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CASE REPORT

A rare case of a child with X-linked opitz G/BBB syndrome caused by a novel partial microduplication in the *MID1* gene: implications for genetic diagnosis

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ABSTRACT

Background: Opitz G/BBB syndrome (XLOS) is a rare X-linked recessive disorder caused by mutations in midline-1 (*MID1*) gene, characterized by midline congenital anomalies. Here, we report a novel *MID1* duplication associated with unique phenotypic features.

Case Presentation: A 2-year-old Saudi male had prenatally oligohydramnios and was born with rectovesical fistula, hypospadias, anorectal malformation, and congenital heart defects (atrial septal defect/patent ductus arteriosus). Family history revealed an X-linked inheritance pattern (multiple affected maternal male relatives). He also exhibited developmental delay and growth parameters below the 3rd percentile.

Methods: Chromosomal microarray (CMA) and whole-genome sequencing were performed using Agilent 4 × 180 K comparative genomic hybridization array and MGI-BGI platform (30× coverage), respectively.

Results: CMA identified a novel 224-kb hemizygous duplication in *MID1* (Xp22.2), overlapping exons 1-3 and the 5' untranslated region. The variant was maternally inherited (heterozygous in the mother) and absent in population databases. This duplication encompasses regions encoding a Really Interesting New Gene (RING), B-box 1 and 2, and part of the coiled-coil domain, suggesting potential disruption of domain integrity and MID1 function, though the precise mechanism remains uncertain.

Conclusion: This is the first report of a *MID1* duplication involving exons 1-3, associated with rectovesical fistula and oligohydramnios, broadening the phenotypic spectrum of XLOS. We recommend that *MID1* testing be considered in males with atypical midline defects (including urogenital anomalies), and prenatal testing should be offered for at-risk pregnancies.

Keywords: Opitz G/BBB syndrome, congenital midline defects, *MID1* gene duplication, X-linked intellectual disability, case report.

Introduction

X-Linked Opitz G/BBB syndrome [XLOS; midline-1 (MID1) - OMIM **300552*] is a rare X-linked recessive disorder characterized by congenital midline anomalies (1,2). The clinical presentation is highly variable, with major features such as hypertelorism, hypospadias, cleft lip/palate, laryngo-tracheo-esophageal defects, and intellectual disability, and minor features including

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congenital heart defects, imperforate/ectopic anus, and brain anomalies (3). Notably, female carriers may exhibit mild manifestations, most commonly hypertelorism (4-6).

XLOS is caused by pathogenic variants in the midline-1 (*MID1*) gene (Xp22.2), which encodes a 667-amino-acid protein critical for embryonic midline development (7). Reported pathogenic variants include missense and nonsense variants, small deletions, intronic splicing variants, or insertions located along the entire length of the gene, with the most clustering in the 3' region. In addition, whole-gene deletions and single-exon deletions or duplications have been documented (8-13).

Structurally, MID1 protein contains an N-terminal tripartite motif comprising a Really Interesting New Gene (RING) domain, two B-boxes, and a Coiled-coil (CC)region, followed by the C-terminal domains including C-terminal subgroup One Signature (COS) domain, fibronectin type III (FN3) repeat and B30.2 domain (composed of PRY/Spla kinase Ryanodine receptor subdomains) (1,9,14).

The RING domain confers E3 ubiquitin ligase activity, enabling MID1 to regulate protein degradation, while the B-box domains mediate protein–protein interactions and proper subcellular localization. The CC domain mediates M1D1 oligomerization, facilitating the formation of protein complexes essential for its function (1,15).

Although most reported variants are point mutations, only a few rearrangements of *MID1* gene have been reported to date, including duplications/deletions of entire exons or deletion of the entire coding region (11). Large exon-level duplications involving *MID1* remain exceptionally rare; only three cases were reported prior to 2013 (10). For example, a duplication of 600-700 bp comprising exon 1 has been identified by *MID1* transcript analysis and confirmed on the genomic level in a patient with XLOS (10), and a 160 bp tandem duplication resulted in a premature termination codon (16). Additionally, a 57-kb duplication of exon 2 was associated with a mild phenotype (craniofacial dysmorphism, swallowing difficulties, and normal development), suggesting that in-frame duplications in the CC domain may retain partial protein function. This contrasts with more severe phenotypes observed in deletions or truncating mutations, underscoring the importance of variant location in genotype–phenotype correlations (10).

Here, we report a Saudi male patient with XLOS harboring a novel 224-kb hemizygous duplication involving exons 1-3 of *MID1* (Xp22.2), associated with a previously unreported rectovesical fistula, and oligohydramnios in the proband of a mildly affected carrier mother. This case broadens the phenotypic and mutational spectrum of XLOS and highlights the disorder's variable expressivity.

Case Presentation

A 2-year-old Saudi male was referred to our genetics clinic for evaluation of genitourinary anomalies and dysmorphic features. The patient's clinical course, summarized in Table 1 and Figure 1, highlights key prenatal, neonatal, and developmental milestones.

He was born prematurely at 34 weeks via cesarean section, following preterm premature rupture of membranes (PPROM). Prenatal ultrasound at 30 and 32 weeks showed oligohydramnios and dilated bowel loops. Renal anatomy and function were normal at birth, and no evidence of bladder outlet obstruction was documented. Therefore, the olighydramnios was most likely related to PPROM rather than the underlying genetic abnormality, although the mother's two previous pregnancies were uncomplicated.

The neonatal course was complicated by respiratory distress syndrome, requiring 3 days of mechanical ventilation. Multiple congenital anomalies necessitated surgical interventions, including anorectoplasty for imperforate anus, repair of rectovesical fistula, and orchidopexy for undescended testes. Hypospadias repair is planned to use meatoplasty but has not yet been performed.

The patient is the third live-born child of non-consanguineous parents (same tribe). Family history revealed four maternal male relatives with anorectal malformations, suggesting an X-linked inheritance pattern; however, those relatives were not genetically tested (Figure 2).

Table 1. *Clinical timeline of the patient.*

Period	Key events	Interventions/findings
Prenatal	-Oligohydramnios - Dilated bowel loops (US at 30, 32 weeks)	• Maternal ultrasound findings
Birth	- Premature delivery (34 weeks) - Respiratory distress	• NICU admission, mechanical ventilation (3 days)
Neonatal	- Anorectal malformation - Rectovesical fistula - Hypospadias	• Anorectoplasty • Fistula repair • Orchiopexy
Infancy	- Developmental delays (head control: 6 months, sitting: 9 months, walking: 18 months)	• Physiotherapy referral
Cardiac	- Systolic murmur	• Echocardiography: small ASD/PDA (no intervention)
2 years	- Growth parameters <3rd percentile - Mild intellectual disability	• Brain MRI: normal Genetic testing initiated

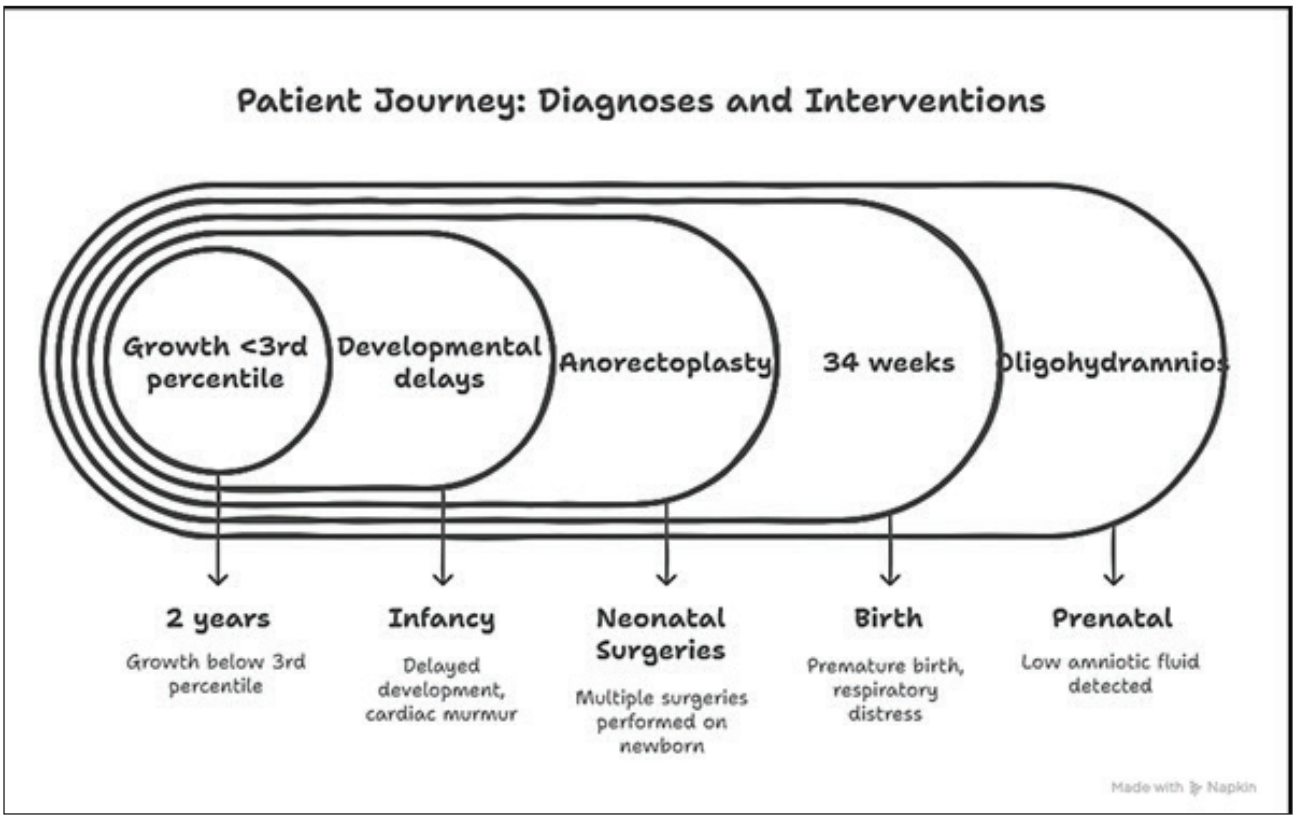

Figure 1. *Clinical timeline from prenatal period to diagnosis.*

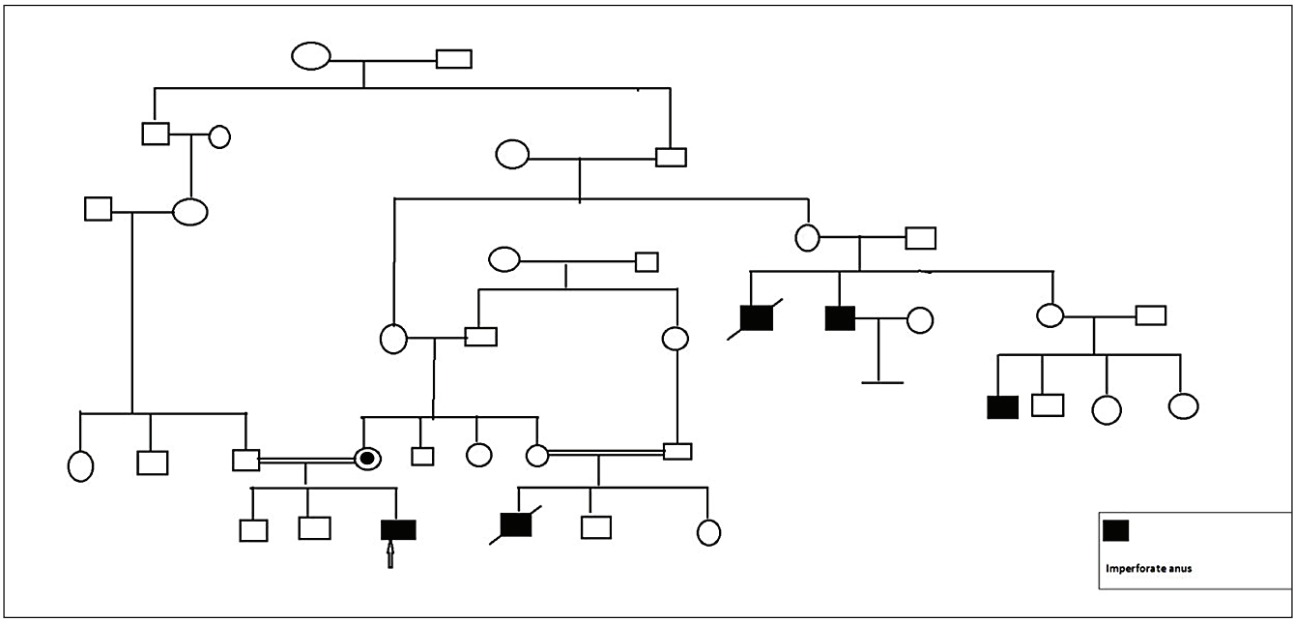

Figure 2. *The pedigree of the family demonstrating X-linked inheritance of imperforate anus. Four maternal cousins who are affected males. The mother of our index case is confirmed as a carrier. The index case (arrow) is affected male who inherited the causative allele from his mother. Four maternal male relatives with anorectal malformations were not genetically tested.*

At 2 years, his weight, height, and occipitofrontal circumference were all below the 3rd percentile for age. He exhibited mild developmental delays, achieving head control (at 6 months), independent sitting (at 9 months), and walking (at 18 months). Neurologically, he presented mild intellectual disability, although brain MRI was unremarkable. Formal developmental assessment tools (e.g., Bayley or Griffiths) were not documented. Dysmorphic features on examination included hypertelorism, a broad nasal bridge, and posteriorly rotated ears, along with glandular hypospadias and bilateral inguinal hernia scars from orchidopexy. Cardiac examination revealed a soft systolic murmur, and echocardiography revealed a small atrial septal defect (ASD) and patent ductus arteriosus (PDA), both hemodynamically insignificant.

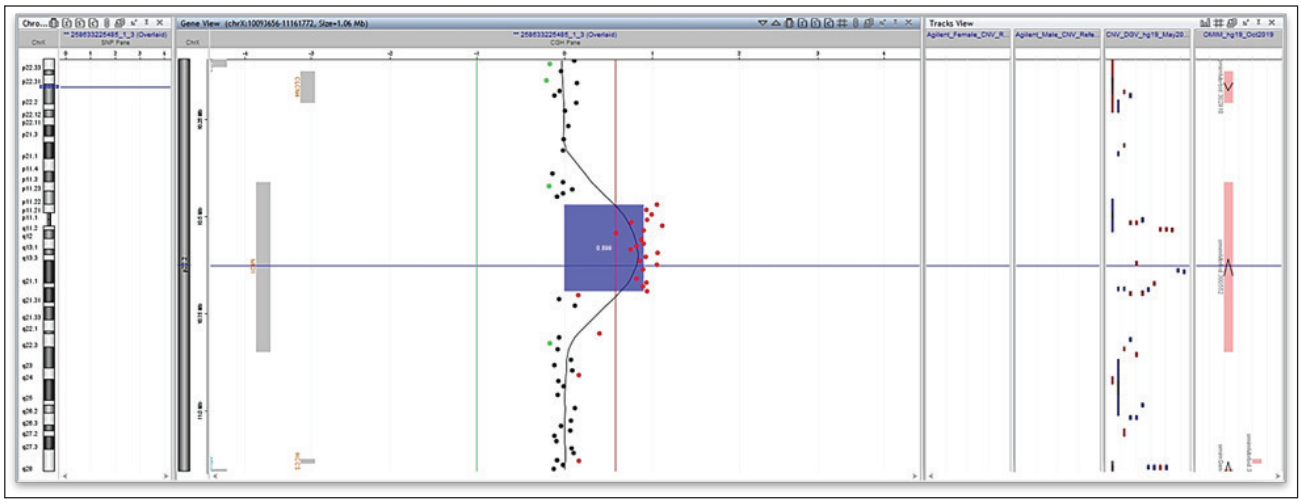

Figure 3. *Array CGH profile indicating an hemizygous duplication into MID1 gene.*

Methods

Array comparative genomic hybridization (Array CGH)

Array CGH was performed using an Agilent 4 × 180 K CGH array (Agilent Technologies, USA) with an average resolution of ~ 50 kb. Data were analyzed using Agilent CytoGenomics Software with GRCh37/hg19 as the reference genome.

Whole-genome sequencing (WGS)

WGS was performed on the MGI DNBSEQ platform. Sequencing reads were aligned to the UCSC hg19 human reference genome using BWA. Variant calling followed a phenotype-driven approach targeting genes associated with monogenic and mitochondrial disorders. Variants were classified according to American College of Medical Genetics (ACMG)/ClinGen guidelines.

Results

Clinical evaluation confirmed multiple congenital midline anomalies in the proband, including hypospadias, anorectal malformations, rectovesical fistula, minor facial dysmorphia, and congenital heart defects (ASD/PDA), consistent with X-linked recessive inheritance affecting maternal male lineage according to the family pedigree (Figure 2). Conventional cytogenetic analysis revealed a normal male karyotype (46, XY). Array CGH identified a hemizygous duplication of approximately 224 kbs at Xp22.2, Spanning from 10470307 bp to 10694513 bp(GRCh37), which includes N-terminal part of *MID1* gene (Figure 3). Segregation analysis confirmed that the patient's mother, who exhibited a mild hypertelorism phenotype, carries the same copy number variant in a heterozygous state. The molecular karyotype was reported as: 46,XY. arr[GRCh37] Xp22.2(10470307_10694513) X2 mat.

WGS refined the duplication breakpoints to ChrX: 10467001 - 10701000 (hg19), defining a ~234 kb hemizygous duplication overlapping the first three exons of *MID1* gene. The proximal breakpoint is located at the upstream region of *MID1* gene and the distal breakpoint is within the intron 3 of the *MID1* gene. No additional pathogenic/likely pathogenic variants were detected as per ACMG criteria. While the duplication spans coding regions for the RING and B-box domains and part of the CC domain, its precise functional impact remains uncertain. Potential effects could include altered transcription, splicing, or protein stability; however, RNA or protein studies were not performed, and mechanistic interpretation should be considered preliminary.

Discussion

Molecular significance of N-terminal MID1 duplications

XLOS is a midline malformation disorder caused by pathogenic variants in *MID1* gene, most commonly loss-of-function mutations. Over 100 pathogenic variants have been reported, including missense, nonsense, insertion/deletion mutations, and deletions - predominantly affecting the gene's 3′ region - consistent with a loss-of-function mechanism (17,18). Notably, no point mutations have been documented in the RING domain of *MID1*, suggesting that such variants may be subject to strong negative selection or other structural constraints (12). While XLOS pathogenesis is generally attributed to loss-of-function mechanisms (11,12), the impact of duplications is less straightforward. Whole-gene duplications often lead to overexpression and gain-of-function effects, whereas partial gene duplications can disrupt protein domains and integrity (13).

In this study, we report a novel duplication spanning exons 1-3 of *MID1* in a male with XLOS. This duplication is absent in the Exome Aggregation Consortium or gnomAD (v2.1) and has not been previously described in the literature. The duplicated segment encompasses critical N-terminal motifs (the RING finger, B-box 1 and 2, and part of the CC domain), which are essential

for MID1's structural and functional integrity (19-23). Although this duplication is predicted to disrupt these domains and potentially alter transcription or translation, the precise pathogenic mechanism remains uncertain.

Structure–function implications

Our findings support a position-dependent effect on phenotype severity. It suggests that N-terminal duplication, such as the exons 1-3 duplication, correlates with more severe anomalies, including the rectovesical fistula observed in our patient. In contrast, previously reported duplication limited to exon 2 (within the CC region) has been associated with much milder phenotypes (10), whereas whole-gene *MID1* deletions produce the most severe phenotypes, consistent with haploinsufficiency as the primary mechanism (12,13).

Disruption of N-terminus of *MID1* (affecting the RING and B-box1 domains and part of the CC domain) may impair MID1's ability to anchor microtubules and target PP2A for degradation (19–23), while more C-terminal mutations might leave some protein functions intact (1,14). Overall, our findings extend the understanding of MID1's role in embryonic development - particularly in urogenital development - and reinforce that the size and location of a duplication, rather than the variant type alone, are key determinants of phenotypic severity. This case effectively bridges the gap between previously reported mild in-frame duplications and the catastrophic whole-gene deletions in the XLOS phenotypic spectrum.

Phenotypic expansion: rectovesical fistula and oligohydramnios

XLOS typically presents with nearly 100% penetrance of hypertelorism, along with hypospadias and laryngo-tracheo-esophageal defects (2). However, our patient demonstrated a previously unreported rectovesical fistula, which broadens the spectrum of XLOS-associated urogenital malformations beyond the classic findings of hypospadias and imperforate anus (1,15,24-27).

A second noteworthy observation was prenatal oligohydramnios. Clinical review confirmed that the mother experienced PPROM, which is a recognized cause of oligohydramnios and likely contributed to the preterm delivery. While this points to a non-genetic etiology, the coexistence of oligohydramnios with a novel *MID1* duplication warrants mention because it raises the possibility - albeit speculative - of an underlying genetic influence on amniotic fluid regulation. Oligohydramnios has not been described in prior XLOS cohorts (28); interestingly, a single case of polyhydramnios was reported in a patient with a duplication of *MID1* exon 1 (13). The occurrence of both oligo- and polyhydramnios in MID1-related cases implies that MID1 may participate in complex amniotic fluid homeostasis pathways, with the specific effect potentially influenced by mutation type or timing of developmental disruption.

Conclusion

This study expands the molecular and clinical spectrum of XLOS by documenting the first ~224 kb duplication involving *MID1* exons 1-3, a novel variant class distinct from previously reported point mutations and C-terminal truncations. Importantly, we describe previously unreported rectovesical fistula, which significantly broadens the spectrum of XLOS phenotypic features associated with urogenital anomalies beyond the classic findings of hypospadias and imperforate anus.

A secondary observation of prenatal findings, such as oligohydramnios and prenatal bowel dilation, were noted. Although the observed oligohydramnios is likely attributed to PPROM, its coexistence with a *MID1* duplication may warrant a potential area for future investigation.

These findings highlight the importance of considering *MID1* testing in males with classic features such as hypertelorism and hypospadias, as well as in those presenting with atypical midline defects (including anorectal and urinary anomalies). Future studies should focus on clarifying the functional impact of N-terminal *MID1* duplications and further exploring MID1's role in urogenital development.

It is notable that our patient represents the first reported XLOS case from Saudi Arabia. We propose that patients presenting with midline congenital defects (e.g., rectovesical fistula) and a family history suggestive of X-linked inheritance should be evaluated for XLOS, with targeted testing for *MID1* mutations.

Limitations

While we report a novel *MID1* duplication associated with XLOS, certain limitations must be acknowledged. First, we did not perform functional assays to assess the duplication's impact on MID1 protein expression or microtubule-binding activity; such experiments would help clarify whether the variant's mechanism is purely haploinsufficiency or involves a dominant-negative effect. Second, the inherent phenotypic variability of XLOS means that milder cases (especially in female carriers or individuals with subtle features) might be underdiagnosed or overlooked. Finally, as a single-case report, our study cannot establish definitive genotype–phenotype correlations for N-terminal *MID1* duplications.

List of Abbreviations

ACMG	American College of Medical Genetics
ASD	Atrial Septal Defect
CC	Coiled-coil
CGH	Comparative Genomic Hybridization
CMA	Chromosomal microarray
MID1	Midline-1
mTOR	mammalian Target Of Rapamycin
PDA	Patent Ductus Arteriosus
RING	Really Interesting New Gene
PPROM	Preterm premature rupture of membranes
SPRY	SPla and the RYanodine receptor
WGS	whole-genome sequencing
XLOS	X-Linked Opitz G/BBB syndrome

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Conflict of interest
The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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Consent for publication
Written informed consent was obtained from the parent/ legal guardian of the patient for publication of the details and any accompanying images.

Ethical approval
Informed written consent was obtained from the guardian of the patient included in the study. According to the rules of the Ethical Committee at the Prince Sultan Military Hospital (IRB approval NO: E-2647 date of approval: 25th Aug 2025), after fulfilling the ethical guidelines outlined by the Declaration of Helsinki 2013.

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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