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ORIGINAL COMMUNICATION

Phenotypic variability related to dominant UCHL1 mutations: about three families with optic atrophy and ataxia

C. Marelli[1] · F. Ramond[2,3] · C. Vignal[4] · C. Blanchet[5] · S. Frost[6] · Q. Hao[6] · B. Bocquet[7] · Y. Nadjar[8] · N. Leboucq[9] · G. Taieb[10] · M. Benkirane[11] · C. Hersent[11] · M. Koenig[11] · I. Meunier[7]

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Abstract

Introduction Ubiquitin C-terminal hydrolase L1 (*UCHL1*) has been associated with a severe, complex autosomal recessive spastic paraplegia (HSP79) [1] [2] [3] [4]. More recently, *UCHL1* loss of function (LoF) variants have been associated to an autosomal dominant disease characterized by late-onset spastic ataxia, neuropathy, and frequent optic atrophy [5].

Methods Routine clinical care whole-genome (WGS) and exome (ES) sequencing.

Results We present three families with autosomal dominant *UCHL1*-related disorder. The clinical phenotype mainly associated optic atrophy, mixed cerebellar and sensory ataxia, and possible hearing loss. We delineated two major phenotypes, even within the same family: (1) juvenile severe optic atrophy followed by a later-onset ataxia, or (2) late-onset ataxia with asymptomatic or mild optic atrophy. The families harboured three novel heterozygous variants in *UCHL1*: two loss of function (p.Lys115AsnfsTer40; c.171_174 + 7del11), and one missense (p.Asp176Asn) involving the catalytic site of the protein and potentially altering the adjacent splice site.

Discussion We confirm the existence of dominantly inherited *UCHL1* pathogenic variants. We describe a considerable intrafamilial phenotypic variability, with two main phenotypes. Optic atrophy was consistently present, but with varying degrees of severity. Neither delayed motor or intellectual development, nor dysmorphic features were part of the dominant phenotype in comparison with the autosomal recessive form. The molecular mechanism appears to be haploinsufficiency. *UCHL1* monoallelic variants should therefore be considered in any case of early-onset optic atrophy or in late-onset complex ataxic syndrome with asymptomatic optic atrophy.

Keywords *UCHL1* · Optic atrophy · Cerebellar ataxia · Autosomal dominant

✉ C. Marelli
c-marelli@chu-montpellier.fr

1 EPHE, INSERM and Reference Center for Neurogenetic Diseases, MMDN, University Montpellier, CHU, 34095 Montpellier, France

2 Service de Génétique, Hôpital Nord, CHU Saint-Etienne, Saint-Etienne, France

3 Laboratoire AURAGEN, Plan France Médecine Génomique 2025, Lyon, France

4 Foundation Adolphe de Rothschild Hospital, Paris, France

5 Reference Centre for Inherited Deafness, Montpellier University Hospital, 34 295 Montpellier, France

6 Clinical Genetics Department, Odense University Hospital, Odense, Denmark

7 National Reference Centre for Inherited Sensory Diseases, INM, Montpellier University, Montpellier, France

8 Department of Neurology, Pitié-Salpetriere Hospital, Paris, France

9 Service de Neuroradiologie, Hôpital Gui de Chauliac, Montpellier, France

10 Department of Neurology, CHU Montpellier, Hôpital Gui de Chauliac, Montpellier, France

11 Laboratoire de Génétique Moléculaire, LGM, Centre Hospitalier Universitaire de Montpellier, IURC-Institut Universitaire de Recherche Clinique, 641 Avenue du Doyen G. Giraud, 34090 Montpellier, France

Introduction

Ubiquitin C-terminal hydrolase L1 (*UCHL1*) has been associated with an autosomal recessive (AR) spastic paraplegia (HSP79) characterized by an early-onset cerebellar ataxia, spastic paraplegia, intellectual deficiency, dysmorphism, and optic atrophy. This is a rare and severe disease with only four families described up to now [1–4]. More recently, *UCHL1* heterozygous loss of function (LoF) variants have been associated to an autosomal dominant (AD) disease characterized by late-onset spastic ataxia, neuropathy, and frequent optic atrophy [5]. We present three independent families (7 subjects) harbouring three novel heterozygous variants in *UCHL1,* confirming the occurrence of an AD form, clinically different from the recessive one, and showing a great intrafamilial phenotypic variability.

Methods

The variations in the *UCHL1* gene were found after genetic investigation in the context of clinical care. Family 1 was analysed by Whole-Genome Sequencing (WGS) using Illumina NovaSeq technology, in the context of the French National Genomic Program (PFMG 2025, AURAGEN platform). Family 2 was analysed by exome sequencing (ES) by Illumina NextSeq technology (https://www.illumina.com/products/by-type/clinical-research-products/trusight-one.html). Sequence alignment and variant calling were performed following the Broad Institute's Genome Analysis Toolkit (GATK4) best practices. Family 3 was analysed by WGS using Illumina DNA PCR-Free Library Prep and Illumina NovaSeq 6000 platform (Illumina, Inc.). Alignment and variant calling were performed using Illumina DRAGEN Bio.IT platform (Illumina Inc.). Clinical sequence interpretation was performed following the guidelines from the American College of Medical Genetics [6].

This study was approved by the institutional review boards of the Montpellier University Medical Centre (Number: IRB-MTP_2021_11_202100959) and was conducted in accordance with the principles of the Declaration of Helsinki. All the presented individuals gave their consent for the genetic analysis, for sharing data in the context of the research about their disease and for the publication of anonymous data.

Results

Family 1 (Fig. 1): the proband is a 71 year-old man presenting at the age of 61 years with late-onset ataxia, due to both cerebellar involvement and mild sensory axonal peripheral neuropathy. He had normal visual acuity (20/20 Right Eye; 20/25 left eye) but ophthalmological examination found bilateral temporal disc pallor, decreased nerve fibre layer thickness, and bilateral mild alteration of the temporal upper visual field. Cerebral Magnetic Resonance Imaging (MRI) showed mild hemispheric cerebellar atrophy (Fig. 2). He also had late-onset progressive bilateral and moderate down sloping hearing loss (hearing thresholds were 15 dB above age and sex normative thresholds (ISO7024), requiring hearing aids since the age of 70 years. The personal history revealed noise trauma exposure in young adulthood (hunting). Tonal and vocal audiometry were concordant. Auditory evoked brainstem potentials (BAEP) (at the age of 72 years) found a prolonged central conduction time on the left and non-reproducible responses on the right for a 70 dB click stimulus. The absence of reproducible response at 70 dB on right ear was concordant with subjective elevated thresholds but prolonged central conduction time on left ear could suggest auditory neuropathy, possibly related to his genetic disease. Neurological examination found moderate ataxia (Scale for the Assessment and Rating of Ataxia – SARA: 13/40) with gait ataxia, mild dysarthria, saccadic pursuit, positive Romberg sign, and decreased deep sensation from the lower limbs.

The complete work-out for genetic and acquired late-onset cerebellar ataxia was negative, including plasma alpha-fetoprotein, vitamin E, ceruloplasmin, lactate, albumin, protein isoelectrofocusing and urinary organic acids analysis; genetic analyses for Friedreich ataxia, SCA1, SCA2, SCA3, SCA6 and SCA7, CANVAS, FXTAS-fragile X tremor ataxia syndrome) were also negative. A DATSCAN was normal. His brother died at 68 years because of a neurodegenerative disease with ataxia and optic atrophy, with an onset at about 45 years. His son presented at 15 years with severe optic atrophy, reduced central visual acuity (20/200) (Fig. 3), and optic nerve atrophy at cerebral MRI (Fig. 2). He denied any other problems but a neurological examination at 36 years showed a mild cerebellar ataxia (SARA = 4/40). Because of juvenile-onset isolated optic atrophy, he was genetically explored and POLG1 and OPA1 were negative, as well as mtDNA sequencing (notably for Leber hereditary optic neuropathy); biotinidase activity was also normal and a muscle biopsy was unremarkable. WGS studies identified in both the father and his son a heterozygous deletion (NM_004181.5: c.345delA) in *UCHL1*, predicted to cause a frameshift followed by

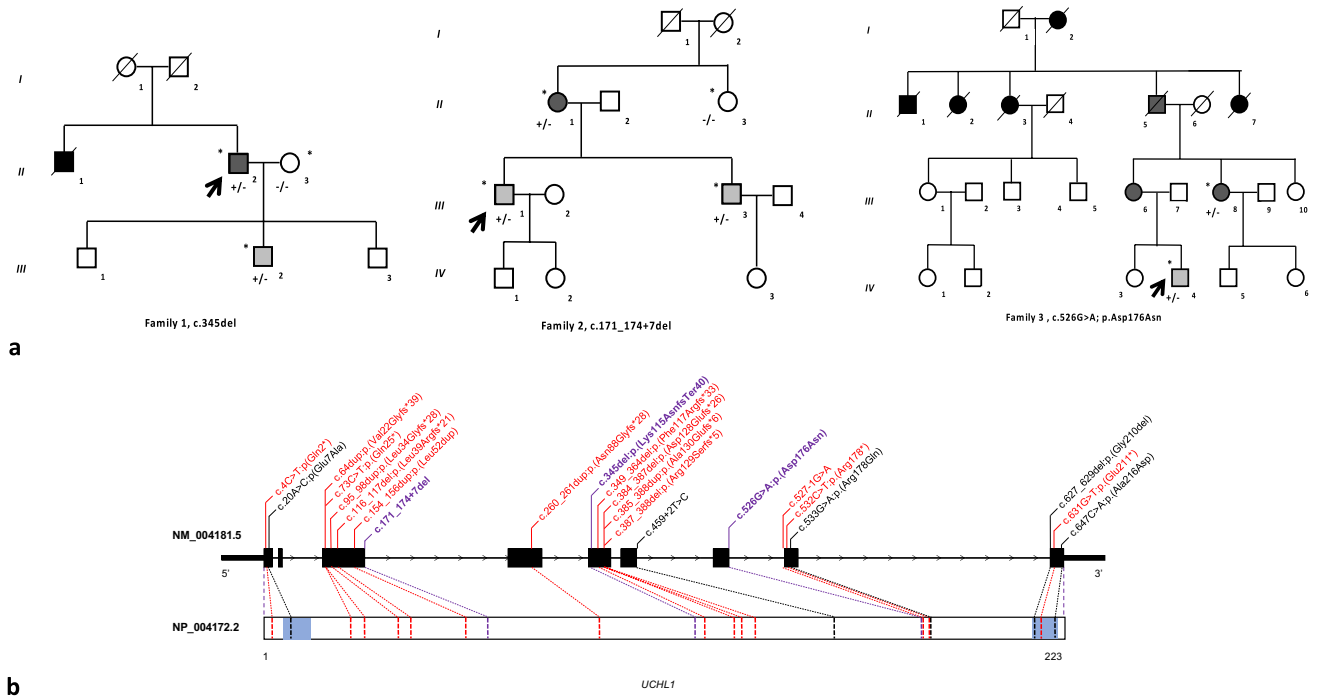

Fig. 1 The pedigree of the three families with dominant *UCHL1*-related disorder and the previously reported *UCHL1* mutations. **a** the pedigree of the three families with the corresponding mutations; the arrow indicates the index case; stars indicate tested family members, with affected presented with closed symbols and unaffected with opened ones. We represented in deep grey the patients with late-onset ataxia, in light grey the patients with juvenile-onset visual loss due optic atrophy, and in black the affected patients with ataxia and optic atrophy for which the phenotype is not better detailed. **b** the *UCHL1* gene (upper) and Uchl1 protein (lower) with mutations described in this report (in purple), previously described recessive mutations (in black), and previously described dominant mutations (in red)

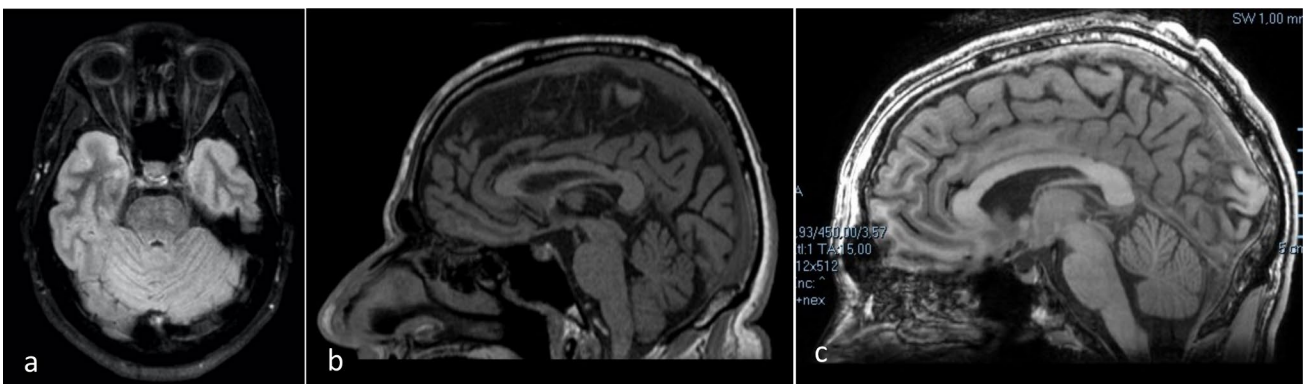

Fig. 2 Cerebral MRI of patients with dominant *UCHL1*-related disease.**a** bilateral optic nerve atrophy without cerebellar atrophy (subject III.2, family 1); **b** very mild hemispheric cerebellar atrophy at the age of 71 years (subject II.2, family 1); **c** no cerebellar atrophy at the age of 40 years (subject III.1, family 2)

a premature stop codon (p.(Lys115AsnfsTer40)) and a truncation of half of the UCHL1 protein. This variant is absent in the general population according to the Genome Aggregation Database (gnomADv4). The variant was classified as pathogenic. No other likely pathogenic variations of *UCHL1* gene were identified in this family.

Family 2 (Fig. 1): the proband is a 52 year-old-man presenting with problems in the colour vision and fluctuating visual acuity (20/25 to 20/20) since his infancy. At the age of 17 years, the visual field showed a central scotoma, initially in the right eye and then bilaterally. Since the age of 30 years, he progressively developed reduced visual acuity, followed by mixed sensory and cerebellar ataxia (SARA = 8/40).

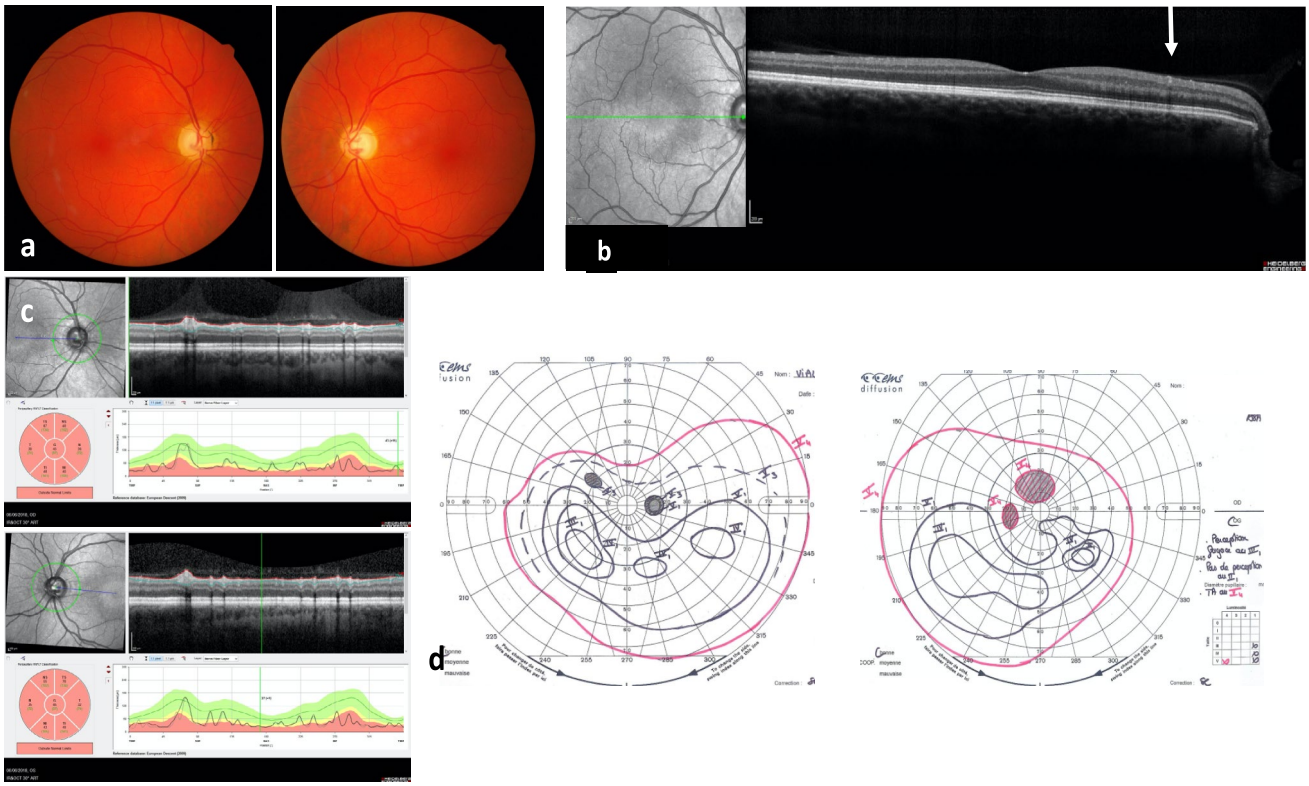

Fig. 3 Ophthalmological findings **a** Slit-lamp examination and Optical Coherence Tomography (OCT) (subject III.2, family 2, at 52 years): the optic disc involvement is very mild compared to the macular OCT slice (**b**), where the maculo-papillary bundle is clearly altered, and compared to the clear reduction of the ganglion fibres on the Retinal Nerve fibre layer (RNFL) (**c**); **d** Visual field analysis showing reduced central visual sensibility (Subject III.2, family 1, at the age of 30 years)

Ophthalmological examination found reduced visual acuity (20/125), optic disc atrophy, and reduced nerve fibre layer thickness. Interestingly, at the ocular fundus the optic disc was only mildly abnormal, whereas optical coherence tomography (OTC) showed marked reduced retinal nerve fibre layer (RNFL) thickness, particularly involving the maculo-papillary bundle (Fig. 3). The cerebral MRI showed severe bilateral optic nerve atrophy, without cerebellar atrophy (Fig. 2). He had no auditory complain (hearing loss or tinnitus). However, in the context of visual and neurological deficiencies, audio-vestibular assessment was performed by the age of 40: audiometry was normal (tonal and vocal, in both quiet and noisy environment); auditory brainstem auditory evoked potential (BAEP) measurements showed normal central conduction time but elevated thresholds (reproducible wave 5 was obtained for 70 dB click stimulus and louder); moreover, distorted otoacoustic emissions were present at 2 et 4 kHz in right ear and at 2 kHz in left ear. These results were in favour of an auditory neuropathy, possibly related to his genetic disorder, without clinical impact. Audiological assessment remained stable 15 years later. Vestibular assessment revealed a left partial deficit in caloric testing, a right directional preponderance (2.5 s) and an alteration of ocular fixation; rotary tests were normal, without any directional preponderance. His brother had optic atrophy with preserved visual acuity. His mother had late-onset (at about 60 years) cerebellar ataxia and optic atrophy. She also complained about late-onset auditory problems but a detailed ORL examination was not available. The initial complete work-out for dominant optic atrophies was negative. ES analysis identified a heterozygous deletion (NM_004181.5: c.171_174 + 7del11) in *UCHL1* in both the patient and his affected mother. Segregation analyses of the deletion in the family revealed that his affected brother also carried the deletion while his unaffected maternal aunt did not, which confirms perfect segregation with the disease. The 11 nucleotide deletion removes all of the exon 3 donor splice site as well as the last four nucleotides of the exon. Skipping of exon 3 as a result of donor splice site loss is predicted to result in an in-frame deletion of 43 amino acids (p.(Val16_Gln58del43)) involving 2 of the 6 highly conserved beta-strands of the UCHL1 protein. This variant is absent in the general population (gnomADv4). The variant was classified as pathogenic. No other likely pathogenic variations of *UCHL1* gene were identified in this family.

Family 3: The proband presented at the age of 17 years with progressive visual loss due optic atrophy. The ophthalmological examination found reduced visual acuity (about 20/200 bilaterally), optic disc atrophy, and reduced nerve fibre layer thickness. At the age of 37 years, he began to present cerebellar ataxia; the cerebral MRI found a mild cerebellar atrophy. Genetic analysis for ataxias due to CAG expansions (SCA 1, 2, 3, 6, 7, SCA17, DRPLA) and for Friedreich ataxia were negative, as well as a panel of 137 genes responsible for cerebellar ataxia, 37 genes responsible for nuclear mitochondrial disorder (including OPA1) and mitochondrial DNA analysis for Leber hereditary optic neuropathy. He had a family history of dominant cerebellar ataxia spanning four generations (Fig. 1, Family 3). A detailed clinical description was not always available because some family members died many years ago. However, his mother was also affected, presenting cerebellar ataxia since the age of 56 years, as well as his grandfather, presenting with cerebellar ataxia since the age of 50 years. His maternal aunt (now 79 years old) was also affected and presented with mixed sensory and cerebellar ataxia since the age of about 55 years; she had no visual complain but detailed ophthalmological examination has never been performed. WGS analysis identified a heterozygous missense change (NM_004181.5: c.526G > A; NP_004172.2: p.Asp176Asn) in *UCHL1* in both the proband and his maternal aunt. His mother was not tested but she was symptomatic and obligate carrier of the same variant. Thus, the variant co-segregates with the phenotype in the family (PP1), with a concordant clinical phenotype (PP4). The p.Asp176Asn variant is absent from the GnomAD v4 database (PM2). Previous mutagenesis studies demonstrated that this variant is deleterious on UCHL1 protein function (PS3) because it impairs ubiquitin binding [7] and virtually eliminates UCHL1 monoubiquitination [8]. Aspartate 176 is conserved in all eukaryotes (PP3, Supplementary Fig. 1). The variant was therefore classified as likely pathogenic (PS3 PM2 PP1 PP3) based on ACMG criteria [6]. In addition, the c.526G > A change is located at the last position of exon 7 and may alter the exon 7 donor splice site (MaxEnt score 7.1 → 2.8, SPIP prediction 98% damaging, SpliceAI Acceptor Loss 0.51, Pangolin Splice Loss 0.76). Unfortunately, protein or mRNA expression studies were not available.

A summary of the demographic, clinical, and radiological features of the three families is presented in Table 1.

Discussion

We present three independent families (7 subjects) harbouring three novel heterozygous variants *UCHL1*. These observations confirm the existence of AD *UCHL1*-related disorders, which are remarkably different from the AR *UCHL1*-related disease, since neither delayed motor or intellectual development, nor dysmorphic features were part of the phenotype. The possible presence of a predominant ataxia and of isolated optic atrophy in AD UCHL1-related disease was already reported in the original paper [5], but with our observation we are able to further precise these phenotypes. In our families, differently from the previously published AD *UCLH1*-related patients, spasticity was minimal or absent. Moreover, we show a large intrafamilial phenotypic variability: from juvenile-onset severe optic atrophy (followed by mild cerebellar ataxia more than 15 years after disease onset) to late-onset ataxia with asymptomatic optic atrophy.

Optic atrophy was constantly present, if searched through detailed ophthalmological examination, but with different severities. In details, optic atrophy was quite particular, showing a relatively mildly pale optic disc (even in patients with severely reduced visual acuity) but a severe reduction of the retinal nerve fibre layer, and particularly of the interpapillomacular bundle (Fig. 3).

Interestingly, hearing assessment in the proband of family 2 showed a sub-clinical auditory neuropathy, with electrophysiological signs but no functional impact during a 15 years' follow-up. The proband of family 1 also had electrophysiological signs of auditory neuropathy but also a bilateral sensorineural hearing loss; the aetiology of this hearing loss remained uncertain and may be multifactorial (age related, noise trauma induced). Although our data were not sufficient to affirm the presence of hearing phenotype in *UCHL1*-related disease, we suggest that a cochleovestibular assessment should be performed in patients with *UCHL1* variants to detect a possible disease-related hearing involvement.

The exact pathophysiological mechanism leading to AR and AD *UCHL1*-related disease is not yet completely elucidated [5]. A loss of function mechanism has been considered for the AR forms. However, it seems that AR disease are mainly related to missense mutations, in-frame deletions, or in-frame splicing variants, probably leading to some residual functional protein. These findings globally suggest that the *UCHL1* variants found in the AR form could be hypomorphic mutations. Instead, up to now, AD *UCLH1*-related disorders were related to predicted loss of function variants suggesting a pathogenic mechanism by haploinsufficiency. The only exception is the c.526G > A p.Asp176Asn variant present in Family 3. However, this variant could still lead to haploinsufficiency, through either altered splicing or alteration of catalytic site activity. Finally, a neurotoxic gain of function mechanism cannot be ruled out for this variant, since UCHL1 has a role in deubiquitination of other proteins and ubiquitin homeostasis, and its absence or dysfunction could cause an accumulation of ubiquitinated proteins,

Table 1 Demographic, clinical, and radiological features of AD UCHL1 patients in the present paper

Family/Subject */ sex/*UCHL1* mutation	Age at onset (years) / symptom at onset	Cerebellar ataxia/age at onset	Visual symptoms/ age at onset	Ophthalmological examination	Polyneuropathy at EMG	Pyramidal signs	Hearing loss	MRI findings
Family 1/II.2 */ M/ p.Lys115AsnfsTer40	61/ataxia	Yes; SARA = 13/61 ys	No	N visual acuity 20/20; bilateral temporal disc pallor, decreased RNFL, altered temporal upper visual field	SM, axonal	Extensor plantar reflex (normal LL reflexes and strength; no spasticity)	Yes; hearing aids at 70 years	Very mild cerebellar atrophy
Family 1/III.2*/M/ p.Lys115AsnfsTer40	15/visual loss	No clinical complains; SARA = 4 at 36 ys	Yes/15 ys	Reduced central visual acuity (20/200); severe OA	NA	Diffused LL reflexes (without spasticity, LL deficit or extensor plantar reflex)	No	Optic nerve atrophy without cerebellar atrophy
Family 1/II.1/M/ NA	45/ataxia	Yes/45 ys	Yes/NA	OA	NA	NA	NA	NA
Family 2/III.2*/M/ (p.(Val16_ Gln58del43))	Infancy/ colour vision problems	Yes/30 ys	Yes/Infancy Optic atrophy at 17 ys	Reduced visual acuity (20/125), mild OA, and markedly reduced RNFL	S, Axonal	None	No/N audiogram/ possible auditory neuropathy at BAEP	Severe bilateral optic nerve atrophy; no cerebellar atrophy
Family 2/III.3*/M/ (p.(Val16_ Gln58del43))	No complains	No	No	OA at 34 years	NA	None	No	NA
Family 2/II.1/F (p.(Val16_ Gln58del43))	60 /ataxia	yes	yes	OA	NA	NA	Yes, late onset	NA
Family 3/IV.4 */M/ p.Asp176Asn	17/visual loss	Yes/37 ys	Yes/17 ys	Reduced central visual acuity(20/200); OA, reduced RNFL	NA	None	NA	Mild cerebellar atrophy
Family 3/III.6/F/ NA (obligate carrier)	56/ ataxia	Yes/56 ys	No	NA	NA	NA	NA	NA
Family 3/III.8 */F/ p.Asp176Asn	55/ataxia	Yes/55 ys	No	NA	SM, axonal	None	NA	NA
Family 3/II.5/M/NA	50 /ataxia	Yes/50 ys	No	NA	NA	NA	NA	NA

BAEP Brainstem Auditory Evoked Potential, *EMG* electromyogram, *F* female, *LL* lower limbs, *M* male, *NA* not assessed, *OA* optic atrophy, *RNFL* Retinal Nerve Fibre Layer, *SARA* Scale for Assessment and Rating of Ataxia, *S* sensory, *SM* Sensory Motor, *Ys* years

*Subjects who underwentdirect neurological examination; for the others subjects clinical data are issued from clinical notes or family history

which is one of the hallmarks of neurodegenerative diseases [9].

In conclusion, we confirm the existence of an autosomal dominant form of *UCLH1*-related disorder, characterized by less severe neurological disorders and two main phenotypes, even in the same family: (1) early-onset optic atrophy followed by mild sensory and cerebellar ataxia; (2) late-onset ataxia with mild or asymptomatic optic atrophy. A subtle hearing loss may also be associated with the disease. The variants associated with AD-UCHL1 disease are mainly, if not all, predicted loss of function. We suggest that *UCHL1* heterozygous variants should be considered in patients with early-onset optic atrophy or in late-onset complex ataxic syndrome with mild or asymptomatic optic atrophy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-024-12574-z.

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Declarations

Conflicts of interest CM received honorary travel to attend scientific meetings (Nutricia and Vitaflo) and honorary for consultant activity (Biogen, Reata Pharmaceuticals, Medesis Pharma); FR, CV, CB, SF, QH, YN, NL, GT, MB, CH, MK, and IM have nothing to disclose. On behalf of all authors, the corresponding author states that there is no conflict of interest.

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