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Case Report

Novel Pathogenic Variants in *IFT140* and *IFT172* Genes in Three Patients with Similar Retinal Dystrophy Phenotypes

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Abstract

Introduction: The intraflagellar transport (IFT) complex plays a key role in protein transport and turnover within photoreceptors. *IFT140* and *IFT172* gene mutations have been associated with skeletal ciliopathies that occur concurrently with retinal dystrophy. These mutations have also been associated with non-syndromic retinal dystrophies. This phenotypic heterogeneity can make diagnosis challenging. Here, we report novel variants in *IFT140* and *IFT172* genes in 3 patients with similar retinal dystrophy phenotypes. ***Case Presentations:*** Two siblings (a 51-year-old male and 46-year-old male) who presented with a similar retinal dystrophy, skeletal abnormalities, and kidney disease were found to have the same novel variant in the *IFT140* gene, along with another, previously reported variant. An unrelated individual with a similar retinal phenotype was found to have a novel variant in the *IFT172* gene, although this was noted as a variant of uncertain significance. The patients underwent testing with the Blueprint Genetics (Blueprint Genetics Oy, Keilaranta 16 A-B, 02150 Espoo, Finland) "My Retina Tracker Program Panel Plus" panel. ***Conclusion:*** Novel variants in the *IFT140* and *IFT172* genes encoding the IFT complex may contribute to similar retinal dystrophy phenotypes, as noted in our case series.

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Introduction

The intraflagellar transport (IFT) complex plays a key role in protein transport and turnover within photoreceptors. The IFT-A complex is responsible for retrograde ciliary transport of proteins and contains a subunit, *IFT140*, which manages photoreceptor outer segment homeostasis and opsin transport. The IFT-B complex, which manages anterograde transport and is mainly responsible for cilium assembly, contains subunit *IFT172* [1].

Both *IFT140* and *IFT172* gene mutations have been associated with skeletal ciliopathies, including short-rib thoracic dysplasia with or without polydactyly (SRTD), which contains several subclasses ranging from SRTD 1–16 [2], including disorders formerly known as the Mainzer-Saldino syndrome, Jeune syndrome, and short-rib polydactyly syndrome [1, 3]. These skeletal ciliopathies occur concurrently with retinal dystrophy and kidney disease in varying degrees and severity [4], which may pose a diagnostic challenge for ophthalmologists. *IFT172* has also been associated with Bardet-Biedl syndrome, which is a ciliopathy characterized by retinal dystrophy, obesity, polydactyly, hypogonadism, cognitive impairment, and genitourinary and renal malformations [5]. Both *IFT140* and *IFT172* mutations have additionally been associated with non-syndromic retinal dystrophies, posing an even greater diagnostic challenge in the absence of systemic findings [3]. In order to shed light on these phenotypes, we present a novel variant in the *IFT140* gene in two brothers with systemic findings, as well as a variant of uncertain significance (VUS) in the *IFT172* gene in an unrelated, non-syndromic individual.

Case Report

Patient 1

This patient is a 51-year-old male with hypertension, a clinical diagnosis of polycystic kidney disease requiring transplantation at age 50 (followed by nephrologist J.S.), and short stature with apparent brachydactyly and hyperextensible finger joints (Fig. 1a). There was no apparent toe involvement. He was diagnosed clinically with an unknown retinal dystrophy in childhood and subsequently underwent long-term surveillance with his optometrist (S.B.). On initial presentation to the retina clinic (T.R.K.), he reported nyctalopia, problems with dark adaptation, and reduced peripheral vision. He reported that these symptoms have been present since he was a child. He denied a history of smoking. There was no family history of consanguinity. He shared that his younger brother had been diagnosed with a similar condition (see patient 2).

On exam, best corrected visual acuity (BCVA) was 20/25 in the right eye (OD) and 20/40 in the left eye (OS) and he was pseudophakic OD. Axial length was 23.56 mm OD and 23.66 mm OS. Dilated fundus exam (DFE) revealed diffuse peripheral bone spicules in both eyes (OU), attenuated retinal vessels and macular atrophy (Fig. 1b, c). There was diffuse hypoautofluorescence in the macula OU (Fig. 1d, e). Macular spectral domain optical coherence tomography (SD-OCT) showed macular atrophy, ellipsoid zone, outer nuclear layer and retinal pigment epithelium (RPE) loss, sparing the fovea, and epiretinal membrane (ERM) formation with vitreomacular traction (VMT) OU (Fig. 1f, g). Goldmann visual field testing (III4e) performed at age 43 showed peripheral field constriction to the central 5–10° OU, without preservation of the temporal crescent on any isopter.

Patient 2

The second patient, the younger sibling of patient 1, is a 46-year-old male with myopia, hypertension, progressive chronic kidney disease, and hyperextensible joints. Like his brother, he was diagnosed clinically with a retinal dystrophy at age 5 and followed with his brother's

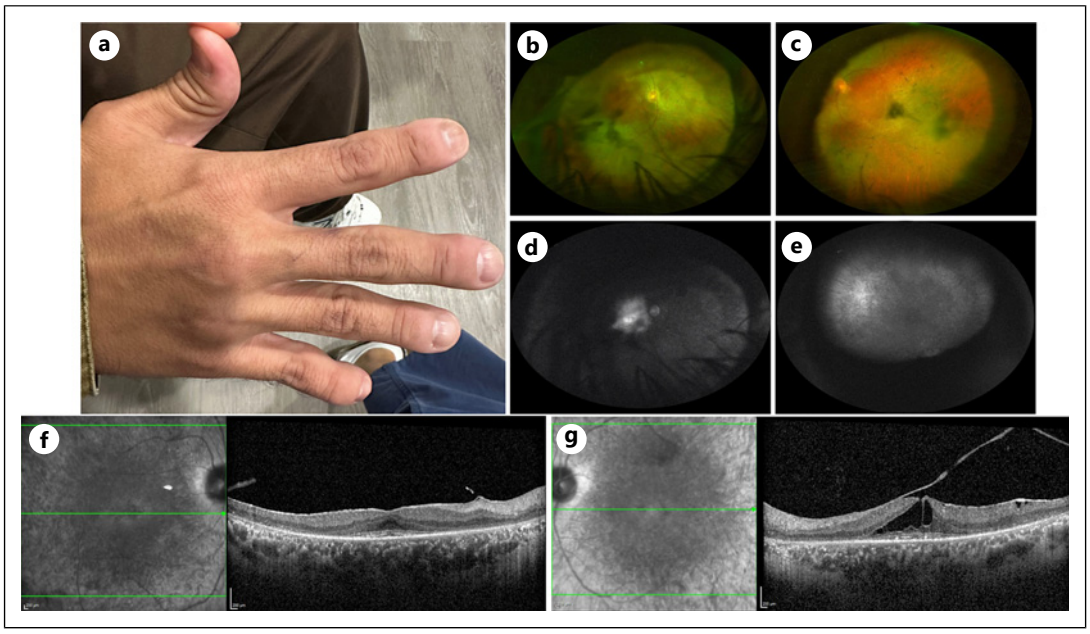

Fig. 1. Patient 1. Clinical photograph of the hand demonstrating apparent brachydactyly and hyperextensible joints (**a**). Fundus photograph OD (**b**) and OS (**c**) showing diffuse peripheral bone spicules, sclerosed retinal vessels, and macular atrophy. Corresponding fundus autofluorescence (FAF; Optos Ultra-Widefield, UWF™, Marlborough, MA, USA) OD (**d**) and OS (**e**) shows diffuse hypoautofluorescence in the macula. SD-OCT (Heidelberg Engineering, Heidelberg, Germany) through the fovea OD (**f**), showing atrophy with EZ and outer nuclear layer (ONL) loss in the macula sparing the fovea, as well as an epiretinal membrane (ERM) with vitreomacular traction (VMT). SD-OCT through the fovea OS (**g**), also shows loss of the EZ and ONL sparing the fovea, and ERM with VMT and a lamellar hole.

optometrist (S.B.). He reports using a cane to ambulate. Unlike patient 1, patient 2 had a tall stature without digit anomalies, though he also had hyperflexible finger joints (Fig. 2a). In the retina clinic (T.R.K.), he reported night blindness, color blindness, and poor vision since age 7 years. On presentation, BCVA was 20/50 OD and hand motion OS with strabismic amblyopia and sensory exotropia in the OS. He also denied a history of smoking. On DFE, there were more extensive peripheral bone spicules than patient 1, as well as attenuated vessels and macular atrophy OU (Fig. 2b, c). Macular hypoautofluorescence was also present OU, albeit less than seen in his brother's fundus imaging (Fig. 2d, e). SD-OCT through the macula showed macular atrophy, loss of the outer retinal layers sparing the fovea, and subretinal deposits in OU (Fig. 2f, g). On visual field testing at age 42, he was noted to have 4 degrees of central vision OD and 2 degrees of central vision remaining OS. Patient 2 was also reported to have severely decreased contrast sensitivity in both eyes. Neither patient 1 or 2 has any children. Their only living family member is their 81-year-old mother who does not have any known ocular diseases, including retinitis pigmentosa, though she has not been examined by the authors.

Patient 3

This unrelated individual is a 77-year-old female who presented to the retina clinic (T.R.K.) with similar retinal findings as patient 1 and patient 2. She was referred to the retina clinic by a general ophthalmologist who noted pigmentary retinal changes during the patient's cataract evaluation. She has a history of HTN and had previously been followed by a different ophthalmologist for low-risk glaucoma suspicion and pseudophakia OD. She noted some new blurry vision over the past several years. She denied any known family history of retinal

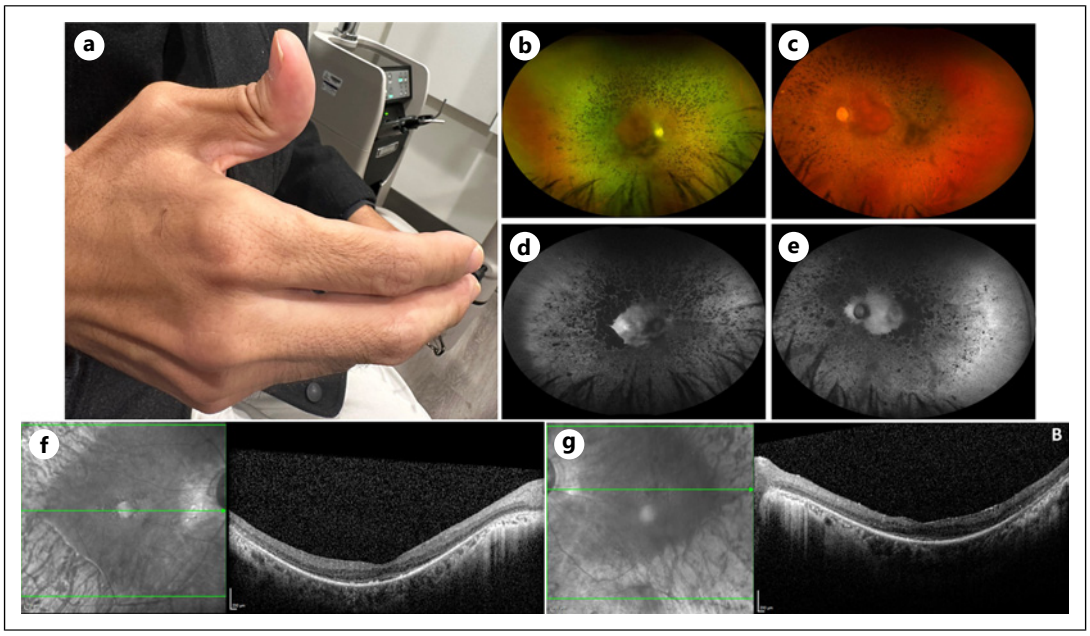

Fig. 2. Patient 2. Photograph of the hand demonstrating lack of digit anomalies, but presence of hyperextensible joints (**a**). Fundus photograph OD (**b**) and OS (**c**) showing macular atrophy and extensive peripheral bone spicules. Corresponding FAF OD (**d**) and OS (**e**) demonstrate hypoautofluorescence in the peripapillary region and nasal macula, as well as in the region of the bone spicules peripherally. SD-OCT through the fovea OD (**f**) showing atrophy and loss of outer retinal layers sparing the fovea as well as subretinal deposits centrally. SD-OCT through the fovea OS (**g**) also demonstrates loss of outer retinal layers sparing the fovea and subretinal deposits centrally.

disease or consanguinity and no family members were available for examination. She had no history of developmental delay or skeletal malformation on presentation, and BCVA was 20/25 OD and 20/25 OS with normal intraocular pressures. Axial length was measured to be 24.28 mm OD and 24.38 mm OS. Posterior segment exam revealed peripapillary atrophy, vascular attenuation and pigmentary changes in the macula and peripheral fundus OU (Fig. 3a, b). There was no distinct bone spicule pigmentation in either eye. Fundus autofluorescence showed a bull's eye-like hyperautofluorescence in the posterior pole with intervening rings of hyper- and hypoautofluorescence (Robson-Holder ring) (Fig. 3c, d). SD-OCT showed macular ellipsoid zone and ONL loss sparing the fovea OU (Fig. 3e, f).

Genetic Testing

Buccal swab was performed on all 3 patients for genetic testing using the Blueprint Genetics (Blueprint Genetics Oy, Keilaranta 16 A-B, 02150 Espoo, Finland) "My Retina Tracker Program" Panel.

Results

In patient 1, sequencing analysis identified two mutations in *IFT140*; a heterozygous nonsense mutation: *IFT140* c.1513C>T, p.(Arg505*) that was noted as likely pathogenic, and a heterozygous missense mutation: *IFT140* c.2720A>C, p.(Tyr907Ser) that was a VUS. Patient 2 had identical results to patient 1 (brother); a heterozygous nonsense mutation: *IFT140* c.1513C>T, p.(Arg505*) that was likely pathogenic; and a heterozygous missense mutation:

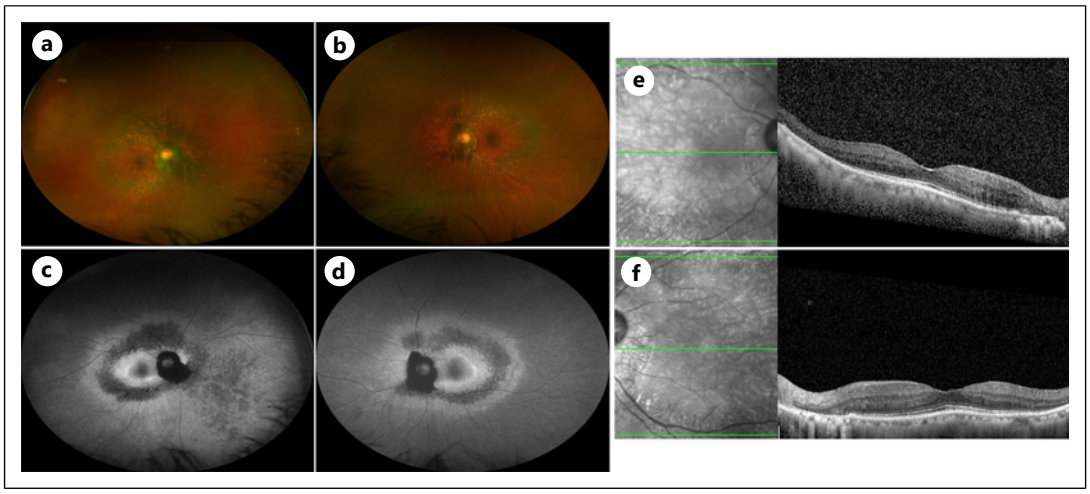

Fig. 3. Patient 3. Fundus photograph OD (**a**) and OS (**b**) showing peripapillary atrophy, vascular attenuation, and hypopigmentation in a circular pattern surrounding the disc and the arcades, sparing the fovea. FAF OD (**c**) and OS (**d**) showing a ring of hypoautofluorescence surrounding the disc and the arcades, corresponding to the region of atrophy seen on the fundus photographs. There is also a thinner ring of hyperautofluorescence surrounding the fovea OD and OS (Robson-Holder ring). Dense hypoautofluorescence is seen surrounding the disc corresponding to the peripapillary atrophy OD and OS, and there is a wedge of inferonasal hypoautofluorescence OD as well. SD-OCT of the OD through the fovea (**e**) showing perifoveal atrophy of the outer retinal layers and a posterior vitreous detachment. SD-OCT through the fovea OS (**f**) showing perifoveal atrophy of the outer retinal layers and a posterior vitreous detachment.

IFT140 c.2720A>C, p.(Tyr907Ser) that was a VUS. In patient 3, genetic testing showed a single heterozygous mutation of *IFT172* c.1993_1994delinsAT, p.(Glu665Met) which was noted to be a VUS.

Discussion

The c.1513C>T, p.(Arg505*) mutation contributes to the formation of a premature stop codon in exon 13 of 31, which likely leads to a loss of normal protein function. To date, there have been 5 reported cases that were heterozygous for this variant in gnomAD, a large reference population database [5]. The c.2720A>C, p.(Tyr907Ser) variant is not found in the gnomAD database and is predicted to be deleterious. Low et al. reported that humans may be unlikely to tolerate deleterious mutations of this gene due to its necessity in embryonic development [6]. Our findings of syndromic retinal dystrophy in two brothers support that the c.2720A>C, p.(Tyr907Ser) variant may also be pathogenic, which has not been previously reported. The *IFT172* c.1993_1994delinsAT, p.(Glu665Met) mutation is also not found in the gnomAD database; however, a biallelic mutation would be necessary to consider it definitively pathogenic.

IFT140 and *IFT172* mutations have been associated with ciliopathies such as SRTD9 and SRTD10, respectively [1–3]. These patients most commonly present with night blindness or difficulty with light-dark adaptation [1], which may be the first sign of underlying retinal dystrophy. Therefore, prompt retinal evaluation is warranted. Skeletal dysplasia in this disease includes shortened ribs and cone-shaped phalangeal epiphyses [1], also noted in patient 1 in our case series. Retinal findings include mid-peripheral hypopigmentation of the

RPE, attenuated vessels, and macular atrophy [7], which were noted in all 3 of our patients. Kidney manifestations may include cystic changes, tubulointerstitial disease secondary to tubular dilation and atrophy, or interstitial fibrosis [8]. *IFT140* and *IFT172* mutations have also rarely been associated with non-syndromic retinal dystrophies [9], which have been shown to have milder manifestations than those with syndromic disease [3, 10]. Of note, it has been shown that the *IFT140* and *IFT172* proteins work together and a functional *IFT172* is therefore necessary for sufficient *IFT140* to enter the cilium [11]. It is believed that *IFT172* is involved in the interaction between the two subcomplexes, IFT-A and IFT-B, and this interaction may help explain some of the clinical similarities between mutations in *IFT140* and *IFT172* genes.

In 2015, Xu et al. [3] identified *IFT140* gene mutations in 7 unrelated individuals with retinal dystrophy using whole-exome sequencing. Although we did not perform segregation analysis, both siblings in our report (patient 1 and patient 2) had the same two mutations in the *IFT140* gene. Additionally, although they had similar retinal findings to each other, they varied in severity, and had otherwise different phenotypes with regards to their systemic manifestations.

Bujakowska et al. [10] reported *IFT172* gene mutations in two siblings that led to a Bardet-Biedl like ciliopathy with elevated BMI, delayed speech development and elevated liver transaminases. One of the sisters also had polydactyly and pancreatitis, while neither had skeletal abnormalities [10]. This report also described, for the first time, *IFT172* mutations in 2 patients with a retinitis pigmentosa-like phenotype and no systemic findings, one of whom reported a family history of consanguinity. These patients demonstrated attenuation of retinal blood vessels, RPE atrophy, and a perifoveal ring of hyperautofluorescence with hypo-autofluorescence outside the vascular arcades, much like our patient 3. However, there were also findings of cystic macular edema and bone-spicule pigmentation not seen in our cases.

Our case series highlights one previously documented pathogenic mutation, c.1513C>T, p.(Arg505*), and one novel mutation, c.2720A>C, p.(Tyr907Ser) associated with syndromic retinal dystrophies, as well as one novel mutation of uncertain significance in *IFT172* c.1993_1994delinsAT, p.(Glu665Met) associated with what appears to be a non-syndromic retinal dystrophy. The same two mutations in the *IFT140* gene found in the two siblings is likely responsible for the syndromic retinal dystrophy in these patients. Although patient 3 in our case series had a single mutation in the *IFT172* gene, this is insufficient to deduce causality of her retinal findings. However, the similarity of her retinal findings compared to patients 1 and 2 may be indicative of the general retinal dystrophy phenotype in patients with IFT mutations, and the *IFT172* c.1993_1994delinsAT, p.(Glu665Met) mutation may be found to play a pathogenic role as genetic testing becomes more widely available and more patient cases are documented.

Given the well-established phenotype heterogeneity in patients with IFT mutations [1], there should be a low threshold to perform genetic testing to reveal possible associated systemic manifestations. Despite the variety of presentations, our case series suggests that the peripheral fovea may highlight possible *IFT140* or *IFT172* involvement. We hope that adding to the paucity of published information regarding these mutations will help identify the retinal component of these ciliopathies and facilitate earlier diagnosis and referral of patients with similar presentations.

While various treatment modalities have been investigated for patients with these retinal dystrophies, none have been consistently successful [9]. These include vitamin A, docosahexaenoic acid, and lutein supplementation, as well as gene therapy and stem cell therapy [9]; however, further research is needed to elucidate the best treatment for these patients.

The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000545390).

Statement of Ethics

Written informed consent was obtained from participants for publication of the details of their medical case and accompanying images. Ethical approval is not required for this study in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.A.: drafting the work and reviewing it critically for important intellectual content, and final approval of the version to be published. S.R.G.: acquisition of data, drafting the work, reviewing it critically for important intellectual content, and final approval of the version to be published. S.B.: acquisition of data, reviewing the work critically for important intellectual content, and final approval of the version to be published. J.S.: reviewing the work critically for important intellectual content, and final approval of the version to be published. T.R.K.: conception and design of the work, drafting the work and reviewing it critically for important intellectual content and final approval of the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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