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CASE REPORT

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C21orf2 variants causing inherited retinal disease: A review of what we know and a report of two new suspected cases

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Abstract

Variants in the *C21orf2* (*CFAP410*) gene have recently been associated with the development of retinitis pigmentosa, an inherited condition characterized by degeneration of the retina. In this article, we describe 34 previously reported cases of *C21orf2* variant-associated retinopathies and present two new suspected cases.

KEYWORDS

C21orf2, CFAP410, ciliogenesis, ciliopathy, retinal dystrophy, retinitis pigmentosa

1 | INTRODUCTION

Variants in the *C21orf2* (*CFAP410*) gene have recently been associated with the development of retinitis pigmentosa, an inherited condition characterized by degeneration of the retina. In this article, we describe 34 previously reported cases of *C21orf2* variant-associated retinopathies and present two new suspected cases.

Retinitis pigmentosa (RP) is an inherited retinopathy characterized by the degeneration of photoreceptors and retinal pigment epithelium (RPE) with subsequent vision loss. It affects approximately 1 in every 4000 people in the United States.[1] The most common presenting symptom is loss of night vision, followed by gradual narrowing of visual fields, loss of color discrimination, and decreased visual acuity. Over 150 genes have been associated with both syndromic and isolated RP,[2] which can be inherited in an autosomal dominant, autosomal recessive, mitochondrial, or X-linked manner.[3–5] Many of these involve ciliary genes, as the photoreceptor outer segment is derived from highly modified cilia and connecting cilium between the inner and outer photoreceptor segments perform essential roles in ciliary signaling.[6–8] One such gene that has been associated with inherited retinal dystrophy is *C21orf2* (also known as *CFAP410*).

C21orf2 maps to chromosome band 21q22.3[9] and encodes a short leucine-rich protein with 256 amino acid residues.[10] It is expressed in both the photoreceptor layer and outer layers of the retina and is involved in ciliogenesis, cilia maintenance, and ciliary cargo transport of photoreceptors.[11] *C21orf2* variant-related retinopathies have two distinct phenotypes: one that solely affects the retina (OMIM #617547) and one with skeletal conditions such as axial spondylometaphyseal dysplasia (SMD) or Jeune Syndrome[12] (OMIM #602271) in addition to retinal manifestations. *C21orf2* variants have also been implicated in the development of amyotrophic lateral sclerosis (ALS),[13] leading to a variety of RP phenotypes. In this report, we describe the ocular and systemic manifestations of previously reported *C21orf2* variant-associated retinopathies in the literature, as well as present two new cases of siblings with a novel homozygous c.26T > C (p.Leu9Pro) variant. By summarizing the clinical presentations of all patients with *C21orf2*-associated RP to date, we hope to highlight the genotype and phenotype correlations of this complex gene and enable providers to better understand, diagnose, and manage patients with these conditions.

1.1 | Case histories and examinations

Patient 1, a 65-year-old African American female, was referred to the ophthalmic genetics specialty service at our institution for a clinical history and physical exam findings consistent with RP. She reported the onset of vision problems approximately 13 years prior, which included nyctalopia and decreased peripheral vision in both eyes. Central vision loss was slowly progressive but became significantly worse 3 years prior, along with new onset of photophobia, fluctuations in vision and color perception, and floaters. Family history was significant for a sister (Patient 2) with a suspected clinical diagnosis of a cone-rod dystrophy (CRD) and a paternal first cousin with premature macular degeneration. Neither of her two children or any of her several grandchildren have significant vision issues to date.

On initial evaluation, Patient 1's best corrected visual acuity was counting fingers at one foot away bilaterally. An accurate visual field assessment was not able to be performed due to her poor visual acuity. Fundus exam was significant for bilateral disc pallor with peripapillary atrophy, bull's-eye macula, diffuse vessel attenuation, diffuse RPE mottling, and peripheral bone spicules throughout the fundus in 360 degrees (Figure 1). Optical coherence tomography (OCT) of the macula was significant for mild epiretinal membranes and pericentral ellipsoid zone loss with subfoveal sparing bilaterally (Figure 2). Fundus autofluorescence (FAF) imaging demonstrated decreased autofluorescence in the subfoveal and perifoveal regions of both eyes (Figure 3). Full-field electroretinography (ERG) recordings were essentially flat appearing bilaterally, suggesting significant impairment in retinal function.

An inherited retinal disease genetic testing panel consisting of 351 genes revealed that Patient 1 had a novel homozygous c.26 T>C, p. (Leu9Pro) variant in *C21orf2*. This variant had never been reported in the medical literature and was classified as a variant of unknown significance (VUS) due to insufficient evidence to evaluate its clinical relevance. However, this variant is rare in control populations and in silico tools have predicted this substitution to be deleterious.

Patient 2, Patient 1's biological full sister with suspected inherited retinal disease, was subsequently evaluated at our clinic. She reported the onset of vision problems when she was around 8-years-old, which included gradual loss of central vision, nyctalopia, and photophobia. Neither of her two daughters have significant vision issues.

On initial evaluation, Patient 2's best corrected visual acuity was counting fingers bilaterally. An accurate visual field assessment was not able to be performed due to her poor visual acuity. Dilated fundus exam was significant for diffusely scattered, hyperpigmented and atrophic RPE changes bilaterally (Figure 4). Full-field electroretinography (ERG) recordings were similarly flat appearing in both eyes. Genetic testing confirmed that she also carried the same homozygous c.26 T>C, p. (Leu9Pro) variant in the *C21orf2* gene as Patient 1.

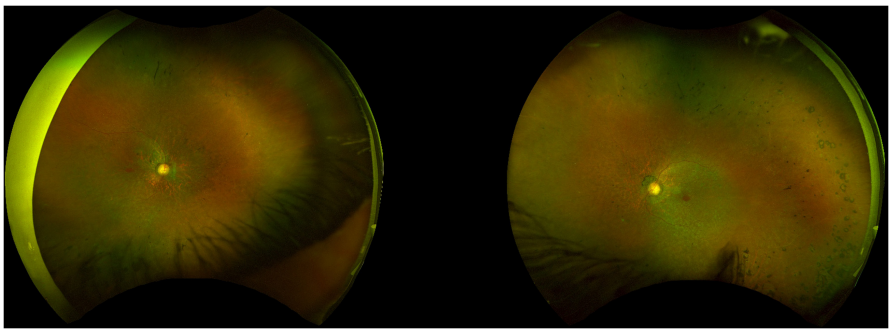

FIGURE 1 Optos photographs of the right and left fundus of Patient 1, notable for bilateral peripapillary atrophy, diffuse vessel attenuation, and peripheral bone spicules.

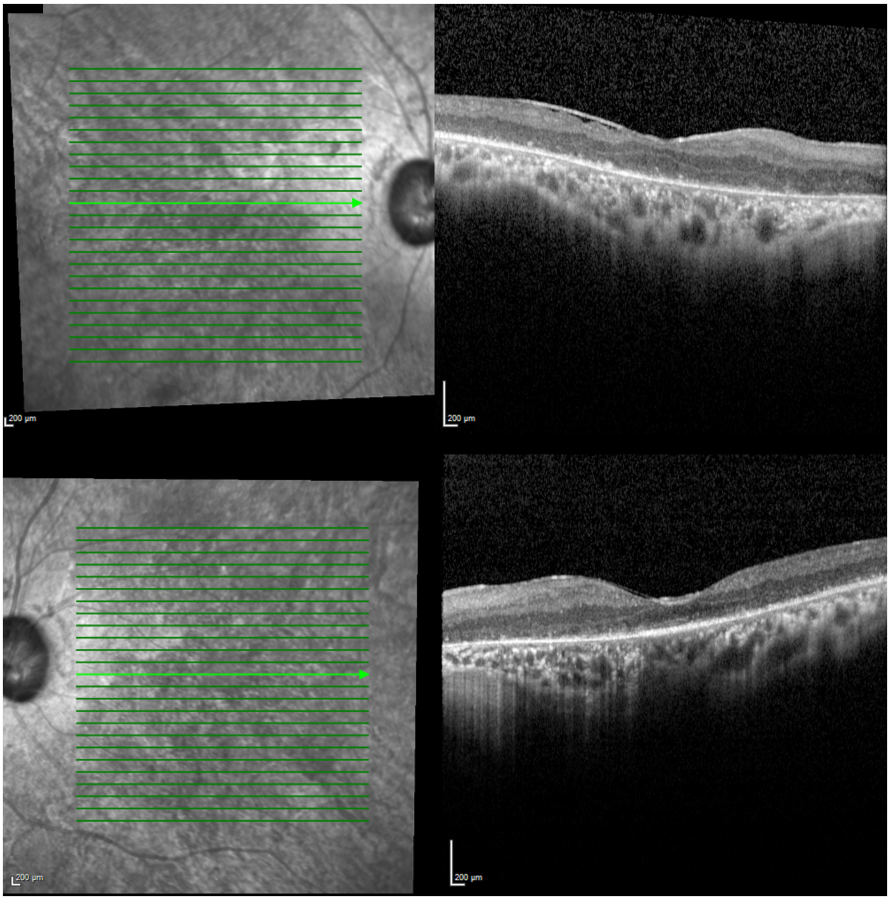

FIGURE 2 Optical coherence tomography images of the right and left macula of Patient 1, notable for ellipsoid zone loss with subfoveal sparing and visually insignificant epiretinal membranes in both eyes.

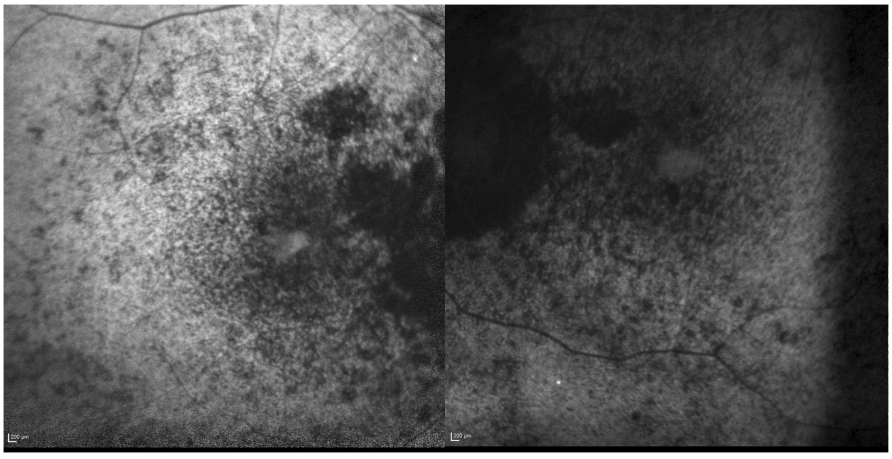

FIGURE 3 On initial evaluation, Patient 2's best corrected visual acuity was counting fingers bilaterally. An accurate visual field assessment was not able to be performed due to her poor visual acuity. Dilated fundus exam was significant for diffusely scattered, hyperpigmented and atrophic RPE changes bilaterally (Figure 4). Full-field electroretinography (ERG) recordings were similarly flat appearing in both eyes. Genetic testing confirmed that she also carried the same homozygous c.26 T>C, p. (Leu9Pro) variant in the *C21orf2* gene as Patient 1.

1.2 | Outcome and Follow-Up

Both patients were provided extensive counseling on genetic testing, genetic variants, patterns of inheritance, and gene-related retinal dystrophies. We explained that their shared c.26 T>C, p.(Leu9Pro) variant was highly suspicious for being the underlying cause of their vision issues given their similar presentations and histories. The sisters were also informed that while treatments for their condition do not currently exist, they may choose to get involved in retinal dystrophy research and ongoing clinical trials with stem cells; the potential benefits and risks of these options

were thoroughly discussed. Going forward, both patients will follow-up with our ophthalmic genetics service annually with continued co-management from retina, primary care, and other specialty services as needed.

2 | MATERIALS AND METHODS

Relevant case reports and review articles were identified through a systematic search of three databases (PubMed, Web of Science Core Collection, and Google Scholar) in September of 2022 with a query of "*C21orf2*" or "*CFAP410*". To be included in this review, articles had to be written in English and describe one or more cases of patients with known *C21orf2* variant-associated retinopathy.

3 | RESULTS

A total of 56 articles published between the years 2010 and 2022 were identified, of which 30 met the inclusion criteria. These 30 articles describe 34 cases of patients with

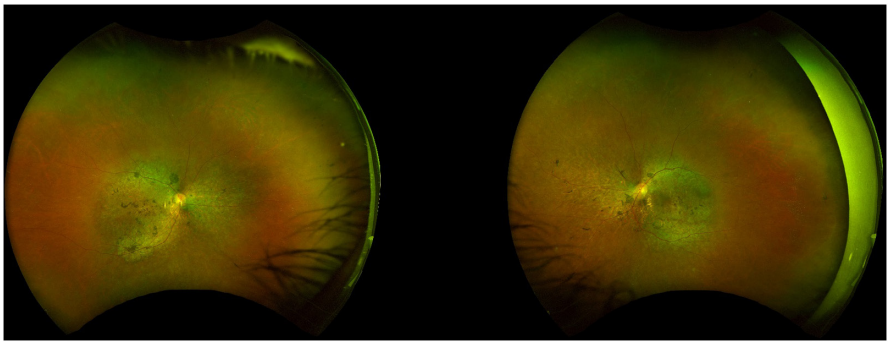

FIGURE 4 Optos photographs of the right and left fundus of Patient 2, notable for diffusely scattered, hyperpigmented, and atrophic RPE changes bilaterally.

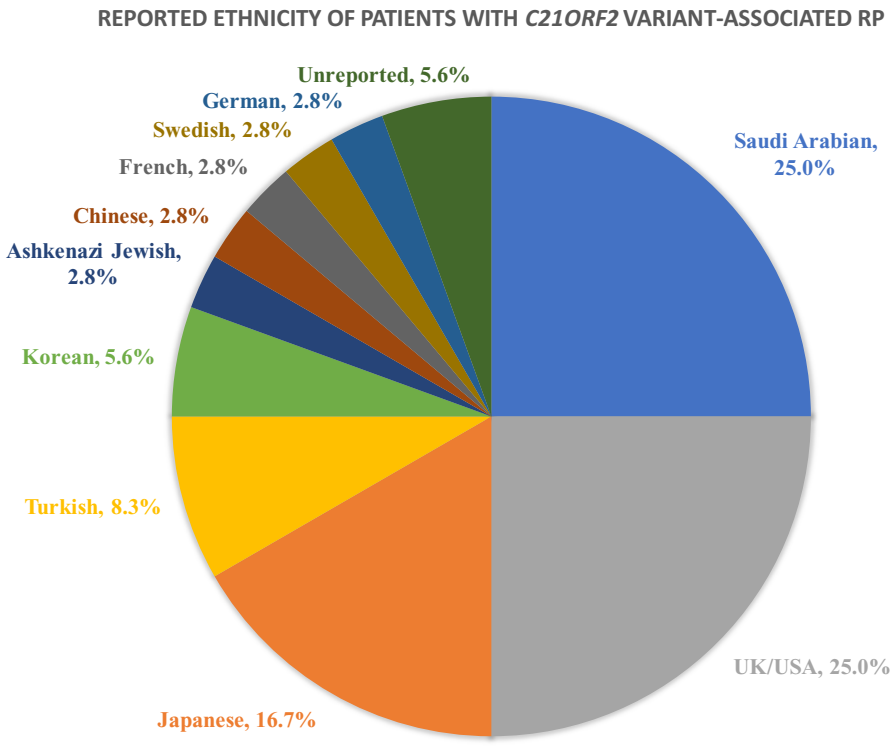

FIGURE 5 Ethnic background of all reported patients with *C21orf2* variant-associated retinopathies.

TABLE 1 Subjective ocular symptoms reported in patients with *C21orf2*-associated retinopathies to date.

Reported subjective ocular symptoms	Male	Female	Total	Percentage
Poor vision	8	14	22	61.1%
Loss of night vision	3	5	8	22.2%
Photophobia	1	3	4	11.1%
Loss of peripheral vision	0	3	3	8.3%

TABLE 2 Objective physical exam and test findings reported in patients with *C21orf2*-associated retinopathies to date.

Reported objective physical exam/ Test findings	Male	Female	Total	Percentage
Reduced ERG Findings	5	10	15	41.7%
Pigmentary changes on fundoscopic exam	1	12	13	36.1%
Retinal thinning or atrophy	3	9	12	33.3%
Staphyloma	1	3	4	11.1%
Cystoid macular edema	0	2	2	5.6%

TABLE 3 All gene variants reported in patients with *C21orf2*-associated retinopathies to date.

C21orf2 variant	Number of patients with variant	Percentage of patients with variant
c.218G>C (p.Arg73Pro)	11	30.6%
c.319 T>C (p.Tyr107His)	6	16.7%
c.331G>A (p.Val111Met)	3	8.3%
c.643-23A>T (p.Asn215Valfs*259)	3	8.3%
c.671 T>C (p.Leu224Pro)	3	8.3%
c.26 T>C (p.Leu9Pro)	2	5.6%
c.103delA (p.lle35Phefs*10)	2	5.6%
c.436_466del (p.Glu146Serfs*6)	2	5.6%
c.A320G (p.Tyr107Cys)	2	5.6%
c.340_351dup	1	2.8%
1.135 kb deletion (Chr21: 45,755,728–45,756,862)	1	2.8%
c.352_353insACCCTGCCGCGC (p.Arg117_Leu118insHisProAlaAla)	1	2.8%
c.(96þ1G>A)	1	2.8%
c.182G>A (p.Cys61Tyr)	1	2.8%
c.347C>T (p.Pro116Leu)	1	2.8%
c.545 + 1G > A (p.Ser183*, A181Glnfs*6)	1	2.8%
c.480_481insT (p.Leu161Serfs*9)	1	2.8%
c.96 + 6 T>A	1	2.8%
c.545 + 1C>T	1	2.8%

ocular symptoms and known *C21orf2* variants, which together with our patients make a total of 36 cases. Reported ethnic backgrounds of patients are displayed in Figure 5.

All of these patients had either homozygous or two heterozygous C21orf2 mutations and consanguinity was present in nine of the 36 patients (25%), suggesting that their ciliopathies were inherited in an autosomal recessive manner. Within the cohort, 22 (61.1%) patients were female, 24 (66.7%) patients had onset of their first ocular symptom before the age of 18 years old, and 25 (69.4%) patients had additional non-ocular phenotypes such as axial SMD (27.8%), Jeune asphyxiating thoracic dystrophy (JATD) (13.9%), or ALS (5.6%).

The subjective ocular symptoms of all 36 patients are summarized in Table 1, with poor vision being the most commonly reported (61.1%). Best corrected visual acuity varied widely and ranged from 20/40 to no light perception. Objective physical exam and test findings of the 36 patients are also summarized in Table 2, with retinal pigmentary changes (41.7%) and reduced ERG findings (36.1%) being the most common.

Table 3 summarizes the 19 different *C21orf2* variants that were identified in these 36 patients, of which 27 (75%) patients were homozygous for the same variant. The most commonly reported *C21orf2* variant was c.218G >C (p.Arg73Pro), which 11 (30.6%) patients had at least one copy of.

4 | DISCUSSION

In summary, we present two siblings with RP who were found to have the same homozygous c.26 T > C,

(p.Leu9Pro) mutation of *C21orf2*, a variant that has never been reported in the medical literature or any disease-related variation databases. Although *C21orf2* variants are associated with both syndromic and non-syndromic retinal dystrophy, the mutation seen in our patients is classified as a VUS. This can be attributed to the lack of both sufficient population-based statistical evidence and functional evidence, making it difficult to interpret the clinical significance of this variant at present. There is, however, a strong association between this gene and the sisters' phenotypes, as evidenced by their shared variant, symptoms, and similar features seen in other patients with known *C21orf2* variant-associated retinal disease (Table S1).[14–22] Future studies to elucidate the role of this variant and other *C21orf2* mutations on the pathogenesis of RP and potential associated skeletal manifestations are warranted.

AUTHOR CONTRIBUTIONS

Meagan Shinbashi: Data curation; methodology; writing – original draft; writing – review and editing. **Ann Jewell:** Writing – review and editing. **Jessica Randolph:** Writing – review and editing. **Natario Couser:** Conceptualization; methodology; project administration; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Meagan Shinbashi: Nothing to disclose. Ann Jewell: Nothing to disclose. Jessica Randolph: Nothing to disclose. Natario L. Couser: Retrophin, Inc./Travere Therapeutics, Inc. (Clinical Trial); National Cancer Institute/Children's Oncology Group (Clinical Trial); Elsevier (Book editor); Patient-Centered Outcomes Research Institute (PCORI; Advisory Panel on Rare Disease); National Institutes of Health/National Eye Institute (Grant Review Panelist).

DATA AVAILABILITY STATEMENT

The data that supports the findings of this article are available in the supplementary material.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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SUPPORTING INFORMATION

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

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