

Global Developmental Delay and Epilepsy Associated with Variants of Uncertain Significance in ALDH18A1 and GABRG2 : A Case Report

Dr. Pooja J Panicker¹, Dr. Reshma Anna Philip², Dr. Manju George Elenjickal³

Dr. Pooja J Panicker
Postgraduate Resident
Department of Paediatrics
Pushpagiri Institute of Medical Sciences & Research Centre
Thiruvalla, Kerala, India

Dr. Reshma Anna Philip
Fellow in Developmental Paediatrics
Department of Paediatrics
Pushpagiri Institute of Medical Sciences & Research Centre
Thiruvalla, Kerala, India

Dr. Manju George Elenjickal
Additional Professor and Head of CDC department
Department of Paediatrics
Pushpagiri Institute of Medical Sciences & Research Centre
Thiruvalla, Kerala, India

Address for correspondence

Dr. Pooja J Panicker
Postgraduate Resident
Department of Paediatrics
Pushpagiri Institute of Medical
Sciences & Research Centre
Thiruvalla, Kerala, India – 689101
Phone No.: 9611537831
E-mail: poojapanicker@gmail.com



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Abstract

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Global developmental delay (GDD) with epilepsy represents a heterogeneous group of neurodevelopmental disorders with significant genetic contribution. The increasing use of next-generation sequencing has improved diagnostic evaluation; however, interpretation of variants of uncertain significance (VUS) remains challenging in clinical practice.

We report a 2½-year-old female child born of a third-degree consanguineous marriage who presented with global developmental delay, recurrent seizures, hypotonia, proximal muscle weakness, and microcephaly. Developmental delay was noted since infancy, with delayed motor and speech milestones. Seizure onset occurred at 9 months of age in the form of febrile tonic seizures, later progressing to generalized tonic-clonic and reflex anoxic seizures. Neurological examination revealed generalized hypotonia and immature pincer grasp. MRI brain demonstrated shallow sulci, mild cerebral atrophy, thinning of the corpus callosum, and reduced hippocampal volume. Whole exome and mitochondrial genome sequencing identified a homozygous missense variant in ALDH18A1 [c.2233A>G; p.Arg745Gly] and two heterozygous missense variants in GABRG2 [c.644G>A; p.Arg215His and c.1357G>T; p.Ala453Ser], all classified as variants of uncertain significance according to ACMG criteria.

The identified genes are associated with neurodevelopmental disorders characterized by developmental delay, hypotonia, and epilepsy. Although the detected variants have not been previously reported, significant genotype-phenotype overlap suggests possible clinical relevance.

This case highlights the complexity of interpreting VUS in paediatric neurogenetics and emphasizes the importance of clinical correlation, parental segregation analysis, and long-term genomic re-evaluation in children with developmental delay and epilepsy.

Introduction:

Global developmental delay (GDD) is defined as significant delay in two or more developmental domains, including motor, language, cognition, and social functioning, in children younger than five years of age. It affects nearly 1–3% of children worldwide^[1] and remains an important cause of long-term neurological disability. Epilepsy commonly coexists with developmental delay and often suggests an underlying structural, metabolic, or genetic disorder.

With the increasing availability of next-generation sequencing (NGS)^[2], the evaluation of children with unexplained neurodevelopmental disorders has changed considerably. Whole exome sequencing (WES) has become particularly useful in children presenting with developmental delay, epilepsy, intellectual disability, or multisystem involvement. Although WES has improved diagnostic yield in paediatric neurology, interpretation of variants of uncertain significance (VUS) continues to be challenging^[3]. These variants lack sufficient evidence to be classified as either pathogenic or benign.

Interpretation becomes even more difficult in children with complex phenotypes and in consanguineous families, where rare homozygous variants are more likely to occur. Correlation of clinical findings with genetic data, segregation studies, and periodic genomic re-evaluation are therefore essential.

The ALDH18A1 gene encodes^[4] delta-1-pyrroline-5-carboxylate synthase, an enzyme involved in proline and ornithine metabolism. Pathogenic variants have been linked to hereditary spastic paraplegia and autosomal recessive cutis laxa syndromes characterized by developmental delay, hypotonia, and progressive neurological involvement. The GABRG2 gene encodes^[5] the gamma-2 subunit of the GABA-A receptor, which plays a key role in inhibitory neurotransmission. Variants in this gene have been associated with febrile seizures, generalized epilepsy with febrile seizures plus (GEFS+), and developmental epileptic encephalopathies.

We report a child with developmental delay and epilepsy in whom WES identified VUS in ALDH18A1 and GABRG2, highlighting the diagnostic and interpretative challenges encountered in clinical neurogenetics.^[6-7]

Case Presentation:

A 2½-year-old girl presented with delayed developmental milestones and recurrent seizures. She was the first child born to parents in a third-degree consanguineous marriage. Antenatal history was significant only for gestational diabetes mellitus in the mother. There was no history of maternal infection, teratogenic exposure, radiation exposure, or birth asphyxia. Delivery and neonatal transition were uneventful.

Developmental delay became apparent during infancy. Gross motor milestones were significantly delayed, with poor head control and delayed sitting. Fine motor development was also affected, and the child demonstrated only an immature pincer grasp. Speech development was markedly delayed, with expressive vocabulary limited to a few meaningful words at presentation. Social interaction, however, was relatively preserved.

At around 9 months of age, the child developed febrile tonic seizures, which later progressed to generalized tonic-clonic seizures occurring during both febrile and afebrile episodes. Reflex anoxic spells were also reported. There was no history suggestive of focal neurological deficits, visual impairment, or hearing loss. Otoacoustic emission testing was normal.

She was evaluated by paediatric neurologists and started on levetiracetam and sodium valproate, following which seizure frequency reduced. However, developmental progress remained slow.

Family history was negative for epilepsy, developmental delay, recurrent pregnancy losses, or other neurogenetic disorders.

Clinical Examination:

On examination, the child appeared undernourished, with anthropometric parameters below expected standards for age. Head circumference was below –3 standard deviations, consistent with microcephaly.

Neurological examination revealed generalized hypotonia with proximal muscle weakness involving both upper and lower limbs. Deep tendon reflexes were preserved. No abnormal involuntary movements or cerebellar signs were noted. Cognitive and fine motor functions were significantly delayed.

There were no dysmorphic facial features, connective tissue abnormalities, cutis laxa, or skeletal deformities. Systemic examination was otherwise unremarkable except for a small hypopigmented lesion over the left hand.

Neuroimaging Findings:

MRI brain demonstrated diffuse structural abnormalities including shallow cerebral sulci, mild cerebral atrophy, thinning of the corpus callosum, and reduced hippocampal volume. These findings suggested impaired cortical maturation and diffuse neurodevelopmental involvement.

Genetic Evaluation:

Considering the combination of developmental delay, epilepsy, hypotonia, and microcephaly, whole exome sequencing and mitochondrial genome analysis were performed.

Table 1: Variants Identified on Whole Exome Sequencing and Their Clinical Significance

Gene ^a (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification ⁵
ALDH18A1 (-) (ENST00000371224.7)	Exon 18	c.2233A>G (p.Arg745Gly)	Homozygous	Cutis laxa, autosomal recessive, type IIIA (OMIM#219150); Spastic paraplegia 9B, autosomal recessive (OMIM#616586)	Autosomal recessive	Uncertain Significance (PM2,PP3)
GABRG2 (+) (ENST00000639213.2)	Exon 6	c.644G>A (p.Arg215His)	Heterozygous	Developmental and epileptic		Uncertain Significance (PM2,PP3)
GABRG2 (+) (ENST00000639213.2)	Exon 10	c.1357G>T (p.Ala453Ser)	Heterozygous	encephalopathy 74 (OMIM#618396); Febrile seizures, familial, 8 (OMIM#607681); Generalized epilepsy with febrile seizures plus, type 3 (OMIM#607681)	Autosomal dominant	Uncertain Significance (PM2)

Abbreviations: VUS – Variant of Uncertain Significance; OMIM – Online Mendelian Inheritance in Man; ACMG – American College of Medical Genetics and Genomics.

The identified variants were classified according to ACMG guidelines. Correlation with clinical phenotype and further segregation analysis were recommended for interpretation of pathogenicity.

Table 2: Summary of Genetic Variants Identified on Whole Exome Sequencing

Gene	Variant	Zygosity	Predicted Protein Change	Clinical Significance	Associated Disorders	Supporting Evidence
ALDH18A1	c.2233A>G	Homozygous	p.Arg745Gly	Variant of Uncertain Significance (VUS)	Autosomal recessive cutis laxa type IIIA, Spastic paraplegia type 9B	Absent in major population databases; deleterious prediction by PolyPhen-2, SIFT, LRT, and MutationTaster2; highly conserved residue
GABRG2	c.644G>A	Heterozygous	p.Arg215His	Variant of Uncertain Significance (VUS)	Febrile seizures, GEFS+, Developmental and epileptic encephalopathy	Extremely low allele frequency; predicted damaging by in silico analysis
GABRG2	c.1357G>T	Heterozygous	p.Ala453Ser	Variant of Uncertain Significance (VUS)	Febrile seizures, GEFS+, Developmental and epileptic encephalopathy	Absent in population databases; deleterious prediction by LRT analysis
KMT2E	c.5323C>A	Heterozygous	p.Pro1775Thr	Variant of Uncertain Significance (VUS)	Uncertain clinical relevance in present case	Insufficient evidence for pathogenicity

No pathogenic variants were identified in the mitochondrial genome, and no clinically significant copy number variations were detected. Parental segregation analysis was recommended for further interpretation of the identified variants (Table 1 and Table 2).

Discussion:

This case highlights the increasing role of genomic medicine in paediatric neurology and the challenges associated with interpretation of VUS. The child demonstrated a phenotype strongly suggestive of an underlying neurogenetic disorder, including developmental delay, epilepsy, hypotonia, microcephaly, and structural brain abnormalities.

The homozygous ALDH18A1 variant is particularly noteworthy given the parental consanguinity and the overlap between the patient's phenotype and previously described ALDH18A1-related disorders. Although classical connective tissue manifestations such as cutis laxa were absent, phenotypic variability is well recognized in neurogenetic syndromes. The rarity of the variant and damaging computational predictions increase the likelihood of pathogenicity, though definitive evidence is lacking.

Similarly, the seizure phenotype in this child showed considerable overlap with GABRG2-associated epilepsy syndromes. GABRG2 plays an important role in inhibitory neurotransmission,

and dysfunction can result in neuronal hyperexcitability and epilepsy. The presence of two heterozygous variants raises the possibility of cumulative functional impairment, although their exact contribution remains uncertain.

Consanguinity remains an important contributor to inherited neurological disorders, particularly in developing countries. In such settings, rare homozygous recessive variants are encountered more frequently, emphasizing the value of genomic evaluation in children with unexplained developmental delay and epilepsy.

Despite advances in sequencing technology, interpretation of VUS remains one of the greatest challenges in clinical genetics. Computational prediction tools alone are insufficient to establish pathogenicity. Reclassification often requires parental segregation studies, functional analysis, identification of additional affected individuals, and accumulation of literature evidence over time.

In the present case, parental testing was recommended to determine inheritance patterns and improve interpretation of the identified variants.

Although a definitive molecular diagnosis could not be established, the genomic findings were clinically valuable. They supported a neurogenetic basis for the disorder, guided counselling, reduced the need

for further invasive investigations, and provided a framework for future reinterpretation of genetic data.

Management of such children requires a multidisciplinary approach involving paediatric neurologists, developmental therapists, physiotherapists, nutritionists, and genetic counsellors^[8-13].

Conclusion:

We report a child with global developmental delay, epilepsy, hypotonia, microcephaly, and cerebral atrophy associated with variants of uncertain significance in *ALDH18A1* and *GABRG2*. Although the pathogenicity of these variants remains uncertain, the clinical phenotype showed substantial overlap with previously described gene-associated disorders.

This case underscores both the diagnostic utility and interpretative limitations of whole exome sequencing in paediatric neurogenetics. Continued clinical follow-up, parental segregation studies, and future genomic re-evaluation may help clarify the significance of these variants and improve understanding of rare neurodevelopmental disorders.

Conflict of Interest: None

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