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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

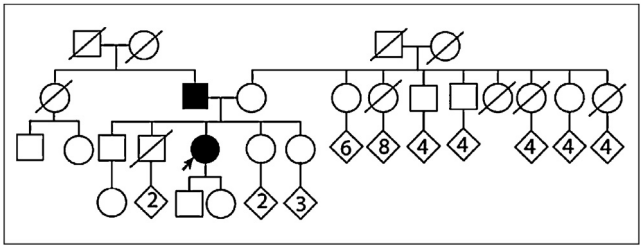

Fig. 1 – Pedigree structure of the proband's family. Standard symbols were used. Round symbols indicate females, squares indicate males, and diagonal lines indicate that the individual is deceased. Diamonds were used to disguise sex, and numbers inside symbols indicate number of children. The arrow indicates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

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