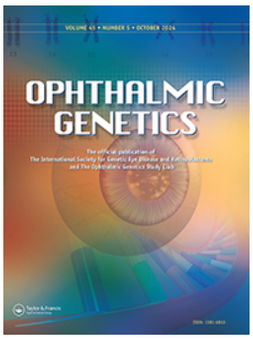

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CASE REPORT

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Mild retinitis pigmentosa, including sector retinitis pigmentosa associated with 2 pathogenic variants in *CDH23*

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ABSTRACT

Background: Biallelic pathogenic variants in *CDH23* can cause Usher syndrome type I (USH1), typically characterized by sensorineural hearing loss, variable vestibular areflexia, and a progressive form of rod-cone dystrophy. While missense variants in *CDH23* can cause DFNB12 deafness, other variants can affect the cadherin 23 function, more severely causing Usher syndrome type I D. The main purpose of our study is to describe the genotypes and phenotypes of patients with mild retinitis pigmentosa (RP), including sector RP with two pathogenic variants in *CDH23*.

Materials and methods: Clinical examination included medical history, comprehensive ophthalmologic examination, and multimodal retinal imaging, and in case 1 and 2, full-field electroretinography (ERG). Genetic analysis was performed in all cases, and segregation testing of proband relatives was performed in case 1 and 3.

Results: Three unrelated cases presented with variable clinical phenotype for USH1 and were found to have two pathogenic variants in *CDH23*, with missense variant, c.5237 G > A: p.Arg1746Gln being common to all. All probands had mild to profound hearing loss. Case 1 and 3 had mild RP with mid peripheral and posterior pole sparing, while case 2 had sector RP. ERG results were consistent with the marked loss of retinal function in both eyes at the level of photoreceptor in case 1 and case 2, with normal peak time in the former.

Conclusion: Patients harbouring c.5237 G > A: p.Arg1746Gln variants in *CDH23* can present with a mild phenotype including sector RP. This can aid in better genetic counselling and in prognostication.

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Usher syndrome; ciliopathies; genetic hearing loss; sector retinitis pigmentosa; dystrophy; inherited retinal dystrophy; inherited retinal disease; retinitis pigmentosa

1. Introduction

Usher syndrome type 1 (USH1) is an autosomal recessive genetic disorder, usually characterised with severe to profound congenital sensorineural hearing loss, vestibular areflexia, and a progressive form of retinal dystrophy called retinitis pigmentosa (RP), with onset in the first decade of life (1,2).

To date, six genes have been identified as responsible for USH1: cadherin-23 (*CDH23*), protocadherin-15 (*PCDH15*), harmonin (*USH1C*), sans (*USH1G*), motor protein myosin 7a (*MYO7A*) and calcium- and integrin-binding protein 2 (*CIB2*) (3).

CDH23 encodes a cell adhesion protein of the cadherin superfamily (4). Pathogenic variants in this gene are associated with both nonsyndromic hearing loss (DFNB12, OMIM 601386) and syndromic Usher type 1D (USH1D, OMIM 601067) phenotypes (5,6).

We describe here a case series with mild or profound congenital hearing loss and mild RP, including sector RP in patients who were found to have compound heterozygous variants in *CDH23*, with one missense, variant c.5237 G > A; p.Arg1746Gln common to all cases. This is the first report with predictable mild expression of the retinal phenotype associated with *CDH23*. Moreover, one of our cases had only mild hearing loss, rather than the typical severe loss associated with *CDH23*.

2. Material and methods

The protocol of the study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Moorfields Eye Hospital. In all three cases, a medical history was obtained, and a complete ophthalmologic examination was performed. Colour fundus photography and fundus autofluorescence (FAF) imaging were performed with wide-field confocal scanning laser imaging (Optos PLC, Dunfermline, UK). Macular scans of the posterior pole were performed with spectral-domain optical coherence tomography (SD-OCT, Heidelberg Engineering, Heidelberg, Germany).

The electrophysiological assessment included international-standard full-field electroretinography (ERG) performed with gold foil corneal electrodes in case 1 and skin; Dawson, Trick, and Litzkow electrodes in case 2.

The molecular confirmation of USH1D was obtained through targeted next-generation sequencing (Molecular Vision Laboratory, Oregon, United States; North East Thames Regional Genetic Laboratory, London, UK; St Georges Genomic Service, London, UK; NIHR BioResource Rare, London, UK). Segregation analyses was performed in two families.

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3. Results

Below follows a succinct description of three individuals identified from three unrelated families with two pathogenic variants in *CDH23*. All three cases presented with congenital profound to mild sensorineural hearing loss and variable symptoms. A summary of the clinical data is presented.

Case 1 was a 45-year-old woman with congenital sensorineural deafness and at least one subjective episode of worsening of her deafness in her adulthood. She benefitted to some degree from hearing aids and developed relatively normal speech, though preferred communicating with sign language. She was diagnosed with myeloproliferative disorder at the age of 43 for which she received bone marrow transplantation and chemotherapy. She had some mild peripheral field loss since age 16 and nyctalopia at age 20. Her best-corrected visual acuity (BCVA) was 6/9 in both eyes with hypermetropic correction of +7 spherical dioptre and was stable over a period of 14 -year follow-up.

Retinal examination showed pigmentary changes in the inferior, nasal, and temporal sectors, in both eyes, while additionally in left eye, retinal pigment extension was present superiorly (Figure 1a,c). The pigmentary changes corresponded to areas of decreased FAF (Figure 1b,d). SD-OCT showed bilateral preservation of the foveal ellipsoid zone but mottling extra foveally (Figure 1e,f).

Her parents and younger sibling were healthy. The proband has three children (from two different partners, both being hearing impaired), with two being hearing impaired. Although limited details were available, this is probably to have been transmitted from each father.

Her binocular Esterman visual fields showed superior field defects, reaching the horizontal meridian (Figure 4a).

Pattern ERGs were normal for both eyes and in keeping with normal macular function.

Rod specific ERGs and maximal a and b wave amplitude were reduced bilaterally (left eye more than the right eye) without delay. The light-adapted 30 Hz and single-flash ERGs were greatly reduced in amplitude bilaterally without peak-time change. The results were consistent with marked loss of retinal function in both eyes at the level of photoreceptor, with unusual finding of cone system probably more affected than the rod system.

Case 2, a 28-year-old male (referred to us at age 19), with congenital profound hearing loss with bilateral cochlear implantation at an early age, was visually asymptomatic.

His BCVA over a follow-up period of 9 years remained stable at 6/5 in each eye.

Ultra-wide field fundus images of the right and left eye revealed pigmentary changes along the inferior arcade (Figure 2g). The FAF imaging demonstrated bilateral decreased autofluorescence noticeable along the inferior arcade (Figure 2h). Corresponding fundus images (Figure 2i) and FAF images (Figure 2j) at approximately 5-year periods showed mild progression. SD-OCT scans showed bilateral preservation of the ellipsoid zone (Figure 2k,l).

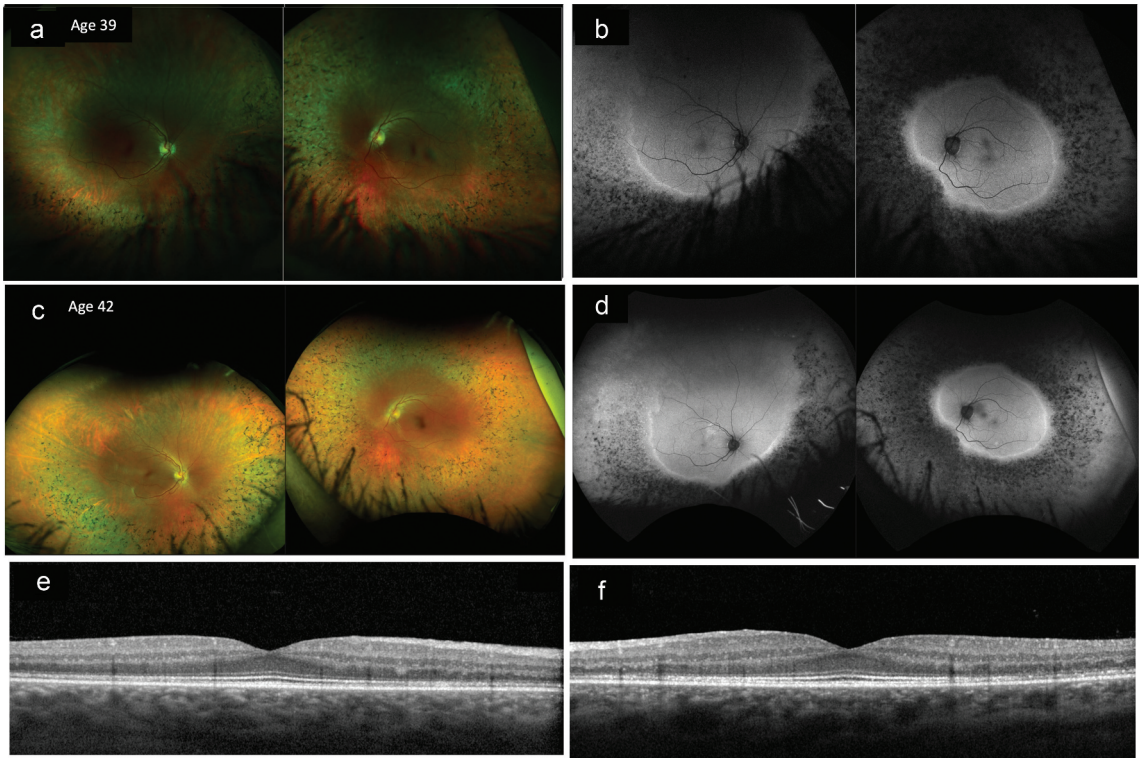

Figure 1. Ultra-wide field fundus images showing inferior, nasal, and temporal sectors of pigmentary change, in both eyes, while additionally in left eye, retinal pigmentation extension was present superiorly, (a). Widefield FAF imaging showing decreased autofluorescence from the retinal pigment epithelium in regions conjugate to pigmentary changes, (b). Corresponding fundus images, (c) and FAF images, (d) at approximately 3-year follow-up showed no obvious progression. SD-OCT scans showing bilateral preservation of the foveal ellipsoid zone but mottling extra foveally, (e, f).

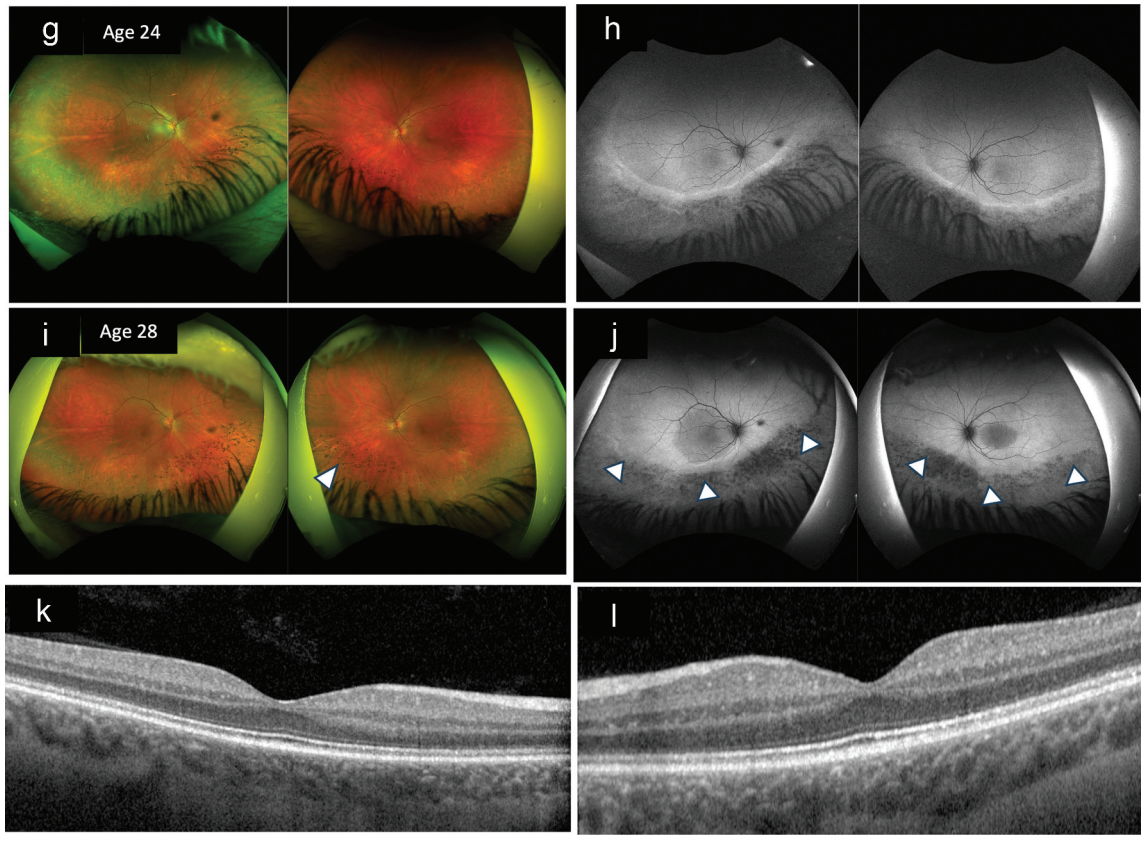

Figure 2. Ultra-wide field fundus images of right eye and left eye showing pigmentary changes along the inferior arcade, (g). Widefield FAF imaging showing decreased autofluorescence noticeable along the inferior arcade, (h). Corresponding fundus images, (i) and FAF images, (j) at approximately 5-year follow-up, with white arrow heads showing areas of progression. SD-OCT scans showing bilateral preservation of the ellipsoid zone, (k, l).

With binocular Goldmann field testing the upper field defect dipped down towards the horizontal meridian at 55-degree eccentricity on the either side of central fixation but did not extend below the horizontal meridian with kinetic testing (Figure 4b).

Full-field ERGs responses (done elsewhere) at 7 years were within normal range in both eyes, although repeat testing at 15 years showed deterioration. There was a decreased rod driven and photopic b-wave, with increased time to peak. The 30-Hz flicker amplitudes were subnormal, with peak time just within normal time.

This unusual phenotype of case 2 has also been previously briefly reported by us (7).

Case 3 is a female who at the age of 17 was visually asymptomatic and was incidentally noted to have symmetrical inferior pigmentary changes by her optometrist. She had mild balance and hearing loss, with no history of nyctalopia, and normal speech. She was born to normal sighted, nonconsanguineous parents, and of the two siblings, she was the only one to be affected. A follow-up of 4 years showed stable BCVA of 6/6 in both eyes.

The fundus examination showed bilateral pigmentary change prominent inferiorly, as well as in the temporal and nasal periphery (Figure 3m,o). Widefield FAF imaging showed decreased autofluorescence in regions corresponding to pigmentary changes (Figure 3n,p). SD-OCT scans showing bilateral preservation of the ellipsoid zone (Figure 3q,r).

Humphrey visual field 24–2 in the right eye showed no obvious field loss, while that in the left eye showed defect in superior two-third of visual field (Figure 4c,d).

4. Molecular genetics

All cases had two pathogenic variants in *CDH23* with one variant c.5237 G > A, p. Arg1746Gln, being common to all cases. In cases 1, 2, and 3, the second variant was c.1369C > T (p. Arg457Try), c.9278 + 2T > G, and c.7823 G > A (p. Arg2608His), respectively. The segregation analysis revealed that the two variants were *in trans* and inherited from different parents in cases 1 and 3.

5. Discussion

Biallelic pathogenic variants in *CDH23* cause Usher type 1D, usually characterised by profound congenital deafness, vestibular areflexia in addition to signs of RP manifesting prepubertally (1,4,8–11).

Although in most cases of USH1D, nonsense, splice-site, and frameshift variants may produce a severe phenotype, as compared to missense variants, this may not be sufficient to predict the clinical presentation (4,6,9).

In the present study, we have identified mild phenotype of RP, including sector RP, associated with mild or profound hearing loss due to two pathogenic variants in *CDH23*, with

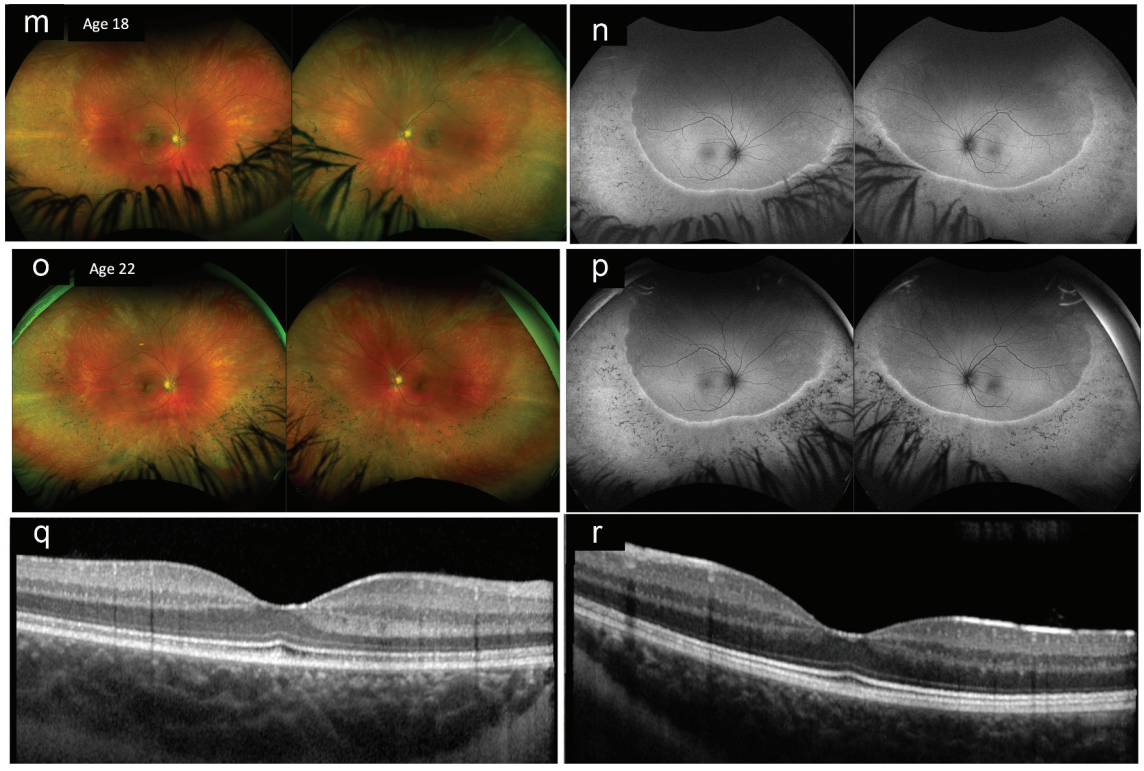

Figure 3. Ultra-wide field fundus images of right eye and left eye showing of pigmentary change prominent inferiorly as well as in the temporal and nasal periphery, (m). Widefield FAF imaging showing decreased autofluorescence from the retinal pigment epithelium in regions corresponding to pigmentary changes, (n). Corresponding stable fundus images, (o) and FAF images, (p) at approximately 4-year follow-up. SD-OCT scans showing bilateral, preservation of the ellipsoid zone (q, r).

the variant common to all cases being c.5237 G > A, p. Arg1746Gln. The feature of retinal degeneration in these cases was well delineated on FAF imaging, showing an area of hypoautofluorescence separated from the rest of the well-preserved area of normal autofluorescence by a clear cut hyperfluorescent line. A follow-up of between 4 and 14 years in our cases showed stable visual acuity over time.

Usher syndrome1D can demonstrate considerable variation in hearing. However, most patients have congenital profound deafness on testing, though few can deviate, ranging from moderate to severe deafness with some progression and asymmetry at times (6). Apart from case 3, who had mild hearing loss on audiologic evaluation, with development of normal speech, all other patients in our case series had profound congenital sensorineural deafness, needing cochlear implants or hearing aids. An effect of modifier genes or epigenetic factors cannot be excluded in case 3.

In previous studies, the pathogenic role of p. Arg1746Gln was found to be uncertain. Bolz et al. described a large family, in which two patients harbouring *CDH23*, and p.Arg1746Gln variant in homozygous state had a mild ocular phenotype, with one patient showing normal visual function with subnormal ERG, while the other patient presented with night-blindness and bone-spicule-like pigmentation of the fundus. In contrast, other patients from this family with p.Arg1746 Gln in the compound heterozygous state with a null mutation showed variable expression of the retinal phenotype ranging from normal vision to typical RP (4).

Similarly, Astuto et al. reported cases with the *CDH23*, p. Arg1746Gln missense variant presenting with atypical Usher syndrome. Homozygous cases for this variant presented with mild, late-onset RP, while a second case, heterozygous for p. Arg1746Gln, presented with severe to profound asymmetric hearing loss and normal vestibular function. At the age of 29, the subject was found to have typical RP and subnormal ERG despite a 10-degree visual field.

Another case in this case series with compound heterozygous p.Arg1746Gln and 1112delT revealed a severe course of RP (6).

This contrasts with our case 2, which presented with a mild phenotype with another variant being a splice variant and unless a functional analysis is performed, and it will remain inconclusive for the variation seen in these two cases.

However, detailed fundus description and imaging of these aforementioned cases are not provided, and it is not clear if patients with subjective normal vision and mild fundus changes had sector RP associated with this variant as seen in our series.

Using functional splicing assays, the p.Arg1746Gln variant has been shown to alter splicing, thereby creating a novel acceptor site resulting in-frame exclusion of 17 amino acids, including a Ca2±binding motif of CDH23 protein (12). The mild retinal affection was presumed by Becirovic et al. due to the preservation of the reading frame (12).

There have been previous reports of sector RP in patients with Usher syndrome (7,13–15), with a single case report associated with two novel compound heterozygous variants

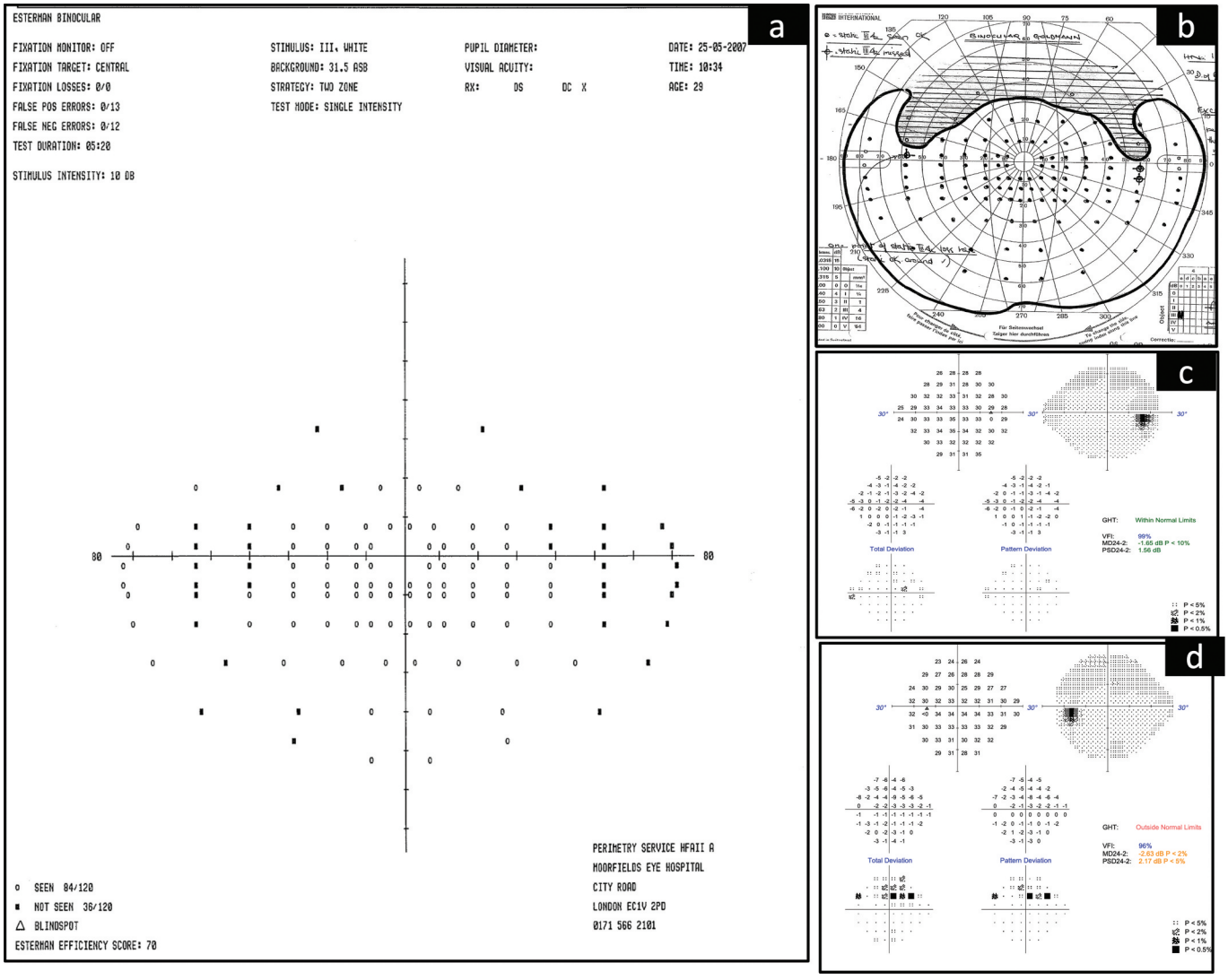

Figure 4. Binocular Esterman visual fields showing superior field defects, reaching the horizontal meridian (a). Binocular Goldmann field showing upper field defect dipping down towards the horizontal meridian at 55-degree eccentricity on either side of central fixation but not extending below the horizontal meridian with kinetic testing (b). Humphrey visual field 24–2 in the right eye showed no obvious field loss, while that in the left eye showed defect in superior two third of visual field (c, d).

in *CDH23*, including one missense (c.8530C > A; p. Pro2844Thr) and one splice-site (c.5820 + 5 G > A) variant (16).

In our case series, a predictable expression of mild RP phenotype, including sector RP, was seen in patients with combination of p.Arg1746Gln, as one pathogenic variant in *CDH23*, irrespective of the second variant. Over follow-up period of 4 to 15 years, all cases maintained stable vision with the lesion area not changing significantly. Moreover, inferior field was well preserved in all three cases. ERG findings in case 1 showed decreased amplitude but no peak delay, more in favour of localised than generalised retinal pathology. In case 2, ERG responses showed deterioration at 8-year follow-up, both for the rod and cone system.

Our cases have a favourable visual prognosis compared to typical RP associated with pathogenic biallelic variants in *CDH23*, thus having an implication for genetic counselling and the prognostication.

In short, we describe a genotype-phenotype correlation, with p.Arg1746Gln variant associated with mild phenotype of RP,including sector RP, although more cases will help in confirming our prediction.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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References

1. Smith RJ, Berlin CI, Hejtmancik JF, Keats BJ, Kimberling WJ, Lewis RA, Möller CG, Pelias MZ, Tranebjærǵ L. Clinical diagnosis

of the Usher syndromes. Am J Med Genet. 1994;50(1):32–8. doi: 10.1002/ajmg.1320500107.
2. de Guimaraes TA, Arram E, Shakarchi AF, Georgiou M, Michaelides M. Inherited causes of combined vision and hearing loss: clinical features and molecular genetics. Br J Ophthalmol. 2022;107:1403–14. doi: 10.1136/bjo-2022-321790.
3. Mathur P, Yang J. Usher syndrome: hearing loss, retinal degeneration and associated abnormalities. Biochim Biophys Acta - Mol Basis Dis. 2015;1852(3):406–20. doi: 10.1016/j.bbadis.2014.11.020 .
4. Bolz H, von Brederlow B, Ramírez A, Bryda EC, Kutsche K, Nothwang HG, Seeliger M, Cabrera MD, Vila MC, Molina OP, et al. Mutation of CDH23, encoding a new member of the cadherin gene family, causes Usher syndrome type 1D. Nat Genet. 2001;27(1):108–12. doi: 10.1038/83667.
5. Xu T, Zhu W, Wang P. The p. P240L variant of CDH23 and the risk of nonsyndromic hearing loss: a meta-analysis. Eur Arch Otorhinolaryngol. 2019;276(1):11–16. doi: 10.1007/s00405-018-5160-8.
6. Astuto LM, Bork JM, Weston MD, Askew JW, Fields RR, Orten DJ, Ohliger SJ, Riazuddin S, Morell RJ, Khan S, et al. CDH23 mutation and phenotype heterogeneity: a profile of 107 diverse families with Usher syndrome and nonsyndromic deafness. Am J Hum Genet. 2002;71(2):262–75. doi: 10.1086/341558.
7. Georgiou M, Grewal PS, Narayan A, Alser M, Ali N, Fujinami K, Webster AR, Michaelides M. Sector retinitis pigmentosa: extending the molecular genetics basis and elucidating the natural history. Am J Ophthalmol. 2021;221:299–310. doi: 10.1016/j.ajo.2020.08.004.
8. Kimberling WJ, Möller C. Clinical and molecular genetics of Usher syndrome. J Am Acad Audiol. 1995;6(1):63–72. PMID: 7696679.
9. Bork JM, Peters LM, Riazuddin S, Bernstein SL, Ahmed ZM, Ness SL, Polomeno R, Ramesh A, Schloss M, Srisailpathy CS, et al. Usher syndrome 1D and nonsyndromic autosomal recessive deafness DFNB12 are caused by allelic mutations of the novel cadherin-like gene CDH23. Am J Hum Genet. 2001;68(1):26–37. doi: 10.1086/316954.
10. von Brederlow B, Bolz H, Janecke A, La O, Cabrera A, Rudolph G, Lorenz B, Schwinger E, Gal A. Identification and in vitro expression of novel CDH23 mutations of patients with Usher syndrome type 1D. Hum Mutat. 2002;19(3):268–73. doi: 10.1002/humu.10049.
11. Vaché C, Besnard T, Blanchet C, Baux D, Larrieu L, Faugère V, Mondain M, Hamel C, Malcolm S, Claustres M, et al. Nasal epithelial cells are a reliable source to study splicing variants in Usher syndrome. Hum Mutat. 2010;31(6):734–41. doi: 10.1002/humu.21255.
12. Becirovic E, Ebermann I, Nagy D, Zrenner E, Seeliger MW, Bolz HJ. Usher syndrome type 1 due to missense mutations on both CDH23 alleles: investigation of mRNA splicing. Hum Mutat. 2008;29(3):452. doi: 10.1002/humu.9526.
13. Haim M, Rosenberg T. Retinitis pigmentosa and allied disorders in Denmark: IV. Ophthalmic features in systemic and non-systemic cases. Acta Ophthalmol. 1993;71(5):597–605. doi: 10.1111/j.1755-3768.1993.tb04648.x.
14. Osman SA, Aylin Y, Gul A, Celikel H. Photodynamic treatment of a secondary vasoproliferative tumour associated with sector retinitis pigmentosa and Usher syndrome type I. Clin Experiment Ophthalmol. 2007;35(2):191–3. doi: 10.1111/j.1442-9071.2007.01440.x.
15. Saihan Z, Stabej PL, Robson AG, Rangesh N, Holder GE, Moore AT, Steel KP, Luxon LM, Bitner-Glindzicz M, Webster AR. Mutations in the USH1C gene associated with sector retinitis pigmentosa and hearing loss. Retina. 2011;31(8):1708–16. doi: 10.1097/IAE.0b013e31820d3fd1.
16. Branson SV, McClintic JI, Stamper TH, Haldeman-Englert CR, John VJ. Sector retinitis pigmentosa associated with novel compound heterozygous mutations of CDH23. Ophthalmic Surg Lasers Imaging Retina. 2016;47(2):183–6. doi: 10.3928/23258160-20160126-14.