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Compound heterozygous variants in *IFT140* as a cause of non-syndromic Retinitis Pigmentosa

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Introduction

Retinitis pigmentosa (RP) refers to a group of inherited disorders that affect the retina's ability to respond to light, leading to progressive visual loss. Retinitis pigmentosa sine pigmento is a variant of RP in which there is an absence of characteristic peripheral bone-spicule like pigmentary changes.

One of the genes found to be responsible for RP is *IFT140*, a ciliary transporter gene (OMIM *614620). Homozygous and compound heterozygous *IFT140* variants have commonly been reported in Mainzer-Saldino syndrome and Jeune syndrome.[1] However, in recent literature, non-syndromic *IFT140*-related RP have been reported.

IFT140 encodes a sub-unit of intraflagellar transport complex A (IFTA), which is involved in retrograde ciliary transport.[2] It was previously referred to as *KIAA0590* and located on chromosome 16p13.3. It is highly expressed in kidneys with moderate expression in ovary, testis, lung, prostate. Schmidts et al., 2013 demonstrated high expression of Ift140 in renal and retinal tissue in mouse embryos.[3] Although the phenotype associated with *IFT140* variants is still emerging, it appears to encompass

a variable spectrum ranging from non-syndromic, isolated RP (as demonstrated in this clinical report) to Short-rib thoracic dysplasia 9 with or without polydactyly (SRTD9; OMIM # 266920).

Case Report

We present a case of a 22-year-old female who attended her opticians for a frequent headaches review. It was found that her visual fields were restricted, with a slightly abnormal retina with greying and mottling (Fig 1). However, night-time vision was not reduced. An optical coherence tomography suggested likely RP, and electrodiagnostic testing confirmed the diagnosis.

She was the first child of healthy, non-consanguineous, White European parents and had a younger sister who was fit and well with no family history of RP. A recent ophthalmology follow-up review found that the patient had visual acuities of 6/6 with patchy visual defects in bilateral eyes, but no significant decrease in visual fields.

Materials and Methods

Genomic DNA was obtained from patient and both parents with appropriate consent. A total of 176 genes associated with retinal dystrophy were targeted using Retinal dystrophy v3 Agilent SureSelect Custom Design and sequenced on the HiSeq2500 (Illumina) system according to manufacturer's protocols. The target enrichment design consisted of coding region of the transcripts, including the immediate splice sites (+/- 5 bases) for these genes. Sequence data was subsequently mapped with GenomeAnalysis ToolKitLite-v2.0.39 (GATK) and with hg19 human genome as a reference. Known polymorphisms were filtered using bioinformatic analysis.

Results

Compound heterozygous variants in *IFT140* NM_014714.3: c.4182G>C p.(Thr1394Thr) and c.212C>T p.(Pro71Leu) were identified, and confirmed by

Sanger sequencing. *IFT140* c.4182G>C p.(Thr1394Thr) is a synonymous change which has not previously been reported in the literature or any of the mutation/ variant databases. However, it affects the last base of exon 30 and *in silico* prediction tools using Alamut Visual version 2.6 (Interactive Biosoftware, Rouen, France) indicates that this change may reduce or abolish the splice donor site of intron 30. *IFT140* c.212C>T p.(Pro71Leu) has previously been reported in the compound heterozygous state in a patient with non-syndromic RP. The proline residue at codon 71 is highly conserved and *in silico* analysis using Polyphen2 and SIFT predicts this change to be damaging. Parental analyses confirmed that the father carried the *IFT140* c.4182G>C p.(Thr1394Thr) and mother carried the *IFT140* c.212C>T p.(Pro71Leu), showing that the variants are in trans in the proband.

Discussion

IFT140 is a protein coding gene, variants in this gene are often associated with a group of autosomal recessive syndromic ciliopathies also known as short rib thoracic dysplasia 9 with or without polydactyly (SRTD9). Human IFT140 protein contains WD40 (WD) and TPR (tetratricopeptide) repeat domains. There does not appear to be specific genotype-phenotype correlation based on existing literature and variants within TPR and WD repeat domains in IFT140 protein give rise to both a syndromic ciliopathy and a non-syndromic RP. It has also been reported that the *IFT140* missense variants in Mainzer-Saldino syndrome and Jeune syndrome were mainly found in the N-terminus and WD repeat domains.

The principle of genetics in RP is complex as locus and allelic heterogeneity exists. The use of multi-gene panels and next-generation sequencing currently yield an 80% success rate in the identification of the pathogenic variant(s). It is worth noting that individuals with RP often do not present with the classical appearance of bone spicule

pigmentation, which may lead to a delay in diagnosis. Indications such as poor night vision and positive family history should guide physicians to request electrodiagnostic tests for further investigation.

Since the use of next generation sequencing for retinal disorders, in clinical practice, we are able to identify more individuals with genetic forms of RP and provide diagnostic confirmation, information on prognosis and informed recurrence risks. This aids in genetic counselling, especially where there is no relevant family history and particularly helpful to clarify recurrence risks in unaffected family members. This report adds to the emerging literature of *IFT140* causing a non-syndromic RP.

Figure Legend

Fig 1. Retinal photographs demonstrating mottled appearance with greying of retina.

Acknowledgement

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