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CASE REPORT

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ITPR1: The missing gene in miosis–ataxia syndrome?

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Abstract

The association of early-onset non-progressive ataxia and miosis is an extremely rare phenotypic entity occasionally reported in the literature. To date, only one family (two siblings and their mother) has benefited from a genetic diagnosis by the identification of a missense heterozygous variant (p.Arg36Cys) in the *ITPR1* gene. This gene encodes the inositol 1,4,5-trisphosphate receptor type 1, an intracellular channel that mediates calcium release from the endoplasmic reticulum. Deleterious variants in this gene are known to be associated with two types of spinocerebellar ataxia, SCA15 and SCA29, and with Gillespie syndrome that is associated with ataxia, partial iris hypoplasia, and intellectual disability. In this work, we describe a novel individual carrying a heterozygous missense variant (p.Arg36Pro) at the same position in the N-terminal suppressor domain of *ITPR1* as the family previously reported, with the same phenotype associating early-onset non-progressive ataxia and miosis. This second report confirms the implication of *ITPR1* in the miosis–ataxia syndrome and therefore broadens the clinical spectrum of the gene. Moreover, the high specificity of the phenotype makes it a recognizable syndrome of genetic origin.

KEYWORDS
anterior segment dysgenesis, Gillespie syndrome, *ITPR1*, miosis, ocular malformation, spinocerebellar ataxia

1 | INTRODUCTION

The association of early-onset non-progressive ataxia and miosis has been reported a few times in the literature, making it a potential new syndromic entity that lacked a clear genetic cause until recently (Casey et al., 2017; Dick et al., 1983; Timby et al., 2008). Casey et al. (2017) detected a likely pathogenic missense variant in the N-terminal suppressor domain of the *ITPR1* gene (inositol 1,4,5-trisphosphate receptor type 1) in a family with dominant early onset ataxia and miosis, without cerebellar hypoplasia. However, to date, this potential new genetic association has not yet been replicated. The *ITPR1* gene encodes a protein that assembles into a homotetramer, forming a calcium channel at the endoplasmic reticulum membrane (Gerber et al., 2016). It mediates calcium release from the endoplasmic reticulum following stimulation by inositol 1,4,5-trisphosphate (IP_3). Pathogenic variants in *ITPR1* have already been associated with various syndromes that share ataxia as part of the phenotype (McEntagart et al., 2016). Although some genotype–phenotype correlations have been observed, they are imperfect and remain to be deciphered (McEntagart et al., 2016; Zambonin et al., 2017). Heterozygous

deletions of the *ITPR1* gene have been associated with spinocerebellar ataxia (SCA) 15, a slowly progressive adult onset ataxia with cerebellar atrophy. Then, heterozygous missense variants affecting the IP_3-binding or the coupling domain have been associated with SCA29, an early-onset non-progressive ataxia with cerebellar atrophy and mild intellectual disability (ID) (Huang et al., 2012). Finally, both mono-allelic and bi-allelic variants, either truncating or missense, mainly within the transmembrane domain, have been associated with Gillespie syndrome (GS), which associates partial iris hypoplasia, early-onset non-progressive cerebellar ataxia, and variable ID (Gerber et al., 2016; McEntagart et al., 2016). GS is likely caused by both effects: a dominant negative effect with perturbation of calcium trafficking across the channel and a recessive loss-of-function mechanism. In the same way, the molecular mechanism leading to SCA29 seems heterogenous with a distribution of variants across the protein suggesting both loss-of-function and gain-of-function mechanisms (Ando et al., 2018; McEntagart et al., 2016; Tolonen et al., 2023). We describe here a second family with a disease-causing missense variant in *ITPR1* associated with early-onset non-progressive ataxia and the ocular phenotype of miosis.

2 | MATERIALS AND METHODS

The full medical and familial history of the patient was collected. She underwent general and ophthalmological examination with slit lamp examination, static pupillometry (Metrovision©, France), intraocular pressure measurement using applanation tonometer (Goldmann), and ocular ultrasound with A-scan and B-scan ultrasonography and ultrasound biomicroscopy (UBM) (Absolu, Quantel Medical, France). Cerebral MRI was conducted at the age of 68 using a 3 T scanner, employing sequences without and with gadolinium injection. The patient also benefited from genetic testing consisting of the analysis of 182-ocular development genes using a dedicated next-generation sequencing (NGS) panel, screening for both single nucleotide variants (SNVs) and copy number variants (CNVs), as previously described (Chesneau et al., 2022). She also had an array-CGH with 180 k resolution (SurePrint G3 Custom CGH Microarray, 4 × 180K, with enrichment in ocular development genes, Agilent) to explore chromosomal imbalances.

Confirmation of variants was performed by direct Sanger sequencing. The study was designed in compliance with the tenets of the Declaration of Helsinki and informed consent from the patient and her legal guardian was obtained.

3 | RESULTS

3.1 | Clinical description

We report a 68-year-old woman presenting with non-progressive moderate cerebellar ataxia and discrete pyramidal signs with lightly brisk osteotendinous reflexes. She is the second child of three siblings from unrelated parents of Caucasian origin. Both of her parents died at an advanced age, with neither ataxia nor miosis. Neither her deceased brother nor her living sister displayed ataxia or miosis. The proband did not have children.

She grew up with early-onset ataxia, neurodevelopmental delay (walking from the age of 7 years old, language delay), and mild ID. Ophthalmological examination at the age of 10 years revealed strabismus and pinpoint pupils without the possibility of dilation with topical atropine (the test was stopped due to systemic signs).

The clinical examination at the time of diagnosis of the 68-year-old reveals a moderate short stature (height 150 cm (−2.2SD), weight 52 kg (25^{e}p), head circumference 52 cm (−2 SD), arm span 155 cm). She has craniofacial dysmorphism (Figure 1a–c) with deeply set eyes, a high palate, and diastema between the maxillary central incisors. Neurological examination shows spastic ataxic gait with moderate upper limb incoordination, mildly increased generalized limb tone, and brisk reflexes but with normal power, normal cranial nerve examination, and plantar reflexes in flexion. Cerebral MRI was normal for her age, demonstrating only mild, unspecific white matter hyperintensities but no significant atrophy, especially of the cerebellum (Figure 1d,e). Ocular examination shows small pupils (2 mm diameter) without light reactivity and without transillumination. On UBM, both iris dilator muscles were very thin (Figure 2). The rest of the ocular examination was normal (fundus examination was not possible because of narrowed pupils). She does not have any other known pathologies. Of note, echocardiography was normal except for mild aortic dilatation (38 mm, +2.6 SD according to Campens et al., 2014 at the Valsalva sinus base).

3.2 | Genetic data

Genetic analysis revealed a heterozygous variant in *ITPR1*: NM_001378452.1: c.107G>C p.Arg36Pro. This variant is absent from GnomAD (v3.1.2) and literature. It is located within the N-terminal suppressor domain of the protein, affects a highly conserved amino acid (PhyloP100way conservation score 9.519, https://hgdownload.soe.ucsc.edu/goldenPath/hg38/phyloP100way/), and predicted deleterious by multiple prediction tools (CADD phred = 32, REVEL = 0.956). Interestingly, a substitution affecting the same amino acid (NM_001378452.1: c.106C>T p.Arg36Cys) has been previously described by Casey et al. (2017) in a heterozygous state in a dominantly transmitted atypical SCA29 phenotype without cerebellar atrophy and with pinpoint pupils from a mother to two children (Table 1). This latter variant has also been reported in three other individuals, but with limited relevant or available clinical information, except for early-onset non-progressive ataxia (Kuperberg et al., 2016; Tolonen et al., 2023). Parental samples of the individual that we describe here were not available for segregation. The p.Arg36Pro variant was classified as pathogenic (PM2, PM5, PP3, and PP5) according to ACMG criteria (Richards et al., 2015). We did not find any other variant of interest in our NGS panel analysis or array-CGH.

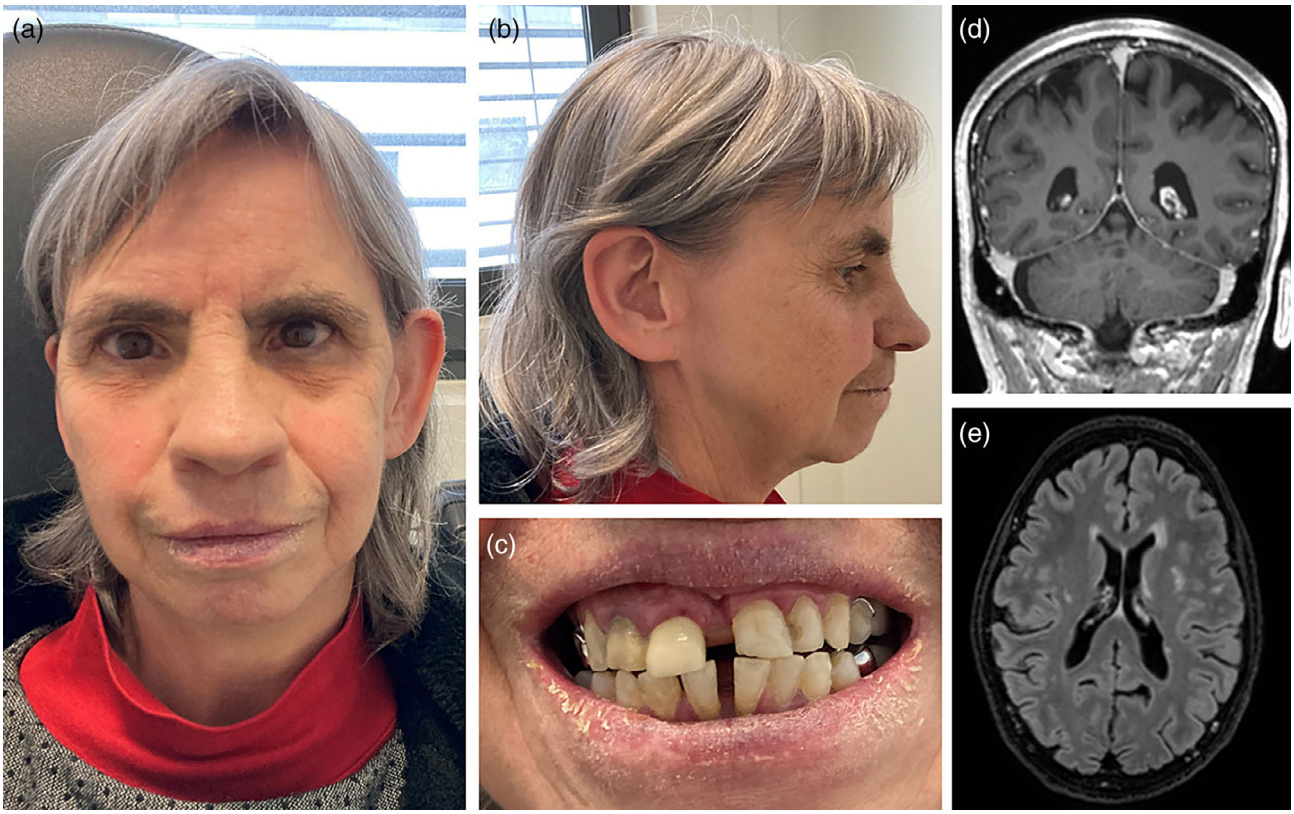

FIGURE 1 Extra-ocular features observed in the 68-year-old patient with a heterozygous *ITPR1* pathogenic variant. (a–c) Photographs showing miosis and craniofacial dysmorphism with diastema between maxillary central incisors. (d–e) Cerebral MRI. (d) Contrast-enhanced coronal T1-weighted image showing normal volume of the brain and cerebellum. (e) Axial FLAIR image revealing only mild non-specific white matter hyperintensities.

4 | DISCUSSION

We report here the second family with a genetically elucidated association between miosis and early-onset non-progressive ataxia (Casey et al., 2017). Affected individuals from both families share a very similar medical history marked by the absence of any events in the neonatal period, the presence of congenital or early-onset miosis, early-onset non-progressive gait ataxia without cerebellar atrophy, and variable ID. Craniofacial dysmorphism does not, however, appear to be consistent between the two families: deeply set eyes, a high palate, and central diastema were observed in our patient, whereas epicanthus, depressed nasal bridge, and hypoplastic teeth were described in the Irish family by Casey et al. (2017). The moderate growth delay presented by our patient is not reported in other patients with a variant affecting arginine 36 and has only been rarely described in *ITPR1* genetic defects (Tolonen et al., 2023). Therefore, it does not appear to be an a priori sign within the phenotypic spectrum associated with this gene. Furthermore, the discrete pyramidal signs observed in our patient are rare among individuals with *ITPR1* pathogenic variants (Tolonen et al., 2023). In the individual that we report here, it remains uncertain whether these signs have always been present or if they are recent and possibly associated with another unknown medical condition, especially considering her advanced age. Interestingly, subtle pyramidal signs, notably brisk reflexes, have been frequently reported in individuals with the miosis–ataxia association without molecular diagnosis (Dick et al., 1983; Timby et al., 2008). These discrete signs might therefore be part of the clinical entity. The mild aortic dilatation is however only displayed in our patient but aortic dilatation is not unusual after 60 years old (Campens et al., 2014). The specificity of the shared clinical signs, namely, early-onset ataxia without cerebellar hypoplasia and miosis, makes it a recognizable syndrome. Moreover, this clinical presentation is very similar to that described in other few case reports available in the literature, which lack any genetic diagnosis to date (Dick et al., 1983; Timby et al., 2008). These cases might possibly be explained by a variant affecting an amino acid within the same region (or even at the same position) of *ITPR1*.

Strikingly, in both cases, the likely causal variant affects the same amino acid in ITPR1 (Arg36) in the head of the suppressor domain of the protein, suggesting the possibility of a specific mechanism (Bosanac et al., 2005; Casey et al., 2017). In addition to the Irish family (Casey et al., 2017), seven other individuals have been described in literature and ClinVar database with a missense variant at the same position (Arg36) in association with early-onset non-progressive ataxia (Kuperberg et al., 2016; Tolonen et al., 2023) (Table 1). Detailed clinical data were only available for two cases reported by Tolonen et al.

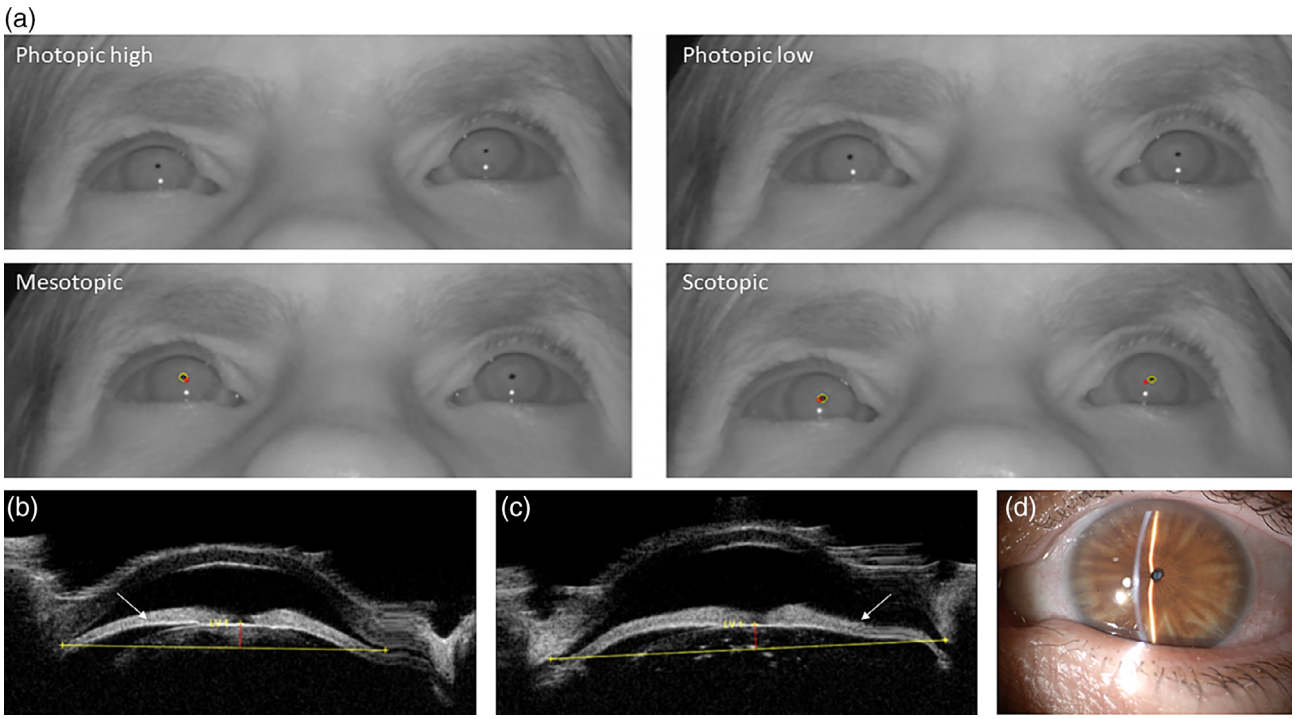

FIGURE 2 Eye phenotype associated with an *ITPR1* pathogenic variant in the proband. (a) Static pupillometry showing pinpoint symmetric pupils (diameter too small to be measured) with no pupil dilation between high photopic and other conditions. (b,c) Ultrasound biomicroscopy of the anterior segment of right and left eye, respectively, with thin iris dilator muscles (arrows). (d) Slit-lamp photograph of the anterior segment of the left eye, showing miosis.

TABLE 1 Reported individuals with a variant affecting the arginine 36 amino-acid of ITPR1 (NM_001378452.1, NP_001365381.1).

Variant	Miosis	Ataxia	Cerebral MRI	Other signs	Number of individuals	Study
c.106C>T p.Arg36Cys	Yes	Early onset (6–24 months)	Normal (2/3)	Mild ID, hypotonia, CFD, atrial septal defect (1/3), keratoconus (1/3)	3	Casey et al. (2017)
	NA	Yes	No MRI	Hypotonia	1	Kuperberg et al. (2016)
	Normal pupils	Early onset (6 months)	NA	Mild ID, hypotonia, tremor	2	Tolonen et al. (2023)
c.107G>A p.Arg36His	NA	NA	NA	NA	4	ClinVar 372854
c.107G>C p.Arg36Pro	Bilateral, early onset	Early onset	Normal for age	Mild ID, CFD, mild pyramidal syndrome	1	This study

Abbreviations: CFD, craniofacial dysmorphism; ID, intellectual disability.

(2023), which indicated normal cerebral MRI and eye examinations. The descriptions of the other reported individuals were either absent or very succinct, indicating only developmental delay and early-onset ataxia. Therefore, we do not know if these patients had miosis and a normal MRI or not. The absence of miosis in the two individuals reported by Tolonen et al. (2023) suggests that this sign may be inconsistently present, and other factors may be involved in the penetrance of this specific ocular phenotype. A precise characterization of the iris phenotype in other individuals carrying a variant affecting the Arg36 residue (and more globally, a variant in *ITPR1*) would provide answers regarding the penetrance of this ophthalmological sign, which has been poorly described so far and probably not sought after in individuals carrying variants in this gene. The suppressor domain, located in the cytoplasmic portion of the protein, might play an important role in regulation of IP_3 binding as variations within this domain result in higher affinity for IP_3 (Bosanac et al., 2005; Casey et al., 2017). Bosanac et al. (2005) have indeed shown that bacterial cells (*Escherichia coli*) expressing *Itpr1* with variation within the head of the suppressor domain, in particular p.Arg36Glu, showed higher affinity to IP_3. This affinity was similar to the one observed in Itpr1 lacking the entire suppressor domain (Δ1-223). Moreover, Casey et al. (2017) showed that cells expressing p.Arg36Cys mutant ITPR1 showed increased

IP_3-binding and enhanced Ca^{2+} release activity, which is in favor of a gain-of-function mechanism. Of note, only one other likely pathogenic variant has been reported in the suppressor domain of ITPR1 (p.-Glu106Lys) in an individual with early-onset ataxia, mild ID, normal MRI, and apparently normal eye phenotype (Tolonen et al., 2023).

The miosis described here is very different from the iris phenotype classically known in association with *ITPR1* variants, which consists of iris hypoplasia with a characteristic "scalloping" of the pupillary edge as observed in GS (McEntagart et al., 2016). GS is indeed a differential diagnosis of *PAX6* aniridia, a panocular condition in which the most specific findings are the total or partial failure of development of the iris. Furthermore, mydriasis has also been reported in a patient with SCA29 (Zambonin et al., 2017). Moreover, miosis associated with *ITPR1* variants has to be distinguished from congenital microcoria. This malformation of the iris is characterized by the partial or total absence of the dilator muscle, which also manifests with congenital miosis. However, it is associated with iris hypopigmentation and transillumination (Angée et al., 2021), findings that were absent in our patient. Microcoria has been linked to structural variations in chromosome 13q32.1 in several families (Angée et al., 2021). Of note, the 180 k custom array CGH ruled out any CNV within this region. In the same way, our patient has very thin iris dilator muscles (Figure 2), which could also result from failure of the muscles to develop. However, it is difficult to determine whether there is a developmental component to the observed eye phenotype, which is likely of neurologic origin.

The phenotype of individuals with miosis–ataxia is close to the early onset non-progressive ataxia observed in SCA29, that is also associated with *ITPR1* variations (Zambonin et al., 2017). But while SCA29-associated variants appear to be responsible for decreased IP_3 binding and channel activity, miosis–ataxia-associated variants appear to be responsible for increased IP_3 binding and calcium transport across the endothelial membrane (Ando et al., 2018; Casey et al., 2017). In addition, they do not share the cerebellar atrophy, which is frequent in SCA29 but not observed in our patient nor in the other family (Casey et al., 2017).

In conclusion, our genetic findings show that miosis–ataxia is a clinically recognizable entity associated with heterozygous missense variants in the suppressor domain of *ITPR1*. This new phenotypic association broadens the already wide phenotypic spectrum of the *ITPR1* gene, which is also associated with GS and two types of ataxia (SCA15 and SCA29). Further studies are thus needed to better understand and possibly elucidate the putative links that might exist between the different phenotypes and genotypes related to this gene, particularly regarding its role in iris development and functions.

AUTHOR CONTRIBUTIONS

All the authors have critically revised the manuscript and have approved its final version. BC and JP wrote the first draft of the manuscript. MC, FV, and PF performed the ophthalmological examination. FB performed the IRM interpretation. PC and JP performed the rest of the clinical examination. BC, J-MR, NC, LFT, and JP performed the genetic analysis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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