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Commentary

An understanding of spinocerebellar ataxia

Advances in molecular genetics techniques have given several approaches to diagnose most common complex genetic disorders and also these advances have helped to diagnose the rare complex disorders. Autosomal dominant cerebellar ataxias are a group of hereditary neurodegenerative disorders and are characterized by a generalized incoordination of gait, speech, and limb movements[1]. Autosomal dominant spinocerebellar ataxias (SCA) form a group of cerebellar degenerative disorders characterized by clinical and genetic variability, that share the feature of progressive ataxia. These disorders share many pathological features beyond a common genetic mechanism, and have a prevalence of 1 to 4 affected for every 1,00,000 individuals[2]. SCAs are classified genetically according to a specific mutation or mapped locus, and also based on the clinical data. Accordingly, 24 autosomal dominant ataxias - SCA1– SCA8, SCA10– SCA19, SCA21– SCA23, SCA25, dentatorubral-pallidoluysian atrophy (DRPLA) and ataxia caused by mutations in the gene that encodes fibroblast growth factor 14 (*FGF14*) have been identified. Six SCA subtypes (SCA1, SCA2, SCA3, SCA6, SCA7 and SCA17) and DRPLA are caused by CAG trinucleotide repeat expansions in the respective genes[3]. The more common SCAs are due to translated CAG repeat expansions that code for an elongated polyglutamine tract within the respective proteins[4]. However, SCAs are highly heterogeneous, the prevalence of specific subtypes varies between different ethnic and continental populations. Among these SCAs, SCA3 is the commonest subtype worldwide followed by SCA1, SCA2, SCA6, SCA7 and SCA8 with a prevalence of over 2 per cent, and the remaining disorders are considered to be rare with a prevalence of <1 per cent[5].

SCA7 is the only autosomal dominant ataxia that presents with unique combination of gait ataxia and progressive vision deterioration[6]. The phenotype of SCA7 patients varies with onset in infancy to an accelerated condition and early death to onset in the fifth or occasionally sixth decade with slowly progressive retinal degeneration and cerebellar ataxia[7]. The key genetic cause for SCA7 has been identified as mutation in the *ATXN7* on chromosome 3p21.1 leading to expanded CAG repeat, which has been implicated to cause neuronal loss in cerebellum, regions of brain stem and retina[6]. CAG40 repeats expand with most transmissions and the alterations often include jumps of >l0, sometimes >20, and occasionally >100 repeats[8]. Normal alleles of *ATXN7* display 19 or fewer CAG repeats. Nearly 75 per cent of normal alleles have shown to exhibit 10 CAG repeats whereas mutable normal alleles span from 28 to 33 CAG repeats. The "intermediate alleles," mutable normal alleles are meiotically unstable and not convincingly associated with a phenotype. Because of the instability of alleles in the mutable normal range, an asymptomatic individual with a mutable normal allele may be predisposed to having a child with an expanded allele[9]. Alleles spanning 34-36 CAG repeats could be defined as alleles with reduced penetrance. When present in an individual with a reduced penetrance allele, symptoms are more likely to be later in onset and milder than average, whereas full penetrant alleles range from 36 to 460 CAG repeats[7].

Advances in genetic research has improved the diagnosis of genetic disorders and brought new possibilities for prevention and treatments. The CAG repeat expansions in *ATXN7* are known to promote repressive chromatin modification of the ataxin-7 promoter which is mainly due to suppressed transcription of an antisense non-coding RNA which further results in an increased expression of the mutant protein[10]. Furrer *et al*[11] have reported that the

suppression of mutant protein expression by 50 per cent in transgenic mice is known to reverse several aspects of the mouse SCA7 phenotype, which suggests avenues for potential therapy. Removal of accumulated mutant polyQ proteins has been shown to ameliorate the disease phenotype in several model organisms studied including *Caenorhabditis elegans,* mouse and *Drosophila*, which is consistent with a toxic gain-of-function disease mechanism[12-14]. However, some studies have also reported that wild-type protein function may be affected by the presence of the mutant which may result in an additional loss-of-function mechanism contributing to disease pathogenesis. Several therapeutic approaches that involve RNA interference (RNAi) result in the suppressed expression of toxic polyQ proteins which have been shown in mouse models of polyQ disorders that include SCA1 and SCA3[13].

Faruq and colleagues[15], in this issue have described the clinico-genetic characteristics of nine SCA7 families of Indian origin and have made a cross-comparison with the worldwide studies. The authors mainly focused on the CAG repeat distribution and showed the association with the age at onset of the disease which was carried out among 35 individuals from these nine affected families including 22 affected, 1 symptomatic and 12 unaffected, and 382 controls from 21 diverse Indian populations based on ethnic, linguistic and geographical location. This approach indicated that the CAG repeats of < 49 correlated with earlier age at onset of SCA7 in South East Asian in comparison with European populations. Interestingly, the authors also identified intermediate alleles at SCA7 locus in controls which was shared among SCA7 families of the same ethnic background. The study also emphasizes the rarity and ethnic specific occurrence of the disorder. The authors further indicated the need for sequence analysis of *ATXN7* in the affected families and intermediate alleles to identify the genetic mechanism that could be implicated in recurrent generation of these intermediate alleles.

India is highly diverse in its population structure with anthropologically well defined 4,635 populations that include 532 tribes along with 72 primitive tribes[16]. These populations differ from one another with respect to their language, social structure, dress and food habits, marriage practices, physical appearance and genetic architecture[16]. Reich *et al*[17] showed the existence of two ancestral groups in the pre-historic India, an 'ancestral North Indian (ANI)', which shared genetic affinity with the populations of the Middle East, Central Asia and Europe (30 - 70%), and an 'ancestral South Indian (ASI)', which had no relation with any population outside India, thus indicating that the present-day Indian populations are the admixture of both ANI and ASI. Governed by various socio-cultural, religious, geographical and linguistic demarcations, Indian population has eventually led to firm endogamy practices which subsequently, along with several evolutionary forces have resulted in higher differences in allele frequency between the groups in India, which has remained intact for thousands of years. The unique genetic diversity in the Indian population has frequently shown surprising results in various association studies. The single nucleotide polymorphisms (SNPs)/ mutations associated with disease among populations of others countries are not usually associated in Indian population[16]. The genetic studies carried out on specific Indian population has pointed towards diverse genetic structure of present-day Indian populations which is mainly due to the social boundaries, strict endogamy practices and evolutionary forces. Thus, obtaining accurate and detailed patient information and the family history from the study population becomes very crucial to the diagnostic process, in order to enable and assist in developing therapeutic and patient management strategies. Further, with respect to SCAs the most effective and widely applicable therapies are likely to be those designed to remove/reduce the production of the mutant protein upstream of these deleterious effects. In view of this, RNA-based approaches are promising therapeutic strategies for polyglutamine diseases, offering the potential to suppress gene expression in a sequence-specific manner both at the transcriptional and post-transcriptional levels[18]. In particular, based on disease-linked polymorphisms or CAG repeat length, the gene silencing therapies capable of discriminating between mutant and wild type alleles prove crucial in cases where a loss of wild type function is deleterious. Novel methods, such as gene knockdown and replacement therapy, might also eliminate the technical difficulties associated with allele-specific silencing by avoiding the need to target specific mutations.

N.B. Ramachandra* & Kusuma L.
Genetics and Genomics Laboratory
Department of Studies in Zoology
University of Mysore, Mysore 570 006,
Karnataka, India
**For correspondence:*
nallurbr@gmail.com
ramachandra@zoology.uni-myosre.ac.in

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