# High prevalence of spinocerebellar ataxia type 1 in an ethnic Tamil community in India

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Objective: To study the prevalence, clinical and molecular genetic characteristics of cerebellar ataxia in an ethnic Tamil community in India. Methods: An epidemiological study of cerebellar ataxia was done in two villages in the Indian state of Tamilnadu where its prevalence was observed to be high. All the people were screened and the clinical characteristics of those with ataxia were recorded. Genetic analysis was done in those with ataxia and in two asymptomatic control groups - group I belonging to the affected community and group II belonging to the unaffected community. The clinical and genetic results are correlated. Measures to help the community are suggested. Results: The total population of the two villages was 378. Among them 345 belonged to Vanniyakula Kshatriyar community and 33 to another. Cerebellar ataxia was found in 25 individuals belonging only to the former community (7.2%). The mean age of onset was 39.8 years and the salient features were ataxic gait (100%), dysarthria (100%), pyramidal signs (72%), slow saccades (48%) and bleeding diathesis (12%). Genetic studies were done in 17 of the study group. All showed pathological expansion of CAG repeats above 40, in chromosome 6p, diagnostic of SCA1. 7 of the 18 in the control group (I) and none in control group (II) had CAG repeats above 40. Conclusion: The prevalence of SCA1 is high (7.2%) in this ethnic Tamil community with a large asymptomatic group waiting to manifest. The symptomatic individuals need social support and rehabilitation. Appropriate counseling, prenatal evaluation and therapy will prevent the spread of disease to the next generation.

**Key words:** Clinical features; genetics; India; prevalence; SCA1.

# Introduction

Spinocerebellar ataxia type 1 (SCA1) is characterized by progressive cerebellar ataxia, dysarthia and eventual bulbar dysfunction with abnormal CAG trinucleotide repeat expansion of the SCA1 gene in chromosome locus 6p23.<sup>[1]</sup> In community-based studies the prevalence rate is 1 to 2 per 100,000 populations.<sup>[1]</sup> Most of the hospital-based studies in India showed SCA2 and SCA3 to be more common.<sup>[2,3,4,5,6]</sup> In this paper, we report a population-based study of SCA1 in an ethnic Tamil community inhabiting two small villages in the state of Tamilnadu.

# Materials and methods

Rajapalayam (village 1) and Kottamedu (village 2) are two small adjacent villages near Vellore about 150 km from Chennai. Most of the people living here belong to the Vanniyakula Kshatriyar community. Agriculture is the main occupation. One patient from Rajapalayam reported to our department with progressive unsteady gait. Clinical and imaging studies confirmed degenerative ataxia. Genetic studies showed CAG repeats above 40 in chromosome 6p23 diagnostic of SCA1. He revealed that quite a few of his villagers have similar disorder. This prompted us to conduct the epidemiological survey in the above villages.

The survey team comprised two neurologists, two residents and five paramedical persons, who were adequately trained. The study was carried out between January and April 2004. A houseto-house survey was done in all the houses using standard proforma.<sup>[7]</sup> Neurological assessment was done in all the inhabitants of the two villages. Detailed examination was done in those who had ataxia and the findings were recorded. All the symptomatic individuals were given genetic counseling. Genetic testing was done in those symptomatic individuals who were willing. After informed written consent, 5ml of heparinized blood was taken and sent for analysis to Saha Institute of Nuclear Physics, Kolkata. For control, blood was taken from two groups of asymptomatic volunteers, (neither randomized nor blinded) group I, belonging to the same community, (IA-below 40 years of age, IB- above 40 years of age), group II belonging to a different community residing in the same village.

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308

Genomic DNA isolation from heparinized blood samples was done by the standardized method. The method used to determine the CAG repeat number was essentially same as reported earlier using the PCR primer Rep1 and Rep2.<sup>[5]</sup> Genetic and clinical correlation was done at the end.

# Results

The total population in both villages was 378; among them 345 belonged to the Vanniyakula Kshatriyar community and the remaining 33 to another single community. Among the 345, 180 were men and 165 women. The age-adjusted distribution of the population and symptomatic individuals is given in [Table 1].

The mean age of onset of the illness was 39.8 years (range 23 - 57 years). The first symptom was unsteadiness on walking in 20(80%), slurring of speech in five (20%). Pyramidal signs were found in 18(72%), sensory neuropathy in seven (28%), cognitive decline in four (16%), slow saccades in 12(48%), deafness in two (8%), nystagmus in two (8%) and optic atrophy in one (4%). None had extra pyramidal involvement. Bleeding diathesis was noted in three (12%) of them in whom the exact cause could not be identified. MRI done in two patients showed cerebellar atrophy.

Genetic testing was done in 17 of the symptomatic group.

Table 1: Age adjusted population and symptomatic individuals   - Vanniyakula Kshatriyar community									
	Population			Symptomatic individuals					
Age	М	F	Т	%	М	F	Т	%	
0–10	37	25	62	18.0	-	_	-	-	
11–20	24	32	56	16.2	-	_	-	-	
21–30	31	35	66	19.1	1	1	2	3.0	
31–40	25	36	61	17.7	2	6	8	13.1	
41–50	34	22	56	16.2	7	3	10	17.9	
51–60	19	10	29	8.4	3	2	5	17.2	
>60	10	5	15	4.4	-	-	-	-	
Total	180	165	345		13	12	25	7.2	

Table 2: Age of onset and number of CAG repeats in						
symptomatic individuals						

No in pedigree	Age	Age of onset	CAG repeats
4	32	30	36, 45
5	33	32	33, 44
6	34	32	33, 47
8	38	33	41, 45
10	40	35	30, 40
12	43	42	30, 43
13	43	42	32, 44
16	47	40	29, 48
17	47	42	33, 42
18	49	30	31, 44
19	49	48	26, 43
20	50	45	36, 42
21	52	40	32, 42
22	53	50	30, 41
23	54	47	31, 45
24	56	40	41, 43
25	58	57	33, 44

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All had CAG repeats above 40 (mean 43.6, range 40 - 48). Two of them were homozygous. The number of CAG repeats in symptomatic individuals and the age of onset of the illness are shown in Table 2. The regression analysis showing inverse relationship between age of onset of ataxia and number of CAG repeats is shown in [Figure 1]. The family pedigree of all those symptomatic individuals is given in Figure 2. In the control group IA belonging to the affected community below 40 years of age six out of ten (60%), and in control group IB above 40 years of age one out of eight (12.5%) had CAG repeats above 40. In control group II, belonging to the different community, all had normal CAG repeats.

## Discussion

In the published literature on spinocerebellar degeneration



Figure 1: Regression estimate for number of CAG repeats and age of onset



Figure 2: Pedigree of symptomatic individuals

309

from India SCA1 was reported to be less common. In the pioneering study of Wadia all the 14 individuals had SCA2 and none SCA1.<sup>[2]</sup> Later in a study of 70 patients of degenerative ataxia by Ambar Chakravarthy only two were SCA1.<sup>[3]</sup> Ghosh has reported 3 cases and Basu 5 cases.<sup>[4,5]</sup> However in a recent report from NIMHANS, Bangalore among 84 genetically tested ataxic individuals 15 belonged to SCA1.<sup>[6]</sup> These studies were hospital-based. In this present community based study SCA1 was found to be prevalent in 7.2% of the members of the Vanniyakula Kshatriyar community. Such a high prevalence has not been observed in any one of the previous studies. This is probably because all the members of the two villages have a common origin from a single family with the affected gene, consanguineous marriage and remaining in the same area for their livelihood.

This disorder was observed more in individuals between 41-50 years (18%) of age, comparable to other studies.<sup>[8]</sup> The presenting symptom was unsteady gait as in other studies.<sup>[9]</sup> Pyramidal signs were found in 18 (72%) in the later stages in contrast to previous reports.<sup>[10]</sup> Sensory neuropathy observed in 28% of the patients by five years of the disease duration was similar to the previous studies.<sup>[10]</sup> Four patients (16%) had cognitive decline correlating well with duration and severity of the disease as reported earlier.<sup>[11]</sup> Extrapyramidal signs in the form of tremors were observed in almost all cases by Won Yong Lee et. al.<sup>[12]</sup> But in the present series none had this manifestation. Bleeding diathesis in the form of profuse bleeding gums was seen in three patients (12%). The exact cause of it could not be identified, as none were willing for further investigations. From the available history bulbar dysfunction, aspiration and respiratory failure were the common endpoints in most of the patients. The mean age of death was around 55 years as reported by the elders of the village.

Earlier studies have shown the number of CAG repeats in SCA1 was between 39-91. In this present series it was between 40-48 (mean 43.6).<sup>[12]</sup> There were two symptomatic individuals with homozygous pathological CAG expansions but they did not differ from others in disease manifestation, severity and progression. Similar observation has already been reported by Ranum et. al.,<sup>[13]</sup> Previous studies have reported a correlation between the number of repeats and the severity of disease; the larger the repeat the earlier the onset and more severe the disease.<sup>[13]</sup> However in this series there was no definite correlation between the age of onset and the severity of illness with CAG repeats. Even though the regression analysis had shown an inverse relationship between numbers of CAG repeats and age of onset of ataxia it was not statistically significant (P = 0.02). The sample is too small for it to be statistically significant.

Whereas all the normal persons (control group II) had CAG repeats less than 36, 60% of the unaffected volunteers in control group IA had CAG repeats above 40. This indicates a large number of asymptomatic young persons, who genotypically positive are likely to manifest the disease later. One (57-year old female) in control group1B with 41 repeats was asymptomatic. She may manifest still later, as the longest age of onset in our series was 57 years, or may remain asymptomatic as shown by Goldfarb et al, in whose study, a woman with 44 CAG repeats was asymptomatic even at an age of 66 years.<sup>[14]</sup>

The disease has affected the community to such an extent that the affected persons are unable to perform their work and dependent on others for the livelihood at middle age itself. The community can be helped by adequate support and rehabilitation of the symptomatic individuals by government and non-governmental organizations. Appropriate genetic counseling and prenatal testing will help to eliminate the disease in the coming generation.

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Autosomal dominant spinocerebellar ataxias (SCA) are phenotypically and genotypically heterogeneous group of disorders. Some of the clinical features have some specific values for predicting a gene defect. However the clinical diagnosis of subtypes of SCAs is complicated by the salient overlap of some of phenotypes between genetic subtypes. Thus genotypic diagnosis is of importance.

Our knowledge of the molecular mechanisms SCAs is rapidly growing. Several identified mutations correspond to expansions of repeated trinucleotides (CAG repeats in SCA1, SCA2, Machado-Joseph disease (MJD)/SCA3, SCA6, SCA7, SCA17, and dentate-rubral-pallido-luysian atrophy (DRPLA) and CTG repeats in SCA8). A pentanucleotide repeat expansion is associated with SCA10. Missense mutations have also been found recently. Anticipation is a main feature of SCAs, due to instability of expanded alleles. It is estimated that extensive genetic testing leads to the identification of the causative gene in about 60-75% of cases.<sup>[1]</sup> As on today molecular genetic studies have identified about twenty-seven subtypes. Current molecular classification corresponds to the order of gene description.

India is an ethnically and religiously diverse population. The ethnic diversity may have a bearing on the prevalence of SCA subtypes. In this issue of the journal Rengaraj et al<sup>[2]</sup> report a high prevalence of SCA1 in an ethnic. Tamil Vanniyakula Kshatriyar community. The most common type of SCA reported in India is SCA2.<sup>[3-5]</sup> The populations in these studies were of mixed ethnicity. Of the 124 families reviewed by Chakravarty and Mukherjee,<sup>[6]</sup> 47 (38%) families belonged to SCA2. Most of the patients with SCA12 reported were from India and it seems SCA12 is typically an Indian disease (Dr K K Sinha, Indian Academy of Neurology Oration, 2005). SCA12 accounted for 25 (9%) of the 212 families of autosomal dominant cerebellar ataxia studied.<sup>[5]</sup> However this needs to be confirmed by other studies. MJD/SCA3 is the common type of SCA worldwide whereas the reported prevalence of MJD/SCA3 from India is very low.<sup>[5,7,8]</sup> Of the 212 families studied by Srivastava et al<sup>5</sup> MJD/SCA3 mutation was seen in 6 (2.8%) pedigrees. However the reported prevalence of MJD/SCA3 was high in ethnic Bengalees in West Bengal.<sup>[6,9]</sup> Of the 19 families with autosomal dominant SCA studied in West Bengal till 2001, MJD/SCA3 mutation was seen in 7 (37%) families. In the patients with MJD/SCA3 studied by Chakravarty and Mukherjee<sup>[6]</sup> many did not have any extrapyramidal features or ophthalmoplegias. MJD/SCA3 showing racially different expressivity has been described in several families of African origin. The phenotype ranged from ataxia with parkinsonian signs to a syndrome clinically almost indistinguishable from idiopathic, L-dopa-responsive Parkinson's disease. These parkinsonian phenotypes are rare in those of European descent.<sup>[10]</sup> The observed low prevalence of MJD/SCA3 in India could be because of the low prevalence of large normal alleles that might act as the reservoir for the expanded alleles. MJD/SCA3 mutation in Indian populations had the same origin as found worldwide.<sup>[7]</sup>

There is an urgent need to do genetic studies of SCAs and genotypic-phenotypic correlation in different ethnic population in India to resolve some of the Genotypic testing even though expensive allows precise classification of genotypic subtype thus allows genetic counseling and predictive testing. It also allows genotype-phenotype correlation, study of natural history and prognosis of specific subtypes of SCA. The development of relevant animal models of SCAs may bring hope for effective therapies in human to resolove some of these issues.

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311