs *5	Pathogenic	Seizures and intellectual disability
44	<i>SCN2A</i>	c.5645G>A	p.Arg1882Gln	Likely pathogenic	Lack of normal physiological development, autism spectrum disorder, and intractable epilepsy
45	<i>SCN2A</i>	c.2558G>A	p.Arg853Gln	Pathogenic	Failure to thrive, developmental delay, speech delay, autism, seizures, dystonia, microcephaly, and gastroesophageal reflux disease
46	<i>SCN2A</i>	c.1178C>A	p.Thr393Lys	Likely Pathogenic	Seizures and developmental regression
47	<i>SCN2A</i>	c.2713A>G	p.Lys905Glu	Likely Pathogenic	Epileptic encephalopathy
48	<i>SCN8A</i>	c.3985A>G	p.Asn1329Asp	Likely pathogenic	Intractable epilepsy
49	<i>SCN8A</i>	c.2287A>G	p.Ile763Val	Likely Pathogenic	Seizures and developmental delay
50	<i>SLC2A1</i>	c.997C>T	p.Arg333Trp	Pathogenic	Febrile seizures, ataxia, hypotonia, hypermobility, and a family

					history of seizures.
51	<i>SLC2A1</i>	c.1006C>G	p.Leu336Val	Likely Pathogenic	N/A
52	<i>SLC9A6</i>	c.508-1G>A		Pathogenic	N/A
53	<i>STXBP1</i>	c.1029+1G>T		Pathogenic	Seizures, developmental delay, and cognitive impairment.
54	<i>STXBP1</i>	c.364C>T	p.Arg122Ter	Pathogenic	Infantile/epileptic spasms and tonic seizures
55	<i>STXBP1</i>	c.548T>C	p.Leu183Pro	Likely Pathogenic	N/A
56	<i>STXBP1</i>	c.704G>A	p.Arg235Gln	Likely Pathogenic	Generalized, absence, and tonic-clonic seizures, infantile spasms, hypotonia, developmental delay, and cerebral palsy
57	<i>SYN1</i>	c.377G>A	p.Trp126Ter	Pathogenic	N/A
58	<i>TPP1</i> *	c.509-1G>C		Pathogenic	N/A
59	<i>TPP1</i>	c.509-1G>C, c.1016G>A	p.Arg339Gln	Pathogenic	Seizures and speech delay
60	<i>TSC2</i>	c.4415delG	p.Gly1472Alafs*4	Pathogenic	Seizure disorder and intellectual disability
61	<i>TSC2</i>	c.3598C>T	p.Arg1200Trp	Pathogenic	Infantile spasms and global developmental delay
62	<i>ZEB2</i>	c.1876G>T	p.Gly626Ter	Pathogenic	Developmental delay and psychomotor epilepsy
Potentially Causative Variants					
Case No.	Gene	Nucleotide	Protein	Classification	Phenotype (if provided)
63	<i>CACNA1A</i>	c.5017C>T	p.Arg1673Cys	Unknown	Generalized convulsive epilepsy and hemiplegia
64	<i>CACNA1A</i>	c.4177G>A	p.Val1393Met	Unknown	Global developmental delay, seizures, and tremor
65	<i>CACNA1A</i>	c.4177G>A	p.Val1393Met	Unknown	N/A
66	<i>CDKL5</i>	c.541G>A	p.Glu181Lys	Unknown	N/A
67	<i>HCN1</i>	c.990G>C	p.Trp330Cys	Unknown	Epileptic encephalopathy, abnormal EEG, and other clinical features suggestive of

					Ohtahara syndrome
68	<i>FLNA</i>	c.4237G>A	p.Glu1413Lys	Unknown	Hypotonia, epilepsy, and abnormal MRI
69	<i>KCNQ2</i>	c.1627G>A	p.Val543Met	Inherited	Developmental delay, seizures, a ventricular septal defect, unilateral cryptorchidism, and macrocephaly
70	<i>KCNQ2</i>	c.1627G>A	p.Val543Met	Unknown	N/A
71	<i>KCTD7</i>	c.190A>G, c.793G>A	p.Thr64Ala, p.Gly265Arg	Inherited from both parents	Status epilepticus, generalized, tonic-clonic, and myoclonic seizures
72	<i>MEF2C</i>	c.121T>C	p.Cys41Arg	Unknown	Generalized and myoclonic seizures, intellectual disability, hypotonia, spasticity, and muscle weakness
73	<i>NRXN1</i>	c.3619C>T	p.Arg1207Ter	Unknown	Autism, epilepsy, and developmental delay
74	<i>PNKP*</i>	c.1324G>A	p.Gly442Ser	Unknown	N/A
75	<i>RELN</i>	c.1817C>T, c.2201T>A	p.Thr606Ile, p.Val734Asp	Inherited from both parents	Cerebral palsy, abnormal EEG, developmental delay, and lack of coordination
76	<i>SCN1A</i>	c.638C>G	p.Ser213Trp	Unknown	Febrile and afebrile seizures and developmental delay
77	<i>SCN1A</i>	c.1703G>A	p.Arg568Gln	Unknown	Seizures
78	<i>SCN1A</i>	c.2923G>C	p.Val975Leu	Unknown	Seizures and developmental delay
79	<i>SCN2A</i>	c.4156T>G	p.Cys1386Gly	Unknown	Seizures, speech and developmental regression
80	<i>SCN8A</i>	c.491C>T	p.Thr164Met	Inherited from affected mother	Focal seizures, developmental delay, failure to thrive, and a maternal family history of seizures
81	<i>SCN8A</i>	c.605T>A	p.Ile202Asn	Unknown	Seizures, developmental delay, dysmorphic

					features, pica, paroxysmal behavior with nonspecific encephalopathy on EEG, and a brother who also has seizures
82	<i>SCN8A</i>	c.1241A>T	p.Tyr414Phe	Unknown	N/A
83	<i>TPPI</i> ^{*†}	c.523C>T	p.Arg175Cys	Unknown	Infantile spasms, learning disability, developmental delay, seizures, and hypotonia

N/A, phenotype was not available

* Indicates a homozygous variant

† This individual also had a novel homozygous missense variant in *SLC25A22*