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Lethal neonatal respiratory failure due to biallelic variants in *BBS1* and monoallelic variant in *TTC21B*

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Abstract

Background—Bardet-Biedl syndrome (BBS) is a rare, autosomal recessive ciliopathy characterized by early onset retinal dystrophy, renal anomalies, postaxial polydactyly, and cognitive impairment with considerable phenotypic heterogeneity. BBS results from biallelic pathogenic variants in over 20 genes that encode key proteins required for the assembly or primary ciliary functions of the BBSome, a heterooctameric protein complex critical for homeostasis of primary cilia. While variants in *BBS1* are most frequently identified in affected individuals, the renal and pulmonary phenotypes associated with *BBS1* variants are reportedly less severe than those seen in affected individuals with pathogenic variants in the other BBS-associated genes.

Case-Diagnosis—We report an infant with severe renal dysplasia and lethal pulmonary hypoplasia who was homozygous for the most common *BBS1* pathogenic variant (c.1169 T > G; p.M390R) and also carried a predicted pathogenic variant in *TTC21B* (c.1846C > T; p.R616C), a genetic modifier of disease severity of ciliopathies associated with renal dysplasia and pulmonary hypoplasia.

Conclusions—This report expands the phenotypic spectrum of BBS with the first infant with lethal neonatal respiratory failure associated with biallelic, pathogenic variants in *BBS1* and a monoallelic, predicted pathogenic variant in *TTC21B*. BBS should be considered among the ciliopathies in the differential diagnosis of neonates with renal dysplasia and severe respiratory failure.

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Code availability Not applicable.

Ethics approval This study was reviewed and approved by the Human Research Protection Office at Washington University School of Medicine. We obtained informed written consent from the parents for participation in this study and publication of the findings.

Conflict of interest The authors declare no competing interests.

Keywords

Bardet-Biedl syndrome; *BBS1* ; Neonatal respiratory failure

Introduction

Bardet-Biedl syndrome (BBS) (OMIM 209900) is a rare, autosomal recessive ciliopathy that results from biallelic pathogenic variants in more than 20 genes important for the function or assembly of the BBSome, a heterooctameric protein complex that is critical for primary cilia assembly and homeostasis. The phenotypic heterogeneity of BBS (from fetal demise to a near-normal life expectancy albeit with health impairments) is likely attributable to widespread expression of the BBSome, the diverse functions of primary cilia, and genetic modifiers [1–4]. Major diagnostic criteria for BBS include at least four of the following major criteria: renal abnormalities, postaxial polydactyly, retinal degeneration, cognitive impairment, hypogonadism, or truncal obesity, or three of these major criteria and two secondary features including hepatic fibrosis, diabetes mellitus, neurological deficits, speech and lingual deficits, ataxia, facial dysmorphism, dental anomalies, developmental delay, hypertension, brachydactyly or syndactyly, cardiovascular anomalies, reproductive anomalies, endocrine abnormalities, short stature, or hearing loss [4].

The incidence of BBS varies by geography and ethnicity from ~ 1/160,000 births in North America and Europe to ~ 1/3700 births in the Faroe Islands, Denmark, the latter incidence due to a founder effect [3]. The two pathogenic variants most commonly associated with BBS, *BBS1* c.1169 T > G; p.M390R and *BBS10* c.271dupT;p.C91fs*95, account for 23% and 20%, respectively, of the molecularly confirmed cases [3]. While there is considerable phenotypic heterogeneity among BBS individuals, kidney disease present in ~50% of affected patients and includes vesicoureteral reflux, hydronephrosis, dysplastic cystic disease, absent, duplex, horseshoe or ectopic kidneys, and defective tubular concentrating ability [1]. The BBS phenotype does not include severe neonatal respiratory distress [5, 6]. While the majority of published BBS cases exhibit autosomal recessive inheritance, variants in other genes likely modify disease penetrance [7, 8].

Here we report a male neonate with a severe phenotype that included markedly dysplastic kidneys, anhydramnios, and lethal pulmonary hypoplasia. Trio exome sequencing revealed that the infant was homozygous for the pathogenic *BBS1* missense variant (c.1169 T > G, p.M390R) and carried a heterozygous, predicted pathogenic variant in *TTC21B* (c.1846C > T; p.R616C). This report of an infant with lethal neonatal respiratory failure and marked renal dysplasia expands the phenotypic spectrum observed with biallelic pathogenic *BBS1* variants and suggests that *TTC21B* may contribute to increased disease severity.

Case report

A 34-year-old G2 P3 mother delivered a male infant at 37 weeks' estimated gestation by repeat cesarean section. Her pregnancy was complicated by anhydramnios noted during the third trimester, enlarged and dysplastic fetal kidneys, and maternal hyperthyroidism treated with methimazole. The infant's Apgar scores were 3 and 7 at 1 and 5 min after

birth, respectively. However, he developed respiratory distress within an hour after birth and required intubation and mechanical ventilation. His physical examination was notable for normal intrauterine growth (weight 3140 g (65th percentile), length 49 cm (60th percentile), head circumference 34.5 cm (80th percentile)), palpable bilateral renal masses, postaxial polydactyly of the hands and right foot, and low set, posteriorly rotated ears.

The infant developed bilateral pneumothoraces for which thoracostomy tubes were placed. His chest radiographs demonstrated small lung volumes suggestive of lung hypoplasia. Echocardiogram demonstrated normal cardiac anatomy but near systemic right ventricular systolic pressures. Despite maximum ventilatory support, he developed progressive respiratory failure. After discussion with his parents, he was compassionately extubated and died at approximately 24 h after birth.

Pulmonary autopsy findings included lung weights within normal limits for body weight likely attributable to congestion and pulmonary hemorrhage (lung to body weight ratio of 0.23), chest circumference 32.7 cm (normal for gestational age), immature lung parenchyma with widened alveolar septa, variably enlarged airspaces, and pulmonary hypoplasia with decreased numbers of alveoli between terminal bronchioles and pleural surface most apparent in the right lower lobe (Fig. 1a). Sufficient inflation was present in the right lower lobe for determination of a radial alveolar count (RAC) of 2.8 ± 0.83 (n = 17) in non-atelectatic areas of lung (normal 4.5 for 37 weeks' infant [11]). An incomplete fissure was present between the right upper and middle lobes. On gross examination, the kidneys were markedly enlarged (right 69.7 g, left 64.8 g, combined average for gestational age 23.3 g ± 9.9 g) without obvious cysts on cut section. Microscopic examination, however, revealed numerous cystic, dilated tubules lined by immature primitive appearing cuboidal epithelium and surrounded by collarettes of condensed mesenchyme with stromal hyperplasia characteristic of renal dysplasia (Fig. 1b). Immature glomeruli were present at the periphery of lobules. Renal arteries, urethra, bladder, renal pyramids, calyces, and pelvises were normal. Tissue was not obtained for electron microscopy. The retinae, testes, and brain were not examined.

Clinical testing of the proband for variants in *PKHD1* was non-diagnostic. Chromosomal microarray analysis was notable for a de novo 222 kb duplication at 16q23.1 which included exons 6–8 of the *WWOX* gene of unknown clinical significance.

After informed parental consent, we performed trio whole exome sequencing (WES) as part of an ongoing study to identify genetic etiologies of birth defects in infants. This study was approved by the Human Research Protection Office at Washington University. Using genomic DNA extracted from proband skin fibroblasts and parental saliva samples, we performed WES using the Nimblegen VCRome v2.1 Exome kit (Roche, Madison, WI) with paired-end sequencing (2 × 125 base pairs) on an Illumina HiSeq 2500 instrument (Illumina, San Diego, CA). Sequence reads were aligned to the human reference genome sequence (GRCh37/hg19), and greater than 90% of the exome had at least 20X coverage. We annotated variants using Annovar (http://annovar.openbioinformatics.org/en/latest/). We identified novel or rare variants (minor allele frequency (MAF) less than 0.01 in the Genome Aggregation Database (gnomAD, https://gnomad.broadinstitute.org))

in coding regions and near exon–intron junctions and predicted pathogenicity using in silico algorithms that included CADD: Combined Annotation Dependent Depletion (https://cadd.gs.washington.edu) and REVEL: Rare Exome Variant Ensemble Learner (https://sites.google.com/site/revelgenomics/). We reviewed candidate genes and gene modifiers for associations with the clinical phenotype (Asper Biogene Nephrology: https://www.asperbio.com/asper-nephrology/, accessed January 2022) [9–11].

WES revealed that the infant was homozygous for the most common pathogenic variant in *BBS1* (c.1169 T > G; p.M390R (gnomAD MAF 0.0016, no homozygotes, accessed January 2022)) and that each parent is a heterozygous carrier (Supplement Fig. 1A). The infant was also noted to have a paternally inherited, predicted pathogenic variant in *TTC21B* (c.1846C > T; p.R616C, gnomAD MAF 0.0040), a recognized genetic modifier of the severity of ciliopathies which can result in renal dysplasia (Supplementary Fig. 1B) [2]. *TTC21B* encodes a retrograde intraflagellar transport protein, and autosomal recessive variants in *TTC21B* are associated with short-rib thoracic dysplasia and nephronophthisis (OMIM 613819, 613820, respectively). We did not identify any additional variants in *TTC21B*, and no deletions or duplications involving the *TTC21B* locus were detected with chromosomal microarray analysis. We did not identify any coding variants in other BBS-associated genes, but did identify three rare intronic variants in BBS-associated genes that were not predicted to affect splicing [12]: a maternally inherited variant in *BBS2* and two variants (one maternally inherited, one paternally inherited) in *BBS9*. We did not identify any coding variants in genes associated with pulmonary hypoplasia (*FOXF1, FGFR2, FGF10, TBX2, TBX3, TBX4*, or *TBX5*).

Discussion

The BBSome is a heterooctameric ciliary transport complex that is evolutionarily conserved across most ciliated organisms [1, 3]. The BBSome core complex is comprised of eight integral subunits: BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, BBS9, and BBS18 [1]. The remainder of the known BBSome-associated proteins aid in assembly or are required for recruitment of the BBSome to ciliary membranes [1]. The most common disease-associated variants occur in one of the eight integral subunits of the BBSome, and most pathogenic variants have been identified in *BBS1* [1]. Pathogenic variants in other genes that encode key components required for BBSome assembly or regulation of intraflagellar transport-dependent cycling of the BBSome through cilia have been identified in patients with ciliopathies [1]. Many genes contribute to ciliary assembly and function, and the widespread expression of primary cilia contributes to the phenotypic variability and penetrance in children and adults with BBS. A recent meta-analysis of BBS disease-associated variants suggested that individuals with pathogenic variants in *BBS1* typically have milder phenotypes, fewer renal anomalies (< 30% of affected individuals), exhibit fewer of the major diagnostic criteria, and typically present later in childhood with retinal degeneration [1]. Pulmonary findings among reported individuals with BBS and homozygous for the p.M390R variant are rare and include asthma in an adult (Supplementary Table). Neonatal presentation of BBS due to pathogenic variants in *BBS1* is extremely rare in cohorts from England and France [5, 6].

Renal histology among individuals with BBS also demonstrates considerable variability. Those diagnosed antenatally with BBS typically have nephromegaly with preserved lobar organization, kidney cysts, and renal hyperechogenicity [13, 14]. Multiple cysts, both medullary and corticomedullary, can be present with loss of corticomedullary differentiation [13, 14]. Interestingly, infants with antenatal findings of enlarged kidneys and polydactyly who received postnatal genetic diagnoses of BBS (some of whom underwent kidney biopsy) were more likely to have pathogenic variants in *BBS2, BBS4, BBS6*, or *BBS10* [13].

BBS1 is widely expressed and conserved across species (gtexportal.org, www.ncbi.nlm.nih.gov/blast; accessed January 2022). While *BBS1* is expressed in the lung, most individuals with biallelic pathogenic *BBS1* variants do not have pulmonary symptoms. Given the milder renal and pulmonary phenotypes typically associated with biallelic pathogenic *BBS1* variants, we speculate that the pathogenic variant in *TTC21B*, a genetic modifier of ciliopathies [2], may have contributed to the severity of kidney disease and pulmonary hypoplasia in the proband. Biallelic pathogenic variants in *TTC21B* result in recessive phenotypes including nephronophthisis and Jeune asphyxiating thoracic dystrophy, and heterozygous *TTC21B* variants may modify other inherited ciliopathy phenotypes [2]. However, we cannot exclude other unrecognized genetic modifiers that may have contributed to the proband's phenotype. While we did not identify any coding variants in other BBS-associated genes, variant burden of *trans*-acting rare nonsynonymous secondary variants across BBS-associated genes may contribute to phenotypic heterogeneity among BBS patients [15]. WES permitted molecular diagnosis, informed counseling regarding recurrence risk, and prompted assessment of the proband's healthy older brothers with kidney ultrasound, serum creatinine measurement, and urinalysis. BBS should be considered among the ciliopathies in the differential diagnosis of neonates with renal dysplasia and severe respiratory failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data sharing not applicable to this article as no datasets or analyses were generated during the current study.

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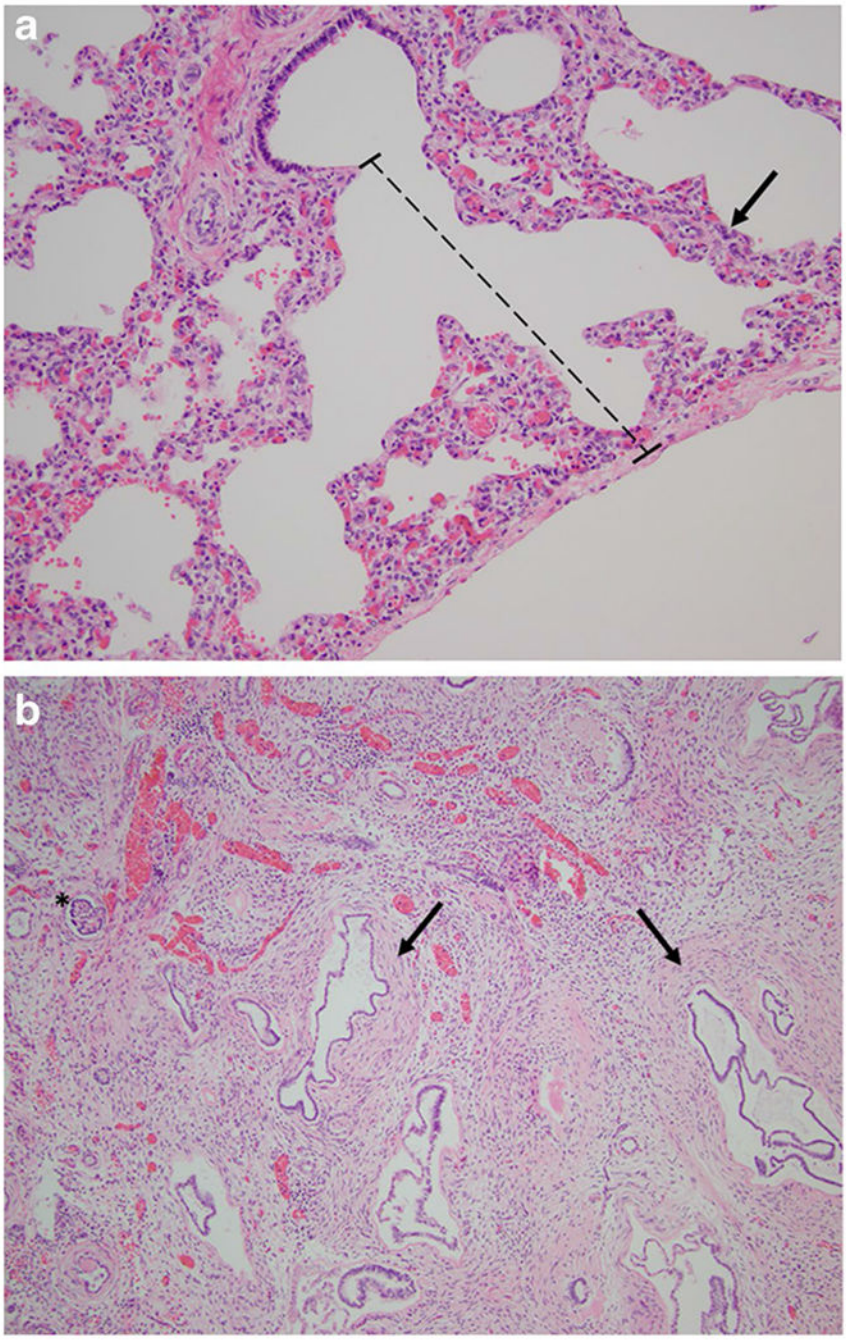

Fig. 1.

a Lung histology shows immature parenchyma with alveolar septal widening and hypoplasia with decreased number of alveoli between terminal bronchiole and pleura as indicated by dotted line (right lower lobe, H&E, 20X , arrow indicates thickened alveolar septa).

b Renal histology shows numerous cystically dilated tubules lined by immature primitive appearing cuboidal epithelium and surrounded by collarettes (as indicated by arrows)

of condensed mesenchyme with stromal hyperplasia characteristic of renal dysplasia. An immature glomerulus is present at the periphery of the lobule (*) (H&E, 20X)