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Whole Exome Sequencing in Children with Neurodevelopmental Disorders: A Case Series of a Novel Mboat7 Variant and Autism Spectrum Phenotype

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Abstract

Background: Neurodevelopmental disorders are a major cause of childhood disability and may present with developmental delay, speech and language impairment, behavioral abnormalities, intellectual disability, and features of autism spectrum disorder. Advances in genomic technologies, particularly whole exome sequencing (WES), have helped in the identification of genetic causes in children with unexplained developmental disorders.

Case Series

We described two children evaluated for neurodevelopmental abnormalities in whom genetic and neuroimaging investigations were undertaken.

Case 1 was a 9-year-old female with delayed speech and language development and delayed developmental milestones. A similarly affected sibling raised suspicion of an inherited neurodevelopmental disorder. Whole exome sequencing identified a novel homozygous frame shift deletion in exon 3 of the MBOAT7 gene, c.168del, resulting in p. Ile57Serfs*52. The variant was absent from population and disease databases and was classified as likely pathogenic according to American College of Medical Genetics and Genomics (ACMG) criteria. The same variant was identified in an affected sibling, supporting familial segregation and autosomal recessive inheritance.

Case 2 was a 13-year-old male evaluated for language delay and behavioral abnormalities, including restlessness, hyperactivity, and lack of eye contact, with autism spectrum disorder considered clinically. MRI brain screening demonstrated no significant intracranial abnormality, with mild inflammatory changes in the paranasal sinuses and right-sided mastoid disease. Phenotype-based exome analysis identified three heterozygous missense variants involving NLGN1, TRNC6B, and ITPR1.

Conclusion

This case series shows the clinical utility of genomic evaluation in children with unexplained neurodevelopmental abnormalities. The first case illustrates the identification of a novel likely pathogenic homozygous MBOAT7 frame shift variant associated with MRT57, while the second demonstrates the complexity of interpreting heterozygous variants of uncertain significance in a child with autism spectrum features. Integration of clinical findings, family history, neuro imaging, molecular findings, and appropriate segregation studies is essential for accurate diagnosis, genetic counseling, and informed reproductive planning.

Keywords: MBOAT7, MRT57, Developmental Delay, Intellectual Disability, Whole Exome Sequencing, Autism Spectrum Disorder, Variants of Uncertain Significance, Neurodevelopmental Disorder.

Introduction

Neurodevelopmental disorders are a major cause of childhood disability worldwide. Advances in genomic technologies, particularly whole exome sequencing (WES), helps in the identification of numerous genes associated with intellectual disability and developmental delay. Among these, MBOAT7 (Membrane Bound O-Acyltransferase Domain Containing 7) has become an important gene implicated in autosomal recessive intellectual developmental disorder-57 (MRT57).[1]

MBOAT7 codes lysophosphatidylinositol acyltransferase-1 (LPIAT1). This enzyme is involved in phospholipid remodeling and maintenance of neuronal membrane integrity. Loss-of-function variants disrupt neuronal development and cortical organization causing intellectual disability, delayed psychomotor development, severe speech impairment, seizures, behavioral abnormalities, and variable neuro imaging findings.[2,3]

Neurodevelopmental disorders may, however, demonstrate considerable genetic heterogeneity. Children presenting with speech delay, developmental delay, behavioral abnormalities, hyperactivity, impaired social interaction, and autism spectrum features may harbor pathogenic variants, susceptibility variants, or variants whose significance is uncertain. So, molecular diagnosis frequently requires correlation between phenotype and genotype and where appropriate, familial segregation studies.

We described two children with neurodevelopmental abnormalities who underwent genetic evaluation. The first child had delayed speech and language development and delayed developmental milestones, in whom WES identified a novel homozygous frame shift deletion in MBOAT7, establishing the diagnosis of MRT57.[4] The second child presented with language delay, hyperactivity, restlessness, and poor eye contact, with autism spectrum disorder(ASD) considered clinically. Genetic analysis identified three heterozygous variants of uncertain significance involving NLGN1, TRNC6B, and ITPR1.

Case Presentation

Case 1

A 9-year-old female child was referred for genetic evaluation because of delayed speech and language development and delayed attainment of developmental milestones. The clinical presentation raised suspicion of an underlying neurodevelopmental disorder, prompting further molecular investigation.

The patient had a similarly affected sibling who also presented with delayed speech and language development and delayed developmental milestones. The occurrence of comparable clinical manifestations in both siblings suggested a possible inherited disorder.

To investigate the genetic basis of the phenotype, Whole Exome Sequencing (WES) was done.

Genetic Investigations – Case 1

Genomic DNA was extracted from peripheral blood collected in EDTA vacutainers using standard Qiagen nucleic acid isolation kits. Library preparation was performed using the Twist 2.0 Exome Kit, including mitochondrial genome coverage, and sequencing was carried out on the Illumina Nova Seq X Plus platform.

Sequence reads underwent quality control assessment and were aligned to the human reference genome (hg38). Variant calling for single nucleotide variants (SNVs) and small insertions/deletions (InDels) was done using Illumina DRAGEN v4.0 software. Variant annotation and interpretation incorporated information from OMIM, Clin Var, db SNP, 1000 Genomes, Ex AC, gnom AD, and ESP databases together with in silico prediction tools including REVEL, Mutation Taster, PolyPhen-2, and SIFT. Variant classification was done according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Analysis found a homozygous frame shift deletion variant in exon 3 of the MBOAT7 gene (NM_024298.5): c.168del (p.Ile57Serfs*52). The variant was detected at chromosomal position chr19:54188254:TG>T with sequencing coverage of 40× and was present in all sequencing reads covering the locus (40/40 reads).

The identified deletion is predicted to result in premature protein truncation 52 amino acids downstream of cod on 57. The normal MBOAT7 protein consists of 472 amino acids. The variant was absent from Clin Var, db SNP, gnom AD, and Ex AC databases.

As per the ACMG criteria (PVS1 and PM2), the variant was classified as Likely Pathogenic. No clinically relevant copy number variations (CNVs) or mitochondrial DNA variants were detected.

The same homozygous MBOAT7 variant was found in the affected sibling, providing more evidence on the pathogenicity and autosomal recessive inheritance.

Diagnosis – Case 1

Based on the clinical phenotype of delayed speech and language development, delayed developmental milestones, and the identification of a homozygous likely pathogenic MBOAT7 variant, a diagnosis of Intellectual Developmental Disorder-57 (MRT57; OMIM #617188) was established.

Management and Genetic Counseling – Case 1

Clinical correlation of the identified variant with the patient's phenotype was recommended. Genetic counseling was advised to facilitate understanding of the molecular diagnosis and its inheritance pattern. Further testing of parents and other affected or unaffected family members was recommended to assess carrier status and familial segregation of the variant.

Long-term clinical follow-up and supportive multidisciplinary management were advised according to the patient's developmental requirements.

Case 2

A 13-year-old male child was evaluated in a neurology setting for developmental and behavioral concerns. The patient presented with language delay. The clinical assessment documented restlessness, hyperactivity, and absence of eye contact. Autism spectrum disorder was clinically suspected.

The available history documented non-consanguinity, hospital delivery, and crying immediately after birth. The child was referred for further neurological and genetic evaluation because of the developmental and behavioral abnormalities.

Neuro imaging – Case 2

MRI brain screening was done on 26 March 2026 using multiplanar and multi sequence non contrast imaging.

There was no restricted diffusion to suggest acute infarction. There was no evidence of acute intra- or extra-axial hemorrhage, midline shift, or hydrocephalus. Grey-white matter differentiation was maintained with normal myelination. The ventricular, cisternal, and sulcal structures were normal. Arterial and venous flow voids were normal.

The vestibulocochlear structures and seventh and eighth nerve complexes were normal bilaterally. The posterior fossa, including the cerebellum and brainstem, fourth ventricle, and foramen magnum region showed no acute abnormality.

Minimal periorbital cerebrospinal fluid collections with kinking of the optic nerves were described without scleral cupping. The sellar and parasellar structures were normal. Mild inflammatory changes were present in the visualized paranasal sinuses along with right-sided mastoiditis. The calvarium and visualized skull base were unremarkable.

The overall impression was no significant intracranial abnormality, but there is inflammatory sinus and right mastoid disease.

Genetic Investigations – Case 2

Genetic analysis identified three heterozygous missense variants involving NLGN1, TRNC6B, and ITPR1. The report recommended parental testing to ascertain the significance of the detected variants.

The first variant involved the NLGN1 gene (NM_001365931.2), with the variant reported as c.167G>A (p.Ala56Asp). The variant was heterozygous and absent from gnomAD. The reported computational evidence showed a REVEL score of 0.093. ClinVar did not report the variant, and the laboratory classified it as a variant of uncertain significance. The report associated NLGN1 with autism susceptibility.

The second variant involved the TRNC6B gene (NM_0012501.2), reported as c.1346A>G (p.Asn449Ser). The variant was heterozygous and absent from gnomAD. The reported REVEL score was 0.087. ClinVar did not report the variant, and it was classified as a variant of uncertain significance. The associated phenotype described in the report was global developmental delay with speech and behavioral abnormalities.

The third variant involved the ITPR1 gene (NM_001378452.1), reported as c.5394G>A (p.Met1798Ile). The variant was heterozygous and absent from gnomAD. The reported REVEL score was 0.459. ClinVar did not report the variant, and it was classified as a variant of uncertain significance. The associated phenotype listed in the report was spinocerebellar ataxia 29/congenital nonprogressive cerebellar ataxia.

No definitive molecular diagnosis was established from these findings in the available report. Parental testing was recommended to determine the significance and possible inheritance of the identified variants.

Diagnosis – Case 2

The clinical presentation of language delay, hyperactivity, restlessness, and poor eye contact was considered consistent with an autism spectrum/neurodevelopmental phenotype. MRI brain screening did not demonstrate a significant intracranial structural abnormality.

Genetic testing identified three heterozygous variants of uncertain significance involving NLGN1, TRNC6B, and ITPR1. Since these variants were classified as uncertain significance and parental testing was recommended, they cannot be considered definitively causative on the basis of the available data.

Management and Genetic Counseling – Case 2

Clinical correlation of the identified variants with the patient's phenotype was recommended. Parental testing was advised to establish the significance and inheritance pattern of the detected variants.

Given the clinical features of language delay, hyperactivity, restlessness, and impaired eye contact, continued developmental and behavioral assessment and proper multidisciplinary supportive management were recommended.

Discussion

MRT57 is a rare autosomal recessive neurodevelopmental disorder resulting from biallelic pathogenic variants in MBOAT7. The disorder was 1st recognized through studies of consanguineous families showing intellectual disability and developmental delay. The phenotype associated with MBOAT7 deficiency includes moderate-to-severe intellectual disability, delayed psychomotor development, markedly impaired or absent speech, motor delay, seizures, hypotonia, behavioral abnormalities, and occasionally autism spectrum features. Brain imaging may show cortical atrophy or malformations like polymicrogyria, although normal neuro imaging has also been documented.[5]

The clinical features documented in Case 1, particularly delayed speech and language development and delayed developmental milestones, are consistent with previously reported MBOAT7-associated neurodevelopmental disorders. The most prominent documented manifestations were delayed speech and language development and delayed developmental milestones, both recognized features of MRT57. Though seizures and major structural brain abnormalities were not documented in this case, phenotypic variability is well recognized among affected individuals.[6]

The identified variant in Case 1, c.168del (p.Ile57Serfs*52), represents a truncating mutation predicted to abolish normal protein function. MBOAT7 plays a crucial role in phospholipid remodeling and neuronal membrane homeostasis. Loss of enzymatic activity disrupts membrane composition, affecting neuronal signaling, cortical development, and synaptic function. These molecular mechanisms likely contribute to the neurodevelopmental phenotype observed in affected subjects. The identified c.168del (p.Ile57Serfs*52) variant was absent from ClinVar, dbSNP, gnomAD, and ExAC databases at the time of analysis, supporting its rarity and suggesting that it may represent a previously unreported pathogenic variant.

In case 1, identification of the same variant in an affected sibling strengthens the evidence for causality.[7]

Case 2 shows different aspect of genomic evaluation in neurodevelopmental disorders. The patient presented with language delay, hyperactivity, restlessness, and lack of eye contact, leading to clinical consideration of autism spectrum disorder. The genetic evaluation did not identify a clearly pathogenic variant. Instead, three heterozygous missense variants involving NLGN1, TRNC6B, and ITPR1 were reported as variants of uncertain significance.

NLGN1 has been associated with neurodevelopmental phenotypes and autism susceptibility.[8] The TRNC6B finding was reported in association with global developmental delay with speech and behavioral abnormalities, andITPR1 is associated with cerebellar and ataxic phenotypes.[9]But the variants identified in the present child were classified as uncertain significance, and the available report specifically recommended parental testing. So, genotype-phenotype correlation and

segregation analysis are important before assigning pathogenic significance to these variants.

The normal brain MRI in Case 2 is also relevant in the context of neurodevelopmental disorders. The absence of a significant intracranial abnormality does not exclude a genetic neurodevelopmental disorder. Neurodevelopmental phenotypes may occur despite structurally normal conventional brain imaging, particularly in children whose major manifestations involve language, behavior, social communication, and developmental function.

Overall, the two cases show the range of outcomes that may be encountered during genomic evaluation of children with neurodevelopmental abnormalities. Case 1 resulted in identification of a novel likely pathogenic homozygous variant and a definitive molecular diagnosis of MRT57. Case 2, showed multiple heterozygous variants of uncertain significance, showing the challenge of distinguishing potentially relevant genetic findings from variants that cannot yet be established as disease-causing.

Genetic counseling is an important component of the evaluation. In Case 1, the homozygous MBOAT7 variant and affected sibling support an autosomal recessive pattern and provide an important basis for familial counseling and reproductive planning. In Case 2, parental testing is particularly important because the currently identified variants are of uncertain significance.

Conclusion

This case series shows the clinical utility and interpretive complexity of whole exome sequencing in children with neurodevelopmental disorders.

Overall, early molecular diagnosis and appropriate interpretation of genomic findings are essential for appropriate management, prognostication, genetic counseling, and informed reproductive planning in families affected by neurodevelopmental disorders.

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