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Guest Editorial

Medical genetics of ciliopathies

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Neither of us had heard about the existence of cilia during biology or genetics courses in high school or university. Nonetheless, these evolutionarily conserved, antenna-shaped organelles of the cell appear to be essential for human development and proper functioning of our organs. Inheritance plays an important role, because genetic defects causing disruption of cilia or ciliary signaling pathways have been shown to result in more than twenty human disorders, collectively known as ciliopathies. While these disorders are each individually rare, many pediatricians and geneticists encounter patients with a ciliary disorder in the clinic. It is therefore important to educate clinicians about cardinal signs of ciliopathies, ciliary disease genes and molecular disease mechanisms. After reading this special ciliopathies issue, specialists should have a good perspective on how to diagnose, manage and treat ciliary disorders occurring in the pediatric clinic in a multidisciplinary team.

The disorders that are discussed in this issue are quite diverse, but can be categorized in two groups based on the occurrence of two types of cilia, i.e. motile (actively moving) cilia and immotile (sensory or primary) cilia. The differences in function and ultrastructure between motile and immotile cilia are discussed in detail in the first review. With respect to disease, the majority of ciliopathies result from defects in sensory cilia that occur almost ubiquitously throughout the human body. The only "motile" ciliopathy that is discussed in this issue is primary ciliary dyskinesia, a disorder that affects the upper and lower respiratory system (and often coincides with sub- or infertility). The non-motile ciliopathies that are reviewed in this issue include ciliary chondrodysplasias (short rib-polydactyly syndromes, cranioectodermal dysplasia, Jeune syndrome and Ellis-van Creveld syndrome), neurological disorders (Joubert- and Meckel-Gruber syndrome), isolated- and syndromic obesity (Bardet-Biedl and Alström syndrome), and renal cystic disorders such as autosomal recessive polycystic kidney disease and nephronophthisis. Finally, since it is slowly becoming clear that neoplasms and tumor predisposition syndromes, like von Hippel-Lindau disease, are part of the ciliopathy spectrum as well, this review also presents a hypothetical model about the connection of cilia and tumorigenesis.

A recurrent theme in this issue is how next-generation sequencing has revolutionized gene identification and genome diagnostics in the ciliopathy field. Given the enormous heterogeneity in nearly all ciliopathies, this new technology that allows us to screen gene panels, all coding DNA or even whole genomes in a single experiment, is a great help for clinicians to provide patients and their relatives with a fast, early and accurate diagnosis and prognosis. Moreover, options for genetic counseling and preimplantation genetic diagnostics for ciliopathy families also tremendously improve after mutation detection. Finally, genetic insights into the underlying causes

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of ciliary disorders open avenues for the development of targeted and personalized treatments. The latter is in particular important for disorders with a relatively late-onset and/or slow progression where there is a window of opportunity to delay or prevent disease, e.g. renal cystic disease, primary ciliary dyskinesia or cancer. However, while identification of pathogenic mutations in known and new ciliary genes through next-generation sequencing is advancing rapidly (more than 100 ciliopathy genes have thus far been identified), translation of genetic insights into (personalized) therapy is the next hurdle to take. Nonetheless, advances in gene therapy and pharmacogenetic testing support that we can increasingly use genetics for personalized medicine in ciliary disorders.