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ORIGINAL ARTICLE

Maculopathy and adult-onset ataxia in patients with biallelic *MFSD8* variants

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Abstract

Background: Biallelic variants in the major facilitator superfamily domain containing 8 gene (*MFSD8*) are associated with distinct clinical presentations that range from typical late-infantile neuronal ceroid lipofuscinosis type 7 (CLN7 disease) to isolated adult-onset retinal dystrophy. Classic late-infantile CLN7 disease is a severe, rare neurological disorder with an age of onset typically between 2 and 6 years, presenting with seizures and/or cognitive regression. Its clinical course is progressive, leading to premature death, and often includes visual loss due to severe retinal dystrophy. In rare cases, pathogenic variants in *MFSD8* can be associated with isolated non-syndromic macular dystrophy with variable age at onset, in which the disease process predominantly or exclusively affects the cones of the macula and where there are no neurological or neuropsychiatric manifestations.

Methods: Here we present longitudinal studies on four adult-onset patients who were biallelic for four *MFSD8* variants.

Results: Two unrelated patients who presented with adult-onset ataxia and had macular dystrophy on examination were homozygous for a novel variant in MFSD8 NM_152778.4: c.935T>C p.(Ile312Thr). Two other patients presented in adulthood with visual symptoms, and one of these developed mild to moderate cerebellar ataxia years after the onset of visual symptoms.

Conclusions: Our observations expand the knowledge on biallelic pathogenic *MFSD8* variants and confirm that these are associated with a spectrum of more heterogeneous clinical phenotypes. In *MFSD8*-related disease, adult-onset

recessive ataxia can be the presenting manifestation or may occur in combination with retinal dystrophy.

KEYWORDS

ataxia, CLN7, MFSD8, NCL7, neuronal ceroid lipofuscinosis, retinal degeneration

1 | INTRODUCTION

The neuronal ceroid lipofuscinoses (NCLs) were first described in the beginning of the nineteenth century and are now recognized as a group of rare neurodegenerative disorders in children and young adults. Their classic presentation consists of a progressive clinical course with seizures, visual loss, motor deterioration, ataxia, and cognitive regression, leading to premature death (Haltia, 2006; Kousi et al., 2009). The NCLs were originally divided into four subtypes based on age of onset: infantile, late-infantile, juvenile (Batten-Spielmeyer-Vogt/Sjögren disease), and adult (Kufs disease) (Haltia, 2006; Topcu et al., 2004), and diagnosis was confirmed by detection of intralysosomal accumulation of autofluorescent lipopigments in neuronal and peripheral tissue (Haltia, 2006; Mole et al., 2005). Advances in genetics made it possible to classify the NCLs by affected gene and the different effects of mutations; 13 genes are now identified (Gardner & Mole, 2021; Mole et al., 2005; Williams & Mole, 2012).

Neuronal ceroid lipofuscinosis type 7 (MIM 610951 at www.omim.org, CLN7) is caused by biallelic pathogenic variants in the gene *MFSD8* (MIM 611124, previous designation also *CLN7*) and typically has late-infantile symptom onset, usually between 2 and 6 years of age. Late-infantile CLN7 disease usually presents with drug-resistant seizures or developmental regression. Within months after the first symptoms, the disorder progresses, eventually leading to blindness, loss of motor skills, and the emergence of a dementia-like syndrome with mood and behavioral problems (Adams & Mink, 2013). Most patients with late-infantile CLN7 disease also develop prominent cerebellar ataxia and present with cerebellar-over-cerebral atrophy on neuroradiological examination (Biswas et al., 2020). More than 75 disease-causing variants are known in *MFSD8* (www.ucl.ac.uk/ncl-disease/mutation-and-patient-database) (Aiello et al., 2009; Aldahmesh et al., 2009; Bauwens et al., 2020; Beckman et al., 2023; Birtel et al., 2018; Gardner & Mole, 2021; He et al., 2023; Hosseini Bereshneh & Garshasbi, 2018; Jilani et al., 2019; Khan et al., 2017; Kim et al., 2019; Kolesnikova et al., 2023; Kose et al., 2021; Kousi et al., 2009, 2012; Kozina et al., 2018; Mandel et al., 2014; Panjeshahi et al., 2023; Patiño et al., 2014; Qiao et al., 2022; Reith et al., 2022; Roosing et al., 2015; Siintola et al., 2007; Stogmann et al., 2009; Zare-Abdollahi et al., 2019).

Biallelic pathogenic variants in *MFSD8* are also associated with milder phenotypes, including non-syndromic (without extra-ophthalmological disease manifestations) retinal dystrophies presenting in childhood or adulthood. The specific retinal dystrophy pattern that was associated with *MFSD8* in the Online Mendelian Inheritance in Man database is *macular dystrophy with central cone involvement* (MIM 616170), but several other types of retinal dystrophies have been described in carriers of biallelic *MFSD8*-variants (Gardner & Mole, 2021).

In this article, we report longitudinal studies on four adult patients with biallelic *MFSD8* variants, adding to existing knowledge of *MFSD8*-related ophthalmological disease and describing a novel intermediate phenotype of *MFSD8*-related neurological disease presenting with adult-onset ataxia.

2 | SUBJECTS AND METHODS

2.1 | Ethical compliance

Informed consent was obtained from all participants. P1 was enrolled in a research study on rare neurological disorders approved by the Regional Ethics Review Board in Lund, Sweden (Dnr 2013/516 and 2021-00884). P3 and P4 were included in a research study on inherited retinal degenerations approved by the Regional Ethics Review Board in Lund, Sweden (Dnr 2015/602). All patients underwent clinical examinations at the authors' clinics, and information is provided here with patients' informed consent and in accordance with the Helsinki Declaration. Patients have agreed to the publication and online dissemination of the video material that accompanies this article.

We describe four patients from four unrelated families. Two are male; individual P1 originated from Pakistan was examined at the Dept. of Neurology in Lund, Sweden, and P2 was of Indian (Hindi) descent and was examined in Ahmedabad, India. Two females (P3 and P4) originating from Sweden were identified at the Dept. of Ophthalmology in Lund and were also seen by neurologists within this study. Blood samples were obtained from all patients in this study, and DNA was isolated from peripheral blood leukocytes using standard procedures. In total, three different genetic laboratories have been used to obtain the genetic results

within clinical or research analyses. P1 was examined genetically at Centogene GmbH, Rostock, Germany, and P2 at the Foundation for Research in Genetics and Endocrinology at the Institute of Human Genetics in Ahmedabad, India. P3 and P4 underwent genetic examination for retinal dystrophy (277 genes) via Asper Biotech, Tartu, Estonia. All variant designations refer to the RefSeq transcript NM_152778.4 or the predicted protein NP_689991.1.

From patient P1, a 4 mm cylindrical skin biopsy was acquired and preserved in glutaraldehyde, and EDTA blood was used to extract buffy coat. Electron microscopy of the skin and buffy coat was performed and interpreted by G.A. at the Department of Histopathology, Great Ormond Street Hospital NHS Foundation Trust, London.

3 | RESULTS

Table 1 summarizes the key findings. Detailed individual descriptions are provided below.

Patient P1: This 28-year-old man was referred to our neurology clinic due to increasing balance and

TABLE 1 Summary of four new cases of adult-onset *MFSD8*-related disease characterized by visual disturbances, radiological finding, and neurological symptoms.

	P1	P2	P3	P4
Gender	M	M	F	F
Country of origin/ethnicity	Pakistan	India	Sweden	Sweden
DNA variant	c.935T>C	c.935T>C	c.1006G>C c.1444C>T	c.1006G>C c.1394G>A
genotype	Homozygous	Homozygous	Comp het	Comp het
Protein variant	p.(Ile312Thr)	p.(Ile312Thr)	p.(Glu336Gln) p.(Arg482*)	p.(Glu336Gln) p.(Arg465Gln)
Consanguinity	+	+	−	−
Age of onset (neurological symptoms; years)	Approx. 25	Approx. 25	Approx. 65	No symptoms at the age of 32
Seizures	−	−	−	−
Cerebellar ataxia	+	+	+ (mild)	−
Cognitive regression	+	−	−	−
Dysarthria	+	+	−	−
Sara score	15	Not assessed	4	0
Nystagmus	Horizontal nystagmus and slow saccades	+	Horizontal	−
Visual disturbance	+	+	+	+
Visual acuity	RE 0.8[a] LE 1.0	RE 6/6[b] LE 6/6	RE 0.7[a] LE 0.4	RE 0.2[a] LE 0.25
Visual fields	Supertemporal constriction of the 20-degree isopter	Not performed	Central scotoma	Central scotoma
OCT	Attenuation of EZ	Not performed	Attenuation and punched out lesions of EZ	Attenuation and punched out lesions of EZ
Disturbance of color vision	Discrete reduction	Not performed	Normal	Normal
Full field erg	Normal	Not performed	Delayed implicit time for 30 Hz cone responses	Normal
Multifocal erg	Reduced	Not performed	Reduced	Reduced
Radiological findings	Cerebellar and vermis atrophy	Cerebellar atrophy	No focal atrophy of cerebellum, mild general cerebral atrophy	Not performed

Note: Variant designations refer to the RefSeq transcript NM_152778.4 or the protein isoform NP_689991.1.

Abbreviations: Comp het, compound heterozygous; ERG, electroretinogram; EZ, ellipsoid zone corresponding to the photoreceptors; LE, left eye; OZT, optical coherence tomography; RE, right eye.

[a]Best corrected decimal visual acuity measured at 3 m.

[b]Best corrected visual acuity measured at 6 m.

gait disturbance since his mid-twenties. The patient was of northern Pakistani origin. His parents were first cousins. He reported that there was no history of neurological diseases in the family. The patient had an advanced-level university degree from his home country and resided in Sweden for further university studies. The patient denied any history of seizures, developmental delays, or cognitive difficulties during childhood or early adulthood.

At the first clinical visit, the patient stated that during the previous year he had increased difficulty concentrating and completing more advanced tasks in his studies. On examination, he had mild dysarthria, horizontal nystagmus, and slow saccades. Dysmetria and dysdiadochokinesia were seen bilaterally in the upper extremities. His gait was broad-based and atactic (Video S1). The patient reported unspecified visual difficulties. Full ophthalmological examination including multimodal imaging and electrophysiological measurements revealed central cone degeneration in both eyes, reflected by reduced multifocal electroretinogram (mfERG) signals and attenuation of the ellipsoid zone and total paramacular thickness on optical coherence tomography (OCT; Figure 1a–c). Consistently, visual fields were constricted for small objects. Color and red-free fundus images showed mild granular pigmentary changes and blunt foveal reflexes, while blue light fundus autofluorescence (FAF) images were mainly normal. The full-field ERG (ffERG), reflecting total retinal function, was within normal limits. Brain MRI at age 28 years revealed marked cerebellar atrophy of both hemispheres and vermis, but normal findings in the brainstem and medulla oblongata (Figure 2). There was no evidence of white matter changes.

Whole genome sequencing and analyses for variants in genes related to the patient's Human Phenotype Ontology terms (https://hpo.jax.org/app) were performed on clinical grounds, and the formal result was negative. However, a homozygous variant in MFSD8 NM_152778.4:c.935T>C p.(Ile312Thr) was reported as a potentially relevant finding. In gnomAD v4.0.0, this variant was present in a heterozygous state in 26 of 1,613,710 alleles internationally; all 26 were from 91,024 South Asian alleles (allele frequency 0.00029), none from alleles of other origins. Several in silico tools predicted a damaging effect of this variant and a high degree of species conservation at this site. The formal interpretation was that it was a variant of uncertain significance. ClinVar listed 4 individuals carrying this variant (variation ID: 211495, accession: VCV000211495.11), of whom one patient was reported to have autosomal recessive disease with ataxia.

Analyses for copy number variants using the Infinium™ Global Diversity Array with Cytogenetics kit (Illumina; Centogene, Germany) showed 29 areas on the genome with a copy number neutral absence of heterozygosity between 3.1 and 72.6 Mbp in length, consistent with parental consanguinity (Sund & Rehder, 2014). One of these regions included the *MFSD8* gene: arr[GRCh37] 4q27q31.21(122,013,739–144,050,795)×2. No other possible candidate variants were found.

Histopathological examination of the blood in buffy coat preparation revealed a good yield of lymphocytes (200 cells examined). No convincing storage cytosomes were identified. A skin biopsy demonstrated two clusters of eccrine sweat glands, blood vessels, and peripheral nerves. On electron microscopy, sweat gland epithelial cells showed no storage material or atypical vacuolation. However, there were prominent deposits of lipofuscin material with an electron-dense component and large lipid droplets; they were considered unusual in the ratio of lipid to dense material (Figure 3). Blood vessels, smooth muscle, and endothelial cells showed no vacuoles or storage cytosomes. Myelinated and unmyelinated peripheral nerves and fibroblasts had a regular appearance.

Patient P2 had been reported to ClinVar in 2019 with the same genotype as P1, homozygous MFSD8 c.935T>C p.(Ile312Thr), by FRIGE's Institute of Human Genetics, Ahmedabad, India; contact was established with J.S. from that institute, who re-examined the patient for the present study. The patient was a man in his mid-30s of Indian Hindi origin, born from a consanguineous marriage. There was no history of neurological disorders in the family. He denied any history of seizures, developmental delays, or cognitive difficulties during childhood. The patient underwent normal school education and obtained a college degree. According to the patient, the initial symptoms of poor balance and gait started after his 25th birthday. During the initial examination, the patient had nystagmus and dysdiadochokinesia. The gait of the patient was broad-based and atactic. The patient reported visual problems and underwent an examination by an ophthalmologist who reported "angular vision problems" and myopia. More detailed neurological or ophthalmological re-examinations within this study, such as OCT and mfERG, could not be performed. An MRI examination of the brain showed cerebellar atrophy (not shown). According to the patient, speech problems appeared after the age of 34, although dysarthria was already observed earlier by others. The patient had not reported any cognitive issues until his most recent examination at the age of 42. Video S2 shows his atactic movements when recontacted by the genetic laboratory at age 42.

Patient P3: This 66-year-old female was referred to our ophthalmological clinic due to central scotoma and difficulty reading at the age of 62. Her previous disease history included chronic obstructive pulmonary

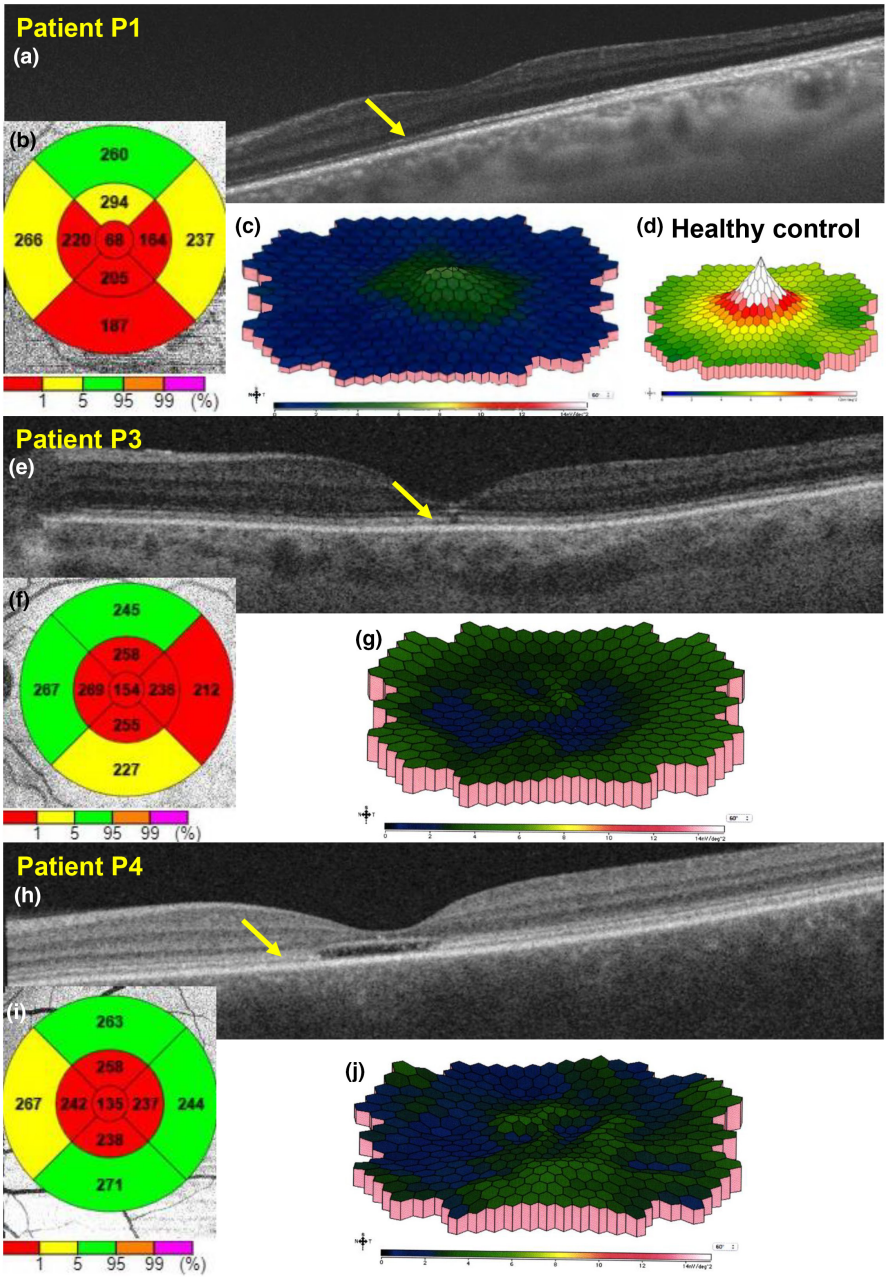

FIGURE 1 Abnormal central retinal structure and reduced macular function in patients P1 (a-c), P3 (e–g), and P4 (h–j). (a, e, and h) show cross-sectional images of the macula captured with an optical coherence tomography (OCT) B-scan. In patient P1 (a), the OCT b-scan shows a subtle attenuation of the ellipsoid zone (yellow arrow) corresponding to the junction of inner and outer photoreceptor segments, indicating a mild structural change to the photoreceptor layer in the macular region. (b, f, and i) are OCT macular maps comparing the thickness of nine separate central macular segments in the patient to a control material. Segments with significantly reduced retinal thickness are shown in red or yellow. For patient P1, (b) reveals central macular thinning compared to controls. (c, d, g, and j) are density plots recorded with multifocal electroretinography (mfERG) reflecting photoreceptor activity in the macular region and thereby the isolated macular function. Patient P1 (c) had quite severely reduced macular function compared to a normal mfERG from a control subject (d). In patient P3, the OCT-b scan (E) shows an interruption of the ellipsoid zone corresponding to a focal loss of photoreceptors. General macular thinning is also evident (f), with a corresponding reduction of macular function on mfERG (G). The OCT B-scan of P4 (h) reveals a broader interruption of the ellipsoid zone, accompanied by macular attenuation (i) and reduced macular function (j).

disease, hypertension, type 2 diabetes, and osteoporosis. Ophthalmological examination, including multimodal imaging and electrophysiological measurements, revealed blunt foveal reflexes and mild pigmentary changes on color and red-free fundus images. FAF images showed slightly reduced autofluorescence in the central macula, surrounded by a halo of increased autofluorescence. OCT demonstrated a central interruption in the ellipsoid

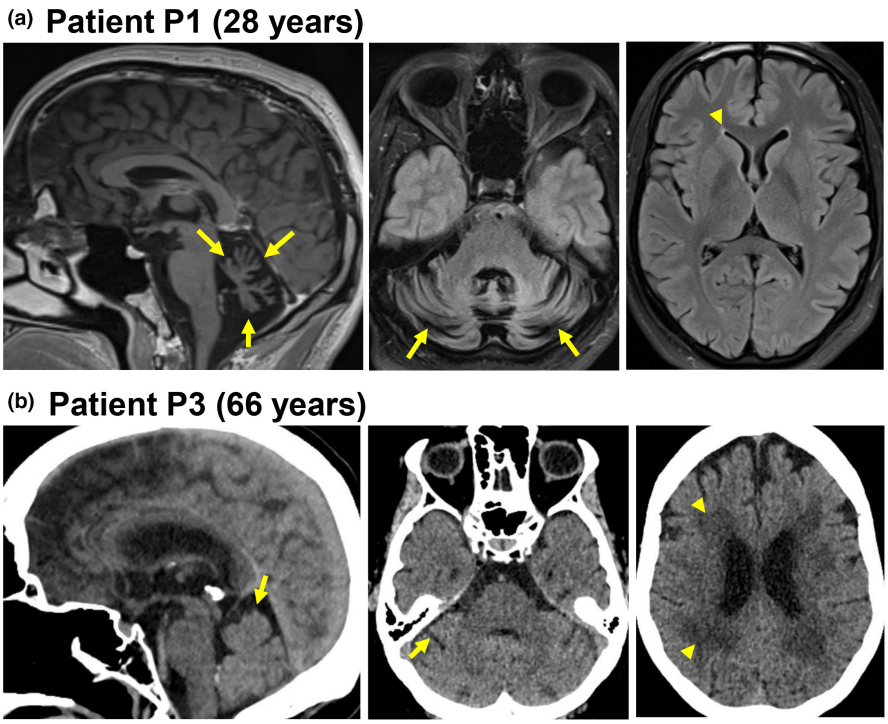

FIGURE 2 Brain imaging of patients P1 and P3. MRI or CT was available for these two patients. Cerebellar atrophy (arrows) was marked in P1 (a) and mild in P3 (b). P3 had marked white matter hypodensities on CT (arrowheads); P1 had possibly pathological hyperintensities around the frontal horns of both lateral ventricles (arrowhead) but not in other parts of the brain (not shown).

zone (Figure 1e), corresponding to a focal loss of photoreceptors in the central macula, and general macular attenuation was also evident on the OCT macular map (Figure 1f). Correspondingly, mfERG responses were reduced (Figure 1g), confirming impaired macular function, while ffERG measurements reflecting general retinal function were normal. Genetic panel examination for retinal dystrophy within her clinical workup revealed two heterozygote variants in *MFSD8* classified as pathogenic: NM_152778.4 c.1006G>C p.(Glu336Gln) and c.1444C>T p.(Arg482*). P3's unaffected daughter carried one of these variants, providing evidence that they were in a compound heterozygote state in P3. p.(Glu336Gln) had previously been identified in 16 patients presenting in adulthood with non-syndromic retinal or macular dystrophy or cone dystrophy without neurological symptoms; these carried different second disease alleles, including other nonsense variants (Gardner & Mole, 2021; Khan et al., 2017; Poncet et al., 2022; Priluck & Breazzano, 2023; Roosing et al., 2015; Stone et al., 2017). p.(Arg482*) had been identified in three patients with childhood-onset CLN7, each carrying different second disease alleles (Gardner & Mole, 2021). P3 had not noticed any neurological symptoms, but her ophthalmologist noted she had developed mild balance problems. There was no history of neurological disorders or symptoms in her family. On neurological examination, the patient had mild horizontal gaze-evoked nystagmus, mild to moderate intention tremor on finger-nose testing (Video S3), discrete irregularities in alternating pro- and supination of her hands, and was swaying when walking or standing in tandem.

Patient P4: This 33-year-old female was referred to the ophthalmological clinic due to central scotoma, difficulty reading, and photophobia that had appeared in early adulthood. She had no problems during her schooling. She reported no neurological disorders or symptoms concerning herself or her family. Her vision was normal at the age of 18 when examined before obtaining her driver's license. Ophthalmological assessment at 33 years of age showed moderate pigmentary changes on color and red-free fundus images. OCT revealed the same kind of structural macular changes as in P3, but more pronounced, with interruptions in the ellipsoid zone corresponding to a focal absence of photoreceptors in the central macula (Figure 1h) and central macular attenuation (Figure 1i). FAF images demonstrated central, round, sharply delineated areas of reduced autofluorescence surrounded by a halo of increased autofluorescence. MfERG signals were reduced (Figure 1j), reflecting impaired macular function, while ffERG was normal. Clinical genetic panel testing for retinal dystrophy revealed two heterozygote variants in the *MFSD8* gene classified as pathogenic: Like P3, she also carried NM_152778.4 c.1006G>C p.(Glu336Gln), as well as the variant c.1394G>A p.(Arg465Gln) that had previously been described in combination with another disease allele in several individuals with adult onset retinal dystrophy, and in homozygous form in one patient with juvenile-onset CLN7, with neurological involvement (Jilani et al., 2019; Khan et al., 2017; Kousi et al., 2012). The patients' unaffected mother carried one of these variants. During the regular follow-up visits of this patient until age 33, no neurological symptoms had been noticed.

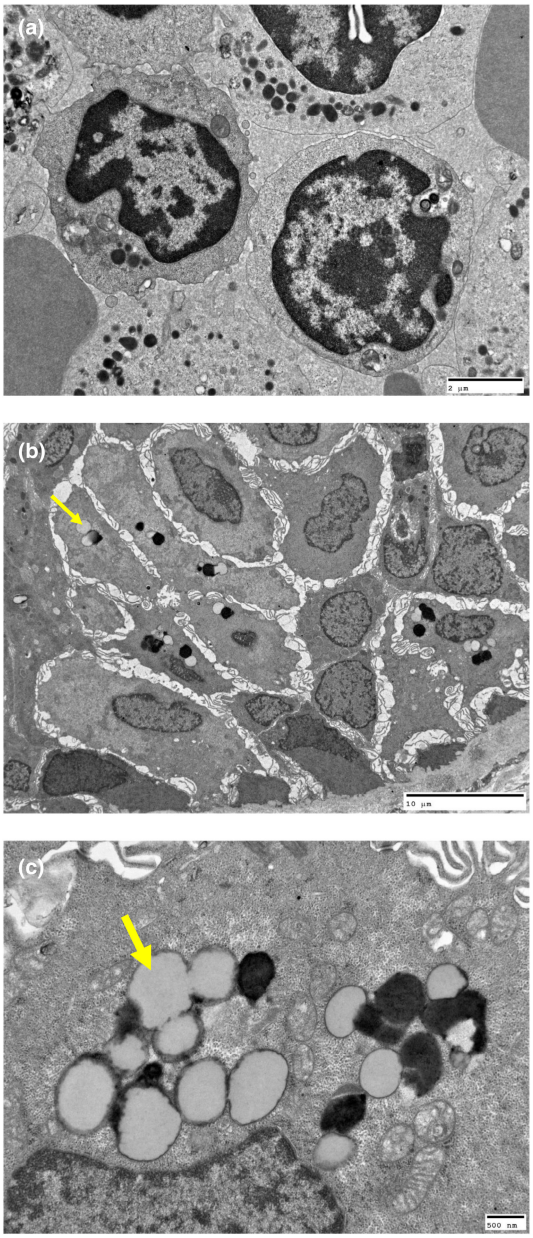

FIGURE 3 Electron microscopy of patient P1. (a) Buffy coat lymphocytes showing normal lysosomes and no storage material. Magnification ×2500. (b) Skin biopsy eccrine sweat gland epithelial cells with numerous lipofuscin granules (arrow). Magnification ×800. (c): Higher power of an epithelial cell with a lipofuscin deposit, including an electron-dense region and prominent pale lipid droplets (arrow). Magnification ×5000.

4 | DISCUSSION

The known disease entities arising from biallelic variants in *MFSD8* fall into several disease types, including a long-recognized largely homogenous pediatric disorder with a similar age of onset in childhood and clinical presentation, and a more recently identified milder phenotype with retinal dystrophy presenting in early to mid-adulthood, without neurological symptomatology. This report adds to the phenotypic understanding of variations in the *MFSD8* gene by describing longitudinal studies on four adult-onset cases characterized by visual disturbances, of whom three also developed neurological features, either before or after visual symptoms. Two patients had late-onset ataxia as the presenting sign for *MFSD8*-related disease and one patient with adult-onset retinal disease developed mild–moderate ataxia years after the onset of visual symptoms.

When the genetic workup from patient P1 was obtained, the result was classified as a variant of uncertain significance according to the ACMG guidelines, and late-onset ataxia as the key finding was not known to be associated with *MFSD8*. However, a detailed entry of the clinical phenotype of the Indian patient in the ClinVar database helped identify P2 as a second patient with the same genotype and very similar clinical presentation of adult-onset cerebellar ataxia and cerebellar atrophy on radiological examination. As alternative genetic causes for the patients' ataxia were ruled out, using whole genome sequencing, we suggest that the homozygous *MFSD8* c.935T>C p.(Ile312Thr) variant, not previously reported from patients with *MFSD8*-related disease, caused the clinical phenotype of these two patients, including marked adult-onset cerebellar ataxia. The specific ophthalmological findings in P1, which were very similar to what is seen in P3 and P4 or other reported patients with *MFSD8*-related maculopathy, further supported the pathogenicity of this variant and genotype. The clinical phenotype of P1 and P2 was much milder than late-infantile CLN7 disease but clearly more severe than non-syndromic retinal dystrophy. This phenotype includes macular dystrophy, but neurological (balance) problems presented before retinal disease and progressed to include speech problems and notable cerebellar atrophy. Thus, the p.(Ile312Thr) variant in homozygotes causes adult onset neurological and ophthalmological disease presenting in early adulthood (20s–30s), compatible with a dosage effect and partially remaining MFSD8 protein function. This can be referred to as adult CLN7 disease.

Patients P3 and P4 were known to our ophthalmology clinic; both had been found to be compound heterozygote carriers of previously reported pathogenic *MFSD8* variants (Aiello et al., 2009; He et al., 2023; Kousi et al., 2012; Priluck & Breazzano, 2023; Ren et al., 2019; Roosing et al., 2015). P3 had visual problems and subsequently developed ataxia; P4 did not develop neurological symptoms during the study period.

The visual symptoms in P3 had a late onset, manifesting in the patient's 60s. The mutations in this patient were p.(Arg482*), which was found as one disease allele in several patients with late-infantile CLN7 disease (Aiello et al., 2009), consistent with truncated and/or nonfunctional proteins, and p.(Glu336Gln), which also was found

in P4. The mild form of disease in P3 and P4 is therefore probably due to a relatively milder effect of p.(Glu336Gln) in combination that does not completely abolish MFSD8 function. Of the other previously reported patients carrying p.(Glu336Gln), five also presented with maculopathy in late adulthood (50s–60s) and eight in early to mid-adulthood (late 20s to 40s) (Khan et al., 2017; Poncet et al., 2022; Roosing et al., 2015). Like P3, one family with five affected siblings also carried a truncating variant, p.(Glu381*), on their second allele; interestingly, the ages of onset in that family varied from 29 to 65 years (Roosing et al., 2015). Two patients presenting at ages 37 and 55 years carried the recurrent p.(Thr294Lys) on their second alleles, a variant that, in homozygous form, causes late-infantile CLN7 disease (Poncet et al., 2022). One additional patient carrying a different variant that affects residue 336, p.(Glu336Lys), in compound heterozygosity with a different mutation (c.750A>G) affecting splicing, presented by age 12 years (Poncet et al., 2022). One patient carrying a different variant that affects residue 482, p.(Arg482Pro), in homozygous form presented with ophthalmological disease described as retinitis pigmentosa at age 31 (Birtel et al., 2018; Zare-Abdollahi et al., 2019), consistent with some MFSD8 function remaining with this missense change.

P4 carries this "mild" p.(Glu336Gln) variant in compound heterozygosity with p.(Arg465Gln). This combination of variants was reported in three sibling patients presenting with visual problems around the age of 28–30 years (Khan et al., 2017) and no other neurological features. p.(Arg465Gln) probably has a larger biological effect because a patient homozygous for p.(Arg465Gln) developed late-infantile CLN7 disease at age 5 (Jilani et al., 2019), and a different missense variant affecting the same residue, p.(Arg465Trp), was found in homozygous form in a child presenting with CLN7 disease at age 4.5 years (Kousi et al., 2009).

Very few patients with CLN7 disease developing neurological symptoms at juvenile or adult ages have been described (Bauwens et al., 2020; Dozières-Puyravel et al., 2020; Jilani et al., 2019; Kousi et al., 2009; Reith et al., 2022). A range of ages of onset has been reported in *MFSD8*-associated retinal disease, where first symptoms appeared in childhood and teenage years, or in the early to mid-20–40s and later adult years (>50 years) (Poncet et al., 2022), but there are very few previous reports of milder or later onset neurological symptoms in patients who are biallelic *MFSD8* variant carriers and who present with visual problems: A Dutch patient developed vision difficulties at the age of 11 years and then motor impairment and seizures in the mid-twenties, and at the age of 28, ataxia was noticed. Cognitive regression started in the early 30s and, by the age of 39, the patient had become wheelchair-dependent. The patient was homozygous for c.468_469delinsCC p.(Ala157Pro); this has not been described in any other reports (Kousi et al., 2009). A second case report describes a Turkish family with two affected siblings, one who developed speech delay at 4 years of age, retinal disturbances at age 10, and thereafter other neurological symptoms including seizures, and the other who presented with epilepsy at age 19, retinal disturbances at age 22, and ataxia and myoclonus when examined at age 26. Both were homozygotes for *MFSD8* c.750A>G p.(Glu250Glu), which is considered to affect splicing and cause exon skipping (Reith et al., 2022).

In cases of late-infantile CLN7 disease, inclusions in skin biopsy typically contain a mixture of fingerprint-profile inclusions and pure curvilinear bodies or rectilinear profiles (Anderson et al., 2013). We were able to examine a skin biopsy in one of our patients, P1. These features were not identified in this skin biopsy, but there were prominent lipofuscin deposits with large lipid droplets, and the ratio of lipid to dense material was unusual. We assumed this may represent regular lipofuscin, as seen in older individuals without storage disease. In general, lymphocytes in CLN7 disease demonstrate membrane bound storage inclusions with a fingerprint pattern and a small adherent lipid droplet. This feature can vary, and storage may only be identified in 2%–10% of lymphocytes (Anderson et al., 2006). An extensive examination of P1's blood sample did not reveal any atypical storage. The pathological inclusions of late-infantile CLN7 disease may therefore not be typically found in patients with a later onset phenotype.

Our data suggest that patients with *MFSD8*-related retinal dystrophy presenting later in life may still go on to develop balance problems and cerebellar signs and therefore fall into the class of adult CLN7 disease. This might have remained unnoticed either because doctors, patients, and their families assumed a connection with the visual loss or because they were not aware of a potential connection between these seemingly unrelated disease manifestations. Furthermore, our report shows that ataxia, starting in mid-adult life, can be the presenting sign of *MFSD8*-related disease. A number of other neurological disorders with ataxia affect retinal function or vision (Almasoudi et al., 2023; Gorcenco et al., 2017, 2019; Hugosson et al., 2009; Reith et al., 2022).

Our study faced several limitations. One was the rarity of individuals in whom pathogenic variants in the *MFSD8* gene have been identified. This remains a common problem for the study of rare monogenic disorders, although increasing use of genetic diagnostics in clinical practice and research internationally leads to an ever-larger number of patients being identified. The geographical distance between Sweden and India meant that not all four individuals could be examined in the same way.

The *MFSD8* gene encodes a protein of 518 amino acids (Siintola et al., 2007) that contains 12 transmembrane domains, including a major facilitator superfamily (MFS) domain (Sharifi et al., 2010; Steenhuis et al., 2010). Some major facilitator superfamily proteins are active in the transport of different solutes via chemiosmotic ion gradients in cell membranes (Drew et al., 2021). The exact function of the MFSD8 protein is still unclear, but it may function as a transport protein in the lysosome perimeter membrane (Siintola et al., 2007). As in other forms of neuronal ceroid lipofuscinoses and generally other recessive diseases, a gene dosage effect is apparent whereby combinations of variants that cause relatively milder biological effects on protein function may lead to milder symptomatology and a later age at onset. New treatments, including gene therapy, are being developed for the recessive *MFSD8*-related diseases (Chen et al., 2022; Kim et al., 2019), which is why it is important to diagnose patients early, as these therapies are likely to be most effective when delivered early in the disease course.

AUTHOR CONTRIBUTIONS

Sigurd Dobloug: Conceptualizing, methodology, writing—original draft, writing—review & editing, data collection, investigation. Ulrika Kjellstöm: Writing:—review & editing, data collection, investigation. Jayesh Sheth: Writing—review & editing, data collection, investigation. Glenn Anderson: Writing—review & editing, data collection, investigation. Sara E. Mole: Writing—review & editing, data collection, investigation, resources. Emily Gardner: Writing—review & editing, investigation. Andreas Puschmann: Supervision, conceptualizing, methodology, writing—review & editing, investigation.

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CONFLICT OF INTEREST STATEMENT

S.E.M. and E.G. are supported by Biomarin for maintaining the NCL mutation database. The other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

All relevant data are presented in the article.

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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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