De novo truncating mutation in SCN1A as a cause of febrile seizures plus (FS+)

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ABSTRACT – SCN1A is one of the most relevant epilepsy genes. In general, de novo severe mutations, such as truncating mutations, lead to a classic form of Dravet syndrome (DS), while missense mutations are associated with both DS and milder phenotypes within the GEFS+ spectrum; however, these phenotype-genotype correlations are not entirely consistent. Case report. We report an 18-year-old woman with a history of recurrent febrile generalized tonic-clonic seizures (GTCS) starting at age four months and afebrile asymmetric GTCS and episodes of arrest, suggestive of focal impaired awareness seizures, starting at nine months. Her psychomotor development was normal. Sequencing of SCN1A revealed a heterozygous de novo truncating mutation (c.5734C>T, p.Arg1912X) in exon 26.

Conclusion. Truncating mutations in SCN1A may be associated with milder phenotypes within the GEFS+ spectrum. Accordingly, SCN1A gene testing should be performed as part of the assessment for sporadic patients with mild phenotypes that fit within the GEFS+ spectrum, since the finding of a mutation has diagnostic, therapeutic and genetic counselling implications.

Key words: SCN1A, epilepsy, truncating mutation, febrile seizures plus

SCN1A (OMIM #182389), the most relevant epilepsy gene, encodes the alpha subunit of the voltage-gated sodium channel (Nav1.1). More than 700 epilepsy related mutations have been reported to date (SCN1A Variant Database; available at http://www.molgen.vib-ua.be/SCN1AMutations/). SCN1A has been linked to several epilepsy syndromes with overlapping clinical characteristics but divergent severity (Gambardella and Marini, 2009; Meisler et al., 2010). In general, de novo severe mutations, such as truncating and missense mutations in the pore-forming parts of the channel, lead to a classic form of Dravet syndrome (DS) (OMIM #607208), while missense mutations have been associated with both DS and milder phenotypes within the genetic epilepsy with febrile seizures plus (GEFS+) (OMIM #607208), while missense mutations have been associated with both DS and milder phenotypes within the genetic epilepsy with febrile seizures plus (GEFS+) (OMIM #604403) spectrum such as febrile seizures plus (FS+) (Kanai et al., 2004; Myers et al., 2018). However, these phenotype-genotype correlations...
are not entirely consistent and genetic, epigenetic, and environmental modifiers may have a significant impact on the final phenotypic expression (Yu et al., 2006; Makinson et al., 2015). Here we report a de novo truncating mutation in a patient with a phenotype consistent with FS+.

Case study

The patient was an 18-year-old woman born to non-consanguineous healthy parents. Pregnancy and delivery were uneventful and there was no family history of epilepsy. At the age of four months, during a post DTPa vaccination febrile episode, she presented with a generalized febrile seizure, possibly prolonged, however her mother was not completely sure about the seizure duration. Thereafter, she experienced monthly brief generalized tonic-clonic seizures (GTCS) related to fever. At the age of nine months, she presented with a first afebrile asymmetric GTCS and episodes of arrest suggestive of focal seizures with impaired awareness. Routine EEGs were normal, and transfontanellar ultrasound and brain MRI showed a perimesencephalic cyst. She was treated with sodium valproate (VPA), but she persisted with one seizure per month. A combination of treatment with VPA and carbamazepine (CBZ) was used but shortly discontinued due to worsening of seizure frequency to one attack per week. Topiramate (TPM) was started and her seizure frequency decreased gradually (details concerning doses were unavailable).

Over the next years, she had a seizure-free period of two years. Since the patient reached the development milestones at expected times, psychomotor evaluations were not performed. Seizure semiology changed to unresponsiveness, left oculocephalic deviation, oro-alimentary automatisms, generalized stiffness and secondary generalization that started with a scream. At age 10 years, TPM was switched to levetiracetam (LEV), 1000 mg bid, and seizure frequency was two to three attacks per year. At the age of 16 years, seizure frequency increased to one per month. TPM, 50 mg qd, was added with significant improvement and the patient had a seizure-free period of one year.

At the age of 18 years, the patient, then a university student, came to our epilepsy unit. She complained of distractibility, poor academic performance and anxiety related to treatment with TPM. The neurological examination was unremarkable. Further brain MRI showed the perimesencephalic cyst previously described. Repeated EEGs and a four-day video-EEG recording did not reveal any abnormalities. A psychometric evaluation showed a normal Hopkins verbal learning test. The Rey-Osterriech complex figure test revealed normal visual-constructional ability and impaired visual memory with an immediate recall score of 25/36 (60th percentile) and delayed recall score of 10/36 (10th percentile). The Boston Naming Test showed normal language skill, the digit symbol substitution test revealed normal executive function, and the Wechsler intelligence scale (WAIS) showed mild attention deficit. Genetic analysis revealed a heterozygous de novo truncating mutation in exon 26 of SCN1A (GenBank Accession Number NM_001165963.1: c.5734C>T, p.Arg1912X) (figure 1). This variant was detected with a frequency of 8.246e-06 in 121278 alleles annotated in the Exome Aggregation Consortium (ExAC) database. Analysis of the inheritance pattern of 25 microsatellite markers confirmed paternal inheritance.

Discussion

SCN1A truncating mutations lead to haploinsufficiency of Na\textsubscript{V}1.1 channels, typically causing DS. Approximately 95% of patients with DS have a de novo heterozygous mutation, which explains the unaffected status of many siblings and parents (Vadlamudi et al., 2010). However, in this patient, the absence of frequent seizures, myoclonic seizures, psychomotor delay, cognitive impairment, behavioural disorders, and motor deficits (Gambardella and Marini, 2009; Dravet, 2011) did not support the diagnosis of borderline DS. Rather, her phenotype, consisting of recurrent febrile GTCS, afebrile asymmetric GTCS and focal impaired awareness seizures, fitted best within the GEFS+ phenotype spectrum, specifically FS+ (Myers et al., 2018). It is important to highlight that despite the typical familial nature of GEFS+, this condition is not always an inherited syndrome (Myers et al., 2017) and it can be associated with mutations in others genes as PCDH19 or HCN1 (Marini et al., 2018; Smith et al., 2018).

In existing databases (SCN1A Variant Database; available at http://www.molgen.vib-ua.be/SCN1AMutations/), the p.Arg1912X mutation has been reported in five patients, all of whom had a DS phenotype. Fukuma et al. (2004) described a case with seizure onset before the age of one year, with myoclonic seizures and mild psychomotor retardation. Depienne et al. (2009) described two patients with normal cognitive and motor development prior to seizure onset, seizure onset before one year of age, long-lasting seizures mainly triggered by fever, later occurrence of various seizure types, and later regression of cognitive. Löfgren and de Jonghe (2010) reported (personal communication) another patient described with DS, but the phenotype description is not available in the database.

The reduced severity in this patient could be explained by the position of the mutation in the C-terminus,
outside the pore region or the voltage sensor; the critical regions responsible for the biophysical properties of the channel (Kanai et al., 2004). Nevertheless, missense and nonsense mutations in almost the same location have been reported as a cause of DS (SCN1A Variant Database; available at http://www.molgen.vib-ua.be/SCN1AMutations/). Another explanation could be related to the influence of the genetic background on the development of the phenotype, as has been demonstrated in animal models of epilepsy. Heterozygous and homozygous knockout mice (SCN1A+/+ and SCN1A−/−) develop an upregulation of NaV1.3 channel (SCN3A). This upregulation compensates partially for the loss of NaV1.1 channels, and may be sufficient for normal firing of single-action potentials but not for firing of sustained trains of action potentials (Yu et al., 2006). In addition, Makinson et al. (2015) showed that a SCN8A variant can confer seizure protection in mice with a SCN1A mutation. Given these findings, it seems possible that different degrees of compensation can lead to different phenotypes. Another possibility is that the patient is a mosaic carrier. Marini et al. (2009) reported a case with a milder phenotype whose genetic analysis revealed mosaicism. The mutation was present in only about 65% of the ectoderm derived cells, which could explain the reduced severity.

Our findings have clinical relevance, since our patient had focal seizures and, as Liao et al. (2010) reported, some AEDs such as sodium channel blockers may induce seizure worsening in patients with GEFS+ spectrum phenotypes, as is the case in DS. Furthermore, since the mutation has been reported with an autosomal dominant inheritance pattern (available at https://www.ncbi.nlm.nih.gov/clinvar/variation/496124/), it seems reasonable that the patient has a 50% chance of having a child with the mutation for each pregnancy, with a phenotype within the GEFS+ spectrum, including DS.

In conclusion, truncating mutations in SCN1A may be associated with milder phenotypes within the GEFS+ spectrum. Therefore, it may be reasonable to perform SCN1A gene testing as part of the assessment for sporadic patients with mild phenotypes that fit within the GEFS+ spectrum (in this case, recurrent febrile and afebrile asymmetric generalized tonic-clonic and focal impaired awareness seizures without confirmed prolonged febrile seizures), since the finding of a mutation may have diagnostic, therapeutic, and genetic counselling implications.

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
AJ and RGL have no conflicts of interest to declare. BGG has received honoraria for activities organized by UCB and Eisai. JS has received honoraria from UCB, Esteve, Eisai, GSK, Sanofi, Bial, Merck Sharp & Dohme, Johnson & Johnson, and GW Pharmaceuticals for participation in advisory boards or industry-sponsored symposia.

References


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**TEST YOURSELF**

(1) What is the most common phenotype associated with SCN1A truncating mutations?

(2) Why should SCN1A gene testing be performed as part of the assessment for sporadic patients that fit within the GEFS+ spectrum?

(3) Why is it important to avoid some AEDs, such as sodium channel blockers, in patients with GEFS+ spectrum phenotypes?

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section “The EpiCentre”.*