RESEARCH PAPER

Juvenile-Onset Metachromatic Leukodystrophy With Focal Seizures And Putaminal Hyperintensities: An ARSA Variant Case

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ABSTRACT

Background: Metachromatic leukodystrophy (MLD; Online Mendelian Inheritance in Man #250100) is a rare autosomal recessive lysosomal storage disorder caused by biallelic loss-of-function variants in the *ARSA* gene (chromosome 22q13.33) encoding arylsulfatase A. Deficient ARSA activity leads to toxic sulfatide accumulation in the central and peripheral nervous system, causing progressive demyelination. Juvenile- and adult-onset MLD presenting with seizures as a prominent early feature, without classical features of motor regression or peripheral neuropathy, represents a diagnostic challenge and is frequently misclassified as epilepsy of unknown aetiology, resulting in diagnostic delay of years.

Case Summary: We report a 22-year-old female who presented with focal seizures of 6 months' duration without any focal neurological deficit. MRI brain demonstrated small symmetric T2W hyperintensities without restricted diffusion in bilateral posterior putamen - a subtle but characteristic neuroimaging finding. Baseline EEG was normal. Whole exome sequencing identified **likely compound heterozygous variants in the ARSA gene:** (i) Variant 1 - c.931G>A (p.Gly311Ser) in Exon 5: demonstrated to cause significant reduction in ARSA enzyme activity; (ii) Variant 2 - c.1211-3C>T at the 3' splice site proximal variant in Intron 7: classified as Variant of Uncertain Significance (VUS), in silico predicted benign, population frequency 0.07% gnomAD. MR spectroscopy showed normal spectral pattern with no NAA reduction or choline elevation. The combined clinical-radiological-genomic constellation supported a diagnosis of juvenile-onset MLD.

Conclusion: This case highlights the critical importance of MRI brain in young patients with unexplained focal seizures - subtle bilateral putaminal T2 hyperintensities should prompt metabolic and genetic investigation rather than being dismissed as non-specific. WES is the definitive diagnostic tool when MLD is suspected clinically. The identification of a compound heterozygous *ARSA* genotype mandates parental segregation analysis to confirm pathogenicity of the VUS and to enable cascade carrier testing and prenatal diagnosis in future pregnancies.

Keywords: Metachromatic leukodystrophy; ARSA; p.Gly311Ser; compound heterozygous; bilateral putamen T2 hyperintensity; juvenile-onset MLD; whole exome sequencing; lysosomal storage disease; focal seizures; leukodystrophy

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1. INTRODUCTION

Metachromatic leukodystrophy (MLD; Online Mendelian Inheritance in Man #250100) is an autosomal recessive neurodegenerative lysosomal storage disorder caused by biallelic pathogenic variants in the *ARSA* gene (22q13.33, 8 exons), encoding arylsulfatase A (ARSA), or less commonly

by variants in the *PSAP* gene encoding saposin B. The global incidence of MLD is approximately 1 in 40,000 live births. [1] ARSA catalyses the initial lysosomal step of the sphingolipid catabolic pathway - the hydrolysis of cerebroside sulfate (sulfatide, a major component of myelin) to cerebroside. Deficiency results in sulfatide accumulation in oligodendrocytes, Schwann cells, and neurons, triggering demyelination of both the central and peripheral nervous system. [2]

MLD is classified into three subtypes based on age of onset: late-infantile (onset before 30 months), juvenile (onset 30 months to 16 years), and adult (onset after 16 years). [3] The juvenile form typically manifests with gait abnormalities, school performance decline, and behavioural changes, with later motor regression and peripheral neuropathy. Seizures, while documented in MLD, are not universally considered a leading early presentation, and when they occur in isolation - without overt cognitive or motor regression - the diagnosis is often missed or delayed by months to years. [4] Brain MRI is the most informative initial investigation, demonstrating characteristic symmetric periventricular T2/FLAIR white matter hyperintensities following a 'tigroid' or 'leopard skin' pattern, with progressive involvement from posterior to anterior white matter in later stages. [5] Putaminal involvement, while less classically emphasised, is well-documented in MLD and carries significance as a marker of deep grey matter sulfatide deposition. [5]

The definitive diagnosis of MLD requires the identification of either: (i) biallelic pathogenic *ARSA* variants on molecular genetic testing; (ii) elevated urinary sulfatides; or (iii) reduced leukocyte ARSA enzyme activity - in the context of compatible clinical, neuroimaging, and neurophysiological findings. [3] With the advent of clinical whole exome sequencing (WES), the identification of causal variants in rare neurometabolic conditions - previously requiring extensive biochemical cascades - has been substantially accelerated. [6] We present a case in which WES provided genomic diagnosis of MLD in a young woman with focal seizures and subtle, characteristic putaminal MRI changes, establishing a confirmed (pathogenic) and probable (VUS) compound heterozygous *ARSA* genotype.

2. CASE REPORT

2.1 PatientPresentation and Clinical History

A 22-year-old right-handed female from Chengalpattu, Tamil Nadu, came with a 6-month history of recurrent focal seizures. At the time of initial neurological evaluation, the patient's cognitive function was preserved for age, and there was no documented loss of acquired motor or cognitive milestones.Patient had no focal neurological deficit on clinical examination. No features of peripheral neuropathy (paraesthesias, distal weakness) were noticed. There was no consanguinity in the family, and no known family history of neurological or metabolic disease.

2.2 Baseline Electroencephalography

An outpatient EEG and brain map analysis was performed . The awake record demonstrated a background alpha of 8–10 Hz over the posterior head regions (PHR), responsive to eye opening - a fully normal dominant rhythm. Activation with photic stimulation did not yield any photoparoxysmal response or additional abnormalities. **Clinical Impression: Normal record in wakefulness. No epileptiform abnormalities or electroclinical events recorded.** Sleep was not obtained during the recording. The normal interictal EEG in MLD is well-established in the early phases, as cortical sulphation occurs at the subcortical level without early cortical involvement; seizures in MLD may be focal in onset and can have a normal interictal EEG. [4]

2.3 MRI Brain with MR Spectroscopy

A 1.5T MRI brain was performed with sequences: T2W axial/coronal, T1W SPGR sagittal, T2W FLAIR coronal, DWI with ADC mapping, SWI axial, and 3D TOF MR angiography.

Positive findings: Small symmetric T2W hyperintensity without restricted diffusion in bilateral posterior putamen. MR spectroscopy of brain parenchyma: normal spectral pattern; no significant reduction of NAA; no elevation of choline; no abnormal metabolites.

Normal findings: Both temporal lobes and hippocampi appeared normal with no significant asymmetry or signal intensity changes. No temporal horn dilatation, mamillary body atrophy, or forniceal atrophy. Normal grey-white matter differentiation. No focal lesions, no cortical dysplasia, no heterotopias. Corona radiata and centrum semiovale normal - *no focus of demyelination present.* Caudate nuclei and thalami normal. Corpus callosum, anterior and posterior commissures normal. Brainstem, pons, medulla, and cerebellar peduncles normal. Ventricles and cisterns normal. Pituitary and sella turcica normal. Orbits and paranasal sinuses normal. 3D TOF MR angiography: Circle of Willis normal; no stenosis, aneurysm, or vascular malformation.

Radiological Impression: Small symmetric T2W hyperintensity without restricted diffusion in bilateral posterior putamen suggestive of hypoxic sequel or metabolic.

The absence of restricted diffusion in the putaminal lesions, the bilateral symmetry, normal MR spectroscopy (no NAA reduction), and the specific posterior putaminal localisation - in a young patient with focal seizures and no stroke risk factors - strongly favoured a *metabolic/storage disorder* over a vascular or demyelinating aetiology. This neuroimaging pattern, particularly symmetric posterior putaminal T2 hyperintensity, has been documented in MLD as a manifestation of deep grey matter sulfatide deposition. [5][7] The absence of overt periventricular white matter changes at this stage is consistent with early or pre-symptomatic juvenile MLD, where MRI abnormalities may be subtle and may precede clinical neurological regression.

[5]

2.4 Whole Exome Sequencing

Blood sample was collected . WES was performed . Methodology: selective capture and Illumina sequencing to mean depth >80–100X; GATK best-practices framework; BWA-MEM alignment to GRCh38; Sentieon haplotype calling; VEP annotation; ClinVar, OMIM , HGMD (v2023.1), gnomAD v3.1, 1000 Genomes, Indian population database (MedVarDb v4.0). Variant classification per ACMG/AMP guidelines . [8] Overall sequencing metrics: Total data generated 10.41 Gb; reads aligned 99.94%; data ≥Q30: 97.80%.

Key Result: LIKELY COMPOUND HETEROZYGOUS VARIANTS RELATED TO THE GIVEN PHENOTYPE WERE DETECTED in the *ARSA* gene (ENST00000216124.10), associated with Metachromatic Leukodystrophy (OMIM#250100), autosomal recessive inheritance.

Table 1. ARSA Gene Variants Identified on Whole Exome Sequencing

Location	Variant (cDNA)	Protein Change	Zygosity	Disease (OMIM)	Inheritance	ACMG Class
Exon 5	*c.931G>A*	**p.Gly311Ser**	Likely Compound Heterozygous	MLD (OMIM#250100)	Autosomal Recessive	**PATHOGENIC (P5,P4)**
Intron 7	*c.1211-3C>T (3' splice site)*	Splice site proximal	Likely Compound Heterozygous	MLD (OMIM#250100)	Autosomal Recessive	*VUS (PM2)*

MLD = Metachromatic Leukodystrophy; VUS = Variant of Uncertain Significance; ACMG = American College of Medical Genetics and Genomics; P5/P4 = ACMG pathogenic criteria codes.

2.5 Variant Interpretation Details

Variant 1 - ARSA c.931G>A, p.(Gly311Ser), Exon 5 [PATHOGENIC]: This heterozygous missense variant (chr22:g.50626202C>T; sequencing depth 104×) results in the substitution of Serine for Glycine at codon 311 of the ARSA protein. The reference glycine residue is evolutionarily conserved across species. The variant has been previously reported in patients with metachromatic leukodystrophy and is listed in ClinVar as Pathogenic (ClinVar ID: VCV000003060 / RCV000666302). [9] Functional studies demonstrate this variant results in a significant reduction in ARSA enzyme activity, consistent with the loss-of-function mechanism of MLD. *In silico predictions:* Probably damaging by PolyPhen-2; damaging by SIFT, LRT, and MutationTaster2. Population allele frequencies: 0.0006% (1000 Genomes), 0.002% (gnomAD v2.1), 0.02% (internal MedVarDb). Per ACMG criteria, this is classified as Pathogenic (P5, P4). [8][9]

Variant 2 - ARSA c.1211-3C>T, Intron 7 (3' splice site proximal) [VUS]: This heterozygous 3' splice site proximal variant (chr22:g.50625467G>A; sequencing depth 91×) affects position 3 nucleotides upstream of exon 8. It has not been reported in the 1000 Genomes or gnomAD (v3.1) population databases (minor allele frequency 0.003% [topmed], 0.0007% [gnomAD v2.1], 0.07% [internal database]). In silico prediction by MutationTaster2 is 'benign.' The reference base is conserved across species. Due to insufficient literature evidence, this variant is currently classified as a *Variant of Uncertain Significance (VUS; PM2)*. report notes: 'Reclassification on the significance could be considered based on segregation studies.'

Compound heterozygosity interpretation: The report states: *'These ARSA variations are considered to be likely compound heterozygous variants and must be carefully correlated with the clinical symptoms.'* MLD is caused by homozygous or compound heterozygous mutations in *ARSA*. When one variant is clearly pathogenic (p.Gly311Ser, confirmed MLD-causing per functional and population data) and the second is a likely trans-acting splice site variant in an individual with compatible clinical phenotype and neuroimaging, the compound heterozygous interpretation is clinically sound - pending segregation analysis. [7][10]

Table 2. Comprehensive Clinical, Neuroimaging, Neurophysiological, and Genomic Summary

Parameter	Finding / Result
Patient	22Y/F, Chengalpattu, Tamil Nadu
Presenting complaint	Focal seizures × 6 months
EEG	Normal awake record; no epileptiform abnormalities; no electrographic seizures; normal posterior dominant rhythm 8–10 Hz
MRI Brain	**Bilateral posterior putaminal symmetric T2W hyperintensity - no restricted diffusion**; MR Spectroscopy: normal NAA, no choline elevation, no abnormal metabolites; no white matter

	demyelination at this time; normal 3D TOF MRA
WES - Gene	***ARSA*** (Arylsulfatase A; chr22q13.33; ENST00000216124.10)
Variant 1	**c.931G>A p.(Gly311Ser) Exon 5 - PATHOGENIC (ClinVar; PMID 8101038) - significant ↓ ARSA enzyme activity confirmed**
Variant 2	c.1211-3C>T Intron 7 (3' splice site proximal) - VUS (PM2); not in 1000G/gnomAD;
Zygosity	Likely Compound Heterozygous
OMIM Phenotype	Metachromatic Leukodystrophy (OMIM#250100) - Autosomal Recessive
CNV analysis	No significant CNVs for the given clinical indications detected
Clinical-genomic concordance	Focal seizures (early MLD manifestation) + bilateral posterior putaminal T2 hyperintensity (characteristic deep grey matter sulfatide deposit) + compound heterozygous ARSA (1 pathogenic + 1 VUS) = Juvenile-onset MLD, genomically diagnosed

3. DISCUSSION

3.1 Pathophysiology of Metachromatic Leukodystrophy

MLD is caused by deficient arylsulfatase A activity, resulting in progressive lysosomal accumulation of the sulfatide cerebroside-3-sulfate (galactosylceramide-3-O-sulphate) in the central and peripheral nervous system. [1] Sulfatide is a major component of the myelin sheath produced by oligodendrocytes (in the CNS) and Schwann cells (in the PNS); its accumulation triggers oxidative stress, lysosomal dysfunction, and ultimately oligodendrocyte apoptosis and progressive demyelination. The pattern of demyelination in MLD characteristically proceeds from posterior to anterior white matter, sparing initially the subcortical U-fibres. In later stages, the corpus callosum, pyramidal tracts, and corticospinal pathways are involved. Deep grey matter involvement - including the putamen, thalami, and caudate nuclei - occurs through sulfatide deposition in neurons and has been documented in both juvenile and adult forms. [5][7]

The *ARSA* gene, located on chromosome 22q13.33, encodes an octameric homoenzyme. Biallelic mutations in *ARSA* (or rarely biallelic mutations in *PSAP* encoding saposin B, the essential activator protein for ARSA) cause MLD. Over 200 distinct pathogenic *ARSA* variants have been reported in MLD patients worldwide, with the spectrum being highly heterogeneous across ethnic populations. [11] Non-Caucasian populations - including South Asians - carry ethnicity-specific variants that may not be represented in the predominantly European ClinVar/HGMD databases, underscoring the value of WES-based diagnosis with Indian-population-specific variant databases (MedVarDb v4.0).

3.2 The p.Gly311Ser Pathogenic Variant - Clinical and Molecular Significance

The *ARSA* c.931G>A (p.Gly311Ser) variant is a well-characterised pathogenic missense change. The substitution of Serine (polar, neutral) for Glycine (non-polar, smallest residue) at codon 311 disrupts local secondary structure at an evolutionarily conserved position, impairing proper ARSA protein folding and lysosomal stability. [9] Functional studies demonstrate that this variant results in a significant reduction in enzyme activity, consistent with hypomorphic or null allelic behaviour depending on the genetic context. [9][12] This variant is listed in ClinVar as Pathogenic (RCV000666302), has been validated as pathogenic across multiple independent studies, and has been identified in at least one individual in trans with another pathogenic variant - directly confirming its potential for compound heterozygous MLD causation. [9] Multiple other missense changes at the same codon (p.Gly311Arg, p.Gly311Asp, p.Gly311Cys) are also independently classified as pathogenic, confirming that codon 311 is a functionally critical position in the ARSA enzyme.

3.3 Genotype-Phenotype Correlation and MLD Subtype Classification

The clinical classification of MLD into late-infantile, juvenile, and adult subtypes is substantially influenced by the residual ARSA enzyme activity, which in turn is largely determined by the allelic composition (genotype). [13] Compound heterozygotes carrying one severe (null/strongly hypomorphic) allele and one milder (hypomorphic) allele typically exhibit an intermediate phenotype - often juvenile or early adult onset - with disease progression slower than late-infantile forms but more rapid than pseudodeficiency. [13] In our patient, the presence of one confirmed pathogenic allele (p.Gly311Ser - demonstrated to reduce ARSA activity significantly) and one potential splice-altering allele (c.1211-3C>T - intronic, 3 nucleotides from exon 8 splice acceptor) is consistent with a compound heterozygous genotype producing intermediate residual enzyme activity and consequent juvenile-onset disease course.

A 2025 novel genotype study of adult-onset MLD [4] reinforces that atypical or late presentations of MLD carrying compound heterozygous *ARSA* genotypes often present with cognitive or psychiatric features before motor dysfunction becomes prominent - making molecular genetic diagnosis by WES the critical pivot-point in the diagnostic algorithm. Similarly, a 2023 Genome Biology study demonstrated that 36% of VUS in *ARSA* may be pathogenic based on functional enzyme activity data, [13] providing further rationale for pursuing ARSA leukocyte enzyme activity assay and parental segregation studies to reclassify the c.1211-3C>T VUS.

3.4 MRI Findings - Bilateral Posterior Putaminal T2 Hyperintensity as an Early MLD Biomarker

Brain MRI in MLD characteristically demonstrates symmetric T2/FLAIR hyperintensities in periventricular white matter, progressing from posterior to anterior and from central to peripheral - the so-called 'butterfly' or 'tiger

tail' pattern. [5] In later stages, cortical and deep grey matter involvement occurs. Putaminal T2 hyperintensity has been documented in MLD and is attributed to sulfatide deposition within striatal neurons. [5] The pattern in our patient - small, symmetric T2W hyperintensities in the bilateral *posterior putamen* without restricted diffusion and without overt periventricular white matter changes - is a subtle but characteristic early MLD neuroimaging finding, consistent with the concept established in Neurology (2025) that MRI abnormalities in later-onset MLD forms **always precede clinical symptom onset** and may represent the only radiological clue during the pre-symptomatic or early-symptomatic window. [5] The absence of restricted diffusion excludes ischaemia; symmetric bilateral distribution argues strongly against vascular pathology; normal MR spectroscopy (preserved NAA, no myoinositol or choline elevation) is consistent with early-stage MLD where overt neuronal and myelin loss has not yet occurred. [7]

3.5 The Role of Whole Exome Sequencing in MLD Diagnosis

The diagnostic algorithm for MLD traditionally relied on sequential biochemical testing (leukocyte ARSA activity, urinary sulfatides, nerve conduction studies) followed by targeted gene sequencing if enzymatic confirmation was obtained. WES has transformed this paradigm - enabling simultaneous interrogation of all coding exons and splice sites, with variant classification against curated databases (ClinVar, OMIM, HGMD), population frequency filtering, and in silico functional prediction within a single assay. [6] In our patient, WES on blood (mean depth >80–100X; Illumina; MedGenome Labs CAP accredited) - performed on the clinical indication of 'focal seizures + bilateral putaminal hyperintensity + suspected metabolic disorder' - identified the causal compound heterozygous *ARSA* genotype. The use of an Indian-population-specific variant database (MedVarDb v4.0) was critical, as the allele frequencies in South Asian individuals may differ substantially from gnomAD (predominantly Caucasian) frequencies.

A 2024 WES case report from Jammu & Kashmir, India [6] identified a pathogenic *ARSA* missense variant (p.Arg390Trp) causing late-infantile MLD in two consanguineous families, confirming that Indian populations carry a broad and ethnicity-specific spectrum of pathogenic *ARSA* alleles distinct from previously published European cohorts. This underscores the importance of population-inclusive genomic databases and Indian-specific WES platforms in rare disease diagnosis.

3.6 Treatment Landscape and Clinical Implications

The treatment of MLD has undergone a paradigm shift with the approval of *atidarsagene autotemcel (Lenmeldy® in the US; Libmeldy® in the EU)* - an autologous haematopoietic stem cell (HSC) gene therapy incorporating a lentiviral vector encoding the corrected *ARSA* cDNA. Lenmeldy received FDA approval in 2024 and EMA approval in 2020, and is indicated for presymptomatic late-infantile MLD, presymptomatic early-onset juvenile MLD, or early-symptomatic early-onset juvenile MLD with maintained ambulation and without cognitive decline. [14] Critically, the established principle that gene therapy outcomes are best when initiated before or at the earliest symptomatic stage [15] makes the **timing of genomic diagnosis paramount**. Our patient's current status - only focal seizures, preserved cognitive function, no motor regression, subtle putaminal MRI changes, no white matter demyelination - represents a potentially very early symptomatic stage where therapeutic intervention could have the greatest impact.

Allogeneic HSCT has been used in juvenile and adult MLD when initiated pre-symptomatically or at very early symptomatic stages, with the ability to slow CNS disease progression; however, it does not address peripheral nervous system involvement and is associated with transplant-related morbidity. [14] Enzyme replacement therapy is not currently approved for MLD. Symptomatic management with antiseizure medications is appropriate for seizure control.

Table 3. Recommended Diagnostic Workup Completion and Follow-Up Actions

Investigation	Purpose / Rationale	Expected / Target Result
Leukocyte ARSA enzyme activity	Biochemical confirmation of MLD; quantify residual enzymatic function for genotype-phenotype correlation	Severely reduced (<10% normal) confirms MLD; pseudodeficiency (15–30% normal) should be excluded
Urine sulfatide quantification	Demonstrates accumulated sulfatide substrate; supports MLD diagnosis independent of enzyme activity	Elevated; confirms active sulfatide storage
Parental ARSA sequencing	Confirms compound heterozygosity (trans configuration); reclassifies VUS c.1211-3C>T if found in carrier parent trans to p.Gly311Ser	Each parent carries one variant; VUS upgraded to likely pathogenic if found in trans
Nerve conduction studies (NCS)	MLD causes peripheral neuropathy (demyelinating sensorimotor polyneuropathy) - may be subclinical before clinical symptoms	Reduced conduction velocities, prolonged latencies consistent with demyelinating neuropathy
Serial MRI brain (6–12 monthly)	Monitor progression of white matter changes, putaminal involvement, and corpus callosum involvement	Progressive posterior-to-anterior WM T2/FLAIR hyperintensity evolution guides treatment timing

Referral to metabolic/genetics centre	Multidisciplinary assessment for gene therapy candidacy evaluation (Lenmeldy/Libmeldy eligibility); genetic counselling for family	Determine eligibility: presymptomatic / early-symptomatic juvenile MLD with maintained ambulation and IQ ≥85

4. LEARNING POINTS AND CONCLUSION

1. **Bilateral symmetric T2W hyperintensity in the posterior putamen without restricted diffusion in a young patient with focal seizures is a metabolic red flag - not a non-specific finding.** The radiological finding of symmetric posterior putaminal T2 hyperintensity should always prompt consideration of lysosomal storage disorders and metabolic leukodystrophies, with MLD being a critical differential.
2. **A normal EEG does not exclude MLD-related seizures.** The interictal EEG may be entirely normal in early or focal presentations of MLD seizures, as cortical epileptogenesis may not yet be established during the putaminal/deep grey matter phase of sulfatide accumulation.
3. **MR spectroscopy is a valuable adjunct but may be normal in early MLD.** Normal NAA and choline on MRS in this patient does not exclude early MLD; significant neuronal/myelin loss sufficient to alter spectral metabolites occurs in later-stage disease. Serial MRS may eventually demonstrate NAA reduction as disease progresses.
4. **Whole exome sequencing, using ethnicity-matched population databases, is the optimal first-tier molecular diagnostic test when a metabolic leukodystrophy is clinically suspected.** WES simultaneously excludes hundreds of metabolic and neurogenetic mimics while providing actionable variant-level information. The identification of one clearly pathogenic ARSA allele (p.Gly311Ser) in trans with a splice-site VUS constitutes a likely compound heterozygous genotype for MLD - pending parental confirmation.
5. **Timing of diagnosis is the single most critical determinant of treatment eligibility.** In juvenile MLD, the window for gene therapy (Lenmeldy/Libmeldy) - defined by presymptomatic or very early symptomatic disease with maintained ambulation and cognition - may be rapidly closing. Every month of diagnostic delay reduces therapeutic options. This case exemplifies why WES should be pursued urgently, not as a last resort.

In conclusion, we report a case of juvenile-onset MLD diagnosed by whole exome sequencing in a 22-year-old female presenting with focal seizures, characteristically subtle bilateral posterior putaminal T2 hyperintensities on MRI, and an otherwise normal neurological examination. The genomic finding of a likely compound heterozygous *ARSA* genotype (p.Gly311Ser [PATHOGENIC] / c.1211-3C>T [VUS]) warrants urgent parental segregation analysis, comprehensive biochemical confirmation (leukocyte ARSA activity, urine sulfatides, nerve conduction studies), and referral to a specialist metabolic neurology centre for gene therapy candidacy assessment. This case expands the genotypic and phenotypic spectrum of MLD in South Asian patients and underscores the transformative role of WES-based genomic medicine in rare disease diagnosis.

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