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OPHTHALMOLOGY
Editorial

Ciliopathies and Revisiting Syndromes

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Received: October 20, 2015; **Published:** December 01, 2015

The word "syndrome" (An abnormal condition or disease that is identified by a set group of physical signs and symptoms) has been fascinating, yet tiring for all those studying medicine. The number and variety of syndromes we have to know and study has been overwhelming thanks to the descriptive use of the term. Sometimes more than 5 different names were used to describe the same disease presenting by different clinical manifestations each time.

The great advances in cytogenetics in the last 50 years, is promising to put an end to this dilemma by re-classifying syndromes according to "specific" genetic defects.

What complicate the current knowledge in cytogenetic and gene-related classification of diseases and syndromes are that several genes, and hence several protein products, when defective, can have the same clinical presentation or phenotype.

A disease as classic as retinitis pigmentosa (pigmentary retinopathy or pigmentary retinal dystrophy), can result from more than 10 genetic defects affecting different genes on different chromosomes.

I cannot forget wondering what links retinitis pigmentosa, an accessory finger (polydactyly) and hypogonadism in the same child presenting with Bardet-Biedel syndrome when I saw the first case more than 20 years ago.

Finally I got the answer after all those years it is the "same" protein that links all these manifestations and it is not in those diverse structures but it is a protein of "cilia".

Ciliopathies are diverse developmental and degenerative single-gene disorders such as polycystic kidney disease, nephronophthisis, the Bardet-Biedl syndrome, the Joubert syndrome, and the Meckel syndrome- a recent concept that describes diseases characterized by dysfunction of a hair-like cellular organelle called the cilium [1].

The notion of a "ciliopathic" disorder was first attributed to Bardet–Biedl syndrome (BBS), when Ansley and colleagues identified genetic mutations in BBS8 whereby the encoded protein was noted to have a pilF domain, suggesting a conserved role for BBS8 in prokaryotic pilus formation. Subsequent immunohisto chemical analysis confirmed the localisation of BBS8 to centrosomes and basal bodies within human embryonic kidney cells, spermatids and the cilium connecting the inner and outer segment of photoreceptors [2].

Bardet–Biedl syndrome

Primary features of Bardet–Biedl syndrome include rod-cone dystrophy, polydactyly, obesity, learning disabilities, hypogonadism and renal anomalies. Renal malformations and abnormal renal function leading to end-stage renal disease (ESRD) can be a major cause of morbidity and are present in at least 40% of cases.

Sixteen genes are known to be associated with BBS. Furthermore, previous studies have shown that the BBS phenotype can vary considerably within affected families. Some of this intrafamilial variability can be accounted for by the presence of mutations at more than one BBS locus as well as the presence of additional modifying genes that exert an epistatic effect on known BBS loci. For example,

heterozygous mutations in MGC1203, which encodes a pericentriolar protein that interacts with BBS proteins, have been described in BBS patients [3].

Ciliary dysfunction and retinal disease

Degeneration of the retinal photoreceptors is a common feature of ciliopathies. Fundoscopic appearances include optic disc pallor, arterial attenuation, pigmentary changes within the peripheral retina and bone spicule formation. Several proteins implicated in human ciliopathic diseases have been localised to the photoreceptor cilium that connects the outer and inner segments of photoreceptors. Arrestin, transducin and opsin molecules are synthesized within the inner segment and are then transported in a light-dependent manner along the connecting cilium to the outer segment [4]. About 2,000 rhodopsin molecules per minute are transported to the outer segment via the connecting cilium to compensate for lost material each day when at least 10% of the distal ends of the photoreceptor outer segments are shed and phagocytosed by the surrounding retinal pigment epithelium [4].

Retinal degeneration has been associated with increased cell death in murine models of Bbs [5]. A range of photoreceptor abnormalities has been described in several murine ciliopathy models and includes the absence of outer segments, disorganised outer segments or photoreceptor degeneration without any obvious abnormalities in photoreceptor morphology. Future studies will need to address the specific molecular defects that become dysregulated in ciliopathic retinal degeneration.

When I last saw a new case of Bardet-Biedl syndrome a couple of weeks ago, I was no longer perplexed by the diverse manifestations of the disease, as I now know what links our eyes, hands, hearts and sperms, it is that protein present at the base of our non-motile cilia. Thanks to all those scientists who cleared the way.

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Volume 3 Issue 1 December 2015