Supplementary table 1: Phenotypic details, variant information and presence of the gene on commercial gene panels for the 14 probands with identified likely pathogenic or pathogenic variants

Gene	***PACS2***	***NSUN2***	***CACNA1A***	**del 6q21-22.31**	***TDP2***	**del 9q34.11**	***NEXMIF***	***SCN1A***	***SCN1A***	***CHD2***	***KDM6B***	***NUS1***	***ALDH7A1***	***TANGO2***	***CTCF***	***SYNGAP1***
Patient Identifier	**784**	**922**	**952**	**1165**	**1218**	**1229**	**1239**	**1260**	**1328**	**1344**	**1348**	**1356**	**1621**	**1625**	**1703**	**1728**
Sex	male	male	female	male	female	female	female	female	female	female	male	female	male	female	male	female
Age (years)	24	27	23	49	21	23	34	24	30	27	31	24	23	21	22	38
Family History																
Consanguinity	No	Yes (parents are cousins)	No	Yes (parents are cousins)	Yes (parents are cousins)	No	No	No	No	No	No	No	Yes (maternal great-grand-mother and paternal grandmother were cousins)	No	No	No
Family history of epilepsy	No	No	Father and paternal half-sister affected	Paternal aunt and father's cousin and aunt	No, but brother has severe intellectual disability	No	No	No	No	No	No	No	Father and paternal aunt affected	No	No	Monozygous twin affected
Risk factors																
Prenatal problems	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Perinatal problems	No	No	No	Forceps	Cyanosis after birth	No	No	No	No	No	No	No	Breech position, cyanosis after birth	Suction cup	No	No
Spontaneous birth/caesarean section	Spontaneous	Caesarean section (planned, triplets, other two are healthy)	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Unknown	Spontaneous	Unknown	Emergency caesarean section	Spontaneaous	Unknown	Spontaneous
Premature birth	32 weeks	36 weeks	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Postnatal intensive care	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Febrile seizures	No	No	Yes (multiple simple febrile seizures, age unknown)	Yes (18 months)	No	No	Yes (single febrile seizure, age unknown)	No	Yes (febrile seizures from 6 mths-6 yrs, 1/8 weeks), different from epileptic spasms	No	No	No	No	No	No	No
Meningitis/ Encephalitis	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Traumatic brain injury	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No
Other neurological conditions	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Epilepsy																
Age of onset (years)	0	2	2	4	14	10	2.5	0.3	0.5	3	18	3	0.1	17	11	2.5
Epilepsy type/location	Focal	Generalized	Generalized	Unknown	Unknown	Multifocal	Generalized	Multifocal	Multifocal	Generalized	Generalized	Multifocal	Generalized	Generalized	Focal, right temporal lobe	Generalized

Gene	*PACS2*	*NSUN2*	*CACNA1A*	del 6q21-22.31	*TDP2*	del 9q34.11	*NEXMIF*	*SCN1A*	*SCN1A*	*CHD2*	*KDM6B*	*NUS1*	*ALDH7A1*	*TANGO2*	*CTCF*	*SYNGAP1*
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Epilepsy syndrome		LGS									JME	CSWS				Doose syndrome
Seizure types																
Semiology I	Generalized atonic seizures	Unknown onset tonic seizures	Absence seizures	Myoclonic-atonic seizures	Unknown onset behavioral arrest seizures	Unknown onset tonic seizures	Absence	GTCS	Focal aware motor seizures (versive seizures)	Absence seizures	Myoclonic seizures	FIAS (dyscognitive seizures)	Generalized tonic seizures	Absence seizures	FIAS (dialeptic/automotor seizures)	Myoclonic-atonic seizures
Semiology II	FIAS	Unknown origin behavioral arrest	GTCS	Myoclonic seizures	Unknown atonic/tonic seizures	Focal aware motor seizures (versive seizures)	Myoclonic seizures		Epileptic spasms (seizure free since the age of 6 years)	GTCS	GTCS	GTCS	GTCS	GTCS	FBTCS	Absence with eyelid myoclonia
Semiology III	FBCTS	Epileptic spasms		GTCS	FBTCS	Unknown onset behavior arrest			FBTCS							
Age at last seizure (years)	21	Ongoing	Ongoing	Ongoing	Ongoing	19	Ongoing	22	Ongoing	26	20	13	Ongoing	21	21	15
Seizure free for > 1 year	Yes	No	No	No	No	Yes	No	Yes	No	No	Yes	No	No	No	No	Yes
Frequency (per month, over the last three month)	0	45	6	3	15	0	3	0	30	0	0	Ongoing ESES	0.3	0	0	0
Status epilepticus																
Type and frequency	None	None	None	None	None	None	None	None	Focal status epilepticus	Absences status epilepticus	None	ESES, every night	Several	Absence status epilepticus	None	None
Age (years)									29	23		Ongoing	Last at 21	17		
Diagnostic tests																
Age at EEG (years)	24	21	23	44	14	19	31	22	29	23	25	20	21	19	22	35
Non-epileptic abnormalities	Mild encephalopathy	Severe encephalopathy	Mild encephalopathy	Mild encephalopathy, left lateral cerebral dysfunction	None	Moderate encephalopathy	Moderate encephalopathy, right lateral cerebral dysfunction	None	Moderate to severe encephalopathy	Mild encephalopathy	None	None	Moderate encephalopathy	Moderate encephalopathy	Right temporal cerebral dysfunction	Mild encephalopathy
Interictal epileptiform discharges (localization, frequency)	None	Generalized sharp-slow-wave complexes (2.5/s). Generalized sharp waves with bifrontal and frontopolar maximum	Generalized spike-waves complexes with bifrontal maximum	Generalized spike-wave complexes	Bifrontal (right>left) sharp waves, temporal sharp waves with bifrontal and bioccipital spread	Bifrontal sharp waves	Generalized poly-spike wave (right temporal maximum). Right temporal sharp wave and poly-spike wave. Breach rhythm right temporal.	Generalized sharp waves, left temporal seizure onset	Sharp waves left central, seizure onset zone both frontal and frontocentral	Generalized spike waves complexes with bifrontal maximum	None	Repetitive, left-hemispheric sharp waves with maximum at F3, P3, and T3, increased in sleep stages 3 and 4 (80% of EEG). Single sharp waves also in wakefulness	Generalized spikes waves with bifrontal maximum	Generalized 3 Hz spikes wave complexes, polyspikes	None	Generalized 3 Hz spikes wave complexes

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Photic stimulation (Waltz et al 1992)	No effect	NA	Photoparoxysmal reaction grade IV	No effect	NA	NA	NA	Photoparoxysmal reaction grade IV	NA	No effect	NA	NA	NA	NA	Photic driving	No effect
Hyperventilation effect	No effect	NA	No effect	No effect	No effect	No effect	Increased frequency of sharp waves	No effect	No effect	No effect	No effect	No effect	NA	NA	No effect	No effect
Age at MRI (years)	17	2.75	21	44	13	15	31	22	Unknown	18	18	5	NA	19	20	Childhood
Results	Right mesiotemporal cystic lesion, suspicious of a ganglioglioma	Normal	Normal	Nonepileptic abnormality: non-specific white matter lesions bilaterally	Normal	Normal	Nonepileptic abnormality: Arachnoid cyst right temporal with displacement of the right temporal pole, hippocampus and amygdala	Normal	Normal	Nonepileptic abnormality: Pinealis cyst	Normal	Nonepileptic abnormality: Left lateral cystic thalamic lesion	NA	Nonepileptic abnormality: Lacunar defect in the right thalamus. Small calcifications at the tentorium on the right and at the falx cerebri frontal without pathological value.	Normal	Normal
Antiseizure medication																
Antiseizure medications tried	LTG	PB, VPA, VGB, Nitrazepam, PHT, ESM, TPM, PRM, LTG, LEV, ZNS, PER, BRV, ZNS, CLZ, Petinutin, MSM, ZNS	VPA, ESM, BRV, TPM, PER, LEV, LTG	PHB, CZP, PHT, PRM, VPA, LEV, TPM, LCM	LTG, ZNS, BRV, OXC, ESL, LEV, STM, VPA	TPM, OXC, LEV, LCM, V	LCM, VPA, ZNS, TPM, LEV, BRV, PER	BR, PB, LTG, VPA, LEV, ZNS	PB, CLB, ESM, MSM, LTG, AZA, VGB, CBZ, PHT, PRM, TPM, LEV, STM, RUF, LCM, PGB, ZNS, BR, VPA, STP	STM, LCM, LEV, PER, LTG, VPA	OXC, LTG, TPM, VPA	STM, VPA, CLB, ESM, LTG, PHT, MSM, TPM, GBP, LEV, ZNS, CLZ	VPA	LTG, BRV, LEV, VPA	LTG, LEV, LCM, BRV	PB, ESM, VPA
Pharmacorefractory	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No
Responsive on these antiseizure medications	LTG	NA	VPA	NA	None	LTG	None	VPA	None	Unknown	VPA	Unknown	VPA	VPA	BRV	VPA
Comorbidities																
Psychiatric disorders	None	None	Depression	Visual and acoustic hallucinations on topiramate	None	Autistic features	Psychobehavioral side effect with perampanel	Aggressive behavior, psychosis on zonisamide	Behavioral disorder, autistic traits	None	Autistic spectrum disorder	None	None	None	Early childhood autism	Organic behavioral disorder
Age of onset (years)			21	44		1	31	19	NA		NA				NA	Unknown
Status at last follow up (remitted, persistent, unknown)			Remitted	Remitted		Persistent	Remitted	Remitted	Persistent		Persistent				Persistent	Persistent
Therapy			Psychotherapy, antidepressant	Withdrawal of topiramate		None	Withdrawal of perampanel	Risperidone, withdrawal of zonisamide	Citalopram		Risperidone				None	Opipramol/risperidone, now: Clonazepam

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Other comorbidities/organ involvement	Scaly exanthema of unclear etiology, hallux valgus	Dyskinetic cerebral palsy, short stature, microcephaly, nephrocalcinosis, kidney stones in infancy, leuko- and thrombocytopenia most likely induced by mesuximide	Migraine, cerebellar ataxia	chronic viral hepatitis C, hemophilia A (factor VIII residual activity approx. 4-5%), diabetes mellitus type 2	Arthrogryposis	secondary microcephaly, cholelithiasis	Chronic allergic asthma, acquired left facial nerve paresis, puncture of the right temporal arachnoid cyst at age 6 years	Ataxia, scoliosis with surgical treatment	Hypothyroidism, steatosis hepatis, obstructive sleep apnea			Right-sided renal agenesis, celiac disease		Suspected congenital myasthenia with compound heterozygous variants of uncertain significance in the ARGN gene, mild sensorineural hearing loss, phonetic-phonological disorder, orofacial myofunctional disorder, latent hypothyroidism	Microcephaly, slim statue with long extremities and joint hypermobility, pneumonia age 4 years (intensive care)	
Intellectual development																
Age of onset developmental delay (years)	0.25	0	4	8	0	1	1	0.3	2	0	0	3.5	0.1	3	0.75	2.5
Neonatal/childhood																
Intellectual development until first seizure	NA	Delayed	Normal	Normal	Delayed	Delayed	Delayed	Normal	Normal	Delayed	Delayed	Normal	Normal	Delayed	Delayed	Normal
Intellectual development after onset of seizures	Delayed	Regression	Delayed	Delayed	No further alteration	Delayed	No further alteration	Delayed	Delayed	No further alteration	No further alteration	Regression	Delayed	No further alteration	No further alteration	Regression
Milestone: Verbal ability (age first words)	NA	NA	NA	NA	NA	1.5	4	NA	2	NA	NA	1.25	NA	3.4	NA	NA
(School) education / graduation	Secondary school	NA	Regular primary school, then special school	Special school	Special school	Special school	Special school	Special school	Special school	Special school	Special school	Special school	None	Regular school until age 15 years, afterwards special school	Special school	Special school
Learning difficulties	Reading, writing and arithmetics with limitations	No reading, writing and arithmetics	Basic writing and reading, arithmetics with numbers <20	Basic writing and reading, no arithmetics	Speaking word by word without understanding content, writing simple words in print, counting to 10	No reading, writing and arithmetics	No reading, writing and arithmetics	No reading, writing and arithmetics	No reading, writing and arithmetics	No reading, writing and arithmetics	No reading, writing and arithmetics	Deficits in spatial-constructive abilities, non-verbal memory and visual-spatial memory, detained executive function	No reading, writing and arithmetics, amnestic memory deficits	Dyscalculia	Reading and writing rudimentary, arithmetic with numbers <10	No reading, writing and arithmetics

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Current verbal ability	Regular language production and comprehension	Very limited language production (3-4 words)	Good language comprehension, speaking slowly and with limited vocabulary	Good language comprehension, speaking slowly and with limited vocabulary	Good language comprehension, speaking slowly and with limited vocabulary	Basic language comprehension, very limited language production (3-4 words)	Short sentences, severe speech impairment	Basic language comprehension and interaction	Basic language production and comprehension	Slow and simply structured language	Good language comprehension, language production: one-word sentences, minimal vocabulary: yes, no, mom, dad	Simply structured language	Basic language comprehension and interaction	Simply structured language	Can understand slow speech, stuttering, sometimes chanting speech	Basic language production and comprehension
Severity of intellectual disability	Mild	Profound	Moderate	Moderate	Moderate	Severe	Severe	Moderate	Profound	Severe	Moderate	Moderate	Profound	Mild	Mild	Severe
IQ and age of testing (years)	NA	NA	NA	NA	52-65 (6.6)	NA	NA	NA	"below normal" (6)	NA	NA	NA	NA	76 (13)	60-70 (unknown)	NA
Motor development																
Age of regression (if applicable)	NA	0	8	8	0	1	1	0.4	2	0	0	3	0	3	0.75	2.5
Neonatal/ childhood/ adult																
Milestones: Age of walking (months)	NA	20	Normal	Normal	NA	60	48	NA	18	NA	NA	12	Not achieved	11	NA	NA
Current motor disabilities	None	Dyskinetic cerebral palsy with unsteady gait, mostly wheelchair-bound	Ataxia including gait	Ataxia especially gait (walker dependent)	Unsteady gait	Standing instability, delayed fine motor skills	Unsteady gait, delayed fine motor skills	Ataxia including gait	Gait ataxia, delayed fine motor skills	Gait ataxia	Small stepped gait	Mild gait and stand instability and central coordination disorder	Sitting with corset, standing with two persons as support	Delayed fine motor skills, reduced muscle strength on exertion at age 15 years	Unstable gait	None
Neurological examination	Mild strabismus divergens on the right, hyperreflexia	Lateral gaze deviation of the right eye, can walk a few steps	Saccadic gaze, gaze-evoked nystagmus to both sides, bradydiadochokinesia bilaterally	Saccadic gaze, bradydiadochokinesia bilaterally	Duchenne gait, unsteady gait, no one-leg stand	Stereotypical hand movements and rocking of the upper body	Finger-nose test dysmetric bilaterally, mild postural tremor of hands, dysdiadochokinesia bilaterally, extended gait testing not possible	Pronounced exophthalmos, saccadic gaze, finger-nose attempt dysmetric, ataxic gait	Unsteady gait, increased tone with spasticity, dysdiadochkinesis	Finger-nose and heel to shin test slightly ataxic, gait slightly unsteady	Small stepped gait, otherwise unremarkable	Fine motor skills limited on both sides, finger-nose test bilaterally dysmetric dysdiadochokinesia, gait and stand slightly ataxic	Basic language production, severe spasticity of all limbs	Unremarkable	Unsteady extended gait testing, otherwise unremarkable	Not orientated, otherwise unremarkable
Pathogenic mutation/phenotype																
Gene	*PACS2*	*NSUN2*	*CACNA1A*	del 6q21-22.31	*TDP2*	del 9q34.11	*NEXMIF*	*SCN1A*	*SCN1A*	*CHD2*	*KDM6B*	*NUS1*	*ALDH7A1*	*TANGO2*	*CTCF*	*SYNGAP1*
Position	14:105834449 G>A (heterozygous)	5:6632711 C>T (homozygous)	19:13476179 C>T (heterozygous)	Del chr6:113,970,857-119,349,116	6:24653368 C>- (homozygous)	Del chr9:127,523,499-128,122,472	X:73963698 G>A (heterozygous)	2:166900409 AG-GAATCTCT>- (heterozygous)	2:165998037 T>A (heterozygous)	15:92997300 G>C (heterozygous)	17:7852225 C>T (heterozygous)	6:117694030 G>A (heterozygous)	5:126555970 TT>- (homozygous)	22:20055941 A>G (homozygous)	16:67611443 AAAC>- (heterozygous)	6:33443307 C>T (heterozygous)
Reference	hg19	hg19	hg19	hg38	hg19	hg38	hg19	hg19	hg38	hg38	hg38	hg38	hg38	hg38	hg38	hg38

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Nucleotide and amino acid change	NM_001100913:exon6:c.G625A:p.E209K	NM_017755:exon2:c.254+1G>A	NM_001127221:exon5:c.G736A:p.E246K	NA	NM_016614:exon6:c.650delG:p.G217Efs*7	NA	NM_001008537:exon3:c.C694T:p.Q232X	NM_001353948:exon12:c.1813_1822del:p.R605Cfs*15	NM_001202435:exon25:c.4476+1A>T	NM_001271:exon30:c.G3782C:p.W1261S	NM_001080424:exon19:c.C4357T:p.R1453C	NM_138459:exon3:c.542-1G>A	NM_001182:exon12:c.1054_1055del:p.K352Gfs*144	NM_001283106:exon7:c.381-2A>G	NM_001363916:exon3:c.608_611del:p.T204Rfs*17	NM_001130066:exon14:c.C2713T:p.Q905X
Variant type	Missense (known pathogenic variant, CADD score 26.1)	Splicing	Missense (CADD score 28.9)	Deletion	Truncation	Deletion	Truncation	Truncation	Splicing	Missense (CADD score 31)	Missense (CADD score 31)	Splicing	Truncation	Splicing	Truncation	Truncation
Inheritance	Unknown	Parents and sister heterozygous	Not present in mother, father unavailable	Unknown	Parents heterozygous	De novo (paternity confirmed by trio exome)	De novo (paternity confirmed by microsatellite maker panel)	Not present in father, mother unavailable	De novo (paternity confirmed by trio exome)	Not present in mother and brother, father unavailable	De novo (paternity confirmed by trio exome)	Unknown	Parents not available, must be heterozygous	Mother heterozygous, father not available, must be heterozygous	Not present in mother, father unavailable	De novo (paternity confirmed by trio exome), twin sister heterozygous as well
ACMG interpretation	Likely pathogenic (PS1, PM2, PP3)	Pathogenic (PVS1, PM2, PM3)	Likely pathogenic (PM1, PM2, PP2, PP3)	Pathogenic (1A, 2A, 2H, 3B)	Pathogenic (PVS1, PM2, PM3)	Pathogenic (1A, 2A, 3A, 4L)	Pathogenic (PVS1, PS2, PM2)	Pathogenic (PVS1, PM2, PP5, ?PS1)	Pathogenic (PVS1, PS2, PM2, PP5)	Likely pathogenic (PM2, PM5, PP2, PP3)	Likely pathogenic (PS2, PM2, PP3)	Likely pathogenic (PVS1, PM2)	Pathogenic (PVS1, PM2, PM3)	Pathogenic (PVS1, PM2, PM3)	Likely pathogenic (PVS1, PM2)	Pathogenic (PVS1, PS1, PS2, PM2, PP1)
Frequency of epilepsy in patients with pathogenic variants in the respective gene	Seizures typical	7% seizures (1/11 Abbasi-Moheb et al. American Journal of Human Genetics 2012;90:847-855, 0/3 Khan et al. American Journal of Human Genetics 2012;90:856-863)	Broad phenotypic spectrum including seizures	NA	Seizures typical	NA	83% seizures (Stamberger et al. Genetics in Medicine 2021;23:363-373)	Seizures typical	Seizures typical	96% seizures (Carvill GL, Mefford HC. CHD2-Related Neurodevelopmental Disorders. GeneReviews January 21, 2021)	17% febrile or afebrile seizures (1/12 patients had focal seizures and 1/12 febrile seizures in Stolerman et al. American Journal of Medical Genetics 2019;179A:1276-1286	Seizures typical	Seizures typical	75% seizures (2/3 in Kremer et al. American Journal of Human Genetics 2016;98:358-362, 4/5 in Lalani et al. American Journal of Human Genetics 2016;98:347-357)	11% (4/38 Konrad et al. Genetics in Medicine 2019;21:2723-2733)	84% seizures (Holder JL, Hamdan FF, Michaud JL. SYNGAP1-Related Intellectual Disability. GeneReviews, Feb 21, 2019)
Notes							Patient published in Stamberger et al. Genetics in Medicine 2021;23:363-373									
Inclusion of gene in simulated gene panels																
Ambry Genetics Epilepsy Next Panel (accessed April 22, 2022, 124 genes)	No	No	Yes	NA	No	NA	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes
GeneDx Comprehensive Epilepsy Panel (accessed May 1, 2022, 144 genes)	No	No	Yes	NA	No	NA	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes

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Invitae Neurodevelopmental Disorders Panel (accessed April 23, 2022, 241 genes)	Yes	Yes	Yes	NA	No	NA	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes
Invitae Epilepsy Panel (accessed April 23, 2022, 320 genes)	Yes	No	Yes	NA	No	NA	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Blueprint Comprehensive Epilepsy Panel (accessed, April 23, 2022, 511 genes)	Yes	No	Yes	NA	No	NA	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Prevention Comprehensive Epilepsy and Seizure Panel (accessed April 23, 2022, 1478 genes)	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ambry Genetics Neurodevelopmental Next Expanded Panel (accessed April 23, 2022, 1527 genes)	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

AZA: acetazolamide, BR: bromide, BRV: brivaracetam, CBZ: carbamazepine, CLB: clobazam, CLZ: clonazepam, CSWS: epileptic encephalopathy with continuous spike-and-wave discharges during sleep, ESES: electrical status epilepticus in sleep, ESL: eslicarbazepine, ESM: ethosuximide, FBTCS: focal to bilateral tonic-clonic seizure, FIAS: focal impaired awareness seizure, GBP: gabapentin, GTCS: generalized tonic-clonic seizure, JME: juvenile myoclonic epilepsy, LCM: lacosamide, LEV: levetiracetam, LGS: Lennox Gastaut syndrome, LTG: lamotrigine, MSM: mesuximide, NA: not available/applicable, OXC: oxcarbazepine, PB: phenobarbital, PER: perampanel, PGB: pregabalin, PHT: phenytoin, PRM: primidone, RUF: rufinamide, STM: sultiam, STP: stiripentol, TPM: topiramate, VGB: vigabatrine, VPA: valproate, ZNS: zonisamide