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Case report

Developmental encephalopathy concomitant with aphasia associated with a pathogenic variant in the *GRIN2A* gene

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Abstract

Introduction: Mutations in the *GRIN* gene family, which encode subunits of the NMDA (N-methyl-D-aspartate) receptor, have been increasingly associated with a spectrum of neurodevelopmental disorders. Among them, *GRIN2A* mutations play a crucial regulatory role in the receptor's function, affecting synaptic transmission and brain plasticity.

Aim: This case study presents the clinical and genetic profile of a pediatric patient with a pathogenic *GRIN2A* mutation, highlighting the associated neurological phenotype, diagnostic process, and treatment approach.

Case study: Clinical data were collected through neurological assessments, EEG, MRI, and comprehensive genetic testing, including next-generation sequencing (NGS), with confirmation by Sanger sequencing. The patient's symptoms, including developmental delay, epileptic episodes, and behavioral abnormalities, were analyzed in the context of current literature on *GRIN*-related disorders

Results and discussion: The identified pathogenic *GRIN2A* mutation correlated with a neurodevelopmental phenotype characterized by early-onset epilepsy, hypotonia, and intellectual disability.

Conclusions: The above case highlights the importance of early genetic testing in children with neurodevelopmental disorders and aphasia, as well as co-occurring epilepsy. Understanding the functional impact of specific *GRIN2A* mutations can guide personalized treatment strategies and contribute to a better characterization of the *GRIN*opathy spectrum.

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1. INTRODUCTION

Advances in sequencing technology (WES – whole exome sequencing and WGS – whole genome sequencing) are an important tool for identifying causal genetic variants in developmental and epileptic encephalopathies. These methods enable the diagnosis of many rare diseases, including pathogenic de novo missense variants in *GRIN* genes encoding N-methyl-D-aspartate receptors (NMDARs). To understand the clinical consequences of rare genetic variants, functional analysis of the variant receptor in model systems is necessary. In the case of NMDAR, this analysis should include the evaluation of multiple properties, which can then be used to determine whether the overall effects will increase or decrease charge transfer via NMDAR.[1] In recent studies, significant genetic variability in N-methyl-D-aspartate receptors (NMDAR) has been documented, with the identification of numerous de novo variants. This receptor plays a pivotal role in brain development, and defects in this receptor are thus of significant relevance to the etiology of neurological diseases. N-methyl-D-aspartate receptors (NMDARs) are ligand-gated cation channels that play a pivotal role in the normal development and function of the brain. This includes plasticity, neuronal development, learning and memory processes. The *GRIN* gene family is responsible for the encoding of three distinct classes of NMDAR subunits. These classes are comprised of glycine-binding GluN1 (*GRIN1* gene product), glutamate-binding GluN2 (*GRIN2A*, *GRIN2B*, *GRIN2C* and *GRIN2D* genes), and glycine-binding GluN3 (*GRIN3A* and *GRIN3B*). The process of NMDAR activation is subject to a number of regulatory mechanisms. The primary regulatory mechanism necessitates the occupation of two glycine-binding sites on GluN1 and two glutamate-binding sites on GluN2. It is evident that NMDAR dysfunction is associated with a number of pathologies, including, but not limited to, Parkinson's disease, Alzheimer's disease, Huntington's disease, various forms of epilepsy, and neurodevelopmental disorders. Determining whether a given missense variant enhances the overall function of the target protein as a gain-of-function (GoF) or reduces its function as a loss-of-function (LoF) is an important aspect of the diagnostic and therapeutic process and crucial for understanding the mechanisms underlying the genetic aetiology of ER. Despite certain limitations, this allows us to link the variant to the neurobehavioural phenotype and provide information about possible therapeutic options.[1,2] It is important to establish whether the variant increases or decreases the overall function of the target protein and, if so, by how much. The first pathogenic variants in NMDAR were identified in 2010.[3,4] To date, approximately 500 variants in all *GRIN* genes have been identified (249 in *GRIN2A* and 204 in *GRIN2B*). These genes[5] encode different NMDAR GluN subunits.

2. AIM

This study aims to present the clinical, laboratory, electrophysiological, and neuroimaging findings in a paediatric patient with a pathogenic *GRIN2A* variant, and to emphasise the importance of early molecular diagnostics in developmental encephalopathy associated with aphasia.

3. CASE STUDY

The patient was an 11.3-year-old male with a family history of speech disorders and intellectual disability (mother, an aunt on the maternal side, and maternal grandfather). The patient had gestational and perinatal risk factors (CII, PI, PSN, with Apgar scores of 9/9) and showed delayed development (did not crawl, walking at around 14–15 months, first words at around 3 years of age). The subject presented with his first seizure episode at the age of 2, which lasted up to 3 minutes. This episode was characterized by a seizure with focal onset, followed by a disturbance of consciousness,

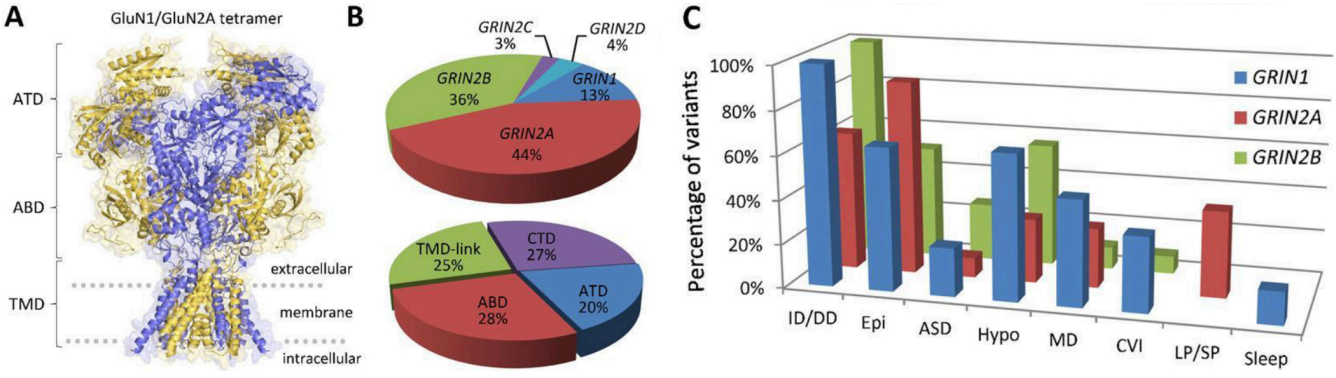

Figure 1. A) Domain structure and organization for NMDAR. B) A summary of NMDAR variants in different *GRIN* genes and protein domains. C) A summary of phenotypes associated with *GRIN* variants. These include ID/DD (intellectual disability/delayed psychomotor development), Epi (epilepsy), ASD (autism spectrum disorders), hypo (hypotonia), MD (motor disorders), LP/SP (speech disorders) and sleep (sleep disorders).

upward turning of the eyeballs, gurgling, and drooling. The episode resolved spontaneously. At 4.7 years of age, during photo stimulation (i.e., watching a cartoon), another episode occurred, this time longer lasting up to 5 minutes. The boy abruptly lost consciousness and presented with impaired consciousness, including rightward involuntary eye movements, and clonic seizures within the area of limbs and head. Subsequent to the occurrence of the seizure, the child exhibited hypotonia and was observed to be in a state of disarray for approximately 15 minutes, followed by vomiting and recovery of consciousness. Consequently, the patient was admitted to the Pediatric Department. A neurological examination was conducted, which revealed no overt dysmorphic features, with the exception of generalized hypotonia. Tendino-periosteal was found to be present. There were no signs of focal CNS damage, but motor clumsiness was evident. Motor aphasia was diagnosed and confirmed by neuropsychological examination. Brain MRI revealed no structural abnormalities. EEG showed numerous paroxysmal abnormalities located in both hemispheres, with greater intensity observed in the medial and posterior temporal leads on the left side. These lesions increased in intensity during sleep and drowsiness. Carbamazepine was included in the treatment, at therapeutic doses. Due to the fact that the boy exhibited episodes of nocturnal hypersalivation, which were reported by his parents and were periodically observed, and that these episodes were followed by prolonged sleep the following day, the treatment was modified to include a oxcarbazepine preparation (OXC). A follow-up awake EEG revealed age-related diminished baseline activity accompanied by sporadic, focal paroxysmal changes in the form of acute-slow wave syndromes in the frontotemporal, middle temporal and posterior parietal leads with predominance of the left side (Figure 2).

The initial assessment at the psychological and educational counseling center (PPP) revealed delayed psychomotor development. The boy was provided with early development support. Subsequent evaluations before the start of compulsory schooling revealed non-harmonious development and below-normal cognitive functions. Consequently, modification of the treatment regimen led to the cessation of nocturnal salivation. No other seizure disorders were observed. However, the boy exhibited substandard academic performance, characterized by impulsivity, excessive mobility, and pronounced attentional difficulties. Re-evaluation at 8.5 years of age confirmed mild intellectual disability. For this reason and because of worsening behavioural disorders, the patient was provided with psychological support, therapy and special education at school. Repeated EEG examinations performed at that time still showed abnormal recordings with a slower baseline activity in relation to age, but with a quantitative decrease in epileptiform graphoelements and a predominance of changes on the right side (Figure 3).

Magnetic resonance imaging of the brain controlled at that time showed no abnormalities. At 10.7 years of age, during an excursion in the mountains (tiredness, the boy drank and ate little), the child had another seizure episode with a focal onset, lasting up to 1 minute. It began with immobility, postural distension accompanied by jaw clenching and upward turning of the eyes. Consequently, treatment with OXC was continued.

Conventional cytogenetic analysis revealed a normal male karyotype (46,XY). Genetic testing identified a heterozygous missense variant in the *GRIN2A* gene: NM_000833: c.2179G>A (p.Ala727Thr), located in exon 12 and confirmed by Sanger sequencing. The variant is also represented in public databases using the MANE Select transcript NM_001134407.3: c.2179G>A, ensuring consistency across genomic resources. This variant has been reported in the ClinVar database (Variation ID: 433124; dbSNP: rs1555488144) and corresponds to previously described pathogenic variants in *GRIN2A*.[6] According to current evidence, *GRIN2A* variants are associated with epilepsy-aphasia spectrum disorders and are typically inherited in an autosomal dominant manner.[7]

Table 1. Characteristics of c.2179G>A (p.Ala727Thr) mutation.

Gene	*GRIN2A*
Variant	NM_000833 c.2179G>A
Variant location	Exon_12/14
Amino acid change	p.Ala727Thr
Zygosity	heterozygote
Population frequency (PL)	0.000 (per Warsaw Genomics)
Population frequency (EU)	not observed
Reference No. ClinVar	433124
Reference No. dbSNP	rs1555488144

The same variant was identified in the patient's mother and described using HGVS nomenclature as NM_000833: c.[2179G>A];[2179=], where the "=" symbol indicates no sequence change in one allele. She had no history of epileptic seizures or significant dysmorphic features but presented with an expressive language disorder. The variant was not detected in the patient's father. This finding indicated that the variant present in the patient is of maternal origin. Consequently, the probability of transmitting this variant to offspring is 50%.

4. RESULTS AND DISCUSSION

GRIN genes[5] encode different GluN subunits of NMDARs. The *GRIN* gene family includes *GRIN1*, *GRIN2A-D*, *GRIN3A-B*. Only *GRIN1*, *GRIN2A*, *GRIN2B* and *GRIN2D* gene variants have been identified with various neurological or psychiatric disorders (Figure 1B), while the role of *GRIN2C* and *GRIN3* variants is questionable. The majority of identified variants in the *GRIN* family are *GRIN2A* (46%) and *GRIN2B* (38%), followed by *GRIN1* (14%).[2]

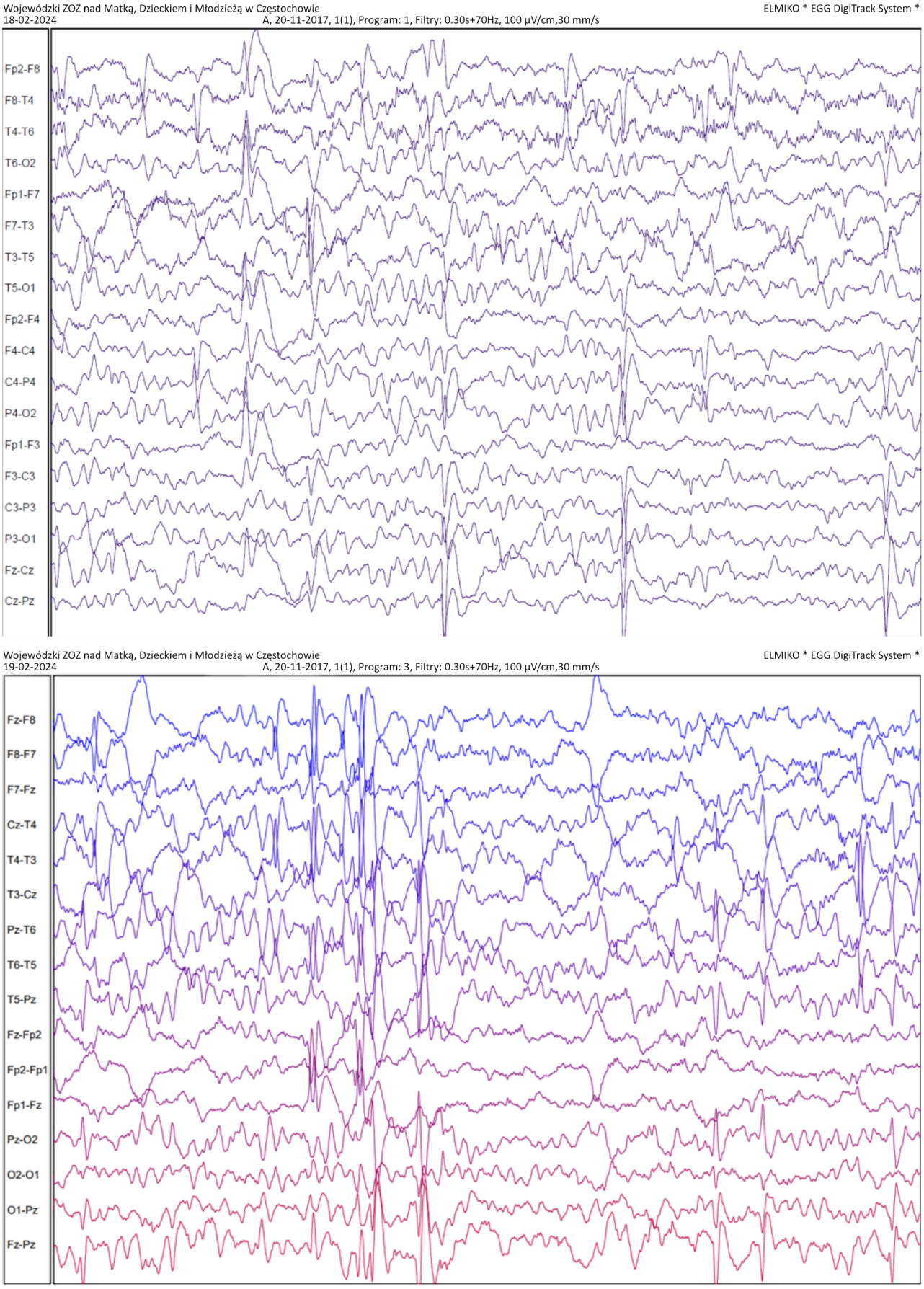

Figure 2. EEG recording in wakefulness with FS and HW.

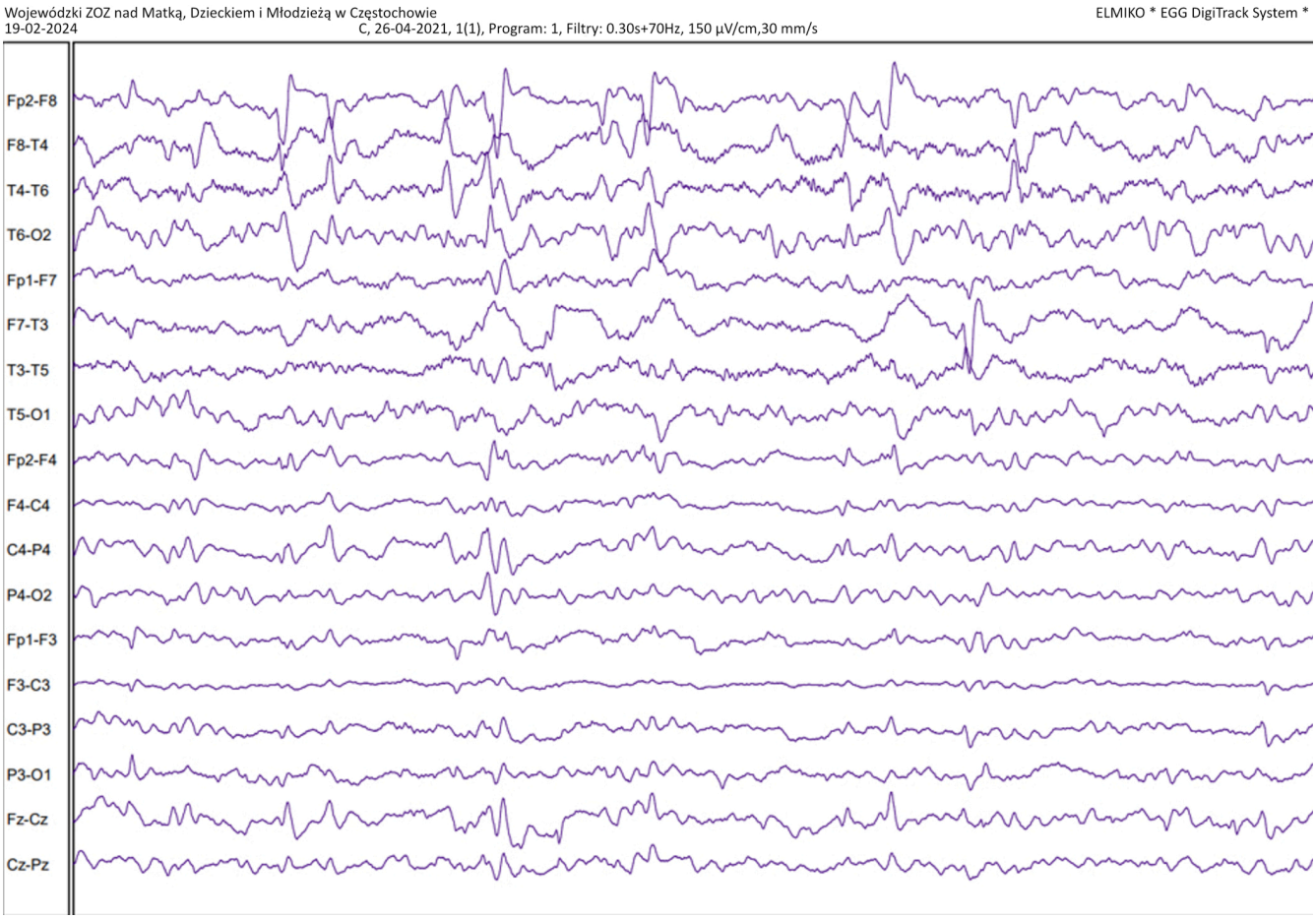

Figure 3. EEG recording in wakefulness with FS and HW.

Comprehensive diagnostic evaluation remains essential in patients presenting with developmental encephalopathy and seizures.[8] In this context, whole-exome sequencing (WES) is currently one of the preferred diagnostic methods, particularly when the clinical presentation includes epilepsy, speech disorders, behavioural abnormalities, and neurodevelopmental delay.

The described familial *GRIN2A* variant, c.2179G>A (p.Ala727Thr), corresponds to dbSNP identifier rs1555488144 (dbSNP/Ensembl). According to the ACMG (American College of Medical Genetics and Genomics) classification, the variant is classified as pathogenic/likely pathogenic (P/LP). The mutation is not incidental, demonstrates a confirmed impact within this family, and is responsible for the observed spectrum of clinical symptoms. It represents an ultra-rare variant in the Genome Aggregation Database,[9] however reported (ClinVar Variation ID: 433124) and functionally characterized. It affects the GluN2A subunit of the NMDAR. This missense mutation causes an alanine-to-threonine substitution at position 727 in the NMDAR protein. This change occurs at the site connecting the ligand-binding domain with the ion channel, which may affect a protein's conformation, signal transduction, and receptor gating. Variants in this region most commonly result in a loss-of-function (LoF) effect, resulting in reduced NMDAR activity. This manifests as reduced ion channel opening, impaired signal transmission after glutamate binding, and decreased calcium ion influx into the neuron. The NMDAR containing the *GRIN2A* subunit plays a vital role in synaptic plasticity, normal speech development, and neuronal maturation. Variants in this gene are linked to epilepsy, speech development disorders, and cognitive difficulties. Weakened receptor activation leads to impaired synaptic plasticity. Typically, loss-of-function (LoF) variants are associated with a milder clinical course than gain-of-function (GoF) variants.[10] Determining whether a molecular variant causes a loss-of-function (LoF) or gain-of-function (GoF) effect enables the selection of personalised anti-seizure therapy, which may improve seizure control, support normalisation of the EEG recording, and minimise adverse effects. Importantly, in patients with reduced protein function, the use of a drug that further decreases its activity may not yield the expected therapeutic effect. A better therapeutic effect can be achieved by using drugs that increase protein function or expression. When selecting anti-seizure medications, the most important factors are seizure morphology, the nature of changes in the EEG recording, the patient's age, and the type of mutation. In the case of the described loss-of-function (LoF) variant, due to

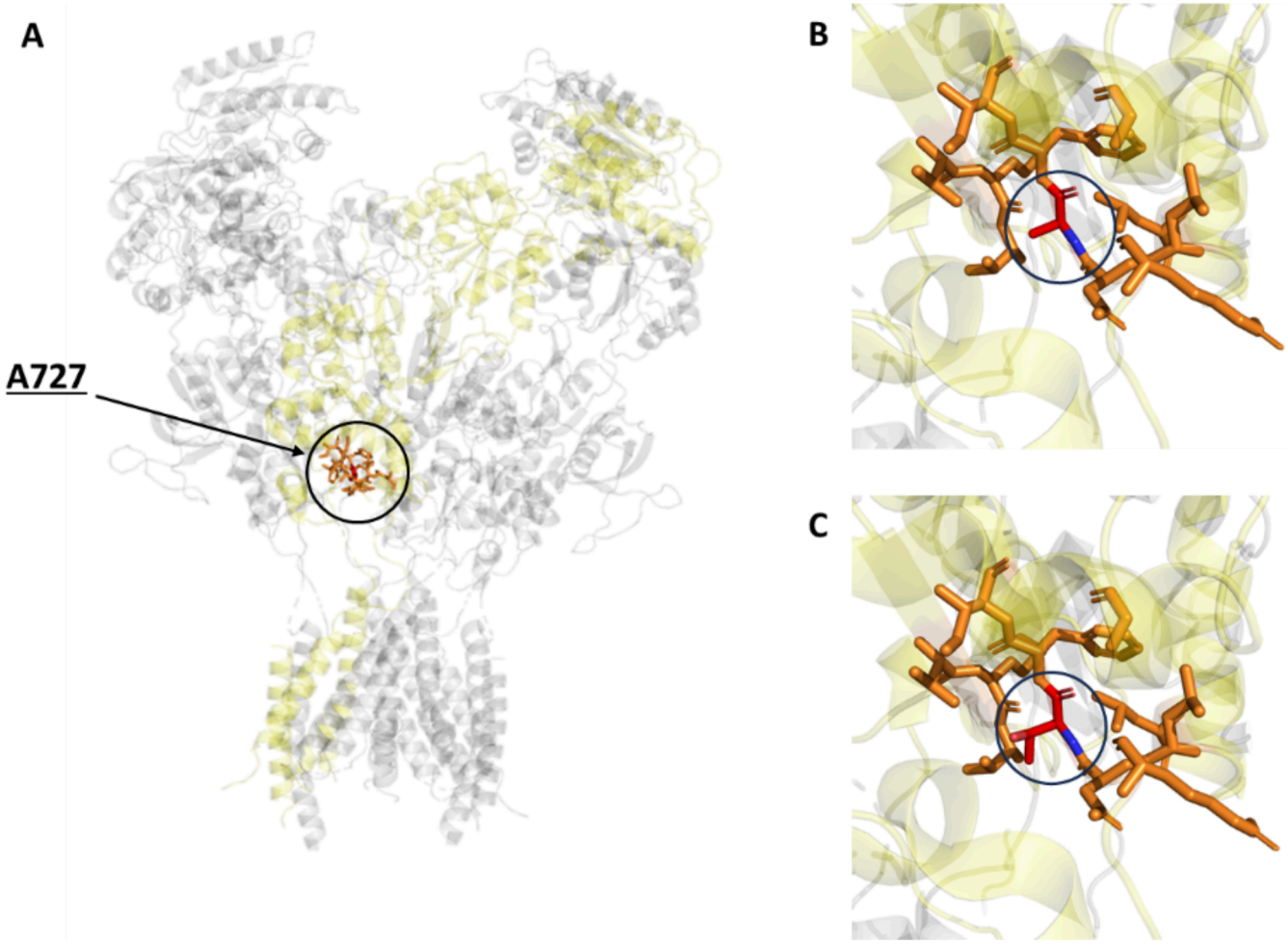

Figure 4. A) Overall structure of the NMDAR (GluN1/GluN2A tetramer) with localisation of the Ala727 residue in the GluN2A subunit. B) Local structural environment of the reference Ala727 residue in the GluN2A subunit. C) Local structural environment of the mutant Thr727 residue in the GluN2A subunit.

Source: Own development, PyMol open-source visualization system.

the weakened activity of the NMDAR, excessive inhibition of the glutamatergic system is avoided. Instead, drugs that stabilise the activity of GABAergic networks or act on sodium channels are preferred. Such drugs include Levetiracetam (acts on neurotransmitter release (SV2A), neutral towards NMDAR), Valproic acid (increases GABA inhibition, stabilises the neuronal network, in both focal-onset and generalised seizures), Lamotrigine (stabilises sodium channels, reduces cortical excitability), Clobazam (used particularly in Continuous Spike-Waves during Slow Wave Sleep CSWS), and Oxcarbazepine/Carbamazepine (blocks sodium channels, more commonly used in focal-onset seizures). On the other hand, drugs such as Felbamate, which shows partial antagonistic activity towards NMDARs, as well as Topiramate and Zonisamide, which affect glutamatergic. The effectiveness of L-serine supplementation was also noted in individuals with LoF-type variants in the *GRIN2A* gene.[11] In a large study published in 2024 using L-serine at a dose of 500 mg/kg/day (maximum 30 g/day) in patients with this variant, improvements were observed in motor functions, quality of life, and EEG readings with better seizure control.[12]

Patients with the *GRIN2A* variant mainly represent neurodevelopmental disorders, which are predominantly (88%) associated with epilepsy, with the initial seizures manifesting between birth and the age of 8 years. It is noteworthy that these symptoms may subside between the ages of 8 and 20 years. The seizures observed were predominantly focal in nature, constituting 57% of the total seizures, with a predilection for the medial temporal region. In 34% of the electroencephalograms (EEGs) of patients with this variant, slow-wave sleep abnormalities consistent with CSWS were recorded. Approximately 37% of patients with the *GRIN2A* mutation demonstrate normal intellectual development. Among 63% of patients with an intellectual disability, 46% were found to have mild neurocognitive impairment (NI), 22% moderate, 11% severe and 21% profound.[5] Further abnormalities were identified in this patient cohort, including muscular hypotonia (29%), movement disorders (27%), autism

spectrum disorders (9%), and psychiatric disorders, notably schizophrenia (3%).[13] A significant feature associated with *GRIN2A* variants is speech impairment, including dysarthria, dysphasia, dyspraxia of speech or its regression, and aphasia, which has been described in 19% of patients.

Table 2. Summary of phenotypes associated with *GRIN* variants.[5]

	GRIN1	*GRIN2A*	*GRIN2B*
Intellectual disability	100%	**63%**	100%
Epilepsy/convulsions	65%	**88%**	57%
Muscle hypotonia	66%	**29%**	56%
Movement disorders	48%	**27%**	56%
Autism spectrum disorders	22%	**9%**	26%
Cortical visual impairment	34%	**–**	8%
Language/speech problems	–	**39%**	–
Schizophrenia	–	**3%**	–
Sleep disorders	15%	**–**	–

Disorders associated with mutations in the *GRIN2A* gene are inherited in an autosomal dominant manner, with generally high penetrance and variable expressivity. Within a single family, a broad spectrum of symptoms may occur, ranging from isolated speech disorders, often with a mild or even unrecognized course, to severe epileptic encephalopathies. Currently, accurate prediction of phenotype remains challenging. The variability of the clinical presentation likely results from differences in brain development, the influence of modifying genes, environmental factors, and additional genetic variation. In the case described above, a patient with a confirmed mutation in the *GRIN2A* gene presented with features of developmental encephalopathy, including mild intellectual disability, muscle hypotonia, and impulsivity, accompanied by aphasia and epilepsy. In contrast, only mild speech impairment was observed in the mother, illustrating the variable expressivity characteristic of *GRIN2A*-related disorders. Although additional functional validation of the identified variant was not performed in the present case study, the available clinical and genetic findings support its potential relevance to the observed phenotype. Further clarification of the functional impact of *GRIN2A* variants may also support the development of model systems, including cell lines and animal models, thereby contributing to future research and drug discovery.[1]

5. CONCLUSIONS

In the case of a patient with developmental encephalopathy, especially with co-occurring speech disorders, hyperactivity, behavioural disorders, and epilepsy, genetic diagnostics for a pathogenic variant in the *GRIN* gene are indicated. Although functional validation of the identified variant was not performed in the present case study, the available clinical and genetic findings support its potential relevance to the observed phenotype. Future functional studies would be valuable to further clarify its biological effect and confirm its contribution to the clinical presentation.

Ethics approval

All procedures performed in this study involving human participants were conducted in accordance with institutional ethics committee standards and the Declaration of Helsinki.

Informed consent

Informed consent was obtained from all participants included in the study.

Conflict of interest

None declared.

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None declared.

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Author contributions

Study design: AB, JP
Data collection: AB
Statistical analysis: AB
Data interpretation: AB, DL, PL
Manuscript preparation: AB, DL, PL
Literature search: AB, DL, PL

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