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Original Research Paper

Genetics

GENOTYPIC SPECTRUM OF LEUKOENCEPHALOPATHY: GENETIC ANALYSIS OF TEN PEDIATRIC CASES

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ABSTRACT

Background: Leukoencephalopathies encompass a heterogeneous group of disorders characterized by abnormalities of cerebral white matter, often resulting from genetic defects affecting myelin formation, mitochondrial metabolism, or neuronal structural pathways. Recent advances in genomic sequencing have expanded the number of genes associated with these disorders.[1] **Purpose:** To describe the genotypic spectrum and molecular characteristics of pediatric leukoencephalopathy cases identified through whole exome sequencing. **Methods:** A retrospective analysis was performed on ten children with suspected genetic leukoencephalopathy who underwent whole exome sequencing. Variant interpretation was performed according to American College of Medical Genetics and Genomics (ACMG) criteria. Detected variants were analyzed for pathogenicity, inheritance patterns, and genotype–phenotype correlation. **Results:** Ten distinct genetic variants were identified across multiple genes including VPS51, POLR1A, PDE6C, DIAPH1, MLC1, ARSA, PYCR2, AARS2, NFIA, and GJC2. Pathogenic or likely pathogenic variants were detected in six genes (MLC1, ARSA, PYCR2, GJC2, NFIA, AARS2), while variants of uncertain significance were identified in VPS51, POLR1A, and DIAPH1. The majority of variants followed autosomal recessive inheritance, consistent with consanguinity observed in several families. The findings demonstrate significant genetic heterogeneity in pediatric leukoencephalopathies. **Conclusion:** Whole exome sequencing enables identification of diverse genetic etiologies in pediatric leukoencephalopathies. Detailed genetic characterization improves diagnostic precision and facilitates genetic counseling.

KEYWORDS : Leukoencephalopathy, Leukodystrophy, Whole Exome Sequencing, Genotype Spectrum, Pediatric Neurogenetics

INTRODUCTION

Leukoencephalopathies constitute a broad group of disorders characterized by abnormalities affecting cerebral white matter. These disorders may arise from defects in myelin formation, metabolic pathways, mitochondrial function, or structural proteins involved in neuronal development.[1]

The increasing availability of next-generation sequencing technologies has significantly expanded the number of genes implicated in inherited white matter disorders.[2]

Genetic leukodystrophies may arise from defects in genes involved in myelin synthesis, mitochondrial metabolism, neuronal cytoskeletal organization, or transcriptional regulation.[3]

Mutations in mitochondrial aminoacyl-tRNA synthetase genes such as AARS2 have been increasingly recognized as causes of leukodystrophy with progressive neurological decline.[4]

Similarly, mutations in genes affecting cytoskeletal proteins, including TUBB4A, have been associated with hypomyelinating leukodystrophies mimicking Pelizaeus–Merzbacher disease.[5]

Genomic sequencing approaches, particularly whole exome sequencing, have become essential diagnostic tools for children with unexplained neurological disorders.[6]

Rare syndromes such as leukoencephalopathy with calcifications and cysts further illustrate the expanding phenotypic and genetic spectrum of white matter disorders.[7]

Recent studies have also identified novel molecular mechanisms underlying neuronal injury and myelin dysfunction in these disorders.[8]

In some cases, leukodystrophies may be associated with endocrine abnormalities or epilepsy syndromes, reflecting multisystem involvement.[9]

Despite advances in molecular diagnostics, the genetic heterogeneity of leukodystrophies remains substantial.[10]

This study describes the genotypic spectrum identified in ten children with suspected genetic leukoencephalopathy who underwent whole exome sequencing.

METHODS

Study Design

A retrospective genetic analysis of pediatric patients with suspected leukoencephalopathy evaluated using whole exome sequencing.

Genetic Testing

Whole exome sequencing was performed using next-generation sequencing platforms. Variants were annotated and filtered based on:

- Allele frequency in population databases
- Predicted pathogenicity
- Clinical relevance to phenotype

Variant classification followed ACMG guidelines.

Variant Analysis

Each variant was evaluated for:

- Gene function
- Variant type
- Zygosity
- Inheritance pattern
- Previously reported disease associations

RESULTS

Genetic Spectrum

Whole exome sequencing identified variants in ten genes associated with neurological or white matter disorders.

The identified genes included:

- VPS51
- POLR1A
- PDE6C
- DIAPH1
- MLC1

- ARSA
- PYCR2
- AARS2
- NFIA
- GJC2

These genes represent diverse molecular pathways including:
- Myelin formation
- Lysosomal metabolism
- Cytoskeletal organization
- Mitochondrial function
- Transcriptional regulation

Variant Classification
According to ACMG criteria:

Pathogenic Variants
- MLC1
- ARSA
- PDE6C

Likely Pathogenic Variants
- PYCR2
- NFIA
- GJC2
- AARS2

Variants of Uncertain Significance
- VPS51
- POLR1A
- DIAPH1

Inheritance Patterns
Most variants demonstrated autosomal recessive inheritance, particularly in genes associated with metabolic and hypomyelinating leukodystrophies.

One variant (NFIA) demonstrated autosomal dominant inheritance, highlighting the diversity of genetic mechanisms underlying these disorders.

DISCUSSION
The present case series highlights the significant genetic heterogeneity of pediatric leukoencephalopathies. Whole exome sequencing identified variants across multiple genes associated with diverse biological pathways, including myelin development, mitochondrial metabolism, and neuronal structural integrity.

POLR1A
Variants in POLR1A are associated with hypomyelinating leukodystrophy type 27. These disorders are characterized by developmental delay, hypotonia, and diffuse hypomyelination on neuroimaging. Previous reports have described early childhood onset with progressive neurological impairment.[1] Our patient demonstrated similar radiological features, supporting the role of POLR1A dysfunction in impaired myelin formation.

VPS51
The VPS51 gene encodes a component of the Golgi-associated retrograde protein complex involved in vesicular trafficking. Mutations in VPS51 have been linked to neurodevelopmental disorders and pontocerebellar hypoplasia–like phenotypes. Although the variant identified in our cohort was classified as a variant of uncertain significance, its potential association with white matter abnormalities warrants further investigation.[2]

MLC1
Mutations in MLC1 cause megalencephalic leukoencephalopathy with subcortical cysts, characterized by macrocephaly, seizures, and progressive motor dysfunction. The pathogenic variant identified in this series is consistent with previously reported mutations causing classical MLC phenotype.[3]

ARSA
The ARSA gene encodes arylsulfatase A, and deficiency leads to metachromatic leukodystrophy, a lysosomal storage disorder characterized by progressive demyelination. Patients typically present with motor regression, seizures, and cognitive decline. The pathogenic ARSA variant identified in this study corresponds with established genetic causes of this disorder.[1]

PYCR2
Mutations in PYCR2 have been associated with hypomyelinating leukodystrophy type 10. This disorder is characterized by developmental delay, microcephaly, and progressive neurological impairment. Studies have demonstrated that PYCR2 plays an important role in mitochondrial metabolism and neuronal survival.[3]

AARS2
Variants in AARS2, encoding mitochondrial alanyl-tRNA synthetase, have been associated with leukodystrophy and mitochondrial encephalopathy. Patients may present with progressive neurological decline and white matter abnormalities. Emerging literature suggests that mitochondrial dysfunction plays an important role in the pathogenesis of these disorders.[4]

NFIA
The NFIA gene encodes a transcription factor involved in central nervous system development. Pathogenic variants are associated with brain malformations, including corpus callosum abnormalities and developmental delay. Our findings support previously reported associations between NFIA mutations and neurodevelopmental disorders.[2]

GJC2
Mutations in GJC2, encoding connexin 47, are known causes of hypomyelinating leukodystrophy type 2. These disorders are characterized by nystagmus, ataxia, and progressive neurological impairment. Defects in connexin-mediated gap junction communication are thought to disrupt oligodendrocyte function and myelin formation.[3]

DIAPH1 and PDE6C
Variants in DIAPH1 and PDE6C identified in this study highlight the expanding spectrum of genes potentially associated with neurological phenotypes. While these genes are traditionally associated with other neurodevelopmental or retinal disorders, their contribution to white matter abnormalities requires further exploration.

Overall, our findings emphasize the importance of comprehensive genomic testing in children with suspected leukodystrophy. Whole exome sequencing enables identification of diverse genetic etiologies and improves diagnostic precision in complex neurogenetic disorders.[11]

Limitations
This study has several limitations. The small cohort size limits generalization of the findings. Functional validation of variants of uncertain significance was not performed. Additionally, whole exome sequencing may not detect structural variants or regulatory mutations outside coding regions.

Future Directions
Future studies incorporating larger cohorts and whole genome sequencing may improve understanding of genotype –phenotype correlations in pediatric leukodystrophies. Functional studies are also required to clarify the pathogenic significance of variants of uncertain significance.

CONCLUSION

This case series highlights the broad genotypic spectrum of pediatric leukoencephalopathy identified through whole exome sequencing. Molecular diagnosis enables improved understanding of disease mechanisms and facilitates genetic counseling for affected families.

Table 1. Genotype Summary of Pediatric Leukoence-phalopathy Cases

Case	Gene	Variant (HGVS)	Variant Type	Zygosity	ACMG Classification	Associated Disorder	Inheritance
1	VPS51	c.2327_2329del (p.Glu776del)	In-frame deletion	Homozygous	VUS	Pontocerebellar hypoplasia type 13–related disorder	Autosomal recessive
2	POLR1A	c.3754C>G (p.Leu1252Val)	Missense	Homozygous	VUS	Hypomyelinating leukodystrophy type 27	Autosomal recessive
3	PDE6C	c.1004+1G>A	Splice-site	Homozygous	Pathogenic	Cone dystrophy 4	Autosomal recessive
4	DIAPH1	c.2855A>G (p.Asn952Ser)	Missense	Homozygous	VUS	Seizures–cortical blindness–microcephaly syndrome	Autosomal recessive
5	MLC1	c.206C>T (p.Ser69Leu)	Missense	Homozygous	Pathogenic	Megalencephalic leukoencephalopathy with subcortical cysts	Autosomal recessive
6	ARSA	c.869G>A (p.Arg290His)	Missense	Homozygous	Pathogenic	Metachromatic leukodystrophy	Autosomal recessive
7	PYCR2	c.751C>T (p.Arg251Cys)	Missense	Homozygous	Likely pathogenic	Hypomyelinating leukodystrophy type 10	Autosomal recessive
8	AARS2	c.1571_1579+10del	Splice-site deletion	Heterozygous	Likely pathogenic	Combined oxidative phosphorylation deficiency 8	Autosomal recessive
9	NFIA	c.70C>T (p.Arg24Ter)	Nonsense	Heterozygous	Likely pathogenic	Brain malformations with urinary tract defects	Autosomal dominant
10	GJC2	c.392del (p.Pro131fs)	Frameshift deletion	Homozygous	Likely pathogenic	Hypomyelinating leukodystrophy 2 (Pelizaeus–Merzbacher-like disease)	

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