The Ciliopathies: An Emerging Class of Human Genetic Disorders

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Abstract

Cilia and flagella are ancient, evolutionarily conserved organelles that project from cell surfaces to perform diverse biological roles, including whole-cell locomotion; movement of fluid; chemo-, mechano-, and photosensation; and sexual reproduction. Consistent with their stringent evolutionary conservation, defects in cilia are associated with a range of human diseases, such as primary ciliary dyskinesia, hydrocephalus, polycystic liver and kidney disease, and some forms of retinal degeneration. Recent evidence indicates that ciliary defects can lead to a broader set of developmental and adult phenotypes, with mutations in ciliary proteins now associated with nephronophthisis, Bardet-Biedl syndrome, Alstrom syndrome, and Meckel-Gruber syndrome. The molecular data linking seemingly unrelated clinical entities are beginning to highlight a common theme, where defects in ciliary structure and function can lead to a predictable phenotypic pattern that has potentially predictive and therapeutic value.

INTRODUCTION

Since their first description in kidneys and the thyroid gland (144), cilia have been observed in a number of organs, such as the liver and pancreas, as well as numerous cell types, including endothelial cells, the myocardium, odontoblasts, photoreceptors in the retina, and cortical and hypothalamic neurons (for examples, see 4, 21, 25, 30, 68, 69, 82; for a comprehensive list of cells and tissues containing cilia see **http://members.global2000.net/bowser/cilialist.html**) (**Figure 1**). Consistent with the broad and varied tissue and cellular distribution, dysfunction of cilia and their anchoring structure, the basal body, has been implicated in numerous human diseases that range from organ-specific disorders such as polycystic kidney disease to broad, pleiotropic phenotypes such as the Bardet-Biedl (BBS) and Alstrom (ALMS) syndromes.

In this review, we discuss the role of cilia in human disease, whose prominence has been elaborated in recent years through the attribution of ciliary and basal body dysfunction to a number of phenotypes. By examining the clinical manifestations and molecular basis of seemingly diverse, yet overlapping human conditions, we attempt to delineate the common phenotypes caused by ciliary dysfunction, thus defining the hallmarks of a ciliopathy, and then extend our observations to assign predictive value for disorders of unknown molecular etiology.

An Overview of the Cilium

Cilia typically project from the apical surface of cells and are composed of a microtubule backbone (axoneme) ensheathed by a membrane contiguous with the plasma membrane (**Figure 2*a*,*b***). Inner and outer dynein arms extend from the A tubules (composed of 13 protofilaments) of each outer microtubule doublet and generate the force needed for motility in an ATP-dependent process (**Figure 2*a*,*b***). (For more information on the structure of cilia and flagella, see Reference 140.) Historically, the geometry and composition of microtubules within the ciliary axoneme have defined the two main ciliary types: "9+2" (motile) and "9+0" (primary, nonmotile) cilia, referring to the axonemal organization of microtubule (mt) pairs. "9+2" cilia contain an axoneme that is formed of nine microtubule doublets surrounding a central pair, whereas "9+0" lack the latter (**Figure 2*a*,*b***). However, newer studies suggest that such distinctions might be naïve. For example, the organization of microtubules along the axoneme varies depending on the position and at least two regions have been distinguished in the cilia of sensory neurons of *C. elegans*, the middle and distal segments, which are composed of nine microtubule doublets and singlets, respectively (75, 79, 109, 122). Even the classic distinction of "9+2" and "9+0" as motile or sensory, respectively, seems to be simplistic and examples of motile primary cilia as well as motile cilia and flagella with sensory roles have been reported. Contrary to the notion that cilia in the renal epithelium are nonmotile and sensory in nature, motile cilia have been reported (95). Furthermore, cilia in the pronephric kidney of zebrafish are required for fluid movement and their dysfunction can lead to cyst formation (58). Additionally, it is likely that the role of motile cilia as sensory organelles has been underappreciated. For example, it was recently shown that transient receptor potential (TRP) channels involved in sensing environmental stimuli of diverse forms localize to both motile and primary cilia in the female reproductive tract in mice (128).

The synthesis of structural and functional components of cilia occurs in the cytoplasm and a specialized system termed intraflagellar transport (IFT), which was first described in the algae *Chlamydomonas reinhardtii* (57), is responsible for moving cargo (IFT particles) toward the axonemal tip or away from it (anterograde and retrograde transport, respectively (**Figure 2*c***). IFT particles are transported by the microtubule-based

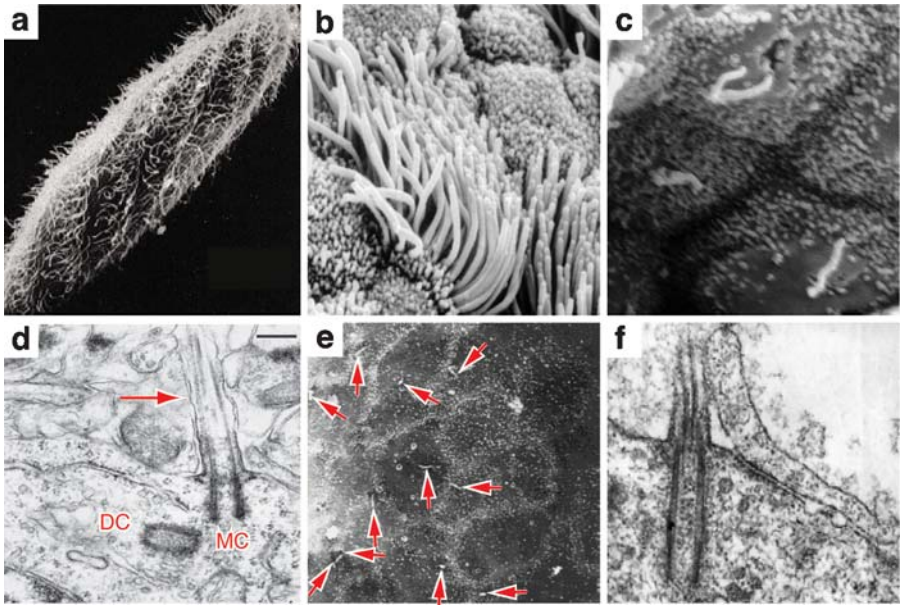

Figure 1

Motile and primary cilia in diverse organisms and cell types. (*a*) The protozoan *Paramecium* is covered with motile cilia that enable swimming. (*b*) Motile cilia in the mammalian trachea. (*c*) Primary cilia in the renal tubules epithelia. (*d*) Electron micrograph of a mouse pyramidal neuron displaying a primary cilium. MC and DC denote the mother and daughter centrioles, respectively. (*e*) Primary cilia in the epithelial cells surrounding the lumen of pancreatic ducts. (*f*) Micograph of a primary cilium emerging from a human odontoblast. Panels are adapted with permission as follows: panel *b* from Reference 114, panel *c* from Reference 105, panel *d* from Reference 138, panel *e* from Reference 4, and panel *f* from Reference 68.

molecular motors kinesin-II and dynein (for a comprehensive review see Reference 114). In *C. elegans*, two types of kinesin molecular motors, kinesin-II and osm3-kinesin, collaborate to build the different parts of sensory cilia (122), not only adding to the complexity of IFT but also introducing new players whose disruption might lead to disease.

The physiological role of motile cilia or flagella in cell locomotion, sexual reproduction, and fluid movement has long been recognized. By contrast, the biological importance of primary cilia has remained relatively obscure until their recent implication in a number of human genetic diseases (reviewed in 19a). A leading example was the Oak Ridge polycystic kidney (*orpk*) mouse model of ARPKD, the *Tg737*^{orpk}, an insertional mutation that disrupts the gene coding for the protein polaris, which localizes to both basal bodies and cilia (81, 127). Furthermore, the *Chlamydomonas* and *C. elegans* orthologs of *Tg737*, *IFT88*, and *osm-5*, respectively, encode intraflagellar transport proteins whose disruption leads to defective flagella in both species (37, 105). Abnormal cilia are also observed in the renal epithelium of *Tg737* mice, a finding not surprising given the localization of polaris in cells and its requirement for ciliogenesis (105).

The role of cilia in human disease has expanded rapidly beyond the PKD field, concordant with their broad tissue distribution and evolutionary conservation. What is more enlightening, however, is the fact that the elucidation of the molecular basis of a number of ciliopathies is uncovering novel roles for

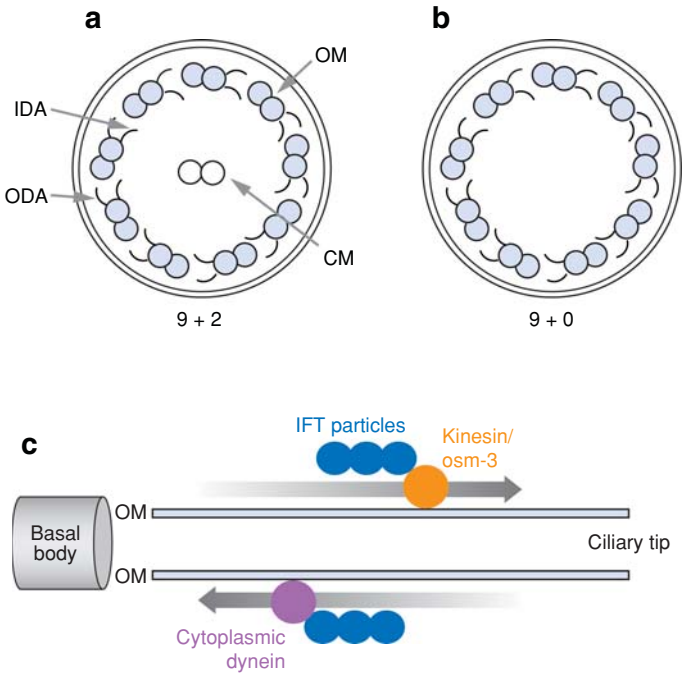

Figure 2

Schematic representation of "9+2"and "9+0" axoneme cross sections and intraflagellar transport. (*a*, *b*) Simplified diagram of the ultrastructure of motile and primary cilia. The axoneme of (*a*) 9+2 cilia is composed of nine outer doublets of microtubules (OM) surrounding a central pair (CM), whereas in (*b*) 9+0 the latter is not present. Inner (IDA) and outer (ODA) dynein arms are responsible for generating force for movement and project from one outer doublet to the next. (*c*) Along the outer microtubule doublets (OM) and under the ciliary membrane, IFT particles are transported toward the ciliary tip (anterograde) by kinesin and back to the basal body and the cell (retrograde) by the molecular motor cytoplasmic dynein.

cilia in mammals, including the regulation of numerous critical developmental signaling pathways.

CILIA IN HUMAN DISEASE

Although the architecture of cilia is much more complex than initially thought, a broad distinction can be made between motile and sensory functions. In some organisms, such as *Chlamydomonas*, cilia serve a dual role; in addition to motile functions, the alga's flagella are required for sensory transduction after flagellar adhesion during the mating process. When mating-type plus and minus gametes of algae mate, interactions between specific adhesion molecules localized to the flagella trigger a signaling cascade that results in an increase in cAMP and the formation of a zygote. In the *fla10*-1 mutant, which is defective in kinesin-II at the restrictive temperature of 32°C, flagellar adhesion is normal but zygotes are not formed due to the inability to increase the levels of cAMP as a response to the stimuli (101, 134). Additionally, the UV-A/blue-light receptor phototropin, which controls the mating behavior of *Chlamydomonas*, localizes to the cell body but also the flagellum (44). In mammals, however, there appears to be a more discrete compartmentalization of motile and sensory functions, where balance has been achieved by the mixing of dedicated cilia within the same anatomical structure, such as the node presenting both types of cilia (72). Likewise, in the olfactory epithelium of most vertebrates sensory and motile cilia are present in discrete regions whereas in humans the two populations are interspersed (80). Phenotypically, there are some immediate distinctions and predictions that result from defects in each ciliary type.

Motile Cilia Dysfunction

The role of motile cilia in a number of physiological processes has been long recognized and thus the consequences of motile cilia dysfunction are perhaps more tractable and specific, with four major manifestations in mammals: early embryonic death due to failure of embryonic turning, respiratory dysfunction, reproductive sterility, and hydrocephalus.

In the embryonic node, a group of motile primary cilia generates a leftward flow of extraembryonic fluid that is thought to generate the first cues to establish the left-right axis of symmetry (89). Furthermore, there appear to be two populations of cilia in this region of the embryo, one motile group generating the flow and a second, nonmotile group sensing it (72). Consequently, defects in ciliary motility can lead to left-right symmetry defects. This has now been shown in several mouse mutants. In

the *inversus viscerum* (*iv/iv*) mouse, disruption of left-right dynein, an axonemal dynein heavy chain important for ciliary motility (125), results in immotile cilia and randomization of the left-right axis of symmetry, with 50% of embryos being normal and 50% presenting *situs inversus* (62). Complete absence of cilia in the node occurs when members of the heterotrimeric kinesin complex, fundamental in IFT, are compromised. Targeting of KIF3A and B in the mouse results in left-right defects, embryonic lethality, and developmental problems (71, 89, 126).

Primary ciliary dyskinesia (PCD) (OMIM: 24,2650) is a group of heterogeneous disorders characterized by bronchiectasis, sinusitis, and infertility, with defects in body *situs* being present in Kartagener syndrome (OMIM: 24,4400). As first described by Afzelius (1976) while studying individuals with immotile sperm, cilia in PCD patients lack dynein arms, as shown by electron microscopy, but can also present with other ultrastructural defects that result in impaired or inefficient motility (1). To date, mutations in a number of genes encoding components of the machinery required for ciliary motility have been reported in PCD and Kartagener syndrome. First, by filtering a candidate gene list with *Chlamydomonas* mutants that result in immotile animals with axonemal defects reminiscent of PCD (absence of outer dynein arms), Pennarun and colleagues (108) identified mutations in *DNAI1*, a gene encoding a dynein intermediate chain. Mutations in *DNAH5* and *DNAH11* encoding two axonemal dynein heavy chains also cause PCD (9, 94).

Ciliary motility is also required for brain development and function. Cilia in the ependymal cell layer surrounding the ventricles maintain a flow of cerebrospinal fluid, the so-called "ependymal flow," necessary to maintain an open aqueduct (47). In *Mdnah5* mouse mutants, the murine ortholog of *DNAH5*, a defect in the axonemal dynein heavy chain that is expressed in ependymal cells, leads to a deficiency in outer dynein arms and results in impaired ciliary beating (47). In the ependymal cell layer, this defective ciliary function translates into failure to produce "ependymal flow" resulting in closure of the cerebral aqueduct and the development of hydrocephalus (47), a condition associated with PCD in humans (49, 56, 110).

The autosomal recessive mouse model of hydrocephalus (hy3) is caused by disruption of the gene *Hydin*, which encodes a protein expressed in the ciliated ependymal cell layer lining the ventricles, the ciliated epithelial cells in the respiratory tract and oviduct, and spermatocytes in the testis (20). Hydin is a novel protein that, based on its expression pattern and mouse phenotype, is a potential candidate for the pathogenesis of some human ciliopathies.

Sensory Cilia Defects

In contrast to the disorders of motile cilia, defects in sensory cilia appear to underlie a broad range of phenotypes, probably due to their nearly ubiquitous presence in almost every cell type of the human body and their emerging role in morphogenetic signal transduction.

The renal phenotype of ciliary dysfunction. In addition to the *Tg737*^{orpk} mouse model of autosomal recessive PKD (ARPKD), other animal models support the link between ciliary dysfunction and renal cyst formation. In the congenital polycystic kidney (cpk) mutant mouse, cystin, the protein product of *cpk*, is present in the cilia of renal epithelial cells (142). Additionally, the identification of genes mutated in various forms of human PKD is also highlighting the central role that primary cilia have in the pathomechanism of the disease.

The process of cyst formation and distribution in the nephron varies, but invariably involves a deregulation of the fine balance between cell proliferation and cell differentiation. In ARPKD, cysts form from the collecting ducts, whereas in autosomal dominant PKD (ADPKD) they can arise in any part

of the nephron, but in both cases cells surrounding the cysts are usually less differentiated (64).

ARPKD (OMIM 26,3200) is a severe, early-onset form of PKD characterized by cystic, enlarged kidneys and hepatic fibrosis and is caused by mutations in *PKHD1* (96, 135, 141). *PKHD1* encodes polyductin, also named fibrocystin, a protein that localizes to primary cilia in MDCK cells and that has been suggested to be a receptor affecting the differentiation of collecting duct cells (64, 96, 135, 136, 141).

In ADPKD, mutations have been found in two genes, *PKD1* and *PKD2* (17, 76). The products of these two genes are polycystin 1 and 2, respectively, two novel proteins able to interact with each other (112, 130) and thought to be part of a Ca^{2+} channel localized in the primary cilium of renal epithelial cells (31, 34, 106, 123, 142). It has been suggested that both polycystin 1 and 2 function as mechanosensors of extracellular fluid flow signaling to the interior of the cell by regulating Ca^{2+} flux (86). These data have raised the intriguing possibility that primary cilia in the renal epithelium might act as environmental sensors to regulate cell growth and differentiation; their failure results in abnormal cell proliferation and the consequent production of renal cysts (86). Consistent with this hypothesis, polycystin 1 can regulate the expression of p21, a tumor suppressor that inhibits cyclin-dependent kinases leading to cell cycle arrest (11).

Nephronophthisis (OMIM 25,6100) is an autosomal recessive cystic renal disease characterized by progressive wasting of the filtering unit of the kidney with or without medullary involvement that can be present in association with retinitis pigmentosa (RP) (Senior-Loken syndrome, see below) (40). To date, five genes have been cloned (*NPHP1-5*), and analysis of their protein products has provided a strong link between ciliary function and the pathogenesis of this disease (41, 77, 93, 98, 100, 118). Mutations in the human *inversin* gene (*INVS*) cause nephronophthisis type 2 (NPHP2) (100). An insertional event in the mouse *inversin* gene, the inversion of embryonic turning (*inv*) murine model, results in pancreatic and renal cysts and a complete inversion of the left-right axis of symmetry, which correlates specifically with an inversion in the expression patterns of genes normally present asymmetrically, such as *nodal* and *lefty* (91, 143). It was shown recently that primary cilia in the node, which move in a clockwise vortical fashion, need to be tilted posteriorly to achieve a net leftward flow (92). This finding highlights the importance of orienting and establishing the polarity of cells in the plane of the tissue to coordinate the correct localization and angle of cilia, a process dependent on noncanonical Wnt signaling, the planar cell polarity (PCP) pathway (reviewed in 132). The nodal cilia in *inv* mutants are defective both in their orientation and movement, thus generating an abnormal, decreased nodal flow (91, 92). Therefore, it is potentially relevant that inversin has been involved in controlling the balance between canonical and noncanonical Wnt signaling cascades (119). Downstream of the receptor frizzled, disheveled (Dsh) is thought to act as a switch between the "canonical," b-catenin-dependent, and "noncanonical" Wnt pathways (132). *Inversin* inhibits the canonical pathway by targeting Dsh for degradation favoring the use of the PCP pathway (119).

Nephrocystin-1 localizes to cell-cell junctions in polarized cells and interacts with focal adhesion proteins such as p130Cas and Pyk2, as well as N-cadherins and catenins, possibly influencing cell polarity (10, 22, 23, 90). Furthermore, inversin can bind to the anaphase-promoting complex (APC), supporting the idea that the cilium plays a role in regulating cell cycle and adding to the evidence from the polycystin 1–regulating p21 (78).

Ciliary dysfunction in the retina. Vertebrate photoreceptors are polarized sensory neurons composed of an inner and an outer segment connected by a highly specialized 9+0 cilium, the connecting cilium. Like other

types of cilia, the synthesis of materials required for the formation, maintenance, and function of the outer segment occurs in the inner segment. Consequently, IFT is responsible for moving cargo across the connecting cilium, is critical for the survival of photoreceptor cells, and underlies the pathogenesis of at least some forms of retinal degeneration (70, 104). For example, specific disruption of kinesin-II in photoreceptors leads to the accumulation of opsin and arrestin in the inner segment, resulting in an increased incidence of apoptotic cell death, a hallmark of RP (70). The requirement of delivering as many as 2000 photopigment molecules per minute to the mammalian outer segment might explain the sensitivity of photoreceptors to IFT defects.

RP is a genetically heterogeneous group of retinal dystrophies that result in night blindness and progressive visual loss. The role of IFT in photoreceptor survival suggests that a number of candidate genes for RP would lie in the still poorly characterized group of moieties involved in the process, including both motors as well as cargo.

Recent studies show that two proteins implicated in RP, RP1 and RPGR, localize predominantly to the photoreceptor-connecting cilium (42, 66). RP1, commonly mutated in some forms of RP, shares a region of similarity with the microtubule-binding domain of doublecortin (DCX), a neuronal microtubule-associated protein involved in neuronal migration (8, 111). RP1 is a microtubule-binding protein that localizes to the photoreceptor axoneme and helps control its length and stability in vivo (67). *Rp1* mutant mice present with misoriented outer segment discs, suggesting that an axonemal protein is involved in their organization, adding another layer of complexity to the role of cilia-associated proteins in the retina and the pathogenesis of RP (65).

The RP guanosine triphosphatase (GTPase) regulator (RPGR) is essential for photoreceptor maintenance and viability and mutations in the human *RPGR* gene cause RP3 (74). RPGR is concentrated in the connecting cilia of both cones and rods and its disruption in mice leads to the mislocalization of opsins, suggesting that RPGR may be involved in protein trafficking across the connecting cilium (42, 43). Some alleles of *RPGR* might also be involved in the function of motile cilia given that mutations in *RPGR* have been found in patients with RP and recurrent respiratory infections, a phenotype characteristic of PCD, with cilia exhibiting ultrastructural problems in the dynein arms and microtubule backbone (131, 133). This association of defects characteristic of motile and sensory cilia are likely to be more common than expected, given the high overlap in protein content between the two types of cilia.

PKD and retinal degeneration. Both retinal degeneration and kidney disease can be caused by defects in cilia formation, maintenance, or function and thus it is not surprising to find an association of these two major phenotypes in human patients. Senior-Loken syndrome (SLSN; OMIM 266900) is a rare autosomal recessive disorder characterized by nephronophthisis and progressive eye disease. SLSN has been associated with mutations in several of the genes responsible for nephronophthisis (*NPHP1*, *3*, *4*) and in particular with *NPHP5/IQCB1* (99). Interestingly, NPHP5 interacts with RPGR in the retina and is localized to the connecting cilia of photoreceptors and to primary cilia of renal epithelial cells (99). These data highlight the fact that the dysfunction of cilia as an organelle can result in a group of related phenotypes. It is likely that a combination of the specific function of individual mutant proteins, their pattern of expression, the level of redundancy in each tissue/cell type, the sensitivity of individual tissues, and the mutational load in additional causative or modifier genes, determines which subset of defects are expressed in each case.

Such variability is better exemplified in more pleiotropic disorders that include not only kidney and retinal defects, but are also defined by defects in other tissues, such as the

limb and the nervous system, as is the case in BBS (see below) and Joubert Syndrome, an autosomal recessive disease (JS; OMIM 21,3300). In some JS cases, the characteristic features of cerebellar vermis hypoplasia, mental retardation, hypotonia, breathing, and eye movement abnormalities are present in conjunction with retinal degeneration and nephronophthisis. Some patients with JS segregate mutations in *NPHP1* (102). Although it is possible that the *NPHP1* deletion unmasks a recessive mutation in this genomic region, the presence of the same deletion in both JS and NPHP patients argues against this alternative.

Cilia in other tissues and cell types. Although the role of cilia in the pathogenesis of cystic kidney disease and retinal degeneration has been well documented, the impact of their dysfunction in a number of other tissues and cell types is just beginning to be appreciated. The analysis of mouse mutants have indicated that the cilium plays a key role in the transduction of several paracrine signaling cascades, a finding supported by the enrichment for proteins involved in signaling observed in the flagellar and basal body proteome (FABB) (63). These signaling pathways are important for diverse functions, including the establishment of cell polarity and axis of symmetry, cell specification and differentiation, limb development, and neural tube formation.

In the neural tube. Several recent lines of evidence indicate a crucial role for ciliary proteins in neural tube development. In a mouse mutagenesis screen of embryonic patterning defects, Huangfu and colleagues (48, 73, 139) identified two mutants with phenotypes characteristic of defective Sonic hedgehog (Shh) activity. Interestingly, the wimple (wim) and flexo (fxo) phenotypes, which include open neural tube, brain defects, and limb abnormalities, are caused by mutations in the IFT proteins IFT172 and polaris/IFT88, respectively, demonstrating that intact IFT, as well as the molecular motor Kif3a (kinesin), are required in Shh signaling downstream of the receptor Patched 1 and the activator smoothened (Smo) (45, 46). Furthermore, Smo, a transmembrane protein, localizes to the primary cilium and its presence in the organelle is required for Shh signaling (18).

Recently, BBS mutant mice have been shown to develop phenotypes characteristic of PCP mutant animals (a pathway required for convergence and extension movements during gastrulation and neurulation in vertebrates), which include neural tube defects, open eyelids, and defective stereociliary bundles in the cochlea (115). Additional evidence for the involvement of the BBS loci in the PCP pathway came from genetic crosses wherein the BBS genes interacted genetically in both mice and zebrafish with *Vangl2*, a known component of the noncanonical Wnt signaling cascade (115).

In the developing limb. Tight regulation of cell growth and differentiation results in the correct patterning of digits. Perturbations in the production, distribution, and interpretation of morphogens can then result in a range of anatomical defects that include post- and preaxial polydactyly (reviewed in 129). Sensory cilia are present in both ectodermal and mesenchymal cells in the limb bud (36), suggesting that they might play a role in sensing and transducing morphogenetic signals, thus offering a potential explanation for the recurrent presence of limb defects in a number of ciliopathies (**Table 1**). The requirement of functional cilia for normal Shh signaling is further supported by the recent work of Haycraft and colleagues in the developing limb. The authors show that defects in polaris/IFT88 result in the defective processing of the glioma (Gli) transcription factors, more specifically Gli3 processing, and that all Gli proteins localize to both the nucleus as well as the tip of the cilium (36).

Cilia and cognitive defects. Several pleiotropic disorders caused by disruption of the

Table 1 The common association of clinical features in five ciliary dysfunction syndromes

Disease	BBS	OFD1	Senior-Loken	Meckel	Joubert
Retinitis pigmentosa	✓		✓	✓	✓
Renal cystic disease	✓	✓	✓	✓	✓
Polydactyly	✓	✓		✓	✓
Situs inversus/Isomerism	✓		✓	✓	✓
Mental retardation/ developmental delay	✓	✓		✓	✓
Hypoplasia of corpus callosum	✓	✓		✓	✓
Dandy-Walker malformation	✓		✓	✓	✓
Posterior encephalocele	✓*			✓	✓
Hepatic disease	✓	✓*	✓	✓	✓
Total number of phenotypes in each disorder	8	5	5	9	9

*In mice.

function of cilia present mental retardation or other cognitive defects as part of their phenotypic spectrum. The presence of cilia in different types of neurons (reviewed in 138) supports the notion that dysfunction in specific neuronal populations might explain, at least in part, such defects. Whether cilia act as sensors of extracellular stimuli or whether some of the proteins involved might have additional extraciliary roles needs further evaluation. The somatostatin receptor 3 (sst3) localizes to the cilia of neurons in the hippocampus, amygdala, cortex, and thalamus (35). Serotonin receptor 5-HT_6 also localizes to cilia in different neurons of the rat brain,-supporting a functional role for this cellular compartment in the central nervous system (14).

Defects in ciliary proteins have not yet been found to cause any of the above phenotypes in isolation. This might reflect the relative youth of the field and in due course sporadic, isolated limb deformities (for instance) might be attributed to ciliary disruption in that tissue. However, a more parsimonious explanation is that the same signaling cascades are typically involved in the development of many tissues; therefore, it is unlikely that disruption of Wnt or Shh signaling, for example, will have local phenotypic manifestations. In addition, disruption of cilia-mediated signaling might lead to the impairment of multiple pathways and thus is likely to result in broad and variable phenotypes.

GLOBAL CILIARY DYSFUNCTION IN HUMAN PLEIOTROPIC DISEASE

An increasing volume of information is highlighting the role of cilia in a wide range of defects that include but extend beyond the well documented ciliary defects in the eye and the kidney. This is well documented by the emerging realization that several human pleiotropic disorders are caused by ciliary dysfunction.

BBS (OMIM 20,9900) is a multisystemic disorder characterized by obesity, polydactyly, mental retardation, retinal degeneration, and renal and gonadal malformations. Additionally, patients often present a number of other features that vary in prevalence including anosmia, asthma, diabetes, *situs inversus*, and congenital heart disease (51, 60).

Ten BBS proteins have been identified to date (BBS1–10) (3, 6, 15, 26, 52, 63, 83, 84, 87, 88, 120, 123a) and all of those tested localize to ciliated cells and tissues (3, 7, 26, 54, 55, 63). However, the function of the BBS proteins, although important for the formation, mantainance, and function of cilia, might not

be restricted to the biology of this organelle. Several of the BBS proteins localize to both centrosomes and basal bodies in ciliated cells (3, 54, 55). BBS4 interacts in mammalian cells with the p150-glued subunit of dynactin, thus directly implying a role in microtubule transport. Furthermore, BBS4 is required, perhaps as an adaptor protein for the correct localization of pericentriolar material 1 (PCM1), the major component of pericentriolar satellites and a protein required for both centrosome function and ciliogenesis (19, 54, 59). BBS3 is a member of the RAS superfamily of GTP-binding proteins that localizes to the cytoplasm and is thought to play a role in vesicle trafficking. However, studies in *C. elegans* demonstrate that Bbs-3 localizes to the cytoplasm and the basal body and is involved in IFT in the cilia of sensory neurons (26). *Bbs-1*, *bbs-2*, *bbs-7*, and *bbs-8* in *C. elegans* localize to the transition zones of cilia, basal bodies in the worm, and loss of bbs-7 and bbs-8 affects cilia both structurally (shortened) and functionally (impaired IFT) (13).

These data suggest that at least some of these proteins might have a dual or broader function that includes, but is not limited to, their role in ciliary biology and could provide a functional link between different structures and subcellular compartments. Importantly, a centrosomal dysfunction might underlie some of the phenotypic aspects of BBS that are not easily reconciled with a ciliary defect. Besides its role during cell division, the centrosome is thought to have a role in diverse cellular processes that include protein degradation, neuronal migration, axonal guidance, and vesicular transport (8). By affecting the function of cilia and other microtubule-based processess, defects in the BBS proteins may thus result in a global impairment of those ciliary functions that depend both on the structure as well as the ability of the organelle to sense and transduce diverse extracellular signals, perhaps explaining, at least in part, the pleiotropy observed in this syndrome (**Figure 3**).

A similar example is ALMS (OMIM 20,3800), which is caused by mutations in *ALMS1* (16, 38). ALMS patients present with a number of phenotypes reminiscent of BBS, including RP, obesity, and diabetes, but are distinguished from the latter in that they develop significant sensorineural deafness and do not have polydactyly. ALMS1 was identified in a proteomic analysis of the human centrosome (2) and was shown to localize to both centrosome and basal bodies in a pattern highly reminiscent of that of the BBS proteins (39). These data may indicate that BBS and ALMS could belong to a discrete group of disorders based on both cilia and centrosomal dysfunction that are distinct from other ciliopathies.

Orofaciodigital syndrome type I (OFD1; OMIM 31,1200), an X-linked disorder characterized by malformations of the face, oral cavity, and digits with PKD and variable involvement of the central nervous system, is caused by mutations in *OFD1* (27). OFD1 localizes to both centrosomes and basal bodies, suggesting that this syndrome might also fall into this broader category of ciliary diseases (2, 53, 113).

The most recent example of ciliopathy is Meckel-Gruber syndrome (MKS; OMIM 24,9000). MKS is a lethal condition characterized by cleft palate, renal cysts, hepatic fibrosis, polydactyly, and central nervous system defects, including occipital encephalocele. Importantly, mutations in several of the BBS genes have been found in fetuses with Meckel-like phenotypes, raising the possibility that the MKS and BBS loci might interact genetically (50). Recently, the first two genes that cause MKS were cloned (61, 121) and their encoded proteins are found in the predicted ciliary proteome (63), supporting the hypothesis that ciliary dysfunction likely underlies the pathogenesis of MKS (see predicting ciliary diseases) (61, 121).

DISSECTING CILIARY DISEASES

A better understanding of ciliary structure and function is likely to have significant consequences both at the basic research and clinical

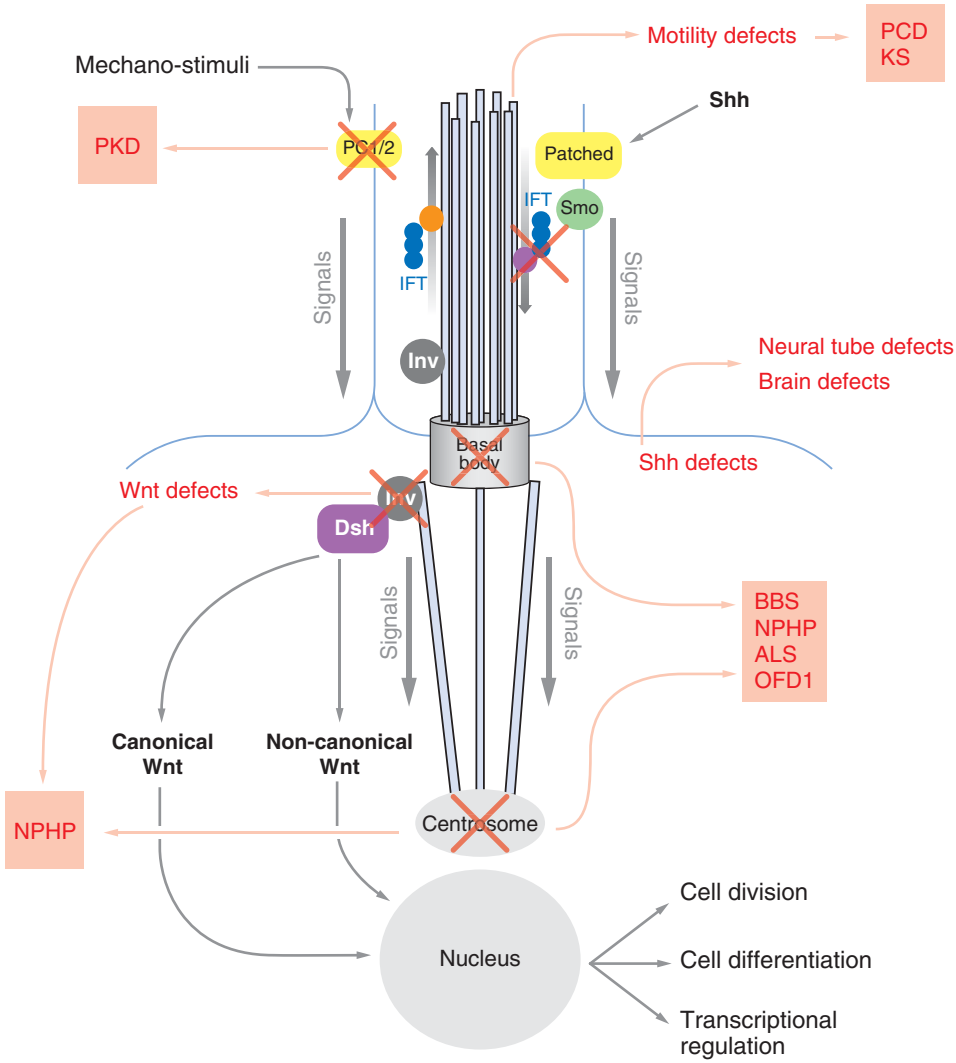

Figure 3

Representation of the microtubule continuum extending from the nucleus to the ciliary tip. Schematic representation of the cilium as a signaling device through which different external signals (Wnt, Shh, mechanical, and possibly others) are sensed and transduced into the cell, ultimately reaching the nucleus to affect gene regulation, cell division, and differentiation. In this context, the phenotypic outcome of different ciliary perturbations depends on how globally ciliary function is affected. In motile cilia, mutations in the force generating molecules lead to inmotile cilia and disorders such as primary ciliary dyskinesia and Kartagener syndrome. Defects in specific receptors localized to the ciliary membrane have a more restricted effect. For example, mutations in polycystin 1 and 2 (PC1 and 2) cause polycystic kidney disease. However, perturbation of basal body proteins might result in structural, intraflagellar transport, and functional defects such as impaired Wnt and Shh in addition to the defective localization of membrane receptors. This global defect in ciliary function might then translate into nephronophthisis or pleiotropic human disorders such as Bardet-Biedl syndrome, Alstrom syndrome, and Orofaciodigital syndrome type I.

levels. To this end, multiple groups have engaged in proteomic and comparative genomic studies to elucidate the complete protein complement of cilia (5, 12, 24, 26, 63, 97, 103, 124).

An *in silico* comparative approach between the proteome of a nonflagellated/ciliated organism such as *Arabidopsis* and that of ciliated organisms such as humans and *Chlamydomonas* resulted in the identification of a group of 688 proteins likely involved in the biology of cilia and basal bodies (63). Furthermore, identification of all *C. elegans* genes and their human orthologs that contain an X box, the recognition site for the cilia-specific transcription factor Daf-19, resulted in additional loci that overlap and expand the previous list (12, 24, 26). Additionally, transcriptional and mass spectrometry analysis in both *C. reinhardtii* and human cells further increased the list, resulting in a combined ciliary proteome data set that contains more than 1300 genes (97, 103, 124; our unpublished data).

The availability of the ciliary proteome is proving to be a powerful resource to expedite the cloning of suspected ciliopathies by prioritizing positional candidates by their presence in the data set. This has facilitated the cloning of both novel causative and modifier genes. For example, in BBS, the cloning of *BBS3*, *BBS5*, and, more recently, the BBS modifier *MGC1203*, was achieved by sequencing a reduced set of positional or BBS-interacting candidates, respectively (7, 15, 26, 63), as was the case for the cloning of *MKS1* (61). This resource is not only facilitating the identification of novel human disease genes, but also promises to help unravel the genetic basis of other suspected ciliopathies.

THE HUMAN CILIOPATHIES: PHENOTYPES AND PREDICTIONS

The clinical manifestations of the known ciliopathies have the potential to provide us with a set of phenotypic parameters that can be used as a training set to predict ciliary involvement in disorders of unknown molecular etiology. By comparing the ontological descriptions of five syndromes for which function has already been ascribed to disordered cilia (**Table 1**), we can devise core search terms by which to query databases such as OMIM or the London Dysmorphology Database (LDDB, formerly known as the Winter Baraitser Dysmorphology Database).

As described earlier, phenotypes such as RP, renal cystic disease, left-right axis determination, and polydactyly can be caused by structural and functional abnormalities of cilia. Additionally, the observation of global levels of cognitive impairment or developmental delay in many of these syndromes highlights the importance of primary cilia in neurological function, although their exact role remains to be determined.

Perhaps more difficult to explain are the reports of specific structural changes within the brain, such as agenesis of the corpus callosum and Dandy-Walker malformation (DWM) associated with four of the five conditions listed in **Table 1**. One possibility might be that the activity of *ZIC* genes (zinc fingers in the cerebellum) relies on the cilium. Mutations in *ZIC* genes were recently implicated in a wide variety of congenital malformations including DWM, holoprosencephaly, neural tube defects, and heterotaxy (reviewed in 32). Mice doubly heterozygous for inactivating mutations in both *Zic1* and *Zic4* give rise to cerebellar hypoplasia and foliation defects similar to DWM in human patients whereby the cerebellar hemispheres are relatively unaffected (33). Additionally, loss of function of *ZIC2* has been associated with holoprosencephaly (HPE), a phenotype that can be caused by Shh defects, and neural tube defects (reviewed in 32). Furthermore, *Zic2* mutants also display phenotypes reminiscent of ciliary dysfunction including neural tube closure defects such as exencephaly, anencephaly, and spina bifida (85). Likewise, mutations in *ZIC3* cause heterotaxy and neural tube defects (29, 137). Although the exact relationship of the *ZIC* family of genes with cilia remains to

Table 2 Representation of core features. The table represents the pairwise analysis of the number of conditions with any two features (using the London Dysmorphology Database)

	RP	RCD	Po	MR	SI	CC	DWM	PE	HF
RP	409*	20	12	73	5	10	12	9	68
RCD	20	128	22	16	6	4	9	9	40
Po	12	22	119	22	7	5	10	9	13
MR	73	16	22	599	7	49	29	5	34
SI	5	6	4	4	27	3	4	2	8
CC	10	4	5	49	3	62	19	2	5
DWM	12	9	10	29	4	19	45	9	5
PE	9	9	9	5	2	2	9	46	7
HF	68	40	13	34	8	5	5	7	288

*Gray box = total number of entries with given feature.

Table 3 Core features represented as a percentage of the total number of conditions with any given feature [e.g., the percentage of RCD and RP cases relative to the total number of conditions with RP = 5% (20/409)]

	RP	RCD	Po	MR	SI	CC	DWM	PE	HF	Mean %
RP		5	3	17	1	2	3	2	16	6
RCD	15		17	12	4	3	7	7	31	12
Po	10	18		18	6	4	8	7	11	10
MR	12	3	4		1	8	5	1	5	5
SI	18	22	26	26		11	15	7	29	16
CC	16	6	8	79	5		30	3	8	19
DWM	26	20	22	64	9	42		20	11	27
PE	19	19	19	10	4	4	19		15	13
HF	24	14	4	12	3	2	2	2		8

be elucidated, their role in "ciliary" phenotypes as well as their sequence similarity to *Gli1* and *Gli3* (32) suggests that these encoded transcription factors might be involved in Shh signal transduction.

Using the nine features common to BBS, JS, OFD1, MKS, and SLSN (**Table 1**), we queried the LDDB. Initially, we tested each feature individually to determine the number of entries in which it coincided with each of the remaining eight. For example, the number of conditions featuring RP totaled 409; however, the number with RP and multiple cystic kidneys (RCD) was 20, the number with RP and polydactyly was 12, and so forth (**Table 2**). In this way we established a weighting for each feature by determining the proportion (%) of disorders with, for example, RP and RCD relative to the total with RP (**Table 3**). By averaging the number of times each feature was associated with another from the list we could gauge the relative likelihood of any one clinical feature to predict ciliary dysfunction.

Surprisingly, RP, which one might intuitively expect to be a strong predictor, came second to last, only marginally higher than mental retardation (MR) (**Table 4**). Like MR, this lack of specificity probably reflects the multiple etiologies of retinal degeneration. Conversely, DWM scored as the greatest predictor for ciliary dysfunction. To test these observations we took two of the highest-scoring features from different

Table 4 Weighting (in descending order) of each feature and its likely relevance to predict ciliary involvement

1	Dandy-Walker Malformation
2	Agenesis of Corpus Callosum
3	*Situs inversus*
4	Posterior encephalocele
5	Multicystic renal disease
6	Post-axial polydactyly
7	Hepatic disease
8	Retinitis pigmentosa
9	Mental retardation

organ systems—DWM (a brain deformity) and *situs inversus* (cardiac)—and queried the LDDB again. This time four conditions were returned: Ellis-van Creveld (EVC; OMIM 22,5500), Jeune asphyxiating thoracic dystrophy (JATD; OMIM 20,8500), Marden-Walker (MWS; OMIM 24,8700), and Meckel-Gruber (MKS) syndromes. MKS was already associated with ciliary dysfunction (see above). EVC is characterized by short stature with short limbs, postaxial polydactyly, and congenital cardiac defects, whereas JATD is a rare chondrodysplasia that often leads to death in infancy because of a severely constricted thoracic cage and respiratory insufficiency. Cystic lesions occur in the kidney, liver, and pancreas, and several cases with retinal degeneration have been described in JATD. MWS is comprised of blepharophimosis, microcephaly, micrognathia, multiple joint contractures, arachnodactyly, camptodactyly, kyphoscoliosis, and delayed motor development and is often associated with cystic dysplastic kidneys, dextrocardia, DWM, and agenesis of the corpus callosum. Clearly, EVC, JATD, and MWS have overlapping features with BBS, Joubert, SLSN, and OFD1 and it remains to be confirmed that these conditions might also be caused by fundamental defects in ciliary function. This should be possible to determine for EVC as two genes (*EVC* and *EVC2*) were recently identified (28, 116, 117).

CONCLUDING REMARKS

A growing body of literature is demonstrating the impact of ciliary dysfunction in human disease. From animal models to human studies, sensory cilia are at the heart of disorders that range from PKD and retinal degeneration to pleiotropic disorders such as BBS and ALMS. This observation raises the question of how disruption of the same cellular organelle can lead to overlapping but distinct phenotypes. Based on our limited knowledge of the function of the proteins involved in this group of disorders, the answer to that question might lie in the specific role of each protein and its effect on the overall function of the organelle.

If we consider the cilium as an extension of the highly organized microtubule network of the cell, we find a continuum that extends from the centrosome located in close proximity to the nucleus, to the basal body, and into the cilia. Complete disruption of the IFT process is incompatible with life, because it blocks ciliary biogenesis, as is the case for the *Polaris* null mutant. By contrast, defects in specific axonemal receptors, such as the ADPKD proteins, seem to have a fairly restricted effect in a discrete range of tissues. A plausible explanation is that they only impede discrete ciliary functions. However, defects at the basal body, as with BBS and ALMS, result in a number of phenotypes that extend beyond kidney cysts and RP (**Figure 3**). However, the question remains of whether all clinical manifestations of ciliopathies can be truly ascribed to the organelle, or whether they reflect multiple functions of the same group of proteins. Inversin localizes to the ciliary axoneme, but has also been reported to localize to the nucleus and centrosome as well as to the basolateral membrane of renal cells (90). The plasma membrane–associated inversin interacts with N-cadherin and catenins and such localization is perturbed upon cell-cell contact disruption (90). In neurons, some of the BBS proteins appear to be present in the axon, as well as the cilium (our unpublished data), raising the possibility that axonal transport, not just

intraflagellar transport, might be involved in the development of the complex cognitive phenotype characteristic of the syndrome. Generating mutants that selectively fail to localize to some but not all physiologically relevant regions of the cell (e.g., the basal body but not the centrosome) will be required to dissect the potential distinct roles of the same protein and better address these questions. In addition, in vivo models that enable us to specifically block and unblock ciliogenesis in a tissue- and cell-specific manner will be invaluable.

Remarkable progress has been achieved in assigning function to cilia in different cell types. However, there are still a large number of tissues in which the role of these cellular structures is less clear and for which the identification and study of pleiotropic human ciliary disorders promises to provide important clues. For example, in odontoblasts, cilia might have a mechanosensory role sensing fluid forces within dentinal tubules and regulating dentine deposition (68). Syndromes such as BBS present dental crowding and other dental anomalies as components of their phenotypes, highlighting the importance and expanding the putative role of cilia in this tissue. Likewise, the presence of different types of receptors in neuronal cilia and the common association of cognitive defects with ciliary disease suggest an important role of cilia in the still poorly understood central nervous system.

Defining the hallmarks of a ciliopathy and classifying a human disease as such will be important both for understanding the pathomechanism of the disease and for the clinical management of patients. Identifying ciliopathies in humans can be aided by the administration of noninvasive, yet informative tests, as exemplified by the identification of anosmia and defective otoacoustic emissions as additional features of BBS (60, 115). Finally, a unified view of the phenotypic characteristics of a ciliary dysfunction and the availability of the ciliary proteome are likely to facilitate the identification of yet unrecognized ciliary disorders and the genes and proteins involved in their pathogenesis.

SUMMARY POINTS

1. Cilia and flagella are evolutionary conserved organelles involved in a number of cellular processes that range from whole cell locomotion, chemotaxis, and fluid movement to signal transduction.
2. The identification of several animal models and human disorders caused by defects in these organelles has highlighted the roles of cilia in a range of biological functions including the intracellular interpretation of several paracrine morphogenetic signals.
3. The association of an increasing number of human disorders with ciliary dysfunction is offering the possibility of unifying diverse phenotypic manifestations under the common theme of the ciliopathies, where each discrete clinical entity manifests a subset of overlapping clinical features.
4. The phenotypic parameters that define a ciliopathy can be used to both recognize the cellular basis of a number of genetic disorders and to facilitate the diagnosis and treatment of some diseases of unknown etiology.

FUTURE ISSUES

1. Although cilia have been found in almost every tissue and cell type in mammals, their role is typically obscure, as are the consequences of their dysfunction.

2. Do ciliary proteins have additional roles in the cell, and if so what are they?
3. How can ciliary dysfunction lead to variable and diverse phenotypes? Is it a question of specific protein dysfunction, the fact that some of the moieties involved are expressed in different cells and tissues, or the variable redundancy and/or buffering capacity of individual systems?
4. Despite a number of clues as to the function of several ciliary proteins, the exact role of this group of molecules is largely unknown.

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The structure and function of cilia have been studied for more than 100 years and hence we apologize to those scientists whose contribution could not be properly cited in this work due to space limitations. We also thank Jantje Gerdes and Erica Davis for their thoughtful comments on the manuscript. This work was supported by grant R01HD04260 from the National Institute of Child Health and Development (N.K.), grant R01DK072301 from the National Institute of Diabetes, Digestive and Kidney disorders (N.K.), a grant from the Polycystic Kidney Disease Foundation (J.L.B. and N.K.), and the Medical Research Council (P.L.B.). P.L.B. is a Senior Wellcome Trust Fellow.

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