


CLINICAL REPORT

Commonalities and distinctions between two neurodevelopmental disorder subtypes associated with *SCN2A* and *SCN8A* variants and literature review

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Abstract

This study was aimed to analyze the commonalities and distinctions of voltage-gated sodium channels, Nav1.2, Nav1.6, in neurodevelopmental disorders. An observational study was performed including two patients with neurodevelopmental disorders. The demographic, electroclinical, genetic, and neuropsychological characteristics were analyzed and compared with each other and then with the subjects carrying the same genetic variants reported in the literature. The clinical features of one of them argued for autism spectrum disorder and developmental delay, the other for intellectual disability, diagnoses confirmed by the neuropsychological assessment. The first patient was a carrier of *SCN2A* (p.R379H) variant while the second was carrier of *SCN8A* (p.E936K) variant, both involving the pore loop of the two channels. The results of this study suggest that the neurodevelopmental disorders without overt epilepsy of both patients can be the consequences of loss of function of Nav1.2/Nav1.6 channels. Notably, the *SCN2A* variant, with an earlier expression timing in brain development, resulted in a more severe phenotype as autism spectrum disorder and developmental delay, while the *SCN8A* variant, with a later expression timing, resulted in a less severe phenotype as intellectual disability.

KEYWORDS

autism spectrum disorders, EEG, epilepsy, intellectual disability, *SCN2A*, *SCN8A*, whole-exome sequencing

1 | INTRODUCTION

Voltage-gated sodium channels (VGSC) exert a key function in neuronal excitability and their specific clustering

at axon initial segments (AISs) and nodes of Ranvier is essential for effective action potential initiation and propagation (Catterall, 2012; O’Brien & Meisler, 2013). The most genes linked with epilepsy frequently investigated are

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SCN1A, *SCN2A*, *SCN3A* (located on 2q24.3), and recently *SCN8A* (located on 12q13.13) which encode $Na_v1.1$, $Na_v1.2$, $Na_v1.3$, and $Na_v1.6$ respectively. Overall, they are responsible for a significant number of early-onset genetic epilepsies characterized by a wide phenotypic spectrum, ranging from mild treatable seizure disorders to severe epileptic encephalopathies (EEs). Notably, epileptic phenotype *SCN1A*-related ranges from benign febrile seizures (FS) to severe Dravet syndrome, epileptic phenotype *SCN2A*-related ranges from self-limiting benign familial neonatal-infantile epilepsy (BFNIE) to severe Ohtahara syndrome, the *SCN8A*-related epileptic phenotype is linked to a spectrum ranging from severe early infantile epileptic encephalopathies (EIEE) to benign familial infantile epilepsy (BFIE) (Brunklaus et al., 2020; Musto et al., 2020; Wolff et al., 2017). VGSCs share a similar amino acid sequence and structure, but their genetic variants lead to different dysfunctions as *SCN1A* is mostly expressed in inhibitory neurons, whereas *SCN2A/8A* is mainly expressed in excitatory neurons. In addition, *SCN1A*-related epileptic phenotype is mainly linked to loss of function (LoF) of $Na_v1.1$, whereas the *SCN2A/8A*-related epileptic phenotypes are mostly linked to gain of function (GoF) of $Na_v1.2$, and $Na_v1.6$.⁴ Further, $Na_v1.2$ and $Na_v1.6$, while being structurally and functionally similar, differ from each other in the age of expression, being $Na_v1.2$ present early from the prenatal late second trimester to 1–2 years of age, when it is largely replaced by $Na_v1.6$ (Sanders et al., 2018).

During the last decade, the increasing use of next-generation sequencing (NGS) technologies, including whole-exome sequencing (WES) for the diagnostic evaluation of patients with epileptic syndromes, led to more than 300 patients diagnosed with *SCN8A* mutations and 276 subjects with *SCN2A* mutations with gain-of-function hyperactivity as the predominant pathogenic mechanism (Meisler, 2019; Sanders et al., 2018; Solé et al., 2020). In addition, a broadening of the phenotypic spectrum *SCN2/8A*-related, that includes heterogeneous neurodevelopmental disorders (NDD), is arising in a way quite evident (Larsen et al., 2015; Wagnon et al., 2017). Interestingly, a case series of 21 patients with *SCN2A*-associated Episodic Ataxia (EA) and epilepsy have been recently described suggesting a feasible upcoming identification of a specific phenotype/genotype also supported by an increasing targeted therapeutic approach such as acetazolamide in some patients (Dilena et al., 2017; Schwarz et al., 2019).

These findings made it difficult to outline a genotype/phenotype correlation due to increasing phenotypic variability since today carriers of *SCN8A* variants include individuals with distinct clinical features ranging from EE until isolated cognitive impairment, the latter linked to loss of channel function as the predominant pathogenic mechanism. In the same way, no precise correlation

between phenotypic severity and genetic variant has been highlighted despite more than 150 missense mutations of *SCN8A* has been identified (Meisler, 2019; Solé et al., 2020). So, the electrophysiological analysis is a useful procedure to predict the clinical consequences and the pathogenic mechanism of a variant since, today, it represents a crucial step for a more specific and effective treatment.

However, although the functional characterization gives the obvious benefits, it entails challenging laboratory investigations that currently interfere with widespread use in clinical care and as a result, only 14 functional characterizations of missense $Na_v1.6$ variants are reported today, 12 of which recognized as GoF (Solé et al., 2020). Similarly, only about 20 *SCN2A* variants have been electrophysiologically assessed (Sanders et al., 2018). To overcome these limitations, studies aimed at identifying the relationship between phenotype and location of known and functionally characterized variants have recently been carried out. The results revealed that LoF missense variants with channel loss of function often localize to the pore region (especially the S5–6 region); while variants with a gain-of-function are identified in the voltage sensor (S4), in DIII–IV linking, and in C-terminal regions. The former was identified in individuals with neurodevelopmental disorders without epilepsy, the latter in patients with the epileptic phenotype (O'Brien & Meisler, 2013; Wagnon et al., 2017).

The growing number of identified *SCN2A/SCN8A* variants, against the few available functional studies, have opened new investigative hypotheses aimed to build a powerful and accurate map of pathogenic variants as a surrogate of functional analysis and with positive effects on the therapeutic choice (Gardella & Møller, 2019; Johannesen et al., 2019).

We think that strengthening recent research lines, focused on the identification of distinct hotspots with recurrent mutations and on their concurrent increase in size, could be a productive way to identify and better understand the role of the environment, of the genetic background, and/or of the modifier genes on phenotypic expression (Schwarz et al., 2019). As previously suggested, an overall assessment that takes into account both genetic data and detailed clinical features such as developmental delay/regression, electroclinical pattern with the age of onset, sensitivity to AEDs, neuropsychological profile, other comorbidities, and the clinical outcome would also facilitate systematic identification and a better understanding of the *SCN2A/SCN8A*-related phenotypic spectrum.

Here we report two patients, carrying *SCN8A* E936K and *SCN2A* R379H variants, with NDD and distinct EEG patterns without epilepsy, notably the former suffers from an intellectual disability (ID) and the latter from development delay (DD) and autism spectrum disorder (ASD).

2 | METHODS

An observational study was performed enrolling patients with neurodevelopmental disorders without overt epileptic seizures due to missense *SCN2A/8A* variants referred to the Child Neuropsychiatry Unit of University Hospital of Palermo, Italy. Clinical information was retrospectively and prospectively collected by interviews with patients and their families and from clinical documents. The patients underwent neurological and psychiatric evaluation, electroencephalographic recording, and detailed neuropsychological assessment with standardized formal tools.

Written informed consent, including an agreement for publication of data in scientific journals, was obtained from the patient's parents. This study was approved by the ethics committee Palermo 1 of "Paolo Giaccone" University Hospital of Palermo, Italy.

3 | RESULTS

We identified 4 patients carrying *SCN2A/8A* variant referred to the Department of Child Neuropsychiatry. Two of them, mother and daughter, carrying a de novo *SCN8A* (NM_014191.3) c.5630A>G; p.N1877S variant in C-terminal, had moderate ID and rare epileptic focal seizures responsive to antiepileptic drugs. These features were suggested to be more consistent with the diagnosis of intermediate *SCN8A*-related epilepsy subtype, so both patients were excluded from the study. Then, we included in the study a subject with *SCN8A* variant and ID and a child with *SCN2A* variant and DD and ASD.

3.1 | Patient 1

The proband, a 10-year and 5 months-old girl, was the third offspring born to healthy Italian unrelated parents whose cognitive, social, and academic functioning was adequate. Her family history was remarkable for learning disability and psychiatric disorder in her mother's sister and brother respectively. She was born at the 38th week of gestation by elective cesarean section following an uneventful pregnancy. Her birth weight was 3500 g (75th percentile), height cm 49 (10th percentile), head circumference 33 cm (25th percentile) and her clinical postnatal course was uneventful. Head control, sitting without support, and walking were achieved at 3, 10, and 22 months, respectively; she spoke the first words at 1 year followed by slow lexical development. Her academic skills remained impaired, and she received permanent educational support at school.

At the age of 5 years and 10 months, she was referred to our Child Neuropsychiatric Department, because of developmental delay, learning, and language difficulties. At last admission (age 10 years and 5 months), the neurological examination showed head circumference 48,5 cm (<3rd percentile), height cm.129 (<3rd percentile), weight kg 25 (3rd percentile), normal deep tendon reflexes, moderate motor, and coordination impairment, clumsiness with specific difficulties such as get off the sidewalks or stairs, but she was able in the basic tasks of daily activities; in addition, she exhibited shyness, low frustration tolerance, irritability.

The level of intellectual abilities, assessed with the Wechsler Intelligence Scale for Children IV Edition (WISC IV), showed that all Index scores were in the extremely low range except the Verbal Comprehension Index that was in the extremely low-borderline range (VCI 63–77) emerging as a significant individual strong point.

The NEPSY II, a neurodevelopmental neuropsychological battery, administration showed affected attention, memory, learning, visuospatial, and visuomotor abilities (scaled score 1–3). The child's performances fell in the "well below expected level." However, the child maintained some control of execution and ability to monitor her own behavior showing herself capable of formulating basic thoughts.

Adaptive functioning was assessed using the Vineland Adaptive Behavior Scale-Second Edition (VABS-II). Adaptive Behavior Composite, Communication, and Daily Living Skills scores were 35, 30, and 43 respectively showing a low adaptive level. On Socialization domain her scores were in the moderately low adaptive level (60) (Table 1 and Supplementary material).

Brain MRI performed at 6 years of age showed no abnormalities.

Wakefulness and sleep EEG showed bilateral discharges of high amplitude sharp waves and slow waves in the parieto-temporo-occipital regions increasing during sleep associated with generalized sequences of 3 Hz spike and wave complexes well identified in the anterior regions without related clinical events. These abnormalities were low sensitive to intermittent photic stimulation and hyperventilation (Figure 1a,b).

Panel NGS sequencing studies for 171 genes associated with developmental and brain malformations, was performed in trios (proband and his parents) and showed a heterozygous de novo *SCN8A* (NM_014191: c. 2806G>A p.E936K2) variant. The *SCN8A* p.E936K emerged as the explanation for the disease pathophysiology, being fully consistent with the phenotype of *SCN8A* encephalopathy and confirmed de novo in the trio by Sanger sequencing. The variant c.2806G>A results in the substitution of negatively charged Glutamic

TABLE 1 Neuropsychological profile patient 1

WISC IV	Standard score	95% CI	Classification	NEPSY II	Scaled score	Classification	Scaled score
IQ	40	37–49	Extremely low	<i>Attention/executive</i>			
							List memory immediate 1 Impaired
VCI	68	63–77	Extremely low-borderline	Auditory attention	<2 percentile	Impaired	List memory delayed 1 Impaired
PRI	50	46–62	Extremely low	Visual attention	4	Impaired	Memory for names immediate 1 Impaired
WMI	49	46–64	Extremely low	Design fluency	6	Borderline	Memory for names delayed 1 Impaired
PSI	47	45–65	Extremely low	Inhibition A composite	1	Impaired	Narrative memory 2 Impaired
GAI	54	50–62	Extremely low	Inhibition B composite	1	Impaired	Sentence repetition 2 Impaired
CPI	36	—	Extremely low	Inhibition C composite	1	Impaired	<i>Social perception</i>
<i>Verbal comprehension tasks</i>	Scaled score			Animal sorting	5	Borderline	Theory of mind 1 Impaired
Similarities	5	Borderline	Borderline	<i>Language and communication</i>			Affect recognition 1 Impaired
Vocabulary	4	Impaired	Impaired	Comprehension of instructions	1	Impaired	<i>Visuospatial functions</i>
Comprehension	5	Borderline	Borderline	Speeded naming composite	4	Impaired	Design copying 1 Impaired
Information	1	Impaired	Impaired	Phonological processing	1	Impaired	Block construction 1 Impaired
<i>Perceptual reasoning tasks</i>				Semantic fluency	2	Impaired	Picture puzzles 1 Impaired
Block design	1	Impaired	Impaired	Phonological fluency	4	Impaired	Geometric puzzles 1 Impaired
Picture concepts	1	Impaired	Impaired	Repetition of nonsense words	1	Impaired	Visuomotor precision composite 4 Impaired
Matrix reasoning	5	Borderline	Borderline	Oromotor sequences	1	Impaired	
<i>Working Memory tasks</i>				<i>Learning and memory</i>			Vineland-II
Digit Span	1	Impaired	Impaired	Memory for faces immediate	1	Impaired	Scaled score
Letter/number sequencing	1	Impaired	Impaired	Memory for faces delayed	2	Impaired	Classification
							Communication 30 Low adaptive level
							Daily living skills 43 Low adaptive level

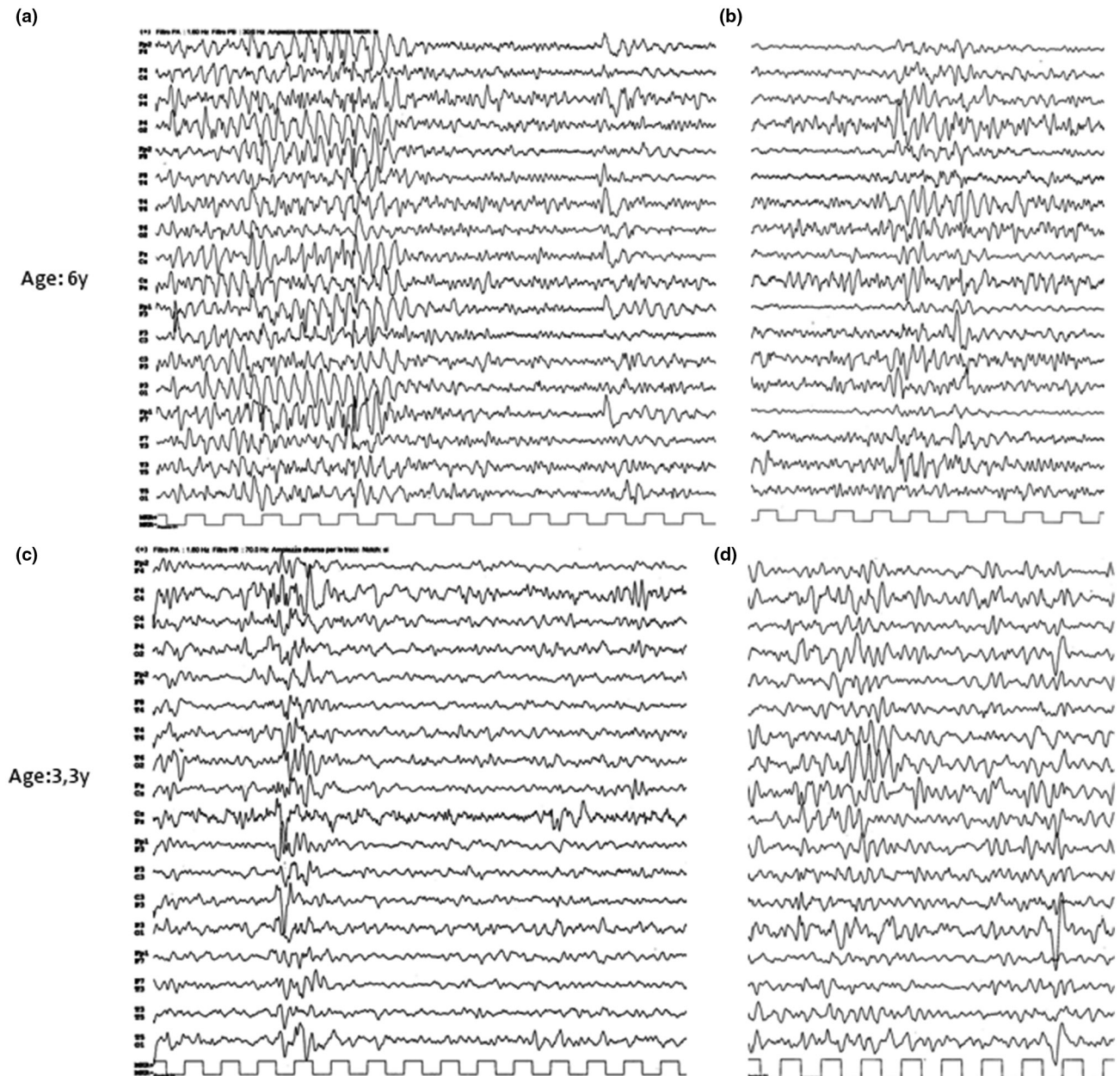


FIGURE 1 EEG: SCN8A patient (a,b); SCN2A patient (c,d). Both EEG showed bilateral discharges of high amplitude sharp waves and slow waves in the parieto-temporo-occipital regions increasing during sleep associated with right frontal-central short sequences of 3.5–4 Hz spike and wave complexes

occasionally exhibited a very low variety of conventional gestures.

To assess the developmental functioning was administered the Bayley Scales of Infant and Toddler Development Third Edition (Bayley III; Ferri et al., 2015) where all composite scores fell into the extremely low range of functioning: Cognitive scale 55, Language scale 49, Motor scale 42, Socioemotional scale 60, and General Adaptive Composite 55. Motor and language skills were delayed to a greater degree than cognitive and social skills ($p < 0.05$). The Adaptive Behavior Subscale Communication was significantly worse compared to

other adaptive skills ($p \leq 0.05$). Short Sensory Profile (McIntosh, 1999), which measures the sensory processing patterns, showed atypical sensory reactivity, predominantly in sensory modulation (Table 2 and Supplementary material). Communication, social interaction, play, and restricted and repetitive behaviors were investigated by a semistructured, standardized assessment instrument (ADOS 2 module 1) which showed impairment in social–emotional reciprocity, poor empathy, and comments on others' emotions, reduced use of eye contact, poor initiation of social interaction, along with repetitive games and use of objects. Scores in the

TABLE 2 Neuropsychological profile patient 2

Bayley III		
Scale	Composite score	Classification
Cognitive	55	Extremely low
Language	49	Extremely low
Motor	42	Extremely low
Socioemotional	60	Extremely low
General adaptive composite	55	Extremely low
Ados 2 toddler module		
Social affect	15	
Restricted and repetitive behaviors	2	
Combined domain total	17	>Cut off autism
Sensory profile		
Factors	Score	
Sensory seeking	67	Typical performance
Emotionally reactive	58	Typical performance
Low endurance/tone	31	Definite difference
Oral sensory sensitivity	27	Probable difference
Inattention/distractibility	17	Definite difference
Poor registration	24	Definite difference
Sensory sensitivity	9	Definite difference
Sedendary	13	Typical performance
Sensory processing		
Auditory	29	Probable difference
Visual	32	Typical performance
Vestibular	46	Typical performance
Tactile	73	Typical performance
Multisensory	23	Probable difference
Oral sensory	40	Probable difference
Sensory modulation		
Sensory processing related to endurance/tone	31	Definite difference
Modulation related to body position and movement	32	Definite difference
Modulation of movement affecting activity level	22	Typical performance
Modulation of sensory input affecting emotional responses	11	Definite difference
Modulation of visual input affecting emotional responses and activity level	16	Typical performance
Emotional-social responses	63	Probable difference
Behavioral outcomes of sensory processing	18	Probable difference
Items indicating thresholds for response	7	Definite difference

domains of social affect (15), restricted and repetitive behaviors (2), and combined (17) supported a diagnosis of autism (cut off >16). The comparison score (6) indicated a moderate level of autism-related symptoms (Table 2 and Supplementary material).

Wakefulness and sleep EEG showed bilateral discharges of high amplitude sharp waves and slow waves in the parietal-temporal-occipital regions increasing during

sleep associated with right frontal-central short sequences of 3,5–4 Hz spike and wave complexes (Figure 1c,d).

Panel NGS sequencing studies for 171 genes associated with developmental and brain malformations, was performed in trios (proband and his parents) and showed a heterozygous de novo *SCN2A* (NM_021007.2: c.1136G>A; p.R379H) variant. The *SCN2A* p.R379H emerged as the explanation for the disease pathophysiology, being fully

consistent with the phenotype of *SCN2A*-related syndrome and confirmed de novo in the trio by Sanger sequencing. The variant c.1136G>A causes the substitution of positively charged Arginine residue 379 with a positively charged Histidine. This variant is predicted to cause loss of normal protein function being in the DI S5-S6 linker, pore loop. Additionally, the c.1136G>A variant is not observed in large population cohorts (GnomAD database, ClinVar). The c.1136G>A variant in the *SCN2A* was previously reported only twice as a pathogenic variant in patients with *SCN2A*-related ASD (De Rubeis et al., 2014). The variant is predicted “disease causing” by Mutation Taster, “probably damaging” by Polyphen 2, “Pathogenic” by Varsome.

4 | DISCUSSION

The VGSCs are complex proteins consisting of primary pore-forming α subunits of 250 kDa and one or two auxiliary β subunits of 30–40 kDa. The channel proteins of α -subunit include nearly 2000 amino acid residues organized in four homologous domains (DI-DIV), each of which contains six transmembrane segments (S1-S6). They are characterized by similar structural and functional properties that confer a high degree of protein sequence conservation (Anderson & Greenberg, 2001; Catterall, 2012; Sanders et al., 2018).

The recent interest aroused by the involvement of LoF $\text{Na}_v1.2$ and $\text{Na}_v1.6$ in the two most important and frequent neurodevelopmental phenotypes, such as ASD and ID, has led to justified expectations for its future therapeutic options. Since we believe that objective assessments of the different cognitive and behavioral domains can identify specific and more homogeneous clinical characteristics, therefore more suitable for comparison in case studies, they can better facilitate the understanding of the pathophysiological mechanisms underlying the aforementioned disorders. So, we sought to compare the clinical findings of two of our subjects with ID and ASD respectively with each other, and then with those reported in the literature. Both *SCN8A* E936K and *SCN2A* R379H variants are located in the S5-S6 linker (P loop) of DII and DI respectively. Notably, *SCN8A* E936K alters the DEKA ring responsible for control ion selectivity. Almost all variants across different VGSCs reported in this region appear to be mainly LoF, and notably, the most *SCN2A/8A* variants associated with NDD without epilepsy are de novo (Ben-Shalom et al., 2017; Larsen et al., 2015). The phenotypes of our patients seem consistent with this last statement as the individual carrying the *SCN2A* R379H variant shows developmental delay and ASD, while the individual carrying the *SCN8A* E936K variant has ID.

It is emerging that *SCN2A* is among the genes most frequently associated with ASD, but the underlying neuropathological mechanisms are yet largely unknown. Multiple lines of evidence relative to analyses of spatio-temporal coexpression of ASD genes converge in the early to mid-fetal brain development (10–24 postconceptional weeks); notably, in layer 5/6 of prefrontal and primary motor-somatosensory cortical glutamatergic projection neurons, among first involved in synaptic connections, in striatal medium spiny neurons, and in thalamus and cerebellum during postnatal development, which overall contribute to the formation of cortico-striatal-thalamic circuits, underlying several motor, emotional, cognitive behaviors especially impaired in ASD (Chang et al., 2015; Sanders, 2015; Willsey et al., 2013).

Recently, it has been shown that $\text{Na}_v1.2$, in addition to early role in action potential initiation and propagation at AISs and at nodes of Ranvier, respectively, is selectively effective in backpropagation of action potential from proximal AISs into soma and dendrites of both immature and mature neocortical pyramidal neurons. Thus, the LoF of $\text{Na}_v1.2$ results in a persistent deficit in dendritic excitability leading to structural and functional changes in synaptic stability, plasticity, integration, and strength. Therefore, it is likely that chronic reduction of neuronal activity may change the dynamics of synaptic plasticity during maturation resulting in aberrant cerebral circuitry that may be detrimental to brain development in ASD and ID patients (Sanders et al., 2018; Spratt et al., 2019).

Among the consequences of the mutated channel protein, a key role concerns the changes associated with the development of early connectivity which typically appears to be characterized by increasing weakening of short-range connections and a simultaneous strengthening of long-range ones. An early imbalance between these two processes due to the LoF of the channel, which leads to a weakening of long-range connections underlying the information integration (Conti et al., 2017), could be influenced by the dysfunction of the *SCN2A* R379H variant.

However, ASD genes are expressed in multiple cell types and brain areas resulting in atypical patterns of connectivity that vary across systems and time and are not specific to any single brain region or behavioral domain. These findings may account for the phenotypic variability and its different severity, also found among the patients with *SCN2A* mutations, notably, stronger functional insults lead to more severe ASD phenotypes. Therefore, it is likely that the distinct phenotypes of our patients, ID, and DD-ASD, may result from different degrees of dysfunction expressed by the relative gene mutations (Chang et al., 2015).

The early haploinsufficiency of $\text{Nav}1.2$ can result in severe impairment of arising connectivity and is consistent

with severe development delay of patient 2, whereas, the haploinsufficiency of Nav1.6 can result in less detrimental impairment of late development and tuning of the connectivity, consistent with the level of the ID of patient 1. In addition, the Nav1.6 patient, exploiting the backpropagation of action potential Nav1.2 mediated, important for proper synaptic development and function, shows a less severe cognitive profile than Nav1.2 patient, and further, the lack of behavior and social impairment predominantly mediated by the backpropagation of action potential Nav1.2 related (Spratt et al., 2019). Although it is now accepted that LoF of *SCN2A* variants results in ASD/ID, one third of patients also develop late-onset epileptic seizures whose pathophysiological mechanism remains unclear being they are usually associated with GoF of *SCN2A* variants. It is likely that these events may be related to impaired connectivity or to factors other than the channel functions of *SCN2A*.

In addition, haploinsufficient *SCN2A*-mice were found to exhibit a mild absence-like epileptic phenotype caused by Na_v1.2 deficiency in cortical excitatory neurons leading to hypoexcitation of downstream inhibitory neurons in the thalamic reticular nucleus which in turn fails to suppress excitatory thalamocortical relay neurons, the hallmark of the pathogenic mechanism of absence epilepsy (Ogiwara et al., 2018). Similarly, Nav1.6-mediate hypoexcitation of cortical circuits results in non-convulsive absence epilepsy in mice and humans (Berghuis et al., 2015; Papale et al., 2009). Notably, loss of *SCN8A* from inhibitory neurons of the thalamic reticular nucleus in mice leads to hyperexcitation (hypersynchrony) of thalamocortical circuits and non-convulsive absence seizures (Makinson et al., 2017). Both our patients showed an EEG pattern characterized by bilateral discharges of high amplitude sharp waves and slow waves in the parietal-temporal-occipital regions increasing during sleep associated with short sequences of 3–4 Hz spike and wave complexes, generalized in the first patient and focal in the other one, without associated clinical events, supporting the experimental data above mentioned (Makinson et al., 2017).

In addition, the anterior predominant EEG pattern without overt epileptic seizures could mirror a weakness of the synchronous firing spreading, which seems consistent with impaired neuronal connectivity through the cerebral networks (Kaczmarek, 2019; Spratt et al., 2019).

Among the patients with *SCN8A* variants reported in the literature, we found only an 8-year-old individual with *SCN8A* E936K, likely inherited by the father suffering from ID and ADHD, whose electroclinical feature was characterized by focal seizures, atypical absence, febrile seizures, beginning at 5 years, sensitive to Levetiracetam, interictal spike-wave in the left frontal, central, and right parietal regions associated with autistic features and behavioral

problems (Johannesen et al., 2019). The comparison between the two patients shows that our girl exhibits a less severe phenotype although both could likely share the interictal EEG pattern which in the reported patient has not been described in detail anyway.

Sadly, the comparison between our patient carrying the *SCN2A* R379H variant with other subjects reported in the literature is not feasible as the other two identical variants so far identified among a series of autistic subjects are lacking in further clinical details of their relative phenotypes (De Rubeis et al., 2014). However, while the delay in the developmental milestone of our *SCN2A* carrier patient seems consistent with early expression of Na_v1.2, from the prenatal late 2nd trimester, conversely, the early development delay of our *SCN8A* carrier patient remains to be elucidated. As the expression of Na_v1.6 typically peaks between the first and second year by replacing a large extent to the Na_v1.2 functions, we would have expected a normal psychomotor development in the first 2 years supported by the typical early neuronal excitability by Na_v1.2 and by its compensatory function extended over time.

Despite the knowledge of the pathophysiological mechanisms of Na_v channels are growing, the variability of the genotype/phenotype correlation remains unclear. On the other hand, the understanding of phenotypic variability always suggests carefully considering the epistasis phenomenon resulting from other genetic factors such as in other conditions where the coincidence of different mutated genes could share common targets implicated in the same phenotype (Nardello et al., 2020).

In addition, a recent study documented that biallelic *SCN1B* variants, leading to alterations in Nav channel gating or kinetics, are predicted to increase neuron excitability and to cause the early infantile epileptic encephalopathy 52 (Scala et al., 2021).

Further, the altered relation of the Nav auxiliary β subunits and Nav channel, the additional effects of reduced early axonal excitability on network functioning, and possibly different environmental factors can play an important role in the phenotype characterization. However, as there is not always a phenotypic overlap, even when the different characteristics of substituting amino acid are taken into account, detailed analyses of the clinical features of patients with recurrent mutations could be useful in characterizing the phenotype for personalized therapeutic options (Brunklau et al., 2020; Dilena et al., 2017; Schwarz et al., 2019). Therefore, the detailed knowledge of the functioning of the Na channels appears to be an interesting goal that could lead to the discovery of effective molecules in restoring their functions even in the mature brain. Lastly, the current rarity of these disorders would suggest developing an international network, as is usually the case

with some rare diseases, which allows the exchange of clinical data and helps to identify personalized therapeutic approaches.

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CONFLICT OF INTEREST

None of the authors has any declaration of interest to disclose.

DATA AVAILABILITY STATEMENT

Data can be made available upon request.

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