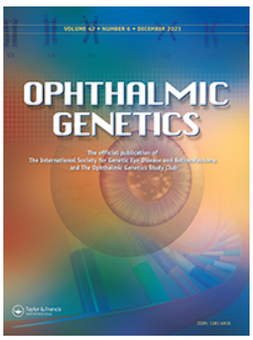

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REVIEW

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A novel frameshift variant in *CEP78* associated with nonsyndromic retinitis pigmentosa, and a review of *CEP78*-related phenotypes

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ABSTRACT

Background: Pathogenic variants in the *CEP78* gene can present as atypical Usher syndrome or as retinitis pigmentosa. Here, we present a review of all reported cases of *CEP78* variants in the literature to date and present a novel variant of *CEP78*, c.1261_1262delinsA, in a consanguineous northern Finnish family with two individuals.

Materials and methods: Our patients were first discovered in a registry-based study. Later, they gave their written consent for this study. In order to describe the genotype and phenotype, their historic clinical patient data and genetic data were gathered, and a clinical ophthalmic examination and an audiogram were performed. For this review, a PubMed search using the keyword CEP78 was carried out. The first article on *CEP78* was published in the year 2007, and the publications from the years 2007–2021 were included.

Results: A large gene panel identified a homozygous *CEP78* c.1261_1262delinsA variant in two affected siblings. In addition to the classical signs of retinitis pigmentosa, both siblings had large round atrophic spots in the mid periphery, and hyperautofluorescence of the macula. Patient 1 had age-related hearing impairment; patient 2 had normal hearing. In total, 20 articles have been published about *CEP78*. Eight of these papers report patient data with the affected individuals typically having retinal dystrophy combined with sensorineural hearing impairment, classified as atypical Usher syndrome.

Conclusions: Here, we present a comprehensive review of *CEP78* and expand the knowledge of pathogenic *CEP78* variants and the phenotypic variety.

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CEP78; inherited retinal dystrophy; retinitis pigmentosa; consanguineous; autosomal recessive

Introduction

Inherited retinal diseases (IRD) are a genetically and clinically heterogeneous group of diseases that all have in common the dystrophy of cone and rod cells of the retina and the heredity of the disease (1). IRD can present as syndromic, e.g., Usher syndrome, or nonsyndromic, such as Leber congenital amaurosis or retinitis pigmentosa (RP). The genetics of IRD has been studied intensively during the past 15 years, and remarkable allelic and locus diversity has been verified. Nearly 300 different genes associated with IRD have been identified (RetNet, https://sph.uth.edu/retnet/, 2).

Pathogenic biallelic variants in the *CEP78* (OMIM 617110) gene are known to cause an atypical Usher syndrome characterized by cone-rod dystrophy (CRD) and bilateral sensorineural hearing impairment (BSNHI). CEP78 is a centrosomal protein implicated in formation of the cilia and ciliary length control. Pathogenic *CEP78* loss-of-function variants have been shown to result in almost undetectable levels of CEP78 in patient cells (3). CEP78-deficient patients have longer primary cilia, suggesting impaired functionality (3,4). In addition, depletion of CEP78 in retinal pigment epithelial (RPE1) cells reduced the proportion of ciliated cells and affected primary cilium assembly, as well as increased the length of remaining cilia (5,6).

The *CEP78* encodes a component of the centrosome, the major microtubule-organizing center of the cell. The centrosome influences cell shape, polarity, and motility, and it has a pivotal role in cell division. CEP78 plays a role in the centrosome-related events during the cell cycle, such as PLK4-induced overduplication of centrioles (7). In addition, CEP78 promotes ciliogenesis by negatively regulating CP110 levels (6,8). Thus, *CEP78*-related disorders belong to the growing number of heterogeneous diseases called primary ciliopathies, ranging from a single organ disturbance to complex pleiotropic syndromes.

Here, we report a novel frameshift variant in *CEP78*, c.1261_1262delinsA, in a consanguineous northern Finnish family presenting with a non-syndromic retinitis pigmentosa and review the current literature of *CEP78*-related disease. This study reaffirms the phenotypic heterogeneity of the disease.

Methods

Patient 1 was referred and consented to genetic testing with a 266-gene retinal dystrophy panel in a CAP- and ISO-accredited laboratory (Blueprint Genetics, Finland). Variants were classified

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according to a point-based modification of the Association for Molecular Pathology/American College of Molecular Genetics and Genomics guidelines (9).

Patient 2 was referred for targeted variant testing in a CAP- and ISO-accredited laboratory (Blueprint Genetics, Finland). The targeted testing of the *CEP78* c.1261_1262delinsA, p.(Gly421Ilefs*4) variant was performed with bidirectional Sanger sequencing using DNA extracted from whole blood. The genomic DNA from patient 1 was included in the targeted *CEP78* c.1261_1262delinsA, p.(Gly421Ilefs*4) variant testing.

The *CEP78* variant nomenclature is based on the accession number NM_001098802.3 from the RefSeq database (10).

Results

Clinical delineation of the patients

Patient 1 (Figure 1, V-1) is a 70-year-old man who is the first child of healthy consanguineous Finnish parents. At the age of 7 years, he got his first pair of glasses and had good vision wearing them. At 18 years of age, he was issued a driver's license and continued to have no visual problems. Also, at the age of 30 years, he had an eye examination for driving and was still noted as seeing well. When he was 33 years old, his younger sister was diagnosed with retinitis pigmentosa. Approaching 40 years of age, he himself started noticing deterioration of vision. His eyes became sensitive to light, and adjustment to dim light was poor. He worked as a salesperson in a furniture store, and paperwork was particularly laborious. At the age of 43, retinal changes and opacity of the posterior capsule of the lens were diagnosed bilaterally, and the patient was referred to an eye clinic.

The diagnosis of retinitis pigmentosa was made based on narrow retinal arteries and pigment deposits in the retinal periphery. The optic disks appeared fairly normal at that time. The visual acuities were 0.2 (logMAR 0.7) and 0.06 (logMAR 1.2), with the refractive error being +0.25 cyl +0.5 ax 100°/-0.25 cyl +1.25 ax 85°. Dark adaptation showed missing rod adaptation. Goldmann perimetry (II/4) showed tunnel vision of less than 10 degrees in diameter. Color vision was practically absent. Electroretinograms showed no rod responses. The subject was soon forced to retire. Visual aids were fitted.

Cataract surgeries were performed at 50 and 51 years of age, and right-sided YAG laser capsulotomy for secondary cataract was later performed. During the following years, glare became increasingly troublesome, and the use of absorption glasses became important.

At the age of 70 years, his visual acuity is light perception and he is using the techniques of the blind. He has mild hearing impairment in the high frequencies, which appears identical to typical age-related presbycusis (Figure 2A). He has not reported subjective hearing problems. Otherwise, his physical health is good, and he has no regular medication.

Patient 2 (Figure 1, V-2) is a 66-year-old woman who is a younger sister of patient 1. In her late twenties, she started to have difficulties seeing at night and noted loss of peripheral vision. She experienced a minor ocular trauma at 28 years of age and, therefore, had an ophthalmic examination in which retinal changes suggestive of retinitis pigmentosa were detected.

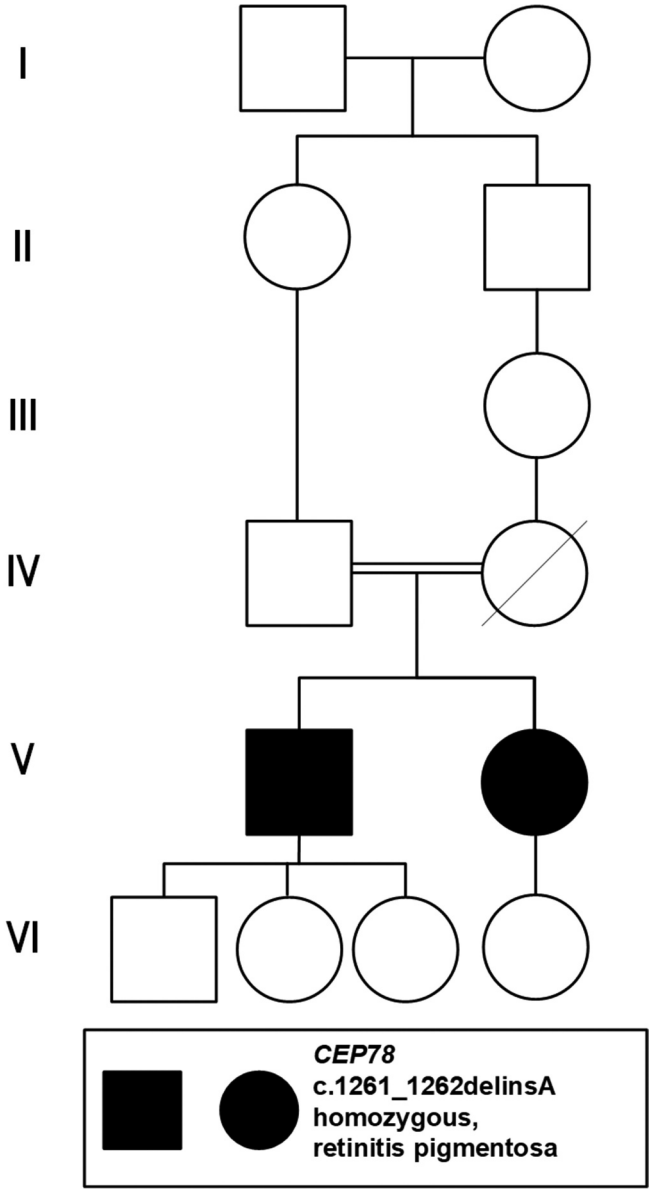

Figure 1. Pedigree of the family.

The diagnosis was confirmed based on retinal pigment deposits, missing dark adaptation, and narrow central visual fields with circular scotomas in the mid periphery combined with normally extending fields in the far periphery. Color vision was normal.

Ten years later, Goldmann (II/4) perimetry revealed tunnel vision, the diameter of the central visual field being less than 10 degrees. The visual acuity was 0.3 (logMAR 0.52)/0.5 (logMAR 0.3) with correction of −0.75 cyl +1.75 ax 85°/-0.5 cyl +1.5 ax 85°. At the age of 42 years, bilateral posterior subcapsular cataract was diagnosed, and cataract surgeries took place at the age of 47. She retired from her work as a secretary at the age of 50 years. Photophobia became increasingly disabling, and absorption glasses were necessary.

The patient has been diagnosed with hypothyroidism, high blood pressure, asthma, irritable bowel syndrome, spinal stenosis in the lumbar region due to disk degeneration and protrusion, and dystonia. Brain MRI at the age of 64 showed mild fronto-temporomedial atrophy. At the age of 66 years, she is able to see

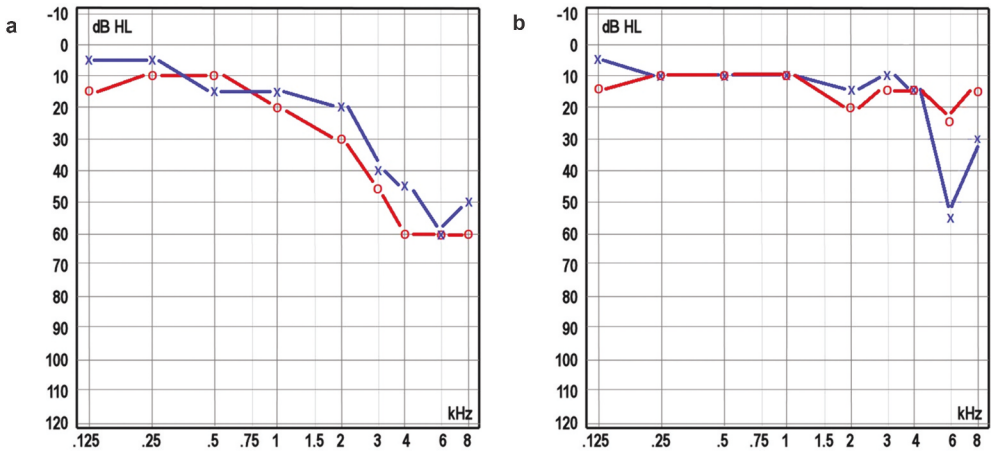

Figure 2. A.Pure tone audiogram (PTA) of patient 1 at age of 70 years shows mild hearing impairment in the high frequencies, which was assessed to be age related. B. PTA of patient 2 at the age of 66 years shows normal hearing.

her smartphone with visual acuities of hand motion in her right eye and 0.125 (logMAR 0.9) in her left eye and a small central field remnant of the left eye. There is alternating exotropia. The ocular fundi have pigmentary deposits and atrophic spots or patches, and the optic disks are pale, and the vessels narrow. This is demonstrated in the color and autofluorescence images of the fundi, and the appearance is seemingly similar to the fundi of her brother (Patient 1). She has problems moving around and is making use of the white cane, the guidance of her family, and absorption glasses. Her hearing is normal (Figure 2B).

Genetic results

Both patients were found to carry a homozygous c.1261_1262 delinsA, p.(Gly421Ilefs*4) variant in exon 11 of the *CEP78* gene (NM_001098802.3, GRCh38 g.9:78254842_78254843delinsA, rs777459097). The variant is present in the Genome Aggregation Database (gnomAD, v.2.1.1), with a minor allele frequency of 0.00002532, including no homozygotes. The deletion/insertion variant generates a frameshift leading to a premature stop codon at position 4 in a new reading frame. It is predicted to cause a loss of normal protein function either through protein truncation (423 out of 722 aa) or nonsense-mediated mRNA decay. To our knowledge, the variant has not been published previously in the medical literature or reported in the disease-associated databases such as Clinvar or the Human Gene Mutation Database. According to the ACMG/AMP criteria (8), the CEP78 c.1261_1262delinsA, p.(Gly421Ilefs*4) variant is classified as pathogenic, based on the segregation data (PP1), extremely low frequency in the control population (PM2), and the truncating nature of the variant (PVS1).

In addition, *IFT140* c.2824C>G p.(Leu942Val) (rs774563994) variant was identified heterozygously in patient 1 and homozygously in patient 2. The variant is classified as likely benign based on lack of segregation (BS4), in silico predictions (BP4). Also, *CYP4V2* c.414–1 G > A variant was found heterozygously in patient 2 and absent in patient 1. As variants in *CYP4V2* cause autosomal recessive retinal dystrophy, the variant is not assessed to be causative.

Review of the literature

Clinical and genetic details of published patients with *CEP78*-related retinal dystrophy are summarized in Table 1. Original accompanying reports described altogether nine patients with biallelic truncating *CEP78* variants causing CRD and BSNHI (3,11). De Castro-Miro et al. screened patients with IRD and identified a homozygous frameshift variant, c.1056delT, p.(Thr353Leufs*5), in a patient with autosomal recessive retinitis pigmentosa (14). However, a detailed clinical description of this patient's phenotype was not available, and the association between RP and *CEP78* variants remained obscure. Later, Fu et al. suggested that pathogenic biallelic *CEP78* variants cause a distinct type of Usher syndrome (12). Sanchis-Juan et al. used whole-genome sequencing to screen patients with IRD, and identified homozygous deletion-inversion-deletion affecting *CEP78* in association with typical CRD and BSNHI (13), confirming that complex genomic structural variants can also cause *CEP78*-related disorder. Ascari et al. demonstrated the pathogenic nature of the first *CEP78* missense variant c.449 T > C, p.(Leu150Ser) causing CRD and BSNHI (4). To date, altogether 28 patients with pathogenic biallelic *CEP78* variants have been reported in eight different studies (3,4,11–16). Twenty-one patients had CRD or CD by the age of 50 years, and four patients, including the patients presented in this study, had RP or RCD. Twenty-one out of 28 patients had BSNHI by the age of 45 years. Two patients without hearing impairment were relatively young. Hearing impairment was not reported in the remaining five patients (3,4,11–16). These eight studies reported 18 distinct pathogenic intragenic variants of *CEP78*, including one nonsense variant, four intragenic single nucleotide deletions resulting in a frameshift, eight splice site variants, and five missense variants (3,4,11–16). In addition, three different structural pathogenic genomic variants were reported as causative, including deletion-inversion-deletion, whole gene deletion, and inversion affecting *CEP78* (Table 1, Figure 4) (3,4,11–16).

Table 1. Pathogenic variants of *CEP78* and associated clinical phenotypes reported in medical literature to date.

Study	Genotype	Phenotype	Age (in years) when visual loss symptoms started	Age (in years) when hearing loss symptoms started	Other
This study, female subject	c.1261_1262delinsA/ c.1261_1262delinsA	RP	28	Hearing is normal for a person of this age	Asthma, high BP, hypothyreosis, IBS, stenosis L3-L4
This study, male subject	c.1261_1262delinsA/ c.1261_1262delinsA	RP	40	Hearing is normal for a person of this age	
(11)	c.893–1 G > A/ c.893–1 G > A	CRD and BSNHI	10	45	DM, high BP, obesity, tinnitus, and occasional vertigo
	c.893–1 G > A/ c.893–1 G > A	CRD and BSNHI	10	11	High cholesterol, BPH
	c.893–1 G > A/ c.893–1 G > A	CRD and BSNHI	20	42	
	c.534delT/ c.534delT	CRD and BSNHI	35	36	
	c.534delT/ c.534delT	CRD and BSNHI	30	20	Tinnitus in the right ear
	c.893–1 G > A/ c.534delT	CRD and BSNHI	28	10	Tinnitus and balance issue
(3)	c.499 + 1 G > T/ c.499 + 1 G > T	CRD and BSNHI	18	NA	Nystagmus
	c.499 + 5 G > A/ c.633delC	CRD and BSNHI	NA (individual has deceased)	Hearing impairment from a young age	
	c.499 + 5 G > A/ c.633delC	CRD and BSNHI	NA	NA	
(12)	c.1254 + 5 G > A/ c.1254 + 5 G > A	CRD and BSNHI	13	30	
	c.1254 + 5 G > A/ c.1254 + 5 G > A	CRD and BSNHI	11	40	
	c.1629–2A>G/ c.1629–2A>G	Vision impairment and BSNHI	10	8	
	c.1629–2A>G/ c.1629–2A>G	Vision impairment and BSNHI	NA	NA	
(13)	homozygous delINVdel affecting *CEP78* gene	CRD and BSNHI	50	NA	Nystagmus
(4)	c.449 T > C/ c.449 T > C	CRD and BSNHI	17	17	Reduced male fertility and DM
	c.449 T > C/ c.449 T > C	CRD and BSNHI	15	15	
	c.449 T > C/ c.449 T > C	CRD and BSNHI	20	20	
	c.449 T > C/ c.1462–1 G > T	CRD and BSNHI	6	6	Reduced male fertility
	c.449 T > C/ c.1462–1 G > T	CRD and BSNHI	6	6	
(14)	c.1056delT/ c.1056delT	RP	NA	NA	
(15)	c.830 T > C/ c.830 T > C	CRD	32	No***	
(16)	Whole deletion/ c.211delG	N/A	35	Birth	
	c.254–1 G > T/ c.323 T > G	N/A	18	18	
	c.1629–7C>A/ c.1629–7C>A	N/A	Teens	15	
	c.635 G > A/ Whole deletion	CRD and BSNHI	40	Birth	
	Inversion der (9)(q21.2)/ Inversion der (9)(q21.2)	CRD and BSNHI	46	50	
	c.440C>T/ c.440C>T	RCD and BSNHI	18	12	
	c.1175C>T/ c.1175C>T	CD	11	No**	

Abbreviations: RP = retinitis pigmentosa, CRD = cone-rod dystrophies, BSNHI = bilateral sensorineural hearing impairment, BP = blood pressure, IBS = irritable bowel syndrome, DM = diabetes mellitus, BPH = benign prostatic hyperplasia.
Transcript: NM_001098802.3
**Age was 25 years old at last visit
***Age was 43 years old at last visit

In the Clinvar, there are 31 pathogenic or likely pathogenic variants and 108 variants of uncertain significance (https://www.ncbi.nlm.nih.gov/clinvar/), whereas in the Varsome database there are 39 pathogenic variants of *CEP78* with known pathogenicity and 110 with uncertain significance (Varsome, https://varsome.com/gene/cep78, 8 November 2021).

Discussion

We report a novel homozygous frameshift variant in *CEP78* causing classical retinitis pigmentosa with the first symptoms appearing in the third or fourth decade of life. The disease led to severe visual impairment and disability to work in the fifth decade and, further, to near blindness by the seventh decade.

Inherited retinal dystrophies display striking locus and allelic heterogeneity. Previous studies have demonstrated that as many as two-thirds of variants causing inherited retinal dystrophies are private and unique to the pedigrees (14). In addition, pathogenic variants in genes involved in IRDs can cause variable clinical phenotypes, adding another layer of complexity to the diagnostics.

In addition to IRD, concurrent progressive hearing impairment has been reported in most patients with pathogenic biallelic *CEP78* gene variants. Unlike most cases in previous reports, neither subject here has experienced problems with hearing. This is verified by the current audiograms that are typical for their age. Previous studies have suggested that cone-rod dystrophy associated with sensorineural hearing impairment is a hallmark of *CEP78*-related disorder. Previously, only one patient with autosomal recessive retinitis pigmentosa phenotype has been associated with pathogenic homozygous truncating *CEP78* c.1056delT variant (14). Our study confirms that the phenotypic spectrum caused by *CEP78* variants varies from typical cone-rod dystrophy associated with sensorineural hearing impairment to adult-onset retinitis pigmentosa. Similar truncating loss-of-function *CEP78* variants can result in either classic non-syndromic retinitis pigmentosa or cone-rod dystrophy associated with sensorineural hearing impairment. On the other hand, the *CEP78* p.(Leu150Ser) missense variant resulted in typical cone-rod dystrophy with hearing impairment (4). It is possible that modifying genetic or even environmental factors contributes to the phenotypic presentation of the patients.

The patients in this study have pigment deposits in the mid periphery as well as pale disks and narrow retinal vessels, which are classical signs of retinitis pigmentosa and have been documented in patients who also have *CEP78* variants (11). In addition, they have large round atrophic spots in the mid periphery, and hyperautofluorescence in the macula. These lesions appear to be more unique and can be pathognomonic to the variant described here (Figure 3).

CEP78 is ubiquitously expressed, and its expression is enhanced in cone and rod photoreceptor cells (https://www.proteinatlas.org/, 17), consistent with the strong association of CEP78 deficiency and cone-rod dystrophy. *CEP78* is also expressed in the inner ear and spermatocytes, explaining the causal relationship between pathogenic *CEP78* variants and sensorineural hearing impairment and male infertility, although this association has variable penetrance and expressivity. *CEP78*-related sensorineural hearing impairment varies from congenital hearing impairment to normal hearing. The male patient presented in this study had three healthy children, and there was no medical history of infertility, suggesting that the male infertility phenotype also has incomplete penetrance.

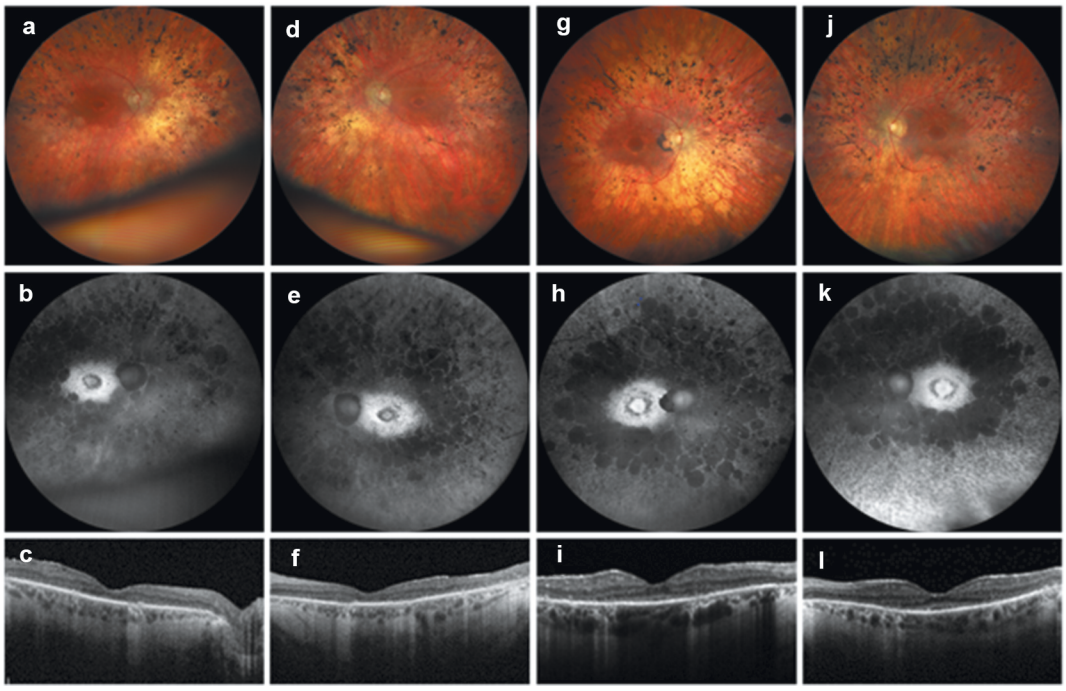

Figure 3. Fundus photographs, autofluorescence photographs, and macular OCT images of the right and left eye of patient 1 (A–C and D–F) at the age of 70 years and patient 2 (G–I and J–L) at the age of 66 years. Pigment epithelial changes in the mid periphery are seen in colour fundus photographs and fundus autofluorescence photographs of both patient 1 and patient 2. Atypically large atrophic punched-out lesions are seen in both patients, which might be pathognomonic to the mutation described in this article. More typical to RP, a pale optic nerve head and diminished retinal vessel caliber are seen in both patients. Both patients also presented with macular hyperautofluorescence. Patient 1 had severe outer retinal atrophy in the macular area on OCT, correlating to the poor visual acuity found at the time. Patient 2 had a slightly better visual acuity and a slightly more normal macular structure on OCT.

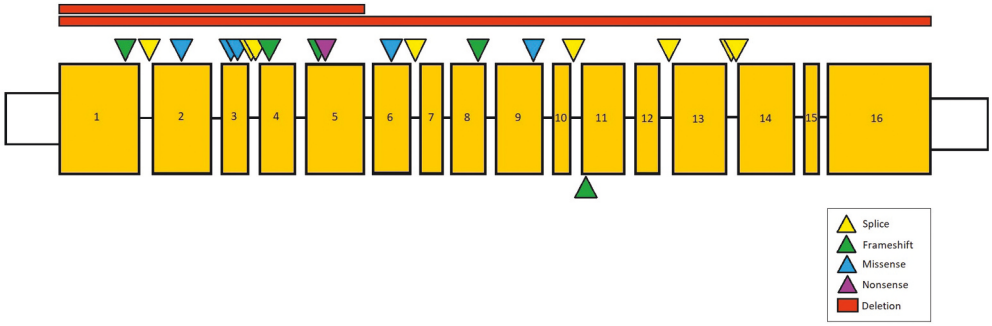

Figure 4. Known pathogenic variants in *CEP78* gene. Exons are to scale, whereas the introns and UTRs are not to scale. Pathogenic *CEP78* variants described in the literature are shown above the *CEP78* gene (3,[10–16]). *CEP78* c.1261_1262delinsA variant described in this study is shown below the gene. Different pathogenic variant types, including splice site, single nucleotide deletions resulting in frameshift, missense, nonsense, and deletions, are indicated by specific color-coded symbols. In addition, a pathogenic inversion with a breakpoint within the *CEP78* has been described in the literature (16). Isoform reference is *CEP78*: NM_001098802, ENST00000376597.4.

In conclusion, this study expands the knowledge of the phenotypic consequences of pathogenic *CEP78* variants. Pathogenic variants in *CEP78* can cause both classical non-syndromic retinitis pigmentosa and cone-rod dystrophy associated with sensorineural hearing impairment. The identification of the genetic variants causing IRD allows accurate genetic counseling for patients and paves the path to developing tailored therapies in the future.

Acknowledgments

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Disclosure statement

LL, SH, OK, TP, ER and AF disclose no conflict of interest. ST is employed by Blueprint Genetics.

Ethics declaration

Written informed consent was obtained from both patients. The study was approved by the ethics committee of the Northern Ostrobothnia Hospital District (EETTMK: 340/2020).

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