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The Rare Syndrome Aicardi–Goutières 4: A Case Report and Literature Review

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ABSTRACT

Aicardi–Goutières syndrome (AGS) is a genetically heterogeneous type of interferonopathy resulting from defects in the processing or sensing of nucleic acids. The AGS phenotype encompasses a broad range of neurological and non-neurological findings. It presents with a congenital or subacute onset, manifesting as microcephaly, spasticity, dystonia, seizures, cortical blindness, and psychomotor retardation in the first year of life. The radiological and laboratory findings of AGS are generally accompanied by intracranial calcification, white matter abnormalities, cerebral atrophy, and cerebrospinal fluid lymphocytic pleocytosis. A case diagnosed as AGS type 4 among patients presenting to the Balikesir University Medical Faculty pediatric neurology clinic, Türkiye, between August 1, 2024, and February 1, 2025, and undergoing genetic testing was included in the study. The patient exhibited a coarse facial appearance, a low ear line, scoliosis, contractures in the upper and lower extremities, hyperactive deep tendon reflexes, an equivocal Babinski response, and upper and lower extremity muscle strength of 3/5. The patient was started on levetiracetam at 20 mg/kg in two doses for epilepsy. Whole exome sequencing revealed a homozygous pathogenic variant in *RNASEH2A*. Parental genetic analyses for the targeted variant were heterozygous. In conclusion, the diagnosis of AGS relies on clinical characteristics and genetic testing. Basic neurological characteristics include developmental delay, dystonia, microcephaly, brain calcification, and leukodystrophy. Although data concerning genotype-phenotype in AGS type 4 have been reported in the literature, these are still limited.

1 | Introduction

Aicardi–Goutières syndrome (AGS) is a genetically heterogeneous type of interferonopathy resulting from defects in the processing or sensing of nucleic acids (Crow 2013). The AGS phenotype encompasses a broad range of neurological and non-neurological findings. It presents with a congenital or subacute onset, manifesting as microcephaly, spasticity, dystonia, seizures, cortical blindness, and psychomotor retardation in the first year of life. The radiological and laboratory findings of AGS are generally accompanied by intracranial calcification, white matter abnormalities, cerebral atrophy, and cerebrospinal fluid lymphocytic pleocytosis (Crow et al. 2005). AGS has to date been linked to nine genes, *ADAR*, *IFIH1*, *RNASEH1A*, *RNASEH2B*, *RNASEH2C*, *TREX1*, *SAMHD1*, *LSM11*, and *RNU7-1* (Uggenti et al. 2020).

Autosomal recessive mutations in *RNASEH2A* lead to AGS type 4 (OMIM#610333). *RNASEH2A*, together with *RNASEH2B* and *RNASEH2C*, constitutes the holoenzyme ribonuclease (RNase) H2 (Cerritelli and Crouch 2009; Sparks et al. 2012). *RNASEH2B* and *RNASEH2C* are used as the scaffold for RNASEH2A, which serves as the catalytic subunit of the RNase H2 complex (Chon et al. 2009). As a ribonuclease, this complex assists the breakdown

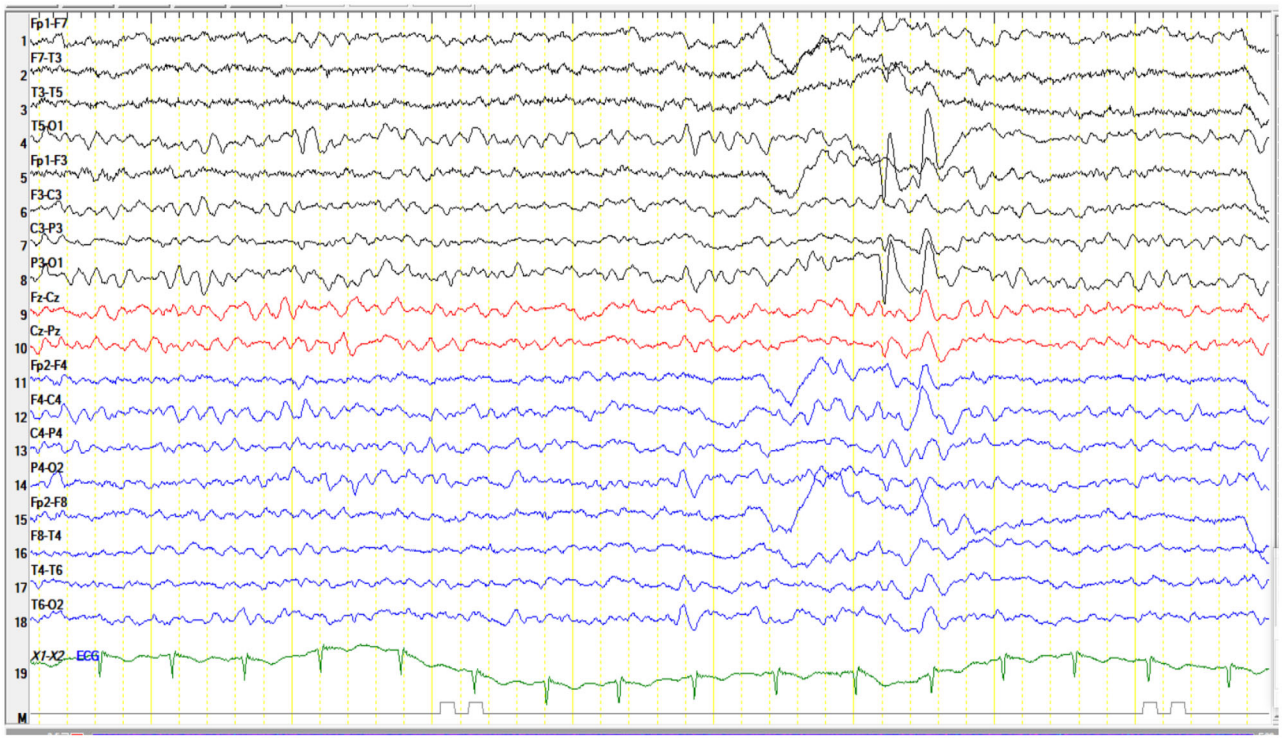

FIGURE 1 | EEG performed 2–3 Hz sharp waves in the left temporoparietooccipital region.

of RNA-DNA hybrid, created during DNA replication, specifically targeting the breakdown of RNA molecules that are chemically related to DNA. Additionally, RNase H2 complex is involved in DNA replication, error repair, and other cellular processes, including helping to prevent inappropriate immune system activation (Crow et al. 2006; Hamperl et al. 2017; Meers et al. 2016). Disruption of RNase H activity affects microRNA turnover, resulting in severe clinical outcomes in the brain that characterize the clinical manifestation of AGS (Rigby et al. 2014).

The aim of this report was to compare our own case of AGS, which exhibited findings of spasticity, seizure, cortical atrophy, and neuromotor development delay causing AGS type 4 associated with a rarely reported variant in the *RNASEH2A* gene, with previous cases of AGS type 4 in the literature.

2 | Materials and Methods

2.1 | Patient

A case diagnosed as AGS type 4 among patients presenting to the Balikesir University Medical Faculty pediatric neurology clinic, Türkiye, between August 1, 2024, and February 1, 2025, and undergoing genetic testing was included in the study. Permission for the study was granted by the local ethical committee (decision No. 2025/61 dated February 4, 2025).

2.2 | Genetic Testing

Informed consent was received from the family before clinical and genetic evaluation and the collection of blood samples. DNA extraction was performed from these 200-μL peripheral blood samples. Genomic DNA was extracted from peripheral venous blood in line with the manufacturer's instructions using an Exgene TM Blood SV isolation kit (GeneAll Biotechnologie, South Korea).

Genomic DNA was isolated automatically using a HiPurA pre-filled clinical multi-purpose nucleic acid purification kit with HIMEDIA InstaN Mag-96. Measurements for DNA concentration analysis were performed with Qubit (Thermo Fisher Scientific, USA). Whole exome sequencing was performed using a Roche KAPA HyperExome 96 rxn kit with MGI DNBSEQ-G400. FastQ files were analyzed with Genomize's SEQ platform version 8.7.0. The variants were classified according to the American College of Medical Genetics (ACMG) standards and guidelines 2015 recommendations. The variants detected were confirmed using Sanger sequencing.

2.3 | Case

A 7-year-old boy presented to the pediatric neurology clinic due to a 10-min generalized tonic-clonic seizure in which he stared at a fixed point and lost consciousness. His history revealed he had been born at 30 weeks, by cesarean section, weighing 1860 g. He spent 4 months in the neonatal intensive care unit, during which time he was monitored for 20 days on a mechanical ventilator, and intracranial hemorrhage developed. At 22 days of age, a ventriculoperitoneal shunt was inserted, and four shunt revisions were performed. First-degree consanguinity was present between the parents. At physical examination, the patient's body weight was 38 kg (> 97 p), 130 cm (> 97 p), and head circumference 49 cm (0–2 SD). The patient exhibited a coarse facial appearance, a low ear line, scoliosis, contractures

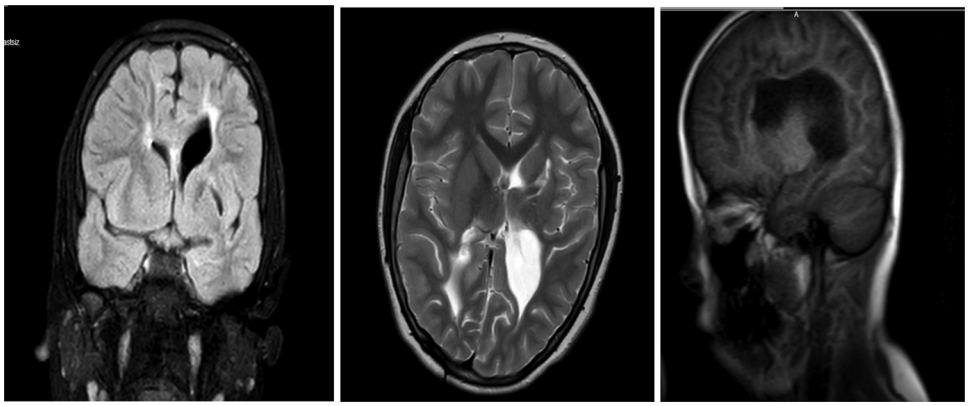

FIGURE 2 | Cranial MRI revealed a widespread gliotic signal increase in white matter, marked atrophy in the right lateral ventricle compared to the left; a hydropic appearance in the left lateral ventricle, particularly in the occipital horn; and corpus callosum dysgenesis.

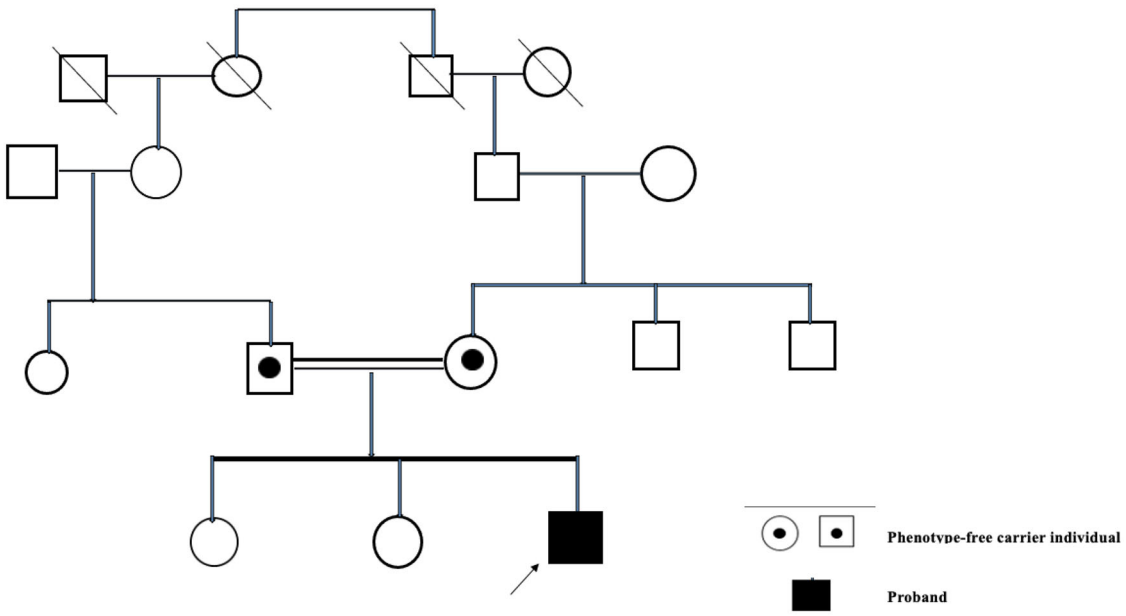

FIGURE 3 | Pedigree of the case carrying *RNASEH2A* variant.

in the upper and lower extremities, hyperactive deep tendon reflexes, an equivocal Babinski response, and upper and lower extremity muscle strength of 3/5. Complete blood count, fingertip blood sugar, blood gas, urine culture, T4, TSH, vitamin B12, vitamin D, ferritin, and folic acid were all normal. Sleep and wake electroencephalography (EEG) performed during the interictal period revealed 2–3 Hz medium/high-voltage sharp waves in the left temporoparietooccipital region (Figure 1). Cranial MRI revealed a widespread gliotic signal increase in white matter; marked atrophy in the right lateral ventricle compared to the left; a linear signal focus compatible with ventriculoperitoneal shunt extending from the right posterior horn to the subcutaneous soft tissue; a hydropic appearance in the left lateral ventricle, particularly in the occipital horn; and corpus callosum dysgenesis (Figure 2). The patient was started on levetiracetam at 20 mg/kg in two doses. Due to an increased seizure frequency at follow-up (2.5 years after commencement of treatment), the levetiracetam dosage was gradually increased. However, the seizure attacks persisted, and topiramate 5 mg/kg/g in two doses was added to the existing protocol. This brought the seizures under control. Full abdomen ultrasound was evaluated as normal. The visual evoked potential of P100 was R: 119 L: 138. A consultation was requested with the ear, nose, and throat department, and no pathology was determined. The patient was referred to the medical genetics department with these findings, and array cGH and chromosome analysis were reported as normal. Whole exome sequencing revealed a homozygous pathogenic variant in *RNASEH2A*. The patient's clinical characteristics are shown in Table 1.

2.4 | Genetic Results

We detected one pathogenic variant in *RNASEH2A* (NM_006397.3). The patient exhibited a homozygous c.502G> T variant. This was classified as pathogenic according to ACMG criteria (Richards et al. 2015). We checked the novel variants in the HGMD and ClinVar (http://ncbi.nlm.nih.gov/clinvar and https://www.hgmd.cf.ac.uk/ac/gen) databases. The variant was

TABLE 1 | Clinical and laboratory characteristics of patients diagnosed with AGS type 4 in the literature.

Age at reports	Sex	Gene	Variant	Location	Zygosity	Clinical manifestations	Referance
14 m	M	*RNASEH2A (NM_006397.3)*	c.229delG (p.E77Kfs*37) c.857G> T (p.R286L)	Exon 3 Exon 8	C Het	Regression, developmental delay, dystonia, intracranial calcification, leukoencephalopathy, cerebral atrophy	(Richards et al. 2015)
5 m	F	*RNASEH2A (NM_006397.3)*	c.370C> T (p.L124F) c.872G> A (p.R291H)	Exon 4 Exon 8	C Het	Developmental delay, dystonia, leukoencephalopathy, microcephaly, cerebral atrophy; intracranial calcification	(Richards et al. 2015)
7.5 y	F	*RNASEH2A (NM_006397.3)*	c.557G> A (p.R186Q)	Exon 8	Hom	Developmental delay, spasticity, white matter disease	(Al Mutairi et al. 2018)
2 y	M	*RNASEH2A (NM_006397.3)*	c.557G> A (p.R186Q)	Exon 8	Hom	Microcephaly, developmental delay, intellectual disability, spasticity, white matter disease	(Al Mutairi et al. 2018)
3 y	M	*RNASEH2A (NM_006397.3)*	c.557G> A (p.R186Q)	Exon 8	Hom	Developmental delay, intellectual disability, spasticity, white matter disease	(Al Mutairi et al. 2018)
5.5 y	M	*RNASEH2A (NM_006397.3)*	c.557G> A (p.R186Q)	Exon 8	Hom	Developmental delay, intellectual disability, spasticity, seizure, brain atrophy, white matter disease	(Al Mutairi et al. 2018)
2.5 y	F	*RNASEH2A (NM_006397.3)*	c.557G> A (p.R186Q)	Exon 8	Hom	Microcephaly, developmental delay, intellectual disability, spasticity, brain atrophy, white matter disease	(Al Mutairi et al. 2018)

(Continues)

TABLE 1 | (Continued)

Age at reports	Sex	Gene	Variant	Location	Zygosity	Clinical manifestations	Referance
NA	F	*RNASEH2A (NM_006397.3)*	c.322C> T (p.R108W)	Exon 3	C Het	Spastic-dystonic tetraparesis, celiac disease	(Garau et al. 2019)
			c.690C> A (p.F231L)	Exon 7			
NA	M	*RNASEH2A (NM_006397.3)*	c.556C> T (p.R186W)	Exon 6	C Het	Spastic tetraparesis, seizure	(Garau et al. 2019)
			c.69G> A (p.V23V)	Exon 1			
8 y	M	*RNASEH2A (NM_006397.3)*	c746C> T (p.Ala249Va)l	Exon 7	Hom	Motor and language regression, spastic diplegia, dysarthria, sitting without support, dystonia, no concerns regarding cognition	(Peixoto de Barcelos et al. 2023)
21 y	M	*RNASEH2A (NM_006397.3)*	c746C> T (p.Ala249Val)	Exon 7	Hom	Spasticity of the right arm and left leg, obsessive-compulsive disorder walk without support, No concerns regarding cognition	(Peixoto de Barcelos et al. 2023)
7.5 y	M	*RNASEH2A (NM_006397.3)*	c.290 C > T (p.S97F)	Exon 3	C Het	Developmental delay, severe mental disability, seizure, nystagmus, brain atrophy at MRI	(Khalilian et al. 2025)
			c.746 C > A (p.A249E)	Exon 7			
Present case 7 y	M	*RNASEH2A (NM_006397.3)*	c.502G> T (p.A168S)	Exon 5	Hom	Developmental delay, seizure, spastic tetraparesis, kyphoscoliosis, a coarse facial appearance, diffuse gliotic signal increase in white matter at MRI, right lateral ventricle significantly atrophic compared to the left, corpus callosum dysgenesis	

Abbreviations: C, compound; Het, heterozygous; Hom, homozygous; y, year, m, month; NA, not applicable.

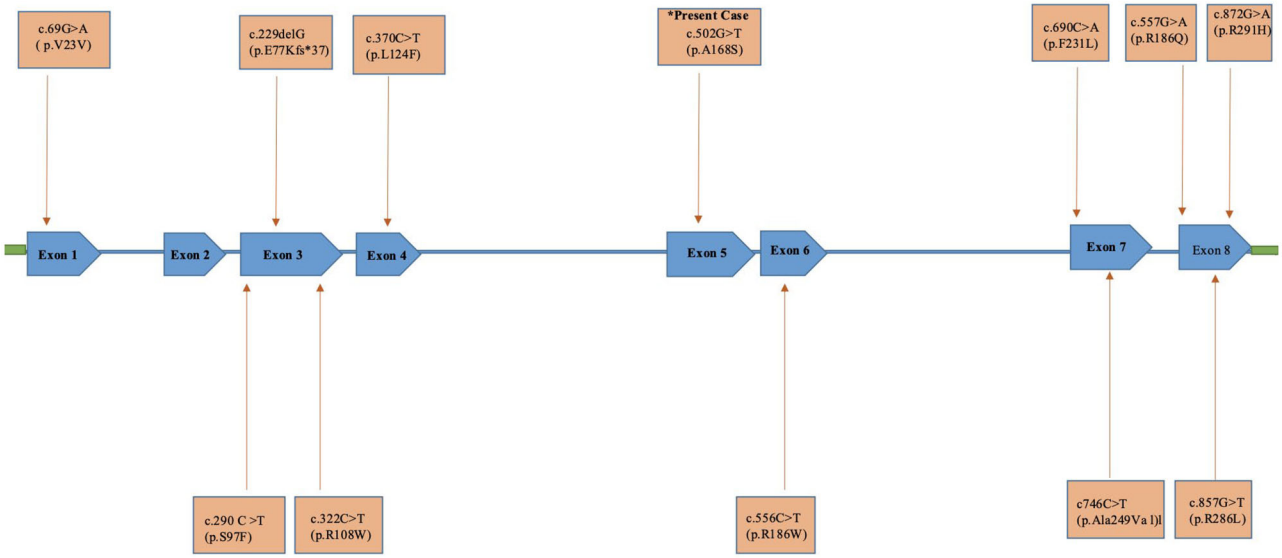

FIGURE 4 | Exon localizations of AGS type 4 cases.

extremely low frequency in the gnomAD population database (0.0001184). The locus was highly conserved in evolution: PhyloP100way 9.103; PhasCons100way 1. In silico predictors (DANN, CADD, Revel, and SIFT) predicted a deleterious effect. The variant was reported in the ClinVar database (Variation ID: 1383789). Parental genetic analyses for the targeted variant were heterozygous (Figure 3).

One variant was associated with AGS 4 in the ClinVar database in 2021 and was evaluated as a variant of uncertain significance (VUS). No association between this variant and clinical findings was reported. This sequence change replaces alanine with serine at codon 168 of the *RNASEH2A* protein (p.Ala168Ser). The alanine residue is highly conserved, and there is a moderate physicochemical difference between alanine and serine. This variant is present in population databases (rs772940870, ExAC 0.02%). However, it has not been reported in individuals affected by *RNASEH2A*-related conditions. Algorithms developed to predict the effect of missense changes on protein structure and function (SIFT, PolyPhen-2, and Align-GVGD) all suggest that this variant is likely to be disruptive.

3 | Discussion

This report describes the genotype–phenotype correlation in a case of AGS type 4 with spasticity, seizure, cortical atrophy, gliosis, and neuromotor development delay associated with a homozygous c.502G> T pathogenic variant in *RNASEH2A* (NM_006397.3) and reviews previous cases with this syndrome in the literature.

AGS, first described in 1984, is a multisystemic disease that generally emerges during birth or infancy. AGS exhibits severe effects on the brain, immune system, and skin in particular. It is generally divided into two types depending on the severity of the characteristics and age at onset, early onset (sometimes known as the classic form) and later onset. The actual frequency of AGS is unknown (Crow et al. 2005).

Neurological characteristics are the most common symptoms in AGS and are generally associated with severe disease and poor prognosis. These neurological characteristics include acute neurological function loss, developmental delay, regression, dystonia, epilepsy, sleep disorder, and microcephaly (Zhang et al. 2024).

Early-onset progressive encephalopathy with intracranial calcification and leukodystrophy of "chilblain-like" cutaneous lesions represent important diagnostic clues, clinical variability can be observed even within the same family, and non-specific presentation makes early diagnosis problematic (Crow and Manel 2015; Crow et al. 2020). Seizures are observed in half of children with AGS and are generally easily brought under control (Crow et al. 2005).

In addition to these findings, patients may also experience hepatosplenomegaly, pulmonary hypertension, interstitial lung disease, hypothyroidism, diabetes insipidus, myopathy and thrombocytopenia, and visual problems including loss of vision and glaucoma (Amari et al. 2020).

AGS 4 results from a homozygous or compound heterozygous mutation in the gene encoding subunit A of ribonuclease H2 (*RNASEH2A*; 606034) on chromosome 19p13. The incidence of *RNASEH2A* is 5% (Amari et al. 2020). The majority of pathogenic variants in *RNASEH2A* are missense, although splicing and frameshift pathogenic variants have also been reported (Crow et al. 2015; Rice et al. 2007). Forty-five mutations were reported in HGM between 2013 and 2024, 33 missense/nonsense, five splicing, three small deletion, two small insertion, and two small indels (https://www.hgmd.cf.ac.uk/ac/gene.php?gene=RNASEH2A). The clinical and laboratory characteristics of the 12 AGS type 4 cases we have been able to access in the literature and our own case are shown in Table 1. Exon localizations of AGS type 4 cases are shown in Figure 4.

Patients with *RNASEH2A* variants in the previous literature were aged 0–21 years, and male gender predominated (Al Mutairi et al. 2018; Garau et al. 2019; Khalilian et al. 2025; Peixoto de Barcelos

et al. 2023; Zhang et al. 2024). Our case also involved a 7-year-old boy. The known onset symptoms in these cases were regression, developmental delay, and spastic diplegia. Almost all cases with *RNASEH2A* variants have been accompanied by developmental delay, spasticity, microcephaly, and cranial imaging abnormalities (leukoencephalopathy, cortical atrophy, and calcification) (Al Mutairi et al. 2018; Garau et al. 2019; Khalilian et al. 2025; Peixoto de Barcelos et al. 2023; Zhang et al. 2024). Seizures are observed in half of children with AGS and are generally easily brought under control (Crow et al. 2005). In addition to these clinical findings, our patient presented with seizures in the first stage. These were brought under control with a single anti-seizure medication. However, a second anti-seizure medication was subsequently added when seizure control could not be achieved at follow-up after 2.5 years. In contrast to the other cases, corpus callosum dysgenesis was also present at cranial imaging.

The limitations of this report include the fact that lumbar puncture could not be performed since the family refused permission and that functional analyses could not be conducted.

In conclusion, the diagnosis of AGS relies on clinical characteristics and genetic testing. Basic neurological characteristics include developmental delay, dystonia, microcephaly, brain calcification, and leukodystrophy. Although data concerning genotype-phenotype in AGS type 4 have been reported in the literature, these are still limited. This variant was associated with AGS type 4 in ClinVar in 2021 and was evaluated as a VUS. We wished to emphasize the relationship with the clinical manifestation of this variant in addition to this case with unknown clinical findings. Further prospective observational and follow-up studies involving larger numbers of patients and centers are now needed on this subject.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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