BBS10-related Bardet-Biedl syndrome with an atypical presentation of diabetes mellitus: A case report

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Abstract. Bardet-Biedl syndrome (BBS) is a rare, autosomal recessive ciliopathy characterized by extensive clinical heterogeneity, which often complicates its diagnosis. The present study reported the case of a 31-year-old woman who presented with longstanding, poorly controlled type 2 diabetes mellitus and its associated complications. The patient exhibited classic features including Class I obesity, retinal dystrophy, postaxial polydactyly, renal dysfunction and hypergonadotropic hypogonadism. A definitive diagnosis was established through whole-exome sequencing, which identified compound heterozygous pathogenic variants in the *BBS10* gene (a nonsense mutation, p.Arg256* and a missense mutation, p.Gly180Glu). This case is novel in presenting with adult-onset diabetes as the primary complaint, highlighting the necessity of including BBS in the differential diagnosis of patients with early-onset metabolic disorders and multisystem involvement. Of note, the patient's glycemic control improved after treatment with a glucagon-like peptide-1 receptor agonist (semaglutide). This observation provides important longitudinal evidence suggesting a promising therapeutic strategy for managing metabolic dysfunction in BBS, potentially by engaging residual G-protein-coupled receptor signaling pathways despite underlying ciliary defects.

Introduction

Bardet-Biedl syndrome (BBS) is a rare autosomal recessive disorder characterized by significant clinical heterogeneity and multi-organ involvement (1). Its prevalence varies geographically, estimated between 1:120,000 and 1:160,000 in European and North American populations (2). The primary cilium is a microtubule-based, immotile organelle that projects from the surface of most mammalian cells, acting as a crucial sensory hub for cellular signaling. Disorders arising from structural or functional abnormalities of the primary cilium are collectively defined as ciliopathies, and BBS is a prototypical condition within this category. As primary cilia are ubiquitously distributed across diverse tissues, their impairment directly accounts for the extensive phenotypic spectrum of the disease. Owing to its multisystemic nature, BBS frequently manifests with progressive vision loss, lifelong obesity, renal dysfunction and cognitive impairment (3).

Establishing a clinical diagnosis of BBS is notably challenging and typically relies on the presence of specific hallmark features, including retinal dystrophy, postaxial polydactyly, truncal obesity, hypogonadism, renal anomalies and developmental delay (4,5). However, the penetrance and severity of these features vary widely across individuals, and many manifestations are age-dependent, often delaying recognition of the disorder. This marked phenotypic variability reflects its intricate genetic basis (6). To date, over 26 disease-causing genes have been implicated in BBS (7). Most of these genes encode components of the BBSome, an octameric protein complex central to the intraflagellar transport machinery. The BBSome ensures targeted trafficking of signaling molecules, such as G protein-coupled receptors (GPCRs), to and from the ciliary membrane (8). Among them, the *BBS10* gene product functions alongside BBS6 and BBS12 within a specialized chaperonin complex, critical for proper BBSome assembly (9). Pathogenic variants in *BBS10* disrupt this process, thereby compromising ciliary signaling pathways downstream (10).

Despite these clearly defined diagnostic criteria, patients with BBS are often first evaluated outside of genetics or rare disease clinics. Due to the syndrome's non-specific early presentations-such as obesity, diabetes, infertility or visual impairment-initial consultations may occur in endocrinology, gynecology or ophthalmology settings (11,12). Atypical feature combinations further increase the risk of diagnostic oversight. The present study reported a case involving a 31-year-old woman who presented with longstanding diabetes mellitus and related complications. Comprehensive clinical workup and molecular testing ultimately revealed compound heterozygous mutations in *BBS10*, confirming the diagnosis of BBS. This case underscores the necessity of including genetic syndromes such as BBS in the differential diagnosis when encountering

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patients with early-onset obesity, metabolic disturbance and multi-organ involvement. Early recognition is pivotal for timely intervention and multidisciplinary management.

Unlike most previously reported cases of *BBS10*-related BBS-which typically present in childhood or adolescence-the present study described a rare adult-onset case in a 31-year-old individual of Mongolian (East Asian) ancestry. To the best of our knowledge, this is the first report providing detailed longitudinal data (over a 6-month period) on metabolic improvements following treatment with a glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA; semaglutide).

Case report

The patient is a 31-year-old Mongolian woman who has been experiencing intermittent abdominal pain for 2 weeks. The patient was admitted for treatment in April 2025. The patient's body height was 159 cm and body weight was 80 kg, resulting in a body mass index of 31.6 kg/m^2, which corresponds to obesity class I (13). Physical examination also revealed craniofacial anomalies and bilateral postaxial polydactyly of the feet (Fig. 1). The patient's medical history was significant for chronic, poorly controlled type 2 diabetes mellitus, which had been diagnosed 9 years earlier during an evaluation for infertility. At that time, the patient was prescribed oral metformin, but reported suboptimal adherence to both pharmacological therapy and dietary recommendations, and did not routinely monitor blood glucose levels. A recent course of empirical antibiotics prescribed by the initial attending physician targeting the intermittent abdominal pain had failed to resolve the symptoms, prompting referral for further investigation (Fig. 2).

Initial laboratory analysis revealed significant hyperglycemia (fasting plasma glucose, 13.75 mmol/l; normal range, 3.9-6.1 mmol/l), elevated serum creatinine (127.8 μmol/l; normal range, 44-84 μmol/l), corresponding to an estimated glomerular filtration rate (eGFR) of 48.1 ml/min/1.73 m^2 (normal, ≥90 ml/min/1.73 m^2) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula 12 (14), indicating chronic kidney disease (CKD) stage G3aA3, and increased blood urea nitrogen (12.85 mmol/l; normal range, 3.2-7.1 mmol/l), which was likely associated with high-protein dietary intake prior to admission. Urinalysis showed marked proteinuria (3+, equivalent to ~3.0 g/l; normal value, negative), leukocyturia (3+, >500 cells/μl; normal value, negative or <5 cells/high-power field) and microscopic hematuria (1+, 10-25 cells/μl; normal value, negative or <3 cells/high-power field). Pelvic magnetic resonance imaging identified a hypoplastic uterus, absence of ovarian visualization and a cystic mass in the right pelvis (Fig. S1). Based on these initial findings, a preliminary diagnosis of type 2 diabetes mellitus with CKD was established (Table I).

Endocrine evaluation confirmed poor glycemic control [glycated hemoglobin A1c (HbA1c), 8.5%; normal range, 4.0-5.6%] and marked insulin resistance (fasting insulin, 25.34 μU/ml; normal range, 2.6-24.9 μU/ml; postprandial insulin, 75.91 μU/ml; normal range, <71.0 μU/ml). Low-normal (24.3 pg/ml; normal range, 20-145 pg/ml) combined with markedly elevated gonadotropins (FSH: 59.1 mIU/ml; normal range, 3.5-12.5 mIU/ml; and LH: 33.9 mIU/ml; normal range, 2.4-12.6 mIU/ml) were indicative of hypergonadotropic hypogonadism. Ophthalmologic assessment confirmed retinitis pigmentosa and bilateral lens opacities. Electromyography detected peripheral neuropathy affecting all four extremities. Cardiac ultrasound showed left atrial enlargement and diastolic dysfunction, while renal sonography revealed increased echogenicity of the renal cortex and bladder wall thickening. Dual-energy X-ray absorptiometry confirmed osteoporotic changes. Conventional karyotyping (46,XX) excluded chromosomal abnormalities (data not shown; based on pathology reports).

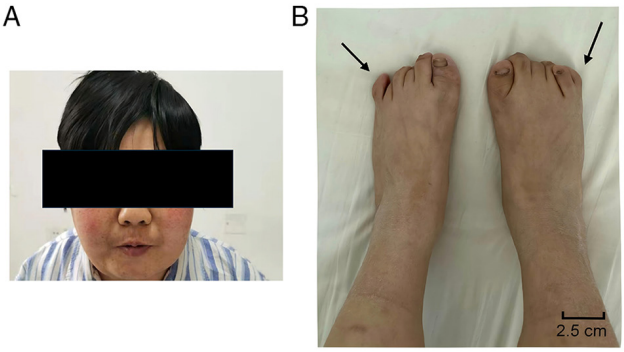


Figure 1. Clinical features of the patient. (A) Craniofacial anomalies: Midface hypoplasia, orbital hypertelorism (with possible telecanthus), with facial flushing and a rounded facial contour. (B) Bilateral postaxial (lateral) polydactyly of the feet: The accessory digits arise lateral to the fifth toes at the level of the distal fifth metatarsals; morphology is suggestive of Type A (well-formed osseous accessory digit articulating with the fifth metatarsal/tarsal). Associated xerosis cutis. Scale bar, 2.5 cm.

Comprehensive genetic analysis by whole-exome sequencing, followed by confirmatory Sanger sequencing, revealed two pathogenic variants in the BBS10 gene (RefSeq: NM_024685.4): A nonsense mutation c.766C>T (p.Arg256*) and a missense mutation c.539G>A (p.Gly180Glu). The missense variant exhibited a Combined Annotation Dependent Depletion (CADD)-phred score of 13.5. CADD is a widely adopted computational framework that integrates diverse annotations into a single quantitative metric to estimate the relative pathogenicity of human genetic variants. In this phred-scaled system, a score >10 indicates that the substitution is predicted to be among the top 10% most deleterious variants in the human genome, thereby strongly supporting the pathogenic impact of the p.Gly180Glu mutation. The patient was found to be a compound heterozygote for these variants. Segregation analysis confirmed the mutations were inherited from both parents, consistent with a biparental inheritance pattern (Fig. 3). This molecular finding, combined with the patient's classic clinical presentation, definitively established the diagnosis of BBS.

Genomic DNA was isolated from EDTA-anticoagulated peripheral blood. The DNA was fragmented using a Covaris focused-ultrasonicator, and libraries were subsequently prepared using the KAPA HyperPrep kit (Roche Diagnostics) strictly according to the manufacturer's instructions. Target capture was performed using the xGen Exome Research Panel v2 (Integrated DNA Technologies, Inc.) in accordance with the manufacturer's protocol. The captured libraries were sequenced on an Illumina NovaSeq 6000 platform

Table I. Metabolic parameters in the patient before and after glucagon-like peptide-1 receptor agonist (Semaglutide) treatment.

Clinical parameter	Normal range	Baseline (pre-treatment)	3-Month follow-up	6-Month follow-up
Glycemic control				
HbA1c, %	4.0-5.6	8.5	7.2	6.1
FPG, mmol/l	3.9-6.1	13.75	8.43	6.99
Insulin resistance				
Fasting insulin, μU/ml	2.6-24.9	25.34	15.54	12.88
HOMA-IR	<2.5	15.5	5.82	4
Anthropometrics				
Body weight, kg	-	80	75	71
BMI, kg/m^2	18.5-23.9	31.6	29.6	28
Renal indices				
eGFR, ml/min/1.73 m^2	≥90	48.1	119	107
Serum creatinine, μmol/l	44-84	127.8	52.2	56.3

All biochemical parameters were measured at the Department of Clinical Laboratory of the Affiliated Hospital of Inner Mongolia Minzu University using standard automated clinical chemistry analyzers. Strict Internal QC procedures were followed to ensure data accuracy. Specifically, FPG was measured using the hexokinase method. HbA1c was determined by high-performance liquid chromatography. Serum insulin levels were quantified using a chemiluminescence immunoassay. Since these data represent clinical diagnostic determinations verified by standard laboratory QC protocols, technical replicates for individual samples were not performed. QC, quality control; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c.

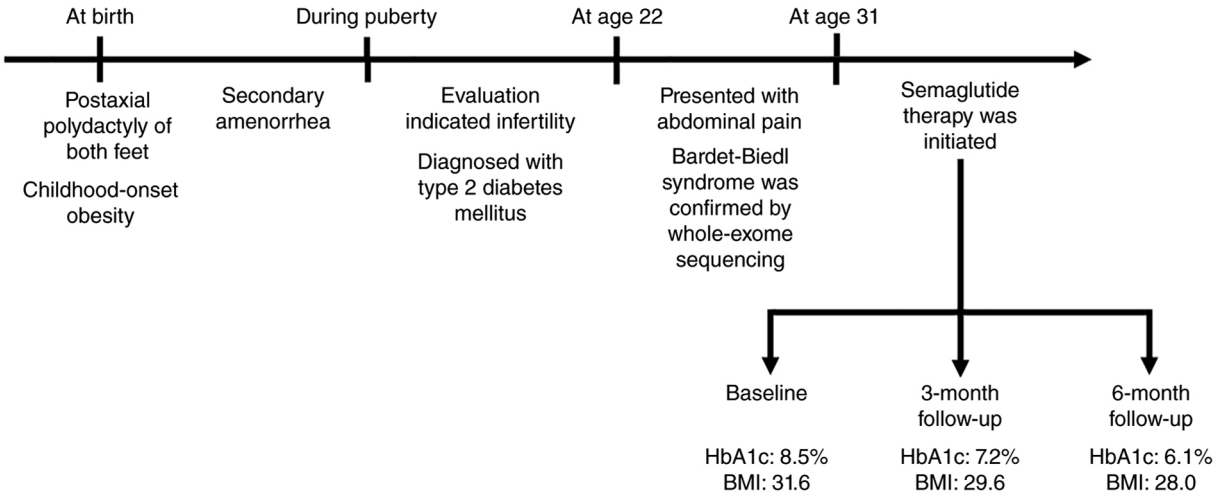


Figure 2. Chronological timeline of the patient's major clinical milestones. The timeline illustrates the progression from early-life manifestations to the current diagnosis and follow-up. Key events include polydactyly present at birth, obesity from early childhood, secondary amenorrhea during adolescence, diagnosis of type 2 diabetes mellitus at age 22 during an infertility workup, and the definitive genetic diagnosis of Bardet-Biedl syndrome at age 31. The timeline also shows the initiation of semaglutide therapy and the subsequent metabolic follow-up points at 3 and 6 months. HbA1c, glycated hemoglobin A1c; BMI, body mass index (units, kg/m^2).

(Illumina, Inc.) with paired-end 150 bp reads. Sequencing achieved a mean on-target depth of 120x; 99% of the targeted bases achieved a coverage depth of at least 10x, and 96-98% achieved a depth of at least 20x. The raw sequencing reads underwent quality control (QC) and trimming using FastQC (v0.11.9; Babraham Institute) and fastp (v0.23.2; Open source). The processed reads were aligned to the human reference genome GRCh38/hg38 using the Burrows-Wheeler Aligner Maximal Exact Matches (BWA-MEM, v0.7.17; Open source). PCR duplicate marking was performed using Picard (v2.27; Broad Institute), followed by base-quality score recalibration using the Genome Analysis Toolkit (GATK, v4.2+; Broad Institute). Small variants were called using the GATK HaplotypeCaller in 'gVCF' mode. This was followed by cohort joint genotyping and hard filtering applying specific thresholds for single nucleotide polymorphisms: QualByDepth (QD) <2.0, FisherStrand (FS) >60, MappingQuality (MQ, defined as the root mean square mapping quality of all reads at the site) <40, MQRankSum <-12.5, and ReadPosRankSum <-8.0, with analogous stringent thresholds for insertions

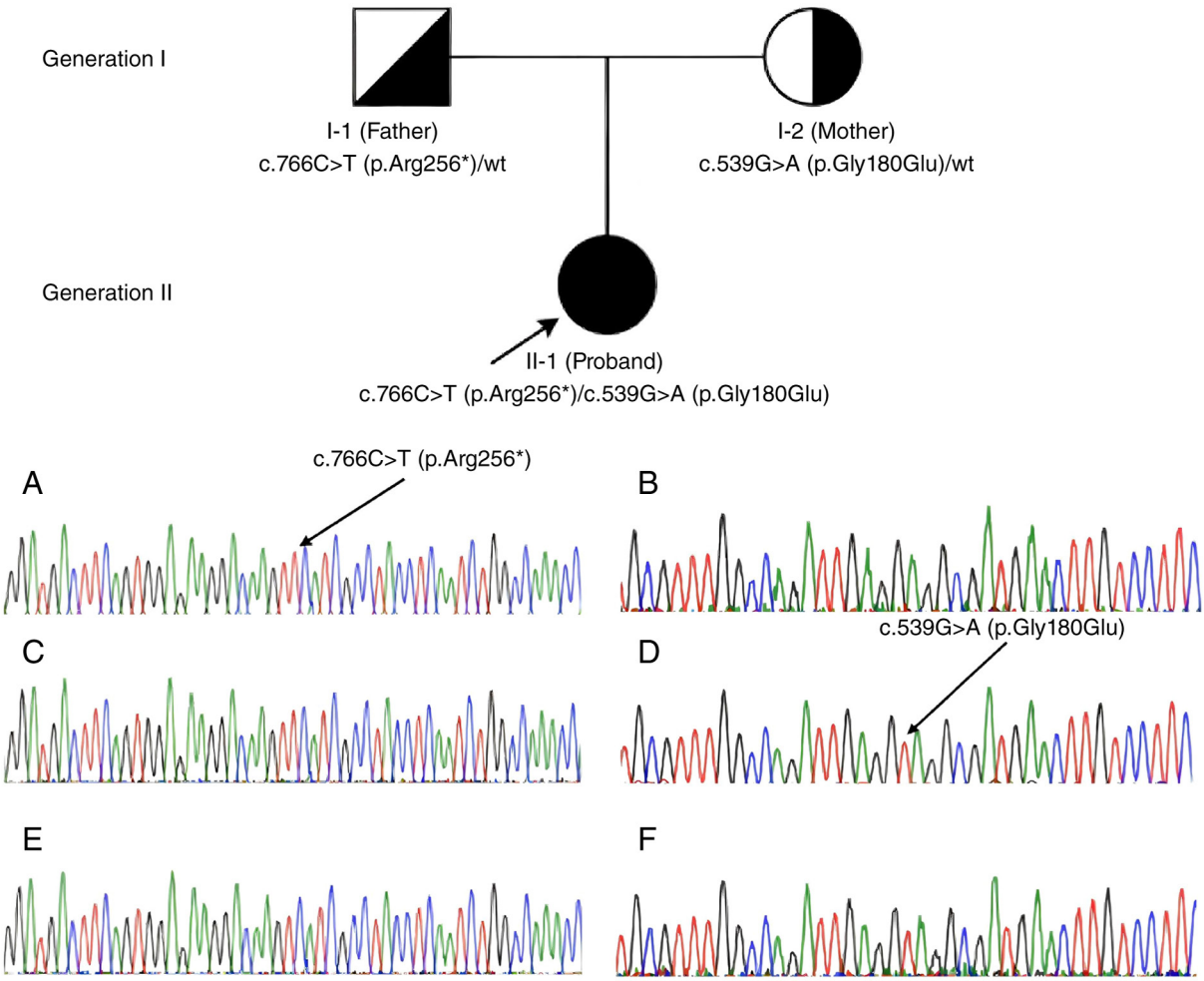


Figure 3. Sanger sequencing segregation analysis of the Bardet-Biedl Syndrome 10 variants. The chromatograms illustrate the genotypes of the proband and the proband's parents at the two pathogenic loci. (A and B) The proband shows heterozygous double peaks at both (A) c.766C>T (black arrow) and (B) c.539G>A (black arrow), confirming the compound heterozygous state. (C and D) The father is (C) heterozygous for the c.766C>T mutation but (D) wild-type for the c.539G>A variant. (E and F) The mother carries (E) the wild-type allele at c.766 but is heterozygous for (F) the c.539G>A mutation. In conclusion, the segregation analysis confirms that the c.766C>T variant was inherited from the father and the c.539G>A variant from the mother, consistent with an autosomal recessive inheritance pattern. Blue, C; Red, T; Black, G; Green, A.

and deletions. Variants were annotated using the Variant Effect Predictor (VEP, v105; Ensembl, European Molecular Biology Laboratory-European Bioinformatics Institute) and ANNOVAR (v.2020-06-08; Open Source). Annotation was performed against population frequency databases, specifically the Single Nucleotide Polymorphism Database (dbSNP) and the Genome Aggregation Database (gnomAD). Candidate pathogenic and likely pathogenic variants were orthogonally confirmed by conventional Sanger sequencing. For Sanger sequencing, the target regions were amplified by polymerase chain reaction and analyzed using an ABI 3730xl DNA Analyzer (Applied Biosystems) following standard laboratory protocols.

The patient's Mini-Mental State Examination score was 18 (15), which is consistent with intellectual disability. The observed familial segregation pattern supports an autosomal recessive mode of inheritance.

Pathogenicity was assessed according to the 2015 American College of Medical Genetics and Genomics standards (16). The BBS10 nonsense variant c.766C>T (p.Arg256*) was classified as pathogenic according to the joint consensus recommendations of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. This classification was established based on two specific evidence criteria: i) Pathogenic very strong 1, defined as a null variant (e.g., nonsense) in a gene where loss-of-function is a known mechanism of disease; and ii) pathogenic moderate 2 (PM2), which refers to a variant that is absent or has an extremely low frequency in large-scale population control databases. The missense variant c.539G>A (p.Gly180Glu) was classified as likely pathogenic on the basis of PM2 (absent or extremely rare in gnomAD), PM3 (observed in trans with a known pathogenic variant in this patient) and pathogenic supporting 3 (multiple *in silico* algorithms predict a deleterious effect-SIFT: Deleterious; PolyPhen-2: Probably damaging; MutationTaster: Disease causing; https://www.ncbi.nlm.nih.gov/sra/SRR36093552), despite a moderate CADD score of 13.5. The patient's clinical phenotype is highly consistent with BBS (PP4).

Semaglutide was initiated at 0.25 mg subcutaneously once weekly for 4 weeks, up-titrated to 0.5 mg once weekly from week 5 and further increased to 1.0 mg once weekly from

week 9 according to glycemic response and tolerability; the treatment was maintained for 6 months (last follow-up in October 2025) at 1.0 mg with injections given on the same weekday each week. No other antihyperglycemic agents were co-administered and no adverse events were observed.

Following the initiation of semaglutide, the patient exhibited a rapid and sustained metabolic response. Over the 6-month follow-up period, objective laboratory evidence demonstrated continuous improvement: HbA1c levels progressively declined from a baseline of 8.5 to 7.2% at 3 months and 6.1% at 6 months, achieving normoglycemia. Notably, the patient's renal function not only stabilized but significantly improved, with the eGFR rising from 48.1 ml/min/1.73 m^2 at baseline to 107 ml/min/1.73 m^2 at 6 months, suggesting a significant recovery of renal function, likely due to the combined effects of improved glycemic control, resolution of acute physiological stressors and the direct renoprotective effects of GLP-1RA (Table I). While the initial 6-month outcomes are highly encouraging, the continuous management of this patient dictates a transition toward a comprehensive, multidisciplinary care model. First, the maintenance of semaglutide therapy at the 1.0 mg weekly dosage is required, alongside rigorous longitudinal monitoring to definitively validate its long-term safety and efficacy in the BBS population. Regular quarterly assessments of glycemic indices and renal biomarkers are mandated to prevent metabolic relapse. Second, proactive surveillance of extra-metabolic manifestations must be enforced. As renal deterioration and cardiovascular complications represent the primary causes of mortality in BBS, annual echocardiography and targeted nephrological tracking are indispensable. Furthermore, aggressive ophthalmological management is warranted to mitigate the progression of the patient's documented retinitis pigmentosa and cataracts. Finally, the treatment paradigm must remain adaptable to precision therapeutics. Emerging interventions, specifically melanocortin receptor agonists targeting the disrupted hypothalamic signaling pathways (setmelanotide), offer a pivotal future strategy to directly counter the underlying ciliopathic defects once conventional pharmacotherapy reaches its efficacy plateau.

Discussion

BBS is a phenotypically heterogeneous, autosomal recessive ciliopathy with widespread involvement of multiple organ systems (5). The clinical diagnosis is established through the presence of either four primary features or three primary manifestations alongside at least two secondary characteristics (17). Core diagnostic criteria include retinal degeneration, postaxial polydactyly, central obesity, cognitive impairments, hypogonadism and renal structural or functional abnormalities (18). Additional supportive features may encompass global developmental delay, ocular anomalies such as strabismus or cataracts, limb malformations, short stature, polydipsia or polyuria, motor incoordination or spasticity, type 2 diabetes, dental irregularities, a high-arched palate, congenital cardiac defects and hepatic fibrosis (19). The prevalence of diabetes mellitus in individuals with BBS increases with age, ranging from ~6% at a mean age of 26 years to 48% at a mean age of 43 years. The overall average prevalence is ~15.8% at a mean age of 33 years (2).

In the current case, the patient exhibited the full clinical spectrum characteristic of BBS. The patient reported progressive visual impairment and nyctalopia, with ophthalmological examination confirming retinitis pigmentosa and bilateral cataracts. Low-light visual acuity and deficit testing were performed, with the final result of >0.7 indicating severe nyctalopia symptoms. Postaxial polydactyly in both feet was present since birth. Secondary amenorrhea, associated with hypergonadotropic hypogonadism, developed during adolescence. A marked predisposition to obesity was evident from early childhood, accompanied by cognitive dysfunction and learning difficulties. Additional manifestations included renal structural or functional anomalies, type 2 diabetes mellitus, xerosis, dental crowding and a high-arched palate. The patient fulfilled all six primary and six secondary diagnostic criteria, which solidified the clinical diagnosis of BBS.

Genetically, >26 causative genes have been associated with BBS. While BBS1 and BBS10 are often the most commonly implicated genes (with BBS10 accounting for ~20% of cases in European cohorts), recent data from Chinese cohorts suggest a different distribution, with BBS10 (11.24%) being less common than BBS7 (24.71%) and BBS2 (22.73%) (3). In the present case, whole-exome sequencing combined with Sanger validation revealed two pathogenic variants in the *BBS10* gene (RefSeq: NM_024685.4): A nonsense mutation c.766C>T (p.Arg256*) in exon 2 and a missense variant c.539G>A (p.Gly180Glu), both occurring in trans. Segregation analysis within the family confirmed biparental inheritance of the mutations, consistent with autosomal recessive inheritance. The compound-heterozygous *BBS10* variants identified in the present case (p.Arg256* and p.Gly180Glu) resemble those recently reported in Chinese cohorts (10); however, the index presentation of the patient of the present study was diabetes mellitus with a relatively late age at onset, which contrasts with the prototypical childhood-onset obesity phenotype of BBS (6).

Currently, therapeutic approaches for BBS remain largely supportive, focusing on glycemic control, weight management, preservation of renal function and interventions for progressive visual loss (4). Molecular diagnosis plays a pivotal role in enabling personalized surveillance strategies and facilitating genetic counseling. Although emerging therapies such as adeno-associated virus-based gene therapy, melanocortin receptor agonists targeting the hypothalamus (e.g., setmelanotide) and mTOR pathway inhibitors have shown potential in preclinical and early clinical studies, their broader clinical application is hindered by the extensive genetic and phenotypic heterogeneity of BBS (20).

Notably, the patient's glycemic control improved substantially after switching to a GLP-1RA (semaglutide). This observation may be biologically plausible given that BBS is a ciliopathy and the primary cilium functions as a hub for GPCR trafficking and signal integration. Disruption of the BBSome can alter GPCR entry/exit at the ciliary membrane and thereby perturb metabolic signaling in islet cells and hypothalamic circuits that regulate appetite and glucose homeostasis. GLP-1R signaling modulates insulin and glucagon secretion via cyclic (c)AMP/Ca^{2+} pathways in pancreatic islets and

exerts central effects on satiety and gastric emptying. Thus, even in the presence of BBS-related defects in ciliary trafficking, a high-affinity GLP-1RA may still engage residual cilia-dependent or alternative (non-ciliary) signaling to produce clinically meaningful metabolic benefit. Future work using patient-derived cells or animal models could test this hypothesis by assessing GLP-1R ciliary localization and downstream signaling dynamics (cAMP/protein kinase A, Ca^{2+} transients), and by exploring genotype-response relationships across distinct BBS variants (21,22). This observation is noteworthy, as it suggests a potential therapeutic avenue for metabolic complications in BBS beyond conventional treatments. This possible mechanism remains hypothetical and should be validated in future cellular or animal models.

The main limitation of this study is that its single-case design precluded statistical hypothesis testing and lacked a control group. Consequently, the observed efficacy of the GLP-1RA is purely descriptive and requires further verification in large-sample cohort studies. Furthermore, the data presented in this report reflect a follow-up period of six months (from April to October 2025). Although the short-term metabolic response was significant, longer-term longitudinal observation is necessary to establish the sustained efficacy and safety of semaglutide in this patient population. This case uniquely highlights that Bardet-Biedl syndrome can present atypically as adult-onset diabetes, underscoring its inclusion in the differential diagnosis for patients with metabolic disorders and multisystem features. Furthermore, the present findings provide crucial preliminary evidence that GLP-1RAs offer a promising therapeutic option for metabolic management in this patient population.

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Availability of data and materials

The pathogenic variants identified in this study have been submitted to the National Center for Biotechnology Information (NCBI) database and are available under accession no. SRR36093552 (https://www.ncbi.nlm.nih.gov/sra/SRR36093552). All other raw clinical data supporting the findings of this study may be requested from the corresponding author.

Authors' contributions

LKH and LZ conceptualized the case report, advised on patient treatment, and acquired funding. GLL, NNS and RNW collected the clinical data, obtained medical images, and managed patient follow-up. HC, YHD and GLL analyzed the patient data, including the interpretation of genetic sequencing results and endocrine laboratory parameters. LZ and NNS wrote the original draft, while LKH, GLL, HC, YHD, NNS and RNW contributed to the critical review and editing of the manuscript. LZ, LKH and RNW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval to report this case was obtained from the Medical Ethics Committee of Affiliated Hospital of Inner Mongolia University (approval no. NM-LL-2025-08-15-01). All diagnostic (including whole-exome sequencing) and therapeutic procedures described were part of standard clinical practice for managing the patient's complex presentation and were not experimental in nature.

Patient consent for publication

Written informed consent was obtained from the patient for participation and the publication of her anonymized clinical data and images. Written informed consent was also obtained from the patient's parents for their participation in the genetic segregation analysis.

Competing interests

The authors declare that they have no competing interests.

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