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SPECIAL REPORT

SCN1A testing for epilepsy: Application in clinical practice

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Summary

This report is a practical reference guide for genetic testing of *SCN1A*, the gene encoding the α1 subunit of neuronal voltage-gated sodium channels (protein name: $Na_v1.1$). Mutations in this gene are frequently found in Dravet syndrome (DS), and are sometimes found in genetic epilepsy with febrile seizures plus (GEFS+), migrating partial seizures of infancy (MPSI), other infantile epileptic encephalopathies, and rarely in infantile spasms. *Recommendations for testing:* (1) Testing is particularly useful for people with suspected DS and sometimes in other early onset infantile epileptic encephalopathies such as MPSI because genetic confirmation of the clinical diagnosis may allow optimization of antiepileptic therapy with the potential to improve seizure control and developmental outcome. In addition, a molecular diagnosis may prevent the need for unnecessary investigations, as well as inform genetic counseling. (2) *SCN1A* testing should be considered in people with possible DS where the typical initial presentation is of a developmentally normal infant presenting with recurrent, febrile or afebrile prolonged, hemiclonic seizures or generalized status epilepticus. After age 2, the clinical diagnosis of DS becomes more obvious, with the classical evolution of other seizure types and developmental slowing. (3) In contrast to DS, the clinical utility of *SCN1A* testing for GEFS+ remains questionable. (4) The test is not recommended for children with phenotypes that are not clearly associated with *SCN1A* mutations such as those characterized by abnormal development or neurologic deficits apparent at birth or structural abnormalities of the brain. *Interpreting test results:* (1) Mutational testing of *SCN1A* involves both conventional DNA sequencing of the coding regions and analyses to detect genomic rearrangements within the relevant chromosomal region: 2q24. Interpretation of the test results must always be done in the context of the electroclinical syndrome and often requires the assistance of a medical geneticist, since many genomic variations are possible and it is essential to differentiate benign polymorphisms from pathogenic mutations. (2) Missense variants may have no apparent effect on the phenotype (benign polymorphisms) or may represent mutations underlying DS, MPSI, GEFS+, and related syndromes and can provide a challenge in interpretation. (3) Conventional methods do not detect variations in introns or promoter or regulatory regions; therefore, a negative test does not exclude a pathogenic role of *SCN1A* in a specific phenotype. (4) It is important to note that a negative test does not rule out the clinical diagnosis of DS or other conditions because genes other than *SCN1A* may be involved. Obtaining written informed consent and genetic counseling should be considered prior to molecular testing, depending on the clinical situation and local regulations.

KEY WORDS: Diagnosis, Epileptic encephalopathy, Guideline, Seizures, severe myoclonic epilepsy in infancy (SMEI), Dravet syndrome, Sodium channel.

Genetic testing has become a powerful tool in clinical epilepsy practice in certain situations. In particular, analyses targeting the gene encoding the α1 subunit of the neuronal

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voltage-gated sodium channel *SCN1A* (protein name: $Na_v1.1$), are clinically valuable in confirming the clinical diagnosis of Dravet syndrome (DS). Mutations of *SCN1A* may also be found as a cause of genetic epilepsy with febrile seizures plus (GEFS+), migrating partial seizures of infancy (MPSI), and rarely in other syndromes. Mutations of *SCN1A* are found in 70–80% of patients with DS and in up to 10% of families with GEFS+ (Scheffer & Berkovic, 2000). The purpose of this report is to provide clinicians with practical guidance for *SCN1A* gene testing. We discuss the Who, Why, What, Where, and How of testing.

Who

Who may have a positive *SCN1A* result?

Suspected Dravet syndrome (DS) is the principal indication for *SCN1A* testing, and 70–80% of cases have a demonstrable mutation. DS typically presents between 4 and 8 months of age (range: up to 15 months) with recurrent prolonged convulsive seizures that may be lateralized (hemiclonic) or generalized (Dravet, 1978; Dravet et al., 1982, 2002). Seizures are often associated with fever or occur shortly after vaccination, which has led to the misdiagnosis of "vaccine encephalopathy" (Berkovic et al., 2006; McIntosh et al., 2010). Myoclonic, focal, and atypical absence seizures may begin between 1 and 4 years. Infants with DS usually develop normally in the first year. Developmental stagnation or regression becomes evident in the second year of life and cognitive outcome is usually poor. It is important to note that the syndromic picture takes time to evolve and early recognition may be challenging (Dravet, 1978; Dravet et al., 1982, 2002).

DS should be considered in infants with febrile seizures (FS) presenting around 6 months of age, especially those with prolonged and recurrent FS (Hattori et al., 2008; Millichap et al., 2009; Fountain-Capal et al., 2011), hemiclonic seizures, and seizures induced by bathing (Oguni et al., 2001; Hattori et al., 2008).

Genetic testing of older patients with an early history consistent with DS helps to confirm the diagnosis of DS, which may have been missed due to the relatively recent recognition of the syndrome or because of difficulties in obtaining a clear early history. Providing a molecular diagnosis is often extremely helpful to the family because it gives them an understanding of the etiology of their relative's epilepsy and intellectual disability. It also informs the prognosis and is key for genetic counseling for family members. Furthermore, recent evidence suggests that optimization of treatment even in later adult life may improve cognition (Catarino et al., 2011).

Individuals with MPSI

Infants with MPSI present with multiple types of focal seizures that begin in early infancy and increase in frequency and prove highly refractory to antiepileptic therapy. The key electroclinical feature is interhemispheric migration during a seizure (Coppola et al., 1995). Electroencephalography (EEG) shows frequent multifocal epileptiform abnormalities. MPSI is more severe than DS, with profound developmental impairment, and is considered one of the most severe forms of early infantile epileptic encephalopathy. The syndrome is much rarer than DS and easily distinguished from DS by its clinical presentation. The main cause appears to be mutations in *KCNT1* (Barcia et al., 2012), but *SCN1A* mutations have been found in a few cases (Carranza Rojo et al., 2011; Freilich et al., 2011). The strategy for genetic testing here is yet to be firmly established, but mutations in *KCNT1* should currently be considered first, and then *SCN1A* may be examined.

Individuals with other severe infantile epilepsies

SCN1A mutations may also be found in approximately 50% of children with disorders that bear some resemblance to DS. These include severe infantile multifocal epilepsy (SIMFE) (Harkin et al., 2007) and intractable childhood epilepsies with frequent generalized tonic–clonic seizures (Fujiwara et al., 2003).

SCN1A mutations are found in a small minority of children (5% or less) with other specific syndromic forms of infantile epilepsy including West syndrome (Wallace et al., 2003), generalized or focal epilepsies of unknown cause (Harkin et al., 2007), epilepsy with myoclonic-atonic seizures (previously called myoclonic-astatic epilepsy) (Wallace et al., 2001), and hemiconvulsion-hemiplegia syndrome (Sakakibara et al., 2009). Routine testing in patients with these syndromes is not currently recommended.

Individuals with epilepsy in families with GEFS+

GEFS+ is a familial syndrome usually with complex inheritance, but sometimes showing autosomal dominant transmission. Family members have extremely variable phenotypes, including typical febrile seizures, febrile seizures plus (FS+), and generalized and focal epilepsies (Scheffer & Berkovic, 1997; Wallace et al., 1998; Scheffer et al., 2009).

The clinical utility of *SCN1A* genetic testing for GEFS+ is limited because few families (approximately 10%) have been found to have mutations, and the identification of a mutation does not predict the phenotype that will develop in an individual (Ottman et al., 2010). At present, therefore, infants and children in families with GEFS+ should not be advised to undergo *SCN1A* testing as it will neither influence management nor provide information regarding the patient's prognosis.

Who is unlikely to harbor an *SCN1A* mutation?

SCN1A mutations are not found in children with confirmed metabolic disorders, genetic syndromes, or those with structural abnormalities of the brain. For a child with

an epileptic encephalopathy with features not found in DS, such as neonatal onset, or developmental delay prior to seizure onset, *SCN1A* testing is unlikely to be helpful. A variety of other genes have been associated with early onset epileptic encephalopathies, including *ARX, STXBP1, and CDKL5* where developmental delay and interictal epileptiform abnormalities in early infancy are usual.

Another differential diagnosis to be considered is epilepsy and mental retardation limited to females (EFMR), perhaps better denoted *PCDH19*-female-limited epilepsies (as not all affected females have mental retardation (Dibbens et al., 2008; Scheffer et al., 2008), which share phenotypic features with DS (Depienne et al., 2009). However, status epilepticus induced by fever is a rare clinical presentation in this syndrome, which presents with clusters of brief febrile seizures continuing over several days (Marini et al., 2010; Higurashi et al., 2011). *PCDH19*-female-limited epilepsies are less likely to be associated with myoclonic and absence seizures, more likely to be associated with autistic features, and carry a better intellectual prognosis than does DS (Dibbens et al., 2008; Scheffer et al., 2008). *PCDH19*-female-limited epilepsies have a distinctive inheritance pattern as only females are affected, so recognition of this pattern in a family suggests that *PCDH19* may be more appropriate for initial testing than *SCN1A*.

Why

Why is *SCN1A* testing useful in DS?

Molecular confirmation of *SCN1A* defects supports the clinical diagnosis and is of considerable importance for genetic counseling. Knowledge of the gene involved will guide the selection of antiepileptic treatment. Some antiepileptic drugs such as specific sodium channel blocking agents, for example, carbamazepine and lamotrigine, are contraindicated as they may aggravate symptoms (Guerrini et al., 1998), whereas stiripentol has been shown to be effective in children (Chiron et al., 2000). Anecdotal evidence suggests that the early use of appropriate drugs, and avoidance of medications that may worsen DS, may lead to an improved long-term outcome, but this needs more rigorous assessment.

When an *SCN1A* mutation is identified, the parents must be investigated for this particular mutation to establish if it has arisen de novo. Among *SCN1A* mutations identified in patients with DS, 90% are de novo (Depienne et al., 2009). The remaining 10% of identified mutations are inherited and family members often have milder GEFS+ phenotypes. It is notable that there are now many well-documented instances of mosaicism (i.e., a mixture of mutation-carrying and noncarrying cells) in the parents of DS patients, either in the germ cells (parental germ line mosaicism) or somatic cells (parental somatic mosaicism). Both forms of parental mosaicism markedly increase the risk of parents having a second child with DS (Depienne et al., 2006). Also notable is that the percentage of abnormal cells in the mosaic parent correlates with whether the parent is affected and the severity of the parent's epilepsy (Depienne et al., 2010). These observations highlight the importance of genetic counseling for families with DS or another *SCN1A*-related epileptic encephalopathy.

What

What do the tests mean?

Comprehensive evaluation for an *SCN1A* mutation requires that two different testing methods be performed (Table 1). Conventional DNA sequencing has the highest yield and should be carried out first to screen the gene's coding regions and associated splice junctions. The approach is based on classic PCR (polymerase chain reaction) methodology followed by Sanger sequencing. Because directed sequencing is limited in coverage and commonly restricted to gene regions likely to affect the encoded protein and previously identified regulatory regions (the coding sequence, all splice junctions, and—in rarer cases—the 5′ and 3′ untranslated regions as well as the proximal and distal promoter, mutations in areas of apparently lesser relevance can be overlooked (Nakayama et al., 2010). Second, multiplex ligation-dependent probe amplification (MLPA) or comparative genomic hybridization (CGH) (Mulley et al., 2006; Suls et al., 2006; Wang et al., 2008; Marini et al., 2009) should be carried out to detect genomic rearrangements, such as microdeletions or microduplications within *SCN1A* and also in the *SCN1A* gene neighborhood of chromosomal region 2q24.

Table 2 explains mutation nomenclature. Truncations of the α1 subunit of $Na_v1.1$, which often result from nonsense mutations, splice site mutations, and small insertions and deletions (indels), are likely to have considerable impact on the function of $Na_v1.1$ and hence to cause severe phenotypes such as DS or MPSI. A missense mutation is a single nucleotide mutation that alters only one amino acid. Compared with truncation mutations, missense mutations generally have less impact on the $Na_v1.1$ function but nevertheless are responsible for about half the cases of DS, so the nature of the mutation does not allow the clinician to confidently predict the phenotype (Zuberi et al., 2011). The *SCN1A* mutations identified in GEFS+ have been largely missense mutations. Missense mutations altering the polarity of the amino acids in the pore-forming and voltage-sensor regions may be more likely to have a severe phenotype (Zuberi et al., 2011).

Genomic rearrangements, typically chromosomal microdeletions and microduplications, may involve several genes contiguous to *SCN1A* and hence result in severe forms of DS and other epilepsies, but sometimes with more extensive features involving other systems.

The *SCN1A* mutations identified are heterozygous, affecting one allele (either the maternal or the paternal gene

Table 1. *SCN1A* mutations and interpretations

Type of variations	Common phenotypes	Uncommon/rare phenotypes	Explanatory examples for the description (Lossin, 2009)
Small scale variations			
Missense mutation	DS, GEFS+	MPSI, SIMFE, ICEGTC	c.3820T>A: p.Y1274N c.5075T>C: p.F1692S
Nonsense mutation	DS	SIMFE	c. 1834 C>T: p.R612X c. 3858 G>A: p.W1286X
Splice-site mutation	DS		c.265-1G>A c.1662+1G>T
Deletion mutation	DS	MPSI	c.429_430delGT: p.V143VfsX149 c.5296_5298delTTT: p.F1766del
Insertion mutation	DS		c.992_993insT: p.L331fsX340 c.1640_1641insA: p.K547fsX549
Large-scale variations			
Microdeletion	DS		
Microduplication	DS	SGE	
cf) Nonpathogenic small-scale variations			
Polymorphism	Nonpathogenic coding variant found in general population	c.1662G>A: p.Q554Q c.5771G>A: p.R1924H	

DS, Dravet syndrome; MPSI, migrating partial seizures of infancy; GEFS+, genetic epilepsy with febrile seizures plus; SIMFE, severe infantile multifocal epilepsy; ICEGTC, intractable childhood epilepsy with generalized tonic–clonic seizures, SGE, symptomatic generalized epilepsy.

(1) Small-scale *SCN1A* variations

Missense mutations are due to single nucleotide exchange resulting in a substitution of a single amino acid. This exchange suggests protein dysfunction using evidence drawn from in vitro or in vivo testing or in silico analysis.

Nonsense mutations generate premature stop codons truncating the α1 subunit molecule, thus named also "truncation mutation." The truncation mutations generally result in DS or related epileptic encephalopathies. They are designated by adding an "X" at the end of their descriptions, for example, c.C1834T: p.R612X, c.429-430delGT: p.V143VfsX149.

Splice-site mutations are located in the vicinity of a splice junction at the intron/exon boundaries. They affect the messenger RNA (mRNA) and lead to considerable changes in the α1 subunit amino acid content (e.g., exon skipping, nonsensical translation of introns) that commonly result in premature truncation due to stochastic occurrence of a stop codon. Determining the effect of splicing abnormalities is challenging and usually exceeds the scope of standard genetic analyses. As such, typical genetic testing will comment only on those splice-site mutations that have been previously extensively studied in a laboratory and have proven functional impact.

Deletions of base pairs have one of two consequences: (1) an in-frame deletion eliminates one or more amino acids from the α1 subunit molecule; (2) a frame-shift mutation recodes all residues downstream of the variation site and frequently results in a premature stop codon. As such they severely impair protein function. Several meta-analyses attempting to identify *SCN1A* genotype–phenotype correlations have found evidence for higher seizure severity with structurally/functionally more significant changes in the $Na_v1.1$ protein.

Insertions are analogous to deletions. They add contiguous nucleotides in the *SCN1A* gene. The consequences are also similar to that of deletion mutations, commonly resulting in DS.

(2) Large-scale *SCN1A* variations

Variations of this kind commonly affect the copy number of the *SCN1A* gene as they involve chromosomal rearrangements that may delete or duplicate entire gene regions.

Microdeletions: Approximately 10% of all individuals for whom conventional sequence analysis of *SCN1A* does not reveal any abnormalities harbor microdeletions that may affect not only *SCN1A* but also adjacent genes (Wang et al., 2008; Marini et al., 2009). Microdeletions typically cause DS, even if adjacent genes (e.g., *SCN2A*, *SCN7A*, etc.) are involved (Wang et al., 2008).

Microduplications: Chromosomal duplications ranging from 1 kb to several Mbp are a rare cause of DS (Marini et al., 2009; Heron et al., 2010; Raymond et al., 2011).

Table 2. Checklist for *SCN1A* genetic test

Explain the potential benefit and harms of the test
Disclose limitations of the test
Provide genetic counseling
Obtain written informed consent depending on local regulations

copy). As noted above, in DS most *SCN1A* mutations are de novo, occurring for the first time as the result of a genetic event either in the germ cell line of one of the parents or during early embryogenesis, since neither parent has the mutation. The possibility of germ line or somatic mosaicism needs to be considered (see above). Detection of *SCN1A* mosaicism is often difficult, especially when it affects the germ line, which complicates genetic counseling for DS (Depienne et al., 2006; Gennaro et al., 2006; Marini et al., 2006). In contrast, cases of GEFS+ with *SCN1A* mutations are usually familial, although de novo cases are known. Occasionally, a patient with DS may be observed in a family where other members have GEFS+ with mild seizure disorders. All the affected family members have the familial *SCN1A* mutation and it is presumed that the more severely affected family member with DS has additional genetic variants that contribute to their severe phenotype.

Databases listing all currently reported variations are available: *The SCN1A Infobase* (http://www.scn1a.info/)

and *The SCN1A Variant Database* (http://www.molgen.ua.ac.be/SCN1AMutations/Statistics/Mutations.cfm).

What does a negative *SCN1A* test suggest in DS and GEFS+?

A negative SCN1A test is found in 20–30% of DS and 90% of GEFS+ families. Mutations in the *SCN2A* gene, which codes for the α2 subunit of the neuronal sodium channel $Na_v1.2$ (Shi et al., 2009), and in *GABRG2*, which encodes the γ2 subunit of the γ-aminobutyric acid $(GABA)_A$ receptor, also lead to severe epileptic encephalopathies resembling DS, as well as GEFS+ (Harkin et al., 2002). Finally, heterozygous mutations of *SCN1B*, the gene encoding the β1 subunit in the voltage-gated Na^+ channel complex, can also cause GEFS+ (Wallace et al., 1998), whereas homozygous mutations in the same gene have been reported to cause DS or an early onset epileptic encephalopathy (Patino et al., 2009; Ogiwara et al., 2012). In females with a Dravet-like phenotype in whom *SCN1A* testing is negative, testing for *PCDH19* mutations should be considered (see above). Negative *SCN1A* testing therefore does not rule out the diagnosis of DS or GEFS+, which are based on their electroclinical phenotypes.

Where

Where can *SCN1A* testing be requested; availability and costs?

A practical concern is that the test may not be commercially available worldwide and when available insurance companies may or may not cover the costs. There are several commercial providers of services that sequence the *SCN1A* gene. Insurance companies may cover the costs associated with molecular diagnosis; this varies between countries and insurance plans and should be checked before ordering. International research laboratories set up for *SCN1A* sequencing (academic or industrial) are an alternative resource imposing a minimal cost or sometimes none at all. They often are not, however, formally approved for providing a diagnostic testing service and may not be allowed to report results back to physicians and families. Laboratory information, both commercial and research, is available at GeneTests http://www.ncbi.nlm.nih.gov/sites/GeneTests/. Hopefully, recent advances in molecular testing may allow commercial companies to significantly lower pricing. The benefits derived from the testing may persuade insurance companies or government providers to fund testing.

How

How must the subject be prepared for the test?

Prior to any *SCN1A* genetic testing, the patient's history should be reviewed to ensure that the phenotype warrants the suggested analysis (Ottman et al., 2010) (Table 2). The benefit and potential harms of the test, as well as its limitations, must be carefully explained to individuals offered *SCN1A* testing. Detailed information on these matters is available elsewhere (Ottman et al., 2010). Genetic counseling should be offered. Written informed consent may be appropriate (and may be required; e.g., in the United States) depending on the clinical context and on specific local regulations; where doubt exists, advice from a medical geneticist is helpful.

DNA for genetic diagnoses can be obtained in a variety of ways, such as ethylenediaminetetraacetic acid (EDTA)-treated peripheral blood, heparinized blood, or saliva; the specific submission details are usually dictated by the diagnostic laboratory.

Conclusions

SCN1A genetic testing for DS and related disorders is a valuable tool in the clinical practice of epilepsy. DS should be suspected in an initially developmentally normal infant presenting with recurrent, febrile or afebrile prolonged, hemiclonic seizures or generalized status epilepticus. Testing can confirm the clinical diagnosis and thus reduce the likelihood of additional, unnecessary investigations. It aids in genetic counseling and assists with prognostic counseling. In contrast, *SCN1A* genetic testing for GEFS+ is not encouraged, because only 10% of families with GEFS+ have mutations, and a positive test in an individual does not provide meaningful information about prognosis.

Detection of *SCN1A* mutations is also useful for treatment because it can guide the selection of antiepileptic medications (Chiron & Dulac, 2011) and may thereby influence outcome, although this needs further validation. If experimental treatments based on genetic information alter the long-term outcome, then earlier genetic diagnosis will become even more important.

Finally, it is noteworthy that the landscape for the detection of *SCN1A* mutations is shifting rapidly given the evolving technology for whole genome sequencing (WGS). The era of "precision medicine," when WGS and surveying for a vast spectrum of susceptibility and pathogenic mutations will be a standard part of the evaluation of an individual's health, will soon arrive. This will undoubtedly make the process related to identification of *SCN1A* mutations in clinical practice simpler, although this will be more than offset by the complexity of understanding the appropriate strategies for counseling and treating patients based on information gleaned from their entire genome.

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Useful Websites

GeneTests: http://www.ncbi.nlm.nih.gov/sites/GeneTests/.

The *SCN1A* infobase: http://www.scn1a.info/.

SCN1A Variant Database: http://www.molgen.ua.ac.be/SCN1AMutations/Statistics/Mutations.cfm.

Recommendations for the description of DNA sequence variants: http://www.hgvs.org/mutnomen/recs-DNA.html.