CERKL related autosomal recessive retinitis pigmentosa - A report on four affected members from a single family

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This case report describes the phenotypes associated with ceramide kinase like protein (*CERKL*) retinitis pigmentosa (RP) in a family with four affected members. We performed a cross sectional study of four members from a single family with RP. The retinal features, electrophysiology findings, and genetic results are discussed. Next generation sequencing based genetic testing was performed in two of the four affected family members. The affected individuals consisted of a 42 year old female proband (II.4), her 39 year old sister (II.6), and her two nephews, aged 10 and 12 years (III.2 and III.3, respectively). The genetic testing of III.2 and III.3 revealed the presence of a pathogenic homozygous frameshift nonsense variant (c. 1045_1046delAT, p.Met349Valfs*19) in exon 7 of the *CERKL* gene. All four family members had central vision problems since childhood. The best corrected visual acuity of the young patients, III.2 and III.3, was 20/30 and 20/80, respectively. The older patients (II.4 and II.6) were able to perceive only hand movements at the time of examination. The common retinal features found in III.2 and III.3 at presentation were minimal optic disc pallor, arteriolar attenuation, early loss of macular photoreceptors, central scotomas, and near extinguished responses in full field electroretinogram (ERG). There were no pigmentary or chorioretinal atrophic changes in the retina noted in individuals III.2 and III.3. The common retinal features in the proband (II.4) and her sister (II.6) in their 5th and 4th decades were prominent vascular attenuation, optic disc pallor, total macular atrophy, peripheral bony spicule pigmentation/scalloped chorioretinal atrophic patches, and a nondetectable ERG. In conclusion, the study of this family highlights the possibility of a severe phenotype in autosomal recessive *CERKL* related RP due to the nonsense variant c. 1045_1046delAT, p.Met349Valfs*19, as observed in our two genetically confirmed patients. Identifying the retinal phenotype and specific pathogenic variant is essential for accurate genetic counselling, personalized visual rehabilitation, and potential targeted therapies.

Key words: *CERKL*, retinal features, retinitis pigmentosa, RP26, single family

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Retinitis pigmentosa (RP) belongs to a group of inherited retinal diseases that show extensive genetic and phenotypic heterogeneity.[1–3] The inheritance pattern of RP can be autosomal recessive, autosomal dominant, X-linked, or mitochondrial. Sporadic cases of RP account for one-third or more of patients. Pathogenic variants in over 100 genes are known to cause RP (https://retnet.org). These mutant genes have reduced or complete loss of function, which in turn affects the health of the photoreceptors/retinal pigment epithelium (RPE) and the visual process.[1,3] Cellular apoptosis is mediated by ceramide kinases, which convert the sphingolipid metabolite ceramide into ceramide-1-phosphate. The defective ceramide kinase-like protein (*CERKL*) gene is known to be associated with autosomal recessive RP (RP26).[4] This gene is located on the long arm of chromosome 2q31.3 and encodes a protein that is part of the ceramide kinase-like family, which is involved in sphingolipid metabolism. It plays a crucial role in the protection of retinal cells against oxidative stress. It also helps by preventing apoptosis of RPE cells. Loss of its function leads to degeneration of photoreceptors and/or RPE.[4–6] *CERKL*-related RP can manifest as early maculopathy, inner retinal dysfunction, and laminopathy.[7,8]

Autosomal recessive *CERKL* RP is known to cause severe central loss of vision with early macular involvement, pauci-pigmentary changes in the retina, scalloped chorioretinal atrophic areas, arteriolar attenuation, and disc pallor.[5,7,9,10] In this study, we present a detailed characterization of phenotypes in four individuals from a single family affected with RP. Genetic testing of two young males affected with RP showed pathogenic variants in *CERKL*.

Subjects and Methods

This is a cross-sectional study, wherein four members of a family affected with RP were examined. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board. Demographic and clinical features with imaging investigations were analyzed. Age, onset of symptoms, and best corrected visual acuity (BCVA) by Snellen distance visual acuity

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chart were evaluated. Color fundus photography (by Optos optomap ultra-widefield (UWF™) or Zeiss Clarus 500), optical coherence tomography (OCT—by swept-source Topcon or Spectralis HRA + OCT), fundus autofluorescence (FAF—by Optos optomap ultra-widefield (UWF™), Zeiss Clarus 500, or Spectralis HRA + OCT), full-field electroretinogram (by Metrovision monopack or hand-held RETeval, LKC technologies), and visual fields (by Humphrey visual field [HVF]) were performed when possible.

Pedigree Analysis and Genetic Diagnosis

The pedigree analysis included collecting a three-generational family tree and information regarding major health issues running in the family. Whole blood (Ethylenediaminetetraacetic acid) samples were collected from two members of the family (III.2 and III.3) after obtaining informed consent from their parents. Genomic DNA was isolated from blood leukocytes and quantified using a Nanodrop spectrophotometer. The genomic DNA samples were used for library preparation. The patient's exomes were sequenced using next-generation sequencing (NGS)-based Illumina MiSeq sequencer to identify the mutations. Clinical exome sequencing (~6705 genes) was performed and covered approximately 96% of all positions at 20× coverage or higher. Paired-end 151 bp reads are aligned to the NCBI reference sequence (GRCh37.75) using the Bowtie2.2.1 short read aligner, and variant calls were made using open-source algorithms. Standard online databases like gnomAD (https://gnomad.broadinstitute.org/) and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar) were used to evaluate the pathogenicity of the variant found.

Results

The family consisted of two older females [II.4-proband and II.6-proband's younger sister] and two young male patients [III.2 and III.3] affected with RP [Fig. 1: Pedigree chart].

Clinical features

Case 1(II.4)

A 42-year-old female presented to us with a history of bilateral progressive blurring of central vision from the age of 6 years, with delayed dark adaptation and peripheral visual field affection. Her BCVA was hand motion appreciation close to the face in both eyes. Anterior segment examination was unremarkable. Dilated fundus examination of both eyes showed optic disc pallor, arterial attenuation, and prominent central macular atrophy with peripheral scalloped chorioretinal atrophic patches and sparse pigmentation. Retinal imaging and ancillary investigations were difficult to perform due to very low vision.

Case 2 (II.6)

A 39-year-old female had a history of reduced central vision from early childhood (from 4 years of age) and defective peripheral vision. On examination, her BCVA in both eyes was hand motion appreciation close to the face. Anterior segment examination was unremarkable. The fundus of both eyes showed pallor of the optic disc, prominent vascular attenuation, bony spicule pigmentation, peripheral scalloped chorioretinal atrophic patches, and central macular atrophy with pigmentation. FAF showed central confluent macular hypoautofluorescence and mid-peripheral and peripheral granular hyper-and hypoautofluorescence. The OCT scan passing through the macula revealed retinal and choroidal thinning, complete loss of photoreceptor and RPE layer, with subretinal hyperreflectivity suggestive of pigmentation [Fig. 2]. Full-field electroretinogram showed nondetectable scotopic and photopic responses.

Case 3(III.2)

A 10-year-old boy (son of II.6) presented with a history of bilaterally reduced central vision (with intact peripheral vision) from the age of 6 years. BCVA at presentation was 20/80, N10 in both eyes. Anterior segment examination was unremarkable. The dilated fundus of both eyes showed minimal arteriolar attenuation. There was neither pallor of the optic disc nor pigmentary or chorioretinal atrophic changes in the retina. The FAF of both eyes showed a hyper autofluorescent ring around the fovea with hypo autofluorescence inside the ring and central sharp speckled hyper autofluorescence. The OCT macula of both eyes showed loss of the central photoreceptor layer with an intact RPE layer and normal retinal thickness. RETeval skin ERG showed flat photopic flicker and single-flash responses. Isolated rod responses were nearly extinguished, and combined rod–cone responses were reduced in amplitude with increased latency. Oscillatory potentials were present. The 30-2 and 10-2 HVF analyses showed predominant affection for the central visual field [Fig. 3].

Case 4(III.3)

An 11-year-old boy presented with a history of predominant night vision problems from the age of 4 years, with progressive bilateral affection of reading vision as well. His BCVA at presentation was 20/30, N12. The anterior segment examination was unremarkable. Fundus of both eyes showed minimal arteriolar attenuation, subtle optic disc pallor, and central foveal abnormalities. There were no pigmentary or chorioretinal atrophic retinal changes. The FAF of both eyes showed a subtle hyperautofluorescent ring around the fovea. OCT passing through the macula showed a symmetric, widespread loss of the ellipsoid zone. ERG showed reduced amplitudes/increased latency of a- and b-waves in both photopic flicker and single-flash responses. There were nonmeasurable isolated rod responses, with maximal combined rod–cone responses showing reduced amplitude and increased latency. The 30-2 and 10-2 HVF analysis showed predominant affection of the central visual field along with peripheral visual defects as well.

Pedigree and genetic analysis

The three-generation pedigree chart revealed four members (II.4, II.6, III.2, III.3) affected with RP who were available for complete ophthalmic examination in this study [Fig. 1]. There was no reported history of consanguineous marriage in the three generations. However, the marriage was within the same ethnic community. Individuals III.2 and III.3 underwent genetic testing, whereas individuals II.4 and II.6 did not have genetic testing due to affordability. Genetic analysis of III.2 and III.3 through NGS-based clinical exome sequencing revealed a pathogenic homozygous nonsense variant, c. 1045_1046delAT, p.Met349Valfs*19, in exon 7 of the *CERKL* gene.

Discussion

This study describes the clinical phenotype of four affected members with RP in a single family. Two of the patients (III.2 and III.3) were genetically tested and confirmed to have *CERKL*-related autosomal recessive RP. The other two patients (II.4 and II.6) did not undergo genetic testing. However, the clinical phenotype of both patients (II.4 and II.6) was similar to what is described for *CERKL*-related autosomal recessive RP in previous literature, i.e., early macular involvement,

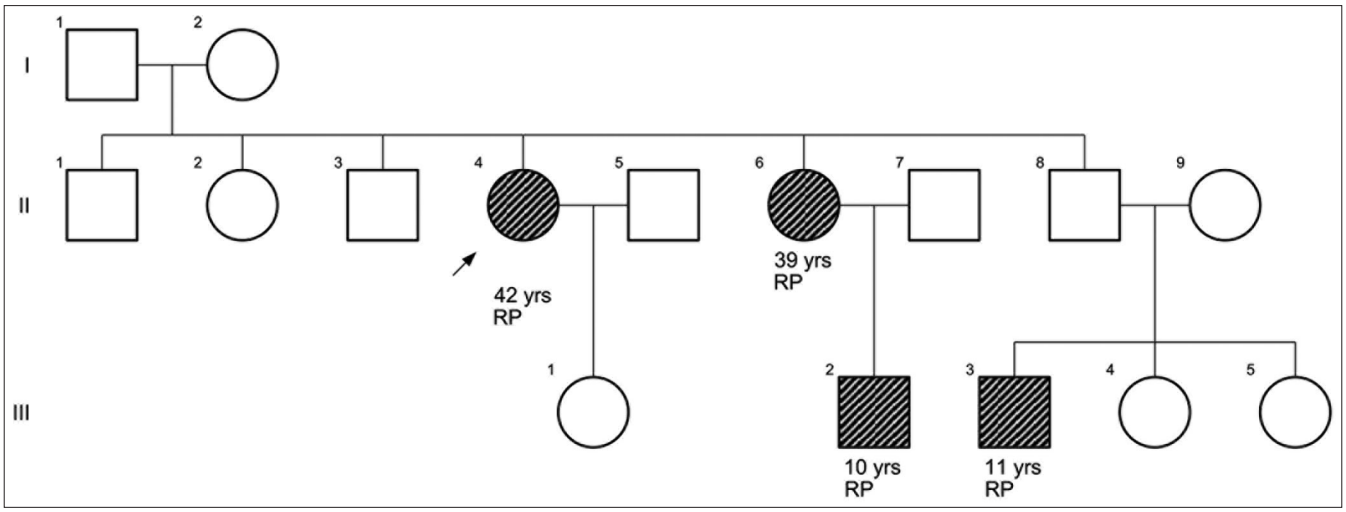

Figure 1: Three-generation pedigree chart revealed four members affected. RP; retinitis pigmentosa

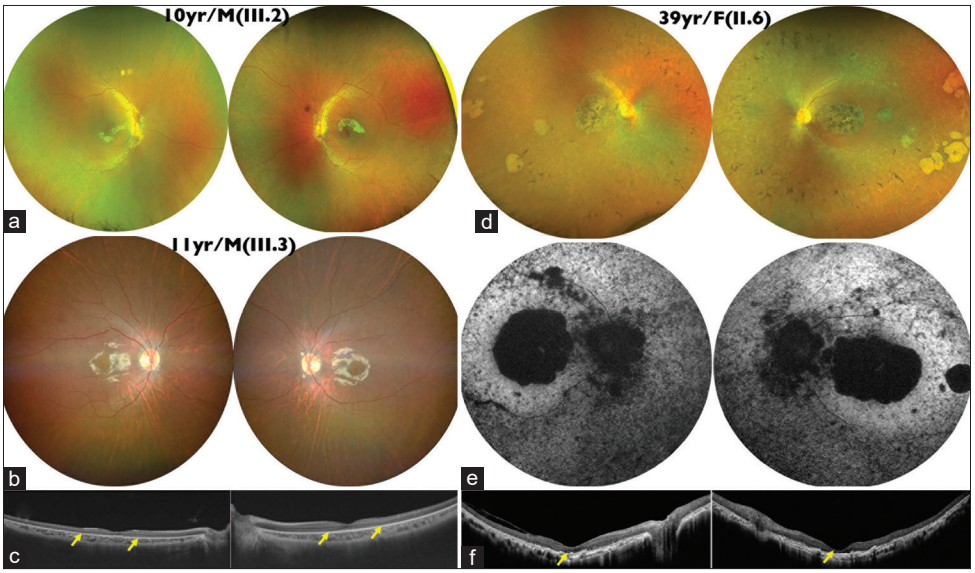

Figure 2: Fundus photographs of a 10-year-old (III.2) (a) and an 11-year-old (III.3) (b) showing minimal optic disc pallor and attenuated vessels without pigmentary changes in both the eyes. Optical coherence tomography (OCT) macula of the 11-year-old (III.3) (c) shows complete loss of the parafoveal ellipzoid zone (yellow arrows) with retinal thinning. Fundus photos (d), autofluorescence (e), and OCT (f) of a 39-year-old female (II.6). Fundus photos show pallor of the optic disc, prominent vascular attenuation, peripheral bony spicule pigmentation, scalloped chorioretinal atrophic patches, and central macular atrophy with pigmentation. Fundus autofluorescence shows central macular hypo autofluorescence and peripheral hyper-hypo autofluorescence. OCT of the central macula shows severe foveal thinning, loss of outer retinal layers (yellow arrows), and hyperreflective deposits correlating with the pigmentation and atrophy seen in the fundus photos

pauci-pigmentary changes in the retina, and scalloped chorioretinal atrophic areas.[5,7,9,10] There was a history of marriage within the same ethnic community. The pedigree did not reveal autosomal dominant or X-linked inheritance. Moreover, III.2, who had genetically confirmed *CERKL* RP, is the son of II.6. Hence, it is likely that even the two patients (II.4 and II.6) without genetic confirmation also have *CERKL-related* autosomal recessive RP. The common phenotypic features in the young patients (III.2 and III.3) in their first and second decades were, predominant affection of central macular functions without evident pigmentary changes in the retina. However, the two adult patients (II.4 and II.6), in the later part of their lives (early 40s), had severely reduced vision (hand motions appreciation), central macular atrophy with pigmentary changes of RP, and peripheral scalloped chorioretinal atrophies.

Pathogenic mutations in the *CERKL* gene lead to apoptotic cell death or oxidative stress in retinal photoreceptor cells, causing RP.[11,12] The genetic variant (c. 1045_1046delAT, p.Met349Valfs*19) found in two of our patients (III.2 and III.3) is reported to be pathogenic in the ClinVar single nucleotide polymorphism database (dbSNP) and the Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER) genome browsers. Our study patients were of North Indian origin, and individuals II.4 and II.6 had severe vision loss by approximately 40 years of age, with a phenotype consistent with *CERKL* RP. Two different studies of unrelated families with *CERKL* RP had shown that North Indian patients with the same nonsense variant had severe loss of vision during adulthood.[7,13] Our cases (III.2 and III.3) strengthen this association of severe visual loss with the c. 1045_1046delAT, p.Met349Valfs*19 variant of *CERKL* RP.

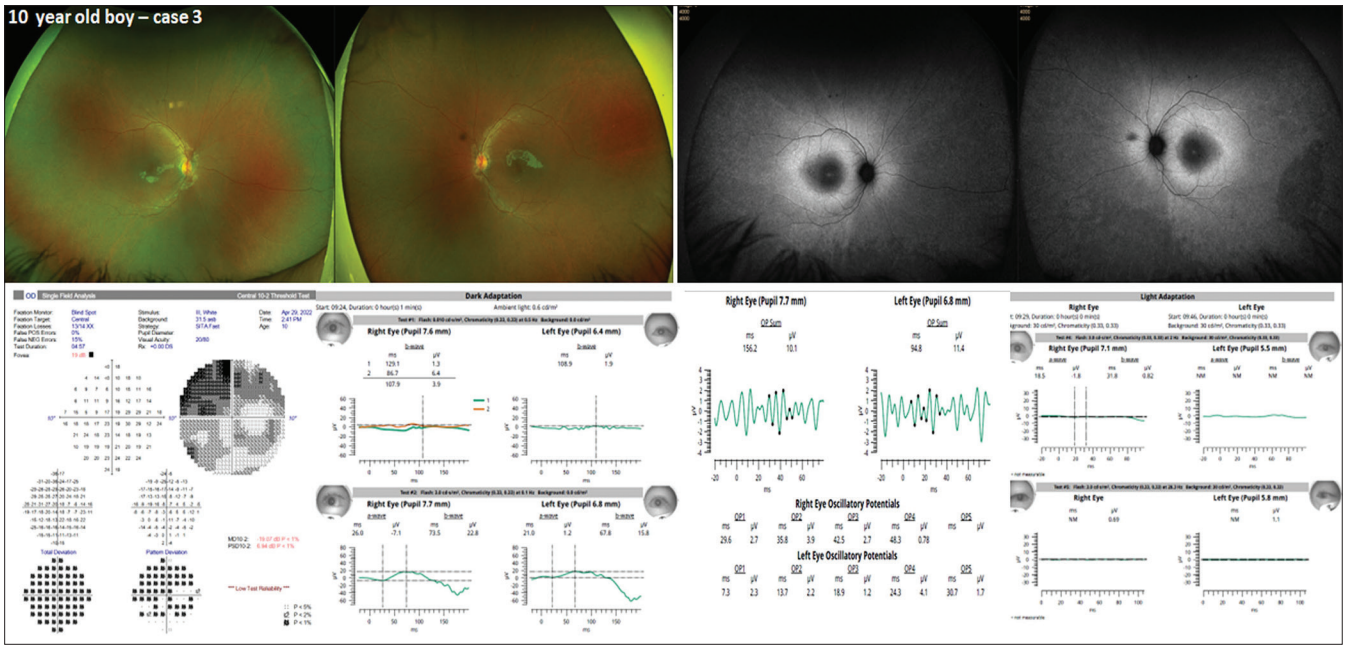

Figure 3: 10-year-old boy (III.2- proband's nephew)(Images in sequence) The fundus of both eyes shows minimal arteriolar attenuation and central macular atrophic changes. There was neither pallor of the optic disc nor pigmentary or chorioretinal atrophic changes in the retina. Fundus autofluorescence showing hyper autofluorescent ring around the fovea. Humphrey's visual field analysis of the right eye shows affection for the central visual field. Full field ERG showing extinguished isolated rod responses, and reduced amplitude in combined rod cone responses with flat photopic flicker and single flash responses. Oscillatory potentials were present

Additionally, this nonsense variant reported in our study may have a high prevalence in Indian populations from the northern part.

Downes *et al.*[13] described six patients (age range 7–45 years) with pathogenic variants in *CERKL* from different families. All but one had a similar presentation to the patients in our study, i.e., early affection of central vision. All our cases also fall within the same age group for vision loss, i.e. onset of visual problems in the first and second decades. Four patients in the study by Downes *et al.* had features of typical RP but with significant variation in presentation and severity. They also found two patients with only macular involvement and no pigmentary changes, like III.2 and III.3 in our study. They also concluded that the *CERKL* phenotype varies with age and severity. Sen *et al.*[7] reported genotype–phenotype correlations in 14 unrelated patients with *CERKL*-associated RP. They noted a bilaterally symmetrical presentation, with all cases having mild to moderate disc pallor, early macular involvement, and attenuation of arteries. Five patients had pauci-pigmentary and peripheral scalloped chorioretinal atrophic patches, similar to II.4 and II.6 in our study. A study by Avela *et al.*[9] reported 18 *CERKL* RP patients out of 55 IRD patients with macular disease, noting the first onset of symptoms in the second decade. Our study (III.2 and III.3) shows that the onset of symptoms can be in the early first decade (4 and 6 years of age). Avila-Fernandez *et al.*[14] identified 7 out of 210 unrelated Spanish families with autosomal recessive RP due to mutations in the *CERKL* gene, with phenotypes similar to those described in our study.

The majority of previous studies with *CERKL* RP involved unrelated individuals. Our study is unique in analyzing the phenotypical features with age in affected family members from the first to fifth decades of life. Patient III.2 in the family may progress to similar features as his mother (II.6), who has *CERKL* RP phenotypically [Fig. 4]. The correct identification of the phenotype, nature of inheritance, and the causative gene can help in many ways in a genetic disease. For example, in this scenario of our study with autosomal recessive *CERKL* RP, the recurrence of RP in the offspring of III.2 and III.3 is higher if their partner is a carrier for any pathogenic variant in the *CERKL* gene, i.e. a 50% risk of having a child with RP at each pregnancy. This knowledge was disclosed during pre- and post-test genetic counselling. The need for prenatal counselling to choose appropriate reproductive options when the young patients (III.2 and III.3) grow older was also explained. Genotyping of unaffected family members was also explained to identify carrier status.

Understanding the severity of the disease and its progression early in life helps in better rehabilitation and planning for the future. The older patients (II.4 and II.6) were advised 4 × magnification telescopes, field expanders, and near vision magnifiers during their second decade, and mobility training is currently being provided at a visual rehabilitation center. The younger patients (III.2 and III.3) are currently managing with larger font sizes on electronic tablets and the use of magnifiers. They are appropriately counselled well in advance before their possible severe visual disability in the future and are in regular follow-up at our visual rehabilitation centre.

Identifying the disease phenotype at a younger age (1st and 2nd decades) in cases of *CERKL*-associated RP is important, as they can be misdiagnosed due to the lack of typical RP features like defective night/peripheral vision and pigmentary changes. Early central visual function affection, with a severe affection of both scotopic and photopic full-field ERG responses in the first decade of life, should point toward the possibility of *CERKL* as a causative gene. Another childhood-onset retinal dystrophy, i.e. Leber congenital amaurosis, can also involve extinguished photopic and scotopic responses in ERG with a near-normal fundus. However, patients with LCA will also have a profound loss of vision from birth or early childhood (<1 year). The presence of nystagmus, eye-poking behavior with wandering movements, and high hypermetropia can differentiate LCA from *CERKL*-associated early-onset retinal dystrophy.

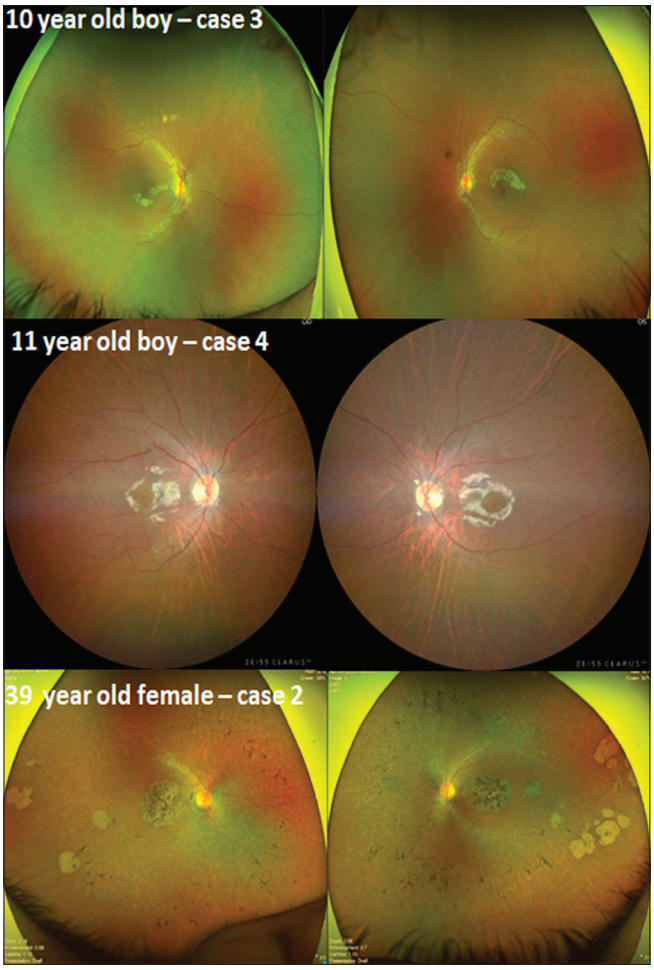

Figure 4: Fundus photographs of III.2, III.3 and II.6 showing a varied phenotypic presentation at different ages from younger to older age

The limitations of the present study are the inability to genotype older patients (II.4 and II.6) due to affordability, and the unavailability of two more affected family members for examination. However, the retinal phenotype of II.4 and II.6 in our study is similar to what is reported in previous *CERKL* RP studies. The lack of examination and genotyping of unaffected family members to identify their carrier status is another limitation of our study.

In conclusion, the phenotypical features of *CERKL*-related RP26, as observed in our study, can range from mild to moderate visual loss, with early macular involvement and an absence of typical retinal pigmentary abnormalities in the first decade of life, as seen in our genetically confirmed patients III.2 and III.3. The nonsense variant (c.1045_1046 del AT, p.Met349Valfs*19) identified in this study may be linked to a more severe phenotype, characterized by significant ERG impairment from early childhood. Profound visual loss, severe macular atrophy, and typical RP changes tend to manifest later in life, as observed in the phenotypically suggestive *CERKL* RP patients II.4 and II.6. The knowledge of changing phenotype due to the *CERKL* gene from early to later life helps in appropriate diagnosis and management.

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Authors' Contributions

PT and DCP were involved in conceptualization, study design, literature review, data acquisition and analysis, manuscript preparation, editing and review. SKP, JB and SJ contributed to manuscript review and editing.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest: There are no conflicts of interest.

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