REVIEW

Ciliary syndromes and treatment

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Received 27 December 2006; accepted 30 October 2007

Abstract

Abnormal visceral patterning has been known for centuries. However, it has not been associated with ciliary dysfunction until recently. Overlapping clinical entities including situs inversus, certain infertility disorders, as well as chronic respiratory infections have their roots in abnormal ciliary function. Current research focuses on causative factors and genes involved in signal transduction pathways that define ciliary function and structure, as well as treatment. In this review, attempts are made to outline selected, yet key topics related to ciliary function in health and disease.

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Keywords: Cilia; Ciliary dysfunctions; Mouse model; Treatment

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doi:10.1016/j.prp.2007.10.013
Cilio- and flagellopathies: two decades of extraordinary discoveries

Driven by realization that numerous proteins involved in mammalian diseases localize to basal bodies and cilia and that the aberrant ciliary function can be linked to a large number of human diseases and syndromes, extraordinary progress has been achieved over the past two decades. Cilia are present on the majority of mammalian cells throughout development and in adult life of an organism, and have been found to be associated with a variety, often overlapping, of clinical abnormalities affecting the function of numerous tissues and organs including epithelium of the respiratory tract, oviduct, testes, brain, kidney, eye, inner ear, and olfactory epithelium. Defects in the respiratory tract manifest as rhinitis, sinusitis, otitis media or bronchiectasis. Male infertility may result from abnormalities in the sperm flagellum, while females can suffer from oviductal cilia defects. In the kidney, defects in renal primary cilia leads to polycystic kidney disease (PKD). Ciliary defects in the choroid plexus of the brain may result in hydrocephalus. Abnormal cilia in hair cells of the ear or nasal epithelium can cause cochlear or olfactory impairment, respectively.

A wide variety of studies of organisms ranging from bacteria to man have greatly enhanced our understanding of the association between cilia and human pathologies. Lower organisms have provided a wealth of knowledge about ciliary structure and function, including basic molecular events such as intraflagellar transport. However, for their genetic malleability and mammalian similarities, rodent models have played a pivotal role. In numerous instances, mouse and rat mutants have proven to be exceptionally useful in recapitulating some of the clinical phenotypes of human ciliopathies. Experiments with rodents continue to provide an increasing supply of disease-causing and modifier genes, which helps elucidate pathogenic mechanisms and test the effectiveness of therapeutic interventions.

Ciliary structure and function

Common ciliary components and their structural arrangement are depicted in Fig. 1. Typical cilia range in size from 5 to 6 μm and are composed of two central and enveloped microtubules with nine microtubular doublets surrounding the central doublet and attached to it by radial spokes [39]. The outer doublet microtubules are connected to one another by nexin. The structural scaffolding of the cilium is composed of central sheath, radial spokes, and nexin molecules, while the dynein arms are responsible for motility.

Cilia are anchored into the cell membrane by cytoplasmic microtubules and the basal body. Orientation of basal root, a part of the basal body, is responsible for the directions of cilial stroke. Propulsion occurs via a two-beat cycle. The first part of the cycle is energy-dependent, where the retracted cilia extend perpendicularly to the cell surface creating characteristic ciliary propulsion. The second part of the cycle is energy-independent, where the cilia return to their resting position near the cell surface. These complex movements are due to dynein arms from the β subunit binding the α subunit of an adjacent microtubule. Hydrolysis of adenosine triphosphate (ATP) is utilized by dynein molecules. Initiation of the beat cycle is an “all-or-nothing” phenomenon [2,93].

Kartagener syndrome and primary ciliary dyskinesia

The discovery of ciliary-associated syndromes and diseases dates back to the 17th century when Hieronymus Fabricius described situs inversus in 1606 and Marco Severino noted the pathology of dextrocardia in 1643. More than 100 years later, Matthew Baillie described the phenomenon of mirror-image reversal of thoracic and abdominal contents. Subsequently, in 1933, Manes Kartagener noted and fully described the triad of symptoms known today to be associated with ciliary dysfunction and referred to as Kartagener syndrome [81].

The body plan and organ layout resulting from congenital ciliary disorders can be categorized based on either situs orientation, asymmetry of unpaired organs, or asymmetry of paired organs. While anatomically correct orientation of organs is known as situs
solitus, complete inversion of thoracic and abdominal contents is known as situs inversus. Complete situs inversus promises good prognosis for the patient, including normal life span and physical capabilities. Syndromes with ambiguous organ positions, or heterotaxia, indicate failure of asymmetry of unpaired organs, where at least one organ shows a reversed orientation along the left–right axis. This condition is often associated with heterogeneity of cardiac defects [32,59]. Heterotaxia is frequently associated with isomerism. This term refers to a defect in asymmetry of paired organs that normally have distinct right and left forms but, in this condition, are mirror images. While left isomerism is often associated with polysplenia [59,138], right isomerism is often coupled to asplenia [32,154].

The incidence of situs inversus is rather rare, averaging about 1:20,000 births with no gender preference. A fraction of these patients are also diagnosed with Kartagener’s syndrome (<25%) [83], a condition manifested by a triad of situs inversus, chronic sinusitis, and bronchiectasis [3,39]. Although the most common form of inheritance is believed to be autosomal recessive, other forms of Kartagener’s inheritance have been noted [111]. Kartagener syndrome is classified as a subset of primary ciliary dyskinesia (PCD) with about 50% of PCD patients typically diagnosed with it. PCD has been extensively studied and linked to genes and proteins responsible for maintaining the structure, mechanical power, and motility of cilia; hence, hindering many physiological processes dependent on cilia and flagella [157]. Mutations in two proteins have been linked to PCD: DNAI1 and DNAH5 [77,158].

**Ciliary function in left–right patterning**

Recent findings have not only implicated cilia in Kartagener syndrome but also in initiation of body-plan layout. It is in the nodal region of the gastrulating embryo that roughly 200–300 ciliated cells are thought to initiate left–right (LR) asymmetrical gene expression leading to proper orientation of viscera [99]. Prior to the era of transgenic mammalian models, it was not clear if cilia might be involved in asymmetrical patterning of viscera. Strong support of this theory was based on studies of knockout mice.

There are two types of cilia in the node: motile cilia containing LR dynein and immotile cilia containing polycystin-2 [100]. It is believed that motile cilia induce the leftward fluid flow, while immotile cilia sense the nodal flow initiating asymmetric calcium signaling at the left border of the node [27]. KIF3A and KIF3B are members of a kinesin superfamily of proteins, which together with an accessory protein (KAP3) form a complex involved in ciliogenesis and organelle transport in many cell types. Ablation of the Kif3B gene coding for microtubule-dependant motor [116] causes lack of monocilia in the node and results in improper LR asymmetry development and gestational lethality [97,145]. A mouse strain carrying a mutation in Kif3A was also obtained [145]. A loss of motile nodal cilia occurs in both these models supporting the notion that cilia-induced fluid movement from the right side of the node to the left side determines the LR asymmetry axis. This fluid flow occurs well in advance of any physiologically detectable LR asymmetry development [118].

In the mouse, the leftward flow of fluid is responsible for breaking the bilateral symmetry of the embryo and is also likely responsible for induction of asymmetrical gene expression via increasing morphogen concentration on the left side of the embryo. Besides factors such as sonic hedgehog, FGF1, and nodal, a large number of genes may be involved in morphogen signaling. For example, there are five members of the RFX family of transcription factors in mammals (RFX1–5). Rfx3-deficient mice have been generated and shown to exhibit frequent LR asymmetry defects leading to a high rate of embryonic lethality and situs inversus in surviving adults [19]. In an ethylnitrosourea screen for genes involved in embryonic patterning, a wimple (wim) mouse mutant was identified [78]. Cilia in nodal cells were absent in these mutants. Genetic analysis has proven that wim is required for hedgehog signaling at a step downstream of Patched1. Shortly after leftward fluid-flow initiation, expression of the nodal gene is restricted to the left side of the node at embryonic day 8.5 [37,94,95]. Lateralization of nodal on the left of the embryonic node is crucial for LR patterning [20,115]. Thus, a large body of evidence indicates that cilia play a critical role in early stages of embryonic development, when LR asymmetry is established.

**Retinitis pigmentosa**

Retinitis pigmentosa (RP) is the most common form of inherited blindness. There is a genetic heterogeneity of retinal dystrophy and a large number of genes (>100) implicated in its pathogenesis. RP occurs as an isolated disease or in association with certain systemic abnormalities such as Usher and Bardet–Biedl syndromes (BBS).

Photoreceptors are highly remodeled neuronal cells with specialized compartments. Synthesis of pigments takes place in the inner segment of the rod, and then these pigments are transported to the outer part for stacking in disks. The transport occurs via a narrow ciliary connection. Being a component of the rod through which the transport of proteins and pigments occur, the connecting cilia are involved in several aspects of RP. Genes that regulate intraflagellar transport have been shown to distort the deposition of various...
photorceptor components leading to cell death. One example is Kif3A, whose disruption accumulates rodopsin and arrestin in the inner segment of the rod [96]. Early degeneration of photoreceptors occurs in Leber congenital amaurosis [5,40,48,61,87], which is caused by mutations in multiple genes. Some of these genes operate within retinal pigmented epithelium, while others are expressed in photoreceptors [40,52]. Examples include retinitis pigmentosa GTPase regulator (RPGR) and RPGR-interacting protein (RPGRIP). Both RPGR and RPGRIP localize to the connecting cilia of rods and cones [74,103] and are involved in protein trafficking. Mouse model of RPGR revealed that disruption of this gene leads to both rod and cone photoreceptor degeneration [76]. This implies a role for RPGR in maintaining the polarized protein distribution across the connecting cilium by facilitating directional transport or restricting redistribution of cellular compounds. RPGRIP ablation revealed more severe degenerative phenotype relative to RPGR [129,162].

With many causative genes of RP identified, the replacement therapy protocols are now under development. The eye is an easily accessible target organ with non-invasive techniques available to monitor the effects of treatment. In the rodent model, several successful gene replacement attempts have recently been reported [75,85,123].

Bardet–Biedl syndrome and ciliary defects

The first cases of BBS, reported in 1866 by Laurence and Moon [89], were marked by overall impairment, mental disabilities, obesity, and retinal degeneration. Several decades later, Bardet and Biedl added additional features of polydactyly and hypogonitalism [11,17] to the list of characteristic phenotypes. It is widely recognized now that the syndrome is highly pleiotropic with poly cystic kidney and complications from obesity, type II diabetes, hypertension, and hypercholesterolemia, most often leading to premature death [14]. BBS is considered to be a developmental and rare disorder averaging ~1:120,000 in the US and Europe [15,41,86] although higher prevalence has been reported in more isolated regions [51,64]. It has been proposed that clinical diagnosis should rely on the presence of four out of six primary symptoms [14]: obesity, rod–cone dystrophy, renal abnormalities, polydactyly, male hypogonadism, and learning disability. While certain symptoms, such as polydactyly or hyperechoic kidneys, may be detectable in utero or at birth [28], other manifestations are recognizable later in life, such as retinal degeneration, genital abnormalities, and obesity.

The pleiotropic nature of BBS is reflected by 12 genes (BBS1–12) identified thus far by linkage analysis and positional cloning [82,107,113,140,142], microarray genotyping [30,143], and other approaches [6,8,31,50,91,110,114]. BBS1 and BBS10 were found to be the most commonly mutated genes in BBS [13,70,109,142]. Most of these genes encode diverse components directly involved in ciliary function including intraflagellar transport (BBS1–8), while others present a challenging molecular conundrum. For example, BBS11 has E3 ubiquitin ligase activity that may play a role in ubiquitin/proteasome system function [30], while BBS12 is a Type II chaperonin [143] likely involved in protein folding. It remains to be established how ubiquitin ligation or chaperonin activities translate into the BBS phenotypes.

For the number of genes involved, the modeling of pleiotropic syndromes is complex. However, two orthologues of human BBS genes, Bbs2 and Bbs4, have been knocked out in mice and analyzed. The Bbs4 disruption recapitulates certain aspects of human BBS such as obesity, infertility, and retinal degeneration [108]. Remarkably, Bbs4−/− mice have normal primary cilia; however, they display compete lack of flagella formation during spermatogenesis. Retinal degeneration via photoreceptor loss was also observed in these mice, indicating involvement of Bbs4 in maintenance of sensory cilia. Similar phenotypes were seen in Bbs2 knockout mouse studies. Bbs2−/− mice reveal retinal degeneration, failure of flagella formation, obesity, and renal cysts development [112].

Polycystic disease

Polycystic diseases (PD) belong to a class of extremely heterogeneous disorders that can be characterized by the formation of cysts. Cysts primarily develop in the kidneys but have also been noted in the pancreas and liver [18,161]. The underlying cystogenesis process involves an ever-increasing list of proteins (reviewed in Refs. [73,139]), many of which are found in clinically distinct conditions such as Bardet–Biedl or Meckel–Gruber syndromes with ciliary hypothesis unifying their biological role.

Much effort has been devoted to studies of PKD and associated defects resulting from abnormal function of the primary cilium present on the luminal face of tubular epithelium. There are basically two forms of PKD: autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD), both debilitating causes of renal failure, morbidity, and mortality in adults and children. ADPKD is common (1/500–1000) [25], with about 50% of patients dying in the fifth to sixth decade of life due to renal failure. The causative genes for ADPKD encode a large membrane protein, polycystin-1 (PC1) [1,23,79] and polycystin-2 (PC2) [69,104]. The latter belongs to the family of transient receptor potential (TRP)
channels that regulate the flow of Ca^{2+} and several other cations (reviewed in Ref. [45]). ARPKD has been linked to a single genomic locus, PKHD1 [119,150,155]. PKHD1 encodes fibrocystin (FC), a membrane glycoprotein with a large extracellular domain. Although different in the pattern of inheritance and basic clinical manifestation, ADPKD and ARPKD share certain similarities, including tubular epithelial proliferation characteristics, elevated apoptosis, and localization of causative proteins in primary cilia [98,124,151,156].

Pathology and genetics of PKD has been extensively reviewed [18,45,67,127,152,161]. Here, it is worth noting that no effective therapy for ADPKD or ARPKD exists. However, numerous animal models of PKD have been developed in recent years, such as cpk, bpk, orpk, pcy, and Pkd2^{WS25} mice [148]. Although none of these models may be entirely satisfactory in recapitulating clinical phenotypes of human ADPKD or ARPKD, this large group of mutant models offers hope for swift progress on mechanistic aspects of PKD and the development of novel, animal-testable pharmacological approaches. Animal testing needs to be considered before clinical trials are attempted. An excellent example has been recently reported where long-lasting arrest of PKD in jck and cpk mice has been demonstrated by the administration of a drug, rescovitine [22].

Recently, several genetic factors involved in pancreatic cyst formation have been identified. One example is the hepatocyte nuclear factor-1β (HNF-1β) that directly controls expression of genes critical for cilia formation in epithelial cells of ducts. Genes under control of HNF-1β include cystic disease genes such as Pkhdl and Pkd2 [65,71,72]. Mice lacking HNF-1β develop cysts in the kidneys and pancreas. Pancreatic cysts were also demonstrated in orpk mice deficient in the ciliary protein polaris [26,159]. Also, knockout mice lacking the transcription factor Hnf6 that regulates HNF-1β expression both in the liver and pancreas have been shown to develop biliary cysts in the liver [33]. Hnf6 is essential for differentiation of certain segments of pancreatic ducts and is required for the formation of primary cilia. In the absence of the gene, cysts develop within the interlobular and intralobular ducts [126].

**Ciliary cells and genes in hydrocephalus**

Hydrocephalus is a condition characterized by the excessive accumulation of cerebrospinal fluid in the brain ventricles. The fluid accumulation is often associated with an impaired fluid flow. The cerebrospinal fluid is produced mainly by a highly specialized secretory neuroepithelium of choroid plexus. The choroid plexus cells contain microvilli and cilia: both important components of the secretory function. The fluid circulation through the brain’s ventricles is thought to depend on orchestrated beating of cilia on these ependymal cells.

Mice with a disrupted E2f-5 transcription factor display congenital non-obstructive hydrocephalus [92]. The expression of E2f-5 is limited to choroid plexus, and in the absence of the gene, epithelial cells seem to display excessive secretory activity. A mutation of Mdnah5 also affects the mouse brain causing hydrocephalus [80]. The Mdnah5 disruption affects ependymal cilia, and this, in turn, inhibits the flow of fluids between the third and fourth ventricles causing the aqueduct of Sylvius to become occluded. The hydrocephalus has also been observed in the mouse mutants of Spag6 or Hydin, the transcription factor Hfh4 (Foxj1), and the intraflagellar transport controlling gene, Tg737, encoding polaris protein [10,26,106,146,159,160]. Yet another gene, Rfx3, whose mutation causes hydrocephalus, has recently been identified [7]. Mice deficient in Rfx3 revealed abnormal differentiation of the ciliated ependymal cells, quantitative ciliary deficit, and poorly developed microvilli within the choroid plexus. Thus, proper aqueduct function relies on cilia-induced movement of fluid.

**Cilia in the Meckel–Gruber syndrome**

Clinical cases of the Meckel–Gruber syndrome (MKS) were first described by Johann Friedrich Meckel in 1822 [102] and then further delineated by Georg B. Gruber [66]. MKS is an autosomal recessive lethal disorder displaying a significant phenotypic variation, but its classical manifestation involves a triad of symptoms: cystic kidneys (100% of cases), occipital encephalocoele (90%), and polydactyly (80%) [4,136,137]. The diagnosis of MKS was based on the presence of two classical symptoms and one associated phenotype [101], or one classic feature and two other relevant anomalies [57]. The MKS-associated anomalies include post-axial polydactyly, cleft lip and/or palate, laterality defects, and congenital heart malformations such as dextrocardia, shortening and bowing of the long tubular bones, ductal malformations of the liver, cystic dysplasia of the kidney, and incomplete development of the male genital organs.

Similar to other ciliary syndromes, the high degree of phenotypic variability in MKS indicates genetic heterogeneity. In humans, three genomic loci have been documented as associated with the disease, and two genes have been identified: MKSI [88] and MKS3 [141]. MKSI is broadly expressed and found in numerous tissues including brain, liver, kidney, and cartilage of the developing digits. Its presence within flagella and basal body proteome offers a mechanistic link between molecular and clinical manifestation of MKS [9,62,120,121]. The MKS3 gene [105] encodes meckelin,
a widely expressed protein with highest levels reported in embryonic adrenal gland, brain, kidney, lung, and spinal cord. In recent studies, both MKS1 and meckelin have been localized to epithelial cells, including proximal renal tubules and biliary epithelial cells [43]. While MKS1 operates primarily in basal bodies, meckelin functions both in the primary cilium and in the plasma membrane of ciliated cell-lines and primary cells. Concerted action of both proteins seems to play an essential role in centriole migration to the apical membrane and consequent formation of primary cilium.

The rat (wpk) model with a missense mutation in MKS3 orthologue [58,141] is available. Wpk animals develop PKD and extensive malformations of the central nervous system such as hypoplasia of the corpus callosum and hydrocephalus. Rodent models of MKS with the disrupted orthologue of MKS1 gene are yet to be developed.

Ciliary dysfunction in oral–facial–digital type I syndrome

First reported by Papillon-Leage and Psaume in 1954 [122], the oral–facial–digital type 1 (ODF1) syndrome was further defined by Gorlin and Psaume [63] in 1962. It is a heterogeneous developmental disorder with a range of characteristic clinical features including facial dysmorphism (facial asymmetry, broad nasal ridge, facial milia, hypertelorism, micrognathia), oral cavity malformations (cleft upper lip, palate and tongue, oral frenulae, thickened alveolar ridges, abnormal dentition), digital abnormalities of the hands and the feet (syndactyly, brachydactyly, clinodactyly or polydactyly), the involvement of the CNS (hydrocephalus, anomalies of cerebellum and corpus callosum, mental retardation, porencephaly [36,46,149,153]), and polycystic kidney [34,36,47,53]. Although other oral–facial–digital syndromes [147] with overlapping clinical manifestations are known, one distinct feature of ODF1 is the causative gene, ODF1 (also known as Cxorf5/71-7a), which maps to chromosome X [54,55,60]. While MKS3 orthologue is available, Wpk animals develop PKD and extensive malformations of the central nervous system such as hypoplasia of the corpus callosum and hydrocephalus. Rodent models of MKS with the disrupted orthologue of MKS1 gene are yet to be developed.

Diagnosis of symptoms associated with primary ciliary dyskinesia

Diagnosis of symptoms associated with primary ciliary dyskinesia

Diagnosis of PCD, which includes situs inversus and/or Kartagener syndrome, is usually made early in life by detecting chronic respiratory infections [117] and, occasionally, by infertility after puberty in males. Early diagnosis is important as it may reduce long-term pulmonary morbidity. It is usually confirmed by electron microscopy, biopsy, CT, MRI, or X-ray imaging [24,38,84,117]. Prenatal diagnosis also can be made through the use of ultrasound imaging. All of these techniques provide for accurate diagnosis; however, operator error and improper labeling of hospital charts should be considered. Additional imaging techniques such as angiography need to be used when cardiac anomalies are suspected.

Due to the requirement of rapid diagnosis, microscopic examination is often performed during surgical intervention [16]. Although tracheal biopsy and light microscopy alone is neither accurate nor sufficient for proper diagnosis, it nevertheless provides a quick means of eliminating PCD from the differential diagnosis list. A combination of biopsy examination with electron microscopy seems more accurate. Electron microscopy continues to be the gold standard [38,117] that is available in specialized centers worldwide.

Other quick means of analysis of PCD include quantification and observation of ciliary beat frequency and waveform. Normal frequency varies from 12 to 14 Hz and can be visualized on high-speed video, laser, or other photoelectric systems. Slow-motion replay of the functional cilia provides for analysis of both beat frequency and waveform [133]. This can be accomplished by collecting nasal mucosa cells from the inferior
turbinate, washing, culturing the cells at 37°C, and subsequent examination [133,134]. Reduced ciliary beat frequency, ~8 Hz, uncoordinated, vibrational, rotary, or diminished movements are all characteristic of PCD [132–135]. This poorly coordinated movement can be exploited clinically to diagnose suspected patients (mainly in specialized centers). It is relevant to note that some patients with PCD have normal ciliary beat.

Ciliary mucus movement transfers saccharine placed on the anterior end of inferior turbinate to the oral pharynx where it can be tasted. In affected individuals, this process takes more than 60 min, while in unaffected people, it takes anywhere from 10 to 20 min [135]. However, the saccharine test is impractical in a pediatric setting because voluntary immobilization of a child over an extended period of time is difficult to achieve.

Given the genetic heterogeneity of PCD in combination with structural and functional complexity of cilia, genetic testing should be considered. Testing for the level of nasal nitric oxide (NO), which is significantly lower in PCD patients, offers a very useful and practical addition to the methods mentioned above [117].

Treatment of patients with ciliary-associated diseases

Treatment of patients with CF and non-CF bronchiectasis, which tries to improve symptoms of cough, sputum production, dyspnea, and prevent the progression of airway damage by recurrent infections (reviewed in Refs. [90,131]), can be extrapolated, in part, to PCD and other ciliary syndromes. In PCD, airway clearance, exercise, and early use of antibiotics are all very important. Medical intervention usually consists of treatment of sinusitis and otitis media. Surgical intervention may be needed to treat localized disease, or when cardiac anomalies are present. Antibiotics are recommendable such as sulfamethoxazole/trimethoprim or amoxycillin/clavulanate. However, prolonged use of these antibiotics may lead to the development of resistant strains. The most efficient selection of drugs is based on culture determination and antibiotic susceptibility testing. Additional similarities to the bronchiectasis treatment include vaccination against influenza viruses, *Streptococcus pneumoniae*, and *Haemophilus*. Some of the more common infections include *Haemophilus influenzae* (most common) followed by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Streptococcus* species [117,125].

Asplenic individuals with ciliary disorders have been documented [12,35,44,68,128]. Asplenia and hypospleenia are relatively rare conditions, often associated with congenital heart disease. Patients without spleen are at lifelong risk of sepsis caused by bacteria and, occasionally, protozoa. The spleen is a major site of antibody production, while splenic macrophages help remove bacteria by phagocytosis. The most common infecting organism is *Streptococcus pneumoniae* and *H. influenzae* type b, but other bacteria such as *Staphylococcus aureus*, *Salmonella* species, *Neisseria meningitidis*, *E. coli*, *Capnocytophaga canimorsus*, and *P. aeruginosa* also present a significant risk [21,29,42].

Advisable prophylaxis and management should include patient and family education, vaccination, and chemoprophylaxis. It is extremely important that asplenic individuals are aware of the risks of not complying with preventive doctor’s recommendations and should avoid traveling to areas where malaria or babesiosis are endemic. It is also recommended that patients be cautioned regarding unexplained fever that must be treated as a medical emergency. After prompt consultation with the primary physician, such an emergency may require “empirical therapy” using antibiotics effective against most frequent bacterial causes [144]. Immuno-preventions should consist of vaccinations routinely prescribed to normal individuals and additional vaccinations directed against encapsulated bacteria. Although there is no agreement in literature regarding the application of chemoprophylaxis in adult asplenic cases, antibiotics should be strongly considered in asplenic children younger then 5 years of age.

Conclusion

Since Hieronymus Fabricius in 1606 first discovered *situs inversus*, a great deal of empirical data has been collected on ciliary dysfunction. Undoubtedly, conclusion of the human genome project in 2003 and the future functional annotation of genes will play a critical role in cataloging key genes and proteins involved in both ciliary dysfunction and *situs inversus*. Current understanding of Kartagener syndrome and uncertainty why only about 50% of people with *situs inversus* display PCD could change in the light of new developments and discoveries. Future experiments on LR patterning of embryos and the role of ciliary cells in mature organisms may yield new procedures and technologies to supplement existing clinical applications. Once most of the genetic factors are identified, novel screening assays for parents-at-risk may be feasible.

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