Supplementary Material
Article title: Genetic diagnosis impacts medical management in pediatric epilepsies

Table S1. Diagnostic yield by additional phenotypic features and types of epilepsy panels. Frequency of additional phenotypic features and panel type in relationship to diagnostic result of epilepsy panel and exome testing (n=602, columns 3-4) and to diagnostic exome after a non-diagnostic epilepsy panel (n=183, columns 5-6).

Phenotype	Phenotypic categories	Diagnostic panel +/- exome n (row %)	P value, Chi-square or Fisher's exact	Diagnostic exome after non-diagnostic panel n (row %)	P value, Chi-square or Fisher's exact
Total cohort		n=602[$], diagnostic in 152		n=183[$$], diagnostic in 54	
Developmental delay (if ≥ 2 y)	Yes	117 (29.7)	<0.0001	48 (34.3)	<0.0001
	No	13 (8.8)		0	
(if < 2 y)	Yes	17 (42.5)	0.4091	6 (60.0)	0.4545
	No	4 (25.0)		0	
Developmental regression (if < 3 y)	Yes, with EE	8 (40.0)	0.6265	2 (33.3)	0.6447
	Yes, independent of seizures/change in EEG	1 (33.3)		1 (100.0)	
	Yes, unknown or other setting	3 (75.0)		0	
	No	29 (39.2)		9 (50.0)	
Movement disorder by category	Choreoathetosis	7 (36.8)	0.2372	3 (37.5)	0.6953
	Dystonia (paroxysmal)	4 (26.7)	1	2 (40.0)	0.6327
	Tremors	6 (24.0)	0.8833	2 (50.0)	0.5826
	Dyskinesias	5 (50.0)	0.0693	3 (75.0)	0.0778
	Tics	1 (9.1)	0.3061	1 (25.0)	1
	Non-epileptic myoclonus	3 (30.0)	0.7187	1 (33.3)	1
	Ataxia	6 (35.3)	0.3335	3 (42.9)	0.4226
	Other	2 (50.0)	0.2656	2 (50.0)	0.5826
	None	122 (24.0)	0.1054	40 (26.5)	0.0518
Stereotypies	Yes	22 (33.3)	0.0993	10 (34.5)	0.5361
	No	128 (24.0)		44 (28.8)	
Brain malformation	Yes	17 (16.7)	0.0270	5 (23.8)	0.5466
	No	134 (27.1)		48 (30.2)	
Brain malformation by category	Polymicrogyria	1 (11.1)		1 (100.0)	
	Heterotopias	1 (14.3)		0	
	Cortical dysplasia	3 (10.3)		1 (16.7)	
	Agenesis of corpus callosum	2 (33.3)		0	
	Posterior fossa/cerebellar malformation	1 (10.0)		0	
	Complex malformation with multiple features	1 (9.1)		1 (25.0)	
	Other	8 (27.6)		2 (40.0)	
EEG encephalopathy pattern	Burst suppression	9 (52.9)	0.0187	3 (75)	0.0778
	Hypsarrhythmia (full or modified)	16 (21.9)	0.4846	8 (25)	0.5382
		61 (30.1)	0.0532	27 (36)	0.1086

	Generalized slowing with multifocal sharp waves and/or generalized epileptiform activity				
	Slow spike and wave +/- fast activity	7 (30.4)	0.5594	4 (44.4)	0.4530
	Electrical status epilepticus in sleep	2 (10.53)	0.1812	1 (16.7)	0.6719
	Other[&]	29 (30.2)	0.2225	10 (34.5)	0.5220
	None	47 (20.7)	0.0458	11 (20)	0.0645
Epilepsy age of onset $\leq$ 1 y	Yes	111 (35)	<0.0001	38 (37.6)	0.0076
	No	41 (14.5)		16 (19.5)	
Epileptic spasms	Yes	40 (25.5)	0.9389	19 (32.8)	0.5114
	No	112 (25.2)		35 (28.0)	
Refractory epilepsy	Yes	112 (26.2)	0.3775	43 (31.4)	0.4686
	No	37 (22.7)		11 (25.6)	
Status epilepticus	Yes	39 (26.9)	0.6097	13 (28.3)	0.8303
	No	112 (24.8)		41 (29.9)	
Seizure frequency at time of panel	Daily	79 (27.3)	0.7123	N/A	N/A
	Weekly	17 (20.0)			
	Monthly	14 (26.9)			
	Yearly	34 (23.9)			
	Seizure free >12 months	8 (24.2)			
Seizure frequency at time of exome	Daily	17 (41.5)	0.9466	14 (42.4)	0.9559
	Weekly	8 (38.1)		8 (44.4)	
	Monthly	3 (27.3)		3 (30.0)	
	Yearly	11 (35.5)		11 (36.7)	
	Seizure free >12 months	6 (37.5)		6 (40.0)	
Systemic malformations	Yes	13 (33.3)	0.2295	8 (47.1)	0.0957
	No	139 (24.7)		46 (27.7)	
Systemic malformation by category	Cardiac	6 (33.3)		4 (50.0)	
	Renal	2 (33.3)		1 (33.3)	
	Extremities	1 (20.0)		0	
	Other	5 (33.3)		4 (57.1)	
Neurocutaneous findings	Capillary malformations	1 (25.0)	0.5197	1 (100.0)	0.0694
	Hypopigmented macules	6 (37.5)		1 (2.05)	
	Hyperpigmented areas	11 (24.4)		6 (60.0)	
	Other	1 (8.33)		0	
	None	133 (25.4)		46 (27.9)	
Muscle tone by category	Diffuse hypotonia	55 (32.7)	<0.0001	23 (39.0)	<0.0001
	Axial hypotonia/ appendicular spasticity	34 (40.5)		19 (52.9)	
	Axial hypotonia only	4 (36.4)		1 (25.0)	
	Asymmetric increased tone	2 (16.7)		1 (25.0)	
	Dystonia, persistent	2 (40.0)		2 (50.0)	
	Mixed	2 (40.0)		0	
	Normal	53 (16.7)		8 (10.5)	
Other diagnoses contributing to epilepsy	Yes	3 (5.36)	<0.0001	0	0.1073
	No	149 (27.5)		54 (30.9)	
If other, genetic?	Yes	2 (7.7)	0.5920	0	N/A
	No	1 (3.3)		0	

Result impacted medical management	Yes No	110 (83.3) 35 (10.8)	<0.0001	30 (76.9) 21 (21.0)	<0.0001
Gene-specific family organization	Yes No	111 (87.4) 41 (66.1)	0.0005	33 (91.7) 21 (65.6)	0.0144
Types of epilepsy panels (EP)*	Comprehensive EP Infantile EP Childhood onset EP STAT EP EpiXpanded Panel Epilepsy Del/Dup Panel Adolescent EP	411 (68.3) 129 (21.4) 36 (5.9) 14 (2.3) 6 (1.0) 5 (0.8) 1 (0.2)	<0.0001	N/A	N/A
Panel yield by year of testing	2012 2013 2014 2015 2016 2017 2018	2/16 (12.5) 6/76 (7.9) 28/128 (21.9) 22/191 (11.5) 15/58 (25.9) 11/35 (31.4) 12/98 (12.2)	0.0035	N/A	N/A

[$]Numbers for cohorts with age cutoffs: ≥ 2 years = 544

[$$]Numbers for cohorts with age cutoffs: ≥ 2 years = 171

[&]Other encephalopathy patterns included discontinuity, frequent/abundant epileptiform activity contributing to encephalopathy (focal or generalized), and generalized slowing with poor organization.

*Includes diagnostic and non-diagnostic panels. Percentages are out of the total cohort (602).

Table S2. Univariate logistic regression analysis for phenotypic predictors of A) diagnostic epilepsy gene panel or exome sequencing and B) diagnostic compared to non-diagnostic exome sequencing after a non-diagnostic epilepsy gene panel. Variables with p-value of <0.25 were included in the initial multivariate regression model prior to backwards selection. Developmental delay was present in all individuals with a diagnostic exome after negative panel and thus could not be used as a predictor; GDD was used instead.

Phenotypic predictor variable	Odds ratio (95% confidence interval) for relationship with diagnostic panel or exome	P value, Wald test
A. Univariate logistic regression model for predictors of diagnostic epilepsy gene panel or exome, combined		
Age of epilepsy onset ≤ 2	4.23 (2.60, 6.90)	<0.0001
Abnormal muscle tone	2.65 (1.81, 3.89)	<0.0001
Strong family history, other than 1st degree relatives First degree family history of epilepsy Consanguinity	0.89 (0.57, 1.38) 1.26 (0.72, 2.20) 1.24 (0.64, 2.40)	0.59 0.42 0.52
Head size Microcephaly compared to normal Macrocephaly compared to normal	 1.31 (0.79, 2.18) 0.71 (0.29, 1.78)	 0.29 0.47
Epilepsy type Generalized or mixed compared to focal	 0.86 (0.58, 1.28)	 0.45
Refractory epilepsy	1.21 (0.79, 1.85)	0.38
EEG encephalopathy pattern (Y/N)	1.49 (1.01, 2.21)	0.05
Malformation of brain development (Y/N)	0.54 (0.31, 0.94)	0.03
Systemic malformations	1.52 (0.76, 3.05)	0.23
Autism spectrum disorder	0.92 (0.57, 1.49)	0.73
Developmental regression	1.15 (0.77, 1.73)	0.49
Cerebral visual impairment	1.95 (1.25, 3.05)	0.003
Dysmorphic features	1.51 (0.92, 2.50)	0.11
Sex, Male	0.97 (0.67, 1.40)	0.88
Seizure types Generalized motor Generalized non-motor Focal motor Focal non-motor	 0.94 (0.65, 1.36) 0.63 (0.39, 1.01) 2.43 (1.65, 3.59) 1.33 (0.91, 1.96)	 0.74 0.06 <0.0001 0.14
Developmental delay, global or in one area	3.86 (2.25, 6.64)	<0.0001
B. Univariate logistic regression model for predictors of diagnostic exome after a negative epilepsy gene panel		

Age of epilepsy onset ≤ 2	5.06 (2.02, 12.70)	0.0005
Abnormal muscle tone	6.41 (2.81, 14.65)	<0.0001
Strong family history, other than 1st degree relatives First degree family history of epilepsy Consanguinity	0.54 (0.24, 1.22) 1.28 (0.51, 3.21) 0.58 (0.21, 1.57)	0.14 0.61 0.28
Head size Microcephaly compared to normal Macrocephaly compared to normal	 2.65 (1.20, 5.85) 1.71 (0.47, 6.21)	 0.02 0.41
Epilepsy type Generalized or mixed compared to focal	 1.24 (0.60, 2.58)	 0.56
Refractory epilepsy	1.33 (0.61, 2.89)	0.47
EEG encephalopathy pattern (Y/N)	1.98 (0.93, 4.22)	0.08
Malformation of brain development (Y/N)	0.72 (0.25, 2.09)	0.55
Systemic malformations	2.32 (0.84, 6.38)	0.10
Autism spectrum disorder	1.11 (0.55, 2.27)	0.77
Developmental regression	1.07 (0.56, 2.06)	0.84
Cerebral visual impairment	1.98 (0.96, 4.10)	0.06
Dysmorphic features	4.48 (1.91, 10.48)	0.0005
Sex, Male	0.99 (0.52, 1.86)	0.96
Seizure types Generalized motor Generalized non-motor Focal motor Focal non-motor	 1.30 (0.68, 2.50) 0.47 (0.19, 1.15) 1.41 (0.74, 2.69) 1.46 (0.76, 2.82)	 0.43 0.10 0.29 0.25
Global developmental delay	11.48 (3.40, 38.74)	<0.0001

Table S3. Genetic information for variants identified on panel or exome that clinically explain epilepsy for 152 individuals.

Study ID	Gene	Zygosity	cDNA	Variant	Transcript ID	Medical management impact category*
B0459	*ACTB*	Het	c.1002G>C	p.Glu334Asp	NM_001101.3	C
B0411	*AGO1*	Het	c.595G>A	p.Gly199S	NM_012199.3	NR
B0249	*ALG11*	Hom	c.1402C>T	p.Arg468Cys	NM_001004127.2	C
B0257	*ALG11*	Hom	c.1402C>T	p.Arg468Cys	NM_001004127.2	C
B0500	*AP4S1*	Hom	c.295-3C>A	IVS4-3 C>A	NM_007077.4	C
B0213	*ARHGEF9*	Het	c.1285delG	p.Glu429Lysfs*19	NM_015185.2	NR
B0091	*ARX*	Hemi	c.1141G>A	p.Ala381Thr	NM_139058.2	NR
B0533	*ARX*	Hemi	c.1612A>G	p.Lys538Glu	NM_139058.2	NR
B0252	*ATP1A3*	Het	c.2219T>C	p.Lys740Pro	NM_152296.4	T
B0205	*ATP6V1A*	Het	c.1123C>A	p.Pro375Thr	NM_001690.3	C
B0241	*BRAT1*	CH	c.419T>C c.171delG	p.Leu140Pro p.Glu57Aspfs*7	NM_152743.4	C, P
B0506	*CACNA1A*	Het	c.4177G>C	p.Val1393Leu	NM_001127221.1	D
B0275	*CACNA1E*	Het	c.5159C>G	p.Ala1720Gly	NM_000721.3	NR
C0003	*CDKL5*	Het	c.1671dupA	p.Arg558Thrfs*9	NM_003159.2	T, C, P
C0005	*CDKL5*	Het	c.533G>A	p.Arg178Gln	NM_003159.2	T, C, P
C0017	*CDKL5*	Hemi	c.2152G>A	p.Val718Met	NM_003159.2	T, C, P
C0023	*CDKL5*	Het	c.1909delG	p.Ala6371Leufs*21	NM_003159.2	T, C, P
C0033	*CDKL5*	Het	c.766C>T	p.Gln256*	NM_003159.2	T, C, P
C0047	*CDKL5*	Het	c.383delA	p.Lys128Argfs*9	NM_003159.2	T, C, P
B0341	*CHAT*	CH	c.620G>A c.635T>A	p.Arg207His p.Val212Asp	NM_020549.4 NM_020549.4	C, P
B0053	*CHD2*	Het	c.2876+3_2876+6delAAGT	IVS22+3_IVS22+6del4	NM_001271.3	NR
B0131	*CHD2*	Het	c.3456-2A>G	IVS27-2A>G	NM_001271.3	NR
B0457	*CHD2*	Het	c.4706_4709delAAGA	p.Lys1569Thrfs*3	NM_001271.3	NR
B0614	*CHD2*	Het	c.4173dupA	p.Gln1392Thrfs*17	NM_001271.3	C
B0631	*CHD2*	Het	c.4893_4905del13	p.His1631Glnfs*179	NM_001271.3	C
B0279	*CHRNA7*	Het	n/a	15q13.3del, incl, at least exons 1-4 of *CHRNA7*	NM_000746.5	NR
B0420	*CNTNAP2*	CH	n/a c.1739G>A	Partial gene deletion including exons 4-6 p.Cys580Tyr	NM_014141.5 NM_014141.5	C
B0295	*COL4A1*	Het	c.943C>T	p.Arg315Cys	NM_001845.4	C
B0659	*DLL1*	Het	c.2048+2T>C	IVS9+2 T>C	NM_005618.3	NR
B0102	*DYNC1H1*	Het	c.1103G>C	p.Arg368Pro	NM_001376.4	C

B0499	*DYNC1H1*	Het	c.3606C>G	p.Phe1202Leu	NM_001376.4	C
B0686	*DYNC1H1*	Het	c.5864G>T	p.Gly1955Val	NM_001376.4	C
B0639	*EEF1A2*	Het	c.1375_1383delCAGAAGGCG	p.Gln459_Ala461del	NM_001958.3	NR
B0049	*ERCC5*	Hom	c.205C>T	p.Arg69*	NM_000123	NR
B0310	*FOXG1*	Het	c.460G>T	p.Glu154*	NM_001165963.1	U
B0200	*FRRS1L*	Hom	c.737_739delGAG	p.Gly246del	NM_014334.2	T
B0437	*FRRS1L*	Hom	c.737_739delGAG	p.Gly246del	NM_014334.2	NR
B0111	*GABRB2*	Het	c.755C>T	p.Pro252Leu	NM_021911.2	NR
B0272	*GABRG2*	Het	c.1000G>A	p.Ala334Thr	NM_000816.3	NR
B0294	*GNAO1*	Het	c.119G>A	p.Gly40Glu	NM_020988.2	C, D
B0044	*GRIN2A*	Het	c.1930A>G	p.Ser644Gly	NM_000833.3	T
B0426	*GRIN2A*	Het	c.2140delG	p.Glu714Argfs*7	NM_000833.3	T
B0460	*GRIN2A*	Het	c.165C>A	p.Trp55*	NM_000833.3	NR
B0206	*HNRNPU*	Het	c.1681C>T	p.Gln561*	NM_031844.2	NR
B0464	*HNRNPU*	Het	c.2014delG	p.Glu672Lysfs*162	NM_031844.2	NR
B0169	*IFIH1*	Het	c.2336G>A	p.Arg779His	NM_022168.4	C
B0178	*IQSEC2*	Het	c.2911C>T	p.Arg971*	NM_001111125.1	NR
B0126	*ITPA*	Hom	c.452G>A	p.Trp151*	NM_033453.3	NR
B0419	*KANSL1*	Het	c.1651dupA	p.Thr551Asnfs*13	NM_001193466.1	C
B0463	*KANSL1*	Het	n/a	17q21.31del, incl. *KANSL1*	NM_001193466.1	C
B0030	*KCNH1*	Het	c.1474G>A	p.Ala492Thr	NM_172362.2	C
B0482	*KCNMA1*	Het	c.1918C>T	p.Arg640*	NM_002247.3	C
B0038	*KCNQ2*	Het	c.1742G>A	p.Arg581Gln	NM_172107.2	T
B0041	*KCNQ2*	Het	c.1742G>A	p.Arg581Gln	NM_172707.2	T, P
B0085	*KCNQ2*	Het	n/a	partial deletion including exons 11-13	NM_172107.2	P
B0128	*KCNQ2*	Het	c.583T>C	p.Ser195Pro	NM_172107.2	T, C
B0150	*KCNQ2*	Het	c.638G>A	p.Arg213Gln	NM_172107.2	T
B0180	*KCNQ2*	Het	c.915C>A	p.Phe305Leu	NM_172107.2	T, P
B0350	*KCNQ2*	Het	c.286dupC	p.His96Profs*24	NM_172107.2	P
B0352	*KCNQ2*	Het	c.902G>T	p.Gly301Val	NM_172107.2	T
B0444	*KCNQ2*	Het	c.740C>T	p.Ser247Leu	NM_172107.2	T
B0564	*KCNQ2*	Het	c.927+1G>A	IVS6+1 G>A	NM_172107.2	U
B0634	*KCNQ2*	Het	c.1709delA	p.Gln570Argfs*50	NM_172107.2	T, C, P
B0651	*KCNQ2*	Het	c.842G>A	p.Gly281Glu	NM_172107.2	T, C, P
B0145	*KCNT1*	Het	c.2688G>C	p.Met896Ile	NM_020822.2	T, C
B0701	*KCNT1*	Het	c.1283G>A	p.Arg428Gln	NM_020822.2	T
B0031	*MECP2*	Het	c.275delG	p.Gly92Aspfs*33	NM_004992.3	C, P
B0243	*MECP2*	Het	c.502C>T	p.Arg168*	NM_004992.3	C

B0697	*MEF2C*	Het	c.44G>A	p.Arg15His	NM_002397.3	T
B0159	*NBEA*	Het	c.4702dupG	p.Val1568Glyfs*14	NM_015678.4	NR
B0487	*NEXMIF*	Het	c.937C>T	p.Arg313*	NM_001008537.1	NR
B0537	*NEXMIF*	Het	c.1493C>A	p.Ser498*	NM_001008537.1	U
B0542	*NHLRC1* *NHLRC1*	CH	c.656G>A c.451G>T	p.Trp219* p.Val151Phe	NM_198586.2	T, C, P
B0055	*NPRL2*	Het	c.57_59delGGGinsCG	p.Gly20Aspfs*45	NM_006545.4	NR
B0046	*NRXN1* *NRXN2*	CH	c.2686C>T c.3176G>A	p.Arg896Trp p.Arg1059Gln	NM_0011335639.1 NM_0011335639.1	NR
B0443	*NRXN1*	Het	n/a	partial deletion including exons 7-10	NM_001135659.1	NR
B0333	*PACS2*	Het	c.625G>A	p.Glu209Lys	NM_001100913.2	U
B0694	*PACS2*	Het	c.631G>A	p.Glu211Lys	NM_001100913.2	P
B0261	*PCDH19*	Het	c.2113C>T	p.Arg705*	NM_001105243.1	C, P
B0307	*PCDH19*	Het	c.695A>G	p.Asn232Ser	NM_001105243.1	T, C
B0217	*PLPBP*	Hom	c.347C>T	p.Thr116Ile	NM_007198.3	T
B0029	*PNPO*	Hom	c.674G>T	p.Arg225Leu	NM_018129.3	T
B0095	*PNPO*	Hom	c.686G>A	p.Arg229Gln	NM_018129.3	T
B0271	*PNPO*	Hom	c.674G>T	p.Arg225Leu	NM_018129.3	T
B0028	*POLG*	CH	c.2800_2801delAA c.3286C>T	p.Lys934Aspfs*10 p.Arg1096Cys	NM_002693.2 NM_002693.2	T, C, P
B0625	*POLG*	CH	c.2243G>C c.3356T>C	p.Trp748Ser p.Leu1119Pro	NM_002693.2 NM_002693.2	T, C, P
B0051	*PRRT2*	Het	c.649dupC	p.Arg217Profs*8	NM_145239.2	C, P
B0065	*PRRT2*	Het	c.649dupC	p.Arg217Profs*8	NM_145239.2	T, C, P
B0067	*PRRT2*	Het	n/a	whole gene deletion	NM_145239.2	T, C, P
B0328	*PRRT2*	Het	c.649dupC	p.Arg217Profs*8	NM_145239.2	C, P
B0434	*PRRT2*	Het	c.629dupC	p.Ala211Serfs*14	NM_145239.2	T, C, P
B0441	*PRRT2*	Het	c.649dupC	p.Arg217Profs*8	NM_145239.2	C, P
B0558	*PRRT2*	Het	c.649delC	p.Arg217Glufs*12	NM_145239.2	T, C, P
B0658	*PRRT2*	Het	c.649dupC	p.Arg217Profs*8	NM_145239.2	T, C
B0278	*RHOBTB2*	Het	c.1448G>A	p.Arg483His	NM_001160036.1	NR
B0068	*SCN1A*	Het	c.2589+3A>T	IVS14+3A>T	NM_001165963.1	T, P
B0069	*SCN1A*	Het	c.986G>T	p.Gly329Val	NM_001165963.1	T, C, P
B0072	*SCN1A*	Het	c.662T>C	p.Leu221Pro	NM_001165963.1	T, C, P
B0079	*SCN1A*	Het	n/a	partial deletion including exon 21	NM_006920.4	T
B0086	*SCN1A*	Het	c.4573C>T	p.Arg1525*	NM_001165963.1	T
B0225	*SCN1A*	Het	c.418A>G	p.Thr140Ala	NM_001165963.1	T
B0226	*SCN1A*	Het	c.2134C>T	p.Arg712*	NM_001165963.1	T
B0175	*SCN1A*	Het	c.4318delG	p.Ala1440Glnfs*36	NM_001165963.1	U

B0304	*SCN1A*	Het	c.1837C>T	p.Arg613*	NM_001165963.1	T, P
B0306	*SCN1A*	Het	c.4786C>T	p.Arg1596Cys	NM_001165963.1	T, C, P
B0312	*SCN1A*	Het	c.5375C>A	p.Ala1792Asp	NM_001165963.1	T, C, P
B0405	*SCN1A*	Het	c.5000T>C	p.Leu1667Pro	NM_001165963.1	T
B0408	*SCN1A*	Het	c.332T>A	p.Leu111*	NM_001165963.1	T
B0525	*SCN1A*	Het	c.2589+2T>C	IVS14+2 T>C	NM_001165963.1	T
B0584	*SCN1A*	Het	c.825T>A	p.Asn275Lys	NM_001165963.1	T, C, P
B0552	*SCN1A*	Het	c.5299delG	p.Val1767Serfs*12	NM_001165963.1	T, C
B0644	*SCN1A*	Het	c.235G>A	p.Asp79Asn	NM_001165963.1	T, C
B0688	*SCN1A*	Het	c.2979_2992del14	p.Ser993Argfs*7	NM_001165963.1	T, C, P
B0698	*SCN1A*	Het	c.2837G>A	p.Arg946His	NM_001165963.1	T, C, P
B0451	*SCN1B*	Hom	c.449-2A>G	IVS3-2 A>G	NM_001037.4	T, C
B0076	*SCN2A*	Het	c.5645G>A	p.Arg1882Gln	NM_021007.2	T, C, P
B0017	*SCN2A*	Het	c.3947C>T	p.Ala1316Val	NM_021007.2	T
B0220	*SCN2A*	Het	c.1301C>A	p.Ala434Asp	NM_021007.2	T
B0008	*SCN2A*	Het	c.2809C>T	p.Arg937Cys	NM_021007.2	T, C
B0345	*SCN2A*	Het	c.643G>C	p.Ala215Pro	NM_021007.2	T
B0620	*SCN2A*	Het	c.4418T>C	p.Ile1473Thr	NM_021007.2	T
B0526	*SCN2A*	Het	c.3149A>G	p.Asp1050Gly	NM_021007.2	NR
B0127	*SCN8A*	Het	c.1228G>C	p.Val410Leu	NM_014191.3	NR
B0168	*SCN8A*	Het	c.5614C>T	p.Arg1872Trp	NM_014191.3	U
B0317	*SCN8A*	Het	c.2525T>A	p.Val842Glu	NM_014191.3	T
B0452	*SCN8A*	Het	c.4873G>T	p.Gly1625Trp	NM_014191.3	T, C, P
B0034	*SEPSECS*	Hom	c.176C>T	p.Ala59Val	NM_016955.3	P
B0386	*SHANK3*	Het	c.3997dupG	p.Val1333Glyfs*28	NM_033517.1	C
B0101	*SLC12A5*	Hom	c.983A>G	p.Asn328Ser	NM_020708.4	T, C
B0212	*SLC2A1*	Hom	c.79G>A	p.Gly27Ser	NM_006516.2	T, C
B0585	*SLC2A1*	Het	c.493G>A	p.Val165Ile	NM_006516.2	T, C
B0048	*SPTAN1*	Het	c.6922C>T	p.Arg2308Cys	NM_001130438.2	NR
B0092	*STXBP1*	Het	c.703C>T	p.Arg235X	NM_003165.3	NR
B0125	*STXBP1*	Het	c.430-1G>T	IVS6-1G>T	NM_003165.2	C
B0518	*STXBP1*	Het	c.1708A>G	p.Thr570Ala	NM_003165.3	U
B0702	*STXBP1*	Het	c.525delG	p.Ile176Serfs*8	NM_003165.3	C
B0448	*SYNGAP1*	Het	c.915_933del19	p.Val306Serfs*35	NM_006772.2	NR
B0503	*TBL1XR1*	Het	c.1108G>A	p.Asp370Asn	NM_024665.4	NR
B0039	*TPP1*	CH	c.1093T>C c.1600C>T	p.Cys365Arg p.Gln534*	NM_000391.3 NM_000391.3	T, C, P
B0484	*TRIM8*	Het	c.1380T>G	p.Tyr460*	NM_030912.2	C
B0078	*TSC2*	Het	c.2410T>C	p.Cys804Arg	NM_000548.3	U

B0251	*TSC2*	Het	c.4747G>A	p.Glu1583Lys	NM_000548.3	C
B0556	*TSC2*	Het	c.3693_3696delGTCT	p.Ser1232Thrfs*92	NM_000548.3	T, C
B0615	*TSC2*	Het	c.2714G>A	p.Arg905Gln	NM_000548.3	T, C
B0557	*TUBB2A*	Het	c.743C>T	p.Ala248Val	NM_001069.2	C
B0610	*UBE3A*	N/A	N/A	15q11.2-q13.3 amplification including *UBE3A* on maternal chromosome	NM_130839.1	NR
B0024	*UPF3B*	Hemi	c.159delGGinsTAC	p.Val54Thrfs*2	NM_080632.2	NR
B0142	*WDR45*	Het	c.700C>T	p.3052delThr	NM_007075	P
B0404	*WDR45*	Hemi	c.752_754delCCT	p.Ser251del	NM_007075.3	T, P
B0536	*WDR73*	Hom	c.750_751delTT	p.Cys251Serfs*3	NM_032856.3	C
B0100	*ZEB2*	Het	c.289delT	p.Trp97GlyfsX11	NM_014795.3	C
B0108	*ZEB2*	Het	c.904C>T	p.Arg302*	NM_014795.3	C

*T = treatment, C = care coordination, P = prognosis, D = correction of diagnosis, U = unknown, NR = None recorded

Abbreviations: CH = compound heterozygous, D = change in diagnosis, Hemi = hemizygous, Het = heterozygous, Hom = homozygous, N/A = not applicable

Table S4. Detailed information on medical impact of genetic diagnosis for 152 individuals.

Study ID	Affected gene(s)	Zygosity	Medical management impact category*	Additional details on medical impact by category
B0459	*ACTB*	Het	C	Recommended echocardiogram and referred to cardiology
B0411	*AGO1*	Het	NR	
B0249	*ALG11*	Hom	C	Monitoring for medical issues associated with congenital disorders of glycosylation
B0257	*ALG11*	Hom	C	Monitoring for medical issues associated with congenital disorders of glycosylation
B0500	*AP4S1*	Hom	C	Recommended multidisciplinary care by ophthalmology, nutrition, orthopedics, and neurology
B0213	*ARHGEF9*	Het	NR	
B0091	*ARX*	Hemi	NR	
B0533	*ARX*	Hemi	NR	
B0252	*ATP1A3*	Het	T	Affected ASM management and movement disorder treatment – clobazam considered given dual improvement in seizures and movement disorders
B0205	*ATP6V1A*	Het	C	Recommended ophthalmology evaluation due to oculomotor apraxia and counseled on issues associated with amelogenesis imperfecta
B0241	*BRAT1*	CH	C, P	C: Counseled on risk of respiratory complications and refractory epilepsy P: Counseled on early lethality associated with compound heterozygous variants, individual was deceased at age 2 years
B0506	*CACNA1A*	Het	D	Mitochondrial disease was suspected, diagnosis changed after genetic testing
B0275	*CACNA1E*	Het	NR	Individual was deceased prior to genetic diagnosis
C0003	*CDKL5*	Het	T, C, P	T: Affected approach to ASM management, with a period off of medication due to highly refractory nature of disorder and serious side effects. Discussed ganaxolone trial. C: Followed in disease-specific multidisciplinary CDD clinic, followed in orthopedics due to scoliosis and neuro-ophthalmology due to CVI, recommended EKG P: Discussed phenotype and poor prognosis of CDD, including risk of early death
C0005	*CDKL5*	Het	C, P	C: Followed in disease-specific multidisciplinary CDD clinic, referred to behavioral neurology, neuro-ophthalmology, and sleep clinic P: Discussed phenotype and poor prognosis of CDD, including risk of early death
C0017	*CDKL5*	Hemi	T, C, P	T: Discussed clinical trial options with family C: Followed in disease-specific multidisciplinary CDD clinic, referred to orthopedics and neuro-ophthalmology, recommended yearly EKG P: Discussed phenotype and poor prognosis of CDD, including risk of early death
C0023	*CDKL5*	Het	T, C, P	T: Discussed clinical trial options with family C: Followed in disease-specific multidisciplinary CDD clinic, referral to orthopedics and sleep clinic, also followed in neuro-ophthalmology and behavioral neurology

				P: Discussed phenotype and prognosis of CDD, including risk of early death
C0033	*CDKL5*	Het	T, C, P	T: Affected ASM management - prescribed cannabidiol (Epidiolex) C: Followed in disease-specific multidisciplinary CDD clinic, referral to neuro-ophthalmology and augmentative communication program, recommended EKG P: Discussed phenotype and prognosis of CDD, including risk of early death
C0047	*CDKL5*	Het	T, C, P	T: Affected ASM management – prescribed cannabidiol (Epidiolex), clinical trial options discussed with family C: Followed in disease-specific multidisciplinary CDD clinic, recommended yearly EKG P: Discussed phenotype and prognosis of CDD, including risk of early death
B0341	*CHAT*	CH	C, P	C: Management related to congenital myasthenic syndrome (e.g. recommended respiratory evaluation). Epilepsy was secondary to hypoxic-ischemic events due to apneas. P: Counseled on prognosis
B0053	*CHD2*	Het	NR	
B0131	*CHD2*	Het	NR	
B0457	*CHD2*	Het	NR	
B0614	*CHD2*	Het	C	Monitored for autism and counseled regarding potential developmental issues
B0631	*CHD2*	Het	C	C: Counseled on range of outcomes including developmental disorders
B0279	*CHRNA7*	Het	NR	
B0420	*CNTNAP2*	CH	C	C: Monitored for autism spectrum disorder and developmental regression
B0295	*COL4A1*	Het	C	C: Screening for renal tubulopathy, referral to cardiology and ophthalmology
B0659	*DLL1*	Het	NR	
B0102	*DYNC1H1*	Het	C	Discussed referral for neuromuscular evaluation
B0499	*DYNC1H1*	Het	C	Referred to neuromuscular clinic due to risk of neuromuscular abnormalities
B0686	*DYNC1H1*	Het	C	Referred to neuromuscular clinic
B0639	*EEF1A2*	Het	NR	
B0049	*ERCC5*	Hom	NR	
B0310	*FOXG1*	Het	U	Individual was not followed after genetic results
B0200	*FRRS1L*	Hom	T	Potential impact on ASM choice – clobazam is potentially helpful, perampanel should be avoided
B0437	*FRRS1L*	Hom	NR	
B0111	*GABRB2*	Het	NR	Individual was deceased prior to genetic results
B0272	*GABRG2*	Het	NR	
B0294	*GNAO1*	Het	C, D	C: Monitoring for movement disorder D: Primary mitochondrial disease was the presumptive diagnosis for many years, diagnosis changed after genetic testing
B0044	*GRIN2A*	Het	T	Treated with dextromethorphan and memantine, memantine having meaningful benefit
B0426	*GRIN2A*	Het	T	Affected ASM management – avoided felbamate and perampanel
B0460	*GRIN2A*	Het	NR	
B0206	*HNRNPU*	Het	NR	
B0464	*HNRNPU*	Het	NR	

B0169	*IFIH1*	Het	C	Referral to neuroimmunology and rheumatology
B0178	*IQSEC2*	Het	NR	
B0126	*ITPA*	Hom	NR	Individual was deceased prior to genetic results
B0419	*KANSL1*	Het	C	C: Recommended renal ultrasound and orthopedics evaluation
B0463	*KANSL1*	Het	C	Recommended renal ultrasound, ophthalmology evaluation and cardiology evaluation
B0030	*KCNH1*	Het	C	Requested EKG due to potential for cardiac complications
B0482	*KCNMA1*	Het	C	Genetic diagnosis contributed to surgical decision-making, leading to corpus callosotomy
B0038	*KCNQ2*	Het	T	Discussed that individuals are often responsive to phenobarbital
B0041	*KCNQ2*	Het	T, P	T: Added oxcarbazepine with good seizure control, eventually individual was seizure free and weaned off medications P: Discussed that diagnosis and clinical course is associated with good prognosis
B0085	*KCNQ2*	Het	P	Discussed optimistic prognosis
B0128	*KCNQ2*	Het	T, C	T: Treated with ezogabine C: Referral to neuromuscular program and neuropsychology
B0150	*KCNQ2*	Het	T	Treated with ezogabine
B0180	*KCNQ2*	Het	T, P	T: Considered treatment with ezogabine P: Counseled on prognosis
B0350	*KCNQ2*	Het	P	P: Counseled on benign prognosis
B0352	*KCNQ2*	Het	T	Affected ASM management – considered treatment with sodium channel blockers, as well as vigabatrin, clobazam, lamotrigine and phenytoin
B0444	*KCNQ2*	Het	T	Affected ASM management, with use of sodium channel blockers and consideration of ezogabine
B0564	*KCNQ2*	Het	U	Individual was not followed after genetic results
B0634	*KCNQ2*	Het	T, C, P	T: Carbamazepine considered as potential ASM choice C: Monitored development and seizures P: Counseled on range of outcomes including persistent seizures and developmental learning problems
B0651	*KCNQ2*	Het	T, C, P	T: Affected ASM management – phenytoin and carbamazepine are particularly beneficial, individual was later treated with ezogabine C: Annual EKG recommended P: Counseled on elevated risk for SUDEP
B0145	*KCNT1*	Het	T, C	T: Considered treatment with quinidine, off-label use based on pathway C: Referral to cardiology due to risk of cardiac arrhythmias
B0701	*KCNT1*	Het	T	Off-label treatment with quinidine, potentially useful due to inhibition of sodium-activated potassium channels
B0031	*MECP2*	Het	C, P	C: Referred to other specialists for management of Rett syndrome P: Discussed the phenotype and prognosis of Rett syndrome
B0243	*MECP2*	Het	C	Referred to disease-specific multidisciplinary clinic for Rett syndrome
B0697	*MEF2C*	Het	T	T: Affected ASM management – treated with valproic acid
B0159	*NBEA*	Het	NR	
B0487	*NEXMIF*	Het	NR	
B0537	*NEXMIF*	Het	U	Individual was not followed after genetic results
B0542	*NHLRC1*	CH	T, C, P	T: Treated with perampanel for seizures based on case reports of Lafora disease, discussed upcoming clinical trials with family C: Coordinated care across multiple specialties

				P: Counseled on poor prognosis in this progressive neurodegenerative disorder
B0055	*NPRL2*	Het	NR	
B0046	*NRXN1* *NRXN2*	CH	NR	Individual was deceased prior to genetic results
B0443	*NRXN1*	Het	NR	
B0333	*PACS2*	Het	U	Individual was not followed after genetic results
B0694	*PACS2*	Het	P	Counseled on optimistic prognosis
B0261	*PCDH19*	Het	C, P	C: Monitoring for cognitive and behavioral concerns P: Discussed phenotype and prognosis of individuals with *PCDH19* variants
B0307	*PCDH19*	Het	T, C	T: Affected ASM management – treated with lamotrigine, considered valproic acid, considered clinical trial options (ganaxolone) C: Monitored for behavioral or learning difficulties
B0217	*PLPBP*	Hom	T	Supplementation with pyridoxine
B0029	*PNPO*	Hom	T	Treated with pyridoxal-5'-phosphate (P5P)
B0095	*PNPO*	Hom	T	Supplementation with pyridoxal-5'-phosphate
B0271	*PNPO*	Hom	T	Treatment with pyridoxal-5'-phosphate is specific to diagnosis
B0028	*POLG*	CH	T, C, P	T: Started on mitochondrial cocktail C: Monitored for progressive liver failure P: Counseled on prognosis, characterized by progressive neurological symptoms and liver failure. Individual was later deceased.
B0625	*POLG*	CH	T, C, P	T: Affected ASM management – avoided treatment with valproic acid C: Monitored for hepatic complications and developmental regression, referred to ophthalmology and neuro-metabolism P: Discussed phenotype and prognosis for individuals with *POLG* variants
B0051	*PRRT2*	Het	C, P	C: Monitored for movement disorders such as PKD P: Discussed optimistic prognosis (benign familial infantile seizures)
B0065	*PRRT2*	Het	T, C, P	T: Discussed that in case of PKD, response to carbamazepine or oxcarbazepine is favorable C: Recommended neuropsychological evaluation P: Discussed optimistic prognosis
B0067	*PRRT2*	Het	T, C, P	T: Discussed treatment with oxcarbazepine or carbamazepine in case of PKD C: Recommended spine films due to the risk of vertebral defects and echocardiogram due to risk of congenital heart disease P: Discussed optimistic prognosis
B0328	*PRRT2*	Het	C, P	C: Counseled/monitored for choreoathetosis P: Counseled on positive prognosis
B0434	*PRRT2*	Het	T, C, P	T: Discussed potential effect on ASM management – oxcarbazepine and carbamazepine have been shown to improve seizures C: Monitored for movement disorders and migraine P: Counseled on overall favorable prognosis
B0441	*PRRT2*	Het	C, P	C: Referred to movement disorder specialist P: Counseled on overall favorable prognosis
B0558	*PRRT2*	Het	T, C, P	T: Affected ASM management, treated with oxcarbazepine with excellent response

				C: Referred to early intervention and monitored for movement disorder P: Counseled on optimistic prognosis
B0658	*PRRT2*	Het	T, C	T: Affected ASM management – treated with oxcarbazepine C: Monitored for movement disorder
B0278	*RHOBTB2*	Het	NR	
B0068	*SCN1A*	Het	T, P	T: Discussed treatment with fenfluramine when in trial stage and initiated treatment once medication was approved for Dravet syndrome P: Discussed higher risk of SUDEP
B0069	*SCN1A*	Het	T, C, P	T: Affected ASM management, counseled against using lamotrigine and other sodium channel medications, suggested valproic acid, clobazam and levetiracetam as possible treatment options C: Suggested EKG and neuropsychological testing P: Discussed risk of cardiac arrhythmias and SUDEP
B0072	*SCN1A*	Het	T, C, P	T: Recommended use of seizure medications effective for Dravet syndrome C: Diagnosis influenced coordination of care with epilepsy surgical team P: Discussed increased risk of SUDEP
B0079	*SCN1A*	Het	T	Participated in fenfluramine open-label trial
B0086	*SCN1A*	Het	T	Considered treatment with cannibidiol (Epidiolex), fenfluramine and ASO trial
B0175	*SCN1A*	Het	U	Followed at another site
B0225	*SCN1A*	Het	T	Affected ASM management - weaned lamotrigine given individual's genetic variant
B0226	*SCN1A*	Het	T	Treated with ASMs known to be helpful in Dravet syndrome, discussed clinical trial with Ataluren
B0304	*SCN1A*	Het	T, P	T: Affected ASM management – treated with levetiracetam, considered clobazam and valproic acid, counseled on avoidance of sodium channel blockers P: Counseled on increased risk of SUDEP
B0306	*SCN1A*	Het	T, C, P	T: Affected ASM management – avoided sodium channel blockers, considered clobazam C: Monitored for possible arrhythmias P: Counseled on increased risk of SUDEP
B0312	*SCN1A*	Het	T, C, P	T: Affected ASM management, considered treatment with clobazam and topiramate C: Referred to cardiology P: Counseled on increased risk of SUDEP
B0405	*SCN1A*	Het	T	Affected ASM management – treated with valproic acid and topiramate
B0408	*SCN1A*	Het	T	Affected ASM management – treated with valproic acid
B0525	*SCN1A*	Het	T	Affected ASM management with avoidance of sodium channel medications
B0552	*SCN1A*	Het	T, C	T: Affected ASM management with avoidance of sodium channel blockers; considered fenfluramine trial C: Impact on surgical decision-making for epilepsy as the family was considering corpus callosotomy
B0584	*SCN1A*	Het	T, C, P	T: Affected ASM management - avoidance of sodium channel medications C: Monitoring for developmental delay P: Counseled on risk of SUDEP and likelihood of continued seizures

B0644	*SCN1A*	Het	T, C	T: Affected ASM management – removed oxcarbazepine, treated with levetiracetam, considered clobazam and valproic acid, counseled against the use of phenytoin and carbamazepine C: Monitored for developmental issues and regression
B0688	*SCN1A*	Het	T, C, P	T: Affected ASM management with initiation of clobazam, discussed fenfluramine trial C: Referred to cardiology P: Counseled on increased risk of SUDEP
B0698	*SCN1A*	Het	T, C, P	T: Affected ASM management - prescribed cannabidiol (Epidiolex) and considered fenfluramine, also treated with ketogenic diet C: Recommended cardiology evaluation P: Counseled on increased risk of SUDEP
B0451	*SCN1B*	Hom	T, C	T: Affected ASM management, with avoidance of sodium channel blockers and consideration of ketogenic diet C: Recommended EKG and cardiology evaluation due to association with Brugada syndrome, prolonged QT syndrome and other arrhythmias
B0008	*SCN2A*	Het	T, C	T: Avoided treatment with sodium channel blockers C: Suggested EKG to detect possible rhythm abnormalities
B0017	*SCN2A*	Het	T	Considered medications with evidence of effectiveness such as phenytoin, phenobarbital, lamotrigine and topiramate
B0076	*SCN2A*	Het	T, C, P	T: Treated with phenytoin, triheptanoin as part of small trial, and riluzole off-label C: Monitoring for movement disorder P: Counseled on the phenotype associated with *SCN2A* variant and prognosis over time
B0220	*SCN2A*	Het	T	Affected ASM management - sodium channel blockers known to be helpful
B0345	*SCN2A*	Het	T	Affected ASM management – treated with oxcarbazepine
B0526	*SCN2A*	Het	NR	
B0620	*SCN2A*	Het	T	Affected ASM management – used sodium channel blockers
B0127	*SCN8A*	Het	NR	
B0168	*SCN8A*	Het	U	Individual was not followed after genetic results
B0317	*SCN8A*	Het	T	Affected ASM management - treated with lacosamide with excellent response
B0452	*SCN8A*	Het	T, C, P	T: Affected ASM management – treated with sodium channel blockers C: Referred to ophthalmology, counseled on movement disorder, monitored for other complications (gastrointestinal issues, autonomic dysfunction, hearing loss, scoliosis) P: Counseled on increased risk of SUDEP
B0034	*SEPSECS*	Hom	P	Counseled on prognosis in this progressive disorder
B0386	*SHANK3*	Het	C	C: Recommended cardiac screening, renal ultrasound, ophthalmological exams and dental exams
B0101	*SLC12A5*	Hom	T, C	T: Discussed ASMs with better evidence for seizure control, including potassium bromide, levetiracetam, rufinamide, stiripentol, clonazepam, and cannabinoids. C: Recommended screening for scoliosis and feeding/speech therapy
B0212	*SLC2A1*	Hom	T, C	T: Treated with ketogenic diet, a specific treatment for this disorder

				C: Management of hemiplegic migraine associated with this disorder, including imaging recommendations. Monitoring for movement disorders.
B0585	*SLC2A1*	Het	T, C	T: Treated with ketogenic diet C: Monitored for movement disorder
B0048	*SPTAN1*	Het	NR	
B0092	*STXBP1*	Het	NR	
B0125	*STXBP1*	Het	C	Monitoring for movement disorder
B0518	*STXBP1*	Het	U	
B0702	*STXBP1*	Het	C	Monitored for developmental delay and ASD
B0448	*SYNGAP1*	Het	NR	
B0503	*TBL1XR1*	Het	NR	
B0039	*TPP1*	CH	T, C, P	T: Discussed that carbamazepine, phenytoin and lamotrigine may exacerbate seizures and myoclonus C: Recommended ophthalmologic evaluation and tissue biopsy P: Counseled on the possibility of presenting a neurodegenerative disorder (NCL)
B0484	*TRIM8*	Het	C	Monitored for renal disease
B0078	*TSC2*	Het	U	Individual was not followed after genetic results
B0251	*TSC2*	Het	C	Referred to disease-specific multidisciplinary clinic for TSC, received related medical monitoring and diagnostic studies
B0556	*TSC2*	Het	T, C	T: Treated with vigabatrin for infantile spasms, with resolution C: Followed in disease-specific multidisciplinary TSC clinic, recommended cardiology and ophthalmology evaluations as well as periodic abdominal and brain MRIs
B0615	*TSC2*	Het	T, C	T: Considered vigabatrin for seizure treatment C: Referred to disease-specific multidisciplinary TSC clinic
B0557	*TUBB2A*	Het	C	Recommended ophthalmologic evaluation due to possible risk of congenital fibrosis of extraocular muscles
B0610	*UBE3A*	n/a	NR	
B0024	*UPF3B*	Hemi	NR	
B0142	*WDR45*	Het	P	Neurodegenerative disorder with reduced life expectancy
B0404	*WDR45*	Hemi	T, P	T: Considered treatment with iron chelator deferiprone P: Counseled regarding prognosis
B0536	*WDR73*	Hom	C	Referred to nephrology
B0100	*ZEB2*	Het	C	Various specialist referrals to follow features associated with Mowat-Wilson syndrome
B0108	*ZEB2*	Het	C	Various specialist referrals to follow features associated with Mowat-Wilson syndrome

*T = Treatment, C = Care coordination, P = Prognosis, D = Change in diagnosis, U = Unknown, NR = None recorded

Note: Rows highlighted in gray indicate individuals with neurotypical development and diagnostic results.

Abbreviations: ASD = Autism Spectrum Disorder, ASM = Anti-seizure medication, CDD = CDKL5 Deficiency Disorder, CVI = Cortical visual impairment, EKG = Electrocardiogram, NCL = Neuronal ceroid lipofuscinosis, PKD = Paroxysmal kinesigenic dyskinesia, SUDEP = Sudden Unexpected Death in Epilepsy, TSC = Tuberous Sclerosis Complex