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Case report

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

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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 reticular membrane and release Ca^{2+}, 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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Abbreviations: *ITPR1*, inositol 1,4,5-triphosphate receptor type 1; $InsP_3$, inositol 1,4,5-triphosphate; SCA, spinocerebellar ataxia; GS, Gillespie syndrome.

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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 reticular 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 homotetramer. Each monomer consists of a N-terminal inositol triphosphate ($InsP_3$) 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.

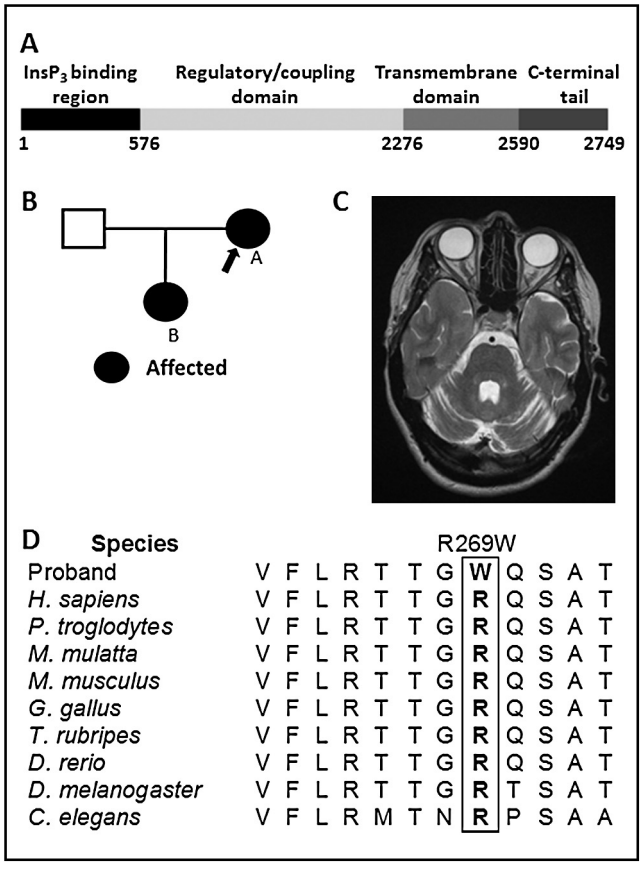

Fig. 1 – (A) Schematic representation of the *ITPR1* protein. (B) Pedigree structure. (C) MRI head of the mother showing cerebellar atrophy. (D) Amino acid sequence of the mutation site is conserved in many species.

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 30 s 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 $InsP_3$ 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 *ITPR1* mutations may not develop any symptoms.

SCA 15 and Gillespie syndrome (GS) are two other well-known phenotypes associated with *ITPR1* mutations. SCA 15, an adult onset very slow progressive pure cerebellar ataxia, is caused by heterozygous complete or partial deletions of *ITPR1*. 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 $InsP_3$ ligand binding affinity without abolishing Ca^{2+} release *in vitro* [26]. The ligand binding to the $InsP_3$ binding domain or the regulatory/coupling domain modulates *ITPR1* 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 $InsP_3$ 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 Ca^{2+} release property of the channel by disrupting its channel pore structure [27,28].

In addition, there are two other lesser known phenotypes of *ITPR1* 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 *ITPR1* presenting with a ataxic cerebral palsy phenotype. Correlations between the *ITPR1* 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.

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None declared.

Appendix A. Supplementary data

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

REFERENCES

[1] Foskett JK, White C, Cheung K-H, Mak D-OD. Inositol trisphosphate receptor Ca2+ release channels. Physiol Rev 2007;87:593–658. http://dx.doi.org/10.1152/physrev.00035.2006

[2] Schorge S, van de Leemput J, Singleton A, Houlden H, Hardy J. Human ataxias: a genetic dissection of inositol triphosphate receptor (*ITPR1*)-dependent signaling. Trends Neurosci 2010;33:211–9. http://dx.doi.org/10.1016/j.tins.2010.02.005

[3] Németh AH, Kwasniewska AC, Lise S, Parolin Schnekenberg R, Becker EBE, Bera KD, et al. Next generation sequencing for molecular diagnosis of neurological disorders using ataxias as a model. Brain 2013;136:3106–18. http://dx.doi.org/10.1093/brain/awt236

[4] Barresi S, Niceta M, Alfieri P, Brankovich V, Piccini G, Bruselles A, et al. Mutations in the IRBIT domain of *ITPR1* are a frequent cause of autosomal dominant nonprogressive congenital ataxia. Clin Genet 2016. http://dx.doi.org/10.1111/cge.12783
[5] Ohba C, Osaka H, Iai M, Yamashita S, Suzuki Y, Aida N, et al. Diagnostic utility of whole exome sequencing in patients showing cerebellar and/or vermis atrophy in childhood. Neurogenetics 2013;14:225–32. http://dx.doi.org/10.1007/s10048-013-0375-8
[6] Sasaki M, Ohba C, Iai M, Hirabayashi S, Osaka H, Hiraide T, et al. Sporadic infantile-onset spinocerebellar ataxia caused by missense mutations of the inositol 1,4,5-triphosphate receptor type 1 gene. J Neurol 2015;262:1278–84. http://dx.doi.org/10.1007/s00415-015-7705-8
[7] Fogel BL, Lee H, Deignan JL, Strom SP, Kantarci S, Wang X, et al. Exome sequencing in the clinical diagnosis of sporadic or familial cerebellar ataxia. JAMA Neurol 2014;71:1237–46. http://dx.doi.org/10.1001/jamaneurol.2014.1944
[8] Huang L, Chardon JW, Carter MT, Friend KL, Dudding TE, Schwartzentruber J, et al. Missense mutations in *ITPR1* cause autosomal dominant congenital nonprogressive spinocerebellar ataxia. Orphanet J Rare Dis 2012;7:67. http://dx.doi.org/10.1186/1750-1172-7-67
[9] Parolin Schnekenberg R, Perkins EM, Miller JW, Davies WIL, D'Adamo MC, Pessia M, et al. De novo point mutations in patients diagnosed with ataxic cerebral palsy. Brain 2015;138:1817–32. http://dx.doi.org/10.1093/brain/awv117
[10] Shadrina MI, Shulskaya MV, Klyushnikov SA, Nikopensius T, Nelis M, Kivistik PA, et al. *ITPR1* gene p.Val1553Met mutation in Russian family with mild spinocerebellar ataxia. Cerebellum Ataxias 2016;3:2. http://dx.doi.org/10.1186/s40673-016-0040-8
[11] Dudding TE, Friend K, Schofield PW, Lee S, Wilkinson IA, Richards RI. Autosomal dominant congenital non-progressive ataxia overlaps with the SCA15 locus. Neurology 2004;63:2288–92.
[12] Storey E, Gardner RJ, Knight MA, Kennerson ML, Tuck RR, Forrest SM, et al. A new autosomal dominant pure cerebellar ataxia. Neurology 2001;57:1913–5.
[13] Knight MA, Kennerson ML, Anney RJ, Matsuura T, Nicholson GA, Salimi-Tari P, et al. Spinocerebellar ataxia type 15 (sca15) maps to 3p24.2-3pter: exclusion of the *ITPR1* gene, the human orthologue of an ataxic mouse mutant. Neurobiol Dis 2003;13:147–57.
[14] Ganesamoorthy D, Bruno DL, Schoumans J, Storey E, Delatycki MB, Zhu D, et al. Development of a multiplex ligation-dependent probe amplification assay for diagnosis and estimation of the frequency of spinocerebellar ataxia type 15. Clin Chem 2009;55:1415–8. http://dx.doi.org/10.1373/clinchem.2009.124958
[15] Hara K, Shiga A, Nozaki H, Mitsui J, Takahashi Y, Ishiguro H, et al. Total deletion and a missense mutation of *ITPR1* in Japanese SCA15 families. Neurology 2008;71:547–51. http://dx.doi.org/10.1212/01.wnl.0000311277.71046.a0
[16] Hara K, Fukushima T, Suzuki T, Shimohata T, Oyake M, Ishiguro H, et al. Japanese SCA families with an unusual phenotype linked to a locus overlapping with SCA15 locus. Neurology 2004;62:648–51.
[17] van de Leemput J, Wavrant-De Vrièze F, Rafferty I, Bras JM, Giunti P, Fisher EMC, et al. Sequencing analysis of the *ITPR1* gene in a pure autosomal dominant spinocerebellar ataxia series. Mov Disord 2010;25:771–3. http://dx.doi.org/10.1002/mds.22970
[18] Iwaki A, Kawano Y, Miura S, Shibata H, Matsuse D, Li W, et al. Heterozygous deletion of *ITPR1*, but not SUMF1, in spinocerebellar ataxia type 16. J Med Genet 2008;45:32–5. http://dx.doi.org/10.1136/jmg.2007.053942
[19] Obayashi M, Ishikawa K, Izumi Y, Takahashi M, Niimi Y, Sato N, et al. Prevalence of inositol 1,4,5-triphosphate receptor type 1 gene deletion, the mutation for spinocerebellar ataxia type 15, in Japan screened by gene dosage. J Hum Genet 2012;57:202–6. http://dx.doi.org/10.1038/jhg.2012.5
[20] Marelli C, van de Leemput J, Johnson JO, Tison F, Thauvin-Robinet C, Picard F, et al. SCA15 due to large *ITPR1* deletions in a cohort of 333 white families with dominant ataxia. Arch Neurol 2011;68:637–43. http://dx.doi.org/10.1001/archneurol.2011.81
[21] Castrioto A, Prontera P, Di Gregorio E, Rossi V, Parnetti L, Rossi A, et al. A novel spinocerebellar ataxia type 15 family with involuntary movements and cognitive decline. Eur J Neurol 2011;18:1263–5. http://dx.doi.org/10.1111/j.1468-1331.2011.03366.x
[22] Synofzik M, Beetz C, Bauer C, Bonin M, Sanchez-Ferrero E, Schmitz-Hübsch T, et al. Spinocerebellar ataxia type 15: diagnostic assessment, frequency, and phenotypic features. J Med Genet 2011;48:407–12. http://dx.doi.org/10.1136/jmg.2010.087023
[23] Novak MJU, Sweeney MG, Li A, Treacy C, Chandrashekar HS, Giunti P, et al. An *ITPR1* gene deletion causes spinocerebellar ataxia 15/16: a genetic, clinical and radiological description. Mov Disord 2010;25:2176–82. http://dx.doi.org/10.1002/mds.23223
[24] Di Gregorio E, Orsi L, Godani M, Vaula G, Jensen S, Salmon E, et al. Two Italian families with *ITPR1* gene deletion presenting a broader phenotype of SCA15. Cerebellum 2010;9:115–23. http://dx.doi.org/10.1007/s12311-009-0154-0
[25] Orsucci D, Ienco EC, Rocchi A, Siciliano G, Mancuso M, Bonuccelli U. Levetiracetam-responsive myoclonus in spinocerebellar ataxia type 15. Mov Disord 2013;28:1465. http://dx.doi.org/10.1002/mds.25433
[26] Yamazaki H, Nozaki H, Onodera O, Michikawa T, Nishizawa M, Mikoshiba K. Functional characterization of the P1059L mutation in the inositol 1,4,5-trisphosphate receptor type 1 identified in a Japanese SCA15 family. Biochem Biophys Res Commun 2011;410:754–8. http://dx.doi.org/10.1016/j.bbrc.2011.06.043
[27] Gerber S, Alzayady KJ, Burglen L, Brémond-Gignac D, Marchesin V, Roche O, et al. Recessive and dominant de novo *ITPR1* mutations cause gillespie syndrome. Am J Hum Genet 2016;98:971–80. http://dx.doi.org/10.1016/j.ajhg.2016.03.004
[28] McEntagart M, Williamson KA, Rainger JK, Wheeler A, Seawright A, De Baere E, et al. A restricted repertoire of de novo mutations in *ITPR1* cause Gillespie syndrome with evidence for dominant-negative effect. Am J Hum Genet 2016;98:981–92. http://dx.doi.org/10.1016/j.ajhg.2016.03.018
[29] Valencia CA, Husami A, Holle J, Johnson JA, Qian Y, Mathur A, et al. Clinical impact and cost-effectiveness of whole exome sequencing as a diagnostic tool: a pediatric center's experience. Front Pediatr 2015;3:67. http://dx.doi.org/10.3389/fped.2015.00067
[30] van Dijk T, Barth P, Reneman L, Appelhof B, Baas F, Poll-The BT. A de novo missense mutation in the inositol 1,4,5-triphosphate receptor type 1 gene causing severe pontine and cerebellar hypoplasia: expanding the phenotype of *ITPR1*-related spinocerebellar ataxia's. Am J Med Genet A 2016. http://dx.doi.org/10.1002/ajmg.a.37962