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Review article

Spinocerebellar ataxia 15: A phenotypic review and expansion

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ABSTRACT

Spinocerebellar ataxia 15 (SCA15) is a clinically heterogeneous movement disorder characterized by the adult onset of slowly progressive cerebellar ataxia. *ITPR1* is the SCA15 causative gene. However, despite numerous reports of genetically-confirmed SCA15, phenotypic uncertainty persists. We reviewed the phenotypes of 60 patients for whom SCA15 was confirmed by the presence of a genetic deletion involving *ITPR1*. The most prevalent symptoms were gait ataxia (88.3%), dysarthria (75.0%), nystagmus (73.3%), and limb ataxia (71.7%). We also present a novel SCA15 phenotype in a woman with an *ITPR1* variant found to have hydrocephalus that improved with ventriculoperitoneal shunting. This is the first reported case of hydrocephalus associated with SCA15. In this review, we analyzed previously reported SCA15 phenotypes and present a novel SCA15 phenotype. We also address important considerations for evaluating patients with complex hereditary movement disorders.

1. Introduction

Spinocerebellar ataxias (SCAs) are a group of complex hereditary movement disorders that are challenging to diagnose due to their clinical heterogeneity. Harding [1] stratified those with autosomal-dominant inheritance into three categories of autosomal dominant cerebellar ataxia (ADCA) based upon clinical presentation. Genetic analyses have led to improved disease classifications, which have enabled the association of SCA with specific genetic disturbances.

SCA15 was first described by Storey et al. [2] in an Australian family with "pure" cerebellar ataxia. There have been several reports of patients with SCA15, and each has been phenotypically different. However, the genetic specificity of this disease increases as the efficiency of genetic analyses improves. Genetic analysis of the original Australian family (AUS1)

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revealed a deletion within the region 3p24.2-3pter of the *ITPR1* (inositol triphosphate receptor 1) gene [3]. This was further specified within the same family by van de Leemput et al., who described a deletion involving exons 1–10 of *ITPR1* and half of the neighboring *SUMF1* (sulfatase modifying factor 1) gene [4]. Despite thorough reporting of SCA15 phenotypes [2,5–13], there is no consensus on a specific constellation of SCA15 symptoms. Therefore, diagnosis is made by genetic analysis.

The purpose of this review is to list previously reported SCA15 phenotypes matched with the their most current genetic analyses, present a novel SCA15 phenotype, and propose a diagnostic approach to this disorder.

2. Characterizing SCA15

SCA15 is defined by a specific genetic locus. Since the locus was identified, clinicians have tried to define the SCA15 phenotype so that it may be clinically differentiable from other diseases.

2.1. *The SCA15 locus and SCA16*

In 2007, van de Leemput described three SCA15 families, including the original AUS1 family, whose genotyping revealed deletions involving the *ITPR1* and *SUMF1* genes [4]. Synofzik et al. reported five SCA15 families, and four had deletions involving both genes, but one family's deletion included only *ITPR1* [9]. Since that time, all reported SCA15 families have had deletions involving *ITPR1* thus establishing it as the causative gene of SCA15.

SCA16 was first described in 2001 by Miyoshi et al. in a Japanese family with nine affected individuals, and all had nystagmus and truncal ataxia [5]. Magnetic resonance imaging (MRI) of the affected individuals showed cerebellar atrophy without brainstem involvement, and genetic analysis suggested linkage to a locus on chromosome 8q22.1-24.1. The locus was later reassigned to 3p26.2-pter, and a point mutation was identified within the *contactin 4* gene (*CNTN4*) [14]. This region overlapped with the SCA15 3p24.2-3pter locus identified three years earlier [3]. Further analysis of this family by Iwaki et al. yielded a heterozygous deletion limited to exons 1–48 of *ITPR1*, indicating that haploinsufficiency of *ITPR1* was the cause of both SCA15 and SCA16 [15]. Gardner proposed designating SCA16 a "vacant SCA" and that any adult onset *ITPR1*-associated cerebellar ataxia should be referred to as SCA15; however, the nomenclature of SCA15/16 continues to be used [16]. This is important because the SCA15 phenotype is not clearly defined. Excluding phenotypes from SCA15 by mislabeling them as SCA16 artificially limits the phenotypic spectrum of disease.

2.2. *Phenotypes*

Since the first report by Storey et al. [2], several phenotypic descriptions have been documented. A recent systematic review of ADCAs showed that when compared to other SCAs, there was a significantly higher proportion of SCA15/16 patients with intention/postural tremor at disease onset. This review showed that throughout the disease course, higher proportions of SCA15/16 patients had nystagmus, but visual impairment was not as common in these patients [17]. We present the most current compilation of SCA15 phenotypes in Table 1, which contains only publications with detailed phenotypic descriptions. We also noted the most specific genetic deletion information, which in some cases, was obtained from subsequent publications. A complete list of reported SCA15 phenotypes matched to specific genetic alterations has never been published. Within these reports, we found sixty individuals whose phenotypes were described in detail. There is considerable variability among the phenotypic descriptions; however, the high prevalence of some traits helped define the SCA15 phenotype. At least three-fourths of the individuals had gait ataxia and dysarthria, while more than half exhibited limb ataxia and nystagmus. Other features frequently seen included tremor, pyramidal signs, and truncal ataxia. Table 2 shows percentages of patients exhibiting each clinical feature. Because pertinent negatives are not regularly reported, phenotype prevalence data is based on the assumption that if an exam finding was not reported then it was absent.

3. Novel case of SCA15

The proband, a 59-year-old woman, presented with chronic, progressive gait ataxia. Physical examination revealed lower extremity spasticity with mild hyperreflexia, bilateral ankle clonus, and positive Babinski's sign bilaterally. She had reduced touch, pinprick, temperature, and vibration sensations in a distance-dependent manner up to the elbows and knees bilaterally. Her gait was spastic, and she had a resting tremor in her right hand. The patient's father had dementia, a shuffling gait, and normal-pressure hydrocephalus. The pedigree structure is presented in Fig. 1. MRI of the brain showed severe enlargement of the lateral and third ventricles, which was compatible with hydrocephalus that was likely secondary to aqueductal stenosis (Fig. 2).

3.1. *Genetic evaluation*

Whole-exome sequencing (WES) was performed using a blood sample from the proband and saliva samples from both of her

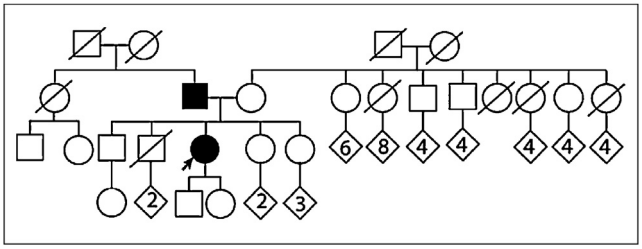

Fig. 1 – Pedigree structure of the proband's family. Standard symbols were used. Round symbols indicate females, squares indicate males, and diagonal lines indicate that the individual is deceased. Diamonds were used to disguise sex, and numbers inside symbols indicate number of children. The arrow indicates the proband. Black symbols indicate individuals with clinical features of ataxia.

Table 1 – SCA15 and SCA16 study summaries.

Study	SCA subtype	Phenotype description	Neuroimaging	Ethnicity	Genetics
Storey et al., 2001 [2], van de Leemput et al., 2007 [4]	SCA15	Limb ataxia, gait ataxia, titubation, dysphagia, dysarthria, dysmetric saccades, VOR gain <1, failure to suppress VOR, pyramidal signs, tremor	Cerebellar vermal hypoplasia	Australian (AUS1)	Deletion of *ITPR1* exons 1–10 & *SUMF1* exons 1–3
Miyoshi et al., 2001 [5], Miura et al., 2006 [14]	SCA16	Gait ataxia, limb/truncal ataxia, nystagmus, titubation, dysarthria	Cerebellar atrophy particularly at the vermis	Japanese	Deletion of 3p26.2-pter and one point mutation (4256C: T) in the 3′ untranslated region of (*CNTN4*) on 3p26.2-26.3.
Hara et al., 2004 [6], Hara et al., 2008 [18]	SCA15	Limb/truncal ataxia, nystagmus, pyramidal signs, hyporeflexia, tremor	–	Japanese	414 kb deletion including entire *ITPR1* and exon 1 of *SUMF1*. C->T substitution at position 8581 of *ITPR1*
van de Leemput et al., 2007 [4]	SCA15	Cerebellar ataxia	–	English	1. Deletion of *ITPR1* exons 1–40 & *SUMF1* exons 1–3 2. Deletion of *ITPR1* exons 1–44 & *SUMF1* exons 1–3
Iwaki et al., 2008 [15]	SCA16	–	–	Japanese	Deletion of *ITPR1* exons 1–48
Ganesamoorthy et al., 2009 [19]	SCA15	Cerebellar ataxia	–	Australian	*ITPR1* exons 1–38 & *SUMF1* intron 1
Novak et al., 2010 [7]	SCA15/16	Truncal ataxia, gait ataxia, dysdiadochokinesia, nystamgus, impaired smooth pursuit, dysarthria, dysmetric saccades, pyramidal signs, tremor	Predominantly vermal cerebellar atrophy with mild parietal/temporal volume loss	English	346,487 bp deletion including *SUMF1* exons 1–3 & *ITPR1* exons 1–48
Di Gregorio et al., 2010 [8]	SCA15	Limb/truncal ataxia, gait ataxia, nystagmus, dysphagia, dysarthria, pyramidal signs, buccolingual dyskinesia, facial myokymia, hypopallesthesia, cognitive/psychiatric symptoms, tremor	Predominantly vermal cerebellar atrophy	Italian	1. Deletion of *ITPR1* exons 1–39 2. Deletion of *SUMF1* exon 7 – *ITPR1* exon 59
Synofzik et al., 2011 [9]	SCA15	Gait ataxia, nystagmus, dysphagia, dysarthria, dysmetric saccades, pyramidal signs, hyporeflexia, upward gaze palsy, cognitive/psychiatric symptoms, tremor, abnormally evoked motor & somatosensory potentials, dysmetria	Vermal cerebellar atrophy	German	1. Heterozygous deletion of entire *ITPR1*. 2. Partial deletion of both *ITPR1* and *SUMF1*
Marelli et al., 2011 [10]	SCA15	Limb ataxia, gait ataxia, nystagmus, impaired smooth pursuit, dysphagia, dysarthria, pyramidal signs, tremor	Global or predominantly vermal cerebellar atrophy	Mostly Western European	1. Deletions involving only *ITPR1* 2. Deletions involving *ITPR1* and *SUMF1* 3. Deletion involving *ITPR1*, *SETMAR*, and *SUMF1*
Castrioto et al., 2011 [11]	SCA15	Gait ataxia, impaired smooth pursuit, titubation, dysphagia, dysarthria, hypophonia, pyramidal signs, hypotonia, cognitive/psychiatric symptoms, dysmetria, chorea	Cerebellar atrophy with verbal involvement	Italian	Deletion of *SUMF1* exon 5 through *ITPR1* (*ITPR1* exons 34–52 & *SUMF1* exons 6–8 were not tested)
Obayashi et al., 2012 [12]	SCA15	Gait ataxia, pyramidal signs, cognitive/psychiatric symptoms, tremor	–	Japanese	ITPR1 deletion preserving exon 48 & 59 and SUMF1 exon 1 & 2
Orsucci et al., 2013 [13]	SCA15	Gait ataxia, myoclonic jerks, hyporeflexia	Atrophy of dorsal cerebellar vermis	–	Deletions in exons 3 & 4 of ITPR1

Abbreviations: VOR, vestibuloocular reflex; SUMF1, sulfatase-modifying factor 1; CNTN4, contactin 4, "-" indicates that the study did not report this information.

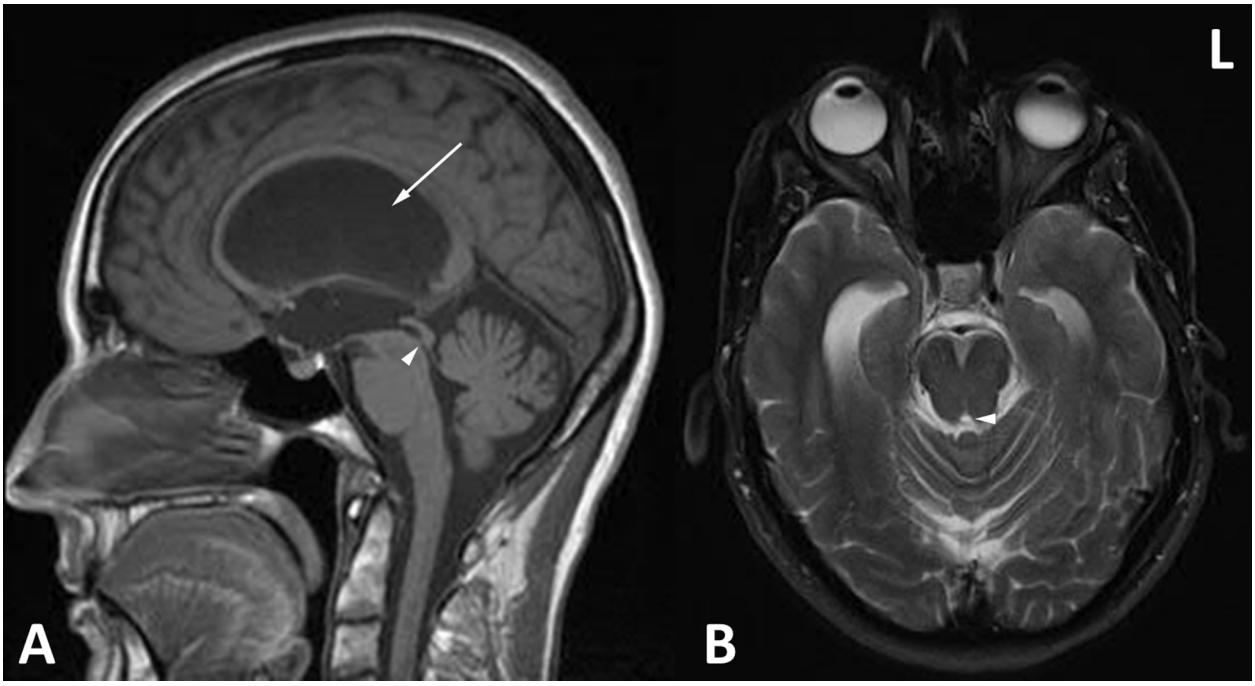

Fig. 2 – Magnetic resonance images of the proband. (A) Sagittal T1-weighted, and (B) axial T2 weighted images with fat saturation showing ventriculomegaly (white arrow) and aqueductal stenosis (white arrow heads). L = left side.

parents. All examinations were performed for diagnostic purposes only, and no approval from the local institutional review board was sought or required. Exome sequencing of a family trio resulted in an average of 11–15 giga base pairs of sequence per sample, and approximately 90% of the bases were expected to have a quality score of Q20 or higher.

A variant designated as c.4402G>A (p.Val1468Ile) was detected in exon 34 of *ITPR1*. Capillary electrophoresis confirmed the presence of this variant in the proband. Next-generation sequencing revealed the same variant in the proband's father. This missense variant has been reported in 3 European-American individuals in the NHLBI ESP database, which indicates that there is an allele frequency of 0.00036337209. It has also been reported in 15 of 66,732 European alleles in the ExAC dataset, indicating an allele frequency of 0.0002248. It has not been reported in the 1000 Genomes population. In silico models were discordant with regard to prediction of pathogenicity, and the variant was classified as a variant of uncertain significance.

Table 2 – SCA15 phenotype characteristics.

Symptom	Patients affected, *n* (%)
Gait ataxia	53 (88.3)
Dysarthria	45 (75)
Nystagmus	44 (73.3)
Limb ataxia	43 (71.7)
Tremor	28 (46.7)
Truncal ataxia	25 (41.7)
Pyramidal signs	24 (40)
Dysphagia	15 (25)
Dysmetric saccades	15 (25)
Impaired smooth pursuit	13 (21.7)
Dysmetria	10 (16.7)
Cog/Psych	7 (11.7)

Abbreviation: Cog/Psych: cognitive/psychiatric test.

3.2. *Treatment*

Prior to a therapeutic lumbar puncture, the patient had reduced arm swing bilaterally and multiphase turning but was able to recover on the pull test (Supplemental video 1). The opening pressure was 128 mm of water. The patient's gait significantly improved following the lumbar puncture, and she underwent placement of a ventriculoperitoneal shunt. The improvement has persisted through our most recent follow up (Supplemental video 2).

There are no previous reports of SCA15-associated hydrocephalus. Moreover, there is no known link between the SCA15 locus and aqueductal stenosis or hydrocephalus. This case adds to the diverse phenotype of SCA15 and illustrates the importance of thorough genetic investigation.

4. Practical application and clinical considerations

Because of the significant phenotypic variation, the diagnosis of SCA15 requires more than clinical symptomatology. Based upon our analysis of previously reported SCA15 phenotypes, we propose that SCA15 should be considered in cases of adult-onset, chronic, progressive ataxia with dysarthria and evidence suggesting an autosomal-dominant inheritance

pattern. Other symptoms that should increase the suspicion for SCA15 include limb ataxia and nystagmus, but other findings including tremor, pyramidal signs, and truncal ataxia may also be present. Compared to other SCAs, SCA15 has a significantly higher proportion of intention/postural tremor and nystagmus, while visual impairments, neuromuscular disorder, and autonomic dysfunction are present in fewer patients [17]. The next stage in diagnosis should include testing to rule out the most common nongenetic etiologies. Our case suggests that even when significant findings such as hydrocephalus are identified; it is prudent to conduct a genetic evaluation if supported by a strong family history. While trinucleotide-repeat disease represents the majority of SCAs, SCA15 was reported as the most common nontrinucleotide-repeat SCA in Central Europe representing 8.9% of the remaining SCAs [9]. Therefore, one should rule out trinucleotide repeat expansions with commercially-available genetic testing prior to moving on to other genetic studies, such as WES.

Genetic testing may uncover a novel variant, but there may not be sufficient evidence to prove pathogenicity. These variants of uncertain significance should not be interpreted as clinically insignificant. Our patient's variant is located within the causative gene for SCA15. This was clinically significant because SCA was in the differential diagnosis of her condition. An advantage of genetic testing is that as data accumulates in genetic databases, variants previously designated as having uncertain significance can be reanalyzed in a stronger database and have a better chance of significance. Moreover, the quality of genetic testing is rapidly improving. This concept of improved genetic analysis is illustrated in Table 1 by the genotype found by Hara and colleagues in their Japanese family. In 2004, they reported a deletion of 3p26.1-25.3, and four years later were able to further specify a 414-kb deletion, including entire *ITPR1* and exon 1 of *SUMF1* [6,18].

Another question of many practicing neurologists is whether testing patients for diseases that have no cure or treatment is valuable. In the age of exponentially rising healthcare costs, this point is well taken; however, some important considerations should be made when choosing to have a patient genetically tested. We propose that genetic testing would actually save money by ending the patient's diagnostic odyssey. Further diagnostics such as expensive imaging studies would not be needed if genetic testing reveals disease. Additionally, in diseases where effective treatments are lacking, the ability to identify a disease would provide prognostic information and help patients make informed decisions regarding reproductive planning. Disease identification also helps patients take action. Knowing what disease a patient has may allow him or her to join appropriate support organizations and establish their candidacy for research studies. This can be empowering and therapeutic for patients with currently incurable diseases.

5. Conclusions

SCA15 is an autosomal dominant movement disorder characterized by slowly progressive cerebellar ataxia. Like many other clinically heterogenous movement disorders, SCA15 presents a significant diagnostic challenge to clinicians. We reviewed the literature and summarized the phenotypic findings of 60 individuals with *ITPR1*-related ataxia. Among the reported cases, the most common findings were gait ataxia, dysarthria, nystagmus, and limb ataxia. We also presented the case of a patient with a novel presentation of treatable SCA15-associated hydrocephalus. When SCA is suspected, genetic testing should be performed. Whole-exome sequencing is a cost-effective tool that should be in the practicing neurologist's armamentarium of diagnostic tests.

Authors' contribution

PT wrote the manuscript and coordinated author contributions. KG wrote the genetics portion of the manuscript. AS obtained patient consent and coordinated scheduling for patient visits. RR aided in writing and editing the manuscript. ZW aided in editing the manuscript. All authors reviewed and agreed upon the final manuscript.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.pjnns.2016.10.006.

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