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Case Report

A Rare Case of Antenatally Diagnosed Tay-Sachs Disease

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ABSTRACT

Background: Tay-Sachs disease (TSD) is a rare autosomal recessive lysosomal storage disorder caused by mutations in the *HEXA* gene that encodes the alpha subunit of the lysosomal enzyme β-hexosaminidase A (Hex A).
Case Report: The case presented is of a 19-week pregnant 30-year-old female with a bad obstetric history. Her two previous female children expired at 11 months and 5 years of age, respectively, with suspected metabolic or neurodegenerative disorders. The third female child presented at 4 years of age with a history of seizures and global developmental delay and had facial dysmorphism and macrocephaly. Considering the past obstetric history and history of consanguinity, whole-exome sequencing (WES) of both parents and Sanger sequencing of the fetus were carried out.
Conclusion: Whole-exome sequencing of the parents and prenatal genetic testing revealed one pathogenic mutation, NM_000520.6(HEXA):c.1274_1277dup (p.Tyr427fs), in the *HEXA* gene in this family. The parents were heterozygous, while the fetus was homozygous for this mutation, which manifests as Tay-Sachs disease.

Keywords: β-hexosaminidase A, Frameshift mutation, Sanger sequencing, Tay-Sachs disease, Whole-exome sequencing

Introduction

Tay-Sachs disease (TSD: OMIM 272800) is an autosomal recessive lysosomal storage disorder that results from mutations in the gene encoding the alpha subunit of β-hexosaminidase A, a lysosomal enzyme. β-hexosaminidase A consists of α- and β-subunits that are encoded by the *HEXA* and *HEXB* genes, respectively. The deficiency of functional β-hexosaminidase A results in an accumulation of GM2 gangliosides, causing GM2 gangliosidosis (1). GM2 gangliosidosis is characterized by progressive neurodegeneration manifested as TSD (mutations in the *HEXA* gene), Sandhoff disease (OMIM 268800, mutations in the *HEXB* gene), and GM2 activator protein deficiency (OMIM 272750, mutations in GM2-activator) (2). The infantile form of TSD is characterized by progressive psychomotor retardation and is fatal by the age of 2 or 3 years (3). More than 100 mutations have been identified in the *HEXA* gene (4).

Case report

A 30-year-old female (G4P4L1D2), consanguineously married, presented at 19 weeks of gestational age with a bad obstetric history. Her first child is female, normal, and alive. The second female child presented with seizures and expired at 11 months of age. A clinical diagnosis of suspected metabolic or neurodegenerative disorder was made, but no investigation was done. The third female child presented at 4 years of age with a history of seizures and global developmental delay. She had facial dysmorphism and macrocephaly with an open anterior fontanelle. She suffered from hypertonia, multifocal tonic-clonic seizures, and status epilepticus. The EEG was abnormal, showing a temporal epileptiform abnormality. A

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focal lesion involving ipsilateral white matter/diffuse cortical dysfunction due to a toxic-metabolic or systemic cause, neurodegenerative disorder, or cortical injury was suspected. MRI of the brain favored the possibilities of leukodystrophy, Krabbe's disease, Alexander disease, or metabolic diseases. There were elevated levels of alanine, lactic acid, pyruvic acid, and hippuric acid, with suspicion of mitochondriopathy. Biotinidase enzyme activity and carnitine levels were normal, and the free/acylcarnitine ratio was low, ruling out glycogen storage disorder. This female child died at the age of 5 years.

The female presented to us during her fourth pregnancy [G4]. The mid-trimester ultrasound scan was normal, with no identifiable congenital anomaly or growth retardation. After a detailed evaluation and genetic counseling, invasive testing was done in the 17th week. As the first line of testing, karyotyping was done, which was found to be normal. Considering the past obstetric history and history of consanguinity, whole-exome sequencing (WES) of both parents was carried out, followed by Sanger sequencing of the fetus. DNA extracted from blood and amniotic fluid was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to a mean coverage of >80-100X on the Illumina NovaSeq platform.

DNA was extracted and fragmented, with fragments from the coding regions of the selected gene panel targeted for amplification and sequencing. Reads from the sequence output were aligned to the human reference genome (GRCh37) using the Burrows-Wheeler Aligner (5). Duplicate read identification and removal, base quality recalibration, and realignment of reads based on indels were done using the inbuilt DRAGEN bio-IT pipeline. Variants to the reference were called using the Genomic Analysis Tool Kit (6). The variants were annotated and filtered using the VarSeq™ version 2.2.2 (Golden Helix Inc., Bozeman, MT, USA) and Varsome analysis workflow (7), implementing the American College of Medical Genetics (ACMG) guidelines for interpretation of sequence variants. The ClinVar database (8) was used for clinical assertions on variants' pathogenicity and multiple lines of computational evidence on conservation and functional impact. All variants with a minor allele frequency of less than 1% in the gnomAD database (9) and disease-causing variants reported in the Human Gene Mutation Database (HGMD) (10) and ClinVar were considered. The investigation for relevant variants was focused on coding exons and flanking +/-10 intronic nucleotides of genes with clear gene-phenotype evidence (based on OMIM information). For exome analysis, the autosomal recessive mode of inheritance was used as a filter because the patients were from a consanguineous family. Final analysis revealed a heterozygous variant, NM_000520.6(HEXA):c.1274_1277dup (p.Tyr427fs), in the parents. Sanger sequencing of the amniotic fluid sample revealed a homozygous mutation NM_000520.6(HEXA):c.1274_1277dup (p.Tyr427fs) (Figure 1).

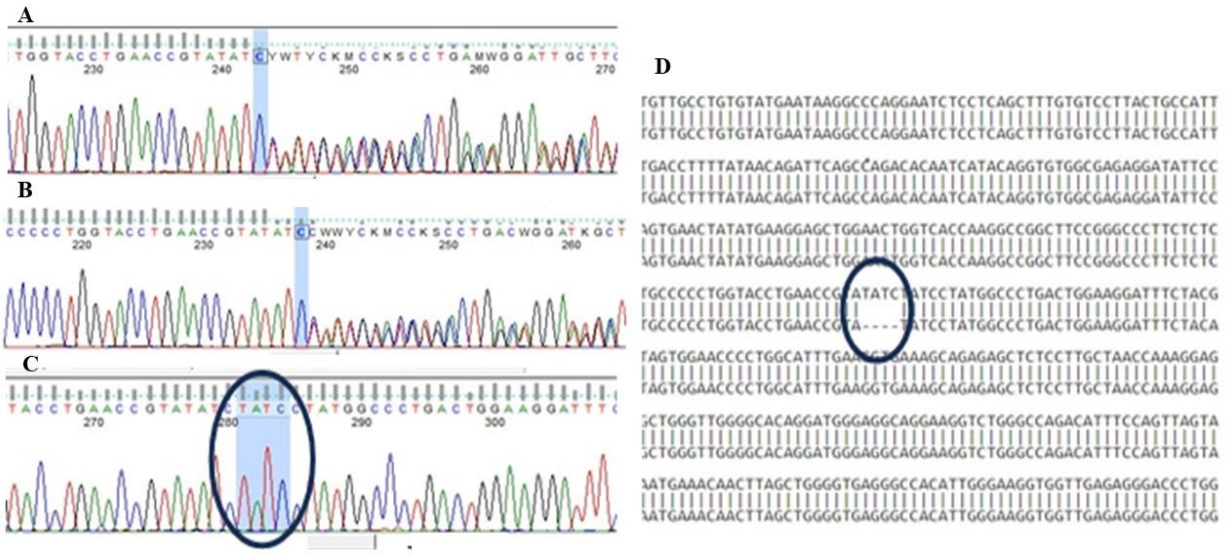

Figure 1. Chromatogram of the patients. Heterozygous c. 1274_1277dupTATA in *HEXA* gene in (A) father and (B) mother, (C) Homozygous c. 1274_1277dupTATA in *HEXA* gene in fetus. (D) Sequence alignment showing TATC duplication

Ethical Approval

Written informed consent was obtained from the patient for publication of this case report. Patient identity has not been disclosed in this case report. Retrospective case reports are exempt from institution review committee.

Discussion

TSD is a rare autosomal recessive lysosomal storage disorder caused by mutations in the *HEXA* gene. The genetic location of TSD is 15q23-q24 (11). In this case report, we present one Indian consanguineous family with a proven case of Tay-Sachs disease. In this family, two female children expired at the age of 11 months and 5 years, respectively. Due to a bad obstetric history, whole-exome sequencing of the parents and Sanger sequencing of the fetus were carried out. The sequencing revealed a pathogenic heterozygous and homozygous mutation in the parents and the fetus, respectively. Since the parents were carriers of this pathogenic mutation, there was a 25% chance that the fetus would be affected. The variant in the current report, NM_000520.6 (HEXA):c.1274_1277dup (p.Tyr427fs), is a known variant of TSD (12) and is reported to be present at a high allele frequency of about 8×10^{-4} (13). The variant causes a shift in the reading frame, leading to nonsense-mediated decay. The frameshift mutation/duplication of the TATC nucleotide (c.1274_1277dupTATC: p.Tyr427fs) creates a premature translational stop signal, resulting in premature termination at tyrosine (427th amino acid; p.Tyr427fs). This results in the formation of a truncated protein of 426 amino acids, which leads to a loss of function. According to ACMG guidelines, the variant is classified as pathogenic (criteria: PVS1, PM2).

Conclusion

Although TSD is a rare genetic disorder, timely genetic screening of the fetus can prevent the birth of affected individuals. Genetic testing for TSD plays an important role in preventing and managing this disease within affected families. The mutation identified in this study, NM_000520.6(HEXA):c.1274_1277dup (p.Tyr427fs), is a known pathogenic mutation that is lethal in the homozygous condition. This case report of a rare homozygous condition is also helpful in creating awareness about TSD.

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Conflicts of interest

The authors declare that no competing interest exists.

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