Research Article

Genetic testing for clinically suspected spinocerebellar ataxias: Report from a tertiary referral centre in India

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Abstract

Spinocerebellar ataxias (SCAs) are a heterogeneous group of neurodegenerative syndromes, characterized by a wide range of muscular weakness and motor deficits, due to cerebellar degeneration. The prevalence of the syndromes of SCA varies across the world and is known to be linked to the instability of trinucleotide repeats within the high-end normal alleles, along with susceptible haplotype. We estimated sizes of the CAG or GAA repeat expansions at the SCA1, SCA2, SCA3, SCA12 and the Frataxin loci among 864 referrals of subjects to Genetic Counselling and Testing (GCAT) clinic, NIMHANS, India with suspected SCA. The most frequent mutations detected were SCA1 [N=100 (11.6%)] and SCA2 [N=98 (11.3%)] followed by SCA3 [N=40 (4.6%)], FRDA [N=20(2.3%)] and SCA12 [N=8 (0.9%)].

Key words: SCA, Genotyping, CAG repeats, India

Introduction

The ataxia syndromes include inheritable spinocerebellar ataxias (SCA), which are a spectrum of neurodegenerative syndromes characterized by loss of balance, motor incoordination, speech and ocular disturbances (Harding 1983; Maschke et al. 2005; Rossi et al. 2014). Currently, more than 43 genetic loci related to SCAs have been described, and these are inherited in either the autosomal dominant or recessive manner. Neurological symptoms and signs overlap between different types of SCA, and even within the specific SCA genotype, and are highly variable. Each SCA is usually attributable to a specific mutation, or a pathological expansion in the specific gene (Martins et al. 2006; Subramony and Dürr 2012) and individuals who carry multiple pathological expansions are quite rare. However, to understand the biology of disease, the molecular diagnosis of the overlapping mutations, high end normal alleles among SCAs and understanding the specific haplotype structure are useful, as this may also provide additional insight on the origins of the disease, as well as therapeutic management.

Earlier reports of SCA types had shown variation in prevalence across geographical regions of India, Europe and Eastern Asia. A few Indian studies have reported the occurrence of SCA phenotypes in eastern India where SCA2 was found to be more prevalent followed by SCA1 and SCA3 (Basu et al. 2000; Mukerji et al. 2000; Sinha et al. 2004). Most epidemiological studies on the prevalence of SCA are from European and Eastern Asian populations (Basri et al. 2007; Ruano et al. 2014; Wang et al. 2010). While, SCA1 is common in southern India (Krishna et al. 2007), SCA2 is widespread in northern and eastern regions of India (Basu et al. 2000; Pang et al. 1999; Sinha et al. 2004; Wadia et al. 1998), in Srilankan population (Sumathipala et al. 2013) and in South Korea (Lee et al. 2003). SCA3 is common in Cambodian (Jayadev et al. 2006), Thai (Sura et al. 2009), Chinese (Tang et al. 2000), Taiwanese (Wu et al. 2004), Malay (Tan 2003; Tan et al. 2000) populations, and western and eastern regions of India (Basu et al. 2000; Chattopadhyay et al. 2003; Krishna et al. 2007; Mittal, Sharma, et al. 2005). SCA6 is highly prevalent in the Japanese population (Yabe et al. 1998), and a high prevalence of SCA7 has been reported in African ethnic groups (Bryer et al. 2003). The occurrence of SCA6 (Basu et al. 2000), SCA7 (Kayal et al. 2011), SCA17 (Hire et al. 2011) and other SCAs appears to be rare in India, while the founder mutation for SCA12 has been seen to occur almost exclusively in a particular ethnic group from northern India (Bahl et al. 2005).

Friedreich's ataxia (FRDA) is an autosomal recessive neurodegenerative disorder with clinical features that overlap with different SCA types, along with cardiac and ocular defects. Earlier reports on FRDA in Indian population have shown low prevalence rates compared to Caucasian population (Chakravarty 2003; Chakravarty and Mukherjee 2003; Mukerji et al. 2000). The occurrence of FRDA appears to be very low or almost absent in sub-Saharan Africans and East Asian populations. Both north Indian and European FRDA patients share a similar pattern of GAA expansion in the Frataxin (FXN) allele, while the occurrence of this mutation in South Indian population might be

due to a very recent admixture event (Singh et al. 2010). The higher prevalence of FRDA in European population despite lower consanguinity, might be due to a higher occurrence of the premutation (at-risk) alleles in European populations (Bidichandani and Delatycki 1993).

Based on the haplotypes (D6S288, SNP9 and SNP1), multiple founder effects have been proposed for the origin of pathological expansions seen in Indian populations for SCA1 (Mittal, Srivastava, et al. 2005) and SCA2 (Pang et al. 1999; Saleem et al. 2000). SCA3 haplotype shows a background haplotype of both Azorean as well as Indian admixture in a large proportion (Martins et al. 2006; Martins et al. 2007; Martins et al. 2012). More haplotype data among SCA types is necessary for describing the distribution of these alleles in the Indian population.

In this study, we provide the sizes of CAG repeats expansion at the SCA1, SCA2, SCA3, SCA12 loci and GAA repeat expansion at FRDA loci and their relative occurrence among 864 clinically suspected cases referred to the GCAT clinic, NIMHANS, India. We also attempted to evaluate the origin of SCA2 mutation through microsatellite marker (D12S1672) at SCA2 loci.

Materials and Methods

Recruitment of samples

Subjects (N=864), were clinical referrals to the genetic counselling and testing centre (GCAT) at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. The patients were assessed according to the International Cooperative Ataxia Rating Scale (IARS). The clinical descriptive was discussed in earlier reports from the centre (Chandran et al. 2014; Jhunjhunwala et al. 2013; Jhunjhunwala et al. 2014; Netravathi et al. 2009; Yadav et al. 2012). Blood sampling was done after written informed consent and counselling prior to enrolment. The healthy controls (N=42) with no lifetime history of neurological and psychiatric signs were recruited by purposive sampling of volunteers belonging to different geographical regions in India. The samples were categorized as of northern, eastern and southern Indian origin based on self-report and geographical origin of their grandparents. The study was approved by institutional ethics committee.

Molecular genetic analysis of SCA and FRDA expansions

The genomic DNA was extracted from whole blood by salting out method (Miller et al., 1988). This DNA was used for polymerase chain reaction (PCR) to amplify the Ataxin (ATXN)-1, 2, 3, 12 and Frataxin (FXN) loci using appropriate primers. The occurrence of CAG or GAA expansions was identified by high resolution agarose gel electrophoresis of the amplified products. The fragment analysis was performed using ABI 3500 XL Genetic analyser (Life technologies, California). The CAG or GAA repeat length was determined using v3.5 gene mapper.

Analysis of D12S1672 microsatellite marker at SCA2 loci

For the analysis of SCA2 microsatellite (D12S1672), 77 controls and 76 SCA2 subjects were considered. Specific primers (FP-56 FAM/ATCAGGCCACTGCACTC -3', RP- 5'- CTGGAAATTCACATCTGCTT-3') were used for PCR to amplify the microsatellite locus. The allele sizes were determined using ABI 3500XL Genetic Analyzer

Result

Relative distribution of SCA and FRDA mutations among 864 clinically suspected subjects referred to the GCAT clinic.

The laboratory offers genetic screening for SCA1, SCA2, SCA3, SCA12 and FRDA. In testing the 864 patient samples, 266 subjects (30.8%) were identified with pathological expansions in the SCA and FRDA loci (Table 1). The most frequent pathological repeat expansions were SCA1 (N=100; 11.6%) and SCA2 (N=98; 11.3%) followed by SCA3 (N=40; 4.6%), FRDA (N=20; 2.3%), SCA12 (N=8; 0.9%) and FRDA (N=20; 2.3%) (Table 1 and Figure 1). Most of the SCAs were heterozygous, except two of SCA2 cases which were homozygous with CAG repeat sizes; 35/37 and 36/38 (lower allele / upper allele). The disease causing SCA genotype could not be detected in two-thirds of the subjects (N=598; 69.2%) (Figure 1), and suggests the need to expand facilities for the same.

Geographical distribution of ataxia types within India

In the subjects who had pathological expansions in SCA1, 78% (N=78) were from southern India and 22% (N=22) were from northern and eastern India (including one from Bangladesh). In SCA2, 67% (N= 66) were of south Indian origin and 33% (N=32) were from the northern and eastern India. In SCA3, 70% (N=28) were from southern India and 30% (N=12) were from northern and eastern India. At the SCA12 locus (though most individuals (N=7) were from a particular ethnic background, and geographically from northern and eastern part of India (Faruq et al. 2009; Faruq et al. 2014), we also identified one SCA 12 positive case from southern India (Table 2).

Out of the patients that tested positive for FRDA, 75% (N=15) were from southern India and 25% (N=5) from northern and eastern India. FRDA has been reported to have a higher prevalence in northern Indian population as compared to southern Indian population (Mukerji et al. 2000; Singh et al. 2010). The age of FRDA mutation has been calculated to be recent in south Indian population as compared to north Indian population (Singh et al. 2010). This might explain possible differences in frequency of FRDA between northern and southern Indian population. In our experience, upto 25% of FRDA cases have been of known consanguineous origin. While the carrier rate in India is not clear, it may be much lower than the 1:60-1:100 which has been reported (Bidichandani and Delatycki 1993).

Distribution of D12S1672 marker at the SCA2 loci in Indian population is similar to European population.

Analysis of D12S1672 microsatellite marker revealed that allele 9 (283 bp) and 11(285bp) were overrepresented in the expanded SCA2 chromosomes (35% and 15%) compared to control chromosomes (7% and 3%), (p=0.0001 and 0.0006) respectively, as also seen in Cuban, French, German and British populations (Didierjean et al. 1999; Pang et al. 1999; Saleem et al. 2000). In contrast, allele 6 (279 bp) and allele 13 (287bp) were overrepresented in control chromosomes (54% and 14%) compared to the expanded SCA2 chromosomes (25% and

7%) (p= 0.0001 and 0.05) respectively. These results suggest that expanded Indian SCA2 alleles overlap with those from the European population.

Discussion

Among clinically suspected 864 subjects for SCA, we confirmed pathological expansions in one-third samples (n=266; 30.8%). We have previously reported a high incidence of SCA1 in southern India (Krishna et al. 2007), while other reports have suggested that SCA2 is most common form of SCA in northern and eastern India (Pang et al. 1999; Saleem et al. 2000; Wadia et al. 1998). Thus, the incidence of specific type of SCAs in India is regionally or ethnically diverse. In this extended sample, we found an almost similar proportion of SCA1 (11.6%) and SCA2 (11.3%) cases, as has also been observed in eastern Indian (Basu et al. 2000), British and Italian populations (Sequeiros, Martins, and Silveira 2012). It is difficult to comment whether our numbers of undiagnosed cases are comparable to other studies as the actual numbers of cases that remain undiagnosed depend on the panel of ataxia types tested for and the strength of clinical suspicion (Ruano et al. 2014). However, SCA1,2 and 3 make up 30-40 % of positive cases in most centres.

The incidence of high end normal alleles and lack of triplet repeat interruptions have been proposed to associate with predisposition of the respective SCAs in many populations (Chattopadhyay et al. 2003; Mittal, Srivastava, et al. 2005; Saleem et al. 2000). The difference in the haplogroups between southern and northern/eastern India has been suggested for the variation in the distribution of SCA1 and SCA2 (Basu et al. 2000; Mittal, Srivastava, et al. 2005; Saleem et al. 2000; Sinha et al. 2004). Previously, it has been proposed that the high end normal and expanded SCA alleles originated independently of each other in India (Mittal, Srivastava, et al. 2005). Multiple CAT interruptions in the high end normal alleles have been linked to the stability of CAG repeats at SCA1 loci, and an ancestral haplotype (C-4-C) found in the high end normal alleles has been suggested for the unstable nature of the high end SCA1 alleles in Indian population (Mittal, Srivastava, et al. 2005).

In the present study, based on the microsatellite (D12S1672) analysis, we found an over representation of allele 9 (283 bp) in the SCA2 chromosomes, which supports the earlier finding that Indian SCA2 loci resemble the haplotype pattern of Cuban and some European populations (Didierjean et al. 1999; Pang et al. 1999; Saleem et al. 2000). High prevalence of SCA2 has been observed in both native African (with low repeat number) and far Eastern population (Boonkongchuen et al. 2014). Therefore, understanding the origins and spread of expanded mutation in both native (Africa and Siberia), as well as admixed (Cuba and south Asia) population could have important implications in studying the population flow, and prevalence of inherited late-onset disorders.

Evidence for a founder effect at the SCA12 loci has been suggested specifically from northern Indian families (Bahl et al. 2005), and a majority of cases seem to occur in one particular sub-group. However, we identified an SCA12 positive case of southern Indian origin, unrelated to that particular population group, which may suggest multiple founder effects of SCA12 in the Indian population. Recently, Faruq et al, have reported the co-occurrence of SCA2 and SCA12 mutations in two cases from India (Faruq et al. 2014). Interestingly we also identified a SCA2 subject with a high end normal allele (41 CAG repeats) at the SCA12 locus.

This study provides evidence that SCA1 and SCA2 are the common ataxia syndromes in India. Of note, we were unable to detect the genetic aetiology for a major portion of this sample (~69%). We have tested for the common SCA types prevalent in India, but the occurrence of other rare types as well as novel mutations have to be explored. Next generation sequencing, association studies and system biology approaches can be useful to identify mutations, and the related biology, underlying these unknown SCAs. This might help to better understand the genotype-phenotype correlates of these ataxia syndromes and enable better treatment for the patients.

Conflict of Interest

All the authors declare no conflict of interest in study undertaken.

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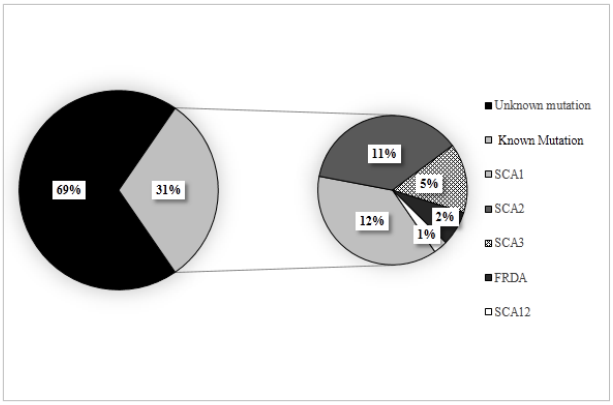
Types of SCA	Cases		Controls	
	Lower Allele Mean±SD Range	**Upper Allele Mean±SD** Range	**Lower Allele Mean±SD** Range	**Upper Allele Mean±SD** Range
SCA1 (ATXN1)	**30±3** 22-35	**53±7** 40-75	**32 ±2** 29-31	**34±2** 29-37
SCA2 (ATXN2)	**22±3** 19-36	**41±6** 30-66	**22**	**22**
SCA3 (ATXN3)	**19±6** 9-28	**70±4** 59-79	**13±4** 8-15	**18±4** 13-29
SCA12 (PPP2R2B)	**13±3** 9-17	**55±8** 48-55	**9±1** 8-10	**12±2** 9-15

Table 1. Distribution of CAG repeats at the SCA loci in cases and healthy subjects. Statistics based on samples that tested positive for SCA1 (N=100), SCA2 (N=98), SCA3 (N=40), SCA12 (N=8) and healthy subjects (N=42). Mean and SD values are nearest whole numbers ATXN1- Ataxin1, ATXN2- Ataxin2, ATXN3 – Ataxin3 and PP2R2B- Protein phosphatase 2, regulatory subunit B, beta isoform.

	SCA1 N(%)	**SCA2 N(%)**	**SCA3 N(%)**	**FRDA N(%)**	**SCA12 N(%)**
Southern India	78(0.78)	64(0.84)	26(0.68)	15(0.79)	1(0.12)
Northern India	5(0.05)	6(0.08)	6(0.16)	2(0.10)	6(0.75)
Eastern India	16(0.16)	6(0.08)	6(0.16)	2(0.10)	1(0.12)

Table 2*:* The table represents the distribution of Spinocerebellar ataxia 1(SCA1), Spinocerebellar ataxia 2 (SCA2). Spinocerebellar ataxia 3 (SCA3), Freidreichs ataxia (FRDA) and Spinocerebellar ataxia 12 (SCA12) in different parts of India. Southern India, Eastern India, Northern India

Figure 1: Proportion of genetically identified SCAs in the study sample with relative frequencies.



The figure represents the distribution of the SCA types that tested positive. Spinocerebellar ataxia 1 (SCA1), Spinocerebellar ataxia 2 (SCA2), Spinocerebellar ataxia 3 (SCA3), Friedreich's ataxia (FRDA) and Spinocerebellar ataxia 12 (SCA12)