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Review: Intraflagellar transport proteins in the retina

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Intraflagellar transport (IFT) is an essential process in all organisms that serves to move proteins along flagella or cilia in either direction. IFT is performed by IFT particles, which are multiprotein complexes organized into two subcomplexes, A and B. The IFT proteins form interactions with each other, with cargo proteins, and with membranes during the transport process. Several IFT proteins are expressed in many parts of the retina, such as the outer plexiform and outer nuclear layers, and function in the transport of photoreceptor proteins between the inner and outer segments. Mutants of IFT protein genes have been characterized in model organisms such as *Chlamydomonas*, C. *elegans*, zebrafish, and the mouse. These mutants have defective ciliogenesis or abnormalities in retinal photoreceptors. Mutations in IFT genes are associated with syndromic and non-syndromic forms of retinal disease in humans, frequently with early onset of disease.

Cilia and flagella are appendages protruding from the cell surface that have a microtubule-based structure. Cilia are generally present in large numbers on the surface of cells and may perform either sensory or motile functions. Flagella are present as single units, are longer than cilia, and primarily function in locomotion. Cilia are of two types: motile cilia and non-motile or primary cilia. Motile cilia perform the task of moving fluids or substances through the organ, for example, cilia in the respiratory tract and fallopian tubes. Primary cilia, however, are present on all cells in mammals. Cilia are made up of doublets of microtubules, organized into an axoneme. The axoneme is surrounded by the plasma membrane. Motile cilia have an axoneme made up of nine microtubule doublets, containing the A and B types of microtubules, surrounding two singlet microtubules in the center (the 9 + 2 arrangement). Primary cilia contain nine microtubule doublets but lack the two central microtubules. The axoneme attaches to the cell surface through the basal body, which also consists of microtubules, present in triplets, containing A, B, and C types of microtubules. Only the A and B microtubules of the basal body continue into the shaft of the axoneme. The basal body is attached to the plasma membrane by protein fibers. The entire structure of the cilia or flagella is estimated to contain more than several hundred proteins, many of which are evolutionarily conserved [1]. The assembly of the axoneme by elongation of the microtubules at its tip necessitates the transport of axonemal subunits along the length of the cilium, from the base to the growing end. In addition, the absence of protein synthesis machinery in the cilia requires that ciliary proteins are made in the cytoplasm of the cell and transported to the cilium. Thus, the intraflagellar transport (IFT) processes serve to move the various protein complexes through the cilium. This is brought about by polymers of IFT particles, known as IFT trains, which are moved along the cilium. Anterograde transport of particles from the base to the tip of the cilium is performed along the microtubule doublets, to transport substances required for axoneme assembly. Retrograde transport serves to recycle IFT particles from the tip to the base of the cilium. Studies on *Chlamydomonas* mutants have suggested that movements of IFT particles are enabled by motor proteins, related to kinesin (heterotrimeric kinesin II) and dynein 2, for anterograde and retrograde transport, respectively [2].

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Intraflagellar transport has several functions that are part of essential processes in all organisms. These functions are cell motility, cytokinesis, and sensory functions in organs such as the kidney and the retina, control of left-right asymmetry during development, cell mating, and control of flagellar length [3].

DISCUSSION

The IFT proteins: Analysis of IFT complexes from *Chlamydomonas* by purification of proteins from wild-type and mutant flagellae enabled the identification of the complexes with two-dimensional gel electrophoresis. There are two IFT subcomplexes, A and B, that are different in their subunit composition and in the functions that they perform (Figure 1A,B). The IFTB complex is involved in anterograde transport, and mutants lacking any of the proteins of the IFTB complex have shortened cilia. However, the IFTA complex

functions in retrograde transport, and IFTA mutants have bulges in their cilia, which contain accumulated proteins [4,5]. The proteins in these IFT complexes are named after their molecular weights, although there are some differences in the components of complexes A and B as described by different authors, in terms of the specific polypeptides that have been designated in these complexes (Figure 1). According to a report by Taschner and coworkers [6], members of the IFTA complex are of high molecular weight (>100 kDa), namely, p144, p140, p139, and p122. For the IFTB complex, there are 11 subunits that are mostly of lower molecular weight (<100 kDa): IFT172, IFT88, IFT81, IFT80, IFT74/72, IFT57/55, IFT52, IFT46, IFT27, and IFT20. In high salt conditions, the dissociation of a few subunits that are more weakly bound, i.e., p172, p80, p57, and p20, from the IFTB complex leaves a salt-stable core complex made up of other nine subunits p88, p81, p74, p72, p52, p46, and p27 [6]. A somewhat similar composition of proteins, although with differences from the above, has also been described. In this configuration, the IFTA complex has six subunits (IFT144, IFT140, IFT139, IFT122, and IFT121) with p43 in addition. The IFTB complex is reported as having two subcomplexes: B1 (consisting of IFT88, IFT81, IFT74, IFT70, IFT56, IFT52, IFT46, IFT27, and IFT25, and IFT22), similar to the salt-stable core complex mentioned above, and B2 with six subunits (IFT172, IFT80, IFT57, IFT54, IFT38, and IFT20) consisting of weakly bound proteins [5,7]. The structure of the IFTB complex in mammalian cells has been elucidated with immunoprecipitation assays in mouse embryo fibroblasts [8].

Protein–protein interactions are crucial to the organization and functioning of the IFT proteins between members of a complex and between IFT complexes and their cargo proteins. Members of the IFTA complex possess interaction domains, such as the tetratricopeptide (TPR) domain, beta-propellers, – expansion of tryptophan-aspartic acid (WD) repeats, and coiled-coil domains [9]. Thus, it appears that the IFTA complex is primarily a structural entity that provides interaction surfaces with other proteins. Apart from protein interaction domains in members of the IFTA complex, interaction with membranes is a property of certain members such as the IFT172 protein, a part of the IFTB complex. IFT172 is capable of remodeling membranes into vesicles. Interaction of IFT172 with membranes appears to be through its N-terminal β-propeller domain [10]. Membrane interaction of IFT proteins may be required during the movement of IFT trains, which are located between the axoneme and the ciliary membrane. In the following sections, we discuss the effects of intraflagellar transport proteins in the retina.

Intraflagellar transport proteins in the retina: Expression of several IFT proteins has been observed in the connecting cilium of the photoreceptors, the inner segments, and the outer plexiform layers of the bovine retina [11]. Studies on the localization of the IFT88 protein in mouse and *Xenopus* retinas suggested that it is present in the basal body and centriole, and additionally, IFT88, IF57, IFT52, and IFT20 proteins are found throughout the length of the axoneme in *Xenopus*. Immunogold labeling of IFT88 in the mouse retina detected IFT88 in particulate or vesicular structures [12]. The kinesin 17 (Kif17) protein, which is the motor component of the IFT particles, was also found to be expressed in all layers of the zebrafish retina, and similar to the other IFT proteins, is found along the axoneme of rods and cones [13]. The IFT particles transport photoreceptor membrane proteins, such as rhodopsin and retinal guanylyl cyclase 1, between the inner and outer segments [14]. IFT complexes from bovine photoreceptors contain IFT88 in association with guanylate cyclase 1 (GC1), rhodopsin, and chaperone proteins, particularly the mammalian relative of DNAJ (the MRJ protein), detectable with yeast two-hybrid and pull-down assays [15]. IFT proteins are also expressed in post-synaptic dendritic terminals of bipolar and horizontal cells of the mammalian retina, as detected with immunoelectron microscopy [16].

Animal models for IFT mutants: Intraflagellar transport is critical to the transport of proteins between the inner and outer segments of photoreceptors through the connecting cilium. The association of retinal disease with mutations at several IFT loci attests to the importance of these proteins in the process of vision. Orthologs of the major IFT proteins found in *Chlamydomonas* are found in the human retina, within the connecting cilia. Mutations in most of the IFT complex genes are associated with defects in ciliogenesis or intraflagellar transport in model organisms, such as *C. elegans, C. reinhardtii, Danio rerio* (zebrafish), and *Mus musculus* (Table 1) [17].

The identification of a mutant mouse model, Tg737, which is an insertional mutant in the *Ift88* (Gene ID 21821) gene, paved the way toward understanding the biologic role of IFT88. *Tg737* was generated by an insertion event affecting one of its exons without any effect on the coding regions of the remaining exons. Thus, the mutation reduced the amount of protein without eliminating it and was hypomorphic [18]. The *Tg737* strain of mice showed ciliary defects in the kidneys and the retina. The outer segments of the photoreceptors were disorganized and smaller than those of healthy controls. Photoreceptors were lost due to apoptotic cell death, and there was a gradual reduction in retinal thickness [11]. The effect of *ift88* knockdown on the retina was also evident

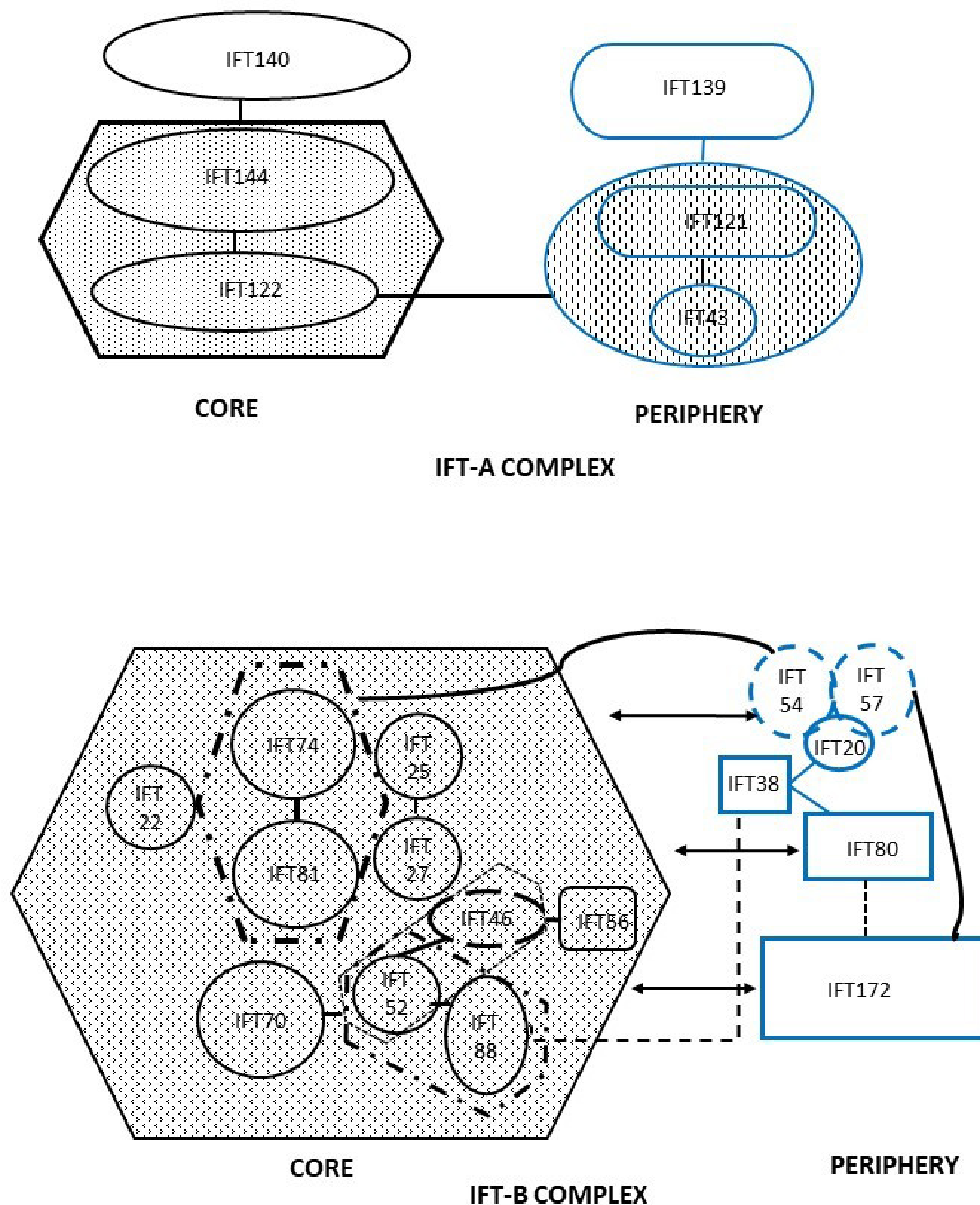

Figure 1. "Schematic representation of IFTA and IFTB complexes showing the proteins comprising each complex and their interactions. Schematic representation of IFTA (**A**) and IFTB (**B**) protein complexes showing the proteins comprising each complex and their interactions. There are variations in the specific interactions between the proteins in each complex as reported in different studies. Based on the data from protein interaction studies with visible immunoprecipitation of the IFTA complex [42], three subunits (IFT122, IFT140, and IFT144) form a stable core complex. IFT140 is proposed to interact with the IFT122–144 dimer. IFT139 and IFT122 connect through the dimer between IFT43-IFT121. In the IFTB complex, protein interactions as detected with visible immunoprecipitation and immunoblotting of human IFT proteins [8] are depicted. The core complex is formed by dimers between IFT25–27, IFT74–81, and IFT46–52. IFT22 can interact with the IFT74-IFT81 heterodimer. IFT56 (TTC26) interacts with the IFT46–52 dimer. IFT70 is proposed to interact with the IFT52-IFT88 dimer [43]. In the peripheral complex, IFT38 connects IFT20 and IFT80.

Table 1. Details of IFT genes and associated phenotypes.

IFT locus	Mutants of IFT loci in model organisms		Retinal dystrophy in humans
	Model	**Phenotype**	
IFT140	R*educed mechanoreceptor potential A* (*rempA;* Drosophila) [44]	Accumulation of IFT-B proteins and defective cilia	Non-syndromic RP, LCA
IFT139, *IFT144*	Genome-editing mediated knockout cell lines [45]	Defects in retrograde transport	-
IFT122 (A, B)	Med1 mice	Knockout leads to IFT-B proteins at ciliary tips; impaired *Sonic* Hedgehog (*Shh*) signaling [46]	-
	jj263 (zebrafish)	Absence of ONL, pronephric cysts, ciliary defects [21]	-
IFT43	ift43 (insertional mutant; *Chlamydomonas*)	Absent or defective flagella. Bulges at flagellar tip [47].	Non-syndromic, early-onset rod-cone degeneration
IFT46	ift46/bld1 mutant (*Chlamydomonas*);	Reduction in IFT-B1 and IFT-B2 proteins, shortened cilia, lack of outer dynein arm	
	Ift46$^{-/-}$ mice	Embryo heart looping, defective patterning of L/R axis [48]	
IFT25, *IFT27*	ift25$^{-/-}$ mice	Defects in transport of opsins and signaling factors *Patched* 1 and *Smoothened* [49]	Bardet-Biedl syndrome
IFT172	C. *reinhardtii* (*fla11ts*)	Accumulation of proteins at tip of flagella.	BBS-like syndromic disease; autosomal recessive RP
	Zebrafish	Disorganized outer & inner segments, PR cell death [20]	
IFT74	ift74-1, i*ft74*-2 (C. *reinhardtii*)	Failure of flagellar assembly. Decrease of IFT-B complex [50].	-
IFT52	ift52/*bld1*(C. *reinhardtii)*	Inability to form flagella. Destabilization of IFT-B1 complex [51].	Syndromic LCA
IFT88	Tg737 (mice)	Defects in photoreceptors with short outer segment, disorganized discs. Defects in cilia of kidneys, cystic kidneys [11,18]	Rod-cone dystrophy
	ift88-1 (*C. reinhardtii*)	Absence of flagellae [52]	
IFT81	-	-	Syndromic rod-cone dystrophy, non-syndromic cone-rod dystrophy
IFT70 (*DYF1*)	Dyf1/*fleer* (zebrafish)	Defects in axoneme. kidney cysts, left-right axis asymmetry, PR outer segment defects [53].	-
IFT56 (*TTC26*/ *DYF13*)	ttc26 knockdown, morpholino (zebrafish)	Left-right asymmetry, other ciliopathy-related phenotypes. Loss of photoreceptor OS.	-
	dyf13 mutant in C. *reinhardtii*	Short flagellae and motility defects [54]	
CLUAP1 (*IFT38*/*FAP22*/qilin)	au^{5} mutant in zebrafish	Curve in body axis, microphthalmia, absence of PR [26].	LCA
	Qilin^{hi3595A}(zebrafish)	Body curvature, kidney cysts, missing outer segments of PR [55]	
	Cluap1$^{-/-}$ mice	Embryonic lethal; absence of cilia in embryos [25].	
KIF3A	Kif3a^{flox}/*Kif3a*^{null} mice	Loss of PR, accumulation of opsin in inner segments [56]	

The table shows details of IFT loci, details of animal models with knockout of IFT loci, and human retinal dystrophies associated with IFT gene mutations.

in an insertional mutation in zebrafish, and mutants developed an absence of outer segments within the first few days of fertilization.

Apart from *ift88*, other intraflagellar transport protein genes appear to be essential for normal photoreceptor function, as observed in the corresponding zebrafish mutants. Knockdown of *ift172* led to similar changes as observed in *ift88* mutants, with a loss of outer segments, while mutants of *ift57* manifested with a milder phenotype of shortened outer segments and mislocalized rhodopsin [19,20]. A retinal dystrophy phenotype was also found in a zebrafish mutant in the *ift122* gene (designated as *jj263*) created with ethyl nitrosourea (ENU)-induced mutagenesis. The *jj263* strain had a nonsense mutation and manifested with early degeneration of photoreceptors leading to the absence of the outer nuclear layer, while the inner nuclear and ganglion cell layers were normal. In addition to the photoreceptor defects, the mutant fish had pronephric cysts within 6 dpf, and ciliary abnormalities in the hair cells of the inner ear [21]. Similar to other IFT mutants, the *ift122* mutants showed mislocalized opsin and disorganization of the outer segments.

In addition to the zebrafish model for *IFT172* knockout (mentioned above), a conditional knockout mouse model for the same gene (*Ift172* $^{fl/fl}$ iCre), showed similar defects in the retina. In this model, Cre recombinase was expressed under the control of the rhodopsin promoter, thus achieving knockout of *Ift172* specifically in the outer nuclear layer. Knockout mice showed mislocalization of rod outer segment proteins and early-onset retinal degeneration that closely followed the loss of *Ift172* expression [22]. These defects in opsin localization have been observed with conditional knockout of *Ift20* and *Ift140* as well, and the mutants had opsins accumulating in the inner segments and the synapses, with gradual degeneration of cones [23,24].

The *IFT38* (Gene ID 23059; OMIM 616787) gene encodes the clusterin-associated protein 1 (CLUAP1) that is part of the IFTB complex in vertebrates. Animal models such as the mouse and zebrafish with knockout of the *Cluap1* gene had multiple defects due to the lack of primary cilia. Homozygous knockout mice (*Cluap1*$^{-/-}$) showed embryonic lethality after 10 dpf. The knockout mouse embryos before 10 dpf showed loss of sonic hedgehog (*Shh*) activity, as well as a marked decrease in the expression of other targets of *Shh* (*Patched1* and *Gli1*) [25]. A zebrafish recessive mutant strain au^{5} carries a nonsense mutation at amino acid 41 of Cluap1, thus truncating the protein in the N-terminal part. The phenotype of the au^{5} mutant strain includes curvature in the body axis, microphthalmia, and abnormal photoreceptors that lack cilia and eventually, degenerated within a few days post-fertilization [26] (see Table 1).

Mutations in IFT genes in retinal disease: There are several genes encoding intraflagellar transport proteins that have been found to have mutations in patients with retinal dystrophies, including syndromic and non-syndromic retinal dystrophy. However, data reported thus far suggests that the mutations in each of these genes are exceedingly rare in the populations tested, with about one mutation-positive patient per 500–1,000 patients, selected for the relevant ciliopathy phenotypes. A common feature among individuals with mutations in any of the IFT genes as described below was the early onset of the disease, within the first few years of life.

Mutations in specific IFT genes occur in patients with syndromic and non-syndromic disease involving different types of retinal dystrophy. A missense change (c.296G>A; pCys99Tyr) in the *IFT27* (Gene ID 11020; OMIM 615870) gene (known as the *BBS19* locus) was identified in a consanguineous Saudi family who had two siblings affected with Bardet-Biedl Syndrome (BBS), both homozygous for this mutation. The affected siblings were in their second decade and manifested with polydactyly, obesity, intellectual disability, renal failure, and retinitis pigmentosa. The pathogenicity of the Cys99Tyr change was confirmed by failure of the mutant transcript to rescue the phenotype of *Ift27* morpholino-treated zebrafish [27]. Mutations in *IFT27* have also been reported in other patients with BBS. Compound heterozygosity for mutations c.104A>G (Tyr35Cys) and a splice site change c.350–2A>G were identified in a patient with typical features of BBS, by targeted next generation sequencing (NGS) with a custom gene panel [28]. In a later report of a patient with BBS, whole exome analysis detected compound heterozygosity for mutations of c.104A>G (Tyr35Cys), and c.349 +1G>T [29]. Prenatal mortality has been observed in cases of severe ciliopathies that are due to mutations in *IFT27*. Compound heterozygous mutations of severe impact-c.118_125del, p.(Thr40Glyfs*11) and a c.352 +1G>T were detected in a fetus with a renal agenesis, short ribs, polydactyly, and imperforate anus. This phenotype shows overlap with Pallister-Hall syndrome [30].

Another syndromic retinal dystrophy of the rod-cone type is associated with mutations in the *IFT81* (Gene ID 28981, OMIM 605489) gene: A deletion (c.2015_2019del (p.Asp672Alafs*15) mutation in *IFT81* was reported in a proband with early-onset rod-cone dystrophy and cerebellar atrophy. The deletion predicted the loss of the stop codon and extension of the reading frame by ten amino acids. In a second proband with a similar syndromic disease in this study, no retinal disease was evident on the fundus evaluation, although

the patient had polydactyly, intellectual disability, and nephronophthisis. The mutation identified in this case was c.1188 +1G>A, involving a conserved splice site [31]. In contrast to the above, compound heterozygous mutations consisting of a missense mutation (Leu614Pro) and a nonsense mutation (Arg405Ter) in the *IFT81* gene were detected in a patient with non-syndromic early onset cone-rod dystrophy. The clinical features were reduced vision and photophobia in childhood, and loss of color vision [32].

Different ciliopathy phenotypes comprising syndromic and non-syndromic disease have been reported in patients with mutations in the *IFT172* (Gene ID 26160; OMIM 607386) gene. Two affected siblings with a BBS-like syndrome consisting of retinitis pigmentosa, obesity, and other systemic abnormalities were compound heterozygous for two mutations in *IFT172*, one splice and one missense variant (c.1525 −1G>A; c.4701C>A (p.His1567Gln)). Further, autosomal recessive non-syndromic RP in two separate isolated cases was associated with missense (c.4815T>G; Asp1605Glu) or with compound heterozygosity for missense (c.770T>C; p.Leu257Pro) and splice (c.3112–5T>A) mutations, respectively, in *IFT172* [33].

Apart from the disorders mentioned above, mutations in *IFT* genes are associated with different forms of LCA. A proband from Saudi Arabia affected with LCA had visual acuity of light perception and nystagmus at 6 weeks of age. No systemic defects were noted. A C>T substitution in the *clusterin-associated protein 1* (*CLUAP1)* gene (Gene ID 23059, OMIM 616787) was identified with whole exome sequencing, as the molecular basis for the disease. This change, which predicts a substitution of phenylalanine for leucine, is designated as either c.817C>T or c.319C>T depending on whether the long or short isoforms of *CLUAP1* are considered, respectively. Thus, it may lead to a missense change of either Leu273Phe or Leu107Phe [34]. Syndromic LCA has also been associated with a mutation in the *IFT52* (Gene ID 51098, OMIM 617094) gene, consisting of c.556A>G leading to a missense substitution (pThr186Ala), discovered with whole genome sequencing. The disease in this patient manifested with severe visual loss from birth, eye rubbing and eye poking signs, mental retardation, growth retardation, and skeletal defects. The pThr186Ala mutation was predicted to be damaging to the protein. In vitro, the mutation appeared to lower the stability of the protein and decrease the length of the cilia in the transfected cell lines [35].

Analysis of non-syndromic, early-onset rod-cone degeneration in a consanguineous Pakistani family with multiple members identified mutations in the *IFT43* (Gene ID 112752, OMIM 614068) gene. The mutation c.100G>A (p.Glu34Lys) in *IFT43* cosegregated with the disease in the family and was absent in various healthy populations [36]. The patients had night blindness by 5 years of age, disc pallor, attenuated vessels, and pigmentary deposits within the retina. The mutation caused defects in the cilia of cells transfected with the mutant gene, with possible aggregation of the protein.

The involvement of the *IFT88* (Gene ID 8100, OMIM 600595) gene in human retinal disease was confirmed with the detection of compound heterozygosity for a nonsense mutation and a missense mutation (Arg266Ter (c796C>T) and Ala568Thr (c.1702G>A)) in two siblings with rod-cone dystrophy, with whole genome sequencing. These mutations were also shown to result in defective or absent cilia when expressed in genome-edited HeLa cells [37]. An apparent difference in the phenotypes in these patients was the age of onset of the disease, which was in the second to third decades of life, unlike the cases with mutations in other *IFT* genes discussed. This feature does not correlate with the nature of the mutations found among all these cases, which include stop and missense changes.

In addition, pathogenic changes in the *IFT140* (Gene ID 9742, OMIM 614620) gene have been reported in families of Han Chinese and European ethnicity with non-syndromic RP and LCA [38]. These changes included various missense and frameshift mutations identified in seven families. In one proband with typical features of RP, compound heterozygosity of missense and frameshift changes (c.T4196C (p. Leu1399Pro) and c. 1898_1901delATAA (p. Asn633Sfs*10)) were found. Another patient with adult-onset RP was compound heterozygous for missense mutations Gly1276Arg and Cys663Trp. A patient with LCA had missense changes of Thr484Met and Cys329Arg. The remaining patients studied were also compound heterozygous for mutations in *IFT140.*

Mutations in the *KIF3B* (Gene ID 9371, OMIM 603754) subunit of the heterotrimeric kinesin-2, the motor component of IFT, were recently reported in a syndromic ciliopathy in two families. Exome sequencing revealed a substitution of c.748G>C leading to missense mutation Glu250Gln in a heterozygous proband with retinitis pigmentosa, polydactyly, and hepatic fibrosis. In addition, a second missense change Leu523Pro (c.1568T>C) was identified in a second family with retinitis pigmentosa. Expression of these mutant transcripts in zebrafish led to the retention of rhodopsin in the inner segment of the photoreceptor (PR), with an increase in ciliary length [39].

Conclusion and remaining questions: The IFT proteins impact a variety of sensory and motor processes through ciliary transport. In addition, these proteins are involved in cellular processes other than transport. For example, IFT188

affects mitosis, and alterations in the expression of this gene lead to deregulation of cell proliferation. Another IFT protein, IFT20, is involved in recycling of T-cell receptors. IFT20 also functions in the Golgi, in the sorting of ciliary proteins [6]. The IFT proteins may also mediate vesicular transport particularly in relation to the Golgi apparatus. IFT20 has been observed to colocalize with the post-Golgi transport vesicles in photoreceptors, secondary neurons, and non-neuronal cells of the retina [16]. These observations suggest a variety of functions performed by the IFT proteins, and these aspects need to be explored further to understand the whole spectrum of their physiologic actions. IFT proteins have been detected in non-ciliary parts of the retina, suggesting that these proteins could have non-ciliary functions. Other critical gaps in this field are in the determination of the factors involved in controlling the length of cilia, which grow to a defined extent during ciliary growth and regeneration. There are yet many unanswered questions regarding which factors control ciliary length [40]. An emerging facet of IFT proteins is their participation in the regulation of autophagy, which is linked to ciliogenesis, and in the modulation of the lysosomal pathway. These effects on lysosomal degradation and autophagy, as observed in an *Ift20* knockout mouse model, in turn, impair the recycling of endosome-associated T-cell receptors and have wider effects on the differentiation of T-cells. These findings ascribe a role for *IFT20* in controlling immune responses as well [41,42]. Knowledge of these and other biologic effects of the IFT proteins will help to further unravel the pathogenic basis of the associated diseases.

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