Eye (2020) 34:2135–2137
https://doi.org/10.1038/s41433-019-0754-y

The ROYAL COLLEGE of OPHTHALMOLOGISTS

CORRESPONDENCE

Analysis of retinal function and structure in autosomal recessive retinal-renal ciliopathy

Moustafa Magliyah[1,2] · Hassan Al Dhibi[1] · Patrik Schatz[1,3]

Received: 4 October 2019 / Accepted: 25 November 2019 / Published online: 7 January 2020

To the Editor:

Cilia are finger-like projections that are present in specialised cells in several organs including the kidney tubules and the retina. In the latter, a ciliary structure termed the connecting cilium connects the inner and outer segments of the rods and cones [1]. The connecting cilium is essential for photoreceptor function and contains several proteins that are encoded by genes incriminated in retinal dystrophies. Recently this structure has been made indirectly observable in vivo as a hyperreflective line in the outer retina, the inner segment ellipsoid (ISe) line, using high resolution spectral domain optical coherence tomography. It is believed that the densely packed mitochondria, required for the transport of molecules and energy production needed for the daily outer segment disc renewal, are the main source of the hyperreflectivity that constitutes the ISe. As cilia in different organs share common structural proteins that are encoded by the same genes, mutations which encode these structural proteins can affect ciliary structures in multiple organs. One example is retinal-renal ciliopathy syndrome, Senior Loken syndrome (SLS, OMIM 266900) [2, 3]. So far, mutations in 13 genes are known to cause nephronophthisis, nine of which are also considered to lead to retinal degeneration [4]. Two such genes are *NPHP4* (OMIM #606966) and *NPHP5* (*IQCB1*) (OMIM #609237). Although their exact function is not known, NPHP4 and NPHP5 are believed to interact with multiple proteins in the transition zone or base of cilium, including with the Retinitis GTPase Regulator (RPGR) and RPGR-Interacting Protein 1 (RPGRIP1), an interaction which may explain the mechanism of retinal degeneration in patients with mutations in these genes. We speculate that this ciliary structure might be affected early on in SLS, and may serve as a marker of the disease.

Five patients (age range 6–42 years) with SLS were identified through a retrospective review of patient encounters and a search of a retinal dystrophy registry including 789 patients, leading to an estimated prevalence of <1% of SLS among retinal dystrophies. All patients came from consanguineous families. The full-field electroretinogram was non-recordable in all except in Patient 3 in whom both scotopic and photopic responses were severely reduced (Table 1). Two novel likely disease causing mutations were detected (Table 1). The retinal phenotype was similar in all patients, including severe central and peripheral degeneration (Fig. 1). Patients 1 and 2 presented with a history of nephronophthisis, while all other patients had normal renal function. The complete syndrome including nephronophthisis may not always be fully penetrant. This variability is believed to be caused by factors such as the complexity of interaction of several of the gene products in the cilia, tissue-specific posttranslational modification and alternative tissue-specific splicing. In conclusion, macular dysfunction and macular structural changes including loss of the ISe were present in all patients with SLS, consistent with ciliopathy. On the other hand, ISe affection can occur in multiple other acquired and hereditary retinal conditions [5]. Assessment of the ISe line may be a surrogate endpoint in future clinical trials on gene therapy for SLS.

Acknowledgements We thank Mr Adolph Cabanas at the Design and Publications Department of King Khaled Eye Specialist Hospital for skilful technical assistance.

✉ Patrik Schatz
pschatz@kkesh.med.sa

[1] Vitreoretinal Division, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia

[2] Ophthalmology Department, Prince Mohammed Medical City, AlJouf, Saudi Arabia

[3] Department of Ophthalmology, Clinical Sciences, Skane County University Hospital, Lund University, Lund, Sweden

Table 1 Retinal function and structure and pathogenetic mutations in five patients with Senior Loken Syndrome.

Patient	Age	Gender	Gene	Mutation	Protein effect	ExAC frequency, accessed 20190523	BCVA	Re-fraction	Fundus	FAF	SD-OCT	ERG
1	40	Male	*NPHP4*	c.673G>T	Missense	0.00001146 (Once only and never homozygously)	4/200 OU	+8.00 OU	Bone spicules, attenuated vessels and pale discs	Parafoveal hyperauto-fluorescent ring	Barely visible ISe at the ring, undetectable beyond it	Flat
2	38	Male	*NPHP4*	c.673G>T	Missense	0.00001146 (Once only and never homozygously)	HM OU	+6.00 OU	Bone spicules, attenuated vessels and pale discs	Parafoveal hyperauto-fluorescent ring	Barely visible ISe at the ring, undetectable beyond it	Flat
3	42	Female	*NPHP4*	c.563C>A and c.1880C>T	Missense	c.563C>A: 0, Not reported. c.1880C>T:0.0003064 but never in homozygous mode	20/300 OU	−3.00 OU	Bone Spicules, attenuated vessels and pale discs, Bull's eye maculopathy	Hypoautofluorescent macula	Undetectable ISe	Reduced
4	6	Female	*IQCB1 (NPHP5)*	c.994C>T	p.Arg332*	0, not reported	HM OU	+7.00 OU	Peripheral retinal depigmentation with minimal pigment depositions, attenuated vessels and small sized optic discs	Parafoveal hyperautofluoresent ring	Barely visible ISe at the ring, undetectable beyond it	Flat
5	14	Female	*IQCB1 (NPHP5)*	c.1278 +1G>A	Frame-shift	0, not reported	HM OU	+6.00 OU	Peripheral retinal depigmentation with minimal pigment depositions, attenuated vessels and small sized optic discs	Parafoveal hyperauto-fluorescent ring	Barely visible ISe at the ring, undetectable beyond it	Flat

All mutations were homozygous, except for those found in patient 3, which were compound heterozygous

HM hand motion, *BCVA* best corrected visual acuity, *ERG* full-field electroretinography, *FAF* fundus autofluorescence, *ISe* inner segment ellipsoid, *OU* in each eye, *SD-OCT* spectral domain optical coherence tomography

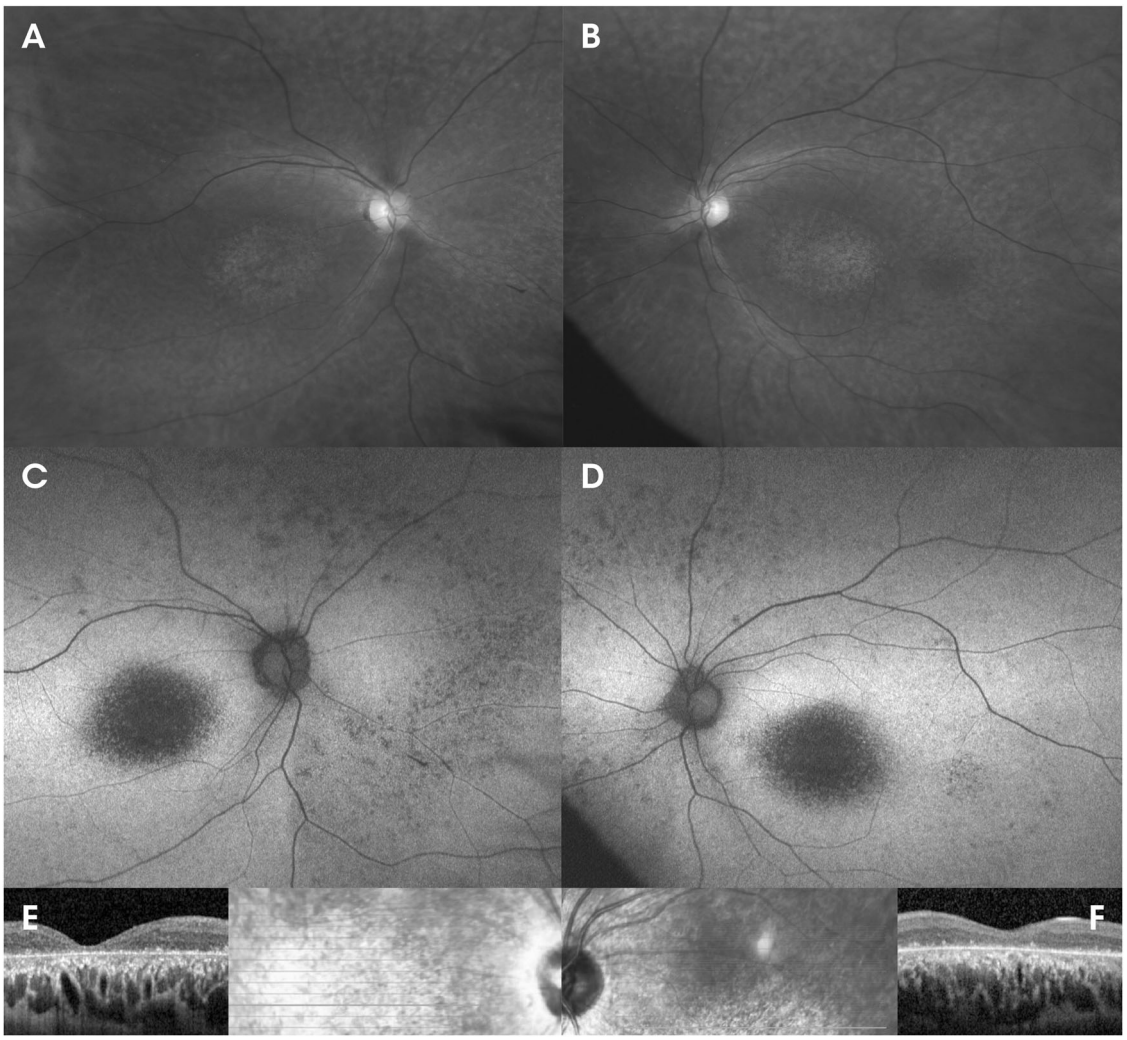

Fig. 1 Multimodal retinal imaging in Senior-Loken syndrome. Upper panel. Wide field fundus imaging of a 42-year-old female with a novel compound heterozygous c.563C>A missense mutation and a previously described c.1880C>T missense mutation in *NPHP4* (Patient 3). Middle panel. Fundus autofluorescence imaging with enlarged macular hypoautofluorescent area corresponding to the maculopathy. Lower panel. Spectral domain optical coherence tomography shows absence of inner segment ellipsoid (ISe) in the macular area.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Horst CJ, Johnson LV, Besharse JC. Transmembrane assemblage of the photoreceptor connecting cilium and motile cilium transition zone contain a common immunologic epitope. Cell Motil Cytoskeleton. 1990;17:329–44.
2. Senior B, Friedmann AI, Brando JL. Juvenile familial nephropathy with tapetoretinal degeneration. A new oculorenal dystrophy. Am J Ophthalmol. 1961;52:625–33.
3. Loken AC, Hanssen O, Halvorsen S, Jolster NJ. Hereditary renal dysplasia and blindness. Acta Paediatrica. 1961;50:177–84.
4. Ronquillo CC, Bernstein PS, Baehr W. Senior-Løken syndrome: a syndromic form of retinal dystrophy associated with nephronophthisis. Vis Res. 2012;75:88–97.
5. Saxena S, Srivastav K, Cheung CM, Ng JYW, Lai TYY. Photoreceptor inner segment ellipsoid band integrity on spectral domain optical coherence tomography. Clin Ophthalmol. 2014;8:2507–22.