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LONGITUDINAL GLOBAL AND DOMAIN-SPECIFIC NEURODEVELOPMENTAL TRAJECTORIES IN *SCN1A*-RELATED DISORDERS

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Abstract

Pathogenic *SCN1A* variants are associated with a broad clinical spectrum, ranging from fever-sensitive seizure phenotypes to Dravet syndrome and developmental and epileptic encephalopathies, with highly variable neurodevelopmental outcomes. We aimed to characterize longitudinal global and domain-specific developmental trajectories in a genetically defined pediatric *SCN1A* cohort. This retrospective longitudinal study included seven children with pathogenic or likely pathogenic *SCN1A* variants who underwent two age-appropriate Griffiths developmental assessments. General Quotient (GQ), longitudinal change in GQ (ΔGQ), and all available domain-specific subquotients (SQs) were analyzed using version-specific interpretation. The cohort comprised four girls and three boys, with a median age at seizure onset of 10 months (range, 0–48). Fever sensitivity was present in all seven children; six had a history of status epilepticus, and four had drug-resistant epilepsy. Median GQ was 84 (range, 42–100) at the first assessment and 80 (range, 38–98) at follow-up, with marked interindividual variability in longitudinal change (ΔGQ, −21 to +9). Across 14 assessments, 73 domain-specific SQs were available. In the five assessments with globally preserved development, 25 of 26 SQs (96.2%) were within the expected or average range, with no recurrent domain-specific deficit. In contrast, assessments with lower global scores showed predominantly heterogeneous multidomain involvement. These findings highlight marked heterogeneity in longitudinal neurodevelopment across the *SCN1A* spectrum and support serial assessment of both global and domain-specific development to capture clinically meaningful change over time.

Keywords: *SCN1A*; neurodevelopment; developmental trajectories; Dravet syndrome; Griffiths Mental Development Scales; developmental and epileptic encephalopathy; febrile seizures.

1. Introduction

SCN1A encodes the pore-forming α1 subunit of the voltage-gated sodium channel NaV1.1, which plays a central role in neuronal excitability, particularly in inhibitory GABAergic interneurons. Pathogenic variants in *SCN1A* are associated with one of the broadest phenotypic spectra among genetic seizure disorders, ranging from febrile seizures and genetic epilepsy with febrile seizures plus (GEFS+) to Dravet syndrome and other developmental and epileptic encephalopathies. *SCN1A* variants have also been implicated in familial hemiplegic migraine and other neurological phenotypes (Rusina, Simonti, Duprat, Cestèle, & Mantegazza, 2024; Scheffer, 2023; Scheffer & Nabbout, 2019).

Dravet syndrome represents the prototypical *SCN1A*-related developmental and epileptic encephalopathy. Seizures typically begin during the first year of life, are frequently triggered by fever, and may be prolonged or evolve into status epilepticus. In the classical course, early development may initially appear preserved, followed during the second and third years of life by increasingly evident developmental slowing, motor and language difficulties, and cognitive impairment (Heineman, Hielkema, Teunissen, & van den Berg, 2025; Sullivan et al., 2026; Vasquez & Wirrell, 2025). Nevertheless, *SCN1A*-related disorders do not follow a uniform developmental pattern. Neurodevelopment may remain within the expected range in milder phenotypes, whereas more severe forms may be associated with early global developmental delay, developmental plateau, or marked slowing in the acquisition of new skills (Battaglia et al., 2021; de Lange et al., 2019; Sullivan et al., 2026).

The relationship between seizure severity and neurodevelopmental outcome is complex. Earlier seizure onset, status epilepticus, drug resistance, and greater seizure burden have been associated with poorer developmental outcomes, yet these factors do not fully account for the substantial interindividual variability observed across the *SCN1A* spectrum (Feng et al., 2024). This supports the contemporary view that the developmental phenotype reflects an interaction between the primary consequences of *SCN1A* dysfunction, the evolution and burden of seizures, and additional genetic or acquired modifying factors.

Genotype–phenotype heterogeneity may further contribute to variability in neurodevelopmental outcome. Classical Dravet syndrome is predominantly associated with loss-of-function of NaV1.1, whereas gain-of-function *SCN1A* variants are described in early-infantile developmental and epileptic encephalopathies and familial hemiplegic migraine type 3. However, particularly for missense variants, functional consequences cannot be reliably inferred from variant type or position alone; electrophysiological evidence and clinical context remain essential for functional interpretation (Brunklaus et al., 2022, 2020). Developmental heterogeneity is therefore likely to reflect the combined

effects of variant-specific channel dysfunction, seizure burden, and additional genetic or acquired modifiers.

Longitudinal studies in Dravet syndrome have demonstrated substantial variability in developmental course and have shown that repeated standardized assessments provide information that cannot be captured by a single developmental measurement. Ragona et al. quantified cognitive evolution through changes in the General Quotient, whereas Battaglia et al. identified distinct neurodevelopmental trajectories, including early visuomotor vulnerability in some individuals and comparatively preserved global developmental quotients with more restricted language or behavioral difficulties in others (Battaglia et al., 2021; Ragona et al., 2011).

More recent natural-history studies have further emphasized developmental slowing and stagnation during early childhood in *SCN1A*-positive Dravet syndrome (Feng et al., 2024; Sullivan et al., 2026). The aim of the present study was to characterize longitudinal neurodevelopmental outcomes in children with pathogenic or likely pathogenic *SCN1A* variants using two serial Griffiths assessments. We focused on changes in the global General Quotient and on domain-specific subquotients across the entire cohort, with particular attention to the domain profiles of assessments showing globally preserved development.

2. Materials and Methods

Study Design and Participants

This retrospective longitudinal single-center study included children followed at the Department of Nervous and Neuromuscular Diseases, University Clinic for Children's Diseases, Skopje, North Macedonia. The retrospective review and data collection were conducted between December 2025 and March 2026.

Seven children with a laboratory-classified pathogenic or likely pathogenic *SCN1A* variant and two available standardized Griffiths developmental assessments were included. Inclusion criteria were: (1) a pathogenic or likely pathogenic *SCN1A* variant; (2) a clinical phenotype within the *SCN1A*-related seizure spectrum; (3) two Griffiths developmental assessments performed at different time points; and (4) available clinical documentation sufficient to characterize the seizure course and developmental trajectory.

Clinical and Molecular Data

Clinical data was extracted from the medical records and included sex, age at seizure onset, seizure types and evolution, fever sensitivity, history of status epilepticus, drug resistance, and relevant neurological and neuroimaging findings.

Genetic testing was performed using NGS-based clinical methods, including whole-exome sequencing and targeted sequencing, depending on the testing period and laboratory. The original laboratory-reported ACMG/AMP classifications were retained for analysis. Parental or segregation testing was available for all included patients.

Neurodevelopmental Assessment

Neurodevelopment was assessed using the Griffiths Mental Development Scales–Revised: Birth to 2 Years (GMDS-R) and the Griffiths Mental Development Scales–Extended Revised: Two to Eight Years (GMDS-ER), according to the child's chronological age and the version of the instrument administered (Ivens & Martin, 2002; Luiz, Foxcroft, & Povey, 2006; Picciolini et al., 2015). The developmental domains comprised A—Locomotor; B—Personal-Social; C—Hearing and Language; D—Eye-Hand Coordination; E—Performance; and F—Practical Reasoning, when applicable in the extended version. For each assessment, chronological age, developmental age, General Quotient (GQ), and all available domain-specific Subquotients (SQs) were recorded. GQ and SQ values are quotient scores and are reported as numerical values. The principal longitudinal measure was the change in GQ between the two assessments: $\Delta GQ = GQ_2 - GQ_1$.

Because two age-specific Griffiths versions with different metric properties were used, longitudinal interpretation was based primarily on the original GQ and SQ values and on individual change in GQ, rather than on a single uniform cut-off applied across all assessments. For GMDS-R, a GQ ≥88 was considered within the expected range, 76–87 mildly reduced, and <76 more markedly reduced; corresponding domain-specific SQ ranges were ≥84, 68–83, and <68 (Picciolini et al., 2015). For GMDS-ER, GQ and domain-specific SQs were interpreted using the common-metric framework described by Ivens and Martin, accounting for differences in the metric properties of the global and individual subscales (Ivens & Martin, 2002).

For the focused domain-level analysis, globally preserved development was defined according to the version-specific expected/average range: GMDS-R GQ ≥88 and GMDS-ER GQ 92–108. Domain-specific SQs were analyzed across all available assessments, with additional attention to the developmental profiles of assessments meeting these criteria.

A developmental plateau was defined as the absence of an increase in developmental age between the two assessments. Developmental slowing referred to continued acquisition of new skills at a rate substantially below chronological maturation, accompanied by a persistently low or declining GQ. Developmental regression was not inferred from a decrease in GQ alone and was reserved for documented loss of previously acquired skills.

Statistical analysis

Given the size of the genetically defined cohort and the longitudinal descriptive design, analyses were performed using descriptive statistics. Continuous variables are presented as median and range, and categorical variables as number and percentage. Within-patient developmental change was quantified as ΔGQ ($GQ_2 - GQ_1$) and interpreted together with the observed longitudinal developmental trajectories. All available domain-specific SQs were included in the analysis and interpreted according to the applicable Griffiths version.

Ethical considerations

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje (No. 03-6470/11, 5 November 2025). All analyses were performed using deidentified clinical and genetic data. Informed consent for clinical genetic testing had been obtained in accordance with local clinical practice and laboratory requirements.

3. Results

Clinical and molecular spectrum

Seven children were included, four girls and three boys. The median age at seizure onset was 10 months with a range of 0 to 48 months. The clinical spectrum extended from milder fever-sensitive SCN1A-related seizure phenotypes to Dravet syndrome and early-onset or neonatal developmental and epileptic encephalopathies. Fever sensitivity was present in all seven children. Six had a history of status epilepticus and four had drug-resistant epilepsy.

The relationship between seizure phenotype and developmental outcome was heterogeneous. Greater neurodevelopmental impairment was observed in several children with more severe seizure phenotypes, although no consistent relationship between clinical severity and longitudinal developmental trajectory was evident. In one child, interpretation of the later developmental outcome was confounded by an arteriovenous malformation-related cerebrovascular event followed by hemiparesis.

Molecular analysis identified six distinct heterozygous SCN1A variants in seven children. Six children carried missense variants, and one carried a frameshift variant. Five children carried inherited variants, three maternally and two paternally, whereas two variants occurred *de novo*. The original laboratory-reported ACMG/AMP classifications were retained. The molecular characteristics of the identified SCN1A variants are summarized in Table 1.

Table 1. Molecular characteristics of SCN1A variants in the cohort

Case	SCN1A variant / type	Inheritance	Class
P1	c.5585T>C, p.(Ile1862Thr) — missense	Paternal	**LP**
P2	c.3925C>T, p.(Leu1309Phe) — missense	Maternal	**LP**
P3	c.4860T>A, p.(Phe1620Leu) — missense	Maternal	**P**
P4	c.3925C>T, p.(Leu1309Phe) — missense	Paternal	**P**
P5	c.5594_5595del, p.(Leu1865Argfs*79) — frameshift	Maternal	**LP**
P6	c.4934G>A, p.(Arg1645Gln) — missense	De novo	**P**
P7	c.350T>G, p.(Leu117Arg) — missense	De novo	**P**

P, pathogenic; LP, likely pathogenic. All variants were heterozygous. Classifications are shown as reported in the original laboratory reports. The recurrent p.(Leu1309Phe) variant was reported as LP in P2 and P in P4.

Global developmental outcome and longitudinal change

The first Griffiths assessment was performed at a median age of 10 months (range, 5–24 months), and the second at a median age of 24 months (range, 18–54 months). Median GQ was 84 (range, 42–100) at the first assessment and 80 (range, 38–98) at follow-up. Individual ΔGQ values ranged from −21 to +9 points.

At the first assessment, when GMDS-R was used in all children, 3 of 7 children (42.9%) had a GQ within the expected range, 1 of 7 (14.3%) had a mildly reduced GQ, and 3 of 7 (42.9%) had a GQ below 76. At the second assessment, using version-specific interpretation, 2 of 7 children had a GQ within the expected or average range, whereas the remaining five had lower global scores ranging from 38 to 82. Because GMDS-R and GMDS-ER have different metric properties, longitudinal interpretation focused on the original GQ values, individual ΔGQ, and the overall developmental trajectory rather than on a single categorical classification applied across both versions.

Longitudinal developmental trajectories were markedly heterogeneous. The observed patterns included stable preserved development, a higher GQ at follow-up, a decline following an initially preserved global score, relative improvement within persistent developmental impairment, a developmental plateau, and persistent severe developmental slowing. In one child, the decline in GQ occurred in the context of an arteriovenous malformation-related cerebrovascular event and was therefore not interpreted as an *SCN1A*-specific developmental change. Individual longitudinal changes in GQ are illustrated in Figure 1.

Patient	T1 GQ age / scale	ΔGQ	T2 GQ age / scale	Developmental trajectory
P1	100 9 mo (R)	→ -2	98 49 mo (ER)	Stable preserved
P2	84 20 mo (R)	↑ +8	92 24 mo (R)	Higher GQ
P3	100 10 mo (R)	↓ -20	80 22 mo (R)	Decline after preserved GQ
P4	97 24 mo (R)	↓ -15	82 54 mo (ER)	Decline; AVM confounding*
P5	56 5 mo (R)	↑ +9	65 24 mo (R)	Relative improvement
P6	63 12 mo (R)	↓ -21	42 18 mo (R)	Developmental plateau
P7	42 10 mo (R)	↓ -4	38 25 mo (ER)	Persistent severe slowing

Figure 1. Individual longitudinal change in General Quotient (GQ)
SCN1A-related disorders: serial Griffiths developmental assessments

Note. Each row connects T1 and T2. P4 follow-up (*) was retained descriptively but was confounded by an AVM-related cerebrovascular event. R, GMDS-R Birth to 2 Years; ER, GMDS-ER Two to Eight Years; ΔGQ = GQ2 − GQ1.

Domain-Specific developmental profiles across all assessments

A total of 73 available domain-specific SQs from 14 Griffiths assessments were included in the analysis. Domain profiles were heterogeneous both across assessments and over time. Domain-specific SQ profiles at the first and follow-up assessments are shown in Figure 2. Five assessments in four children met the version-specific criteria for globally preserved development. Across these assessments, 25 of 26 available SQs (96.2%) were within the expected or average range for the applicable Griffiths version. The only mildly reduced score was observed in Hearing and Language, domain C, with an SQ of 83. No recurrent hidden deficit was identified in language, visuomotor function, or any other single developmental domain among assessments with globally preserved development.

Among assessments with lower global developmental scores, domain-level involvement was predominantly multidomain and heterogeneous. Lower SQs occurred in varying combinations across Hearing and Language, Eye-Hand Coordination, Personal-Social development, Locomotor function, and Performance. Longitudinal patterns included relative improvement, parallel decline across multiple domains in the context of developmental plateau, and persistent broad developmental involvement. No single domain-specific developmental pattern was consistently observed across the *SCN1A* spectrum.

A. First assessment (T1)

Patient	Scale	A Locomotor	B Personal-Social	C Hearing & Language	D Eye-Hand Coord.	E Performance	F Practical Reasoning
P1	R	**100**	**100**	**100**	**100**	**100**	*NA*
P2	R	**90**	**90**	**70**	**80**	**90**	*NA*
P3	R	**100**	**100**	**100**	**100**	**100**	*NA*
P4	R	**100**	**88**	**96**	**100**	**100**	*NA*
P5	R	**40**	**60**	**60**	**60**	**60**	*NA*
P6	R	**67**	**67**	**58**	**58**	**67**	*NA*
P7	R	**50**	**40**	**40**	**40**	**40**	*NA*

B. Follow-up assessment (T2)

Patient	Scale	A Locomotor	B Personal-Social	C Hearing & Language	D Eye-Hand Coord.	E Performance	F Practical Reasoning
P1	ER	**98**	**98**	**98**	**98**	**98**	**98**
P2	R	**100**	**88**	**83**	**88**	**100**	*NA*
P3	R	**91**	**82**	**64**	**73**	**91**	*NA*
P4	ER	**83**	**83**	**87**	**78**	**85**	**78**
P5	R	**58**	**67**	**67**	**67**	**67**	*NA*
P6	R	**44**	**44**	**39**	**39**	**44**	*NA*
P7	ER	**56**	**40**	**32**	**32**	**32**	**32**

Figure 2. Domain-specific Griffiths developmental profiles
Exact Subquotient (SQ) values at first and follow-up assessment

Notes. Values are domain-specific Subquotients (SQs). R, GMDS-R Birth to 2 Years; ER, GMDS-ER Two to Eight Years; NA, not applicable. Shading represents score magnitude only (darker cells indicate lower SQ) and is not a diagnostic or version-specific categorical classification.

4. Discussion

This study demonstrates that neurodevelopmental outcomes in *SCN1A*-related epilepsy are markedly heterogeneous, even within a small genetically defined cohort assessed longitudinally using serial standardized developmental evaluations. Original GQ values and individual ΔGQ revealed distinct trajectories, including stable preserved development, a higher GQ at follow-up, marked decline after an initially preserved global score, relative improvement within persistent developmental impairment, developmental plateau, and persistent severe developmental slowing. Because both GMDS-R and GMDS-ER were used, version-specific interpretation was more informative than mechanically applying a single cut-off across all time points.

These findings are consistent with previous longitudinal studies of Dravet syndrome. Ragona et al. used change in General Quotient as a quantitative measure of cognitive evolution and demonstrated substantial variability between patients. Battaglia et al., in a prospective multicenter study, identified distinct neurodevelopmental trajectories, including early visuomotor vulnerability in some patients and less frequent profiles with preserved global developmental quotients. More recent natural-history studies have further shown that, in *SCN1A*-positive Dravet syndrome, developmental age may progress substantially more slowly than chronological age, resulting in developmental slowing or stagnation (Battaglia et al., 2021; Ragona et al., 2011; Sullivan et al., 2026).

Distinguishing between a decline in GQ, developmental plateau, and true regression is particularly important. A decrease in GQ alone does not demonstrate loss of previously acquired abilities. It may occur when a child continues to acquire new skills, but at a rate slower than expected for chronological age. Our cohort included a clear example of a developmental plateau, with no increase in developmental age during the assessment interval, as well as a profile of severe developmental slowing with only minimal progression in developmental age. This distinction allows more precise clinical interpretation of serial developmental assessments.

Analysis of domain-specific SQs across all patients showed that the developmental profile provides information that is not fully captured by GQ alone. Among assessments with lower global scores, involvement was predominantly multidomain, although the combination and evolution of affected domains varied over time. The marked decline following an initially preserved global score was accompanied by more pronounced reductions in hearing and language and Eye-Hand Coordination, whereas developmental plateau was associated with parallel deterioration across multiple domains. In contrast, among the five assessments meeting version-specific criteria for globally preserved development, only one of 26 available SQs was mildly reduced, in Hearing and Language, and no recurrent visuomotor or language-specific deficit was identified. These findings do not support a single neurodevelopmental signature across the entire SCN1A spectrum and emphasize the importance of evaluating domain-specific performance in all patients rather than only in those with globally preserved development.

The molecular spectrum was also heterogeneous, with six distinct variants identified in seven patients, including both inherited and *de novo* findings and both missense and frameshift variants. Contemporary functional data indicate that classical Dravet syndrome is most commonly associated with loss-of-function mechanisms, whereas gain-of-function mechanisms have been described in some early-infantile *SCN1A*-related encephalopathies. However, the functional effect of an individual missense variant cannot be reliably inferred from the sequence change alone. Accordingly, no LOF/GOF genotype–phenotype correlation was attempted in this cohort

in the absence of direct functional data (Brunklaus et al., 2022, 2020). The same p.(Leu1309Phe) variant was identified in two patients in different clinical and inherited contexts, further illustrating the limitations of simple genotype–phenotype assumptions. In one of these patients, interpretation of the later developmental outcome was additionally confounded by an AVM-related cerebrovascular event with hemiparesis.

Clinically, these findings support serial standardized developmental assessment as an integral component of follow-up in children with *SCN1A*-related epilepsy. Global GQ is useful for monitoring the overall developmental trajectory, but domain-specific SQs should be considered in all patients to identify relative weaknesses, multidomain involvement, and uneven developmental change over time. Importantly, even if GQ is globally preserved at one point, it can still decline later; similarly, a substantial decrease in GQ does not mean true developmental regression unless there is documented loss of previously acquired skills.

The study was conducted at a single center and included a small number of patients of different ages and with varying intervals between developmental assessments. In addition, two age-specific Griffiths versions with different metric properties were used. Accordingly, the primary emphasis was placed on the original GQ and SQ values, ΔGQ, and individual longitudinal developmental profiles, with version-specific interpretation. In one patient, interpretation of the second assessment was additionally confounded by an AVM-related cerebrovascular event. Given the cohort size, relationships between phenotypic severity, variant type, and developmental outcome should be regarded as descriptive rather than predictive.

5. Conclusion

SCN1A-related disorders are associated with a broad spectrum of neurodevelopmental outcomes, ranging from stable preserved development to multidomain developmental delay, developmental plateau, and severe slowing in the acquisition of new skills. Serial Griffiths assessments allow more precise characterization of these patterns when global GQ is interpreted together with developmental age and domain-specific SQs, while accounting for the metric properties of the Griffiths version administered.

Among assessments with globally preserved development, no universal hidden deficit was identified in language, eye-hand coordination, or any other single developmental domain. In contrast, assessments with lower global scores showed heterogeneous and predominantly multidomain involvement. These findings support an individualized longitudinal approach to developmental assessment rather than the assumption of a single characteristic neurodevelopmental profile across the SCN1A spectrum.

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