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AUTOSOMAL DOMINANT CEREBELLAR ATAXIA INCLUDING SCA 2,SCA 3,SCA 7 AND SCA 12 : AN OVERVIEW

Genetics

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KEYWORDS

INTRODUCTION

Spinocerebellar ataxias (SCAs) are a heterogeneous group of neurodegenerative disorders. The CAG repeat expansions in the causative genes are the principal cause of SCAs and these have been used for the classifications and diagnoses of patients with ataxia. Spinocerebellar ataxia (SCA), previously known as autosomal dominant cerebellar ataxia, is a biologically strong group of relatively 30 progressive neurodegenerative diseases. The more prevalent Spinocerebellar ataxias like SCA1, SCA2, SCA3, and SCA6 along with SCA7 and SCA17 are brought about by CAG repeat expansion, that encodes a polyglutamine tract in the affected protein[1]. Present day studies advocate that the mutated protein results in pathogenesis within the context of its "normal" cellular function. Hence, decoding the cellular function of these proteins might help in the development of therapeutics.

Ataxia primarily occurs because of degeneration of neurons in the brain stem, cerebellum, spinocerebellar tracts, and their afferent/efferent connections. As many as 50 different types of inherited ataxias are there that strike during childhood or adulthood (Taroni and DiDonato, 2004; Manto, 2005).

Classification

Autosomal dominant cerebellar ataxias (ADCA) are classified into three categories by Harding in 1981, Type I, Type II and Type III. ADCA Type I includes syndromes such as SCA1- SCA4, SCA8, SCA10, SCA12 - SCA23, SCA25, SCA27, SCA28 and DRPLA. ADCA Type II consists of syndromes associated with pigmentary maculopathies and comprises SCA7. ADCA Type III consists of pure cerebellar syndromes and includes SCA5, SCA6, SCA11, SCA26, SCA29, SCA30 and SCA31[2].ADCA Type I phenotypes are complex and comprises ataxia and other neurological signs. The clinical spectrum is very wide and it ranges from just " pure " cerebellar signs to constellations including peripheral nerve disease, spinal cord syndromes, cognitive impairment, cerebellar or supranuclear ophthalmologic signs, seizure disorders and psychiatric problems[3]. Type I ADCA pathogenesis is not fully understood. Based on proposed pathogenesis, categories of Type I ADCA have been recommended. Thus, there are 3 major subclasses. The first and supposedly most common subclass includes SCA1, SCA2, SCA3, and SCA17; and DRPLA that are associated with expansions of trinucleotide CAG repeat, encoding large nonstop and continuous glutamine tracts. The second important pathogenic subclass comprises those ADCA Type I such as SCA8, SCA10 and SCA12, where expansions of trinucleotide repeat fall outside of the protein coding region of the disease gene. The last sub-class includes SCA13, SCA14, SCA15/16, SCA27 and SCA28 caused by missense mutations, nonsense mutations and specific gene deletions, resulting in neurodegeneration[4].

Our work is basically upon Autosomal dominant spinocerebellar ataxia 2, 3, 7 and spino cerebellar ataxia 12.

Spinocerebellar ataxia 2 (SCA 2)

Spinocerebellar ataxia 2 (SCA 2) belongs to the family of autosomal dominant cerebellat ataxias (ADCA) a genetically heterogenous group of neurodegenerative diseases. Spinocerebellar ataxia type 2 (SCA2) is a disorder indicated by progressive problems with movement. SCA2 occurs because of mutation in the **ATXN2** gene known as a trinucleotide repeat expansion. The length of the repeated CAG segment in the ATXN2 gene is increased because of this mutation. If CAG repeats in the ATXN2 are 32 or more, then SCA2 might occur in the subjects. SCA 2 had located the locus for SCA2 that mapped to chromosome 12q24[5,6].

Spinocerebellar ataxia 3 (SCA 3)

Spinocerebellar Ataxia Type 3 (SCA3), commonly known as **Machado-Joseph Disease (MJD)** is a polyglutamine neurodege nerative disorder which occurs because of expansion of a (CAG)n in the **ATXN3** gene. 11 to 44 CAG repeats are considered normal, whereas pathogenic extensions range from 61 to 87 CAGs[7]. Cerebellar ataxia, ocular rotatory muscles palsy, gaze-evoked nystagmus, pyramidal and extrapyramidal signs, as well as sleep disorders are the characteristic features seen in SCA3. The age of onset of SCA3/MJD is not fixed, but most commonly occurs in the second to fifth decade. This disease is the most common form of autosomal dominant ataxia, globally and several studies related to this disorder, have been reported[8]. ATXN3 gene located on chromosome 14q32.1.[9,10]

Spinocerebellar Ataxia type 7 (SCA 7)

Spinocerebellar ataxia 7 (SCA7) is one of the type, a group of inherited neurodegenerative disorders including spinal and bulbar muscular atrophy/Kennedy's disease, Huntington's disease, spinocerebellar ataxia types 1, 2, 3, 6, 7 and 17, and dentato-rubro-pallidoluysian atrophy[11,12]. This disorder commonly presents with cerebellar ataxia and progressive retinal degeneration and are also related with neuronal loss of Purkinje cells in the cerebellum and loss of cone-photoreceptor cells in the retina are peculiar symptoms of SCA7. The polyQ tract sequence is located at the N-terminal region of **ATXN7** protein. Normally 4–35 cytosine-adenine-guanine repeats are noticed in ATXN7, however 36–306 repeats are seen in pathogenic variants[13]. The gene responsible for the SCA7 phenotype is found to be located at chromosome 3p12-21.1[14,15]. In addition mapping of this region allowed the researchers to test the hypothesis, that a CAG repeat expansion was involved[16]. Initial studies of the ataxin-7 CAG repeat proved that expansions beyond 37 CAG's resulted in SCA7 disease phenotype, and normal persons retains ataxin-7 repeats ranging in size from 7 to 34 CAG's[17]. There is also a interrelationship between repeat length and the type of clinical presentation in SCA7 disorder, with repeat mutations

of < 59 CAGs often shows cerebellar findings first and those > 59 CAGs generally producing visual impairment as the earliest symptom[18].Before gene discovery, on the basis of presence of retinopathy, at the beginning SCA7 was differentiated from the chief category of autosomal dominant cerebellar ataxia (ADCA) as ADCA type II[19]. At present, unstable CAG repeat expansion in the coding zone of the ataxin-7 gene is the only recognized gene defect responsible for ADCA type II[20]. The very common clinical feature and often the first reported symptom of SCA7 is cerebellar ataxia, which is established as troubled walking, speech and manual dexterity[21]. In the due course of time, more comprehensive neurological deficits like dysphagia, dysarthria, hypoacusis and eye movement abnormalities (slow saccades; staring) that can progress to frank ophthalmoplegia, develop in SCA7 patients. Exaggerated deep tendon reflexes, extensor plantar reflexes and spasticity could be present due to the involvement of the cortico-spinal tracts[22]. A pattern of genetic anticipation is noticed in SCA7 families where successive generations establish more severe forms of the disease after inheriting longer repeat expansions than were present in their clan and this occurs because the causative gene in SCA7 is an unstable CAG repeat. SCA7 might present as an early onset rapidly progressive juvenile type or even a very serious infantile type, if very long repeats are inherited. Because of its extensive disease pathology, infantile-onset SCA7 is significant and this includes organ systems outside the central nervous system (CNS).On doing Magnetic Resonance Imaging (MRI) of SCA7 patients, marked atrophy of the cerebellum and pons is typically noticed, although few patients may also exhibit high T2 signal intensity in transverse pontine fibers. Researches have proved that volume loss may occur in the pons before the development of cerebellar atrophy and this suggests that the initial site of disease onset could be in brainstem structures rather than in the cerebellar folia[23]. In SCA7 patients, cerebellar tissue shows considerable loss of cerebellar PCs although only mild changes are observed in the cerebellar granule cell layer. In the inferior olive, there is noticable neuronal loss with gliosis. Demyelination of the posterior columns of the spinal cord and of the pyramidal tracts may also takes place[24]. The presence of nuclear inclusions is one of the pathological feature of SCA7.

Spinocerebellar ataxia 12 / PPP2R2B

SCA 12 disease is also known as PPP2R2B, which occurs because of a CAG repeat expansion in a promoter region of PPP2R2B located on chromosome 5q32 . The most characteristic feature of this disease is action tremor. SCA12 is frequently seen in Caucasians, while few cases have been reported among Indians and Chinese. The disease exhibits inter/intra familial phenotypic heterogeneity. Brain imaging usually reveals both cerebral and cerebellar atrophy with relative sparing of brainstem, thalamus, basal ganglia and other subcortical brain regions[25].

Epidemiology

Autosomal Dominant Cerebellar ataxias are of more than 30 different forms, associated with mutations in over 20 genes, have been described, with a global prevalence of 1:35,000 individuals. SCA2 is more prevalent in Cuba, India, Mexico, and Southern Italy.

To establish the prevalence and distribution of MJD/SCA3 in the Cuba, a clinical and molecular genetic study of a cohort of SCA3 families was developed. SCA3 was not validated in the replication cohorts, probably due to the low prevalence of intermediate alleles at this locus. This was already illustrated in a homogeneous SCA3 Brazilian cohort[26]. The prevalence of SCA3 is 0.26 cases/100 000 and a frequency of 4.1% among the dominant ataxias in Cuba.

SCA7 is mainly a rare disease, with an incidence of less than 1/100,000. The prevalence is of about 6 per 100,000[27]. Although the various genetic subtypes of ADCA are mainly found in various populations worldwide, their frequencies differs because its depending on the population studies.

The prevalence of SCA 12 is unknown. On the other hand, in India, SCA12 is mainly limited to one endogamic population; however, 5–8% of families with SCA12 have been reported from other ethnic communities[28].

DISCUSSION

In this review, we characterize the clinical, molecular, genetic and phenotypic aspects of ADCA. Till date a lot of research has taken place which provides a better platform to understand the genetic and molecular mechanisms related to ADCA. Nonetheless, the Harding classification is still significant, and this is very useful in detecting the type of autosomal dominant cerebellar ataxia. At present, there are no adequate treatments to modify disease progression.

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