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The ciliopathies: A transitional model into systems biology of human genetic disease

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Abstract

The last decade has witnessed an explosion in the identification of genes, mutations in which appear sufficient to cause clinical phenotypes in humans. This is especially true for disorders of ciliary dysfunction in which an excess of 50 causal loci are now known; this discovery was driven in part by an improved understanding of the protein composition of the cilium and the co-occurrence of clinical phenotypes associated with ciliary dysfunction. Despite this progress, the fundamental challenge of predicting phenotype and or clinical progression based on single locus information remains unsolved. Here, we explore how the combinatorial knowledge of allele quality and quantity, an improved understanding of the biological composition of the primary cilium, and the expanded appreciation of the subcellular roles of this organelle can be synthesized to generate improved models that can explain both causality but also variable penetrance and expressivity.

Introduction

Since the recognition of ciliary dysfunction in Kartagener syndrome in 1976 [1], the cilium has been transformed from a largely ignored, sometimes considered vestigial organelle, to a subcellular structure that contributes significantly to the health care burden. This has been especially true for disorders of primary cilia, immotile organelles that are now understood to be near ubiquitous in the vertebrate body plan (for detailed reviews of primary and motile cilia see [2,3]). Subsequent to the identification of mutations in the intraflagellar transport (IFT) protein Ift88 in the *orpk* mouse model of renal cystic disease [4], mutations in ciliary genes have been attributed to human genetic disorders at an accelerating rate.

Tethered to the cell at the basal body and supported by a microtubule-based scaffold, cilia emanate from the apical portion of nearly all vertebrate cell types (Figure 1; for a recent review, see [2,3]). Combined proteomic, comparative genomics, and transcription analysis data in both vertebrate and invertebrate ciliated organisms and cell types have yielded a predicted protein repertoire of ~1000 proteins required for the generation and maintenance

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of cilia (ref [5] and www.ciliaproteome.org). The intersect of these data with candidate gene lists generated from traditional and next-generation sequencing approaches have contributed to the identification of novel ciliopathy genes and clinical entities (Tables 1, 2).

Initially, mutations in the basal body and axonemal protein INVS/NPHP2 were implicated in the isolated renal cystic disease nephronophthisis (NPHP) either with or without *situs inversus* (Table 2) [6]. At the same time, a causal association was demonstrated between the basal body protein BBS8 and Bardet-Biedl Syndrome (BBS), a multisystemic disorder involving both developmental abnormalities (polydactyly, mental retardation and developmental delay; Table 2) and degenerative phenotypes (retinal degeneration and renal cystic disease) [7]. Since these discoveries, an excess of 50 causal loci have been identified for >15 clinically discrete disorders (Table 1). In 2006, recognition of the phenotypic overlap of such disorders led to the conceptual unification of the ciliopathies and the progressive prediction that as many as 100 human rare disorders may be driven (at least in part) by structural and/or functional defects in the primary cilium [8,9]. At present, although each ciliopathy remains individually rare, collectively their contribution to the overall genetic disease burden in humans approaches population frequency similar to that of common defects such as Down syndrome [10], with a minimal estimated collective incidence of ~1:1,000 conceptuses (>100 ciliopathies × average incidence of 1:100,000).

The progress in gene discovery allows us to begin to address one of the next great challenges in human and medical genetics, namely our ability to glean information of prospective value from patient genomes in terms of information, management, and treatment options. Success in this endeavor will be aided by the hyper-acceleration of whole genome sequencing of patients and healthy individuals. At the same time, a paradigm shift is also required, where apparently Mendelian mutations will have to be considered, at minimum, in the background of the entire genome. As we discuss below, the primary cilium and its constellation of human pathologies represents an ideal system to build context-dependent genetic models and to test their capacity to inform and predict the natural course of the phenotype.

Here, we highlight our current understanding of primary locus contribution to disease, ranging from overt to subtle correlations between allelism and phenotype. We also review the accumulating evidence for second-site modification of primary ciliopathy loci and explore the concept of mutational burden within the ciliary protein repertoire as a major modulator of phenotypic determinism. Taken together, these observations begin to outline a model in which a systems-based approach can a) inform the causality of ciliopathy phenotypes; and b) offer a potential paradigm for the study of other disorders that exhibit genetic heterogeneity and clinical variability.

Genetic causality and single locus genotype-phenotype correlations

The ciliopathies are characterized by extensive intra- and inter-familial phenotypic variability. As shown in Table 1, mutations in genes necessary for the elaboration or function of the primary cilium can give rise to dramatically different phenotypes that, crucially, have markedly different clinical outcomes and management requirements (see Table 2 for a summary of hallmark clinical ciliopathy phenotypes). Further, mutations in the same gene can also give rise to radically different clinical phenotypes (see overlaps in Table 1). Nonetheless, in some instances, tenuous phenotype-genotype correlations at a single locus have been possible, where the nature and/or strength of mutational effect on protein function can correlate with specific clinical entities. In two instances, specific mutations have been shown to drive single-organ pathology: a branch site mutation in intron 26 of *CEP290* is sufficient to cause Leber Congenital Amaurosis (LCA), one of the most frequent

causes of non-syndromic early childhood blindness [11], while a mutation in a *BBS8* exon that is expressed in a retina-specific manner is sufficient to cause retinitis pigmentosa [12].

In other cases, the strength of allele effect on protein function at a single locus can correlate well with phenotypic severity and pleiotropy. For example, null alleles in *NPHP3* cause neonatal lethal Meckel-Gruber syndrome (MKS) a pleiotropic disorder hallmarked by a triad of renal cystic disease, central nervous system defects (most commonly occipital encephalocele) and postaxial polydactyly [13]. However, hypomorphic *NPHP3* alleles have been implicated in NPHP [14]. Likewise, essentially all MKS fetuses attributed to dysfunction of *MKS1* bear null alleles at this locus [15], while hypomorphic *MKS1* mutations have been shown to cause BBS [16].

Some reports have also hinted at intermediate phenotype-genotype correlations: although classical associations are not obvious, it has been possible to observe an apparent enrichment for the presence/absence of specific endophenotypes. For instance, mutations in *SDCCAG8* can cause both BBS and NPHP, with no clear enrichment for specific types of alleles or mutated positions in the protein [17]. However, all BBS individuals with causal *SDCCAG8* mutations reported to date exhibit no polydactyly and have a high frequency of end-stage renal disease [18]. The simplest explanation for these data is that *SDCCAG8* mutations establish a range of pathology that straddles unique, perhaps tissue-specific components of the two principal disorders (NPHP and BBS).

At the same time, mutational analyses of clinically diverse patients for some ciliopathy loci have hinted at complex genetic architecture in which affected organ systems, but not severity, can be explained by allelism at a single locus. In several instances, the phenotypic spectrum can be restricted to clinical entities with extensive phenotypic overlap, such as in the case of mutations in *RPGRIP1L* that can cause either MKS or Joubert Syndrome (JBTS), a disorder characterized typically by hypoplasia of the cerebellar vermis, neuroradiologic “molar tooth sign,” and accompanying features including retinal dystrophy, polydactyly, and renal abnormalities (Table 1, 2). However, the severity of disease is highly variable ranging from moderate (JBTS) to severe (MKS) when the primary genetic lesion is functional null in both instances [19-21]. Similarly, mutations in *TMEM216*, give rise to a similar oscillation of phenotypes within and across patient families with JBTS and MKS [22,23].

Even so, the ciliopathy disease spectrum offers accumulating examples in which the type and position of mutations at a causal locus offer little guidance to predict the development of phenotypes. Homozygous null mutations in *Ttc21b* are embryonic lethal in the *alien* mouse mutant [24] and have never been found in humans. However, heterozygous null mutations *in trans* with a hypomorphic allele at this locus have been reported in patients with NPHP (with extra-renal manifestations) or Jeune Asphyxiating Thoracic Dystrophy (JATD), a chondrodysplasia characterized by a constricted thoracic cage, short limbs, polydactyly, and often hepatorenal abnormalities [25]. Mutations in *CEP290* manifest even more extreme clinical variability; in addition to LCA, null alleles at this locus have been shown to cause each of NPHP, JBTS, MKS, and BBS, four clinically distinct entities with markedly different phenotypic characteristics and clinical outcomes [11,16,26-28] (Table 1, 2).

Oligogenic inheritance in ciliopathies

In addition to profound clinical variability, the ciliopathies are characterized by complex relationships between disease genes and alleles that remain partially understood. Despite multiple indirect lines of evidence in favor of epistatic phenomena, such as the frequent lack of correlation between allelism at a single locus with disease severity or particular endophenotypes as described above for *TTC21B* or *CEP290*, the community is still faced with a paucity of direct evidence to enable prediction of phenotype based uniquely on

genotype. Still, there are some notable exceptions in which we have been successful toward dissecting disease modulation.

The earliest direct example of complex inheritance in this group of disorders was the identification of rare asymptomatic individuals with homozygous truncating mutations in BBS genes [29]. At the time of discovery, a digenic (or digenic triallelic) model was proposed by virtue of the fact that affected individuals within non-penetrant families also had heterozygous pathogenic mutations at other BBS loci. Such genetic interactions have since been reported for a significant number of causal ciliary genes and have also been recapitulated in experiments utilizing either genetic crosses or transient multi-gene suppression in model organisms.

Since the initial report of oligogenic phenomena in BBS, which we now know to account for ~25% of BBS families [30], there have been noteworthy instances in which it is possible to explain disease manifestation through two paradigms: the interaction of either two known primary causative loci; or the interaction of one known primary ciliopathy locus with a modulator that is necessary but not sufficient to give rise to disease. One example of the former instance emerged when individuals with JBTS were screened for mutations in three known causative genes: *NPHP1*, *CEP290*, and *AHI1*. This analysis revealed that individuals harboring *NPHP1* mutations had an enriched incidence of pathogenic *CEP290* or *AHI1* lesions *in trans*, which likely explained extra-renal symptoms [31]. Recent functional studies in murine models substantiated these genetic predictions; there is a retinal-specific exacerbation in double transgenic *Nphp1*^{-/-} *Ahi1*^{+/-} mice in comparison to mice with only *Nphp1* ablation [32].

Biochemical interaction studies have assisted with the identification of two additional modifiers of ciliary disease. First, MGC1203/CCDC28B was shown to interact directly with BBS4, co-localize to the centrosome, and resulted in a synergistic increase of early gastrulation defects in mid-somitic zebrafish embryos when both orthologs were co-suppressed *in vivo*. In addition to an enrichment of the mutant allele in patients, the *MGC1203/CCDC28B* 430T variant was shown to segregate with a penetrant phenotype in a *BBS1* family [33]. Second, as part of an unbiased resequencing effort to better understand mutational load at the *RPGRIP1L* locus, a hypomorphic Ala229Thr change of modest allele frequency in the general population (2.8%) was found to be enriched significantly in ciliopathy patients with retinal phenotypes. Moreover, this change diminishes interaction between RPGRIP1L and RPGR, one of the most frequently mutated loci in X-linked retinitis pigmentosa [34], providing initial mechanistic insight for the effects of this modulator of retinal endophenotypes [35]. Taken together, these examples highlight the importance of multifaceted genetic, animal model, and biochemical approaches to enable the dissection of modulators in rare disease.

Although such digenic models are attractive to explain observed variable penetrance (rare) and variability (common) they remain limited in two important ways. First, the activity of alleles at a single locus or in pairwise relationships still occurs in the context of the genetic background of the genome and epigenome. Second, any attempt to apply absolute language that can describe accurately such relationships is an oversimplification of biological reality. The conflict arises in part for the clinical need to ascribe a discrete entity for the benefit of physicians and patients that are at odds with the biological reality of continua of cellular processes and their malfunction.

Admittedly, our understanding of the genetic interactions of ciliopathy loci still remains poor and can be attributable, at least in part, to the difficulty in identifying second-site modifiers. Coincident with causal discoveries, some alleles have been reported across the

ciliopathy spectrum, which are clearly enriched in patients but not sufficient to cause disease under a Mendelian paradigm. Still, we anticipate that this class of molecular lesion is underrepresented in the literature for two reasons. First, this likely represents the classical bias of the human genetics community in which patients for whom causal mutations at a single locus have been discovered are not screened further. Second, patients with *bona fide* pathogenic heterozygous mutations at a single locus are less likely to be reported because of the challenge in interpreting those genotypes in the clinical setting. These are problems that should be overcome as we transition from genocentric sequencing paradigms to whole genome studies. However, this technological leap will not solve, but rather accentuate both our interpretive challenges and the limitations of classical dichotomization of genetic mutations in rare diseases as causal or non-causal.

Further dissection of total mutational load

Although the lack of genotype-phenotype correlations is not unique to this group of disorders, the ciliopathies do represent a potentially unique opportunity to understand such vexing genetic problems such as variable penetrance and expressivity. This is primarily due to four reasons. First, the combinatorial dataset derived from evolutionary genetic studies, transcriptional studies, and mass spectrometry analysis of cilia and basal body across phyla has led to a reasonably populated catalog of the proteins required to build, maintain and operate the primary cilium [5]. Second, by virtue of its architecture, the primary cilium represents a semi-closed system that can now be studied in its (near) entirety, since it is proposed to be strictly regulated by a transition zone complex consisting of MKS and JBTS proteins that regulate ciliogenesis and membrane assembly [36]. Third, significant progress in understanding the subcellular functions of the primary cilium [37] have enabled the scientific enterprise to connect genetics with cell biology and biochemistry, thus enabling us to monitor and assess the functional output of this organelle in cells and in whole organisms. Finally, in large part because of these advances, it is now possible to evaluate the functional consequences of variation found in any given ciliary gene/protein in a physiologically relevant context through the use of genetic mutants [3], *in vivo* complementation assays [16,25,35,38-42], and a constellation of *in vitro* morphometric, protein localization and signaling reporter assays [25,41].

Unbiased medical resequencing studies are beginning to provide an initial glimpse at how mutational burden might be contributing across the ciliopathy disease spectrum, representing a paradigm shift away from examination of distinct clinical entities, or the deployment of narrow genetic approaches that require prior assumptions on the mode of inheritance, such as linkage analysis or homozygosity mapping. Mutational analysis of *TTC21B* was the first large-scale analysis of an axonemal protein-encoding locus across the ciliopathy spectrum ranging from mild (isolated NPHP), moderate (BBS, JBTS) to severe (MKS, JATD), and sequencing data combined with functional assays revealed a five-fold enrichment of pathogenic *TTC21B* variants in the ciliopathy cohort in comparison to healthy controls [25]. Moreover, genetic interaction studies demonstrated that genetic sensitization of retrograde IFT likely exacerbates at least 13 different primary ciliopathy loci. Taken together, *TTC21B* mutations contribute to the mutational burden in 5% of individuals with ciliopathies. Even so, analysis of one single locus was insufficient to understand phenotypic severity across clinical subgroups. Expanded studies involving multi-gene/protein macromolecular complexes such as the BBSome [43], transition zone complexes [36,39], the IFT complex [44], or the entire ciliary proteome [5] are required to achieve enhanced resolution of the combinatorial effect of molecular lesions that drive particular phenotypes (Figure 1).

The observed complex genetic interactions seen in some ciliopathy loci (highlighted as primary and/or modifying loci in Table 1), although challenging to understand and prone to

interpretive bias, have nonetheless given rise to a number of predictions that have been supported by experimental evidence. First, oligogenic interactions have provided a parsimonious means to explain intra-familial variability. Second, deep sequencing of ciliopathy loci, such as *RPGRIP1L* or *TTC21B*, have unearthed a combined enrichment of rare alleles significantly above population average [25,35]. Third, the prediction that some families should manifest clinically discrete ciliopathies has also been shown to be true. Not only are there examples of numerous families with co-segregated MKS and JBTS [45], but some families have also recently been reported with more distantly related phenotypes such as Joubert and Bardet-Biedl Syndrome [46]. Finally, genetic interaction studies in model organisms have supported the notion of *trans* modification; pairwise suppression of orthologous genes in zebrafish embryos has shown epistatic interaction of a multitude of NPHP, BBS and MKS loci [16,23,25,33,39,47-49].

The concept of phenotypic oscillation and its limits

Query of the London dysmorphology database, and the more recent mining of Online Mendelian Inheritance in Man (OMIM) database led to the estimate that at least one hundred discrete disorders were likely ciliopathies, prioritized based on the co-occurrence of multiple core features that include retinitis pigmentosa, renal cystic disease, polydactyly, mental retardation, *situs inversus*, agenesis of the corpus callosum, Dandy-Walker malformation, encephalocele, and hepatic disease [8,9] (Table 2). This information has had intrinsic discovery value because it accelerated the identification of previously unknown ciliopathies and causal ciliopathy genes as exemplified by the uncovering of mutations of *IFT80* as the first causal JATD locus [50]. Just as importantly, however, are the biological lessons on the cellular levels that are emerging from clinical and genetic observations.

Although the current availability of genome wide sequencing data in ciliopathies is limited, we can begin to appreciate some substructure that is of likely biological relevance. For example, causal mutations in components of the IFT complex are heavily enriched in three disorders, JATD, SRP, and Sensenbrenner syndrome (Figure 1), a disorder characterized by craniofacial abnormalities and hepatorenal defects (CED; also known as Cranioectodermal dysplasia; Table 2); the common clinical presentation of these three ciliopathies is defects in bone formation [25,50-53]. Likewise, mutations in genes that are sufficient to cause various forms of isolated or highly penetrant cystic renal disease, such as *NPHP1* [54], have emerged as proteins that encode components of the transition zone (Figure 1). Finally, mutations in the genes that cause BBS are almost always associated with fully penetrant retinal degeneration [9]. Each of these observations might suggest a topological modularity, wherein particular organ systems are most susceptible to defects of specific functional protein complexes. Consequently, the oscillation of accessory phenotypes in addition to the highly penetrant disease phenotype (photoreceptor loss for BBS proteins; renal cystic disease in transition zone mutations; chondrodysplasias for IFT mutations) might be due, at least in part, to the sensitization of other tissues by a combination of stochastic factors and *trans* mutations affecting alternate complexes elsewhere in the cilium.

It is likely that this working model is a vast oversimplification; not all families with mutations in the retrograde IFT protein-encoding gene *TTC21B* have skeletal defects [25]. Also, the ciliary protein complexes that drive additional hallmark phenotypes, such as central nervous system defects, still remain poorly resolved, or may not drive such phenotypes under the direction of specific ciliary macromolecular complexes. Even so, this does represent a framework in which the spatiotemporal involvement of primary causal mutations establishes at least some primary ciliopathy phenotypes that oscillate around a median defined by biological boundaries and whose amplitude is influenced by second site modifiers.

Guilty by association

Amidst the rapid progress in establishing new ciliopathy clinical entities and/or novel contributing loci it is important to ensure that in each case, dysfunction of the primary cilium can be causally attributed to disease. As discussed earlier, cilia play critical roles in a broad range of paracrine signal transduction pathways. Therefore it is not difficult to imagine how perturbation of some of these pathways might also phenocopy ciliopathies. For example, mutations in *KIF7*, the human ortholog of *Drosophila* Costal-2 and an agonist of Shh pathway that interacts with Shh effector protein Smoothened (Smo) cause hydrolethalus (HLS) and acrocallosal (ACLS) syndromes [40]. Further, Kif7 has been shown to traffic within the ciliary axoneme upon Shh stimulation *in vitro* [55]. The subsequent report of *KIF7* mutations in JBTS [56] does support the notion that HLS and ACLS also both belong under the ciliopathy umbrella. However, the marked phenotypic differences between the three disorders may or may not be driven by ciliary related differences in the genomes of these patients or by the function of this protein in a hitherto unknown context.

The NPHP-like locus *XPNPEP3*, encoding an aminopeptidase, further illustrates the conundrum of understanding the cellular basis of a seemingly ciliopathy phenotype. From a clinical perspective, the renal phenotype of patients with recessive mutations in *XPNPEP3* is a hallmark ciliopathy feature broadly indistinguishable from patients with mutations in *bona fide* ciliary genes. However, initial biochemical and immunocytochemical studies suggest that this protein might not have direct ciliary roles [57]. It is an open question therefore, whether this mitochondrial X-prolyl aminopeptidase protein regulates ciliary function through the processing of ciliary proteins with a proline at the third N-terminal position of the peptide, or whether its cystogenic role is driven by an altogether different mechanism.

Some necessary next steps

Our ability to discern the effect of alleles on humans, both in *cis* and *trans* contexts will necessitate the improvement of four key areas. Broadly, these areas will delineate a blueprint of the protein networks within the primary cilium that will allow us to evaluate how specific dysfunction of components, as well as the combinatorial effect of variation across the biological system, can drive specific pathology. It is necessary to compile a higher fidelity list of the proteins required for ciliary biogenesis and function and to accurately map the roles of these proteins in discrete spatiotemporal contexts. This ambitious endeavor could be conceptualized in the following aspects.

First, it will be necessary to understand the composition of the cilium in a cell type and developmental or regenerative stage specific manner, since emerging evidence suggests that not all primary cilia are alike. For instance, loss of members of the tectonic protein family can lead to defective ciliogenesis in certain cell types; *Tctn1*^{-/-} mice lack cilia in the node and neural tube, but do generate cilia in the notochord and early gut epithelium [36]. Immunohistochemical analysis of *Tctn1*^{-/-} has correlated this diverse phenotype with changes in ciliary protein content. Ift20 is differentially localized in the neural tube and perineural mesenchymal cells in a *Tctn1*^{-/-} context, however Ift88, another anterograde IFT protein, is similarly present in both cell types regardless of the presence of TCTN1 [36].

Second, the above observation transitions into a certain critical point, namely the notion that ciliary proteins can have non ciliary functions in specific tissues and cell types. For example, IFT20 localizes to the Golgi complex in ciliated mammalian cells [58]. Moreover, IFT components including IFT20, IFT57, and IFT88 have been found to play critical roles at the immune synapse in non-ciliated human lymphoid and myeloid cells [59]. Some ciliary proteins localize to the nucleus in certain contexts; RPGR has been localized to the nucleus of photoreceptor cells where it can interact with members of the chromodomain family [60],

while several BBS proteins have been shown to have nuclear export signals and to similarly localize to the nucleus to interact with ring finger transcriptional repressors [61]. A major unknown is whether these aspects are related to or independent from ciliary function, and by extension, whether these ciliary-independent roles drive specific pathology seen in some ciliopathies.

Third, in addition to content and cellular context the functional connectivity of ciliary proteins is an area bereft of knowledge. Despite having recognized the presence of two macromolecular complexes required for the anterograde (complex B) and retrograde (complex A) transport of cargo along the ciliary axoneme [44] (Figure 1), the precise stoichiometry (context-dependent variance thereof) of the ~20 proteins that compose the IFT complexes A and B is not yet solved. Likewise, many but not all of the BBS proteins have been shown to assemble into a stable particle, termed the BBSome, in cultured cells [43]. However, we do not know whether this is true *in vivo* and if so, in what cell types. The interaction of several MKS and JBTS proteins has also been shown to regulate ciliogenesis and ciliary membrane assembly [36]. The aggregation of some BBS proteins in subcellular compartments in neurons hints at additional diversity whose biological relevance is unknown [62]. It is not difficult to imagine that as ciliary and ciliopathy proteins are identified, the complexity and the wiring of this system will increase exponentially.

Finally, the primary cilium has emerged as a major driver for the propagation or fine-tuning of a broad range of signaling pathways that are triggered either by small molecules or by paracrine signals [3]. Emerging evidence suggests that different tissues, cell types, developmental, and homeostatic time points have variable tolerance for defects in some but not all of these pathways and it is critical that we understand which pathways might underpin which phenotypes common across all ciliopathies. For example, mounting evidence suggests that PCP (β -catenin independent Wnt signaling), as demonstrated in *Fat4* mutants, plays a major role in the manifestation of renal cystic pathology seen in most but not all ciliopathies [63,64]. At the same time, injury repair in the same tissue can trigger significant canonical Wnt signaling phenotypes in ciliopathy mouse mutants, as shown recently in the *Ahit*^{-/-} murine models [65].

Ultimately, a perhaps idealized endpoint of the ciliopathy field will be the generation of a context-specific protein network onto which both improved phenotype information and genetic variation discovered in patients can be overlaid. We anticipate that the spatial relationship of both Mendelian and non-Mendelian pathogenic alleles in such a construct will help derive predictions of clinical utility and enhance dramatically the predictive power of the genotype.

Acknowledgments

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Figure 1.

Schematic representation of functional ciliary complexes and their components. Four biochemically characterized ciliary complexes have emerged as facilitators of discrete functions in the cilium. First, the BBSome (purple) consists of seven proteins, mutations in which have been implicated in Bardet-Biedl syndrome. The BBSome has been proposed to interact with BBS3/ARL6 at the plasma membrane and sort membrane proteins to the cilium [43,120]. Second, the transition zone complex (orange) has emerged as a regulator of ciliogenesis and ciliary membrane assembly and is comprised of proteins encoded by MKS and JBTS genes [36,39,121,122]. Third, once loaded into the primary cilium, anterograde protein transport is conducted with IFT complex B proteins and heterotrimeric kinesin

motors (green) [44]. Finally, retrograde recycling of proteins from the tip of the cilium back to the cell body is governed by IFT complex A proteins and dynein motors (blue) [44], all of which have been implicated in the skeletal dysplasia ciliopathies including Sensenbrenner syndrome, JATD, and SRP.

Table 1

Phenotypic overlap and genes contributing to total mutational load in ten ciliopathies

Gene	► INCREASING PHENOTYPIC SEVERITY ►										REFERENCE	
	RP MR	KD RP, MR, CH, HD	KD, RP SI, HD	RP, KD, MR, CH P, SI, O, HD	RP, KD, MR, P, O, CH, SI, HD	KD, P, HD, EN SI	P, CF, KD, CNS	P, CF, KD, CED	P, TD, KD, CF	TD, LS, P, RP, KD, HD	Primary locus	Modifying locus
	LCA	NPHP	SLS	JBTS	BBS	MKS	OFD		SRP	JATD	○	○
<i>AIPPL1</i>	○										[66]	
<i>CRB1</i>	○										[67,68]	
<i>CRX</i>	○										[69]	
<i>GUCY2D</i>	○										[70,71]	
<i>IMPDH1</i>	○										[71]	
<i>RDH12</i>	○										[72]	
<i>RPE65</i>	○										[73]	
<i>RPGRIPI</i>	○										[74]	
<i>LCA5</i>	○										[75]	
<i>CEP290</i>	○	○	○	○	○	○					[11,16,26-28]	[31]
<i>NPHP1</i>		○	○	○							[54,76,77]	
<i>INVS</i>		○	○								[6,78]	
<i>NPHP3</i>		○	○			○					[13,14]	
<i>NPHP4</i>		○	○								[79,80]	
<i>NPHP5</i>		○	○								[81]	
<i>GLIS2</i>		○									[82]	
<i>NEK8</i>		○									[83]	
<i>ATXN10</i>		○									[84]	
<i>AH11</i>		○		○							[85,86]	[32]
<i>TMEM67</i>		○		○	○	○					[16,87-89]	[16]
<i>RPGRIPI1</i>		○	○	○	○						[19-21]	[35]
<i>ARL13B</i>	○			○	○						[90]	
<i>OFD1</i>				○			○				[91,92]	
<i>INPP5E</i>				○							[93]	

	► INCREASING PHENOTYPIC SEVERITY ►											REFERENCE	
	RP MR	KD RP, MR, CH, HD	KD, RP SI, HD	RP, KD, MR, CH P, SI, O, HD	RP, KD, MR, P, O, CH, SI, HD	KD, P, HD, EN SI	P, CF, KD, CNS	P, CF, KD	P, TD, KD, CF	TD, LS, P, RP, KD, HD	Primary locus	Modifying locus	
	LCA	NPHP	SLS	JBTs	BBS	MKS	OFD	CED	SRP	JATD			O
<i>TMEM216</i>				○	○	○					[22,23]		○
<i>TMEM138</i>				○							[47]		
<i>TMEM237</i>				○	○						[39]		
<i>TCTN1</i>				○							[36]		
<i>TCTN2</i>				○							[84,94]		
<i>KIF7</i>				○	○	○	○				[56]		[40]
<i>CEP41</i>				○	○						[95]		[95]
<i>BBS1</i>				○	○						[96]		[97,98]
<i>BBS2</i>				○	○	○					[99,100]		[29,97]
<i>BBS3</i>				○	○	○					[101,102]		
<i>BBS4</i>	○			○	○	○					[99,103,104]		[48]
<i>BBS5</i>				○	○						[105]		
<i>BBS6</i>				○	○	○					[99,106]		[29,48,97]
<i>BBS7</i>				○	○						[107]		
<i>BBS8</i>				○	○						[7]		
<i>BBS9</i>				○	○						[108]		
<i>BBS10</i>				○	○	○					[48,109]		
<i>BBS11</i>				○	○						[110]		
<i>BBS12</i>				○	○						[49]		
<i>SDCCAG8</i>		○	○		○						[17,18]		[111]
<i>WDPCP</i>					○						[111]		[33]
<i>MGC1203</i>					○								[16]
<i>MKS1</i>					○	○					[15,16]		
<i>CC2D2A</i>				○		○					[112,113]		
<i>B9D1</i>						○					[114]		
<i>B9D2</i>						○					[38]		
<i>WDR35</i>								○	○		[115,116]		

	► INCREASING PHENOTYPIC SEVERITY ►											REFERENCE	
	RP MR	KD RP, MR, CH, HD	KD, RP SI, HD	RP, KD, MR, CH P, SI, O, HD	RP, KD, MR, P, O, CH, SI, HD	KD, P, HD, EN SI	P, CF, KD, CNS	P, CF, KD	P, TD, KD, CF	TD, LS, P, RP, KD, HD	Primary locus	Modifying locus	
	Gene	LCA	NPHP	SLS	JBTS	BBS	MKS	OFD	CED	SRP	JATD		O
<i>IFT43</i>									○				
<i>IFT144</i>	○								○		○	[51]	
<i>DYNC2H1</i>									○	○	○	[52]	
<i>NEK1</i>										○	○	[53,117]	
<i>IFT80</i>										○	○	[118]	[118]
<i>TTC21B</i>	○				○	○	○				○	[50]	[25]

Ciliopathies- LCA: Leber congenital amaurosis, NPHP: Nephronophthisis, SLS: Senior-Loken Syndrome, JBTS: Joubert Syndrome, BBS: Bardet-Biedl Syndrome, MKS: Meckel-Gruber Syndrome, OFD: Orofacialdigital Syndrome, CED: Sensenbrenner Syndrome, SRP: Short rib polydactyly, JATD: Jeune Asphyxiating Thoracic Dystrophy.

Phenotypic features- RP: Retinopathy, KD: Kidney disease, MR: Mental retardation, P: Polydactyly, O: Obesity, CH: Cerebellar hypoplasia, SI: Situs inversus, HD: Hepatic disease, EN: Encephalocele, CF: Craniofacial defect, TD: Thoracic dystrophy, LS: Limb shortening. Bold type indicates primary characteristics

Table 2

Phenotypic overlap in ten ciliopathies (adapted from refs [8,9]). Prevalence of individual phenotypes (if known) is indicated as dark blue (50-100%; primary clinical diagnostic criteria); and pale blue (0-50%); no shading (no data available).

Ciliopathy Phenotype											
Ciliopathy	Retinitis pigmentosa	Renal cystic disease	<i>Situs inversus</i>	Mental retardation/ developmental delay	Hypoplasia of corpus callosum	Dandy-Walker malformation	Posterior encephalocele	Hepatic disease	Polydactyly	Craniofacial abnormality	Bone malformation
Leber Congenital Amaurosis	○			○				○			
Nephronophthisis		○						○			
Senior Loken Syndrome	○	○	○			○		○	○		
Joubert Syndrome	○	○	○	○		○		○	○		
Bardet Biedl Syndrome [119]	○	○	○	○	○	○		○	○	○	
Meckel Gruber Syndrome		○	○					○	○	○	
Oro-facial-digital Syndrome		○		○	○			○	○	○	
Cranioectodermal Dysplasia	○	○		○	○			○	○	○	○
Short Rib Polydactyly	○	○						○	○	○	○
Jeune Asphyxiating Thoracic Dystrophy											○