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REVIEW ARTICLE

Autosomal dominant spinocerebellar ataxias: An Asian perspective

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Abstract

Autosomal dominant cerebellar ataxias, frequently referred to as spinocerebellar ataxias (SCAs) have been under intense scientific research limelight since expansions of coded CAG trinucleotide repeats were demonstrated to cause several dominantly inherited SCAs. The number of new SCA loci has expanded dramatically in recent years. At least ten genes have been identified for SCAs 1, 2, 3, 6, 7, 8, 10, 12, 17, dentatorubral-pallidoluysian atrophy (DRPLA), and six loci responsible for SCAs 4, 5, 11,13, 14, &16 have been mapped. Genetic testing is essential for diagnosis due to the overlapping and varied phenotypic features of the different SCAs. While there is no effective treatment available, genetic counseling is important for addressing the many ethical, social, legal, and psychological issues facing SCA patients. Researchers have recently provided valuable information on the pathogenesis of the disease and hopefully a cure can be available in the near future.

INTRODUCTION

Autosomal dominant cerebellar ataxias (ADCAs) are a group of neurodegenerative diseases characterized by cerebellar dysfunction either alone or in combination with other neurological abnormalities.[1-4]

CLINICAL CLASSIFICATION

In the past, various authors have classified cerebellar degeneration based on neuropathologic differences.[5] More recently, Anita Harding proposed a clinical classification of cerebellar ataxias into; ADCA I: characterized by cerebellar syndrome with other neurologic involvement (such as pyramidal, extrapyramidal, ophthalamoplegia, dementia), ADCA II: cerebellar syndrome with pigmentary maculopathy, ADCA III: relatively pure cerebellar syndrome.[6]

GENETIC CLASSIFICATION

ADCAs, frequently referred to as SCAs have been under intense scientific research limelight since expansions of coded CAG trinucleotide repeats were demonstrated to cause several dominantly inherited SCAs.[1-4] The number of new SCA loci has expanded dramatically in recent years. At least ten genes have been identified for SCAs 1, 2, 3, 6, 7, 8, 10, 12, 17, dentatorubral-pallidoluysian atrophy (DRPLA), and six loci responsible for SCAs 4, 5, 11,13, 14, &16 have been mapped[7-23] (table 1). In SCAs 1, 2, 3, 6, 7, the mutation is due to CAG repeat expansions within the coding regions of the gene. SCA8 is associated with an expansion of a CTG repeat in the 3' untranslated region (UTR) of the *SCA 8* gene that produces antisense mRNA to the *KLHL1* gene on the complementary strand. In SCA 10, the disease-causing expansion occurs in the ATTCT pentanucleotide repeat of intron 9 of *SCA 10,* a gene of unknown function widely expressed in the brain. In SCA12 there is an expanded CAG repeat in the 5' untranslated region (UTR) of *PPP2R2B*, a gene coding for a brain-specific regulatory subunit of the protein phosphatase PP2A. Episodic ataxia types 1 and 2 (EA-1 & EA-2) are also dominantly inherited cerebellar ataxias caused by point mutations within a voltage-gated potassium channel gene (*KCNA1*) and the cerebral P/Q-type calcium channel alpha 1 subunit gene (*CACNL1A4*), respectively.[24,25] SCA 17 is due to an expanded CAG repeat in TATA box binding protein (*TBP*) gene which gives rise to an elongated

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Table 1: Genetic classification of autosomal dominant cerebellar ataxias

Type	Locus	Mutation	Normal repeats size	Abnormal repeat size	Cryptic Interruptions	Intergenerational expansions
SCA 1	6p	CAG	6-44	39-82	1-3 CAT	p>m
SCA 2	12q	CAG	14-31	33-64	CAA	p>m
SCA 3	14q	CAG	12-40	54-86	GGG/CGG	p>m
SCA 4	16q	?	?	?	-	?
SCA 5	11cen	?	?	?	-	?
SCA 6	19P	CAG	4-18	20-30	-	No
SCA 7	3p	CAG	4-27	37-200	-	p>m
SCA 8	13q	CTG	16-91	107-127	-	m>p
SCA 10	22q	ATTCT	10-22	1000-4500	-	?
SCA 11	15q	?	?	?	-	?
SCA 12	5q	CAG	<29	66-78	-	?
SCA 13	19q	?	?	?	-	?
SCA 14	19q	?	?	?	-	?
SCA 16	8q	?	?	?	-	?
SCA 17	6q	CAG	29-42	47-55	-	?
DRPLA	12p	CAG	7-35	49-88	-	p>m

p:paternal, m:maternal, SCA 9 is not assigned, SCA 15 assigned to an Australian kindred but no linkage analysis done yet

polyglutamine tract in the respective proteins. As a result of these discoveries, a new classification based on the genetic loci of the SCAs has developed. These loci have been numbered based on their order of classification. However, a locus fro SCA 9 has yet to be assigned. Based on Harding's classification, SCAs 1, 2, 3, 4, 8, 12 would be under ADCA I, SCA 7 under ADCA II, and SCAs 5, 6, 10, 11, 14, 16 under ADCA III.

PREVALENCE OF SPINOCEREBELLAR ATAXIA

It is difficult to ascertain with great accuracy the true prevalence of the different subtypes of SCAs because most published studies focused on clinic-based populations and hence their findings were subjected to referral bias. Thus the true prevalence of some late onset SCAs may be underestimated. However, based on available information, SCAs 1,2 and 3 account for more than half of the ADCAs tested in the world. SCA 3/Machado-Joseph disease (MJD), originally described in two MJD families of Azorean descent, has been found in different ethnic populations and appears to be most common in many countries including United States and Germany. SCA 1 and SCA 2 are more common in the United Kingdom and Italy, and SCA 2 in Cuba. SCA 10 has been seen only in Mexicans. DRPLA is rare outside Japan. SCAs 12, 13, and 14 have been reported in German American, French, and Japanese families, respectively. For some countries such as Italy, founder effects may explain why certain SCAs predominate in specific regions of the country.[26-32]

PREVALENCE OF SCAs IN ASIAN COUNTRIES

Relative to the West, there is a paucity of information of SCAs in Asian countries. Most of the published data are from Japan, China, India and South Korea.[32-59] One of the major reasons is the lack of facilities and expertise in diagnosing SCAs in many countries in Asia. The absence of an effective curative treatment does not encourage health authorities to grant priority to develop diagnostic SCA capability in places where provision of basic healthcare is more important.

JAPAN

SCAs 3 and 6 appear common in a number of areas in Japan.[33,36] In a study in Hokkaido, the northernmost island of Japan, the authors found that out of 155 unrelated SCA families, 23.9%

was positive for SCA 3, 29.0% for SCA 6, 9.7% for SCA 1, 7.7% for SCA 2, and 2.6% for DRPLA.[36] However none of their patients were screened positive for SCA 7 and SCA 8. A total of 27.1% of the patients had still unknown SCA mutations. A founder effect of SCA6 was observed in the Chugoku area of Western Japan.[33] In the Tottori prefecture, located in the northeastern part of the Chugoku district, there was a cluster of SCA 6 families within the eastern area. Genotyping with DNA microsatellite markers linked to the CACNL1A4 gene on chromosome 19p13 demonstrated shared allelic characteristics and revealed a common haplotype in the majority of Japanese families. In another study involving117 unrelated SCA families that originated from the Tohoku District in the northernmost part of Honshu Island in Japan, the SCA1 mutation was found to be the most frequent (24.8% of all such families).[34] The relative prevalence of SCA 1 in the Tohoku District is very high relative to other countries. As the population of this area seldom moved, the alleles with SCA 1 mutations are thought to have been present in this area for a long time.

Recently, in a community-based prevalence study involving 613,349 inhabitants in Tottori prefecture, Japan, 109 SCA patients were identified.[32] The prevalence of SCA was 17.8 per 100,000 individuals. The most common was SCA 6 (25%), followed by SCA 1 (15%), SCA 3 (5%) and DRPLA (5%). None of the expanded alleles was found for SCA 2 and SCA 7. Prevalences per 100,000 individuals were: SCA 6, 2.40; SCA 1, 0.48; DRPLA, 0.32, and SCA 3, 0.16. SCA 14 was assigned to a Japanese SCA family.[35] The authors performed linkage analysis in a three-generation Japanese family with a locus or mutation that differed from those of known SCAs. Multipoint analysis and haplotype reconstruction traced this novel spinocerebellar ataxia locus (SCA 14) to a 10.2-cM interval flanked by D19S206 and D19S605 on chromosome 19q13.4-qter. The family members with a late onset exhibited pure cerebellar ataxia, whereas those with an early onset first showed intermittent axial myoclonus followed by ataxia.

CHINA AND TAIWAN

SCA 3 are most among amongst Chinese from China and Taiwan.[40-45] In a large study of 85 autosomal dominant SCAs families and 37 patients with sporadic SCA in China, SCA 1 was found in 4.70%, SCA 2, 5.88% SCA 3 48.23%. Sixty-five patients from 35 kindreds (41.19%) and 37 patients with sporadic SCA did not test positive for SCA 1, SCA 2, SCA 3/MJD, SCA 6, SCA 7, or DRPLA.[43] SCA 2 was found in 2 Chinese patients with familial parkinsonism. Functional imaging revealed reduction of 18F-dopa distribution in both the putamen and caudate nuclei.[39]

INDIA

SCA 2 appears common in India.[51-53] One group analysed the SCA 1, SCA 2, SCA 3, SCA 6, SCA 7 and DRPLA loci for expansion of CAG repeats and detected CAG repeat expansion and found SCA 1 to be present in 10.5%, SCA 2 in 17.5%, SCA 3 in 7%, and SCA 6 in 1.8%. No mutations were detected in the SCA 7 and DRPLA loci.[51] In another study, 77 Indian families with autosomal dominant cerebellar ataxia phenotype was examined and SCA12 was found in 5 families, which included a total of 6 patients and 21 family members. The sizes of the expanded alleles ranged from 55 to 69 CAG repeats, and the sizes of the normal alleles ranged from 7 to 31 repeats.[48] The authors suggest that SCA 12 may not be as rare in some populations as previously thought.

SOUTH KOREA

In the largest published study in this country, the frequency of six types of SCAs in 87 unrelated Korean patients with progressive ataxia were examined. SCA 2 was the most frequent hereditary ataxia (12.6%) and types 3 and 6 accounted for 4.6% and 6.9% of ataxia patients, respectively. DRPLA was found in three patients (3.4%). SCAs 1 or 7 were not detected. DRPLA should be considered in Korean patients who present with progressive ataxia.[59]

SINGAPORE

SCA 3 is most common in Singapore, followed by SCAs 1 and 2.[60] Our preliminary observations suggest that in Singaporean Malays and Indians, SCA 2 should be considered, whereas in Singapore Chinese SCA 3 is more prevalent.

GENOTYPIC FEATURES

SCAs generally share the following features; Firstly, anticipation, where there is progressive increase of expanded CAG repeats in successive generations. Those with larger CAG repeats display earlier ages of onset with greater disease severity than those with relatively smaller repeats. Secondly, there appears a critical size of repeat

for most of the SCAs, above which the disease would manifest. Thirdly, influences of parental origin on repeat size instability. Paternal transmission of many SCAs (such as SCAs 1, 2, & 3) may result in a severe, rapidly progressive phenotype at a young age. This observation is also well recognised in SCA 7 in which increased embryonic lethality in paternal transmission has been postulated.[61]

Not all SCAs display the above characteristics. For example in some SCAs, the disease and normal allele sizes overlap in an intermediate range. Alleles in the intermediate range show reduced penetrance in SCA 2. In SCA 7, the intermediate alleles do not cause disease but can give rise to *de novo* expansion to disease causing size in subsequent generations. Some SCAs (such as SCAs 1 and 2) have non-CAG repeat (CAA, CAT) interruptions. The CAT interruptions introduce histidines in the polyglutamine tract in the protein product, ataxin 1, that may prevent pathogenicity of expanded polyglutamines in SCA 1. The presence of the CAT interruptions on normal alleles is useful for distinguishing normal from diseased alleles for allele sizes of 36-44. The clinical relevance of somatic mosacism seen in some SCAs (1, 3, & 7) is unclear. SCA 8 exhibits instability of repeat with a bias towards expansion in maternal transmission and frequent contraction in paternal transmission. SCAs 1, 2, 3 & 7 may show length changes during intergenerational transmission with a predisposition to expansion in subsequent generations. While anticipation has been reported for SCA 6, the CAG repeat size shows no size instability in parent-to-child transmission. SCAs 1, 2, 3, 5, 10 & 14 also show anticipation, whereas SCAs 8, 12 &13 do not.

PHENOTYPIC FEATURES

There is a wide phenotypic overlap amongst the SCAs and inter-familial and intra-familial phenotypic variability exists even for each SCA subtype. However, there are some characteristic features of each SCAs. For SCA 1, there is hypermetric saccades and hyperreflexia. Markedly reduced velocity of saccadic eye movements, areflexia and changes similar to those seen in olivopontocerebellar atrophy on brain imaging suggest SCA 2. For MJD/SCA 3, combinations of protruded eyes, muscle fasciculations, spasticity, chorea, gaze-evoked nystagmus, parkinsonism and peripheral neuropathy are characteristic features. However, SCA 1 and SCA 2 also share a number of these features. For SCA 4, there is sensory neuropathy in addition to cerebellar ataxia. SCA 7 is distinguished by macular degeneration. SCAs 5, 6, 10 and 11 should be considered in patients with relatively pure cerebellar signs. In SCA 6, there is frequently a lack of family history and late age of onset of symptoms. SCA 8 patients have a mild sensory neuropathy with frequent late onset spasticity. Patients with SCA 13 characteristically show slowly progressive cerebellar ataxia of early childhood onset with mild mental retardation and motor developmental delay. SCA 14 patients have early onset myoclonus. Head and hand tremors are frequently seen in SCA 16, whereas intellectual deterioration and dysphagia are seen in SCA 17. There are some overlapping clinical features between SCA6 and patients with EA-2 and familial hemiplegic migraine. The CAG expansion in SCA 6 is located in the alpha-1A voltage-dependent calcium channel gene and EA-2 is caused by a point mutation in the same gene. If there is a history of seizures with ataxia, DRPLA and SCA 10 need to be considered. For SCA 10, seizures are accompanied by relatively pure cerebellar ataxia. SCA 3 and DRPLA need to be considered in suspected Huntington's disease (HD) patients if HD DNA test is negative. Some SCA 2 and SCA 3 patients may show pure parkinsonian phenotype.

Our experience suggests that the predictive value of some of these characteristic clinical features may increase when applied to a particular ethnic population where the most common SCA subtypes are known. This is illustrated by our recent study (60), where we determined the prevalence of SCA subtypes and predictive features of a positive DNA test in consecutive clinically diagnosed SCA cases in Singapore. Twenty-one consecutive patients from 14 families were evaluated. Thirteen patients (61.9%) from 6 families had a positive DNA test. Eleven of these (all ethnic Chinese) had SCA 3 (abnormal CAG size ranged from 61 to 71), and 2 ethnic Malays had SCA 2 (abnormal CAG size of 39). Clinical features which were highly predictive of a positive DNA SCA test in our population included presence of a positive family history, chorea and dystonia, muscle and tongue fasciculations, gaze-evoked nystagmus, and hypertonia. Our study draws attention to the observation that knowledge of relatively specific features of the most common SCA subtype in a local population can greatly enhance the practical accuracy of the choice of which SCA DNA test to order.

PATHOGENESIS

The gene products of SCA genes are designated ataxins. Ataxin 1, the product of SCA 1 gene is probably the best intensively studied, since transgenic SCA 1 mice model was first developed. The normal function of proteins with glutamine repeats is not entirely clear, though these proteins have been postulated to be responsible for development, neurogenesis or transcriptional activities.[2] Overexpression of a mutant SCA 1 allele in mice resulted in progressive ataxia and Purkinje cell degeneration. However, in mice with targeted deletion of SCA 1 gene no ataxia or neurodegeneration were noted. These observations support the theory that SCA 1 mutation causes disease via a toxic gain of function mechanism.[62-64]

The ataxins are transported from the cytoplasm to the nucleus where they aggregate and form intranuclear inclusions (NII). NI have been demonstrated in SCAs 1, 2, 3 & 7.[65-67] However, there appears no correlation between the distribution of NII and sites of pathology. For instance, NII are distributed in sites of brain involvement in SCA 1 & 3, but the cerebellum is spared in SCA 2. Immunohistological studies suggest that NI are ubiquitin positive and various components of the proteosomes appear to interact with them.[68] This implies that the expanded ataxins are targets for the ubiquitin-proteosome proteolyitic machinery. Aggregates of ataxin 1 stain positively for the molecular chaperone HDJ-2/HSDJ suggesting that that protein misfolding causes the NII in SCA 1. In vitro studies show that there is decreased ataxin 1 aggregation when HDJ-2/HSDJ is overexpressed. HDJ-2/HSDJ may promote recognition of the expanded or aberrant polyglutamine tract resulting in early ubiquitin-proteosome degradation or promote refolding.[69] Thus it appears that a chaperone stress response is being mounted to handle the toxic presence of misfolded polyglutamine proteins.

There was a lot of excitement initially when NI were first described in SCA for it was thought that preventing NI formation would prevent disease formation. However, there is increasing evidence that the mere formation of NI is not the most critical step in cell dysfunction. This is based on the poor correlation between distribution of NII and the sites of pathology. Furthermore, in vitro studies have demonstrated that increased formation of NI do not promote cell death.[69] It does appear that NII represents the "scars" (similar to Lewy bodies in patients with Parkinson's Disease) of damage that had ready occurred. On the other hand, nuclear localisation of the expanded ataxins appear important for pathogenesis for it has been demonstrated in transgenic SCA 1 mice models that prevention of transport of ataxins into the nucleus prevent formation of the disease.[70] Based on available evidence, one hypothesis of a possible chain of events which lead to cell dysfunction include: Firstly, changes in the tertiary structure of the ataxins due to expansion of the polyglutamine tracts. Secondly, aberrant interactions with the abnormal ataxins, Thirdly, transport of ataxins to nuclei of certain cells depending on the cell-specific protein interactions. Fourthly, aggregation (involving the proteosome complex and molecular chaperones) of the ataxins as NII.

CLINICAL IMPLICATIONS

Genetic testing of SCAs has a number of potential clinical roles. First, confirmation of diagnosis allows early institution of genetic counseling. Second, it enables genotype-phenotype correlation. Third, it helps select specific patients for clinical drug trails. Fourth, it leads to better understanding of pathogenesis and long-term clinical outcome of the disease.

At present, DNA testing that can directly detect mutations for SCAs 1, 2, 3, 6, 7, 8, 10, 12 & 17 and DRPLA. As the list of these DNA tests grows, the variable and overlapping phenotypic manifestations of the SCA subtypes make it difficult to select the specific SCA DNA test. We recommend an initial screen for SCAs 1, 2 & 3 to be carried out in suspected cases as they make up the majority of dominantly inherited SCAs. If these are negative, screening can be carried out for the other SCAs. In some cases, the ethnic origin and the presence of certain suggestive clinical signs should provide some guidance. For instance, if seizures accompany ataxia, DRPLA and SCA 10 should be screened first.

To be cost-effective, these tests should be done in SCAs that demonstrate a clear mode of inheritance. For those without family history secondary causes such as Wilson's disease and hypothyroidism should be first excluded. If the family history is unreliable or ambiguous testing in apparent 'sporadic' cases is useful for some sporadic cases have been found to be autosomal dominant. This is particularly relevant in Asian populations for based on our experience, some patients may feel that their disease is a "curse" and may not be willing to volunteer information regarding their family members. At-risk family members may also not want to be associated with their affected relatives and decline genetic testing.

Patients with SCA 6 may not always give a positive history since disease onset is usually late. A *de novo* mutation may cause the disease with clearly negative family history. Early parental deaths, non-paternity, and adoption are also important factors to consider. If all available SCA screen is unyielding, it is worthwhile considering other diseases which can mimic the SCA phenotype such as adrenoleukodystrophy and multiple system atrophy.[71]

There are presently no standard guidelines for SCA testing. However, the importance of genetic counseling cannot be over emphasized. Like other neurodegenerative diseases without a definitive cure, there are a number of ethical, social, legal and psychological issues to consider for SCA genetic testing.[72] These include confirmatory testing, prenatal diagnosis, predictive testing and asymptomatic testing for children, confidentiality, insurability, finances, employment, disability, and marriage. Most clinicians would agree that testing in at risk asymptomatic children is not encouraged. Prenatal testing of SCAs is also available. However issues such as possible termination of pregnancy and follow-up care for psychological problems require careful management by a combined team of experts including the physicians, genetic counselors, psychologists and social workers.

FUTURE DIRECTIONS

Clinical drug trials for SCAs have been disappointing. Treatment has been symptomatic though antioxidants and NMDA antagonists have been used in the hope of preventing further neurodegeneration.[73] On the brighter side, great strides have been made in our understanding of the pathogenesis of the disease. One common theme has emerged in the pathogenesis of SCAs (whether polyglutamine disease or not): there are specific cellular proteins or components that interact with the mutant ataxins which influence its degradation and subcellular distribution. Identification of such proteins and designing drugs to intervene in these interactions may prevent or slow down the disease.

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