Adult phenotype of KCNQ2 encephalopathy

Adult phenotype of *KCNQ2*-Encephalopathy

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ABSTRACT

Background: Pathogenic *KCNQ2*-variants are a frequent cause of developmental and epileptic encephalopathy.

Methods: We recruited 13 adults (between 18 and 45 years of age) with *KCNQ2*-encephalopathy and reviewed their clinical, EEG, neuroimaging and treatment history.

Results: While most patients had daily seizures at seizure-onset, seizure frequency declined or remitted during childhood and adulthood. The most common seizure type was tonic seizures (early) infancy, and tonic-clonic and focal impaired awareness seizures later in life. Ten individuals (77%) were seizure-free at last follow up. In 38% of the individuals, earlier periods of seizure-freedom lasting a minimum of 2 years followed by seizure recurrence had occurred. Of the ten seizure-free patients, four were receiving a single anti-seizure medication (carbamazepine, lamotrigine or levetiracetam), and two had stopped taking anti-seizure medication. Intellectual disability (ID) ranged from mild to profound, with the majority (54%) of individuals in the severe category. At last contact, six individuals (46%) remained unable to walk independently, six (46%) had limb spasticity, and four (31%) tetraparesis/tetraplegia. Six (46%) remained non-verbal, ten (77%) had autistic features/autism, four (31%) exhibited aggressive behaviour, and four (31%) destructive behaviour with self-injury. Four patients had visual problems, thought to be related to prematurity in one. Sleep problems were seen in six (46%) individuals.

Conclusion: Seizure frequency declines over the years and most patients are seizure-free in adulthood. Longer seizure-free periods followed by seizure recurrence are common during childhood and adolescence. Most adult patients have severe ID. Motor, language and behavioural problems are an issue of continuous concern.

Introduction

KCNQ2-encephalopathy is a severe epileptic disorder characterized by early (mostly neonatal) onset therapy-resistant seizures and various degrees of developmental delay, caused by pathogenic variants in the gene *KCNQ2*. *KCNQ2*-encephalopathy was shown to be the most frequent genetic cause of neonatal onset epileptic encephalopathy, with an estimated incidence of 3/100.000 births [1, 2]. *KCNQ2* encodes for the Kv7.2 subunit of the voltage-gated potassium channel that is responsible for the M-current, an important regulator of neuronal excitability. Like other voltage-gated K+ channels, functional Kv7 channels are tetramers of subunits, each having six transmembrane segments (S1–S6) and cytoplasmic N- and C-termini of variable length [3-5]. Heterozygous pathogenic variants in *KCNQ2* are responsible for epileptic disorders with various modes of genetic inheritance and clinical severity [3]. The difference in phenotype can be explained by the different functional effects on the M-current of the respective amino acid substitutions [6, 7]. Inherited *KCNQ2*-variants with pure loss-of-function effects are known to lead to autosomal dominant Benign Familial Neonatal Epilepsy (BFNE) [8-11]. Specific *KCNQ2* missense variants give rise to *KCNQ2*-encephalopathy [6, 12, 13]. These variants arise *de novo* or are inherited from a mosaic parent, and have either a dominant-negative [14] or more rarely, a gain-of-function effect [12]. Both syndromes start early within the first days of life. Patients diagnosed with BFNE have a good prognosis regarding seizure remission and neurodevelopment [8]. *KCNQ2*-encephalopathy patients suffer from early-onset refractory seizures and developmental delay of varying severity [6, 15].

Several studies describe the disease course of children with *KCNQ2*-encephalopathy, but so far, no studies on the outcome in adulthood exist. This impedes the counselling of parents of

young children diagnosed with *KCNQ2*-encephalopathy about the long-term outcome with regards to seizure frequency, neurological impairments, cognitive functioning and behaviour. We describe the adult phenotype of patients with a *KCNQ2*-encephalopathy to inform other parents of children with *KCNQ2*-encephalopathy about the future of their children.

Methods

Patients

This is a retrospective study of adults (age ≥ 18 years at inclusion) with neonatal or early infantile onset epilepsy, genetic testing showing a pathogenic *KCNQ2*-variant as defined by ACMG criteria[16], and clinical histories indicating some degree of neurodevelopmental delay. The presence of some degree of neurodevelopmental delay was an explicit inclusion criterion to exclude individuals with B(F)NE. Patients with additional (likely) pathogenic variants leading to neurodevelopmental disorders or epilepsy were excluded. Eligible subjects were identified from those enrolled in the RIKEE patient and variant registry (www.rikee.org) by their parent or treating physician. Also, individuals fulfilling inclusion criteria were located by contacting collaborating (paediatric) neurologists and medical geneticists. All parents or legal caregivers of recruited patients provided informed consent for inclusion in our study.

Clinical data collection

Referring physicians were provided with a data sheet to collect clinical information. Personal and familial medical history, results of genetic testing, neurological examination, detailed epilepsy and developmental history, and information on EEG and imaging results were obtained. All information was extracted from existing medical files by the treating physicians. Seizure types were classified using International League Against Epilepsy terminology based

on the description provided by the treating physician [17]. Age at epilepsy improvement was defined as the age at which a clinically relevant decrease in seizure frequency was seen, as noted in the medical records of the treating physicians. Intellectual disability was defined based on the level of adaptive functioning as proposed by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[18].

Results

Demographic and genetic features

A total of 24 unrelated adult individuals with *KCNQ2*-encephalopathy were identified and screened. For 11, insufficient clinical data were available, so they were excluded. The clinical features of the 13 individuals where extensive data could be collected are summarized in Table 1 and described in detail in Supplemental Table 1. They originated from Italy, France, Denmark, Belgium, Switzerland and the USA. Five of 13 were male (38%) and eight were female. The age of inclusion in this study ranged from 18 to 45 years old.

Sequencing revealed 10 different heterozygous *KCNQ2* missense variants in 12 patients, and an in-frame trinucleotide deletion in one (c.314_316delCCT, p.Ser105del; patient 1). Three individuals (patients 3, 4 and 5) carried the same missense variant c.619C>T, p.Arg207Trp. Seven missense variants were previously reported in (unrelated) younger patients diagnosed with *KCNQ2*-encephalopathy (Table 1) [6, 13, 15, 19-36]. Three missense variants (c.367G>A, p.Glu123Lys; c.629G>C, p.Arg210Pro; c. 1040A>G p.Tyr347Ser) are, to our knowledge, novel.

In 10 individuals the *KCNQ2*-variants arose *de novo*. Inheritance was unknown for two individuals (patients 4 and 11). The mother of patient four, who also had a mild intellectual disability, declined further genetic testing. The variant identified in patient 11 was not found in the mother, but the father was not available for testing. The in-frame trinucleotide deletion

was inherited from a mosaic mother with self-limiting neonatal seizures, a single seizure during adulthood, and normal development (patient 1). This family has been reported in a genetic study on BFNE in 2004 (prior to description of *KCNQ2*-encephalopathy), but follow-up of the proband revealed clear neurodevelopmental delay [19]. Seven individuals had a family history of seizures in one or more first- or second-degree relatives. The *KCNQ2*-variant segregated in two of these families (family of patient 1 and patient 5). Two individuals had a family history of intellectual disability: The mother of patient 4, who declined genetic testing, and the son of patient 5 who also had a phenotype compatible with *KCNQ2*-encephalopathy.

Evolution of seizure frequency

All but one individual (patient 5) had seizure onset within the first week of life. Age at seizure onset ranged from the first day of life to two months (median: 2nd day).

Seizure frequency decreased with increasing age. At onset, all patients for whom this information was available had one or multiple seizures daily. The age at epilepsy improvement varied from the first month of life until the age of eight years (median: 12 months). Six individuals (46%) had improvement during the first year of life, another four individuals had improvement between the age of one year and two and a half years (31%). In five out of 13 individuals, seizure-free periods of a minimum of two years followed by seizure recurrence had occurred before inclusion in the study.

By the age of 18, six out of 13 individuals were seizure-free for at least two years (46%). At the time of inclusion in the study, eight individuals (62%) were between 2 and 19 years (median 6 years) seizure-free with ongoing anti-seizure medication (ASM) use, and two (15%) were seizure-free for 16 and 20 years respectively, and were no longer taking ASM (patient 7 and 8). Three individuals (4, 11 and 12; 23%) had ongoing seizures in adulthood (Figure 1). One

individual (patient 11) still had several seizures daily. This individual was born prematurely and thought to have suffered perinatal asphyxia. No information on cerebral imaging was however available. The two other individuals had infrequent seizures.

Evolution of seizure types

Seizure types were defined based on the description of the treating physician and available (inter)ictal EEG findings. The onset of tonic, clonic, and tonic-clonic seizures (focal versus generalized) was often not clear from the description and available historical data, therefore onset type was not specified for these categories of seizures. Seizure types include focal impaired awareness, tonic, clonic, tonic-clonic, myoclonic, epileptic spasms and status epilepticus (Figure 2). All individuals had several seizure types, which often changed throughout life. The most frequent types were tonic-clonic, focal impaired awareness and tonic seizures. Tonic seizures were prominent at onset and during infancy, but did not occur in adulthood. In adulthood, the most frequent seizures were focal impaired awareness seizures and tonic-clonic seizures (Figure 2).

Anti-Seizure Medication

As noted, two out of ten seizure-free patients were receiving no ASM at the time of inclusion in our study. In four out of ten seizure-free patients, seizures were controlled with carbamazepine, lamotrigine or levetiracetam monotherapy. The remaining four seizure-free patients used polytherapy in different combinations to control their seizures. In total, seven of the eight seizure-free patients still receiving ASM, were being treated with a sodium channel blocker (SCB): carbamazepine or lamotrigine. One of the three patients who were not

seizure-free in adulthood had never been treated with a SCB (patient 11). Of note, carbamazepine was said to have aggravated seizures in one individual (patient 4).

EEG and Brain imaging

EEG findings at onset were available for nine individuals and included burst-suppression, discontinuous trace, focal, and multifocal epileptiform activity. During childhood, EEG showed multifocal (poly)spikes or sharp waves, spike-wave complexes and slow background activity. Four out of the ten patients with available EEG during adulthood had unremarkable findings.

Brain MRI was performed in eleven individuals at various ages and was normal in six. In five individuals, nonspecific abnormalities were seen, including enlarged ventricles (patient 8), decrease in white matter volume (patient 12) and severe frontal and insular cortical atrophy (patient 6), to bi-occipital ischemic abnormalities and a minor thalamic haemorrhage (patient 4). Patient 10 was diagnosed with right parietal cortical dysplasia. The interictal EEGs at onset and during childhood showed multifocal interictal epileptiform activity and no ictal EEGs were available to support (or exclude) the presence of a seizure onset zone within the dysplastic cortex. Although we thus cannot exclude the role of this dysplastic tissue in seizure generation, the multifocal interictal EEG abnormalities suggest more diffuse brain hyperexcitability.

Neurological examination and development

Intellectual disability ranged from mild to profound (Figure 3). The largest subgroup had severe ID (7/13; 54%). Five individuals (38%) did not receive any type of school education, the other eight (62%) had special education.

Six (46%) individuals did not develop speech and in four individuals (31%), speech was limited to a few words or sentences. Seven (54%) walked independently, four (31%) were wheelchair-

bound, and two (15%) could walk with assistance. All adult individuals needed assistance in daily life activities.

Motor abnormalities were prominent, including limb spasticity in six (46%) individuals and tetraparesis or tetraplegia in four (31%). Other neurological impairments were axial hypotonia, pyramidal signs, dystonia, dysarthria, apraxia and ataxia.

Neuropsychiatric features

Ten individuals (77%) showed autistic features or were diagnosed with autism spectrum disorder (Figure 4). Four (31%) exhibited aggressive behaviour, four (31%) showed destructive behaviour with self-injury and two (15%) had anxiety problems (patients 5 and 7). Patient 10 often needed to be immobilized in his wheelchair to protect him from self-injury during aggressive outbursts. Sleep problems during childhood and adulthood were seen in six (46%) individuals and were described by the treating physician as insomnia, nocturnal restlessness, unspecified uncontrolled movements, bruxism and frequent awakening.

Other findings

Visual problems were reported in four out of thirteen individuals (31%). Patient 8 had cortical blindness despite the lack of lesions on brain MRI. Patient 11 had bilateral optic nerve atrophy, and was born prematurely at 34 weeks gestational age. Medical files described a history of neonatal asphyxia and haemorrhage, but cerebral imaging was unavailable. Other described visual problems were severe visual impairment, convergent strabismus, amblyopia and astigmatism. Four individuals had problems with feeding such as difficulties with chewing (patient 10) and dysphagia (patient 6 and 12). One patient had a percutaneous endoscopic gastrostomy (PEG) tube (patient 11). No cardiac abnormalities were reported.

Three patients (patients 3, 4 and 5) in our study carried the previously described recurrent variant, c.619C>T, p.Arg207Trp [20-23]. All seemed generally less neurologically affected in adulthood, with only limited abnormalities on clinical examination. All three individuals talk fluently with normal vocabulary and can walk independently. They all had special education and can work. Patient 5 became seizure-free at the age of 22, patient 3 at the age of 40, and patient 4 still has monthly seizures at the age of 24.

Discussion

The current study analysed the course of illness and current phenotypes of 13 adult *KCNQ2*-encephalopathy patients. Because of the small sample size, the high degree of allelic and phenotypic heterogeneity, and our retrospective method, this should be regarded as an early effort to begin understanding the *KCNQ2* adult outcome spectrum. Another issue limiting generalization is that clinical care of infants with *KCNQ2*-encephalopathy has changed considerably since the years when this cohort was born, and potentially might influence outcome. Despite these limitations, we highlight three broader conclusions about the adult outcomes, if only to provoke more investigation, namely: (1) seizures become far less frequent, but breakthrough events occur in many patients, (2) intellectual, behavioural, motor and language disabilities persist despite seizure remission, (3) outcome severity remains correlated with the pathogenic variant.

Neonatal seizures in individuals with *KCNQ2*-encephalopathy are highly therapy-resistant at first presentation, and earlier studies [6, 33, 37] showed a high rate of seizure remission within the first year of life. The longer perspective of our study confirms that seizure frequency decreases with age, although the age of clinically relevant epilepsy improvement varied from

the first month of life to the age of eight years (median: 12 months). Importantly, seizure-free periods of two years or more followed by recurrence of seizures were seen in over one-third of the individuals in our study. Previously described children with seizure freedom in the first year of life might have shown later seizure recurrence in longer follow-up studies. The large majority (10/13; 77%) of adult patients were indeed seizure-free for two years or longer at the time of study entry, but most of them (50%) reached prolonged seizure freedom between the age of 11 and 20 years of age only. Seizure type evolved with age, from tonic seizures being most prominent at in early infancy, to focal impaired awareness seizures and tonic-clonic seizures in older children and adults. Noteworthy, patient 11 was born prematurely at 34 weeks gestational age. She was the only patient still having daily seizures in adulthood. Suspicion of neonatal asphyxia and haemorrhage was reported and could have influenced the outcome. Unfortunately, no information on cerebral imaging was available to confirm the presence of perinatal damage. The patient was however reported to have optic nerve atrophy, a symptom not previously reported in *KCNQ2*-encephalopathy, and most likely caused by her premature birth and hypoxic-ischemic encephalopathy [38, 39].

Evidence for favourable response to SCBs has been described in several previous studies and it is generally accepted that they should be considered as first-line treatment in young patients presenting with seizures and *KCNQ2*-encephalopathy [15, 33, 37, 40-42]. The design and sample size of our study does not allow to draw strong conclusions about treatment response. However, reflecting this clinical consensus, all but one of the seizure-free patients still taking ASM were currently on a SCB. Voltage-gated sodium channels and KCNQ potassium channels co-localize and are bound at critical locations of the neuronal membrane [43]. Therefore, the efficacy of SCB could be linked to their modulating effect on this channel signalling complex. Maximizing potential therapeutic benefits for KCNQ2-encephalopathy may depend on early genetic

diagnosis and effective seizure control at disease onset, and is best tested via prospective controlled trials.

Seizure control notwithstanding, most patients in this series continued to exhibit severe ID as adults. Although moderate and mild ID was observed in a few, all adults needed assistance in daily life activities. Nearly half (46%) of the individuals did not develop any speech or walked independently. Additional neuropsychiatric problems in adulthood were common (Figure 4), and 77% of the individuals had either a formal diagnosis of autism spectrum disorder or showed autistic features. The brain mechanisms driving persistent ID, autism, and other behavioural disabilities in *KCNQ2*-encephalopathy are poorly understood. Studies introducing human alleles into model animals may address this gap in knowledge. In one recent study, mice heterozygous for a *Kcnq2* null allele, equivalent to a large group of BFNE patients, showed, in addition to elevated susceptibility to chemoconvulsant-induced seizures, behavioural abnormalities including autism-associated behaviours such as reduced sociability and enhanced repetitive behaviour [(44)]. Behavioural characterization of mice heterozygous for Kcnq2 Thr274Met, a highly recurrent *KCNQ2*-encephalopathy allele, revealed deficits in spatial learning and memory in adults but no gross abnormality during early neurosensory development [(45)]. Rigorous parallel investigation of the developmental trajectories in both humans and model animals is needed to uncover the mechanisms.

No other non-neurological abnormalities were reported in our cohort, which is in line with the fact that *KCNQ2* is only expressed in the central and peripheral nervous system.

Three unrelated subjects in our study (patients 3, 4 and 5) carrying the recurrent missense *KCNQ2*-variant, c.619C>T, p.Arg207Trp, displayed neurodevelopmental problems not compatible with a diagnosis of B(F)NE but had a remarkably milder phenotype compared to

other individuals in the cohort. All had received special education and were at the time of enrolment working in a sheltered workshop or as a part-time volunteer. One patient transmitted the variant to a son who also has a phenotype compatible with *KCNQ2*-encephalopathy. Although significantly disabled, these individuals appear relatively similar to each other, and as a group were more mildly affected than the other study subjects with *de novo* variants. This suggests that disease outcome depends to some extent on the underlying variant, which is in line with previous studies [7]. Remarkably, Arg207Trp has been reported before in BFNE families including individuals with myokymia [20] or severe myoclonus-like dyskinesia [21]. These features were not seen in the individuals described in our study, although none underwent electromyography. Patients with myokymia experience involuntary rhythmic generalized muscle contractions provoked by hyperexcitability of the lower motor neurons. *KCNQ2* is indeed also expressed by spinal motoneurons [20]. Functional studies showed that this variant has a unique functional effect on M-current, markedly slowing opening and closing kinetics, which is in some respects intermediate between the mild current suppression exhibited by variants found in BFNE and the strong suppression characteristic of many variants leading to *KCNQ2*-encephalopathy. We show that some individuals with this variant show a mild to moderate degree of ID. This highlights how *KCNQ2*-related epilepsies now appear as a disease spectrum rather than a dichotomous entity (BFNE vs. *KCNQ2*-encephalopathy). It also shows that despite this increased complexity, the specific *KCNQ2*-variant remains a central factor contributing to outcome, further influenced by environmental and/or genetic factors. In this respect, it is worth noting that the first descriptions of *KCNQ2*-encephalopathy patients were based on sequencing of genetically unsolved patients that were previously diagnosed with MRI-negative Early Infantile Epileptic Encephalopathy (EIEE) [6, 30]. EIEE is defined clinically by burst-suppression EEG, refractory seizures, evolution to hypsarrhythmia, poor

global developmental progression, and high risk of early mortality [46]. Recent case series continue to show *KCNQ2*-variation as the most frequent genetic cause of EIEE, or Ohtahara Syndrome [1, 26]. The current study of adult patients, along with evidence from other work, however emphasize how this patient subgroup has diverged the classical EIEE syndrome in early features, treatment responsiveness, epilepsy evolution and neurodevelopmental outcome.

Some specific limitations of this study were intrinsic to the approach -- data were collected retrospectively from the medical records. Although we clarified issues by contact with current treating physicians, in many instances, older data may be limited in detail or impossible to further validate. We were unable to apply a uniform criterion for the definition of epilepsy improvement since we depended on the impressions and interpretation of the treating physician at prior times, in diverse settings. Similarly, we based seizure classification on the description in the medical file of the patient. Often it was unclear, based on available descriptions or routine EEGs, whether seizures had a focal or generalized onset.

In conclusion, in this study, patients with *KCNQ2*-encephalopathy were mostly seizure-free in adulthood. Years-long seizure-free periods interrupted by seizure recurrences were frequently seen during childhood and adolescence, but seizure frequency generally declines with age. Most adult patients have a severe ID, and language, motor and behavioural problems are still a concern during adulthood. Systematic, prospective natural history studies on *KCNQ2*-encephalopathy should ideally extend into adult life but until the current ongoing improvements in early diagnosis and treatment are implemented more uniformly, this will add an additional dimension of heterogeneity that will challenge analyses of aggregate outcomes.

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DISCLOSURE OF CONFLICTS OF INTEREST

ECC is a consultant to Xenon Pharmaceuticals and Knopp Biosciences; his participation in this work has been reviewed and approved by Baylor College of Medicine in accordance with institutional conflict of interest policies. MKK serves on speakers bureaus for Greenwich, Novartis and Lundbeck, and on an advisory board for Stealth Biotherapeutics. PS received fees from Ultragenyx, Zogenyx, Biomarin, PTC pharmaceuticals, GW pharma, Neuraxpharma and research grants from GW pharma, PTC pharmaceuticals, ENECTA SV, Kolfarma., and has has been investigator for clinical trials for Ultragenyx and Zogenix. SW received speaker and consultancy fees from UCB, Xenon, Zogenix, Lundbeck and Biocodex. None of the other authors has any conflict of interest to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ABBREVIATIONS

Anti-seizure medication (ASM)

Benign familial neonatal epilepsy (BFNE)

Carbamazepine (CBZ)

Clobazam (CLB)

Clonazepam (CLZ)

Day (D)

Diazepam (DZP)

Early Infantile Epileptic Encephalopathy (EIEE)

Gabapentin (GBP)

Intellectual disability (ID)

Lacosamide (LCM)

Lamotrigine (LTG)

Levetiracetam (LEV)

Lorazepam (LOR)

Melatonin (MEL)

Mirtazapine (MIR)

Month (M)

Not applicable (NA)

Olanzapine (OLAN)

Oxcarbazepine (OXC)

Percutaneous endoscopic gastrostomy (PEG)

Phenobarbital (PB)

Phenytoin (PHT)

Pyridoxine (PN)

Retigabine (RTG)

Risperidone (RIS)

Sodium channel blocker (SCB)

Status epilepticus (SE)

Sulthiame (STM)

Topiramate (TPM)

Valproic acid (VPA)

Vigabatrin (VGB)

Year (Y)

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FIGURE LEGENDS

Figure 1: Age at epilepsy offset (Y = Years)

Figure 2: Distribution of seizure types over the different age categories

Figure 3: Cognitive functioning in adulthood

Figure 4: Neuropsychiatric problems in adulthood

Table 1: Key clinical features of patients with *KCNQ2*-encephalopathy

Patient/ Age at last follow-up	*KCNQ2*-variant c.DNA, protein, inheritance	Previous reports of patient/ variant	Age at epilepsy onset	Age at epilepsy improvement	Age at epilepsy offset + Seizure free periods	Neurological examination at last follow up	Cognitive functioning	Behavioural problems
1/23Y	c.314_316delCCT p.Ser105del Inherited from mosaic mother	[19]	2D	1M	16Y 1M-15Y: seizure-free	Stereotypies, increased tonus left arm and legs, motor and speech dyspraxia, nasal atactic speech, uses short sentences, can read but not write, walks long distances, slightly broad-based with inversion of feet, needs assistance with daily activities	Mild ID, concentration problems Special education	Autistic features
2/18Y	c.367G>A, p.Glu123Lys De novo	-	1D	3M	14Y	Axial hypotonia, spasticity lower limbs, reduced fine motor skills, no speech, understands few simple orders, walks with assistance	Severe ID No education	Autistic features
3/45Y	c.619C>T, p.Arg207Trp De novo	[20-23]	1D	3M	40Y 2,5Y-6Y: seizure-free 13Y-22Y: seizure free	Normal with slight spasticity	Moderate ID Special education, works in sheltered workshop	No
4/24Y	c.619C>T, p.Arg207Trp Unknown	[20-23]	3D	Unknown	Not seizure-free	Ataxia Normal speech and gait	Moderate ID Special education, works in sheltered workshop	Autistic features Aggressive behaviour Destructive behaviour with self-injury
5/33Y	c.619C>T, p.Arg207Trp De novo	[20-23]	2M	4M	22Y 4M-13Y: seizure-free	Slightly dysarthric and nasal speech Normal gait	Mild ID Special education, Half-time supervised volunteer work in retirement home	Autistic features Aggressive behaviour (during adolescence) Anxiety attacks Hyperventilation

6/28Y	c.629G>C, p.Arg210Pro De novo	-	2D	2,5Y	20Y	Spastic tetraplegia No speech, no communication No walking, wheelchaired	Severe ID Special education	Autistic features
7/21Y	c.740C>T, p.Ser247Leu De novo	(24)	1D	1Y	1Y	Dystonic posturing, drooling, clumsy, pyramidal signs, walking with stroller. Needs assistance daily activities. No coherent speech, 1000 words, no sentences, points to communicate, not answering most questions, regression in periods of no sleep	Severe ID No education	Autism Aggressive outbursts Destructive behaviour with self-mutilation Anxiety
8/24Y	c.793G>A, p.Ala265Thr De novo	**(15)** (13, 25-28)	2D	9M	8Y	Axial hypotonia, quadriparesis with pyramidal signs, dysarthria, poor eye contact, no speech, only noises, some comprehension No walking, wheelchaired	Profound ID Special education	Autistic features
9/18Y	c.886A>C, p.Thr296Pro De novo	(25)	2D	1,5Y	13Y D19-6M: seizure-free	Stereotypic movements, no active speech, good comprehension, no writing, occupational therapy with very little autonomy Normal gait	Severe ID No education	Severe autism
10/20Y	c.1174C>T, p.Arg333Trp De novo	(13, 25, 29-32)	1D	15M	18Y 1Y3M-3Y: seizure-free 3Y-10Y: seizure-free	Severe visual impairment, reduced fine motor skills, brady-dysdiadochokinesis, mild spasticity, dysarthria, speaks few words. Independent walking, spastic atactic gait	Severe ID Special education	Temper tantrums Aggressive outbursts Destructive behaviour with self-mutilation

11/42Y	c.1040A>C, p.Tyr347Ser Unknown	-	1D	8Y	Not seizure-free 8Y-20Y: seizure-free	Spastic tetraplegia No speech or walking	Severe ID No education	No
12/18Y	c.1678C>T, p.Arg560Trp De novo	(6, 13, 33-36)	Unknown	Unknown	Not seizure-free	Stereotypic head movements, knee contractures, quadriparesis, variable tone. No walking, wheelchaired. Good eye contact, communicates with nodding, used several words but speech regression secondary to seizures	Profound ID, IQ < 20 Special education	Autistic features
13/22Y	c.1687G>A, p.Asp563Asn De novo	**(15)** (23)	1D	2Y	3Y Recurrence when stop ASM at age 5Y and 19Y	Stereotypies, no spasticity, normal strength, incontinent Speaks short sentences Walks on toes	Severe ID No education	Autistic features Destructive behaviour with self-injury (during adolescence)