Thoraco-Abdominal Abnormalities in Bardet-Biedl Syndrome: Situs Inversus and Heterotaxy

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Objectives To characterize the diversity and prevalence of thoraco-abdominal abnormalities in Bardet-Biedl syndrome (BBS), a model ciliopathy for understanding the role of cilia in human health.

Study design The Clinical Registry Investigating BBS, a worldwide registry exploring the phenotype and natural history of BBS, was used to conduct the study. Protected health information was obtained by subject or family interview and Health Insurance Portability and Accountability Act-approved release of data including imaging studies and genetic testing. Echocardiography and imaging findings were independently confirmed by 2 cardiologists.

Results Thoraco-abdominal abnormalities were identified in 6 of 368 (1.6%) subjects with a minimum prevalence of 1 in 60 Clinical Registry Investigating BBS participants. Diverse laterality defects were observed suggesting that the underlying ciliopathy randomly alters embryonic left-right axis orientation. Congenital heart disease, common in heterotaxy, was present in 2 subjects. Additional defects, uncommonly reported in BBS, were observed in the central nervous, genitourinary, gastrointestinal, and musculoskeletal systems in the subjects. No BBS genotype was favored in the cohort. One subject had genetic and clinical phenotype diagnostic of both primary ciliary dyskinesia and BBS.

Conclusions The variety of thoraco-abdominal abnormalities in BBS suggests the pleiotropic nature of these anomalies is not confined to a single pattern or genotype. Clinicians providing care to individuals with BBS should consider the increased prevalence of thoraco-abdominal anomalies in BBS. Individuals with features suggestive of other ciliopathies, such as primary ciliary dyskinesia, should undergo further evaluation for additional genetic disorders. *(J Pediatr 2019;204:31-7).*

Trial registration ClinicalTrials.gov: NCT02329210.

Bardet-Biedl syndrome (BBS) is a rare, autosomal recessive disease with multisystemic features and a member of a diverse group of disorders called ciliopathies.[1,2] The molecular origin of BBS, as well as many other ciliopathies, is a disruption of signaling pathways inherent to primary cilia, a ubiquitous organelle identified in most vertebrate cells.[3,4] The primary cilia first appear early in embryonic development (gastrula stage) and together with nodal cilia, provide critical signals necessary for left-right axis determination.[3-6] Situs inversus totalis, a mirror image of normal thoraco-abdominal organ position, is rarely reported in BBS. Heterotaxy, also known as situs ambiguous, is a disorder composed of both correct-sided and incorrect-sided organs. Laterality defects may be asymptomatic if not accompanied with cardiac disease; however, noncardiac defects may pose a health risk to individuals with BBS.[7] Laterality defects are rare in the general population with a birth prevalence of 1.1 per 10 000 births,[8] therefore, recognition of the association of BBS, and other ciliopathies, with thoraco-abdominal abnormalities may facilitate diagnosis of the syndrome and increased awareness of thoraco-abdominal anomalies in BBS may also improve care of affected individuals.

The connection of laterality disorders and BBS proteins provided researchers in the early 21st century with a critical link in understanding the central role of cilia in BBS and the molecular genesis of the syndrome.[9,10] A growing number of ciliopathies are now recognized to be associated with thoraco-abdominal anomalies, most commonly in primary ciliary dyskinesia (PCD), a motile ciliopathy with overlapping features with BBS. PCD is a recessive disorder characterized predominantly by respiratory phenotypes including respiratory distress in term neonates, early persistent wet cough, recurrent sinopulmonary infections precipitating bronchiectasis—a permanent fibrous thickening of the bronchial walls, and chronic otitis media.[11] There is an increased prevalence of such respiratory symptoms in BBS, though less so than in PCD.[12] Investigations exploring motile cilia in BBS via light and electron microscopy reported essentially normal structure and function, though inclusion bodies of unclear clinical significance and unique to BBS were visualized in

BBS	Bardet-Biedl syndrome
CRIBBS	Clinical Registry Investigating BBS
CT	Computed tomography
PCD	Primary ciliary dyskinesia

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respiratory motile cilia.[12,13] The overlap of PCD with primary ciliopathies such as polycystic kidney disease and nephronophthisis has been previously highlighted.[14-16]

In this study, we use an international registry for BBS to explore diverse thoraco-abdominal abnormalities in children with BBS. Secondary objectives of this study are to report midline anomalies, structural cardiovascular disorders, and additional anatomic findings in subjects with BBS and thoraco-abdominal abnormities. We aim to demonstrate diversity of affected BBS genotypes, suggesting that laterality defects are nonspecific in BBS. Furthermore, we emphasize the importance of considering the possibility that mutations in multiple ciliopathy genes could interact to result in blended phenotypes. Considering the rarity of reported laterality defects in BBS, we present phenotypic and genetic data from 6 individuals to highlight the variety of clinical features.

Methods

The Clinical Registry Investigating BBS (CRIBBS) is an open-enrolling international database that is designed to follow longitudinal health outcomes of individuals with BBS (ClinicalTrials.gov: NCT02329210). As of January 1, 2018, there were 368 individuals enrolled in CRIBBS. Individuals with clinical features meeting established diagnostic criteria for BBS are included in CRIBBS.[17] Prior to inclusion in this Marshfield Clinic Health System Institutional Review Board-approved registry, informed consent was obtained from those enrolled or their legal guardians. CRIBBS data were accumulated via health interviews with study participants. All participants were screened using standardized questions to detect laterality defects and cardiopulmonary disease. Protected health information (PHI) was gathered from medical records obtained in compliance with the Health Insurance Portability and Accountability Act. Available imaging studies, genetic testing, and laboratory results were obtained from the healthcare providers of study participants.

A retrospective review of clinical data from the CRIBBS database was performed to identify subjects with BBS as well as laterality defects and complex or simple cardiac anomalies. Review of health interviews as well as cardiology, pulmonology, surgical records, and imaging reports was conducted. Laterality defects were considered present in individuals with situs inversus or situs ambiguous, which includes heterotaxy. Isolated abnormalities including polysplenia, interrupted inferior vena cava, or cardiac defects (eg, septal defects) were not included in this series. These individuals were further reviewed for symptoms consistent with PCD including respiratory distress in term neonates, early persistent wet cough, recurrent sinopulmonary infections precipitating bronchiectasis, and chronic otitis media.[11,15] PHI was reviewed in all subjects and diagnoses of cardiac anomalies, made prior to this review based on abnormal cardiothymic silhouette on chest radiography, or by screening echocardiography, were independently confirmed by 2 pediatric cardiologists based on review of echocardiography and imaging studies. Molecular genetic evaluation of the individuals with thoraco-abdominal abnormalities was available in CRIBBS for review. Different genetic testing approaches were employed, however, all of subjects were evaluated using multigene next generation sequencing panels or whole exome sequencing. Results from 6 individuals with BBS and thoraco-abdominal abnormalities and other midline defects are reported in this study (**Figure**).

Results

Analysis of CRIBBS data revealed 180 (49%) individuals were examined by both echocardiography and abdominal imaging (ultrasonography, computed tomography [CT], magnetic resonance imaging, and/or autopsy). Echocardiography was available in 273 (74%) participants and retroperitoneal (urinary tract) ultrasonography was performed in 318 (86%) participants. Thoraco-abdominal abnormalities were identified in 6 individuals in the cohort of 368 participants (1.6%) with a minimum prevalence of 1 in 60 subjects enrolled, reflecting a 170-fold higher prevalence of laterality defects in BBS than reported in the general population.[5,8] Heterotaxy was present in 4 subjects and was associated with a variety of cardiac and extracardiac anomalies. Situs inversus totalis was present in 2 subjects and both subjects displayed no other anatomic anomaly other than clinical features consistent with BBS. Genetic characterization of the subjects is presented in **Table I**. In 1 subject, situs inversus totalis was associated with a BBS10 genotype with clinical features consistent only with BBS (case 3). The second individual (case 2) fulfilled diagnostic criteria for BBS and PCD and had confirmatory genetic testing reflecting both BBS and PCD. **Table II** summarizes the 6 cases of thoraco-abdominal abnormalities, and **Table III** delineates how these individuals meet diagnostic criteria for BBS as well as which individuals show features of PCD.

Case 1

A male subject was identified in infancy with an atrioventricular septal defect, single atrium (left) with atrial isomerism, mesocardia, and cleft mitral valve. Vascular anomalies identified were bilateral persistent superior vena cava and interrupted inferior vena cava with hemiazygos continuation. Midline abdominal defects consisting of midline liver, right-sided stomach, and polysplenia were recognized in infancy. Posterior urethral valves and gastrointestinal atresia were identified and surgically corrected during infancy. Consequent to progressive decline in vision, obesity, learning difficulties, and associated birth anomalies, a clinical diagnosis of BBS was made when the subject was 8 years of age and confirmed by genetic testing at 31 years of age.

Case 2

A female subject was identified on prenatal sonography to have situs inversus totalis. Following full-term delivery neonatal respiratory distress required protracted neonatal intensive care hospitalization. Recurrent respiratory infections and year-round nasal congestion necessitated intensive chest physiotherapy, myringotomy, and antibiotic management. Cardiovascular anomalies consistent with situs inversus totalis were identified consisting of dextrocardia, right-sided aorta,

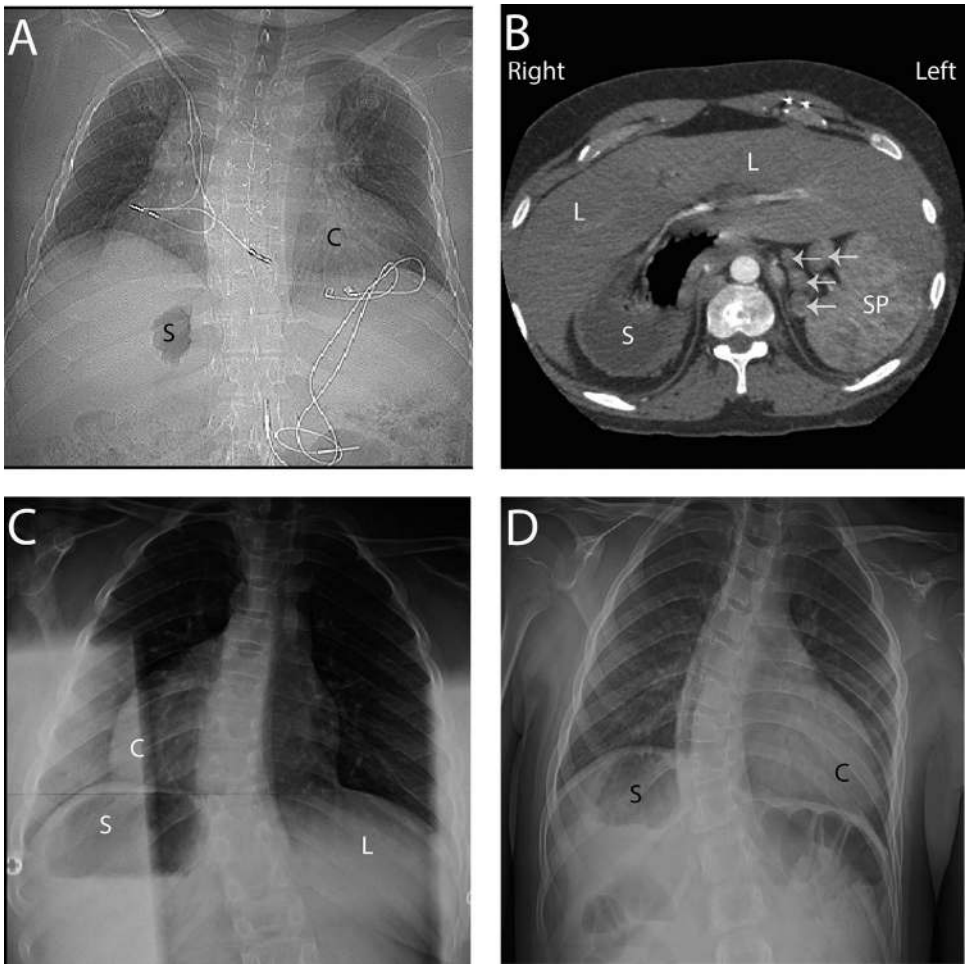

Figure. Examples of laterality defects on radiology imaging in subjects with BBS. **A,** Case 1, patient with mesocardia and right-sided stomach. Pacemaker electrodes are present. **B,** Case 1, demonstrating midline liver, right-sided stomach, and polysplenia (*arrows*). **C,** Case 3, patient with situs inversus totalis with right-sided cardiac apex, right-sided stomach bubble, left-sided liver, and thoracolumbar scoliosis. **D,** Case 5, patient with left-sided cardiac apex, right-sided stomach, polysplenia, and thoracolumbar scoliosis. *C*, cardiac apex; *L*, liver; *S*, stomach; *SP*, spleen.

and left-sided inferior vena cava. Abdominal findings in the setting of situs inversus totalis included left-sided liver, right-sided stomach, and right-sided single spleen. The patient was diagnosed in early childhood with PCD. BBS was subsequently considered based on obesity, polydactyly, learning difficulties, impaired vision, and renal impairment. Genetic diagnosis of BBS was made at 5 years of age. Clinical criteria for both BBS and PCD were present (**Table III**).

Case 3

A female subject was identified with polydactyly and early onset obesity. Genetic diagnosis of BBS was made at 2 years of age. Situs inversus totalis was identified including dextrocardia, right-sided aorta, and left-sided inferior vena cava. Abdominal findings in the setting of situs inversus totalis include left-sided liver, right-sided stomach, and right-sided single spleen. Renal ultrasonography revealed prominent fetal lobulation and poor corticomedullary differentiation. Clinical criteria for BBS included polydactyly, rod-cone dystrophy, learning difficulties, obesity, and urinary tract abnormalities. Clinical features of PCD aside from laterality defects were not present (**Table III**).

Case 4

A female subject was diagnosed with BBS with multiple clinical features including obesity, rod-cone dystrophy, renal anomalies, learning difficulties, speech delay, dental crowding, imbalance, and coordination difficulties, brachydactyly (hands and feet), and hepatic fibrosis. Heterotaxy was present with multiple large splenules, truncated pancreas, and intestinal malrotation with the small bowel in the right hemi-abdomen and colon in the left hemi-abdomen. Vascular anomalies included interrupted inferior vena cava with azygous continuation and hemiazygos blood return from the left renal vein. Absence of the circle of Willis and a right frontal lobe angioma were incidentally identified by CT angiography of the brain.

Table I. Genetic characterization of subjects with thoraco-abdominal abnormalities

Cases	Ancestry	Consanguity of parents	Genetic testing	Gene	DNA variation (inheritance)	Predicted effect	Classification	Reference
1	Northern European	No	Panel	*BBS2*	c.1237C>T(U)	p.Arg413*	Pathogenic	32
					c.1438C>T(U)	p.Arg480*	Pathogenic	33
2	Unknown to family	No	WES	*BBS1*	c.1169T>G(P)	p.Met390Arg	Pathogenic	34
					c.1169T>G(M)	p.Met390Arg	Pathogenic	
				SPAG1	c.897_901delGAGTA(P)	p.Lys301Thrfs*4	Pathogenic	35
					c.897_901delGAGTA(M)	p.Lys301Thrfs*4	Pathogenic	
				DNAH5	c.4961G>A(P)	p.Arg165Gln	VUS	Novel
					c.8999G>A(M)	p.Arg3000Gln	VUS	Novel
3	Western European	No	Panel	*BBS10*	c.273C>G(U)	p.Cys91Trp	Pathogenic	36
					c.118A>T(U)	p.Lys40*	Pathogenic	Novel
4	Unknown to family	No	WES	*IFT172*	c.5068G>C(U)	p.Gly1690Arg	VUS	Novel
					c.5179T>C(U)	p.Cys1727Arg	Pathogenic	37,38
5	Western European	No	WES	*BBS2*	c.823C>T(P)	p.Arg275*	Pathogenic	39
					c.823C>T(M)	p.Arg275*	Pathogenic	
				BBS10	c.424G>A(U)	p.Asp142Asn	VUS	40
6	German, Czech	No	Panel	*BBS2*	c.1770del(U)	p.Phe590Leufs*8	Pathogenic	Novel
					c.943C>T(U)	p.Arg315Trp	Pathogenic	39
				TMEM67	c.1660_1661del(U)	p.Met554Aspfs*3	VUS	Novel

M, maternal; *NGS*, next generation sequencing; *P*, paternal; *Panel*, multigene NGS panel; *U*, unknown; *VUS*, variant of uncertain significance; *WES*, whole exome sequencing.

Progressive renal cystic disease resulted in end-stage renal disease. Genetic diagnosis of BBS was established at 23 years of age.

Case 5

A female subject was noted on prenatal sonography to have enlarged echogenic kidneys. Following birth post-axial polydactyly was identified and a tentative diagnosis of BBS was considered. Genetic confirmation of BBS was established at 2 years of age. Her anomalies include atrial septal defect, interrupted inferior vena cava with hemiazygos return to the innominate vein midline liver, right-sided stomach, and right-sided polysplenia. The patient has scoliosis associated with vertebral and rib anomalies. Clinical criteria for diagnosis of BBS

Table II. Situs inversus totalis and heterotaxy features

Patients	Situs inversus totalis	Heterotaxy	Cardiac	Vascular	Liver	Stomach	Spleen	Other midline anomalies and clinical findings
1	No	LAI	MC, AVSD, cleft mitral valve, single atrium (left)	Bilateral persistent SVC, interrupted IVC, hemiazygos continuation	Midline	Right-sided	Left-sided Polysplenia	Sinus node dysfunction with atrial standstill status post pacemaker insertion; congenital posterior urethral valves and gastrointestinal atresia
2	Yes	NA	DC	Right-sided aorta, left-sided inferior vena cava	Left-sided	Right-sided	Right-sided single spleen	Primary ciliary dyskinesia
3	Yes	NA	DC	Right-sided aorta, left-sided inferior vena cava	Left-sided	Right-sided	Right-sided single spleen	Bilateral renal dysplasia and thoracolumbar scoliosis
4	No	LAI	LC	Interrupted IVC, azygous continuation, hemiazygos return of left renal vein	Right-sided	Left-sided	Left-sided Polysplenia	Venous angioma of the frontal lobe of the brain and absent circle of Willis; pancreatic hypoplasia; biliary ductal hypoplasia; intestinal malrotation; lymphatic malformation in region of celiac axis; renal corticomedullary cystic disease.
5	No	LAI	LC, atrial septal defect	Interrupted IVC, hemiazygos return to innominate vein	Left-sided	Right-sided	Right-sided Polysplenia	Multiple vertebral anomalies; thoracolumbar scoliosis; renal corticomedullary cystic disease
6	No	RAI	LC	Bilateral persistent SVC	Right-sided	Left-sided	Asplenia	None

AVSD, atrioventricular septal defect; *DC*, dextrocardia; *IVC*, Inferior vena cava; *LAI*, left atrial isomerism; *LC*, levocardia; *MC*, mesocardia; *RAI*, right atrial isomerism; *SVC*, superior vena cava.

Table III. BBS and PCD diagnostic features[11,17]

Patients	BBS polydactyly	BBS rod-cone dystrophy	BBS obesity	BBS learning difficulties	BBS urinary tract anomalies	PCD unexplained neonatal respiratory distress	PCD laterality defects	PCD persistent wet cough	PCD persistent nasal congestion
1	No	Yes	Yes	Yes	Yes	No	Yes	No	No
2	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
3	Yes	Yes	Yes	No	Yes	No	Yes	No	No
4	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
5	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No
6	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes

were met though features of PCD aside from laterality defects were not present (**Table III**).

Case 6

A female subject was diagnosed with BBS based on clinical findings at 4 years of age. Cardinal features of BBS include obesity, polydactyly, retinal degeneration, learning difficulties, and renal/urologic abnormalities. thoraco-abdominal anomalies including right atrial isomerism, bilateral persistent superior vena cava, and asplenia. In addition to laterality defects, persistent nasal congestion throughout the year was present but no other features of PCD were present. Genetic confirmation of BBS was made at 22 years of age.

Discussion

We examined the prevalence and variety of thoraco-abdominal abnormalities in patients with BBS. We identify thoraco-abdominal abnormalities in 1.6% of the participants and a minimum estimated prevalence of 1 in 60 CRIBBS subjects. The estimated birth prevalence of nonsyndromic laterality defects is 1.1 per 10 000 live births in the US with heterotaxy twice as likely as situs inversus totalis.[8] Thoraco-abdominal abnormalities are significantly more common in the motile ciliopathy, PCD, and sporadically in other ciliopathies including BBS.[9,14,18,19] The pleiotropic nature of BBS and variation in thoraco-abdominal abnormalities uncovered in this study reflects that laterality defects may stem from multiple BBS genotypes. The discovery of 1 individual with both BBS and PCD establishes that multiple ciliopathies should be considered in complex cases.

The diversity of thoraco-abdominal anomalies in this study highlights the importance of comprehensive evaluation of children with BBS to assess thoraco-abdominal abnormalities and related midline defects requiring medical and surgical management. Genitourinary abnormalities are the most common midline abnormalities reported in heterotaxy.[7] Obstructive uropathy from posterior urethral valves was identified in the only male subject in our cohort. Other anomalies of the kidneys and urinary tract in our cohort included fetal echogenic and enlarged kidneys, persistent fetal lobulation, and renal cystic changes. The presence of congenital heart disease in 2 individuals in our cohort suggests that children with recognized BBS and thoraco-abdominal abnormalities should undergo echocardiography to delineate intra-cardiac lesions.[5,20,21] As observed in the present study, vascular abnormalities may go unrecognized in individuals with thoraco-abdominal abnormalities.[22] CT angiography and other advanced imaging modalities may be a useful tool in planning surgical care of individuals with BBS.[23] Furthermore, children with BBS have an increased incidence of midline-associated defects of the respiratory tract, and advanced airway management techniques may be required in patients with BBS requiring anesthesia.[24]

Pediatricians may suspect BBS based on key clinical features. BBS is a genetically recessive disorder typically diagnosed during childhood. Primary characteristics including rod-cone dystrophy, truncal obesity, postaxial polydactyly, renal anomalies, male hypogonadism, and learning difficulties.[17,25] Retinal degeneration initially causes night-blindness by school-age, followed by progressive tunnel vision and legal blindness by adolescence.[26] Myopia, nystagmus, and strabismus also occur more commonly in children with BBS. Truncal obesity develops during early childhood because of increased caloric threshold of satiation. Screening evaluation of renal anomalies necessitate ultrasonography evaluation in children with BBS.[25] Learning difficulties and educational needs may be assessed through neuropsychological testing. Secondary characteristics include congenital heart disease, cataracts, brachydactyly, syndactyly, diabetes insipidus, diabetes mellitus, speech delay, ataxia, mild spasticity, and dental anomalies (both hypodontia and hyperdontia).[17,25,27] The significantly higher prevalence of thoraco-abdominal abnormalities in BBS compared with the general population in the present study also suggests that individuals discovered to have laterality defects should also be evaluated for ciliopathies such as BBS if additional clinical features are present.

Although clinically distinct, PCD is similar to BBS as it is a rare, genetically recessive ciliopathy. PCD is unique in the sense that it presents with primarily respiratory symptoms. Respiratory distress in term neonates that is unexplained, children with persistent wet cough throughout the year, recurrent sinopulmonary infections, and chronic otitis media should prompt suspicion for PCD.[11,15] Cilia are key in the development of laterality during embryogenesis by interrupting bilateral nodal symmetry resulting in normal asymmetrical gene expression in the organ primordia, and the normal situs solitus

phenotype.[3-6] Dysfunctional cilia may preclude the normal embryogenic process of laterality and are thought to precipitate situs inversus totalis, heterotaxy, and dextrocardia seen in some individuals with BBS or PCD. A phenomenon previously unreported and discovered in our study is an individual with both BBS and PCD in addition to situs inversus totalis. Clinical criteria for both BBS and PCD are present in patient 2 (**Table III**). Genetic testing in patient 2 identified homozygous *BBS1* pathogenic variants, homozygous *SPAG1* pathogenic variants, and compound heterozygous variants of uncertain significance in *DNAH5* (**Table I**). Without electron microscopy of the primary cilia (data not available), it is difficult to determine if *DNAH5* or *SPAG1* are both contributing to the PCD phenotype in this individual. It is possible that *DNAH5* variants are rare benign variants and not contributing to disease; however, it is also possible that the *DNAH5* variants are modifying the presentation. Complex inheritance patterns including triallelic patterns have been described in BBS but not in PCD.[28] It is intriguing to consider that mutations in a small number of ciliopathy genes may interact to impact the phenotype. Given the potential for BBS and PCD to occur in a single patient, overlapping ciliopathies should be considered in patients whose clinical features are not encompassed by a single known genetic disorder.

Posey et al analyzed the relationship between clinical phenotypes and underlying genotypes revealed that up to 4.9% of individuals with a genetic condition actually had involvement of 2 or more disease loci.[29] This conclusion was founded on analysis of clinical characteristics in individuals with genetic diagnoses discovered through whole-exome sequencing. In our study, the discovery of an individual with BBS and PCD suggests that overlapping ciliopathies could be considered if clinical features of both diseases are present. This phenomenon could potentially stem from 2 different genes encoding proteins in overlapping molecular pathways involved in cilia formation and function. The resulting combination of ciliopathies could precipitate laterality defects such as situs inversus totalis and dextrocardia seen in the individual reported in this study.

This retrospective case series is limited by the relatively small sample size, though CRIBBS is one of the largest databases of BBS patients reported in the medical literature. The study reports thoraco-abdominal abnormalities discovered through analyzing CRIBBS data. It is likely that unrecognized thoraco-abdominal abnormalities were present in the CRIBBS subjects because many have not had comprehensive imaging including echocardiography, abdominal ultrasonography, and angiography suggesting that the prevalence of thoraco-abdominal abnormalities may be underestimated in our study. Likewise, it is recognized that the prevalence of asymptomatic thoraco-abdominal anomalies in the general population may be underestimated. Laterality defects were identified in 12.1% of individuals with PCD in a multicenter study.[30] Unlike the report by Shapiro et al, this study does not reflect a systematic collection of prospective imaging studies nor does it include subtle thoraco-abdominal abnormalities that may be overlooked in the present study. The prevalence of laterality defects in BBS would be better determined using a similar research design. Rare disease registries are an important resource for examining rare diseases, however, caution must be employed in registry based evidence.[31] CRIBBS was designed to use a variety of important methodologic tools to ensure data quality including enrollment of a geographically diverse population (35 countries, 6 continents); participant interviews conducted by research professionals and PHI acquisition from healthcare providers to ensure data quality.

We conclude that the minimum prevalence of laterality disorders in a large, international registry of subjects with BBS is a remarkable 170-fold higher than reported in the general population. The anomalies are not confined to a single pattern or BBS genotype. The diversity of thoraco-abdominal anomalies in this study highlights the importance of comprehensive evaluation of children with BBS to identify thoraco-abdominal abnormalities and related midline defects requiring medical and surgical management. We highlight that individuals with features suggestive of other ciliopathies should undergo further evaluation for additional genetic disorders. ■

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