Two novel *WDR19* missense variants associated with a retino-renal ciliopathy

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Introduction

Variants in *WDR19,* a ciliary gene, have been associated with systemic ciliopathies including the retino-renal syndromes: Senior-Løken, Sensenbrenner, Jeune and Caroli syndromes (1-5).

These rare syndromes present in childhood and a *WDR19*-related retinal disease, described in only a handful of these cases, ranges from pan-retinal dystrophy (1) to 'bear-track' maculopathy (2).

Here we report a case of advanced retinitis pigmentosa in an adult patient with WDR19 genotype and unknown systemic associations.

Methods

This case-study involved a patient who underwent detailed clinical evaluation, ophthalmic imaging, genetic testing and renal studies.

Results

We describe a case of a 68-year-old Caucasian female with advanced retinitis pigmentosa. Deep phenotyping demonstrated pan-retinal atrophic changes (Figure 1). Family studies revealed no family history of inherited retinal degeneration or syndromic associations. Next generation sequencing analysis revealed two novel heterozygous missense variants in WDR19 gene, c.2095C>T (p.Arg699Trp) and c.3464A>C (p.His1155Pro), of undetermined pathogenicity (Figure 2). The affected amino acids in both variants are highly conserved across species implicating their importance in protein function. Systemic investigations, including renal function tests and renal ultrasound revealed multiple bilateral renal cysts and mildly impaired renal function, suggesting a new diagnosis of a mild form of Senior-Løken Syndrome.

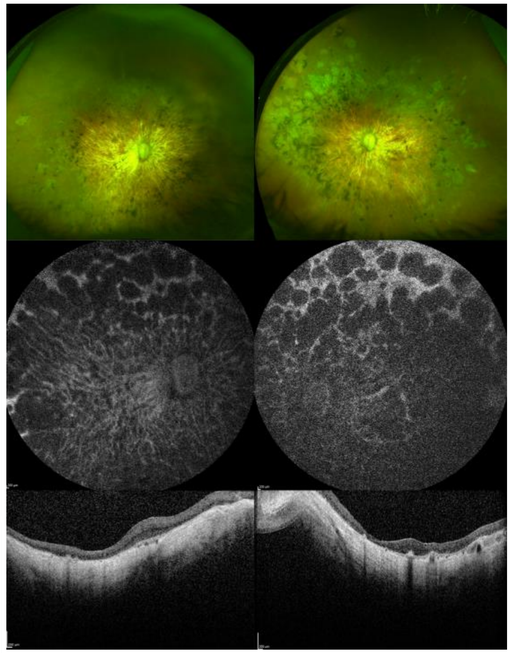


Figure 1. Ultra-widefield retinal imaging (top), fundus auto-fluorescence (middle) and optical coherence tomography (OCT) (bottom) demonstrating advanced retinal dystrophy.

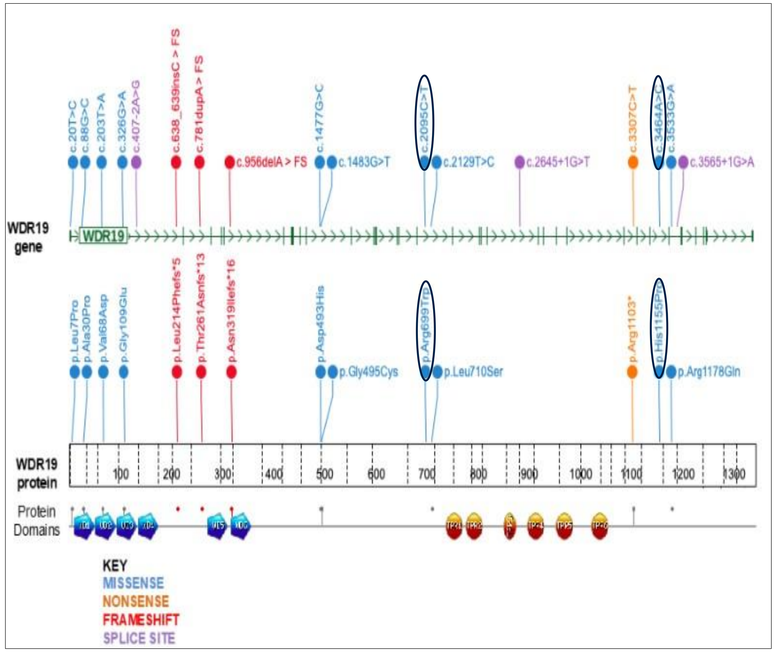


Figure 2. Diagram showing previously reported WDR19 variants associated with retinal phenotypes and the two novel missense mutations (circled) from the present study. WD40 - repeats of 40 amino acids ending in tryptophan–aspartic-acid dipeptides (W–D) Tetratricopeptide (TPR) domains.

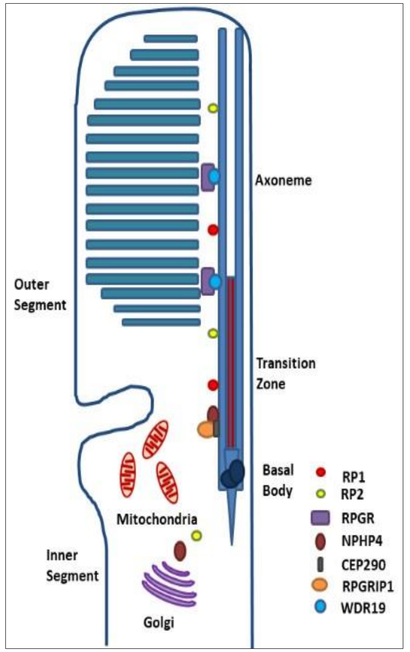


Figure 3. The photoreceptor cilium illustrating salient genes important in photoreceptor function and homeostasis.

Discussion

WDR19 encodes for a ciliary protein that is ubiquitously expressed throughout the body, including the photoreceptor cilia where it plays a key role in photoreceptor function and homeostasis (Figure 3).

This case-study highlights the importance of verifying the genotype with systemic investigations and looking for subclinical phenotypes to help determine the pathogenicity of unknown variants.

With emergence of genetic treatments for inherited retinal degenerations, it is imperative to determine their genotypes.

With this particular gene, *WDR19,* where the cDNA of 4.1kB is beyond current AAV capacity for gene replacement therapy, gene editing tools including CRISPR technology will be more suitable.

References

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