Supplementary

Table S1 General conditions of 60 cases of CLCN4-related epilepsy

Case number	Ethnic background	Gender	Developmental disability	Delayed speech	Appearance	Other abnormalities	Complication
1 (22)	English	M	Moderate ID	LD	–	Left alternating esotropia	Hyperactivity
2 (22)	European Caucasian	M	mild to moderate ID	LD	Almond shaped eyes, short upturned nose Short stature	–	ASD, obsessiveness
3 (22)	Dutch Caucasian	M	Mild ID	LD	High palate, large central incisors	Restricted elbow extension	ASD, ADHD, hyperkinesis and impulsiveness
4 (12)	Lebanese	M	Profound ID, regression	NV	Small head, short stature (<3SD)	Hypoacusis, talipes equinovarus	–
5 (18)	China	F	ID, regression	NV	–	–	–
6 (8,10,13)	Anglo-Australian	M	Moderate ID	Severe LD	long face	–	Depression, gastroesophageal reflux, asthma
7 (22)	Turkish	M	Moderate ID	LD	–	Clumsy movements, tremor	ASD, aggression
8–12 (8,10,18)	Anglo-American [1], China [4]	F [1] M [4]	Moderate [2], severe-profound [3], regression [3]	NV [4], LD [1]	Small head [1]	Hypertonia [3]; Tendon hyporeflexia [1]	–
13 (22)	Caucasian	M	Severe ID	LD	Long face, full cheeks, micrognathia	Global hypotonia	Short attention span
14 (22)	Arabic	M	Profound GD	LD	Small head, abnormal face (details unknown)	Central hypotonia and peripheral spasticity	–
15 (22)	Caucasian	F	Moderate ID	LD	Wide mouth, short eustachian tube, mildly small mandible	Increased peripheral tone and reflection	Hyperactivity and anxiety
16 (22)	Caucasian	M	Moderate ID	LD	–	–	hyperactivity, ASD and anxiety
17 (22)	Caucasian	M	Moderate ID	LD	Long face, strabismus, square jaw, turned out upper lip; tall, overweight	Ataxia	Anxiety
18 (22)	Caucasian	F	GD	LD	Canthus, left eyelid ptosis, astigmatism	Transverse palmar creases	Hyperkinesis, short attention span and impulsiveness, anger outbursts
19 (22)	Mexican	M	Moderate ID	LD	–	Elevated finger pads and clinodactyly of the fifth finger	ADHD, hyperkinesia, inattention, impulsiveness, obsessiveness, rigidity, rage
20 (22)	Belgium	M	Non-verbal learning difficulties	Difficulty in pronunciation	–	Hypermobility of joints, unsteady gait	Hyperkinesia and a short attention span
21 (12) 22 (this case)	southern Asia, China	M [2]	Moderate GD [1]; Mild ID [1]	NV [1]; lack of expressivity [1]	–	–	ASD, aggression (1); hyperactivity (1)
23 (22)	French Canadian	M	ID	LD	–	–	Opposition defiant disorder
24 (22)	European Caucasian	M	Moderate ID	LD	Full cheeks, small jaw, prominent forehead, high hairline, drooping eyelids, wide nasal bridge, anteriorly tilted nostrils, smiling lips, large posteriorly rotated ears	Wide-based gait, Bilateral sensorineural hearing loss, optic nerve hypoplasia	ASD, rigidity, anger outbursts
25 (8)	China	M	Severe ID	NV	Long face, wide forehead, collapsed nose, short stature (<3SD)	Tendon hyporeflexia, abnormal Babinski signs	Repeated head pats
26 (22)	Portugal	M	Mild ID	LD, computational difficulty	Maxillary dysplasia with malocclusion; dwarfism; ‘sandal toe’ gap	–	Short attention span, impulsiveness.
27 (8)	China	M	Severe ID	NV	Long face, small head, short stature (<3SD)	Nystagmus, hypertonia	–
28–29 (7,22)	Portugal, Turkish	M [2]	Moderate ID [1], severe [1]	LD	Round face, bilateral temporal narrowing, collapsed nose, narrow and downward sloping lid fissure [1]	Strabismus, intentional tremor, ataxia [1]	Short attention span [1], difficulties in socialization [1]
30 (8,10)	Northern European	M	Severe ID	LD	Round face, small jaw	Microcephaly, upper limb hypertonia and spasticity, CVI	–
31–38 (8,10,13)	Anglo-Australian	M [7] F [1]	Mild ID [1], Moderate [2], Severe [5]	LD [4]	Slightly ‘rough’ face, long face, protruding chin, collapsed nose [4]	Unsteady gait [2], diplegia [2], ataxia [1]	Aggressive [3], hyperactivity [1], bipolar disorder [1]
39–41 (6,8,10,13,17)	Dutch [1], North American [1], Italy [1]	M [2] F [1]	Severe ID	NV [2], NR [1]	Round face, sloping eyelids [1]; NR [1]; round face, wide forehead, flattened nose, full lips, swivel ears, small hands and feet [1]	Microcephaly [1], Hypotonia, abnormal posture [2], progressive spasticity, unsteady gait [1]	Apathy, motor stereotypies [1], ASD [1]
42 (12)	French-Canadian	M	Severe ID	No communication	–	Crouch gait	–
43 (18)	China	M	Severe ID	NV	Collapsed nose, small jaw	–	–
44 (8)	China	M	Severe ID, regression	Severe LD	Congenital left ptosis	Unsteady gait	Aggressive, hyperactivity, irritability
45 (22)	Caucasian	F	Moderate ID	LD	Obesity, eyelid crease, cheek fullness	Exotropia, nystagmus, hypermetropia, neuropathic spasms	ASD, ADHD, sleep disorder, anxiety
46 (22)	Asian	M	Severe ID	LD	–	Hypotonia	Restlessness, hyperactivity, aggressive, anxiety
47 (19)	China	M	Normal	Normal	–	–	–
48–51 (8,10,14,22)	Scottish [1], China [2], Portugal Italia [1]	M [2] F [2]	Severe ID [2], Moderate [1], NR [1]	NV [2]; LD [1]	Wide forehead, deep set eyes, wide midriff, full lower lip [1]	Scoliosis [1], abnormal Babinski signs, dystonia [1]	Self-abusive [1]; ASD, ADHD and anxiety, sleep disorder [1]
52–53 (16)	Pakistan	M [2]	Moderate ID	LD, dysarthria	–	Hypotonia, ataxia, tendon hyporeflexia	Memory impairment, emotional, aggressive
54 (8,10)	Belgium	M	Moderate ID	Normal	Long face, prominent chin	Shuffling gait	Aggressive
55–56 (8,10)	Kurdish	M [2]	Moderate ID	Normal	Long face, protruding chin, lean body habitus [2]	–	Aggressive
57–58 (10)	Spanish	M [2]	Mild ID [1], Severe [1], regression [1]	Severe LD	High palatal arch [1]	Gait abnormality, CVI, non-progressive upper limb choreiform movements [1]	–
59 (22)	Caucasian	M	Mild to moderate ID	LD	Long face, prominent chin, straight eyebrows, thin lips	–	ADHD, sleep disorder
60 (18)	China	M	boundary	LD	-	–	ASD

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(*Continued*)

Age of EP onset	Type of seizures	Epileptic syndrome	Variant site	Inheritance	EEG	Neuroimaging	Treatment and response
6 m	IS→MS + T	IS	c.87C>G/p. A29G	Maternally	Polyspike and wave	Normal	Control of LEV
3 m	ATS + FS, febrile sensitivity	–	c.100G>A/p. A34A	Maternally	NR	Normal	Drug-resistant
2 y	GTC + AS + FS	–	c.185A>G/p. L62A	Maternally	Focal	NT	Not controlled with monotherapy [ethosuximide]
5–6 m	T + BTCS + FSC	–	c.265G>A/p. A89A	*De novo*	SB + multifocal	Completely absent corpus callosum, ventriculomegaly, underdeveloped pons and small cerebellum	Drug-resistant [VGB + LEV + VPA]
4 m	IS	IS	c.608C>T/p. T203I	*De novo*	HH	Delayed myelination	Controlled on ACTH, TPM, and VGB
infancy	CP	–	c.661C>G/p. L221V	Maternally	SB	Small perivascular spaces	Controlled on CBZ
NR	FS + multifocal	–	c.677C>T/p. P226L	*De novo*	Multifocal	Normal	Controlled on phenytoin + CLB + OXC
3 m, 7 m, 8 m, 13 m, 17 m	GT + MS + CP [1], IS + GTC [1], MS + T+FS [1], T + FS + SE [1], GTC + T+AS [1]	IS [1]	c.823G>A/p. V275M	*De novo* [4] Maternally [1]	SB + high amplitude discharge + absence of posterior rhythm [1]; Focal [2]; PPR [1]	Persistently enlarged 3rd ventricle [1], CCT [1], bilateral dilatation of the lateral and third ventricles [1], dilated ventricles, CCT and small hippocampus [1]	Drug-resistant
4 m	AS + IS (6 m) →FS	IS	c.823G>C/p. V275L	Maternally	HH	CCH	Controlled on LEV
2 m	GTC	–	c.826C>T/p. L276P	Maternally	SB	Severe cerebral and cerebellar atrophy, CCT, mild bilateral thalami atrophy, abnormal white matter signs	Controlled on CLB + LEV + PB, but died at the age of 4
13 m	Atypical GTC, febrile sensitivity	–	c.835C>G/p. L279V	*De novo*	NR	CT [-]	Controlled on CBZ and stopped
8 m	GTC + FS, febrile sensitivity	–	c.840A>T/p. G280A	*De novo*	Focal	Normal	Controlled on LVE + VPA
13 y	FSGS	–	c.926A>G/p. A309S	Maternally	Focal	CCH [2]	Seizure reduction after Tegretol
5 y	NR	–	c.928C>T/p. P310S	*De novo*	NR	Normal	Controlled on ZNS
13 y	FS	–	c.949G>A/p. V317I	Maternally	Focal	Partial CCH, hypoplastic optic nerves and chiasm	Controlled on OXC
9 m	GTC+ AS, with eyelid myoclonic seizures	–	c.956T>C/ p. P319S	Maternally	Focal+ generalize	Normal	Drug-resistant
13 m, 28 m	FSGTC, SE [1], FSC [1], febrile sensitivity [2]	–	c.1024G>A/p. G342A	Maternally [1]; *De novo* [1]	Focal [1]; small spikes [1]	Small perivascular spaces [1]; normal [1]	Drug-resistant [VPA + CLB + TPM] [1], controlled on VPA + LTG [1]
6 y	AS→FS + FSGS	–	c.1090A>G/p. A364G	Maternally	SB+ sharp waves	NR	Controlled on VPA + LEV
<1 y	NR	–	c.1106C>T/p. P369L	*De novo*	Focal	Persistent hyperintense signals of the neurohypophysis, marginal enlargement of the right lateral ventricle and hyperintense signal abnormalities in the periventricular white matter	Controlled on CLB
neonatal	IS + GT + MS + FS	IS	c.1363G>A/p. V455I	Maternally	Multifocal+ atypical HH+ SB	periventricular leukomalacia	Drug-resistant
1 y	Febrile seizure → FSGS + MS	–	c.1576G>A/p. G526S	Maternally	NR	NT	Controlled on VPA
2 m	IS + GT + MS	IS	c.1595C>A/p. T532L	*De novo*	Multifocal+ atypical HH	CCH, reduced white matter in posterior lateral ventricle	Drug-resistant, and died at 2 years 9 months
1 y, 5 y	FS (1); FS + T+NCSE + ABS (1)	–	c.1597G>A/p. V533M	Maternally [2]	Normal [1]; Multifocal+ SB [1]	CCT, Ventricle enlargement and white matter atrophy [1]; NT [1]	Controlled on VPA + TPM [1]; Drug-resistant but controlled on KD [1]
3 m	IS + MS + T+AS	IS	c.1601C>T/p. S534L	*De novo*	Focal→ Multifocal+ SB	Periventricular white matter decreased, lateral ventricle and third ventricle dilated	Drug-resistant
Infancy and early childhood	CP + GTC + ATS	EE (5)	c.1606G>A/p. V536M	Maternally	Epileptiform discharge [1], NT [7]	CA, CCT [2], Ventriculomegaly [1], cortical atrophy, white matter loss [1], NT [6]	Controlled on a single drug [2], drug-resistant [6]; 3 cases died at 12, 16 and 19 years of age respectively
4 m, 6 m, <1 y (1)	CP + FS + GTC [1], AS + GTCS [1], MS + GTC + CP + ABS [1]	EE [3]	c.1630G>C/A/p. G544A	*De novo*	Generalize [1], NR [1], SB+ focal+ generalize [1]	CCH [1]; normal [1], mild craniocerebral asymmetry, small left hippocampus [1]	Controlled on LTG [1]; drug-resistant [1]; controlled on VPA + TPM + CBZ + CZP [1]
2 y	Myoclonic-atonic	LGS	c.1645A>C/p. I549L	Maternally	SB+ multifocal	Normal	Drug-resistant
53 days	IS + FS	IS	c.1807C>T/p. A603T	*De novo*	Multifocal	Ventriculomegaly	Drug-resistant
5 m	IS + MS + GTC	IS	c.1873C>T/p. L625P	Maternally	Multifocal+ generalize+ Intermittent HH	CA	Drug-resistant, but controlled on LTG
2 y	FS + GTC	–	c.1904C>G/p. P635A	Maternally	Normal at 2y	Normal	Controlled on LTG
1 y	Febrile seizure→ FS (7 y)	–	c.2025C>G/p. T675T	*De novo*	Focal	Bilateral middle temporal sclerosis, obvious on the right	Controlled on VPA + CLB, and VPA has been stopped
10 y	AS + GTCS	–	c.2044G>A/p. G682L	Maternally	Generalized	Normal	Controlled on VPA
2 y [1], 6 m [1], 1 m [2]	AS [1], CP [1], MS + GT + FS [1], FS [1]	EIMFS [1]	c.2152C>T/A718T	*De novo* [3] Maternally [1]	SB+ intermittent HH+ multifocal [1]; multifocal [1], NT [1]; SB [1]	CCT [2], white matter decreased, left hippocampus small, ventricle enlargement [1]; possible FCD of the left temporal [1]	Drug-resistant [2], but 1 case of remission; controlled on OXC [1], untreated [1]
NR	Focal myoclonus	–	c.2167C>T/p. A723T	Maternally [2]	NR	NR	NR
NR	AS	–	del13bp/A15S fs*18	Maternally	Normal	NT	Controlled on a single drug [not specified], and stopped
Infancy	GS [2]	–	Insert A/Ile626Asnfs*135	Maternally [2]	NR	NT	Controlled on a single drug [2], and discontinued at age 7-10
6 m, 14 y	FS + GS + MS [1],GTC [1]	–	g. (10182428_10187807) _ (10189796_10201480)	Maternally [2]	Focal+ generalize+ SB [1]; normal [1]	CCT, CA [1]; normal [1]	Drug-resistant [1], controlled on LEV [1]
10 m	GS	–	c.1987_1990del/c.925_928del/ p.Asn309Profs	Maternally	NR	NR	Controlled on LTG + TPM + VPA
16 y	NR	–	c.1576+5(IVS10) G>A	Maternally	NR	NR	Controlled on VPA

ABS, atypical absence seizure; ACTH, adrenocorticotropic hormone; ADHD, attention deficit hyperactivity disorder; AS, absence seizure; ASD, autistic disorder; ATS, atonic seizure; BTCS, bilateral tonic-clonic seizure; CA, cerebellar atrophy; CBZ, carbamazepine; CCH, corpus callosum hypoplasia; CCT, corpus callosum thinning; CLB, clobazam; CP, complex partial seizure; CVI, cortical visual impairment; EE, epileptic encephalopathy; EEG, electroencephalogram; EIMFS, epilepsy of infancy with migrating focal seizures; EP, epilepsy; F, female; FS, focal seizure; FSC, focal seizure with disturbance of consciousness; FSGS, focal secondary generalized seizure; FSGTC, focal secondary tonic-clonic seizures; GD, global developmental delay; GS, generalized seizure; GT, generalized tonic seizure; GTC, generalized tonic-clonic seizures; HH, hypsarrhythmia; ID, intellectual delay; IH, infantile hypotonia; ; IS, infantile spasms; LD, language delay; LEV, levetiracetam; M, male; MS, myoclonus; NCSE, non-convulsive status epilepticus; NR, not report; NT, not test; NV, nonverbal; OXC, oxcarbazepine; PB, phenobarbital; PPR, photoparoxysmal response; SB, slow background; SE, status epilepticus; T, tonic; TPM, topiramate; VGB, vigabatrin; VPA, valproate; ZNS, zonisamide.

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