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Case Report

Identification of a Novel *GBA* Deletion Spanning 20,627bp Associated with Gaucher Disease: A Case Report

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Abstract

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder caused by variants in the *GBA* gene. This study reports a novel pathogenic large deletion in the *GBA* gene identified in a 70-day-old male infant presenting with cholestasis and hepatosplenomegaly, leading to a diagnosis of GD. Comprehensive genetic analysis using whole-exome sequencing (WES) revealed compound heterozygous variants, a maternally inherited c.1448T>C (p.Leu483Pro) missense variant and a paternally derived large deletion encompassing both the *GBAP1* pseudogene and the functional *GBA* gene. The paternal origin of the deletion was confirmed by quantitative PCR (qPCR), and long-range PCR with subsequent sequencing precisely mapped the breakpoints, characterizing the deletion as 20,627 bp in length. A critical diagnostic finding was that standard Sanger sequencing initially failed to detect this deletion, misleadingly suggesting the infant was homozygous for the missense variant. This case highlights a significant limitation of Sanger sequencing, which can misinterpret large heterozygous deletions as false homozygosity due to allele dropout. Consequently, this report underscores the necessity of employing comprehensive genomic methods like WES as a first-line diagnostic test for lysosomal storage disorders such as GD, ensuring accurate detection of complex variants including large structural variants.

Keywords

Gaucher Disease, Gaucher I, *GBA* Gene, Paternal Large Deletion, Whole-exome Sequencing, Enzyme Replacement Therapy

1. Introduction

Gaucher disease (GD), the most prevalent lysosomal storage disorder, is an autosomal recessive condition caused by pathogenic variants in the *GBA* gene [1, 2]. This gene encodes glucocerebrosidase (GCase), which catalyzes the degradation of glucosylceramide (GlcCer). GCase deficiency leads to GlcCer accumulation in macrophages, resulting in hepatosplenomegaly, anemia, thrombocytopenia, and skeletal involvement [3]. GD is clinically categorized into three types: non-neuronopathic (type 1), acute neuronopathic (type 2), and chronic neuronopathic (type 3) [4]. Over 500 *GBA* variants have been documented, with a predominance of missense/nonsense changes (HGMD 2023.6). The variant spectrum exhibits notable ethnic heterogeneity. In the Chinese population, the p.Leu483Pro (historically designated L444P) variant is predominant, accounting for 35–40% of disease alleles, contrasting with the high frequency of p.Asn370Ser in Ashkenazi Jewish populations [5, 6]. While research has focused on these recurrent variants, reports on complex structural variants, such as large deletions, remain limited.

Herein, we report a novel large deletion in *GBAP1*

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pseudogene and the *GBA* gene that escaped detection by conventional Sanger sequencing. This case expands the mutational spectrum of GD, highlights a critical diagnostic pitfall, and provides insights for optimal molecular diagnosis and management.

2. Case Description

A 70-day-old male was referred to our clinic, due to persistent jaundice accompanied with greyish stools for 1 month. Laboratory analysis when aged 49 days revealed elevated serum levels of total bile acids, bilirubin, transaminases and gamma-glutamyl transpeptidase (Table 1). Cholestatic liver disease was diagnosed, and oral glutathione was given but didn't respond well. The patient was the first child born to a non-consanguineous couple by vaginal delivery after an uneventful pregnancy.

Physical examination at referral revealed a body weight of 4.9 kg, head circumference 39 cm and height 58 cm. No abnormal appearance other than jaundice in the skin and sclera. No positive signs were revealed on examination of the heart and lungs, but an enlarged liver 5.0 cm below the right costal margin and 5.0 cm below xiphoid as well as an enlarged spleen 5.0 cm below the left costal margin were palpated.

Biochemical analysis confirmed the elevation of transaminases, total bile acids and bilirubin levels (Table 1).

Table 1. *Biochemical Indices of the Infant Over Time. Abbreviations: D, day, ALT, Alanine Transaminase; AST, Aspartate Transaminase; GGT, Gamma-glutamyl Transpeptidase. TBIL, Total Bilirubin; DBIL, dIrect Bilirubin; IBIL, Indirect Bilirubin; TBA, Total Bile Acids.*

Indices (range)	Ages									
	49D	52D	66D	67D	70D	72D	76D	81D	84D	284D
ALT (5-40U/L)	54.6	66	192.3	302	256	220	618	449	359	60
AST (5-40U/L)	117.5	122	278.1	331	311	285	776	448	289	64
GGT (8-50U/L)	189.6	122	108.9	103	92	74	80	74	70	15
TBIL (2-19μmol/L)	59.9	57.5	31.2	36.6	30.4	22.9	23.5	17.5	15.3	4.9
DBIL (0-6μmol/L)	48.6	35.4	22.9	22.8	23.2	16	16.5	12.3	9.8	1.7
IBIL (2.56-20.9μmol/L)	11.3	22.1	8.3	13.8	7.2	6.9	7	5.2	5.5	3.2
TBA (0-10μmol/L)	57.56	69.2	104.54	113.2	96.6	44.7	42.9	74.9	27.1	3.8

Common infection pathogens including toxoplasmosis, varicella-zoster, parvovirus B19, rubella, and herpes tested negative. Whole-exome sequencing (WES) was performed using a targeted capture approach, achieving a mean coverage depth of 314x (±186x) with >10x coverage for 99.2% of the targeted regions, which included the *GBA* locus. Initial analysis of sequencing depth indicated a heterozygous deletion involving exon 10 of the *GBA* gene (copy number =1) in the proband, in combination with a maternally inherited pathogenic c.1448T>C (p.Leu483Pro) missense variant [7, 8] confirmed by Sanger sequencing (Figure 1A). Quantitative real-time PCR (qPCR) confirmed the presence and paternal origin of this heterozygous deletion (Figure 1B). To characterize the deletion precisely, long-range PCR followed by Sanger sequencing mapped the breakpoints, defining a novel 20,627 bp deletion (NC_000001.10: g.155184891_155205517del) that spans the *GBAP1* pseudogene and *GBA* gene (Figure 2). Systematic searches in major public variant databases (including ClinVar and dbVar) revealed no records of this deletion, supporting its novelty. The diagnosis was functionally validated by a markedly reduced glucocerebrosidase activity (1.71 nmol/(h·mg); reference range 6.56–55.1 nmol/(h·mg)) in peripheral blood.

Based on integrated clinical, enzymatic, and genetic evidence, a definitive diagnosis of Gaucher disease was established. Enzyme replacement therapy (ERT) with intravenous Cerezyme (imiglucerase, 400 IU fortnightly) was initiated, achieving resolution of hepatosplenomegaly, jaundice, and hepatic dysfunction by the 9th infusion. Long-term therapeutic monitoring remains ongoing.

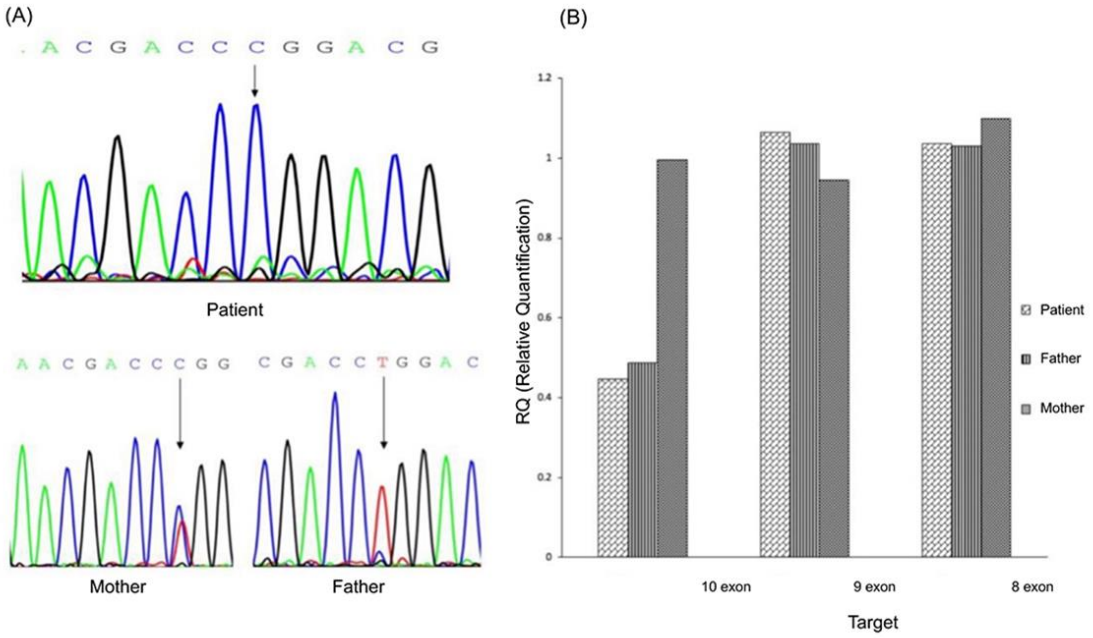

Figure 1. *Genetic findings in the GD patient and parents: A hemizygous c.1448T>C (p.Leu483Pro) variant in exon 10 of the GBA gene was detected in the patient. This variant was heterozygous in the mother and wild-type in the father, as confirmed by Sanger sequencing (Figure 1A). Further real-time PCR analysis of the GBA gene in the family trio showed a normal copy number of exons 8 and 9, but a reduced signal in exon 10 in both the patient and the father, indicating a deletion covering this exon (Figure 1B). The c.1448T>C (p.Leu483Pro) variant is located within exon 10 of the GBA gene.*

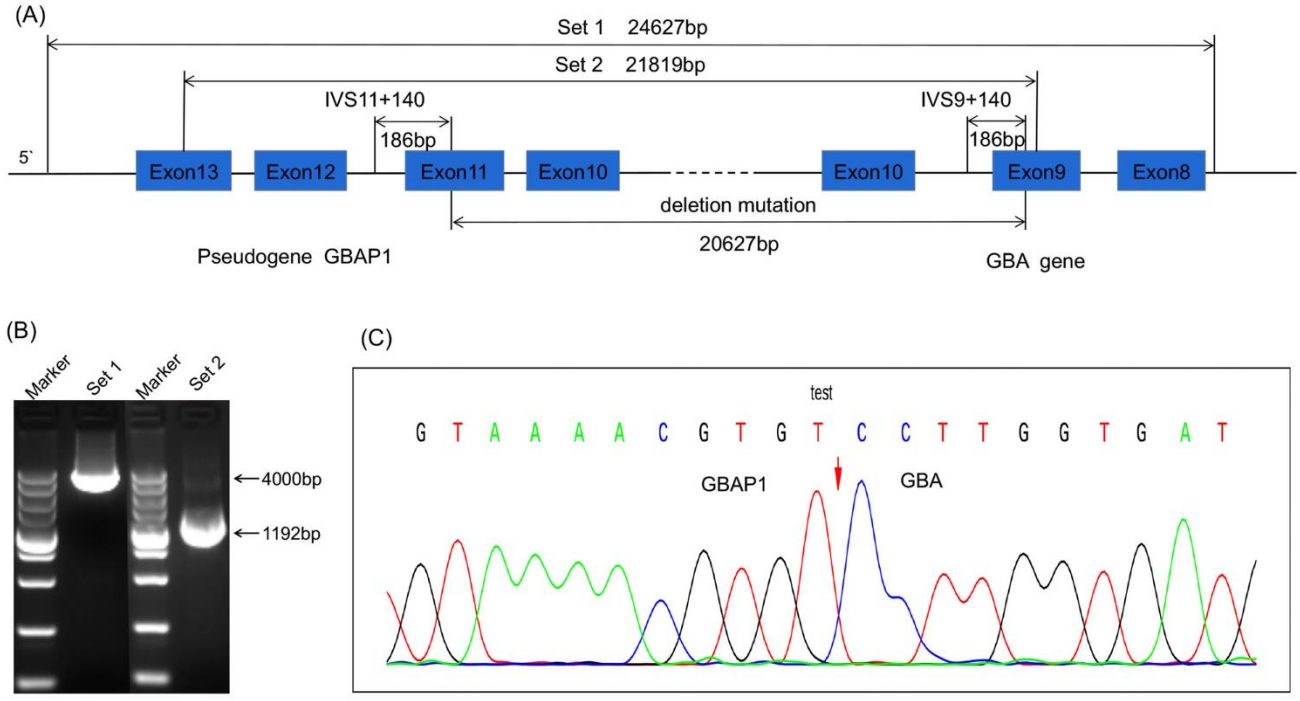

Figure 2. *Characterization of a novel large segment deletion involving the GBAP1 and GBA genes. (A) Schematic of the long-range PCR strategy for breakpoint mapping. Two primer sets flanking the predicted deletion region were employed. (B) Electrophoresis of long-range PCR products. The proband and father showed aberrantly shorter fragments (Set 1: ~4,000 bp vs. the expected ~24,627 bp wild-type; Set 2: ~1,192 bp vs. ~21,819 bp), confirming the heterozygous deletion. (C) Sanger sequencing chromatogram of the breakpoint junction from the purified PCR product. Sequence alignment indicated by the vertical dashed line (GRCh37/hg19: chr1: 155184891_155205517), defining a 20,627 bp deletion that includes GBAP1 and exon 10 of GBA.*

3. Discussion

The novel paternally inherited deletion was classified as pathogenic according to the American College of Medical Genetics and Genomics (ACMG) guidelines [9]. The classification is based on the following criteria: PVS1: The variant is a null variant (a large deletion) resulting in the loss of *GBA* exon 10, a mechanism known to cause loss of function in a gene where loss of function is a well-established disease mechanism for Gaucher disease. PM2: The deletion is absent from population frequency databases (gnomAD, dbVar, and ClinVar), indicating it is not a common benign polymorphism. PM3: The deletion was detected in trans with a confirmed pathogenic variant (the maternally inherited c.1448T>C; p.Leu483Pro) in the proband. PP4: The patient's phenotype—infantile cholestasis, hepatosplenomegaly, and a markedly reduced glucocerebrosidase activity of 1.71 nmol/(h·mg) (reference range: 6.56–55.1 nmol/(h·mg))—is highly specific for Gaucher disease, providing strong phenotypic correlation. The combination of PVS1, PM2, PM3, and PP4 provides strong evidence supporting a pathogenic classification for this deletion.

To establish the novelty of this deletion, we performed a systematic database search using its precise coordinates (GRCh37/hg19: chr1: 155184891-155205517). No records were found in ClinVar or dbVar, indicating it is neither a reported clinical variant nor a common polymorphism. Annotation using the UCSC Genome Browser confirmed that the deletion bridges the *GBAP1* pseudogene and *GBA* gene, a locus known for complex structural variations due to high homology between these sequences. Further analysis yielded two salient observations: first, both the paternal deletion and the maternal p.Leu483Pro variant impact the same C-terminal functional domain (residues 438-445) of β-glucocerebrosidase; second, breakpoint mapping revealed the deletion occurred in a region of low sequence homology and lacked the typical molecular features (e.g., extended microhomology) characteristic of non-allelic homologous recombination (NAHR) [10]. While the *GBAP1-GBA* locus is a known recombination hotspot where NAHR is common [11], the breakpoint structure in this case does not support an NAHR mechanism. Thus, the coincidental targeting of the same protein domain by two independent variants—a large deletion likely arising via a non-NAHR pathway and a classic missense variant—likely compounded the enzymatic defect, leading to the severe deficiency observed. This finding underscores the molecular heterogeneity underlying GD even within a classic recombination-prone locus.

Early identification of GD is critical for improving prognosis, yet its non-specific signs often lead to diagnostic delays amidst a broad differential diagnosis [12, 13]. Our case exemplifies this challenge and its resolution. The patient's severe infantile cholestasis with marked hepatosplenomegaly—a high-risk presentation for early-onset GD—underscores the need for targeted diagnostic suspicion in such a clinical scenario [14]. While definitive diagnosis traditionally hinges on demonstrating deficient glucocerebrosidase activity [15], our experience highlights the transformative role of rapid genomic sequencing. More critically, it exposes a major technical limitation of conventional Sanger sequencing. In the presence of a large heterozygous deletion, PCR amplification of the affected allele often fails due to "allele dropout," resulting in a sequencing readout that artifactually appears homozygous [16, 17]. This artifact can mislead clinicians into overlooking a true compound heterozygous state, as initially occurred here. The risk is further exacerbated in genes like *GBA*, where high homology with the *GBAP1* pseudogene increases the potential for primer disbanding and amplification bias, compromising accurate variant detection [18]. Reliance on Sanger sequencing alone in such contexts, particularly for severe early onset cases, carries a substantial risk of misdiagnosis or significant diagnostic delay.

Given these limitations, a first-tier, comprehensive genomic approach is warranted for suspected GD. WES provides an unbiased survey of coding regions and, through depth-of-coverage analysis, can indicate potential copy-number variations, prompting targeted confirmation [19]. In this case, WES concurrently identified both the point variant and the large deletion, enabling a conclusive molecular diagnosis within weeks and permitting the immediate initiation of enzyme replacement therapy. This strategy averted potential invasive procedures (e.g., diagnostic liver biopsy) and shortened the protracted diagnostic odyssey often experienced in GD [20, 21]. Consequently, we advocate that for infants presenting with hepatosplenomegaly and cholestasis—a constellation highly suggestive of early-onset GD—WES with integrated Copy Number Variation (CNV) analysis, or targeted high-resolution CNV assays, should be considered the primary diagnostic test. This approach ensures the detection of the full spectrum of pathogenic variants, facilitates timely intervention, and provides accurate information for family genetic counseling by clarifying the mechanism and recurrence risk of the identified variants.

4. Conclusions

This case highlights a significant limitation of Sanger sequencing, which can misinterpret large heterozygous deletions as false homozygosity due to allele dropout. Consequently, this report underscores the necessity of employing comprehensive genomic methods like WES as a first-line diagnostic test for lysosomal storage disorders such as GD, ensuring accurate detection of complex variants including large structural variants.

Abbreviations

GD	Gaucher Disease
WES	Whole-exome Sequencing
GCase	Glucocerebrosidase
GlcCer	Glucosylceramide
HGMD	Human Gene Vatiant Database
ERT	Enzyme Replacement Therapy
qPCR	Quantitative Real-time Polymerase Chain Reaction
ACMG	American College of Medical Genetics and Genomics
NGS	Next-generation Sequencing
NAHRCNV	Non-allelic Homologous Recombination Copy Number Variation

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This Written informed consent was obtained from the patient's parents for publication of this case report.

Author Contributions

Ke-yuan Shen: Investigation, Writing – original draft
Phoebe Liao: Validation, Visualization
Yuan-zong Song: Writing – review & editing

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Conflicts of Interest

The authors declare no conflicts of interest.

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