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Brief Communication

A novel inherited *SCN1A* mutation associated with different neuropsychological phenotypes: Is there a common core deficit?

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ABSTRACT

We report a three-generation, clinically heterogeneous family in which we identify a novel inherited splicing mutation of the *SCN1A* gene. Thirteen subjects were submitted to genetic analysis, clinical and instrumental examination, and neuropsychological assessment.
In eight subjects, a heterozygous c.2946+5G>A donor splice site alteration in the *SCN1A* gene was found. Half of them had never had a seizure and showed normal EEG and cognitive profile, whereas the other half had a history of seizures and variable neuropsychological impairments ranging from moderate cognitive disabilities to mild visual–motor impairments. Different clinical phenotypes were identified, including generalized epilepsy with febrile seizure plus (GEFS+), Dravet syndrome, and partial epilepsy with febrile seizure plus (PEFS+).
Remarkable clinical heterogeneity can be found among family members carrying the same *SCN1A* gene mutation. Variable involvement of visual–motor abilities might represent a neuropsychological feature which needs to be further explored in other familial cases.

1. Introduction

The *SCN1A* gene, which encodes the α1 subunit of the neuronal sodium channel, is the most relevant epilepsy gene with the largest number of epilepsy-related mutations. De novo mutations of the *SCN1A* gene are observed in about 80% of patients with Dravet syndrome (DS). Dravet syndrome is a rare and distinct epileptic encephalopathy, which begins with infantile onset of febrile hemiclonic status epilepticus and evolves into a pattern of multiple seizure types including focal, myoclonic, absence, and atonic seizures. Seizure profile is typically associated with marked slowing or stagnation of psychomotor development, often accompanied by behavioral disturbances [1–5]. Inherited *SCN1A* mutations, usually missense, are found in 5% of patients with DS. Families of probands with DS with inherited mutations include milder phenotypes consistent with febrile seizures (FS), febrile seizure plus (FS+), or generalized epilepsy with febrile seizure plus (GEFS+) [6,7]. Mutations of the *SCN1A* gene have also been found in a few patients with partial epilepsy with febrile seizure plus (PEFS+) and, more rarely, in patients with ataxia and coordination defects [6,8].

Familial cases offer a unique opportunity to explore the clinical heterogeneity of *SCN1A* mutations. Previous reports have documented remarkable clinical heterogeneity in both epilepsy-related factors and cognitive level [9,10]. However, variability of neuropsychological functioning in familial cases has been incompletely investigated. More specifically, the neuropsychological profile of those family members who have not experienced seizures, despite carrying the mutation, has not been usually studied. Investigation of both affected and nonaffected family members carrying the same mutation might shed light on the interplay between genetic and epilepsy-related factors in neurocognitive development.

Herein we report a three-generation, clinically heterogeneous family in which we identified a splicing mutation of the *SCN1A* gene and describe neuropsychological findings.

2. Materials and methods

2.1. Clinical assessment

The institutional review board approved the study protocol. Written informed consent was obtained from each subject involved in the study. The proband (IIIa) was referred to the pediatric epilepsy clinic for investigation of a seizure disorder that had a familial distribution. The family

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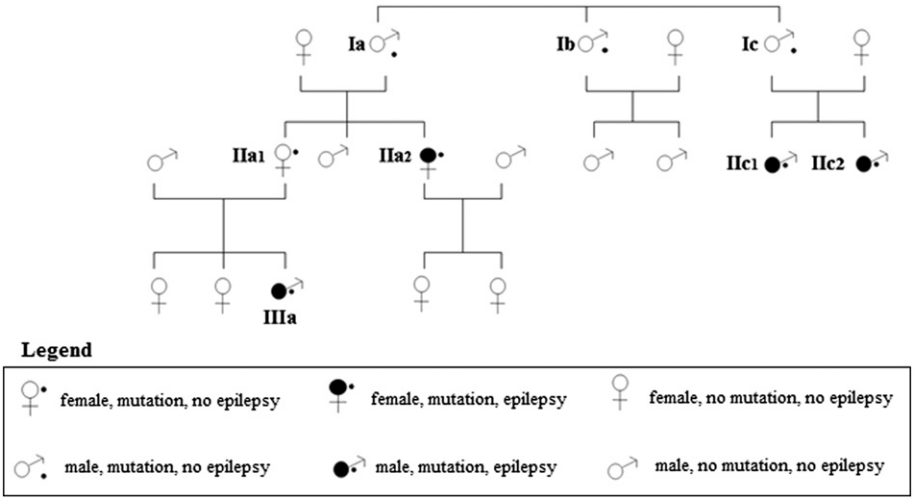

Fig. 1. The diagram represents a family tree. Ordinal numbers identify generations within the same family (I: first generation, II: second generation, III: third generation). Letters identify subjects belonging to the same family nucleus, i.e., a family group consisting of a pair of adults and their children. Cardinal numbers identify birth position within the family nucleus.

originated from central Italy; a pedigree is shown in Fig. 1. Fifteen subjects belonging to the same family as proband IIIa were contacted for a clinical examination and blood sample collection for DNA analysis. Thirteen subjects gave the consent to participate. The clinical history of each family member was collected by direct interview and retrospective review of the original medical records of individuals IIa2, IIb, IIc1, IIc2, and IIIa. Standard electroencephalography (EEG) recording in sleep and awake states (minimum duration: 40 min) was performed in all subjects. In subjects with a history of seizure, a 24-hour video-EEG recording was also carried out. Electroencephalography records were assessed by an expert neurologist. Based on the clinical history, we decided to investigate the possible involvement of the *SCN1A* gene. A formal neuropsychological assessment was carried out at the time of the study in each subject using standardized instruments validated on an Italian sample. The mean age of subjects at testing was 37 years (range: 5–73). Assessment included an evaluation of cognitive level (IQ, intelligence quotient) by means of the Wechsler Preschool and Primary Scale of Intelligence (for subject IIIa) and the Wechsler Adult Intelligence Scale-R (for the remaining subjects), attention and executive functions (Trail-Making Test, Bells test), memory abilities (digit and visual–spatial span, short-story test), visual–motor abilities (Rey Figure test), and linguistic skills (Verbal Fluency test). A psychiatric interview was also performed [11–19].

2.2. Genetic analysis

Molecular analysis was performed on genomic DNA extracted from the blood using a QIASymphony SP robot (QIAGEN, Hilden, Germany). All 26 exons of *SCN1A* (accession NM_001165963.1) were amplified by polymerase chain reaction (PCR) and analyzed by direct sequencing in the proband (patient IIIA) (see Supplemental material for details). The novel *SCN1A* substitution identified in the proband was tested in all the available family individuals to study its segregation. Since the substitution was located near a splice site, we used the Splice Site Prediction by Neural Network (http://www.fruitfly.org/seq_tools/splice.html), Human Splicing Finder (http://www.umd.be/HSF/), and NetGene2 (http://www.cbs.dtu.dk/services/NetGene2/) splicing prediction tools to explore its role in affecting the splicing process. Unfortunately, the *SCN1A* gene is not expressed in easily accessible tissues (i.e., blood or fibroblasts), and therefore it has not been possible to study the impact of the substitution on mRNA splicing.

This *SCN1A* novel splicing substitution was not found in a cohort of 190 Caucasian ethnically matched control DNAs (380 alleles) originating from Italy and was not reported in the ESP6500 (13,006 alleles) and dbSNP137 databases.

3. Results

3.1. Genetic findings

We identified a heterozygous c.2946+5G>A donor splice site alteration in the *SCN1A* gene in eight out of the thirteen subjects examined. Segregation analysis revealed that the mutation showed an incomplete penetrance and variable expressivity. In silico predictions indicated that the substitution likely alters the donor site thus leading to a potential loss of the coding sequence (exon skipping) or to retention of intronic sequence or may lead to a frameshift mutation. Since *SCN1A* is not expressed in easily accessible tissues, we could not study mRNA, and therefore we cannot establish which one of these mechanisms was the one arising from the mutation.

3.2. Subjects' characteristics and neuropsychological findings

Four out of the eight individuals with *SCN1A* gene mutation (Ia, Ib, Ic, IIa1) have never had seizures, whereas the remaining four had manifested their initial seizures between 8 and 11 months of age. In all these cases, seizures were triggered by fever. The first seizure was complex partial (IIIa, IIb), generalized tonic–clonic (IIa2), and generalized tonic (IIc1, IIc2). Patient IIc2 experienced convulsive hemiclonic status epilepticus at the age of two years. In this subject, status epilepticus was triggered by fever >38° which lasted 4 h and required hospitalization in an intensive care unit. At the time of the study, the youngest subject (IIIa) still experienced partial seizures with secondary generalization with a frequency of twice per year. In the remaining three patients, seizures disappeared between three and twenty-four years of age. All patients with epilepsy had been treated with AEDs (IIa2, IIc1, IIb), with two or more AEDs in individuals IIIa and IIc2; three of these subjects (IIa2, IIa, IIc2) were still treated with more than one AED at the time of the study. Electroencephalography showed alterations in four subjects, all having a history of seizures. Electroencephalography abnormalities included spikes and a spike–wave complex predominantly over the right occipital lobe (IIIa), spike and sharp waves over both temporoparietooccipital lobes (IIa2), sharp waves over both temporoparietal lobes (IIc2), and sharp waves over the left temporoparietooccipital lobe (IIc1). No structural alteration was revealed by MRI in any subject.