Table 1. Genetic variants of *IQSEC2* in the patient cohort

Patient ID	Sex	DNA change (hg19) (NM_001111125.3)	AA change	REVEL	Inheritance	Novel/Reported	ACMG
1	Male	*c.2449_2450del*	*p.Asp817Arg fs*8*	–	Maternal	Novel	LP
2	Female	*c.2317C>T*	*p.Gln773**	–	*de novo*	Novel	P
3	Male	*c.3206G>T*	*p.Arg1069Pro*	0.93	*de novo*	Reported	LP
4	Female	*c.895C>T*	*p.Gln299**	–	*de novo*	Reported	P
5	Female	*c.2983C>T*	*p.Arg995Trp*	0.67	*de novo*	Reported	P
6	Female	*c.2776C>T*	*p.Arg926**	–	NA	Reported	P
7	Male	*c.4147C>T*	*p.Gln1383**	–	NA	Novel	LP
8	Male	*ChrX:53242135_53254741del*	–	–	*de novo*	Novel	LP
9	Male	*c.1402-1G>T*	*p.?*	–	Maternal	Novel	LP
10	Male	*c.3576C>A*	*p.Tyr1192**	–	*de novo*	Novel	P
11	Male	*c.1454G>A*	*p.Gly485Glu*	0.12	Maternal	Novel	VUS
12	Female	*c.3227T>C*	*p.Leu1076Pro*	0.78	*de novo*	Reported	LP
13	Male	*c.315C>A*	*p.Ser105Arg*	0.64	NA	Novel	VUS
14	Male	*c.2983C>T*	*p.Arg995Trp*	0.87	*de novo*	Reported	LP
15	Male	*c.1967+1G>C*	*p.?*	–	Maternal	Novel	P
16	Female	*c.2984G>A*	*p.Arg995Gln*	0.52	NA	Reported	LP
17	Female	*c.746del*	*p.Gly249Valfs*8*	–	NA	Novel	P
18	Male	*c.3016-25T>A*	*p.?*	–	*de novo*	Novel	VUS
19	Male	*c.847_848delinsT*	*p.Gly283Serfs*23*	–	*de novo*	Reported	P
20	Male	*c.2681A>G*	*p.Asp894Gly*	0.41	*de novo*	Novel	LP
21	Male	*c.2052C>A*	*p.Cys684**	–	*de novo*	Reported	P
22	Female	*c.2272C>T*	*p.Arg758**	–	*de novo*	Reported	P
23	Female	*c.2354dupC*	*p.Val786Glyfs*40*	–	*de novo*	Novel	P
24	Female	*c.2969_2978delTAGGGTTGCAinsAAC*	*p.Leu990Glnfs*26*	–	*de novo*	Novel	P
25	Female	*c.2272C>T*	*p.Arg758**	–	*de novo*	Reported	P
26	Male	*c.2707del*	*p.Glu903Asnfs*4*	–	*de novo*	Novel	P
27	Male	*c.2563C>T*	*p.Arg855**	–	*de novo*	Reported	P
28	Male	*c.3986_c.3987insC*	*p.Gly1330fs*57*	–	*de novo*	Novel	LP
29	Male	*c.3452-2A>G*	*p.?*	–	*de novo*	Novel	LP
30	Female	*c.631dupA*	*p.Arg211Lysfs*28*	–	*de novo*	Novel	P
31	Male	*c.3119A>T*	*p.Tyr1040Phe*	0.67	Maternal	Novel	VUS
32	Female	*c.2505_2506del*	*p.Leu837Profs*12*	–	*de novo*	Novel	P
33	Female	*c.2027_2040delCTGGGGGTCGGAGG*	*p.Ala676Valfs*12*	–	*de novo*	Novel	P
34	Male	*c.4309_4321del*	*p.Tyr1437Profs*54*	–	Maternal	Reported (ClinVar)	LP
35	Female	*c.2295_2297del*	*p.Asn765del*	–	*de novo*	Novel	VUS

Abbreviations: AA, amino acid; REVEL, rare exome variant ensemble learner; LP, likely pathogenic; P, pathogenic; VUS, variant of uncertain significance; NA, not available.

Table 2. Clinical characteristics and phenotypic features of the patient cohort

Patient ID	Sex	Age at first dx / last FU	Main clinical features	Age of onset	Epilepsy phenotype	Antiseizure medications	Seizure-free (≥6 mo)	Age of DD onset	Speech/Language status	Motor status	Strab.
1	Male	1y/2y5m	DD, refractory epilepsy, hypotonia	1y6m	Unknown onset	VPA, LEV, LCM	No	1y	Nonverbal	Non-ambulatory	Y
2	Female	1y3m/8y3m	DD, stereotypic hand movements	–	–	–	–	10m	Nonverbal	Unsteady gait, inability to negotiate stairs	Y
3	Male	1y7m/2y4m	DD, refractory epilepsy	1y7m	Focal onset seizures	VPA, TPM, CLB	No	1y7m	Speaks single words, unable to combine	Gross motor developmental delay	N
4	Female	2y/4y6m	DD, febrile convulsions	1y6m	–	–	–	1y	Speaks short sentences within 8-10 words, poor comprehension	Fine motor delay	N
5	Female	3y/7y	Severe DD, epilepsy	2y	Focal onset impaired awareness motor onset	VPA, OXC	Yes	2y	Nonverbal	Able to walk independently but requires assistance to negotiate stairs	N
6	Female	1y8m/6y10m	DD, epilepsy	1y6m	Generalized tonic-clonic seizures	LEV	Yes	1y8m	Mild developmental delay	Gross motor skills at borderline with normal fine motor development	N
7	Male	2y/7y	DD, epilepsy	5y	Focal onset impaired awareness motor onset	LEV	Yes	2y	Speaks short sentences within 3-4 words, poor comprehension	Fine motor delay	N
8	Male	9m/1y	DD, esotropia, muscle weakness	–	–	–	–	3m	Non-ambulatory	Severe to profound developmental delay; inability to roll over	Y
9	Male	2m/–	Preterm, ELBW; NRDS; neonatal jaundice; PDA, ASD, PH	–	–	–	–	–	–	–	N
10	Male	3y/–	DD	–	–	–	–	–	–	–	N
11	Male	3y/6y9m	Language DD	–	–	–	–	1y6m	Speaks short sentences; markedly reduced verbal output	Runs, climbs stairs, hops normally	N
12	Female	6y/8y4m	DD, epilepsy	2y4m	Focal impaired awareness seizure	LEV	Yes	2y	Speaks 3-4 word sentences, slow response	Fine motor delay	N
13	Male	3y/3y	Language DD, hypogammaglobulinemia	–	–	–	–	2y	Only says "mom," no other words	Walks, runs, climbs stairs normally	N
14	Male	2y/7y9m	DD, refractory epilepsy, sleep disorder	9m	Infantile epileptic spasms syndrome	ACTH, VPA, TPM	No	6m	Non-ambulatory	Requires assistance to walk	N
15	Male	2y/2y	DD, refractory epilepsy, hypotonia	2y	Epileptic spasms	VGB, Prednisone	No	6m	Non-ambulatory	Sits independently, stands with support	Y
16	Female	3y/4y	DD	–	–	–	–	3y	Capable of simple daily expression but with	Fine motor delay	N

Patient ID	Sex	Age at first dx / last FU	Main clinical features	Age of onset	Epilepsy phenotype	Antiseizure medications	Seizure-free (≥6 mo)	Age of DD onset	Speech/Language status	Motor status	Strab.
									limited spontaneous language		
17	Female	1y/1y6m	DD	–	–	–	–	8m	No active language, responds to sounds	Maintains standing posture with support	N
18	Male	3y/3y	DD, irritability, hyperactivity, hypoalgesia	–	–	–	–	4m	Speaks short sentences	Requires support from the stairs to go down and is unable to hop on one foot	N
19	Male	4m/2y6m	Gross motor DD, hypotonia, poor feeding, ACC	–	–	–	–	4m	Babbles, no meaningful words	Stands independently for a short time	N
20	Male	7m/2y10m	DD	–	–	–	–	4m	Occasional "mom/dad," no coherent language	Independent walking at a slow pace	Y
21	Male	1y1m/1y1m	DD, strabismus, nystagmus	–	–	–	–	6m	Non-ambulatory	Fine motor delay	Y
22	Female	2y8m/4y6m	DD, refractory epilepsy	2y8m	Unknown onset	VPA, CLB, ZNS	No (2-3/mo)	1y4m	Produces sentences of 4-5 words in length	Fine motor delay	Y
23	Female	3y/9y9m	DD, epilepsy	3y	GTCS	VPA, NZP	Yes	1y3m	Speaks short sentences, comprehension poor	Walks, runs, climbs stairs independently	N
24	Female	2y7m/7y3m	DD, refractory epilepsy	2y7m	GTCS	OXC, LEV, NZP, TPM	Yes	1y8m	Produces sentences of 3-5 words in length	Walks independently, runs unsteadily	N
25	Female	3y/4y2m	DD, epilepsy	2y3m	GTCS	LEV	Yes	11m	Expressive language is limited with minimal spontaneous utterances; however, the individual can successfully repeat words or phrases when modeled	Gross motor developmental delay	N
26	Male	9m/3y8m	DD, refractory epilepsy, hypotonia, poor feeding	9m	GTCS/epileptic spasms	VPA, TPM, CLB, PER	No (daily)	6m	Non-ambulatory	Sits with support, unable to sit independently	N
27	Male	3y/6y4m	DD, epilepsy	2y6m	Focal onset seizures	Tibetan remedy	Yes	1y6m	Non-ambulatory	Unable to sit independently	N
28	Male	7m/7m	DD, epilepsy, hypotonia	7m	GTCS	VPA	No	7m	Non-ambulatory	Poor head control; unable to sit independently	N
29	Male	11m/1y10m	DD, refractory epilepsy, VSD, hypotonia	11m	Infantile epileptic spasms syndrome	VPA, CLB, BRV, ZNS	Yes	9m	Non-ambulatory	Unable to sit independently	Y
30	Female	2y/2y1m	DD, mild hypotonia	–	–	–	–	11m	Able to verbalize "dad, mom, grandpa, grandma," but does not use them to refer to specific people	Fine motor delay	N
31	Male	1y1m/1y6m	DD	–	–	–	–	5m	Able to verbalize "dad"	Independent in crawling; non-ambulatory	N
32	Female	2y/8y11m	DD	–	–	–	–	2y	Can engage in daily communication, but is unable to attend mainstream primary school	Fine motor delay	N

Patient ID	Sex	Age at first dx / last FU	Main clinical features	Age of onset	Epilepsy phenotype	Antiseizure medications	Seizure-free (≥6 mo)	Age of DD onset	Speech/Language status	Motor status	Strab.
33	Female	7y/13y	ID	–	–	–	–	7y	Can engage in daily communication, poor academic performance	Fine motor delay	N
34	Male	1y2m/1y2m	Developmental disorder	–	–	–	–	11m	Speech DQ:49	Gross motor DQ:42; fine motor DQ:51	N
35	Female	2y6m/3y4m	DD, ID, epilepsy, sleep disorder	2y6m	GTCS	ZNS	Yes	1y3m	Non-ambulatory	Can walk independently, but lacks the ability to run or navigate stairs	N

Abbreviations: DD, developmental delay; ID, intellectual disability; dx, diagnosis; FU, follow-up; VPA, valproate; LEV, levetiracetam; LCM, lacosamide; TPM, topiramate; CLB, clobazam; OXC, oxcarbazepine; ZNS, zonisamide; NZP, nitrazepam; PER, perampanel; BRV, brivaracetam; VGB, vigabatrin; ACTH, adrenocorticotropic hormone; GTCS, generalized tonic-clonic seizures; ACC, agenesis of corpus callosum; VSD, ventricular septal defect; DQ, developmental quotient; mo, months; y, years; Y, yes; N, no; Strab., strabismus; ELBW, extremely low birth weight; NRDS, neonatal respiratory distress syndrome; PDA, patent ductus arteriosus; ASD, atrial septal defect; PH, pulmonary hypertension.