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WDR34, a candidate gene for non-syndromic rod-cone dystrophy

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CONFLICTOF INTEREST

The authors declare no potential conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The authors declare having full access to the data.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Abstract

Rod-cone dystrophy (RCD), also called retinitis pigmentosa, is characterized by rod followed by cone photoreceptor degeneration, leading to gradual visual loss. Mutations in over 65 genes have been associated with non-syndromic RCD explaining 60% to 70% of cases, with novel gene defects possibly accounting for the unsolved cases. Homozygosity mapping and whole-exome sequencing applied to a case of autosomal recessive non-syndromic RCD from a consanguineous union identified a homozygous variant in *WDR34.* Mutations in *WDR34* have been previously associated with severe ciliopathy syndromes possibly associated with a retinal dystrophy. This is the first report of a homozygous mutation in *WDR34* associated with non-syndromic RCD.

Keywords

KIAA2026; non-syndromic rod-cone dystrophy; retinitis pigmentosa; *WDR34*; whole-exome sequencing

Rod-cone dystrophy (RCD), also called retinitis pigmentosa (RP [MIM #268000]), is the most common inherited retinal disorder (IRD) with a prevalence of 1/3500 to 5000.[1] Patients with RCD initially experience night blindness and gradual visual field constriction, and eventually loss of central vision due to progressive rod-cone degeneration.[1] So far, mutations in more than 65 genes have been implicated in non-syndromic RCD following one of three Mendelian modes of inheritance (https://sph.uth.edu/retnet/). Nevertheless, approximately 40% of RCD cases are still unresolved, demonstrating the need for discovery of new gene defects.[2] Homozygosity mapping in geographic isolates or consanguineous families coupled with whole-exome/-genome sequencing (WES/WGS) is an important method for detecting the remaining genes implicated in RCD[3] as applied in this study.

Our aim was to identify the underlying gene defect of a non-syndromic RCD case, hitherto excluded for mutations in known genes (Data S1). This study followed the tenets of the Declaration of Helsinki and was approved by a national ethics committee.

The proband, a 27-year-old subject (IV-1, Figure 1A), from Portuguese first cousin parents, experienced early onset night blindness with progressive visual field constriction. Visual acuity was 20/500 and counting fingers with a refractive error of −5.75(−2)180° and −5.75(−1.75)15° in the right and left eyes, respectively. Kinetic visual fields were constricted to central 10° in either eye (Figure S1A). Full field electroretinogram was undetectable to all tested stimuli. Fundus examination was in keeping with severe RCD (Figure 1B). He was otherwise fit with only a well-controlled mild asthma since childhood (chest X-Ray was normal, Figure S1B) and a non-clinically significant subtle hearing loss around 4000 Hz within normal limits according to the audiologist (Figure S1C). The case was therefore considered as non-syndromic RCD.

Homozygosity mapping performed in the index patient and his unaffected parents, III-1 and III-2 (Figure 1A) revealed 21 homozygous regions ranging from 9 kb to 77.7 Mb (Data S1).

Homozygous regions included seven IRD genes associated (Table S1) for which Sanger sequencing did not reveal any pathogenic variants. Subsequent WES in the index patient and his unaffected parents (Data S1) identified homozygous variants in two candidates genes: *KIAA2026* (Refseq NM_001017969.2) carrying [c.22G>T, p.(Gly8*)] and *WDR34* [MIM# 613363, Refseq NM_052844.3] with [c.1241A>G, p.(Asp414Gly) (Table S2, Figures 2 and S2). Both changes were in large homozygous regions (10.9 and 12 Mb, respectively) on chromosome 9 and were confirmed by Sanger sequencing. No other variants in known IRD genes (homozygous or compound heterozygous) likely leading to disease were identified (Table S3), though our analysis did not cover copy number variants, changes in distal promoters and deep intronic regions, which may harbor pathogenic variants.

The premature stop codon in *KIAA2026* seemed at first the most promising candidate. But, although this variant is absent in a homozygous state in gnomAD, its frequency is too high to be causal for a new RCD gene (minor allele frequency = 0.0004477 in general and 0.001383 in Ashkenazi Jews). Moreover, an alternative translation start site at codon 10 was identified with an initiation codon (GcgAUGG) downstream of p.(Gly8*) which appears to be preferential to the annotated one (GgcAUGA).[4] The p.(Gly8*) variant in *KIAA2026* therefore unlikely leads to RCD.

Meanwhile, mutations in *WDR34* were reported in severe syndromic ciliopathies occasionally associated with RCD. The variant identified in our patient (c.1241A>G; p.(Asp414Gly)) is absent from gnomAD and leads to the substitution of a conserved residue (Table S2). This genetic form of RCD is extremely rare as screening of 2685 of our autosomal recessive and sporadic RCD cohort did not reveal additional subjects with bi-allelic likely pathogenic changes in *WDR34*.

WDR34 encodes a 539-amino acid protein (WD40 domain repeat protein 34) expressed in many tissues,[5] including retina (Figure 2).[6–11] WDR34 is part of the intraflagellar transport (IFT) complex crucial for the assembly, maintenance and signaling function of the primary cilia, including photoreceptor outer segments.[12,13] Loss of *WDR34* in human telomerase immortalized retinal pigment epithelial (hTERT-RPE1) cells resulted in a deficient ciliary length control, in keeping with the involvement of WDR34 in the retrograde intraflagellar transport.[14] Further studies showed direct interactions with proteins associated with the retrograde motor dynein-2 complex.[13,14] Morpholino knockdown of the *WDR34* ortholog in zebrafish, *dync2-i1,* resulted in a reduction of electrophysiological light responses due to photoreceptor outer segment shortening.[15]

WDR34 contains seven WD40 repeats. The Asp414 residue, located in the fifth WD40 domain is highly conserved and is present in the proximity of five other previously reported pathogenic variants in the same domain (Figure 3). This, together with the fact that a negatively charged aspartic acid is replaced by a small non-polar glycine, suggests that the p.Asp414Gly variant likely affects the structure of this WD40 domain.[18]

Mutations in *WDR34* were previously identified in 17 ethnically diverse probands with severe skeletal ciliopathies such as short-rib polydactyly syndrome type III (SRPS III), asphyxiating thoracic dysplasia (ATD), SRPS and Jeune ATD (JATD) with documented

retinal dystrophy in two cases (Figure 3 and Table S4).[6,7,17–20] Twenty-three different, mostly missense, mutations were described (Figure 3 and Table S4). No case of biallelic null alleles was reported suggesting the requirement of a residual function to WDR34 for survival.[21] Most of the mutations leading to syndromic disease are lethal in early childhood, lead to stillbirth or *in utero* developmental defects.[6,7] Only two patients with JATD had also a retinal phenotype: one was compound heterozygous for c.472C>T p.(Gln158*) and c.1307A>G p.(Lys436Arg), while the other was homozygous for c.1229G>T p.(Ser410Ile) located in the same fifth WD40 domain as our novel variant (Figure 3). The lack of a retinal phenotype in patients with severe ciliopathies may be due to a short life span or a clinical oversight. On the other hand, the isolated retinal phenotype reported here may be explained by a hypomorphic nature of p.(Asp414Gly) or an effect on an interaction with a retina-specific protein.

Other genes coding for retrograde IFT proteins, including *WDR19* and *IFT140,* have been involved in a broad spectrum of ciliopathies affecting major organs, including the retina and also in non-syndromic RCD with a phenotypic variability potentially involving disease modi- fiers.[22] This study adds yet another gene to the broad phenotypic spectrum of ciliopathies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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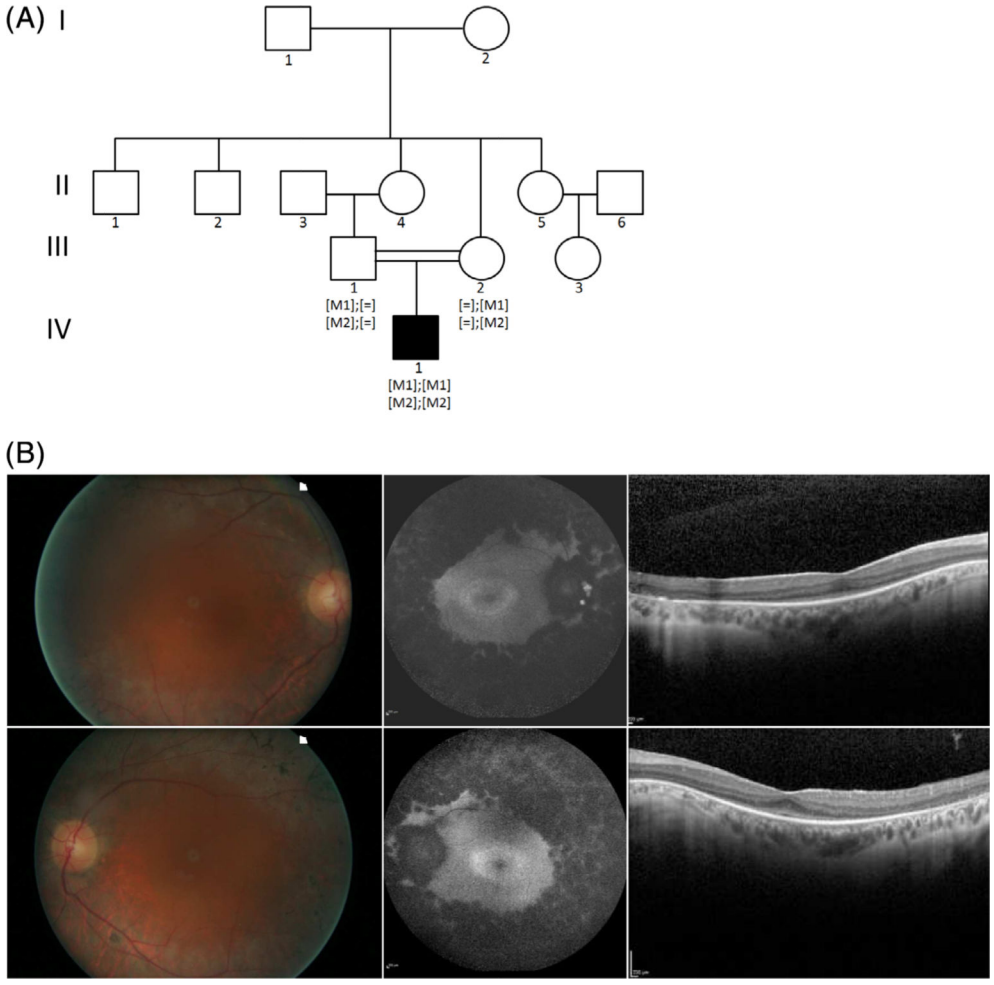

FIGURE 1.

A, Pedigree of a case with biallelic variants in *WDR34* (M1: c.1241A>G, p. (Asp414Gly)) and in *KIAA2026* (M2: c.22G>T, p.(Gly8*)) with co-segregation analysis (whole-exome sequencing and homozygosity mapping were applied to III.1, III.2 and IV.1). B, Retinal phenotype of the right (upper) and left (lower) eye (a) fundus photographs showing a waxy disc pallor, narrowed retinal vessels and pigmentary changes in the retinal periphery; (b) fundus autofluorescence showing loss of peripheral autofluorescence, and an hyperautofluorescent perifoveal ring; (c) spectral domain optical coherence tomography showing thinning of the outer retina (photoreceptor layer) in the periphery with relatively preserved foveal cones

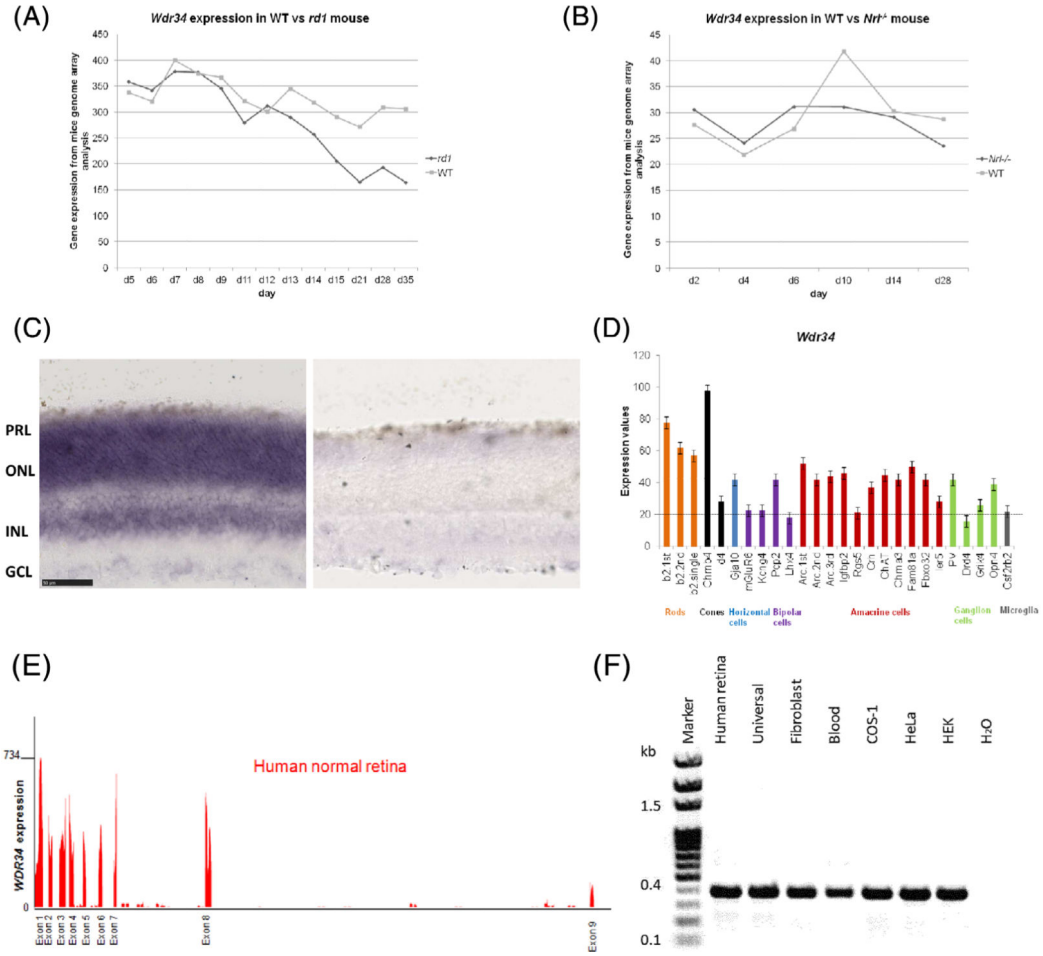

FIGURE 2.

A,B, Decreased expression of *Wdr34* in *rd1,* A, and *Nrl*$^{-/-}$, B, compared to wild-type controls at different stages of post-natal development.[12,13] C, *WDR34* is expressed in normal human retina transcriptomic database.[11] D, *Wdr34* is expressed in all mouse retina cell types including rods and cones.[10] E, RNA *in situ* hybridization of a *Wdr34* antisense and sense probes in adult mouse retinae show an expression in the outer and inner nuclear layers, absent in the sense-control. F, RT-PCR across exons 7 to 9 followed by Sanger sequencing confirms *WDR34* amplification. GCL, ganglion cell layer; INL, inner nuclear layer; ONL, outer nuclear layer; PRL, photoreceptor layer

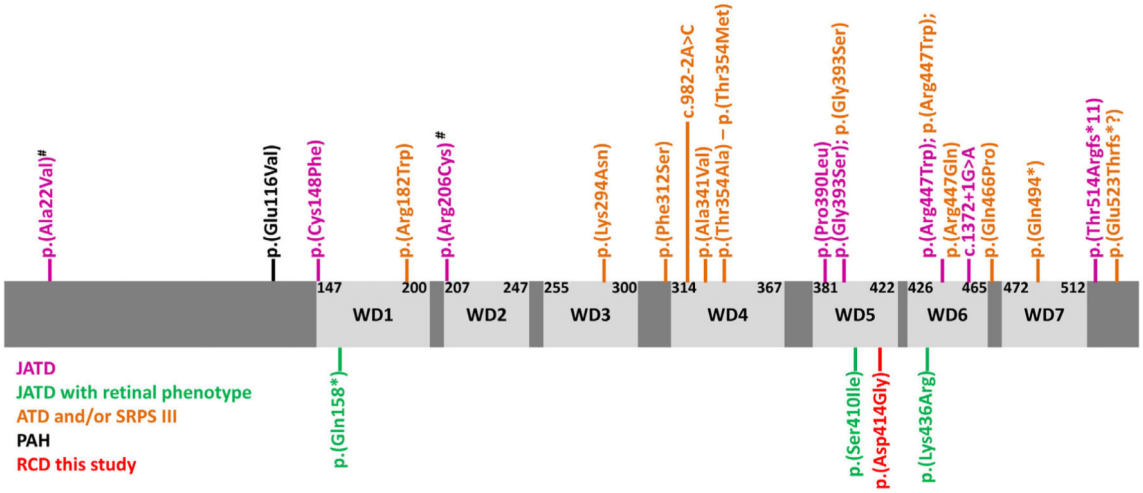

FIGURE 3.

Localization of reported WDR34 variants associated with various phenotypes: Jeune asphyxiating thoracic dystrophy (JATD) (violet), short-rib polydactyly syndrome type III (SRPS III) (orange), severe asphyxiating thoracic dysplasia (ATD) (orange), JATD with retina phenotype (green), pulmonary arterial hypertension (PAH) (black) and the rod-cone dystrophy case described here (red). #Two missense variants (c.65C>T p.(Ala22Val); c.616C>T p.(Arg206Cys)) have now a questionable pathogenicity since they occur homozygous in >8 controls in gnomAD.[25]