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Senior–Løken syndrome: A syndromic form of retinal dystrophy associated with nephronophthisis

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ABSTRACT

Senior–Løken syndrome (SLS) is an autosomal recessive disease characterized by development of a retinitis pigmentosa (RP)- or Leber congenital amaurosis (LCA)-like retinal dystrophy and a medullary cystic kidney disease, nephronophthisis. Mutations in several genes (called nephrocystins) have been shown to cause SLS. The proteins encoded by these genes are localized in the connecting cilium of photoreceptor cells and in the primary cilium of kidney cells. Nephrocystins are thought to have a role in regulating transport of proteins bound to the outer segment/primary cilium; however, the precise molecular mechanisms are largely undetermined. This review will survey the biochemistry, cell biology and existing animal models for each of the nephrocystins as it relates to photoreceptor biology and pathogenesis of retinal degeneration.

1. Introduction

Inherited retinal diseases are estimated to affect up to 200,000 people in the United States (http://www.mdsupport.org/library/numbers.html). A vast majority of these cases are retinitis pigmentosa (RP), which accounts for 40% or 80,000 people. RP is a disease where the photoreceptors, the light-sensing cells of the eye, die (Hartong, Berson, & Dryja, 2006). RP clinically presents with nyctalopia (night blindness) and progresses to significant peripheral visual field reduction (tunnel vision). Central visual acuity and cone function are often preserved until late in the course of the disease. Patients with end stage disease will have no light perception at all. Other clinical findings on a retinal exam include bone spicule formation (retinal pigmentation), peripheral retinal atrophy, waxy pallor of the optic disk and optic nerve head drusen and vascular attenuation (Fig. 1). Diagnosis is done using a detailed clinical and family history, a dilated retinal examination and photography, visual field testing, electroretinography, optical coherence tomography and genetic testing. Currently, there is no therapy that stops progression or restores vision in patients with RP, and therefore, prognosis is poor.

RP may associate with development of pathology in other organs (Sattar & Gleeson, 2011). Examples of syndromic RP include Bardet–Biedl syndrome (BBS), Joubert syndrome (JBTS), Meckel syndrome (MKS), Usher syndrome (USH) and Senior–Løken syndrome (SLS) (Table 1). Bardet–Biedl syndrome is characterized by RP, obesity, polydactyly, cognitive impairment, male infertility, and renal abnormalities, among other pathologies (Zaghloul & Katsanis, 2009). Joubert syndrome presents with hypotonia and ataxia early in life. Other characteristic features are breathing problems, abnormal eye movements, and mental retardation. Joubert syndrome is sometimes associated with RP, kidney, and liver disease, and polydactyly (Doherty, 2009; Juric-Sekhar et al., 2012) (Table 1). Usher syndrome affects mostly hair cells in the ear and photoreceptors in the retina causing hearing loss and RP (Kremer et al., 2006).

Patients with Senior–Løken syndrome develop RP and a kidney pathology called nephronophthisis. Nephronophthisis (NPHP) is an autosomal recessive cystic kidney disease and is the most frequent genetic cause of end-stage renal disease (ESRD) in children and adolescents. A recent review on nephronophthisis can be found in Wolf and Hildebrandt (2011). The median age for ESRD is around 13 years old. Children clinically present with polyuria, nocturia or

Abbreviations: NPHP, nephronophthisis; NPHP5, nephrocystin-5; SLS, Senior–Løken syndrome; RP, retinitis pigmentosa.

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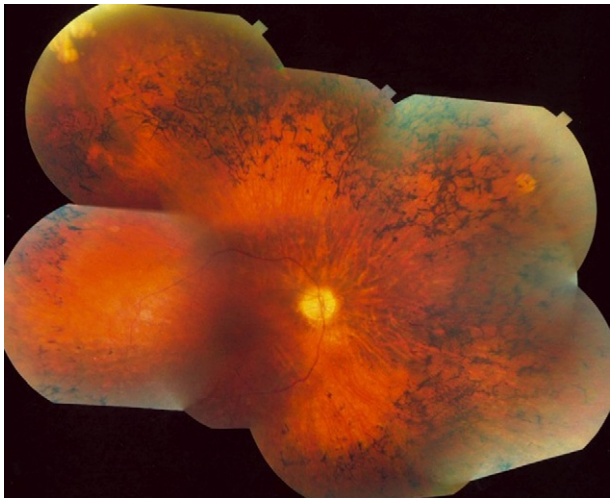

Fig. 1. Fundus photograph of a patient diagnosed with Senior–Løken syndrome. Shown are classic findings in RP: bone-spicule shaped deposits, attenuation of blood vessels with macular sparing.

secondary enuresis. Renal ultrasound scans may initially show normally sized kidneys with increased echogenicity, poor corticomedullary differentiation, and corticomedullary cysts and can progress to atrophic kidneys with more prominent cysts. A kidney biopsy may show the triad of corticomedullary cysts, tubular basement membrane disruption and interstitial fibrosis. NPHP is diagnosed using renal biopsy or by mutational analysis. So far, mutations in 13 genes (NPHP1–13) are known to cause nephronophthisis, and nine mutant genes are associated with development of retinal degeneration (Table 2). However, most of the gene mutations are also associated with development of pathology in other organs besides the kidneys and the retina (Tables 1 and 2). A majority of the nephrocystins associated with development of retinal degeneration or Senior–Løken syndrome are now known to be expressed in the photoreceptor connecting cilium, a structural counterpart of the primary cilium found in most cell types.

2. The photoreceptor connecting cilium

Cilia are composed of nine microtubule doublets (called the axoneme) in a cylindrical arrangement that emanate from basal bodies, the microtubule organizing centers of the cell. There are two types of cilia: motile cilia that are necessary for locomotion and fluid movement, and non-motile (primary) cilia that serve mainly sensory functions. Motile cilia have an additional microtubule doublet found in the center of the axonemal cylinder giving it a characteristic 9 + 2 pattern unlike the 9 + 0 pattern of doublets found in primary cilia. Nodal cilia (a type of motile cilia) that are found on cells of the embryonic node were initially thought to have 9 + 0 arrangement but some have recently been found to be 9 + 2 (Caspary, Larkins, & Anderson, 2007; Novarino, Akizu, & Gleeson, 2011; Okada & Hirokawa, 2009). In addition to the central pair of doublets, motile cilia also have inner and outer dynein arms on the outer doublets that are required for generation of force necessary for motility. The axonemal structure is anchored at the base by the basal body or mother centriole.

The connecting cilium (CC) of vertebrate photoreceptors is a structural homolog of the primary cilium containing the 9 + 0 pattern of microtubule doublets. The CC is 0.5–1.2 μm in length and approximately 0.2 μm in diameter, connects the biosynthetic inner segment (IS) to the sensory outer segment (OS). The entire structure consisting of CC and OS is also called the "photosensitive cilium". It is now recognized that mutations in numerous genes, which are expressed in the photoreceptor connecting cilium cause a group of heterogeneous diseases called ciliopathies. Because of the ubiquitous expression of these genes in primary cilia, ciliopathies often affect multiple organs including kidney, retina, brain, or spermatozoa. The most prominent syndromic diseases that affect the retina are Joubert syndrome, Bardet–Biedl syndrome, and Senior–Løken syndrome (Table 1).

Senior–Løken syndrome and the mutations in the genes that are associated to the development of this disease will be important to study to understand the basic mechanisms of protein transport through the connecting cilium. Therefore, it is important to understand the normal function of each of the nephrocystins to understand pathogenesis of retinal degeneration in these patients.

Table 1
Clinical syndromes associated with development of retinitis pigmentosa. Column 1 shows various clinical syndromes. Column 2 shows mutations in different NPHP genes (with the exception in Usher syndrome – not associated with development of nephronophthisis). Column 3 shows other pathologies in different organs. Links to the sources are shown in blue in column 3.

Syndrome	Gene mutations	Other pathologies besides RP
Bardet Biedl	CEP290 (NPHP6), SDCAAG8 (NPHP10)	Truncal obesity, postaxial polydactyly, cognitive impairment, male hypogonadotropic hypogonadism, complex female genitourinary malformations, and renal abnormalities http://omim.org/entry/209900
COACH	NEK8 (NPHP9), TMEM67 (NPHP11)	**C**erebellar vermis hypoplasia/aplasia, **O**ligophrenia, **A**taxia, **C**oloboma, and **H**epatic fibrosis http://omim.org/entry/216360
Jeune	TTC21B (NPHP12), WDR19 (NPHP13)	Severely constricted thoracic cage (thoracic hypoplasia), short-limbed (brachydactyly), short stature, and polydactyly. It often leads to death in infancy due to respiratory insufficiency (chronic nephritis) http://omim.org/entry/612014http://omim.org/entry/608151
Joubert	NPHP1, CEP290 (NPHP6), RPGRIP1L (NPHP8), NEK8 (NPHP9), TMEM67 (NPHP11), TTC21B (NPHP12)	Abnormally rapid breathing (hyperpnea), decreased muscle tone (hypotonia), jerky eye movements (oculomotor apraxia), mental retardation, inability to coordinate voluntary muscle movements (ataxia) http://omim.org/entry/213300
Meckel	NPHP3, CEP290 (NPHP6), RPGRIP1L (NPHP8), NEK8 (NPHP9), TMEM67 (NPHP11)	Encephalocele, hepatic ductal dysplasia and cysts, and polydactyly http://omim.org/entry/249000
Renal–hepatic–pancreatic dysplasia (RHPD)	NPHP3	Pancreatic fibrosis, renal dysplasia, hepatic dysgenesis http://omim.org/entry/208540
Senior–Løken	NPHP1, INVS (NPHP2), NPHP3, NPHP4, IQCB1 (NPHP5), CEP290 (NPHP6), SDCAAG8 (NPHP10)	Nephronophthisis and Leber congenital amaurosis (LCA) http://www.omim.org/entry/266900
Sensenbrenner	WDR19 (NPHP13)	Microcephaly, narrow thorax, heart defects, liver fibrosis, hypoplasia of the corpus callosum, skeletal abnormalities, including craniosynostosis, narrow rib cage, short limbs, and brachydactyly, and ectodermal defects http://omim.org/entry/614378
Usher	MYO7A, USH1C, CDH23, PCDH15, SANS, USH2A, VLGR1, WHRN, USH3A	Hearing loss and severe balance problems http://omim.org/entry/276900