Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Sequencing and Variant Interpretation

Next-generation sequencing (NGS) based multi-gene panel testing for epilepsy-related genes was conducted as previously described.[6] Briefly, genes from the epilepsy panel were targeted and sequenced via a short-read NGS assay that used genomic DNA extracted from blood or saliva samples. A bioinformatics pipeline aligned sequencing reads and utilized community standard and custom algorithms that identified single nucleotide variants (SNVs), small insertions or deletions (indels), large indels, structural variants, and exon-level copy number variants (CNVs). Variants were classified using the points-based Sherloc framework based on the joint consensus guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[21] A definitive genetic diagnosis was defined as one pathogenic or likely pathogenic (P/LP) variant in a gene with autosomal dominant and X-linked inheritance or two P/LP variants in a gene with autosomal recessive inheritance. A gene reported in the literature with at least 1 published study demonstrating improved clinical presentation (i.e. reduced seizures or movement issues) in a series of human participants was classified as clinically actionable (eTable 2). Reports of a single individual or family or included only animal studies or a hypothetical therapy were not sufficient.

CRF questions sent to healthcare providers

1. Please enter the Invitae RQ number for whom you are completing this survey. Only one RQ number should be associated with each set of questions.
    a. Patient identification number
2. The most actionable finding in this patient was in which gene? Select all that apply:
    a. Select from this list of genes:

ADSL	*CLN3*	*GABRA1*	*KCNB1*	*PCDH19*	*SCN1B*	*ST3GAL5*
ALDH5A1	*CLN5*	*GABRB2*	*KCNC1*	*PIGA*	*SCN2A*	*STRADA*
ALDH7A1	*CLN6*	*GABRB3*	*KCNH2*	*PIGN*	*SCN3A*	*STX1B*
ALG13	*CLN8*	*GABRG2*	*KCNJ10*	*PIGO*	*SCN5A*	*STXBP1*
AMT	*CNTNAP2*	*GAMT*	*KCNMA1*	*PLCB1*	*SCN8A*	*SYN1*
ARHGEF9	*CSTB*	*GATM*	*KCNQ2*	*PNKD*	*SCN9A*	*SYNGAP1*
ARX	*CTSD*	*GCSH*	*KCNQ3*	*PNKP*	*SERPINI1*	*SYNJ1*
ATP1A2	*DEPDC5*	*GLDC*	*KCNT1*	*PNPO*	*SGCE*	*SZT2*
ATP1A3	*DNAJC5*	*GLRA1*	*KCTD7*	*POLG*	*SIK1*	*TBC1D24*
ATRX	*DNM1*	*GNAO1*	*LGI1*	*PPT1*	*SLC2A1*	*TCF4*
BRAT1	*DOCK7*	*GOSR2*	*LIAS*	*PRICKLE1*	*SLC6A1*	*TPK1*
C12orf57	*DYNC1H1*	*GPHN*	*MBD5*	*PRIMA1*	*SLC6A8*	*TSC1*
CACNA1A	*DYRK1A*	*GRIN1*	*MECP2*	*PRRT2*	*SLC9A6*	*TSC2*
CACNA2D2	*EEF1A2*	*GRIN2A*	*MEF2C*	*PTEN*	*SLC12A5*	*UBE3A*
CARS2	*EFHC1*	*GRIN2B*	*MFSD8*	*PURA*	*SLC13A5*	*WDR45*
CASK	*EHMT1*	*HCN1*	*MTOR*	*QARS*	*SLC19A3*	*WWOX*
CDKL5	*EPM2A*	*HNRNPU*	*NEDD4L*	*RANBP2*	*SLC25A12*	*ZDHHC9*

CHD2	*FARS2*	*IER3IP1*	*NEXMIF*	*RBFOX1*	*SLC25A22*	*ZEB2*
CHRNA2	*FLNA*	*IQSEC2*	*NGLY1*	*RELN*	*SLC35A2*	
CHRNA4	*FOLR1*	*ITPA*	*NHLRC1*	*ROGDI*	*SMC1A*	
CHRNB2	*FOXG1*	*JMJD1C*	*NPRL3*	*SATB2*	*SNX27*	
CLCN4	*FRRS1L*	*KANSL1*	*NRXN1*	*SCARB2*	*SPATA5*	
CLN2 (TPP1)	*GABBR2*	*KCNA2*	*PACS1*	*SCN1A*	*SPTAN1*	

3. What is your specialty? Select all that apply:
    a. Behavioral medicine
    b. Endocrinology
    c. Emergency medicine
    d. Epilepsy
    e. Family medicine
    f. Genetics
    g. Hematology-oncology
    h. Internal medicine
    i. Neurology
    j. Neurosurgery
    k. Pediatrics
    l. Unsure
    m. Other (please specify)
4. You, the clinician that ordered this genetic test, work in a (select all that apply):
    a. Private practice
    b. Children's Hospital
    c. Academic Tertiary Care center
    d. Community hospital
5. How was this patient referred to you?
    a. Pediatrician
    b. Family Medicine
    c. Self -referral
    d. Other (please specify)
6. Why did your patient have genetic testing?
    a. Patient has a clinical presentation of epilepsy
    b. Patient does not currently have seizures or a clinical presentation of epilepsy, but is at risk of having a familial epilepsy-causing variant
    c. Patient is at risk of having a child with epilepsy
    d. Other (please specify)
7. **If patient has a clinical presentation per question 6:** At what age did the patient begin to experience seizures?
    a. 0-3 months
    b. 4-6 months
    c. 6-12 months
    d. 1 year old
    e. 2 years old
    f. 3 years old
    g. 4 years old
    h. 5 years old
    i. 6 years old
    j. 7-17 years old
    k. 18 years old or older

8. **If patient has a clinical presentation per question 6:** At what age was the patient clinically diagnosed with epilepsy?
    a. 0-3 months
    b. 4-6 months
    c. 6-12 months
    d. 1 year old
    e. 2 years old
    f. 3 years old
    g. 4 years old
    h. 5 years old
    i. 6 years old
    j. 7-17 years old
    k. 18 years old or older
9. **If patient has a clinical presentation per question 6:** At what frequency did seizures occur BEFORE the patient had a genetic diagnosis?
    a. 1 or more times a day
    b. 1 or more times a week
    c. 1 or more times a month
    d. 1 or more times a year
10. At what age did the patient receive the genetic testing result from Invitae?
    a. 0-3 months
    b. 4-6 months
    c. 6-12 months
    d. 1 year old
    e. 2 years old
    f. 3 years old
    g. 4 years old
    h. 5 years old
    i. 6 years old
    j. 7-17 years old
    k. 18 years old or older
11. How would you describe the result obtained from Invitae? Note: if the variant was reclassified, please refer to the most recent reclassification when answering this question.
    a. It is a clinically actionable molecular diagnosis
    b. It included a pathogenic or likely pathogenic result but was not a clinically actionable molecular diagnosis
    c. It is an uncertain or negative (non-actionable) result
    d. It confirmed previous known clinical genetic testing results for my patient
12. How did you determine whether clinical management (treatment indications or contraindications) were needed based on this diagnosis?
    a. I felt comfortable making clinical decisions for this patient on my own or with others from my practice
    b. I utilized Invitae's genetic counselors to help me evaluate next steps for this patient
    c. I utilized other resources in making clinical decisions for this patient
    d. I have not used any outside resources in making clinical decisions for this patient yet, but I would like to
    e. Other: _____
13. Did the genetic diagnosis lead to a change in clinical management?
    a. Yes
    b. No
    c. Unsure
14. **If Yes to Q13:** In what way did the genetic diagnosis lead to a change in clinical management? Select all that apply:
    a. Started a medication
    b. Added a new medication to one already taking
    c. Stopped one or more medications or treatment

d. Medications stayed the same but dosage was changed
e. Diet change was recommended
f. Surgery was recommended
g. Monitoring for extra-neurological disease (please specify)
h. Referral to a specialist (please specify)
i. Other (please specify)

15. **If No to Q13:** Which of the following best describes the reason why no clinical management change was made?
    a. The result was not informative to clinical management
    b. Current clinical management already consistent with the recommendations based on this genetic result
    c. Recommended treatment refused by the patient
    d. Results useful for informing future treatment possibilities
    e. Other (please specify)
16. **If "Stopped one or more medications or treatment" on Q14":** What medication(s) or treatments was(were) stopped? Select all that apply:
    a. Acetazolamide (Diamox, Diamox Sequels)
    b. ACTH
    c. Brivaracetam (Briviact)
    d. Cannabidiol (Epidiolex)
    e. Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR)
    f. Clobazam (Onfi, Frisium)
    g. Clonazepam (KlonoPIN)
    h. Eslicarbazepine acetate (Aptiom)
    i. Ethosuximide (Zarontin)
    j. Felbamate (Felbatol)
    k. Immunoglobulins
    l. Lacosamide (Vimpat)
    m. Lamotrigine (Lamictal)
    n. Levetiracetam (Keppra, Roweepra, Spritam)
    o. Nitrazepam
    p. Oxcarbazepine (Oxtellar XR, Trileptal)
    q. Perampanel (Fycompa)
    r. Phenobarbital (Solfoton, Luminal)
    s. Phenytoin (Dilantin, Phenytek)
    t. Prednisone (Rayos, Sterapred, Deltasone)
    u. Pyridoxine (Vitamin B6, Vitelle Nestrex, Pyridoxal 5'-Phosphate)
    v. Retigabine (Potiga)
    w. Rufinamide (Banzel)
    x. Steroids
    y. Stiripentol (Diacomit)
    z. Sulthiame
    aa. Topiramate (Topamax, Qudexy XR Sprinkle, Topamax Sprinkle, Trokendi XR, Topiragen)
    bb. Valproate
    cc. Vigabatrin (Sabril, Vigadrone)
    dd. Zonisamide (Zonegran)
    ee. Atkins diet
    ff. Casein free diet
    gg. Gluten free diet
    hh. Ketogenic diet
    ii. Corpus callosotomy
    jj. Gamma knife radiosurgery
    kk. Hemispherectomy
    ll. Lobectomy
    mm. Resection surgery
    nn. Subpial transection

oo. Vagal nerve stimulator (VNS) surgery
pp. Other (please specify)

17. **If any choice on Q14 except for "Stopped one or more medications or treatment", "Medications stayed the same but dosage was changed", "Specialist evaluation (please specify)" or "other":** What new medication(s) or treatments was(were) started? Select all that apply:
    a. Acetazolamide (Diamox, Diamox Sequels)
    b. ACTH
    c. Brivaracetam (Briviact)
    d. Cannabidiol (Epidiolex)
    e. Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR)
    f. Clobazam (Onfi, Frisium)
    g. Clonazepam (KlonoPIN)
    h. Eslicarbazepine acetate (Aptiom)
    i. Ethosuximide (Zarontin)
    j. Felbamate (Felbatol)
    k. Immunoglobulins
    l. Lacosamide (Vimpat)
    m. Lamotrigine (Lamictal)
    n. Levetiracetam (Keppra, Roweepra, Spritam)
    o. Nitrazepam
    p. Oxcarbazepine (Oxtellar XR, Trileptal)
    q. Perampanel (Fycompa)
    r. Phenobarbital (Solfoton, Luminal)
    s. Phenytoin (Dilantin, Phenytek)
    t. Prednisone (Rayos, Sterapred, Deltasone)
    u. Pyridoxine (Vitamin B6, Vitelle Nestrex, Pyridoxal 5'-Phosphate)
    v. Retigabine (Potiga)
    w. Rufinamide (Banzel)
    x. Steroids
    y. Stiripentol (Diacomit)
    z. Sulthiame
    aa. Topiramate (Topamax, Qudexy XR Sprinkle, Topamax Sprinkle, Trokendi XR, Topiragen)
    bb. Valproate
    cc. Vigabatrin (Sabril, Vigadrone)
    dd. Zonisamide (Zonegran)
    ee. Atkins diet
    ff. Casein free diet
    gg. Gluten free diet
    hh. Ketogenic diet
    ii. Corpus callosotomy
    jj. Gamma knife radiosurgery
    kk. Hemispherectomy
    ll. Lobectomy
    mm. Resection surgery
    nn. Subpial transection
    oo. Vagal nerve stimulator (VNS) surgery
    pp. Other (please specify)
18. **If yes to Q13:** When was the clinical management change made?
    a. No clinical management change
    b. 0-3 months after the genetic diagnosis
    c. 4-6 months after the genetic diagnosis
    d. 6-12 months after the genetic diagnosis
    e. 1 year or more after the genetic diagnosis
19. **If yes to Q13:** In the time since the clinical management change was made, how has the patient responded? Select all that apply:
    a. Not enough time has passed since the clinical management change to evaluate the outcome

b. Unknown - have not followed up with the patient
c. No change in patient condition
d. Patient has reduced seizures
e. Patient seizures have stopped
f. Patient has reduced medication side effects
g. Patient has increased seizures
h. Patient has increased medication side effects
i. Patient has other improvements to their condition(please specify)
j. Patient has other decline in their condition (please specify)

20. **If yes to Q13:** At what frequency did seizures occur AFTER the clinical management change?
    a. No seizures have been observed
    b. 1 or more times a day
    c. 1 or more times a weekly
    d. 1 or more times a month
    e. 1 or more times a year
21. Did this result cause you to consider genetic testing in other unrelated patients with a similar phenotype?
    a. No, I was already doing testing for this type of patient
    b. No, I will not test other similar patients
    c. Yes, I have tested / will test additional similar patients

eTable 1. Demographic Information for Study Cohort and Nonresponder Cohort

	Responders (n=418)	**Nonresponders (n=2,992)**	***p*-value**
Age, years			
Mean	6.9	6.1	0.07
Median	4	3	
Sex, males, n (%)	193 (46.2)	1,395 (46.6)	0.83
Date of testing, n (%)[a]			
2016	19 (4.6)	116 (3.9)	0.07
2017	52 (12.5)	365 (12.2)	
2018	95 (22.8)	696 (23.3)	
2019	185 (44.4)	1357 (45.4)	
2020	66 (15.8)	458 (15.3)	
Clinical actionability of genetic findings, n (%)			
Actionable	291 (69.0)	2,026 (67.1)	0.62
Not actionable	131 (31.0)	992 (32.9)	

[a]Date of testing was unavailable for one patient in the responder group

eTable 2. Frequency of Positive Findings by Gene Among the Study Cohort (Responders) and the Nonresponder Cohort

Gene	Responders (n=418) n (%)	Nonresponders (n=2,992) n (%)	Genetic finding associated with management changes[a]	PMID
SCN1A	64 (15.3)	465 (15.5)	Yes	20301494, 26600876, 26339958, 28538134, 24902755, 30061856
PRRT2	41 (9.8)	303 (10.1)	Yes	28056630, 29334453, 32392383
DEPDC5	27 (6.5)	100 (3.3)	Yes	26434565, 30782578, 27683934, 30093711
KCNQ2	19 (4.5)	204 (6.8)	Yes	25880994, 20437616, 27602407
MECP2	16 (3.8)	126 (4.2)	No	–
PCDH19	15 (3.6)	107 (3.6)	Yes	26820223, 23712037
TSC2	14 (3.3)	51 (1.7)	Yes	15563014, 10073425, 33346789, 24053983, 31335226, 32854808
STXBP1	14 (3.3)	79 (2.6)	Yes	27905812, 26865513
KCNT1	10 (2.4)	45 (1.5)	Yes	26369628, 32167590, 31054119
SYNGAP1	10 (2.4)	62 (2.1)	No	–
SCN2A	9 (2.2)	82 (2.7)	Yes	28379373, 26291284
SLC2A1	8 (1.9)	51 (1.7)	Yes	20301603, 32913944
NPRL3	8 (1.9)	71 (2.4)	Yes	26434565, 26285051
CACNA1A	8 (1.9)	47 (1.6)	Yes	20301319, 21734179, 30142438
CHD2	8 (1.9)	63 (2.1)	Yes	31677157, 25672921
CDKL5	8 (1.9)	69 (2.3)	Yes	Pestana-Knight E et al. Abstract 419. Presented at AES. December 2020.
ATP1A3	7 (1.7)	24 (0.8)	Yes	20301294, 25447930, 24996492, 24532324
UBE3A	7 (1.7)	52 (1.7)	No	–
GABRG2	7 (1.7)	29 (1.0)	No	–
ALDH7A1	6 (1.4)	15 (0.5)	Yes	24664145, 20301659, 19142996, 24748525
GRIN2A	6 (1.4)	40 (1.3)	No	–

Gene	Responders (n=418)	Nonresponders (n=2,992)	Genetic finding associated with management changes[a]	PMID
MBD5	5 (1.2)	18 (0.6)	No	–
SCN8A	4 (1.0)	41 (1.4)	Yes	26252990, 26029160, 27559564, 25568300, 30615093
TBC1D24	4 (1.0)	20 (0.7)	No	–
ALG13	4 (1.0)	10 (0.3)	No	–
TPP1	4 (1.0)	32 (1.1)	Yes	2968815, 33604240, 33348105, 33202105
GABRB3 and UBE3A	4 (1.0)	39 (1.3)	No	–
GPHN	4 (1.0)	7 (0.2)	No	–
STX1B	4 (1.0)	13 (0.4)	No	–
SCN1B	3 (0.7)	19 (0.6)	No	–
SLC6A1	3 (0.7)	37 (1.2)	Yes	27600546, 25865495
SLC6A8	3 (0.7)	13 (0.4)	Yes	24953403, 20301745
TCF4	3 (0.7)	18 (0.6)	No	–
WDR45	3 (0.7)	25 (0.8)	No	–
FOXG1	3 (0.7)	27 (0.9)	No	–
KCNA2	3 (0.7)	20 (0.7)	Yes	34516822
NEXMIF	3 (0.7)	17 (0.6)	No	–
SCN9A	3 (0.7)	7 (0.2)	No	–
SMC1A	3 (0.7)	13 (0.4)	No	–
TSC1	2 (0.5)	36 (1.2)	Yes	15563014, 10073425, 33346789, 24053983, 31335226, 32854808
ARHGEF9	2 (0.5)	5 (0.2)	No	–
ATP1A2	2 (0.5)	7 (0.2)	No	–
GLDC	2 (0.5)	6 (0.2)	Yes	20301531, 26749113
HNRNPU	2 (0.5)	23 (0.8)	No	–
KCNH2	2 (0.5)	6 (0.2)	Yes	29097296, 24011539
IQSEC2	2 (0.5)	22 (0.7)	No	–
KCNH5	2 (0.5)	3 (0.1)	No	–
MEF2C	2 (0.5)	10 (0.3)	No	–

Gene	Responders (n=418)	Nonresponders (n=2,992)	Genetic finding associated with management changes[a]	PMID
PIGN	2 (0.5)	7 (0.2)	No	–
GRIN1	1 (0.2)	9 (0.3)	No	–
KCNMA1	1 (0.2)	5 (0.2)	No	–
KCNQ3[b]	1 (0.2)	11 (0.4)	No	–
POLG	1 (0.2)	15 (0.5)	Yes	20301791, 20301791, 21038416
PURA	1 (0.2)	19 (0.6)	No	–
RELN	1 (0.2)	1 (<0.1)	No	–
SLC13A5	1 (0.2)	2 (0.1)	No	–
SPTAN1	1 (0.2)	7 (0.2)	No	–
WWOX	1 (0.2)	6 (0.2)	No	–
ZEB2	1 (0.2)	19 (0.6)	No	–
ARX	1 (0.2)	15 (0.5)	No	–
ATP6AP2	1 (0.2)	0	No	–
ATRX	1 (0.2)	2 (0.1)	No	–
CASK	1 (0.2)	5 (0.2)	No	–
CLCN4	1 (0.2)	3 (0.1)	No	–
CLN3	1 (0.2)	4 (0.1)	No	–
DIAPH1	1 (0.2)	0	No	–
DNM1	1 (0.2)	6 (0.2)	No	–
DYRK1A	1 (0.2)	19 (0.6)	No	–
GABRA1	1 (0.2)	17 (0.6)	No	–
GABRA1 and GABRG2	1 (0.2)	0	No	–
GABRB2	1 (0.2)	2 (0.1)	No	–
KCNB1	1 (0.2)	13 (0.4)	No	–
KCNC1	1 (0.2)	8 (0.3)	No	–
NHLRC1	1 (0.2)	2 (0.1)	Yes	20301563, 25667898
PNKP	1 (0.2)	3 (0.1)	No	–
SLC9A6	1 (0.2)	4 (0.1)	No	–
GABRB3	0	18 (0.6)	No	–
FRRS1L	0	13 (0.4)	No	–

Gene	Responders (n=418)	Nonresponders (n=2,992)	Genetic finding associated with management changes[a]	PMID
GNAO1	0	13 (0.4)	Yes	29661126, 30103967, 31076915
EHMT1	0	12 (0.4)	No	–
EEF1A2	0	11 (0.4)	No	–
CNTNAP2	0	10 (0.3)	No	–
LGI1	0	10 (0.3)	Yes	20301709, 7647791
GRIN2B	0	9 (0.3)	No	–
PPT1	0	7 (0.2)	No	–
SCN5A	0	7 (0.2)	No	–
SPATA5	0	7 (0.2)	No	–
GLRA1	0	6 (0.2)	Yes	20301437, 25356525
HCN1	0	6 (0.2)	No	–
PTEN	0	6 (0.2)	No	–
SYN1	0	6 (0.2)	No	–
CHRNA4	0	5 (0.2)	Yes	32097883
KANSL1	0	5 (0.2)	No	–
SATB2	0	5 (0.2)	No	–
SGCE	0	5 (0.2)	No	–
BRAT1	0	4 (0.1)	No	–
CLN5	0	4 (0.1)	No	–
EPM2A	0	4 (0.1)	Yes	20301563, 27459034
PACS1	0	4 (0.1)	No	–
PIGG	0	4 (0.1)	No	–
SCN3A	0	4 (0.1)	No	–
CLN6	0	3 (0.1)	No	–
KCTD7	0	3 (0.1)	No	–
NRXN1	0	3 (0.1)	No	–
QARS[b]	0	3 (0.1)	No	–
SLC35A2	0	3 (0.1)	No	–
ST3GAL5	0	3 (0.1)	No	–
TBL1XR1	0	3 (0.1)	No	–

Gene	Responders (n=418)	Nonresponders (n=2,992)	Genetic finding associated with management changes[a]	PMID
ADSL	0	2 (0.1)	No	–
GAMT	0	2 (0.1)	Yes	23622406, 20301745
GOSR2[b]	0	2 (0.1)	No	–
KCNJ10	0	2 (0.1)	No	–
MFSD8	0	2 (0.1)	No	–
NGLY1[b]	0	2 (0.1)	No	–
PIGA[b]	0	2 (0.1)	No	–
SZT2	0	2 (0.1)	No	–
C12orf57	0	1 (<0.1)	No	–
CACNA2D2	0	1 (<0.1)	No	–
CHRNB2	0	1 (<0.1)	No	–
DNAJC5	0	1 (<0.1)	No	–
FLNA	0	1 (<0.1)	No	–
FOLR1	0	1 (<0.1)	Yes	20447151
ITPA	0	1 (<0.1)	No	–
KCND2	0	1 (<0.1)	No	–
PNPO	0	1 (<0.1)	Yes	20301659, 20301659. 25639976
RANBP2	0	1 (<0.1)	No	–
ROGDI	0	1 (<0.1)	No	–
SIK1	0	1 (<0.1)	No	–
SYNJ1	0	1 (<0.1)	No	–

[a]All genes except *GLDC*, *RANBP2*, and *SLC13A5* were included in previous literature reviews. [b]These genes were classified as "emerging evidence" previously. Upon re-review of the literature, no studies in humans have indicated positive outcomes.

eTable 3. Genes With Definitive Genetic Diagnoses in This Study Cohort

Gene	hgvs	Variant	n[a]
ALDH7A1	NM_001182.4:c.1279G>C	p.Glu427Gln	3[b]
ALDH7A1	NM_001182.4:c.1301_1302del	p.Tyr434Cysfs	2
ALDH7A1	NM_001182.4:c.246+1G>A	Splice site	1
ALDH7A1	NM_001182.4:c.364C>T	p.Arg122Trp	1
ALDH7A1	NM_001182.4:c.575C>T	p.Thr192Met	3[b]
ALDH7A1	NM_001182.4:c.898A>G	p.Asn300Asp	1
ALG13	NM_001099922.2:c.320A>G	p.Asn107Ser	2
ALG13	NM_001257230.1:c.8A>G	p.Asn3Ser	2
ARHGEF9	NM_015185.2:c.1012C>T	p.Arg338Trp	1
ARHGEF9	NM_015185.2:c.561+1G>A	Splice site	2
ARX	c.426_458dup	p.Gly143_Ala153dup	1
ATP1A2	NM_000702.3:c.1777C>T	p.Arg593Trp	1
ATP1A2	NM_000702.3:c.2936C>T	p.Pro979Leu	1
ATP1A3	NM_152296.4:c.2401G>A	p.Asp801Asn	3
ATP1A3	NM_152296.4:c.2415C>G	p.Asp805Glu	1
ATP1A3	NM_152296.4:c.2443G>A	p.Glu815Lys	2
ATP1A3	NM_152296.4:c.2839G>T	p.Gly947Trp	1
ATP6AP2	NM_005765.2:c.321C>T	Silent	1
ATRX	NM_000489.4:c.1727C>A	p.Ser576*	1
CACNA1A	NM_001127221.1:c.1442del	p.Arg481Profs	1
CACNA1A	NM_001127221.1:c.2360del	p.Leu787Cysfs	1
CACNA1A	NM_001127221.1:c.4177G>A	p.Val1393Met	1
CACNA1A	NM_001127221.1:c.4953+1G>T	Splice site	1
CACNA1A	NM_001127221.1:c.5126T>C	p.Ile1709Thr	1
CACNA1A	NM_001127221.1:c.5588_5589del	p.Leu1863Argfs	1
CACNA1A	NM_001127221.1:c.6193-2A>C	Splice site	1
CACNA1A	NM_001127221.1:c.928_931del	p.Thr310Phefs	1
CASK	NM_003688.3:c.-46-?_*5486+?del	Deletion (Entire coding sequence)	1
CDKL5	NM_003159.2:c.-162-?_*85+?del	Deletion (Entire coding sequence)	1
CDKL5	NM_003159.2:c.-162-?_1944+?del	Deletion (Exons 2-12)	2
CDKL5	NM_003159.2:c.100-2A>G	Splice site	1
CDKL5	NM_003159.2:c.116T>G	p.Val39Gly	1
CDKL5	NM_003159.2:c.2345C>A	p.Ser782*	1
CDKL5	NM_003159.2:c.508G>T	p.Glu170*	1
CDKL5	NM_003159.2:c.533G>A	p.Arg178Gln	1
CDKL5	NM_003159.2:c.854G>A	p.Arg285Lys	1
CHD2	c.1382_1383delinsAAGTCTGAA	p.Leu461Glnfs	1

Gene	hgvs	Variant	n[a]
CHD2	c.3734dup	p.Tyr1246Ilefs	1
CHD2	NM_001271.3:c.1937G>A	p.Gly646Glu	1
CHD2	NM_001271.3:c.3171_3172del	p.Glu1058Argfs	1
CHD2	NM_001271.3:c.3782G>A	p.Trp1261*	1
CHD2	NM_001271.3:c.3787dup	p.Val1263Glyfs	1
CHD2	NM_001271.3:c.3938G>C	p.Arg1313Pro	1
CHD2	NM_001271.3:c.4613C>T	p.Ser1538Phe	1
CLCN4	NM_001830.3:c.2152C>T	p.Arg718Trp	1
CLN3	NM_001042432.1:c.1056+3A>C	Intronic	1
CLN3	NM_001042432.1:c.461-?_677+?del	Deletion (Exons 8-9)	1
DEPDC5	c.1081+2T>G	Splice site	1
DEPDC5	c.1555C>T	P.Gln519*	1
DEPDC5	c.280-1G>A	Splice site	1
DEPDC5	c.3563+1G>C	Splice site	1
DEPDC5	c.562+1G>A	Splice site	3[b]
DEPDC5	NM_001242896.1:c.-60-?_1666+?del	Deletion (Exons 2-21)	1
DEPDC5	NM_001242896.1:c.-60-?_767+?del	Deletion (Exons 2-12)	1
DEPDC5	NM_001242896.1:c.1139del	p.Phe380Serfs	1
DEPDC5	NM_001242896.1:c.1218-1G>C	Splice site	1
DEPDC5	NM_001242896.1:c.147-?_193+?del	Deletion (Exon 4)	1
DEPDC5	NM_001242896.1:c.147-?_363+?dup	Gain (Exons 4-6)	1
DEPDC5	NM_001242896.1:c.1555C>T	p.Gln519*	1
DEPDC5	NM_001242896.1:c.21C>G	p.Tyr7*	2
DEPDC5	NM_001242896.1:c.2548dup	p.Asp850Glyfs	1
DEPDC5	NM_001242896.1:c.3259C>T	p.Arg1087*	1
DEPDC5	NM_001242896.1:c.346C>T	p.Arg116*	1
DEPDC5	NM_001242896.1:c.3868C>T	p.Gln1290*	1
DEPDC5	NM_001242896.1:c.3994C>T	p.Arg1332*	1
DEPDC5	NM_001242896.1:c.4207C>T	p.Gln1403*	1
DEPDC5	NM_001242896.1:c.4446dup	p.Val1483Cysfs	1
DEPDC5	NM_001242896.1:c.4501C>T	p.Gln1501*	2
DEPDC5	NM_001242896.1:c.59-?_146+?del	Deletion (Exon 3)	1
DEPDC5	NM_001242896.1:c.832_833del	p.Phe278Hisfs	1
DIAPH1	NM_005219.4:c.2540_2541del	p.Lys847Argfs	1
DNM1	NM_004408.3:c.1081C>G	p.Arg361Gly	1
DYRK1A	NM_001396.3:c.951+4_951+7del	Intronic	1
FOXG1	NM_005249.4:c.1135del	p.Leu379Serfs	1

Gene	hgvs	Variant	n[a]
FOXG1	NM_005249.4:c.301C>T	p.Gln101*	1
FOXG1	NM_005249.4:c.460del	p.Glu154Argfs	1
GABRA1	NM_000806.5:c.-468-?_*2537+?del	Deletion (Entire coding sequence)	1
GABRA1	NM_000806.5:c.641G>A	p.Arg214His	1
GABRB2	NM_021911.2:c.902A>G	p.Tyr301Cys	1
GABRB3	NM_000814.5:c.-114-?_*4247+?del	Deletion (Entire coding sequence)	4
GABRG2	c.1248_1249delinsG	p.Ser416Argfs	1
GABRG2	NM_000816.3:c.-358-?_*2171+?del	Deletion (Entire coding sequence)	1
GABRG2	NM_000816.3:c.107+1G>A	Splice site	1
GABRG2	NM_000816.3:c.269C>T	p.Thr90Met	1
GABRG2	NM_000816.3:c.429dup	p.Lys144Glufs	1
GABRG2	NM_000816.3:c.530del	p.Arg177Glnfs	1
GABRG2	NM_000816.3:c.571C>T	p.Gln191*	1
GABRG2	NM_000816.3:c.95C>A	p.Ser32*	1
GLDC	NM_000170.2:c.2T>C	Initiator codon	3
GLDC	NM_000170.2:c.499G>T	p.Glu167*	2
GPHN	NM_020806.4:c.1156_1159dup	p.Val387Alafs	1
GPHN	NM_020806.4:c.144-?_201+?del	Deletion (Exon 3)	1
GPHN	NM_020806.4:c.1666C>T	p.Arg556*	1
GPHN	NM_020806.4:c.390-?_456+?dup	Gain (Exon 6)	1
GRIN1	NM_007327.3:c.2530C>T	p.Arg844Cys	1
GRIN2A	NM_000833.4:c.-18-?_414+?del	Deletion (Exon 3)	1
GRIN2A	NM_000833.4:c.1008-?_1122+?del	Deletion (Exon 5)	1
GRIN2A	NM_000833.4:c.1244dup	p.Phe416Ilefs	1
GRIN2A	NM_000833.4:c.1510C>T	p.Arg504Trp	1
GRIN2A	NM_000833.4:c.1961T>C	p.Ile654Thr	1
GRIN2A	NM_000833.4:c.44T>C	p.Leu15Pro	1
HNRNPU	NM_031844.2:c.-218-?_*4150+?del	Deletion (Entire coding sequence)	2
IQSEC2	NM_001111125.2:c.2507C>T	p.Ala836Val	1
IQSEC2	NM_001111125.2:c.2563C>T	p.Arg855*	1
KCNA2	NM_004974.3:c.1214C>T	p.Pro405Leu	1
KCNA2	NM_004974.3:c.193C>T	p.Arg65*	1
KCNA2	NM_004974.3:c.890G>A	p.Arg297Gln	1
KCNB1	NM_004975.2:c.629C>T	p.Thr210Met	1
KCNC1	NM_001112741.1:c.959G>A	p.Arg320His	1
KCNH2	NM_000238.3:c.1096C>T	p.Arg366*	1
KCNH2	NM_000238.3:c.2653_2657del	p.Arg885Alafs	1

Gene	Hgvs	Variant	n[a]
KCNH5	NM_139318.4:c.980G>A	p.Arg327His	2
KCNMA1	NM_002247.3:c.2612del	p.Asn871Ilefs	2
KCNQ2	NM_172107.2:c.-177-?_*455+?del	Deletion (Entire coding sequence)	1
KCNQ2	NM_172107.2:c.-177-?_1023+?del	Deletion (Exons 1-7)	1
KCNQ2	NM_172107.2:c.-177-?_296+?del	Deletion (Exon 1)	1
KCNQ2	NM_172107.2:c.1217+1G>T	Splice site	1
KCNQ2	NM_172107.2:c.1356dup	p.Lys453Glnfs	1
KCNQ2	NM_172107.2:c.144dup	p.Lys49Glnfs	1
KCNQ2	NM_172107.2:c.1708C>T	p.Gln570*	1
KCNQ2	NM_172107.2:c.2245G>T	p.Glu749*	2
KCNQ2	NM_172107.2:c.2361dup	p.Ile788Hisfs	1
KCNQ2	NM_172107.2:c.297-?_1023+?del	Deletion (Exons 2-7)	1
KCNQ2	NM_172107.2:c.583T>C	p.Ser195Pro	1
KCNQ2	NM_172107.2:c.587C>T	p.Ala196Val	1
KCNQ2	NM_172107.2:c.793G>A	p.Ala265Thr	2
KCNQ2	NM_172107.2:c.821C>T	p.Thr274Met	1
KCNQ2	NM_172107.2:c.997C>T	p.Arg333Trp	2
KCNQ2	NM_172107.2:c.998G>A	p.Arg333Gln	1
KCNQ3	NM_004519.3:c.61_77del	p.Gly21*	3
KCNT1	NM_020822.2:c.1193G>A	p.Arg398Gln	1
KCNT1	NM_020822.2:c.1283G>A	p.Arg428Gln	1
KCNT1	NM_020822.2:c.1421G>A	p.Arg474His	1
KCNT1	NM_020822.2:c.1885A>G	p.Lys629Glu	1
KCNT1	NM_020822.2:c.2849G>A	p.Arg950Gln	1
KCNT1	NM_020822.2:c.2849G>T	p.Arg950Leu	1
KCNT1	NM_020822.2:c.73C>T	p.Arg25Trp	2
KCNT1	NM_020822.2:c.862G>A	p.Gly288Ser	2
MBD5	NM_018328.4:c.-556-?_397+?del	Deletion (Exons 6-8)	1
MBD5	NM_018328.4:c.2299_2302del	p.Asn767Leufs	1
MBD5	NM_018328.4:c.2633del	p.Pro878Hisfs	1
MBD5	NM_018328.4:c.397+1G>A	Splice site	1
MBD5	NM_018328.4:c.4455del	p.Lys1486Asnfs	1
MECP2	c.1054_1271delins36	p.Lys352Profs	1
MECP2	c.729_1172delins127	p.Gln244Glufs	1
MECP2	NM_004992.3:c.-226-?_*8554+?dup	Gain (Entire coding sequence)	1
MECP2	NM_004992.3:c.1157_1197del	p.Leu386Hisfs	1
MECP2	NM_004992.3:c.1157_1200del	p.Leu386Glnfs	1

Gene	hgvs	Variant	n[a]
MECP2	NM_004992.3:c.1216C>T	p.Gln406*	1
MECP2	NM_004992.3:c.179G>A	p.Gly60Asp	1
MECP2	NM_004992.3:c.316C>T	p.Arg106Trp	1
MECP2	NM_004992.3:c.455C>G	p.Pro152Arg	1
MECP2	NM_004992.3:c.502C>T	p.Arg168*	2
MECP2	NM_004992.3:c.763C>T	p.Arg255*	5
MECP2	NM_004992.3:c.808del	p.Arg270Glufs	1
MECP2	NM_004992.3:c.916C>T	p.Arg306Cys	1
MECP2	Partial Deletion	Exon 4	1
MEF2C	NM_002397.4:c.-142-?_*4363+?del	Deletion (Entire coding sequence)	1
MEF2C	NM_002397.4:c.908dup	p.Leu303Phefs	1
NEXMIF	c.1783A>T	p.Arg595*	1
NEXMIF	NM_001008537.2:c.3011_3014del	p.Ser1004Ilefs	1
NEXMIF	NM_001008537.2:c.3334del	p.Ile1112Serfs	1
NHLRC1	NM_198586.2:c.1091C>A	p.Ser364*	1
NPRL3	NM_001077350.2:c.-67-?_*904+?del	Deletion (Entire coding sequence)	1
NPRL3	NM_001077350.2:c.-67-?_118+?del	Deletion (Exon 2)	3
NPRL3	NM_001077350.2:c.-67-?_188+?del	Deletion (Exons 2-3)	1
NPRL3	NM_001077350.2:c.1270C>T	p.Arg424*	1
NPRL3	NM_001077350.2:c.630-?_767+?del	Deletion (Exon 8)	1
NPRL3	NM_001077350.2:c.954C>G	p.Tyr318*	1
PCDH19	c.514G>T	p.Glu172*	1
PCDH19	NM_001184880.1:c.-1676-?_*4633+?del	Deletion (Entire coding sequence)	2
PCDH19	NM_001184880.1:c.-1676-?_2616+?del	Deletion (Exons 1-3)	1
PCDH19	NM_001184880.1:c.1019A>G	p.Asn340Ser	1
PCDH19	NM_001184880.1:c.1059_1062del	p.Glu354Leufs	1
PCDH19	NM_001184880.1:c.1300C>T	p.Gln434*	1
PCDH19	NM_001184880.1:c.1720G>T	p.Glu574*	1
PCDH19	NM_001184880.1:c.2502del	p.Asn834Lysfs	1
PCDH19	NM_001184880.1:c.2616+1G>A	Splice site	1
PCDH19	NM_001184880.1:c.2617-2A>G	Splice site	1
PCDH19	NM_001184880.1:c.2619del	p.Glu874Lysfs	1
PCDH19	NM_001184880.1:c.374A>G	p.Asn125Ser	1
PCDH19	NM_001184880.1:c.471dup	p.Ser158Leufs	1
PCDH19	NM_001184880.1:c.659del	p.Gly220Alafs	1
PIGN	NM_176787.4:c.1251+1G>A	Splice site	1
PIGN	NM_176787.4:c.1860-?_2370+?dup	Gain (Exons 21-25)	1

Gene	hgvs	Variant	n[a]
PIGN	Partial Deletion	Exons 5-7	1
PNKP	NM_007254.3:c.1253_1269dup	p.Thr424Glyfs	1
PNKP	NM_007254.3:c.1299-2A>G	Splice site	1
POLG	NM_002693.2:c.2542G>A	p.Gly848Ser	1
PRRT2	NM_145239.2:c.-301-?_*1243+?del	Deletion (Entire coding sequence)	1
PRRT2	NM_145239.2:c.-65-?_*1243+?del	Deletion (Entire coding sequence)	9
PRRT2	NM_145239.2:c.649del	p.Arg217Glufs	3
PRRT2	NM_145239.2:c.649dup	p.Arg217Profs	29
PURA	NM_005859.4:c.697_699del	p.Phe233del	1
RELN	NM_005045.3:c.4901_5797+1405del	Partial Deletion (Exons 33-38)	1
SCN1A	NM_001165963.1:c.1008T>G	p.Cys336Trp	1
SCN1A	NM_001165963.1:c.1028G>C	p.Gly343Ala	1
SCN1A	NM_001165963.1:c.1129C>T	p.Arg377*	1
SCN1A	NM_001165963.1:c.1177C>T	p.Arg393Cys	1
SCN1A	NM_001165963.1:c.1248T>A	p.Asn416Lys	1
SCN1A	NM_001165963.1:c.1278C>A	p.Tyr426*	1
SCN1A	NM_001165963.1:c.1278C>G	p.Tyr426*	1
SCN1A	NM_001165963.1:c.1738dup	p.Arg580Profs	1
SCN1A	NM_001165963.1:c.2134C>T	p.Arg712*	1
SCN1A	NM_001165963.1:c.2495G>A	p.Trp832*	1
SCN1A	NM_001165963.1:c.2593C>T	p.Arg865*	1
SCN1A	NM_001165963.1:c.2624C>T	p.Thr875Met	1
SCN1A	NM_001165963.1:c.264+3G>C	Intronic	1
SCN1A	NM_001165963.1:c.264+4_264+7del	Intronic	1
SCN1A	NM_001165963.1:c.2729A>G	p.Gln910Arg	1
SCN1A	NM_001165963.1:c.2831T>C	p.Val944Ala	1
SCN1A	NM_001165963.1:c.2837G>A	p.Arg946His	1
SCN1A	NM_001165963.1:c.2860G>A	p.Glu954Lys	1
SCN1A	NM_001165963.1:c.2869T>G	p.Trp957Gly	1
SCN1A	NM_001165963.1:c.2947G>A	p.Val983Ile	1
SCN1A	NM_001165963.1:c.2947G>T	p.Val983Phe	1
SCN1A	NM_001165963.1:c.2956C>T	p.Leu986Phe	1
SCN1A	NM_001165963.1:c.2983T>C	p.Phe995Leu	1
SCN1A	NM_001165963.1:c.301C>T	p.Arg101Trp	1
SCN1A	NM_001165963.1:c.3104_3110del	p.Gln1035Profs	1
SCN1A	NM_001165963.1:c.3173_3176del	p.Lys1058Thrfs	1
SCN1A	NM_001165963.1:c.3371_3372del	p.Phe1124*	1

Gene	Hgvs	Variant	n[a]
SCN1A	NM_001165963.1:c.3407C>A	p.Ser1136*	1
SCN1A	NM_001165963.1:c.3637C>T	p.Arg1213*	2
SCN1A	NM_001165963.1:c.3649_3650insTT	p.His1217Leufs	1
SCN1A	NM_001165963.1:c.3715_3721dup	p.Tyr1241*	1
SCN1A	NM_001165963.1:c.3724_3725dup	p.Asp1243Leufs	1
SCN1A	NM_001165963.1:c.379C>T	p.His127Tyr	1
SCN1A	NM_001165963.1:c.3925C>G	p.Leu1309Val	1
SCN1A	NM_001165963.1:c.3925C>T	p.Leu1309Phe	1
SCN1A	NM_001165963.1:c.4057G>T	p.Val1353Phe	1
SCN1A	NM_001165963.1:c.4219C>T	p.Arg1407*	1
SCN1A	NM_001165963.1:c.4295A>T	p.Lys1432Ile	1
SCN1A	NM_001165963.1:c.4352C>T	p.Pro1451Leu	1
SCN1A	NM_001165963.1:c.4372del	p.Tyr1458Thrfs	1
SCN1A	NM_001165963.1:c.4414T>C	p.Phe1472Leu	1
SCN1A	NM_001165963.1:c.4428C>A	p.Asn1476Lys	1
SCN1A	NM_001165963.1:c.4453A>G	p.Asn1485Asp	1
SCN1A	NM_001165963.1:c.4515_4516del	p.Lys1506Ilefs	1
SCN1A	NM_001165963.1:c.4541T>G	p.Leu1514*	1
SCN1A	NM_001165963.1:c.4656T>A	p.Cys1552*	1
SCN1A	NM_001165963.1:c.4787G>A	p.Arg1596His	1
SCN1A	NM_001165963.1:c.4822G>T	p.Asp1608Tyr	1
SCN1A	NM_001165963.1:c.4852+1G>A	Splice site	1
SCN1A	NM_001165963.1:c.487_496del	p.Gly163Leufs	1
SCN1A	NM_001165963.1:c.4907G>A	p.Arg1636Gln	1
SCN1A	NM_001165963.1:c.4966_4969dup	p.Arg1657Hisfs	1
SCN1A	NM_001165963.1:c.4973C>T	p.Thr1658Met	1
SCN1A	NM_001165963.1:c.530G>A	p.Gly177Glu	1
SCN1A	NM_001165963.1:c.5488_5489del	p.Gln1830Valfs	1
SCN1A	NM_001165963.1:c.5656C>T	p.Arg1886*	1
SCN1A	NM_001165963.1:c.5754del	p.Ala1919Leufs	1
SCN1A	NM_001165963.1:c.5781_5782delinsTG	p.Arg1927_Arg1928delinsSerGly	1
SCN1A	NM_001165963.1:c.580G>A	p.Asp194Asn	1
SCN1A	NM_001165963.1:c.673A>G	p.Lys225Glu	1
SCN1A	NM_001165963.1:c.680T>G	p.Ile227Ser	2
SCN1A	NM_001165963.1:c.752T>G	p.Met251Arg	1
SCN1B	NM_199037.3:c.363C>G	p.Cys121Trp	3
SCN2A	NM_021007.2:c.1019dup	p.Asn340Lysfs	1

Gene	hgvs	Variant	n[a]
SCN2A	NM_021007.2:c.2995G>A	p.Glu999Lys	1
SCN2A	NM_021007.2:c.3400-?_*2486+?del	Deletion (Exons 18-27)	3
SCN2A	NM_021007.2:c.3631G>A	p.Glu1211Lys	1
SCN2A	NM_021007.2:c.4879G>A	p.Val1627Met	1
SCN2A	NM_021007.2:c.647T>G	p.Leu216Trp	1
SCN2A	NM_021007.2:c.668G>A	p.Arg223Gln	1
SCN2A	NM_021007.2:c.685T>G	p.Ser229Ala	1
SCN2A	NM_021007.2:c.788C>T	p.Ala263Val	1
SCN8A	NM_014191.3:c.5615G>A	p.Arg1872Gln	1
SCN8A	NM_014191.3:c.5630A>G	p.Asn1877Ser	2
SCN8A	NM_014191.3:c.779T>C	p.Phe260Ser	1
SCN9A	NM_002977.3:c.5843A>C	p.Asp1948Ala	1
SCN9A	NM_002977.3:c.829C>T	p.Arg277*	1
SCN9A	NM_002977.3:c.902-2A>C	Splice site	1
SLC13A5	NM_177550.4:c.1280C>T	p.Ser427Leu	1
SLC2A1	NM_006516.2:c.1198C>T	p.Arg400Cys	1
SLC2A1	NM_006516.2:c.277C>T	p.Arg93Trp	1
SLC2A1	NM_006516.2:c.400G>A	p.Gly134Ser	2
SLC2A1	NM_006516.2:c.667C>T	p.Arg223Trp	1
SLC2A1	NM_006516.2:c.680-11G>A	Intronic	1
SLC2A1	NM_006516.2:c.751_757dup	p.Arg253Hisfs	1
SLC2A1	NM_006516.2:c.884C>T	p.Thr295Met	1
SLC6A1	NM_003042.3:c.1024G>A	p.Val342Met	1
SLC6A1	NM_003042.3:c.1460T>C	p.Met487Thr	1
SLC6A1	NM_003042.3:c.223G>A	p.Gly75Arg	1
SLC6A8	c.1006_1008del	p.Asn336del	1
SLC6A8	NM_005629.3:c.1222_1224del	p.Phe408del	1
SLC6A8	NM_005629.3:c.1659C>G	p.Tyr553*	1
SLC9A6	NM_006359.2:c.1013_1025delinsTCAGCC	p.Trp338Phefs	1
SMC1A	NM_006306.3:c.3103C>T	p.Arg1035*	1
SMC1A	NM_006306.3:c.3249dup	p.Ile1084Aspfs	1
SMC1A	NM_006306.3:c.392del	p.Arg131Leufs	1
SPTAN1	NM_001130438.2:c.6843_6848del	p.Ile2282_Leu2283del	1
STX1B	NM_052874.4:c.-242-?_*3565+?del	Deletion (Entire sequence)	1
STX1B	NM_052874.4:c.106-1G>C	Splice site	1
STX1B	NM_052874.4:c.205+2_205+3del	Splice site	1
STX1B	NM_052874.4:c.281-2A>C	Splice site	1

Gene	hgvs	Variant	n[a]
STXBP1	NM_003165.3:c.1099C>T	p.Arg367*	1
STXBP1	NM_003165.3:c.1162C>T	p.Arg388*	1
STXBP1	NM_003165.3:c.1216C>T	p.Arg406Cys	1
STXBP1	NM_003165.3:c.1217G>A	p.Arg406His	1
STXBP1	NM_003165.3:c.1258G>T	p.Glu420*	1
STXBP1	NM_003165.3:c.1652G>A	p.Arg551His	2
STXBP1	NM_003165.3:c.1702+1G>A	Splice site	1
STXBP1	NM_003165.3:c.22_32dup	p.Glu12Leufs	1
STXBP1	NM_003165.3:c.247-1G>A	Splice site	1
STXBP1	NM_003165.3:c.265del	p.Ser89Valfs	1
STXBP1	NM_003165.3:c.385A>C	p.Thr129Pro	1
STXBP1	NM_003165.3:c.569G>A	p.Arg190Gln	1
STXBP1	NM_003165.3:c.817G>T	p.Glu273*	1
SYNGAP1	NM_006772.2:c.1453del	p.Arg485Alafs	1
SYNGAP1	NM_006772.2:c.1802C>A	p.Ala601Glu	1
SYNGAP1	NM_006772.2:c.2059C>T	p.Arg687*	1
SYNGAP1	NM_006772.2:c.2147G>A	p.Arg716Gln	1
SYNGAP1	NM_006772.2:c.3060del	p.Gln1021Serfs	1
SYNGAP1	NM_006772.2:c.3233_3236del	p.Val1078Alafs	1
SYNGAP1	NM_006772.2:c.333del	p.Lys114Serfs	1
SYNGAP1	NM_006772.2:c.3706C>T	p.Gln1236*	1
SYNGAP1	NM_006772.2:c.91C>T	p.Arg31*	1
SYNGAP1	NM_006772.2:c.937G>T	p.Glu313*	1
TBC1D24	NM_001199107.1:c.457G>A	p.Glu153Lys	1
TBC1D24	NM_001199107.1:c.845C>G	p.Pro282Arg	3
TCF4	NM_001083962.1:c.1169del	p.Leu390*	1
TCF4	NM_001083962.1:c.520C>T	p.Arg174*	1
TCF4	NM_001083962.1:c.923-2A>G	Splice site	1
TPP1	NM_000391.3:c.182T>G	p.Leu61Arg	1
TPP1	NM_000391.3:c.229G>C	p.Gly77Arg	3
TPP1	NM_000391.3:c.509-1G>C	Splice site	3
TPP1	NM_000391.3:c.622C>T	p.Arg208*	1
TSC1	NM_000368.4:c.1439-1G>C	Splice site	1
TSC1	NM_000368.4:c.1498C>T	p.Arg500*	1
TSC2	NM_000548.3:c.1108C>T	p.Gln370*	1
TSC2	NM_000548.3:c.1832G>A	p.Arg611Gln	2
TSC2	NM_000548.3:c.1855_1863dup	p.Leu619_Leu621dup	1

Gene	hgvs	Variant	n[a]
TSC2	NM_000548.3:c.2087G>A	p.Cys696Tyr	1
TSC2	NM_000548.3:c.2108G>A	p.Trp703*	1
TSC2	NM_000548.3:c.2410T>C	p.Cys804Arg	1
TSC2	NM_000548.3:c.2714G>A	p.Arg905Gln	1
TSC2	NM_000548.3:c.336+1G>C	Splice site	1
TSC2	NM_000548.3:c.3598C>T	p.Arg1200Trp	1
TSC2	NM_000548.3:c.4508A>C	p.Gln1503Pro	1
TSC2	NM_000548.3:c.4544_4547del	p.Asn1515Serfs	1
TSC2	NM_000548.3:c.4912_4914del	p.Lys1638del	1
TSC2	NM_000548.3:c.5024C>T	p.Pro1675Leu	1
UBE3A	Gain	Entire sequence	2
UBE3A	NM_130838.1:c.-44-?_*1888+?del	Deletion (Entire coding sequence)	4
UBE3A	NM_130838.1:c.-44-?_*1888+?dup	Gain (Entire coding sequence)	3
UBE3A	NM_130838.1:c.2507_2510del	p.Lys836Argfs	1
UBE3A	NM_130838.1:c.317_321del	p.Thr106Argfs	1
WDR45	c.10C>T	p.Gln4*	1
WDR45	NM_007075.3:c.210_213dup	p.Pro72*	1
WDR45	NM_007075.3:c.873C>G	p.Tyr291*	1
WWOX	NM_016373.3:c.127C>T	p.Gln43*	1
WWOX	NM_016373.3:c.321C>G	p.Tyr107*	1
ZEB2	NM_014795.3:c.1277T>A	p.Leu426*	1

[a]Sum of variants will not equal number of molecular diagnoses patients because patients could have more than one variant in a given gene. [b]Variant observed in multiple individuals of a single family.

eTable 4. Patient Outcomes After Treatment Changes by Gene With Diagnostic Finding

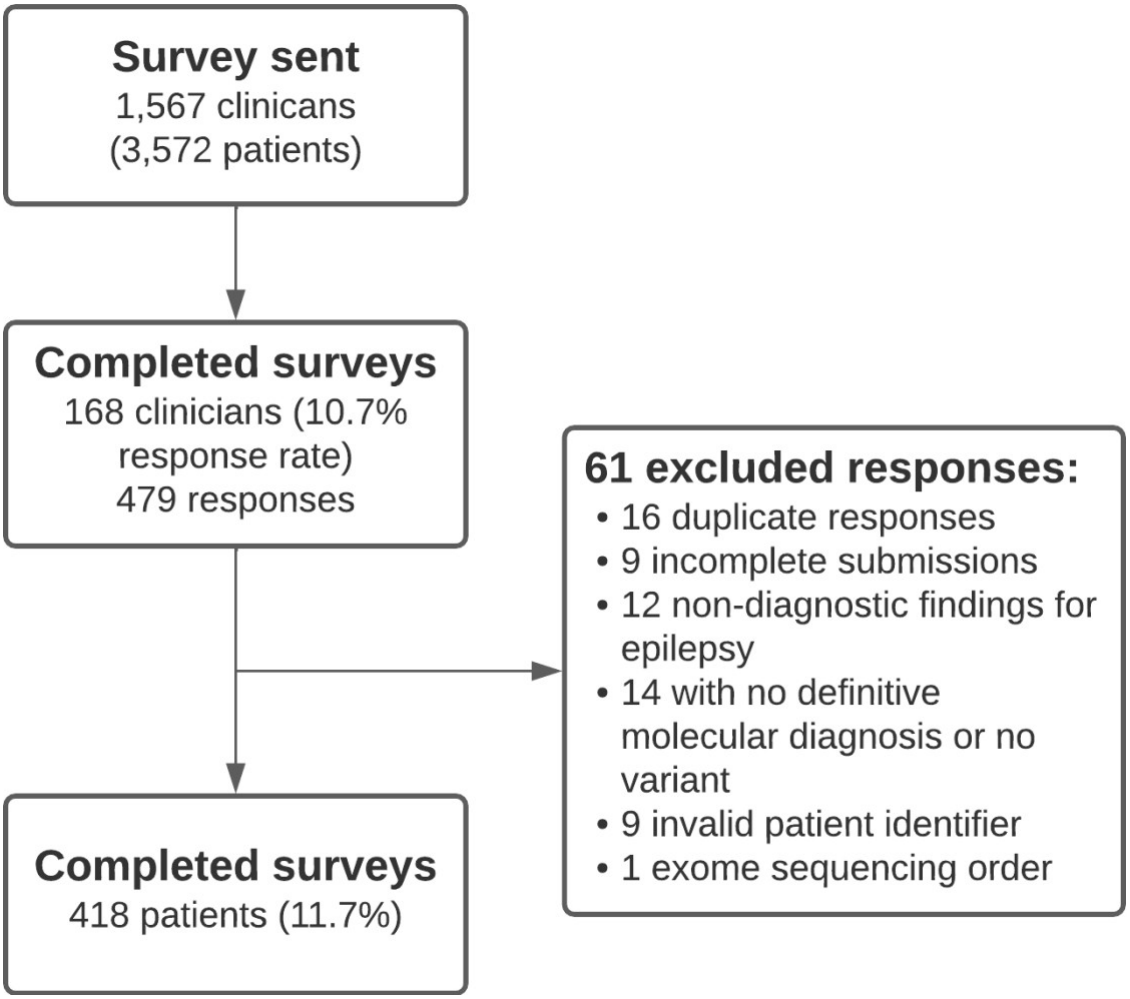
				Patient outcomes, n (% with outcomes available)		
Gene	Diagnostic finding, n	Clinical management change, n (% result)	Outcomes available, n (% changes)	Positive outcome	Negative outcome	No change
SCN1A	64	48 (75.0)	42 (87.5)	35 (83.3)	4 (9.5)	3 (7.1)
PRRT2	41	16 (39.0)	13 (81.3)	12 (92.3)	0	1 (7.7)
TSC2	14	11 (78.6)	9 (81.8)	8 (88.9)	0	1 (11.1)
KCNQ2	19	10 (52.6)	8 (80.0)	8 (100)	0	0
DEPDC5	27	10 (37.0)	8 (80.0)	7 (87.5)	0	1 (12.5)
PCDH19	15	9 (60.0)	7 (77.8)	6 (85.7)	1 (14.3)	0
STXBP1	14	7 (50.0)	7 (100)	3 (42.9)	2 (28.6)	2 (28.6)
SLC2A1	8	7 (87.5)	5 (71.4)	4 (80.0)	1 (20.0)	0
NPRL3	8	5 (62.5)	5 (100)	3 (60.0)	1 (20.0)	1 (20.0)
KCNT1	10	5 (50.0)	5 (100)	2 (40.0)	1 (20.0)	2 (40.0)
CACNA1A	8	4 (50.0)	4 (100)	3 (75.0)	0	1 (25.0)
CHD2	8	4 (50.0)	4 (100)	1 (25.0)	2 (50.0)	1 (25.0)
MECP2	16	10 (62.5)	4 (40.0)	1 (25.0)	1 (25.0)	2 (50.0)
SCN2A	9	5 (55.6)	4 (80.0)	3 (75.0)	0	1 (25.0)
SYNGAP1	10	4 (40.0)	4 (100)	2 (50.0)	1 (25.0)	1 (25.0)
ATP1A3	7	5 (71.4)	3 (60.0)	2 (66.7)	0	1 (33.3)
ALDH7A1	6	4 (66.7)	2 (50.0)	2 (100)	0	0
CDKL5	8	3 (37.5)	2 (66.7)	1 (50.0)	0	1 (50.)
GRIN2A	6	2 (33.3)	2 (100)	1 (50.0)	1 (50.0)	0
SCN1B	3	2 (66.7)	2 (100)	1 (50.0)	0	1 (50.0)
SCN8A	4	2 (50.0)	2 (100)	2 (100)	0	0
TBC1D24	4	2 (50.0)	2 (100)	2 (100)	0	0
TSC1	2	2 (100)	2 (100)	1 (50.0)	0	1 (100)
UBE3A	7	2 (28.6)	2 (100)	2 (100)	0	0
ALG13	4	2 (50.0)	1 (50.0)	0	0	1 (100)
ARHGEF9	2	1 (50.0)	1 (100)	1 (100)	0	0
ATP1A2	2	2 (100)	1 (50.0)	1 (100)	0	0
GLDC	2	1 (50.0)	1 (100)	1 (100)	0	0
GRIN1	1	1 (100)	1 (100)	1 (100)	0	0

				Patient outcomes, n (% with outcomes available)		
Gene	Diagnostic finding, n	Clinical management change, n (% result)	Outcomes available, n (% changes)	Positive outcome	Negative outcome	No change
HNRNPU	2	2 (100)	1 (50.0)	0	0	1 (100)
KCNH2	2	2 (100)	1 (50.0)	1 (100)	0	0
KCNMA1	1	1 (100)	1 (100)	0	1 (100)	0
KCNQ3	1	1 (100)	1 (100)	1 (100)	0	0
MBD5	5	1 (20.0)	1 (100)	1 (100)	0	0
POLG	1	1 (100)	1 (100)	1 (100)	0	0
PURA	1	1 (100)	1 (100)	0	0	1 (100)
RELN	1	1 (100)	1 (100)	1 (100)	0	0
SLC13A5	1	1 (100)	1 (100)	1 (100)	0	0
SLC6A1	3	1 (33.3)	1 (100)	0	0	1 (100)
SLC6A8	3	2 (66.7)	1 (50.0)	1 (100)	0	0
SPTAN1	1	1 (100)	1 (100)	0	0	1 (100)
TCF4	3	1 (33.3)	1 (100)	1 (100)	0	0
TPP1	4	3 (75.0)	1 (33.3)	1 (100)	0	0
WDR45	3	2 (66.7)	1 (50.0)	0	0	1 (100)
WWOX	1	1 (100)	1 (100)	1 (100)	0	0
ZEB2	1	1 (100)	1 (100)	1 (100)	0	0

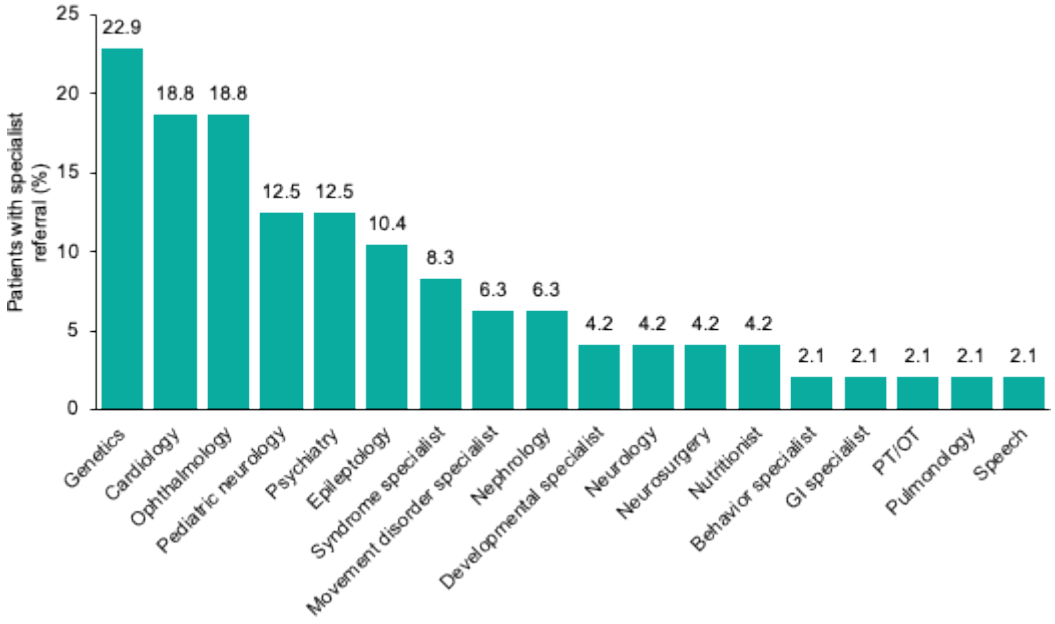
eTable 5. Summary of Treatment Changes Noted for Patients With Seizures That Resolved[a]

Number of Cases	Gene	Example of Treatment(s) Stopped	Example of Treatment(s) Started
11	*PRRT2*	GABA Modulator; Sodium valproate	Sodium Channel Blocker
8	*KCNQ2*	GABA Modulator; Sodium valproate	Sodium Channel Blocker
6	*TSC2*	None	ACTH; GABA Modulator; Sodium valproate
5	*SCN1A*	Sodium Channel Blocker	Calcium Channel Blockers; Cannabidiol; GABA Modulator; Sodium valproate; Vagal nerve stimulator
4	*DEPDC5*	None	Resection surgery; Sodium Channel Blocker
4	*MECP2*	None	None
4	*PCDH19*	GABA Modulator	Calcium Channel Blockers; GABA Modulator; Sodium Channel Blocker; Sodium valproate
3	*ALDH7A1*	GABA Modulator; Sodium Channel Blocker	Pyridoxine
3	*NPRL3*	GABA Modulator	GABA Modulator; Hemispherectomy; Sodium Channel Blockers
3	*SCN2A*	GABA Modulator; Sodium valproate	Sodium Channel Blocker
2	*CACNA1A*	None	Sodium valproate
2	*GABRG2*	None	None
2	*SCN1B*	None	None
2	*STXBP1*	None	Sodium valproate
2	*WDR45*	None	None

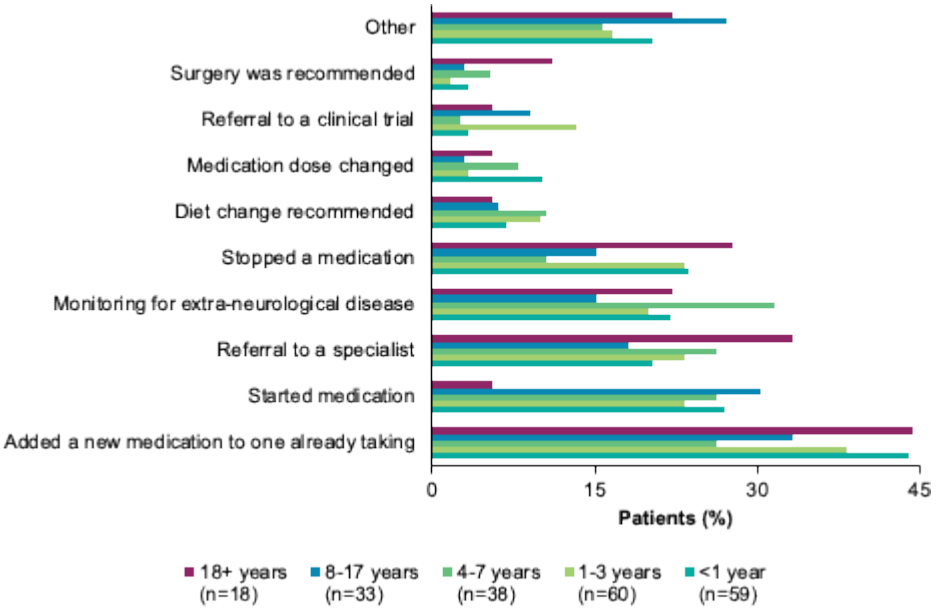
[a]Information not provided for genes with only one patient, including *ATP1A2*, *CHD2*, *GLDC*, *KCNT1*, *POLG*, *RELN*, SLC2A1, *SLC6A8*, *STX1B*, *SYNGAP1*, and *UBE3A*.



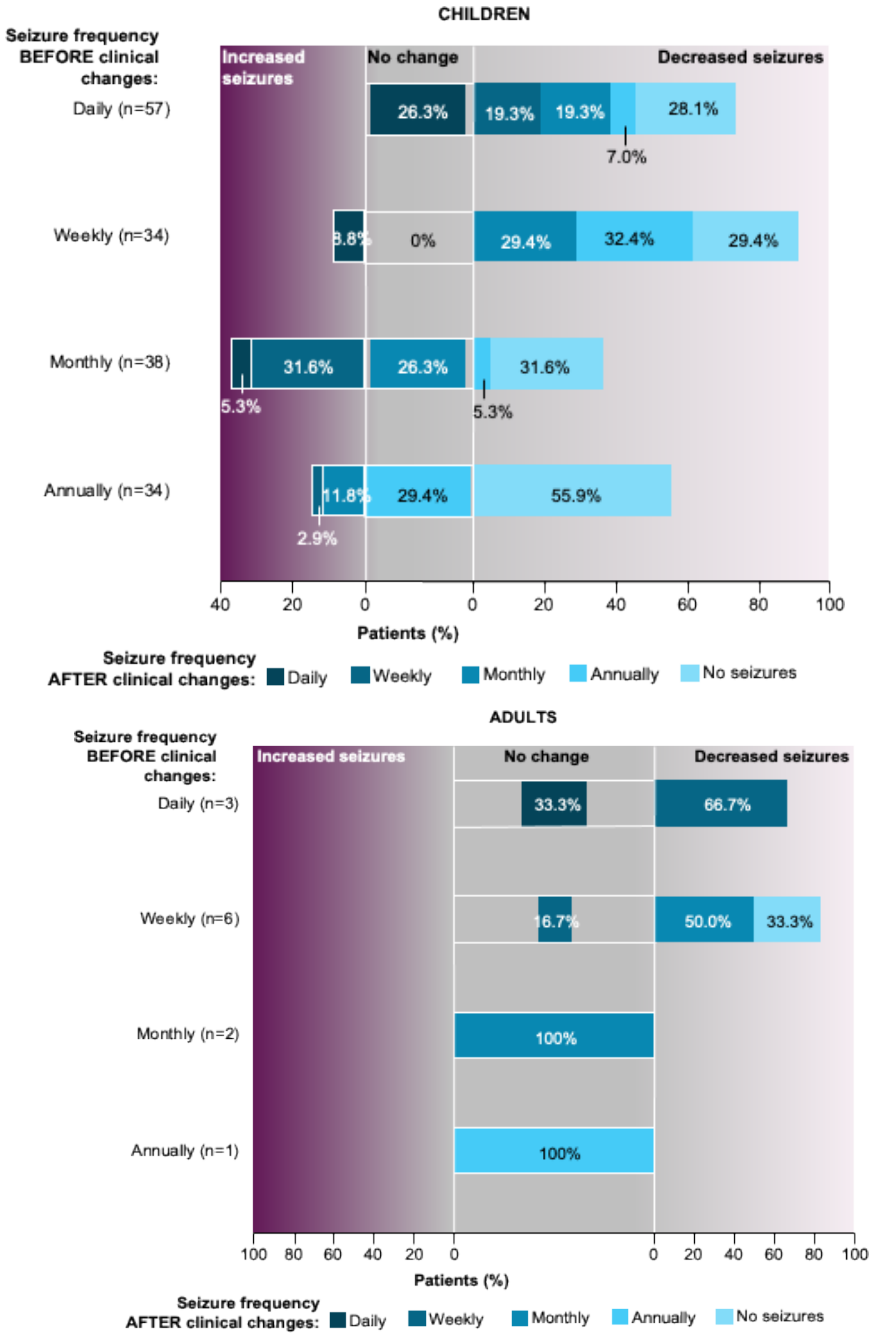
eFigure 1. Flowchart of Cohort Development Three families had more than one related participant: two families with two relatives; one family with three relatives included in the cohort.



eFigure 2. Types of Referrals to Specialists Among 48 patients with a referral to a specialist, the types of referrals are reported. Patients may have had more than one referral, and are included in each appropriate category.



eFigure 3. Clinical Management Changes by Age The percent of patients with each clinical management change after diagnostic genetic testing was calculated by age group. A patient could have more than one recommendation reported and is included in each recommendation category. The most common change for all patient age groups was to add or start a new medication. HCPs also reported referring the patient to a specialist, monitoring for extra-neurological disease, or stopping a medication in 15-30% of patients in all age groups. Less common actions included a change to diet, a medication dose change, referral to a clinical trial or recommendation for surgery.



eFigure 4. Frequency of Seizures Before and After Changes in Clinical Management in Pediatric and Adult Cohorts

Seizure frequency changes after treatment changes in children (top) and adults (bottom). Individuals were grouped by their initial reported seizure frequency (daily, weekly, monthly, annual, or no seizures) prior to genetic testing and treatment changes on the Y axis. The reported seizure frequency after treatment changes is represented on the X axis. Only individuals who had a response provided for both pre- and post-treatment were included in this analysis.