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ARTICLE

Making Sense of Cilia in Disease:
The Human Ciliopathies

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Ubiquitous in nature, cilia and flagella comprise nearly identical structures with similar functions. The most obvious example of the latter is motility: driving movement of the organism or particle flow across the epithelial surface in fixed structures. In vertebrates, such motile cilia are evident in the respiratory epithelia, ependyma, and oviducts. For over a century, non-motile cilia have been observed on the surface of most vertebrate cells but until recently their function has eluded us. Gathering evidence now points to critical roles for the mono-cilium in sensing the extracellular environment, and perturbation of this function gives rise to a predictable panoply of clinical problems. We review the common clinical phenotypes associated with ciliopathies and interrogate Online Mendelian Inheritance in Man (OMIM) to compile a comprehensive list of putative disorders in which ciliary dysfunction may play a role.

KEY WORDS: cilia; ciliopathy; OMIM; Bardet–Biedl; Joubert syndrome

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INTRODUCTION

Mark Twain once proclaimed, "There is something fascinating about science. One gets such wholesale returns of conjecture out of such a trifling investment of fact" (from Life on the Mississippi, 1883). No truer a statement can be made of the astonishing discoveries of the past decade relating to primary cilia and the associated disorders that arise from their dysfunction. With the exception of higher plants and fungi, most eukaryotic cells bear these apical protrusions. In vertebrates, cilia are present throughout each organ; however, among invertebrates they are confined to the sensory neurons, where they serve to sense changes in the environment including chemical stimuli and even vibration.

Additional Supporting Information may be found in the online version of this article.

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For example, cells lining the respiratory tract, oviducts, epididymis, and ependymal surface of the brain bear large clusters of motile cilia, which beat in concert to generate a wave-like motion. In contrast, the ubiquitous immotile or "primary" cilium is present as a solitary cellular extension. It is sessile in nature and was long regarded as a vestigial remnant of its motile cousin [Webber and Lee, 1975]. This view has now been superseded following several studies indicating that primary cilia serve an essential sensory purpose in transducing extracellular information to the cell interior within multiple tissue types both during development and adult life [see Singla and Reiter, 2006, for review]. More recently, studies have indicated that the cilium is a central structure for regulation of key signal transduction pathways, including the Wnt non-canonical (or planar cell polarity—PCP) pathway and the Sonic Hedgehog (SHH) pathway, and for regulation of intracellular Ca^{2+} concentration [reviewed by Michaud and Yoder, 2006].

CILIA BIOLOGY

Structure

To appreciate the role primary cilia play in disease pathogenesis, it is important to understand their structure and function. Motile cilia are long thin protrusions, extending up to 20 μm from the cell surface. They tend to be concentrated in large numbers on the apical surface of cells and beat in coordinated waves to clear mucus from the respiratory epithelium, drive sperm along the Fallopian tube, and move cerebrospinal fluid in the brain ventricles and spinal cord. In cross section, these cilia are constructed from a "9 + 2" arrangement

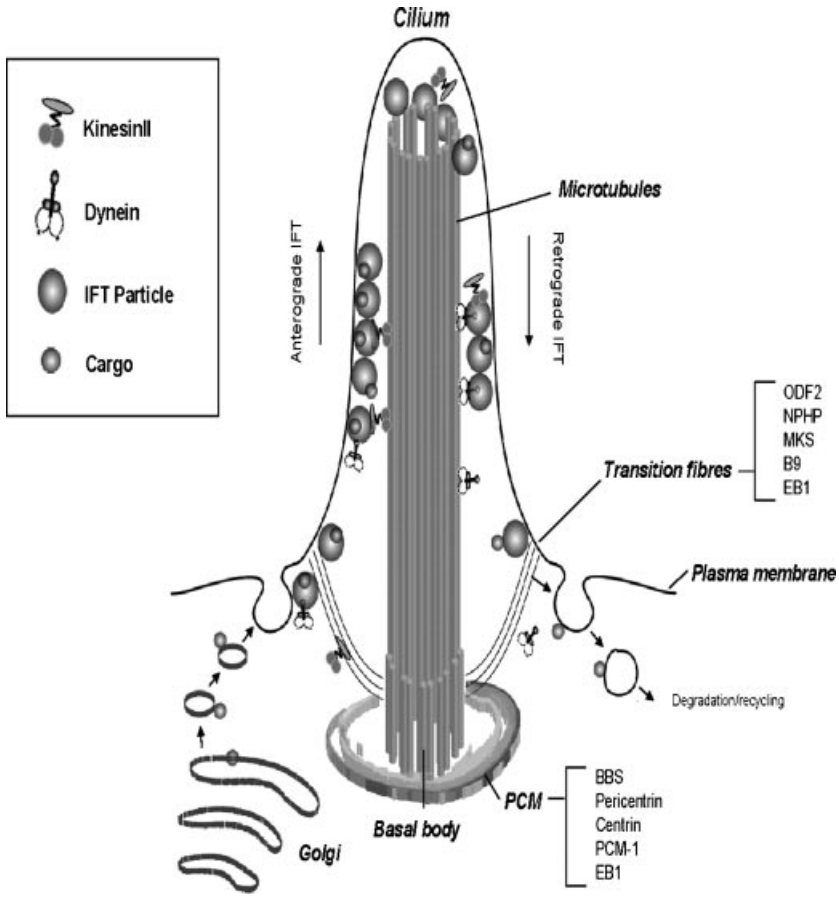

Figure 1. Structure of the cilium.

of microtubules, in which nine microtubule doublets surround a central inner pair (Fig. 1). The outer and inner doublets are connected by radial spokes, which are used to bend the outer doublets relative to the inner, producing a sheer force necessary to bend the cilium. Small dynein arms facilitate this movement.

Primary cilia lack the central microtubule doublet, have a "9 + 0" arrangement, and are generally immotile, with the unusual exception of cilia covering the node (or organizer) of the vertebrate embryo. These nodal cilia move in a circular motion, wafting molecules or nodal vesicular packets unidirectionally, conferring polarity on the node and establishing left–right (L–R) asymmetry in the developing embryo. At the base of the cilium lies the basal body, a cylindrical structure perpendicular to the cell membrane, anchoring the cilium in the cytoplasm. The basal body also acts as a nucleation point from which the cilium extends out from the cell. Microtubule fibers project from the basal body to the proximal region or transition zone, from which a nascent cilium grows.

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Intraflagellar Transport

Cilia are devoid of ribosomes, and so all associated proteins required for ciliary biogenesis or function must be transported from the cytoplasm. A system of ferrying proteins within the cilium either toward the tip (anterograde) and from the tip (retrograde) is employed, termed intraflagellar transport (IFT). Anterograde transport involves the loading of cargo proteins bound for the cilium onto an IFT particle, which in turn is attached to a kinesin motor protein complex [Rosenbaum, 2002]. Retrograde transport is facilitated by the dynein–dynactin motor complex [Rosenbaum, 2002]. Loading of cargo is regulated at the basal body and transition zone.

The best-studied mouse model of defective IFT is the Oak Ridge Polycystic Kidney (ORPK) mouse, originally described as a model for human recessive polycystic kidney disease (PKD) [Lehman et al., 2008]. The ORPK mouse arose through integration of a transgene into an intron of *Ift88* resulting in a hypomorphic allele (Tg737) that disrupts the expression and function of the polaris protein. The phenotype includes scruffy fur, preaxial polydactyly, hepatic and pancreatic ductal cysts, retinal degeneration, skeletal defects, cerebellar hypoplasia, hydrocephalus, growth retardation, and late-onset obesity [Lehman et al., 2008]. This was the first mammalian model to establish a connection between cystic kidney disease and ciliary dysfunction.

Formation and resorption of the primary cilium is dynamic and is linked with the cell cycle. The cilium is withdrawn before mitosis as the basal body is recruited as a microtubule-organizing center to form the mitotic spindle. Cilia tend to protrude from quiescent cells that are not cycling.

Signaling at the Cilium

A recent and novel view of the cilium is that it behaves somewhat like an "antenna," sensing extracellular signaling molecules and transducing signals. The following pathways have been shown, to varying extents, to depend on the cilium for optimal signaling: Sonic hedgehog (Shh), canonical Wnt, non-canonical Wnt, PDGF, and

mTOR [Singla and Reiter, 2006; Pedersen and Rosenbaum, 2008].

CLASSIFICATION OF THE CILIOPATHIES

Perturbation of ciliary proteins can give rise to a broad range of phenotypes in mammals including retinal degeneration, anosmia, renal, hepatic and pancreatic cyst formation, postaxial polydactyly, and situs inversus. But despite this breadth, mutations in different ciliary genes give rise to a remarkable spectrum of disruptions.

Therefore, the ciliopathies form a class of genetic disease whose etiology purportedly lies not with dysfunction in a single-gene product but with dysfunction in an integrated aspect of cellular physiology.

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In sensu stricto the primary ciliary dyskinesias (including Kartagener syndrome), characterized by bronchiectasis, infertility, and occasionally situs inversus/isomerism, can be directly ascribed to motile ciliary dysfunction. However, in an era of advanced molecular techniques, the spectrum has widened to include a much larger number of syndromic entities (the primary ciliopathies) in which either ciliary structure or function has been shown to be abnormal, or a causative gene product has been localized to the ciliary apparatus or to associated complexes and pathways. Most of the disease-related proteins are not expressed in the cilium itself, but rather at its base, in the basal body, transition zone, or centrosome. A growing body of evidence indicates that they likely serve other functions within the cytoplasm. Nevertheless, the common phenotype likely arises out of suboptimal ciliary signaling. The assertion that these syndromes are caused exclusively by ciliary dysfunction is probably overly inclusive but will suffice until such time as the underlying disease-causing mechanisms have been elucidated.

Lumping or Splitting

The argument for nosological splitting or lumping of syndromes applies in equal measure to ciliopathies. Many of the ciliopathies have long been recognized as discrete clinical entities [e.g., Bardet–Biedl syndrome (BBS) was first described in 1866, Laurence and Moon, 1866] and only in the last few years has this seemingly disparate collection of rare and clinically perplexing disorders begun to be reclassified as a group in terms of overlapping phenotype and pathophysiology. These revelations have come about through an incomplete understanding of the underlying complex biology in which multiple factors interact to determine phenotype, perhaps by influencing quantitative and qualitative aspects of ciliary function in different tissues. In support of this view, it has been demonstrated that mutations in the same ciliary gene can give rise to quite different syndromes [Karmous-Benailly et al., 2005; Baala et al., 2007; Hoefele et al., 2007; Tory et al., 2007; Bergmann et al., 2008; Leitch et al., 2008]. Hence, prudent classification and diagnosis on phenotypic, genotypic, and ultimately physiological grounds is challenging but nonetheless important at the clinical level for accurate prognosis, counseling, prenatal screening, and management.

The list of confirmed ciliopathies continues to grow and at present, includes: BBS, nephronophthisis (NPHP), Senior–Løken syndrome (SNLS), Alström syndrome (ALMS), Meckel syndrome (MKS), Joubert syndrome (JBTS), oral–facial–digital syndrome type I (OFD 1), Jeune asphyxiating thoracic dystrophy (JATD), Ellis–van Creveld syndrome (EVC), and Leber congenital amaurosis (LCA). PKDs (both recessive and dominant forms) are also regarded to be ciliopathies but in view of the existing and extensive literature on these disorders, they will not be discussed here in detail and the reader is referred to relevant reviews [Harris, 2009].

PREDICTING CILIOPATHIES

At a clinical level, the ciliopathies share a number of core features which, although they can occur in isolation or in association with other unrelated anomalies, may in combination be predictive of other disorders of ciliary function [Badano et al., 2006]. Indeed, we hypothesized that the greater the number of these core features within any individual, the higher the likelihood of the presence of a ciliopathy (Table I).

To identify potential clinical syndromes as putative ciliopathies, we previously chose to interrogate the London Dysmorphology Database as the search terms were tightly defined [Badano et al., 2006]. In order to gain a more comprehensive view of the ciliopathy landscape, here we have extended our search to the Online Mendelian Inheritance in Man (OMIM, www. ncbi.nlm.nih.gov/sites/entrez?db=OMIM). Each pairwise couplet of nine core features was entered into OMIM, giving a total number of 36 potential pairwise combinations (corresponding to the 36 cells within Table II). Overall, 193 unique OMIM entries were found to belong to one or more cells (i.e., to be associated with at least one of the pairwise combinations of features rather than any individual feature in isolation). Two simple screening criteria were then applied to this list to identify potential ciliopathies. First, any cases of aneuploidy, chromosome rearrangements, or deletion/duplications were excluded as these will not easily implicate a specific gene etiology. This is not to say that ciliopathy genes contained within a deletion interval might not play a pertinent role in the phenotype, but rather, that identification of the causative gene within the interval might be difficult in such a case. Second, any condition known to be

TABLE I. The Common Association of Clinical Features in Five Ciliary Dysfunction Syndromes

Disease	BBS	OFD1	Senior–Løken	Meckel	Joubert
Retinitis pigmentosa	✓		✓	✓	✓
Renal cystic disease	✓	✓	✓	✓	✓
Polydactyly	✓	✓		✓	✓
Situs inversus/isomerism	✓		✓	✓	✓
Mental retardation/developmental delay	✓	✓		✓	✓
Hypoplasia of corpus callosum	✓	✓		✓	✓
Dandy–Walker malformation	✓		✓	✓	✓
Posterior encephalocele	✓[a]			✓	✓
Hepatic disease	✓	✓[a]	✓	✓	✓
Total number of phenotypes in each disorder	8	5	5	9	9

Taken from Badano et al. [2006].
[a]In mice.

definitely associated with a non-ciliary pathophysiology was excluded (e.g., enzyme deficiencies, chromosomal instability syndromes, and mutations in transcription factors not thought to be downstream targets of ciliary signaling).

Following this search and screen strategy, a total of 127 conditions remained. Sixty-one of these conditions were specified by a unique combination of cell memberships. On the basis of clinical features and known gene(s)/protein functions, these 127 conditions, which share phenotypic overlap of at least two features of the core nine, were judged to be either known ciliopathies (n = 14), likely ciliopathies (n = 16), possible ciliopathies (n = 72), or unlikely ciliopathies (n = 25). Tables III–V list these conditions, together with their cell memberships (from Table II), loci, and genes where known, primary systems involved and putative ciliary "likelihood" rating. This list is necessarily and by design, inclusive of all conditions with phenotypic overlap, not all of which will be caused by direct disruption to cilia or indirect disruption to ciliary signaling processes. However, many, if not most, of the genes implicated in the etiology of these conditions do in fact code for proteins with putative ciliary functions or upstream/downstream interactions.

With regard to the hypothesis asserted above regarding the clustering of features within this group of syndromes, there is partial support for the proposition that ciliopathies are associated with a higher degree of phenotypic similarity than non-ciliopathies, but with notable exceptions (Fig. 2). Some of the conditions definitely known to be caused by ciliary disruption, notably BBS, MKS, and JBTS, were identified in a large number of pairwise OMIM searches (belonging to greater than 10 cells in Table II), and were specified by a unique combination of cell memberships (Fig. 3). Conditions unlikely to be ciliopathies (Supplementary Table) were more likely to be identified as members of only one or a low number of pairwise cells and to share their cell membership identity with other syndromes. Conditions judged to be possible or likely ciliopathies tended to be present in an intermediate number of cells, and some were uniquely specified.

However, some known ciliopathies, notably McKusick–Kaufman syndrome (MKKS) and short-rib polydactyly syndrome (SPS) were only identified in a single pairwise comparison (retinitis pigmentosa and polydactyly in the case of MKKS, and renal cystic disease and polydactyly in SPS). Hence, the presence of a ciliopathy cannot be predicted by the total number of features alone, nor can any individual pairwise association reliably predict the presence of a ciliopathy.

CATEGORIZATION OF CILIOPATHIES

As more diseases emerge as non-motile ciliopathies, it is becoming possible to categorize the diseases based on the clinical features of the disease, presumably contingent on the biological role of the protein involved. Excluding kidney diseases, this classification defines two predominant groups: ciliopathies with skeletal involvement (JATD, OFD1, and EVC), and those without, excluding polydactyly (BBS, NPHP, MKS, JBTS, ALMS, and LCA). The clinical phenotypes of some of these are discussed here.

Bardet–Biedl Syndrome

One of the first diseases discovered to have an etiology associated with primary ciliary dysfunction is BBS [reviewed by Zaghloul and Katsanis, 2009]. In fact, BBS patients variably display all the common features of ciliopathies: polydactyly, cystic kidneys, retinitis pigmentosa, and situs inversus.

Clinical diagnosis. The diagnosis of BBS is usually established by clinical findings. Beales et al. [1999] have suggested the presence of four primary features or three primary features plus two secondary features is diagnostic. These can now be updated by expanding the secondary features based on recent reports.

TABLE II.

Total number of syndromes with each core feature (OMIM)														
RP	74	Retinitis pigmentosa												
RCD	a	109	Renal cystic disease											
Po	b	i	153	Polydactyly										
MR	c	j	p	259	Mental retardation									
SI	d	k	q	v	32	Situs inversus								
CC	e	l	r	w	aa	165	Agenesis of the corpus callosum							
DWM	f	m	s	x	ab	ae	72	Dandy–Walker malformation						
PE	g	n	t	y	ac	af	ah	86	Posterior encephalocele					
HF	h	o	u	z	ad	ag	ai	aj	96	Hepatic disease				
Pairwise cell code	RP	RCD	Po	MR	SI	CC	DWM	PE	HF					

Primary Features

- *Cone–rod dystrophy*: The fundus abnormality in BBS has been described as an atypical pigmentary retinal dystrophy with early macular involvement [Ammann, 1970; Bergsma and Brown, 1975; Campo and Aaberg, 1982]. Full-field rod and cone electroretinograms are the investigations of choice and may be abnormal as early as 14 months of age [Runge et al., 1986]. Visual acuity (central retinal function mediated by cones), dark adaptation, and peripheral visual fields (peripheral retina function mediated by rods) are affected. Optic disks and retinal vessels are normal in infancy; disk pallor and attenuated retinal vessels develop with age. Pigmentary changes are observed in the peripheral fundus [Riise et al., 1996]. Significant cone–rod dystrophy is not apparent in most children under 5 years of age and cooperation with ERG testing at that age is often poor. Unless strongly indicated, ERG testing may be deferred until at least 4 years of age.
- *Postaxial polydactyly*: Additional digits on the ulnar side of the hand and the fibular side of the foot.
- *Truncal obesity*: Nearly all BBS patients are obese [~98%; Beales et al., 1999; body mass index (BMI) >30 or >97th centile], the precise reason is unclear but may be linked to a defect in the satiety center of the hypothalamus, whose neurons are ciliated but a role for deregulation of adipogenesis cannot be discounted [Marion et al., 2009; Seo et al., 2009].
- *Learning disabilities*: Cognitive impairment.
- *Hypogonadism/hypogenitalism in males or genital abnormalities in females. Males*: Small penis and/or reduced volume of testes. Males are infertile. *Females*: Hypoplastic fallopian tubes, uterus, and ovaries; partial and complete vaginal atresia; septate vagina; duplex uterus; hydrometrocolpos; persistent urogenital sinus; vesico-vaginal fistula; absent vaginal orifice; and absent urethral orifice [McLoughlin and Shanklin, 1967; Klein and Ammann,

TABLE III. Syndromes With Known Ciliary Pathology

Syndrome	Cell membership	Locus	Gene	Primary systems	Known ciliopathy
Alstrom syndrome	b c h u z	2p13	ALMS1	Retinal, obesity, endocrine	Known ciliopathy
Asphyxiating thoracic dystrophy (Jeune)	i j o p u z	15q13; 3q	IFT80	Skeletal	Known ciliopathy
Bardet–Biedl syndrome	a b c d h i j k o p q u v z ad	Heterogeneous	BBS1-14	Multi-system	Known ciliopathy
Cranioectodermal dysplasia (Sensenbrenner syndrome)	ag			Hepatic; renal	Known ciliopathy
Ellis–van Creveld syndrome	q s v x ab	4p16	EVC	Skeletal; cardiac	Known ciliopathy
Joubert syndrome	r s u w x y z ae af ag ah aj	9q34.3	JBTS1 and others	Neurological and other	Known ciliopathy
Leber congenital amaurosis	c h z	17p13; 11p31	GUCY2D; RPE65	Vision	Known ciliopathy
McKusick–Kaufman (MKKS)	b	20p12	BBS6	Limb; cardiac; urogenital	Known ciliopathy
Meckel syndrome	i l m n o p r s t u ae af ag ah ai aj	17q23 and others	MKS1 and others	Renal; neurological; hepatic	Known ciliopathy
Nephronophthisis types 1–4	a h k o p ad	Multiple	Nephrocyston and others	Renal	Known ciliopathy
Oro-facio-digital syndrome 1	i j r	Xp22.3-p22.2 (and others)	OFD1	Facial	Known ciliopathy
Polycystic kidney disease	o p u	Heterogeneous	Multiple	Renal	Known ciliopathy
Primary ciliary dyskinesia	b c d p q v	Heterogeneous	Multiple	Multi-system	Known ciliopathy
Senior–Løken syndrome 1–5	a o p x z ai	Heterogeneous	Multiple	Renal; retinal	Known ciliopathy
Short-rib polydactyly syndrome	I		DYNC2H1	Skeletal	Known ciliopathy

1969; Nadjmi et al., 1969; Campo and Aaberg, 1982; Srinivas et al., 1983; Cramer et al., 1988; Green et al., 1989; Stoler et al., 1995; Mehrotra et al., 1997].

- *Renal anomalies*: The combination of calyceal clubbing, tubular cystic diverticula, and persistent fetal lobulation is characteristic and may be pathognomonic of BBS.

Secondary features

- *Speech disorder/delay*: Disordered speech refers to delay in onset (individuals often not establishing intelligible speech until 4 years of age) and phonation difficulties such as breathy, high-pitched quality of speech. Disordered speech has been reported infrequently in BBS [Garstecki et al., 1972; Beales et al., 1999]. It has been suggested that substitutions of consonants at the beginning of words and the omission of the final consonant may be distinctive for BBS [Beales et al., 1999]. Videofluoroscopy and palatal articulation studies point to incoordination of the pharyngeal and/or laryngeal muscles as the possible basis of the problem (personal observations).
- Strabismus, cataracts, and astigmatism are common.
- *Brachydactyly/syndactyly*: Brachydactyly of both the hands and feet is common as is partial syndactyly (most usually between the second and third toes).
- *Developmental delay*: Many children with BBS are delayed in reaching major developmental milestones including gross motor skills, fine motor skills, and psychosocial skills (interactive play/ability to recognize social cues).

TABLE IV. Phenotypic Overlap Syndromes With Likely Ciliary Pathology

Syndrome	Cell membership	Locus	Gene	Primary systems
Acrocallosal syndrome	a r s w x	7p13	GLI3 gene (165240)	Neurological
Acromelic frontonasal dysostosis	t r y w af	Unknown		Facial skeleton
Arima syndrome	n o p j i u t z p			Multi-system
Biemond syndrome	c p			Multi-system
Coach syndrome	z af ag aj			Neurological; hepatic
Conorenal syndrome	h o p			Multi-system
Greig cephalopolysyndactyly syndrome	r w	7p13	GLI3	Digital; facial
Hydrolethalus syndrome	s t ae	11q24.2	HYLS1	Digital; neurological
Johanson–Blizzard syndrome	v	15q15-q21.1	UBR1	Multi-system
Mohr syndrome (OFD2)	s			Digital and other
Neu–Laxova syndrome	ae			Multi-system
Opitz-GBBB syndrome	c e f w x ae	del 22q11.2 and others	MID1	
Pallister Hall syndrome	l r w	7p13	Gli3	Hypothal-pit; digital
Papillorenal syndrome	i j p	10q24.3-q25.1	PAX2	Optic disc; renal
Renal–hepatic–pancreatic dysplasia	n q s t ab ac ah	3q22	NPHP3	Multi-system
Varadi–Papp syndrome (OFD type 4)	r s w ae			Skeletal; neurological

- *Polyuria/polydipsia (nephrogenic diabetes insipidus)*: Polyuria and polydipsia may be present in the absence of any renal structural abnormality.
- *Ataxia/poor coordination/imbalance*: A large proportion of individuals demonstrate a degree of clumsiness and often a wide-based gait. Tandem walking (in a straight line with one toe abutting the other heel) is usually impossible. Repetitive supination and pronation of the hands at the wrist is slow (dysdiadochokinesia). Despite occasional reports of cerebellar involvement, there is no indication that cerebellar function (structure?) is abnormal. More likely, a yet-to- be-delineated defect in coordination and processing movements exists.
- Mild hypotonia and muscle flaccidity are common which may manifest with secondary joint laxity. The cause is unknown.
- *Diabetes mellitus*: Diabetes mellitus may be evident in adolescence or adulthood. It is usually non-insulin-dependent diabetes mellitus (NIDDM)/type 2 diabetes mellitus, although occasionally insulin is required for acute control of hyperglycemia. Diabetes mellitus may relate to level of obesity. Impaired glucose tolerance has been described in younger individuals prior to the onset of NIDDM [Green et al., 1989].
- *Dentition*: Dental crowding/hypodontia/small dental roots/highly arched palate occurs [Borgstrom et al., 1996].
- *Cardiovascular anomalies*: Echocardiographic studies of 22 individuals with BBS revealed cardiac abnormalities in 50% [Elbedour et al., 1994]. Valvular stenoses and atrial/ventricular septal defects are the most commonly reported lesions [McLoughlin et al., 1964; Farag and Teebi, 1988; Elbedour et al., 1994; Beales et al., 1999; Slavotinek et al., 2000].
- *Hepatic involvement*: Perilobular fibrosis, periportal fibrosis with small bile ducts, bile duct proliferation (persistence?) with cystic dilatation, biliary cirrhosis, portal hypertension, and congenital cystic dilations of both the intrahepatic and extrahepatic biliary tract have been described in individuals with BBS [Meeker and Nighbert, 1971; Tsuchiya et al., 1977; Pagon et al., 1982; Roussel et al., 1985; Croft and Swift, 1990; Nakamura et al., 1990].
- *Hyposmia/anosmia*: Olfactory deficits in the majority of patients have now been found following initial observations in mouse models [Kulaga et al., 2004; Iannaccone et al., 2005].
- *Nociception/thermosensation*: Relative insensitivity to pain has been reported anecdotally by patients and their relatives. In *Bbs1* and *Bbs4* mouse mutants, defective peripheral thermosensation and mechanosensation were evident [Tan et al., 2007].
- *Infections*: Although not yet proven, there are several reports from parents and patients of increased episodes of serious infection, primarily lower respiratory tract. Given the role of motile cilia in clearing the airways, it is possible they may depend on BBS proteins for optimal function. Such a role has been postulated based on electron microscopy studies of respiratory tract cilia in Bbs mutants [Shah et al., 2008].

Natural history. BBS patients are usually born with postaxial polydactyly [~30% do not have extra digits, Beales et al., 1999, of one or more limbs], and commonly, hypogenitalism. In the first few years of life, there is a tendency to gain weight and eventually develop obesity. Usually by the age of 8 years, night blindness manifests, proceeding to

TABLE V. Phenotypic Overlap Syndromes With Possible Ciliary Pathology

Syndrome	Cell membership	Locus	Gene	Primary systems
Acrofacial dysostosis	s w x			Facial skeleton renal
Acrofrontalfacionasal dysostosis 2	s w x	Unknown		Facial skeleton
Adams–Oliver syndrome	a w y	Unknown		Skin, limbs
Asplenia with cardiovascular anomalies (Ivemark syndrome)	w z aa ad ag			
Autosomal recessive spastic paraplegia	c w	Heterogeneous		Neurological
Barakat/HDR syndrome	c		GATA3 gene	Endocrine, hearing, renal
Basal cell nevus syndrome	r p u z ag	9q22.3; 1p32	PTCH1; PTCH2	Skin, skeleton
Branchio-oculo-facial syndrome	p	6p24	TFAP2A	Facial skeleton
C syndrome (Opitz trigonocephaly)	r p w	3q13.13	CD96	Facial
Carpenter syndrome	p	6p11	RAB23	Facial, digital
Cephaloskeletal dysplasia (MOPDI)	w	2q14.2-q14.3		Severe microcephalic dwarfism
Cerebrofaciothoracic dysplasia	r p			Facial, skeletal
Cerebrofrontofacial syndrome	w x ae			Neurological
Cerebrooculonasal syndrome	r p t y af			Facial, neurological, ocular
Charlevoix-Saguenay spastic ataxia	w	13q12	SACS	Neurological
Chondrodysplasia punctata 2	p s x	Xp11.23-p11.22	EBP	Skeletal
Choroideremia	c	Xq21.2	CHM	Retinal
Chudley–McCullough syndrome	w			Hearing; hydrocephalus
C-like syndrome	ae	3q13.13	CD96	Facial; ocular;
Coffin–Siris syndrome	w x ae			Multi-system
Cohen syndrome	c e	8q22-q23	COH1	Neurological; retinal
Craniofrontonasal syndrome	w	Xq12	EFNB1	Facial; skeletal
Dandy–Walker syndrome	p r s w x ae	3q24	Zic1 and Zic4	Neurological
Dysgnathia complex	aa			Facial
EEC1	p	7q11.2-q21.3		Facial; palate; digits
Endocrine-cerebroosteodysplasia (eco)	i l r	6p12.3	ICK	Endocrine, cerebral, and skeletal
Focal dermal hypoplasia	p r w	Xp11.23	PORCN	Skin; digital;
Frontonasal dysplasia	p r t w y af			Facial
Fryns microphthalmia syndrome	w y af			Facial
Fryns syndrome	j l m x ae			Facial; lung/diaphragm; digital
Genito-patellar syndrome	w			Multi-system
Hemifacial microsomia	p q r t w y aa ac af	14q32	HFM	Multi-system
Hypothalamic hamartomas	t	7p13		Facial; skeletal; neurological
Johnson neuroectodermal syndrome	p			Anosmia; hypogonad; deafness
Kabuki syndrome	z ag			Facial; skeletal; neurological
Kallmann syndrome	w	Xp22.3	KAL1	Anosmia; hypogonad
Lenz–Majewski hyperostotic dwarfism	w			Facial; skeletal
Lissencephaly 3	w	12q12-q14	TUBA1A	Neurological
Marden–Walker syndrome	j l m w x ae			Multi-system
Masa syndrome	w	Xq28	L1CAM	Neurological
Microhydranencephaly	w	16p13.3-p12.1		Neurological
Mowat–Wilson syndrome	w	2q22	ZEB2	Neurological
NDH syndrome	o p	9p24.3-p23	GLIS3	Endocrine
Oculoauriculofrontonasal syndrome	af			Facial
Oculocerebrocutaneous syndrome	w x ae af ah			Eye; brain, skin
Oculodentodigital dysplasia	p	6q21-q23.2	Connexin-43	Facial
Optiz–Kaveggia syndrome	w	Xq13	MED12 (TRAP)	Multi-system
Otopalatodigital syndrome 2	p	Xq28	Filamin A	Facial; digital
Periventricular heterotopia X-linked	w	Xq28	Filamin A	Neurological
Perlman syndrome	l o p			

TABLE V. (*Continued*)

Syndrome	Cell membership	Locus	Gene	Primary systems
Pitt–Hopkins syndrome	w	18q21.1	TCF4	Facial; neurological
Proteus syndrome	j n	10q23.31	PTEN	Overgrowth
Pseudotrisomy 13	t af			Multi-system
Retinal cone dystrophy 1	c	6q25-q26		
Retinitis pigmentosa	b	Heterogeneous	Multiple	Retinal
Robinow syndrome	j	9q22	ROR2	Facial; skeletal; urogenital
Rubenstein–Taybi syndrome	r w	16p13.3, 22q13	CREBBP; EP300	Multi-system
Sakoda complex	y af			Neurological
Schinzel–Giedion midface-retraction syndrome	p r			Craniofacial
Split hand/foot malformation 3	p	10q24		Digital
Spondyloepiphyseal dysplasia congenita	p	12q13.11-q13.2	COL2A1	Spinal
Thanatophoric dysplasia	p	4p16.3	FGFR3	Skeletal
Townes–Brocks syndromes	r	16q12.1	SALL1	Multi-system
Tuberous sclerosis	j o p z	16p13.3, 12q14, 9q34	TSC1 TSC2	Multi-organ hamartoma
Vater association	q t ac	Heterogeneous		
Ven Den Ende–Gupta syndrome	x			Facial; skeletal
Visceral heterotaxia	ad	Heterogeneous		
Walker–Warburg syndrome	j l m n y ae af ah	14q24.3, 9q34.1, 9q31, 22q12.3-q13.1, 19q13.3	POMT 1 and 2 and others	Muscle, neurological
Warburg micro syndrome	w	2q21.3	RAB3GAP	Vision; neurological
X-linked congenital hydrocephalus	w	Xq28	LCAM1	Neurological
X-linked lissencephaly	w	Xq22.3-q23	Doublecortin	Neurological
Young–Simpson syndrome	p			Multi-system

complete blindness by about 15–20 years. Kidney cysts often appear in childhood and some patients require dialysis or transplantation. End-stage renal failure is the most common cause of premature death from BBS, whereas around 30% of patients will develop chronic kidney disease [Alton and McDonald, 1973]. Complications arise from overweight, including hypertension and type 2 diabetes. Hyperlipidemia, especially raised triglyceride levels, is common and may be primary rather than secondary to obesity. A range of endocrine disturbances such as hypothyroidism, growth hormone, and testosterone deficiency are infrequently associated with BBS. A typical facial appearance associated with BBS has been suggested [Beales et al., 1999; Lorda-Sanchez et al., 2001; Tobin et al., 2008]. Finally, there is a significant association of BBS with Hirschsprung disease [Radetti et al., 1988; Islek et al., 1996; de Pontual et al., 2007].

Genetics. BBS has traditionally been considered an autosomal recessive disorder although there are instances of oligogenic inheritance in which more than three mutations in two BBS genes are required for disease manifestation [Katsanis et al., 2001]. Moreover, a number of heterozygous mutations in BBS genes in addition to the two "causative" mutations are considered modifiers of disease expressivity [Badano et al., 2003].

To date, mutations in 12 BBS genes have been identified; *BBS1–12*. It is, however, now apparent that two mutations in other ciliopathy-related genes (e.g., *MKS1*, *MKS3*, and *CEP290*) can also give rise to a BBS phenotype indistinguishable from BBS gene-associated disease [Leitch et al., 2008].

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Alström Syndrome

ALMS is a rare recessive disorder that closely resembles BBS. ALMS is characterized by cone–rod dystrophy, neuro-

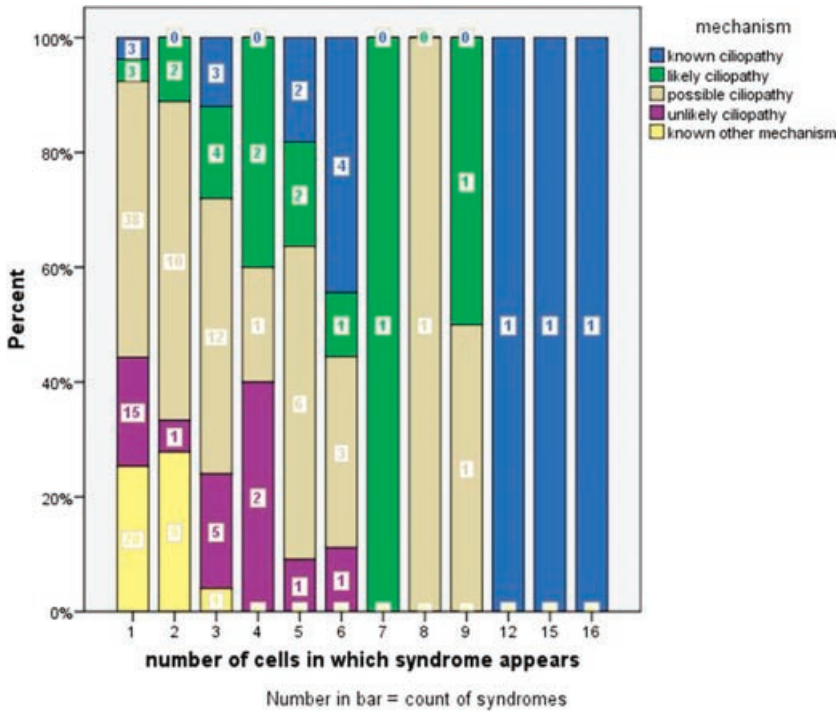

Figure 2. Graphical illustration that ciliopathies are associated with a higher degree of phenotypic similarity than non-ciliopathies.

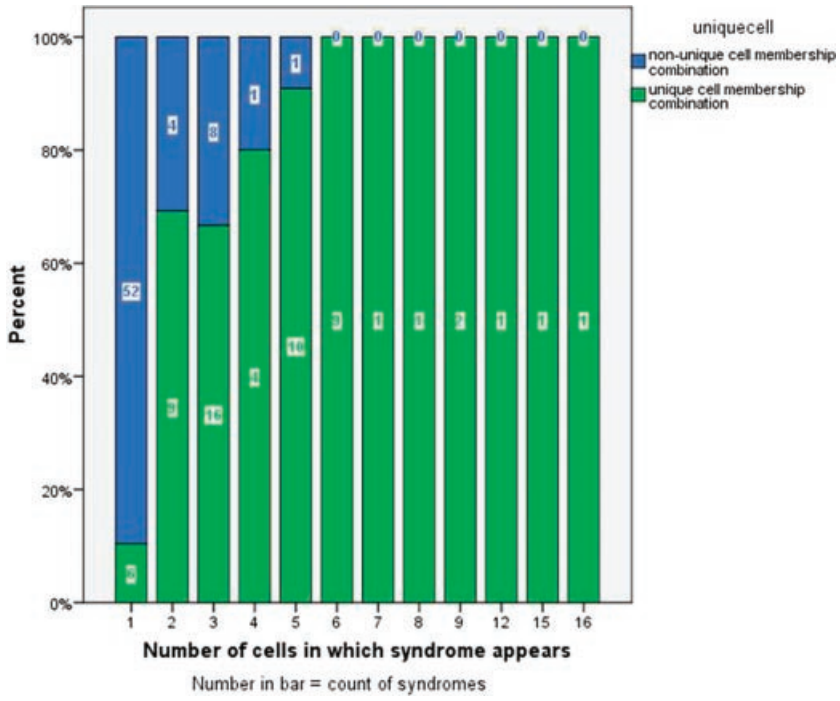

Figure 3. Graphical representation of syndromes with a unique combination of cell memberships.

sensory hearing loss, early-onset obesity, and insulin resistance leading to type II diabetes, but polydactyly is never seen. Additional features such as dilated/restrictive cardiomyopathy, hepatic fibrosis and renal dysfunction, short stature, and male hypogonadism are often present [Joy et al., 2007]. Thus far, ALMS is homogeneous with mutations in *ALMS1* accounting for all known cases of the syndrome. ALMS1 is ubiquitously expressed throughout all organ tissues [Collin et al., 2002, 2005] and is localized to the centrosome and basal body. ALMS1 is required for ciliogenesis [Li et al., 2007]. A role in intracellular trafficking comes from the studies in the mouse mutants *foz* (*fat aussie*), and an *Alms1* knockout mouse [Collin et al., 2005; Arsov et al., 2006]. These mice develop features similar to ALMS patients such as obesity, hypogonadism, hyperinsulinemia, retinal degeneration, and late-onset hearing loss. Males are infertile because of aflagellate spermatozoa.

Nephronophthisis

NPHP is an autosomal recessive cystic renal condition characterized by corticomedullary clustering of cysts and tubulointerstitial fibrosis [see Hildebrandt et al., 2009 for comprehensive review]. The overall size of the kidney in NPHP is normal or diminished in contrast to PKD where enlarged kidneys are a common diagnostic feature. Although NPHP describes a renal histopathology, ~10% of cases also present with extra-renal manifestations such as retinitis pigmentosa (called SLSN), cerebellar vermis hypoplasia (JBTS), oculomotor apraxia (Cogan type), cognitive impairment, hepatic fibrosis, phalangeal cone-shaped epiphyses (Mainzer–Saldino), and situs inversus. NPHP has also been described in cases of BBS, EVC, JATD, ALMS, and MKS [Hoefele et al., 2007]. Three forms of NPHP characterized by time of onset of ESRD are recognized: infantile, juvenile, and adolescent types. Collectively, they constitute the most frequent genetic cause of end-stage renal failure in

the young. Nine causative genes have now been identified (*NPHP1-9*) and protein analysis points to a strong link between ciliary function and disease pathogenesis [Hildebrandt et al., 2009].

Joubert Syndrome

An autosomal recessive condition JBTS is characterized by hypotonia, ataxia, psychomotor delay, oculomotor apraxia, and episodes of rapid breathing. The diagnosis may be supported by the pathognomonic neuroradiological "molar tooth sign" (MTS), which describes horizontally oriented and thickened superior cerebellar peduncles and a deepened interpeduncular fossa combined with cerebellar vermis hypoplasia [Louie and Gleeson, 2005]. The MTS has improved the diagnosis of JBTS and consequently led to the identification a group of JBTS-related disorders (JSRD) with additional organ involvement. Approximately one-quarter of patients develop juvenile NPHP with retinal dystrophy, termed cerebello-oculo-renal syndrome (CORS) or JBTS type B [Valente et al., 2008]. Several reports of additional clinical features include occipital encephalocele, polymicrogyria, cystic kidneys, polydactyly, hepatic fibrosis, and ocular coloboma, thus overlapping with the lethal MKS. At least eight JBTS genes have now been described; again, a clear genetic overlap with other ciliopathies is apparent. The underlying gene for the *JBTS2* loci is not yet identified; however, *JBTS3* is caused by mutations in the *AHI1* gene [Dixon-Salazar et al., 2004; Ferland et al., 2004] accounting for between 7% and 11% of JBTS cases, most of which are accompanied by retinopathy [Parisi et al., 2006; Utsch et al., 2006; Valente et al., 2008]. *JBTS8/ARL13B* mutations have recently been identified in families with a classical form of JBTS [Cantagrel et al., 2008]. ARL13B belongs to the Ras GTPase family and is required for ciliogenesis, body axis formation, and renal function. The lethal *hnn* (*hennin*) mouse (Arl13 mutant) has defective ciliary structure and Sonic hedgehog (Shh) signaling, while the zebrafish *scorpion* (*ARL13B* ortholog) mutant displays renal cysts and a curved tail, both of which are phenotypes commonly seen in morphants with ciliary dysregulation [Sun et al., 2004; Garcia-Garcia et al., 2005; Caspary et al., 2007].

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Meckel Syndrome

The autosomal recessive MKS is characterized by renal cystic dysplasia, hepatic fibrosis with the ductal plate malformation (e.g., occipital encephalocele), and/or other central nervous system malformations. Additionally, polydactyly is frequently reported as is cleft palate and/or lip, cardiac abnormalities, and incomplete development of genitalia and gonads [Salonen, 1984; Paavola et al., 1997; Salonen and Paavola, 1998]. Those patients who survive to term with MKS invariably die from respiratory and/or renal failure. Many examples of mistaken early diagnoses turn out to have BBS [David et al., 1999]. Thus far, MKS has been linked to six loci of which five genes have been identified; *MKS1*, *MKS3–6*. MKS1 interacts with MKS3/meckelin [Dawe et al., 2007]. Meckelin is predicted to be a multi-pass transmembrane protein although its ligand (if it has one) has yet to be identified.

Oral–Facial–Digital Syndrome

OFD type I is an X-linked dominant disorder characterized by malformations of the buccal cavity, face, and digits as well as cystic kidneys. Facial features include hypertelorism, broad nasal bridge, buccal frenulae, cleft palate, lobulated tongue, and lingual hamartomas; in the hands and feet, brachydactyly and rarely polydactyly may be present. PKD is common, and central nervous system malformations include corpus callosum agenesis, cerebellar abnormalities, and hydrocephalus, with accompanying mental retardation. It is presumed lethal in males. Mutations in the novel gene *OFD1* are causative and the OFD1 protein localizes both to the primary cilium and to the nucleus [Ferrante et al., 2001; Giorgio et al., 2007]. Franco and colleagues knocked out *Ofd1* in mice and recapitulated the human phenotype albeit with increased severity, possibly owing to differences in X inactivation patterns between species [Ferrante et al., 2006]. They also showed a failure of left–right axis specification in mutant male embryos, a lack of cilia in the embryonic node, mispatterning of the neural tube, altered expression of *Hox* genes in the limb buds, and cystic kidneys, all of which are indicative of ciliary defects and demonstrate that Ofd1 plays a role in ciliogenesis.

SKELETAL DYSPLASIAS AND CILIOPATHIES

The role of cilia in skeletal and more precisely, chondrocyte development and maturation was initially reported in the polaris mouse model [Lehman et al., 2008]. The first direct evidence of the role of an *IFT* mutation in human disease came with the discovery of the first gene for Jeune syndrome, paving the way for the classification of a subgroup of chondrodysplasias as ciliopathies.

Jeune Syndrome

JATD is an autosomal recessive chondrodysplasia. Affected children often die in the perinatal period owing to respiratory insufficiency, a consequence of abnormal rib cage formation. Up to 50% of all cases have a postaxial polydactyly. The limb shortening is usually rhizomelic and may be confused with achondroplasia. The ribs are short and slender. The pelvic bones have abnormally small ilia and irregularity of the acetabulum,

from which a medial bony projection is often visible. In the newborn, premature ossification of the capital femoral epiphyses is typically seen. In those who survive, renal cystic disease and peri-glomerular fibrosis give rise to end-stage renal failure, a common cause of death. This resembles juvenile NPHP. Biliary dysgenesis with portal fibrosis and bile duct persistence can precede cirrhosis another cause of early morbidity [Hudgins et al., 1992]. Cases have been reported with situs inversus and cardiac malformations [Brueton et al., 1990; Majewski et al., 1996] and retinal degeneration—all hallmarks of a ciliopathy.

These phenotypic clues led to the identification of mutations in *IFT80* in a subgroup of patients presenting with milder disease without renal, liver, pancreatic, or retinal features [Beales et al., 2007]. There is, however, genetic heterogeneity with another, as yet unidentified, locus on 15q. IFT80 is a member of the IFT complex B proteins that are important for ciliary structure and function. *Ift80* knockdown in the multiciliate protozoan, *Tetrahymena*, resulted in fewer cilia and nuclear duplication [Beales et al., 2007]. In *zebrafish*, silencing *ift80* results in convergent extension defects, cystic pronephros and cardiac edema, whereas knockout mice all display early embryonic lethality (unpublished observations).

Ellis–van Creveld Syndrome

Also known as chondro-ectodermal dysplasia, EVC overlaps with JATD as characterized by short ribs, polydactyly, and growth retardation, but with the addition of ectodermal (dysplastic fingernails and teeth) and cardiac defects [Baujat and Le Merrer, 2007]. EVC is a very rare autosomal recessive condition with variable expression. Causative mutations in *EVC1* and *EVC2* genes have been identified, located in a unique head-to-head configuration on 4p16.

Short-Rib Polydactyly

Based on similarities with JATD and EVC, the short-rib polydactyly (SRP) group of disorders is also predicted to be caused by mutations in ciliary components. Classification of SRPS is complex and ascribing cases accurately is difficult [Elcioglu and Hall, 2002].

The short rib-polydactyly syndromes are a group of lethal skeletal dysplasias with autosomal recessive inheritance characterized by markedly short ribs, short limbs, polydactyly, and multiple anomalies of major organs. Distinct radiological findings at both pre- and postnatal assessments may permit classification of cases into one of four types, designated SRPS I–IV.

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The rare Saldino–Noonan type of SRPS (SRPS I) has torpedo-shaped long bones [Saldino and Noonan, 1972] helping to distinguish it from the more common Verma–Naumoff variant (SRPS III), which is described as having a banana-peel shape to the long bones [Verma et al., 1975; Naumoff et al., 1977]. Verma–Naumoff patients may also display a wide range of ancillary features such as cleft lip and/or palate, polycystic kidneys, and urogenital, neurological, or cardiac malformations. Patients with the Majewski syndrome (SRPS II) have characteristically short, oval tibiae [Majewski et al., 1971]. The Beemer type (SRPS IV) resembles the Majewski syndrome, but the tibiae are not as short and polydactyly is rarely present [Beemer et al., 1983]. It is important to involve experienced radiologists to help distinguish early cases of SRPS from the differential diagnosis of JATD and EVC as the prognosis is considerably varied. EVC patients, for example, display acromelic and mesomelic limb shortening with smooth rounded metaphyses.

Recently, two groups identified mutations in *DYNC2H1* in patients with SRPS III and JATD [Dagoneau et al., 2009; Merrill et al., 2009]. DYNC2H1 is a component of the cytoplasmic dynein complex, DYNC2, and closely associates with the light intermediate chain (DYNC2LI1). The dynein complex is important for microtubule transport via its large motor domain and is therefore an integral part of IFT processes both within cilia and the cytoplasm.

CONCLUSIONS AND FUTURE DIRECTIONS

Since the discovery in 2003 of the novel gene, *BBS8*, and the revelations that its protein is localized to the basal body and centrosome and its worm ortholog to ciliated neurons, ciliopathies have come of age. By using a comprehensive search and screen strategy, we present a list of 127 known conditions, most of which are now associated with at least one chromosomal locus and causal gene, with partial phenotypic overlap for the core features associated with the primary ciliopathies. It is of note that several of the genes, which localize to the ciliary apparatus and downstream signaling targets, are associated with more than one clinical phenotype, and that many of the clinical phenotypes are genetically heterogeneous. Modeling ciliopathies across organ systems and development will therefore require multiple approaches, taking into account genotypic and phenotypic heterogeneity, and considering the ciliome as an integrated structural and functional entity. In the future it may be possible and more realistic to base clinical predictions on aspects of ciliary function (e.g., intraflagellar transport, or pathway-specific transduction of extracellular signals such

as Hedgehog) rather than single-gene mutations.

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