Case report

Missense mutation in the ITPR1 gene presenting with ataxic cerebral palsy: Description of an affected family and literature review

Joyutpal Das a,*, James Lilleker b, Hannah Shereef b, John Ealing b

a Department of Neurology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Glossop Road, Sheffield S10 2JF, United Kingdom
b Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Stott Lane, Salford M6 8HD, United Kingdom

ABSTRACT

The inositol 1,4,5-triphosphate receptor type 1 (ITPR1) gene on chromosome 3 belongs to a family of genes encoding intracellular calcium channel proteins. Such channels are located primarily within the endoplasmic reticulum membrane and release Ca2+, an intracellular messenger, which governs numerous intracellular and extracellular functions.

We report a family with infantile-onset cerebellar ataxia with delayed motor development and intellectual disability caused by a heterozygous c.805C>T, p.Arg269Trp missense mutation in ITPR1. Both affected family members had postural tremor, hypotonia and dysarthria, but neither had pyramidal signs. Their neuroimaging revealed cerebellar atrophy.

Several neurological conditions have been associated with ITPR1 mutations, such as spinocerebellar ataxia type 15 and Gillespie syndrome, and the phenotype may vary according to the location and type of mutations. Spinocerebellar ataxia type 15 is an autosomal dominant disorder, which causes late onset pure cerebellar ataxia. Gillespie syndrome is characterised by bilateral iris hypoplasia, congenital hypotonia, non-progressive ataxia and cerebellar atrophy.

In this report, we provide a detailed phenotypic description of a family with a missense mutation in ITPR1. This mutation has only been reported once before. We also provide a literature review of the various phenotypes associated with ITPR1 gene.

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* Corresponding author.

E-mail addresses: j.das@doctors.org.uk (J. Das), james.lilleker@srft.nhs.uk (J. Lilleker), hannah.shereef@nhs.net (H. Shereef), john.ealing@srft.nhs.uk (J. Ealing).

Abbreviations: ITPR1, inositol 1,4,5-triphosphate receptor type 1; InsP3, inositol 1,4,5-triphosphate; SCA, spinocerebellar ataxia; GS, Gillespie syndrome.

http://dx.doi.org/10.1016/j.pjnns.2017.06.012
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1. Introduction

The inositol 1,4,5-triphosphate receptor type 1 (ITPR1) gene belongs to a family of genes (type 1, 2 and 3) that encode for the intracellular calcium channels. Such channels are located primarily within the endoplasmic reticulal membrane and release \(Ca^{2+}\), an intracellular messenger that governs numerous intracellular and extracellular functions. ITPR1 is ubiquitously expressed throughout the body and particularly in cerebellar Purkinje cells [1]. It is hypothesised that the impairment of the calcium buffering leads to Purkinje dysfunction and therefore, the disruption of ITPR1-dependent signalling plays a key role in the development of various forms of cerebellar ataxias [2].

Functionally active ITPR1 is thought to form a homotrimer. Each monomer consists of a N-terminal inositol triphosphate (InsP3) binding domain, a regulatory/coupling domain and a C-terminal transmembrane domain with relatively short cytoplasmic tail (Fig. 1A) [1]. The phenotype associated with ITPR1 mutations may vary according to the location and type of mutation present.

In this report, we provide a detailed phenotypic description of a family with a missense mutation in ITPR1 and a literature review of the various phenotypes associated with mutations in this gene.

![Fig. 1 – (A) Schematic representation of the ITPR1 protein. (B) Pedigree structure. (C) MRI head of the mother showing cerebellar atrophy. (D) Amino acid sequence of the mutation site is conserved in many species.](image)

2. Case description

Patient A (see Fig. 1B, arrowed) was referred to a paediatrician at the age of 27 months with developmental delay. She was diagnosed with 'ataxic cerebral palsy'. She was able to walk unsupported at the age of 9 years and attended a school for children with special needs between the age of 3 and 16 years.

Patient A came to our attention in her 30s after further deterioration in her gait, as the requirement to use a walking aid became evident. At that time examination revealed postural tremor, hypotonia, limb ataxia and cerebellar dysarthria. There was no nystagmus, but she had broken smooth pursuit eye movements and saccades in all directions were slow.

Patient B, the daughter of Patient A, was hypotonic at birth, crawled at the age of 3 years and was only able to walk small distances with a wide-based gait before becoming wheelchair bound in her childhood. In addition to her delayed motor development, she exhibited intellectual disability and cerebellar signs (Supplementary Table 1). Neither exhibited any pyramidal signs. Both had myoclonic jerks and myokymia with normal serum voltage-gated potassium channel antibody levels. The head MRI showed cerebellar atrophy involving the superior vermis and adjacent superior cerebellar surface in both affected individuals (Fig. 1C).

The pedigree was suggestive of an autosomal dominant disorder (Fig. 1B). The proband was screened for inherited ataxia using the 'Inherited Ataxias Next Generation Sequencing – 43 Gene Panel', previously described by Nemeth et al. [3]. This identified the c.805C>T, p.Arg269Trp (Transciption ID: NM_001168272.1) variant in ITPR1 in heterozygous form. Screening of other family members confirmed segregation in affected individuals. p.Arg269 is highly conserved across species and lies within the InsP3 binding domain of the protein (Fig. 1D). Recently this mutation has been reported in association with an autosomal dominant non-progressive congenital ataxia in another family [4].

3. ITPR1 mutations: a detailed review of the literature

Eleven different heterozygous missense mutations in ITPR1, including the p.Arg269Trp mutation described here, have been reported to cause a non-progressive infantile-onset cerebellar ataxia and delayed motor development. This 'ataxic cerebral palsy' phenotype is also known as spinocerebellar ataxia (SCA) 29 [4–11]. The cerebellar dysfunction may become apparent as early as the first day of life and generally within the first year. Common cerebellar features include nystagmus, ataxia, postural tremor, dysarthria and hypotonia. The delayed motor development and the absence of pyramidal dysfunction are the hallmarks of this phenotype (Supplementary Table 1).

Overall, about 75% of individuals with SCA 29 exhibit learning difficulties (Supplementary Table 1). Both affected individuals that described here had intellectual difficulties. However, this was only evident in one of the three affected individuals of the second family with the same mutation [4]. Also all 20 affected individuals in the Australian family with
heterozygous c.4657G>A, p.Val1553Met (mRNA sequence: NM_001099952.2) mutation had intellectual disability, compared to none of the affected Russian family members with this mutation [8,10,11]. Interestingly, a 45-year-old female with heterozygous c.722G>A, p.Arg241Lys mutation did not have pathogenic phenotype except incidental cerebellar atrophy on neuroimaging, but her daughter had cerebellar dysfunction and delayed motor development [4]. Therefore, it is possible that some individuals with ITIPI mutations may not develop any symptoms.

SCA 15 and Gillespie syndrome (GS) are two other well-known phenotypes associated with ITIPI mutations. SCA 15, an adult onset very slow progressive pure cerebellar ataxia, is caused by heterozygous complete or partial deletions of ITIPI. It typically presents with gait ataxia in the third decade of life. The affected individuals remain ambulatory for several decades after their diagnosis. Dysarthria, nystagmus, tremor and relative absent pyramidal signs are other common features of SCA 15. Unlike SCA 29 and GS, it is not typically associated with delayed motor development or intellectual disability. Twenty four families have been identified with this phenotype so far [12–25].

The heterozygous deletion is proposed to cause haploinsufficiency. Interestingly, one heterozygous missense mutation, c.8581C>T, p.Pro1059Leu (GenBank: AAB04947.2) in a Japanese family has also been reported to cause this SCA 15 phenotype [15,16]. None of the affected members in this family had delayed motor development or intellectual disability.

The p.Pro1059 residue is located in the regulatory/coupling domain and has been found to increase the InsP3 ligand binding affinity without abolishing Ca2+ release in vitro [26]. The ligand binding to the InsP3 binding domain or the regulatory/coupling domain modulates ITIPI channel function by integrating other external signals [1]. Therefore, this p.Pro1059Leu mutation is thought to influence channel gating by altering its ligand binding properties. We hypothesise that SCA 29 causing missense mutations located within the InsP3 binding domain and the regulatory/coupling domain, also impair the channel function by altering its ligand binding properties.

GS is characterised by cerebellar ataxia, cerebellar atrophy, aniridia, hypotonia, delayed motor developmental and intellectual disability. It can be caused by homozygous partial deletions, compound heterozygous truncating mutations or heterozygous mutations located within the C-terminal transmembrane domain and its close vicinity (Supplementary Table 2). The latter is thought to be dominant negative mutation. These mutations have been proposed to abolish the Ca2+ release property of the channel by disrupting its channel pore structure [27,28].

In addition, there are two other lesser known phenotypes of ITIPI mutations, which are caused by mutations in the C-terminal transmembrane domain. A heterozygous c.7568C>T, p.Thr2523Met mutation has been reported to cause progressive optic atrophy, ataxia, sensorineural hearing loss, muscle weakness, vertigo, erythrocytosis and nystagmus [29]. Recently another heterozygous c.7649T>A, p.Ile2550Asn (mRNA sequence: NM_001099952) mutation has been associated with non-progressive early onset ataxia, hypotonia, hyperreflexia, delayed motor development, intellectual disability and severe pontocerebellar hypoplasia [30]. Unlike GS, neither of these two mutations was associated with iris hypoplasia, despite being located within the C-terminal transmembrane domain of the protein. At this point it is difficult to determine whether these are incomplete variants of GS or completely new entities and further analyses of these mutations are required.

### 4. Conclusions

We describe only the second reported case of a family with a heterozygous c.805C>T, p.Arg269Trp mutation in ITIPI presenting with a ataxic cerebral palsy phenotype. Correlations between the ITIPI genotypes and phenotypes are increasingly recognised. Although, the phenotypic variation appears to depend on the site and nature of the mutation within the gene, further studies are required to define the precise mechanism of pathogenicity and associated variation in phenotype and disease severity.

### Consent

Written consent has been obtained.

### Conflict of interest

None declared.

### Acknowledgement and financial support

None declared.

### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pjnsa.2017.06.012.

### References


