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SCA-LSVD: A Repeat-Oriented Locus-Specific Variation Database for Genotype to Phenotype Correlations in Spinocerebellar Ataxias

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ABSTRACT: Repeat expansion has been implicated in 10 out of 17 candidate genes identified for autosomal dominant cerebellar ataxias (ADCAs)—commonly referred as spinocerebellar ataxias (SCAs). Though genetically distinct, the SCAs share a large number of features that confound their clinical classification. In addition, there is a difference in the prevalence and phenotypic expression of ataxias between different ethnic groups. We have created a new SCA-locus-specific variation database (LSVD) that aims to catalog and integrate information on SCAs associated with trinucleotide repeat expansion (SCA1, SCA 2, SCA 3, SCA 6, SCA 7, SCA 8, SCA 12, SCA 17, Friedreich's ataxia [FRDA], and dentatorubral-pallidoluysian atrophy [DRPLA]) from all over the world. The database has been developed using the Leiden Open (source) Variation Database (LOVD) software (Leiden University Medical Center, Leiden, the Netherlands). The database houses detailed information on clinical features, such as age and symptom at onset, mode of inheritance, and genotype information, pertaining to the SCA patients from more than 400 families across India. All the compiled genotype data conforms to the HGVS Nomenclature guidelines. This would be a very useful starting point for understanding the molecular correlates of phenotypes in ataxia—a multilocus disease in which related molecular mechanisms converge to overlapping phenotypes. The database is accessible online at http://miracle.igib.res.in/ataxia.
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KEY WORDS: SCA-LSVD; variation database; trinucleotide repeats; ataxia

Introduction

Spinocerebellar ataxias (SCAs) are a group of neurodegenerative disorders presenting with progressive cerebellar ataxia and associated subtle signs [Cummings and Zoghbi, 2000]. Nearly 30 loci have been identified to be associated with ataxia, including candidate linkage regions and characterized genes (Table 1). SCAs have been broadly grouped into three categories, as proposed by Harding based on cerebellar ataxia, ophthalmoplegia, and associated clinical symptoms [Harding, 1993; Duenas et al., 2006; Everett and Wood, 2004]. Autosomal dominant cerebellar ataxia (ADCA)-I, a more heterogeneous group that includes SCA1, SCA2, SCA3, SCA4, SCA8, SCA12, SCA13, SCA18-25, SCA27-29, and dentatorubral-pallidoluysian atrophy (DRPLA), presents with pyramidal features, extrapyramidal signs, and amyotrophy [Orr et al., 1993; Imbert et al., 1996; Pulst et al., 1996; Kawaguchi et al., 1994; Flanigan et al., 1996; Koob et al., 1999; Holmes et al., 1999; Waters et al., 2006; Devos et al., 2001; Verbeek et al., 2004; Knight et al., 2004; Vuillaume et al., 2002; Chung et al., 2003; Schelhaas et al., 2004; Swartz et al., 2002; Stevanin et al., 2005; Yu et al., 2005; van Swieten et al., 2003; Cagnoli et al., 2006; Koide et al., 1994]. Additionally, pigmentary retinal degeneration and seizures are observed in ADCA-II (SCA7) and ADCA-IV (SCA10 and SCA17), respectively [David et al., 1997; Matsuura et al., 2000; Nakamura et al., 2001]. Only ADCA-III (SCA6, SCA5, SCA11, SCA14-16, and SCA26) has pure cerebellar syndrome [Zhuchenko et al., 1997; Ikeda et al., 2006; Worth et al., 1999; Chen et al., 2003; Hara et al., 2004; Miyoshi et al., 2001]. In the initial stage of the disease, each of the SCAs to some extent can be clinically distinguished. However, as the disease progresses, there is a significant overlap of clinical features between members of ADCA.

Among the ADCAs, 10 loci have been associated with repeat instability. The repeats of these loci, the majority of which are triplets, especially CNG (N is any nucleotide), are located either in coding or noncoding regions of respective disease genes (Table 1). SCA10 is an exception, in which there is a pentanucleotide repeat expansion in the noncoding (intronic) region of the ATXN10 gene. These repeats become unstable once they cross a particular threshold leading to disease manifestation [Cummings and Zoghbi, 2000; Zoghbi, 2000]. The trinucleotide repeats are polymorphic with respect to both length and interruption pattern in the normal population. However, the extent of polymorphism differs between loci (Table 1). In some cases, there is an overlap between normal and expanded alleles whereas in some there is a transition range between normal and expanded (mutated) alleles, being either unstable normal alleles or premutation alleles [Hellenbroich et al., 2004; Katayama et al., 2000; Matsuura et al., 2006; Nardacchione et al., 1999; Ranum et al., 1999; Rolfs et al., 2003; Zuhlke et al., 2002). The pathological threshold varies depending on whether the repeat is coding or noncoding. In polyglutamine (polyQ) disorders (caused by expansion of CAG

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Table 1. Molecular Characteristics of SCAs

SCA type	Gene	OMIM ID	Chromosome region	Location	Mutation	Normal repeat range			Expanded repeat range		References
						SN	LN	Unstable/mutable	Atypical phenotype[a]	Pathogenic (typical)	
ADCA-I (cerebellar ataxia with ophthalmoplegia ±pyramidal, ± peripheral neuropathy, ± extrapyramidal features)											
SCA1	*ATXN1*	601556	6p22.3	Coding	(CAG)n	6–29	30–35	36–38	39	40–82	Orr et al. [1993]
SCA2	*ATXN2*	601517	12q24.13	Coding	(CAG)n	13–21	22–28	NR	NR	32–200	Imbert et al. [1996]; Pulst et al. [1996]
SCA3	*ATXN3*	607047	14q32.12	Coding	(CAG)n	13–25	26–36	NR	45–53	61–84	Kawaguchi et al. [1994]
SCA8	*ATXN8OS*	603680	13q21	3′UTR	(CTG)n	15–50	NR	NR	71–80	>80	Koob et al. [1999]
SCA12	*PPP2R2B*	604325	5q32	5′UTR	(CAG)n	4–32	NR	NR	40–41	45–78	Holmes et al. [1999]
DRPLA	*ATN1*	607462	12p13.31	Coding	(CAG)n	7–34	NR	NR	NR	49–88	Koide et al. [1994]
ADCA-II (cerebellar ataxia and retinal pigmentary degeneration)											
SCA7	ATXN7	607640	3p14.1	Coding	(CAG)n	4–19	20–28	28–33	34–36	37–306	David et al. [1997]
ADCA-III (pure cerebellar syndrome ± extrapyramidal features)											
SCA6	CACNA1A	601011	19p13.13	Coding	(CAG)n	4–18	NR	NR	19	20–29	Zhuchenko et al. [1997]
ADCA-IV (cerebellar ataxia with seizures)											
SCA10	*ATXN10*	611150	22q13.31	Intronic	(ATTCT)n	10–29	NR	NR	280–370	500–4500	Matsuura et al. [2000]
SCA17	*TBP*	600075	6q27	Coding	(CAG)n	25–39	40–42	NR	43–48	47–63	Nakamura et al. [2001]
Autosomal recessive cerebellar ataxia[b]											
FRDA	*FXN*	606829	9q13	Intronic	(GAA)n	5–11	12–33	34–65	NR	66–1700	Campuzano et al. [1996]

[a]Atypical phenotypes or reduced penetrance alleles are observed with lower abnormal repeats, and their pathogenic potential also depends on the purity of the repeat track.
[b]FRDA is an autosomal recessive ataxia not classified under ADCAs but its causative mutation is hyperexpansion of the (GAA)n allele and it produces a cerebellar phenotype, so it is included in this list and in the database.
SN, small normal; LN, large normal; NR, not reported.

repeats encoding glutamine), the repeat expansions are generally small (30–40 triplets). In SCA6, repeats as small as 20 triplets are sufficient to cause the disease. In contrast, massive expansions of over thousands are observed in the repeats present in the noncoding regions. The relative frequencies of different subtypes of SCAs also vary between populations of different ethnic backgrounds and geographical locations. Though the majority of SCAs are prevalent in most of the studied populations, a few are restricted to specific populations. For example, SCA3/Machado-Joseph Disease (MJD) seems to be the major subtype worldwide, representing more than 70% of the cases in Portugal [Gaspar et al., 2001]. On other hand, DRPLA is mostly reported from Japan [Sasaki, 2007], and SCA12 from India [Bahl et al., 2005; Srivastava et al., 2001]. The prevalence is probably accounted for by regional founder effects, as evidenced through linkage disequilibrium studies using flanking markers at various loci like SCA1, SCA2, SCA3, SCA6, SCA12, DRPLA, and FRAXA in different populations [Bahl et al., 2005; Basu et al., 2000; Chakravarty and Mukherjee, 2002; Choudhry et al., 2001; Cossee et al., 1997; Eichler et al., 1994; Gaspar et al., 2001; Imbert et al., 1996; Mittal et al., 2005a, 2005b; Rubinsztein et al., 1994; Saleem et al., 2000; Terasawa et al., 2004]. In a few ataxias, disease prevalence correlates with the frequency of repeats in the higher range of normal alleles (LNs) and occurrence of stabilizing interruptions in the repeat stretch [Cossee et al., 1997; Takano et al., 1998; Saleem et al., 2000; Mittal et al., 2005b].

Besides differences in prevalence, there is also variation across different ethnic groups in clinical features, which confound clinical classification of SCAs. Heterogeneity in clinical phenotype also indicates the existence of disease-modifying factors in these disorders. It is therefore imperative to develop an integrated database cataloging variations with clinical features of ataxia from different global populations. Over the last 10 years our group has been involved in genetic studies of various hereditary ataxias and has built up the largest resource of ataxia in India. We have reported differences in their prevalence and have also identified founders for various SCAs in the Indian population [Bahl et al., 2005; Choudhry et al., 2001; Mittal et al., 2005a, 2005b; Padiath et al., 2005; Srivastava et al., 2001]. All the ataxias are not prevalent in India (Fig. 1) and their frequencies vary across different ethnic populations of India [Basu et al., 2000; Krishna et al., 2007; Mittal et al., 2005b]. Keeping this objective in mind, we have built a locus-specific variation database (LSVD) for ataxia (named SCA-LSVD), which is specifically focused toward genes that have repeat involvement. We initiated the LSVD activity with the clinical and genetic information on nearly 400 families of ataxia reported from various parts of Northern India of Indo-European origin.

Figure 1. Frequency of different SCAs in the North Indian population. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Data Source and Organization

The database has information on probands of 400 SCA families from the All India Institute of Medical Sciences (AIIMS), a premier tertiary referral center in north India, in which we screened for various SCAs from 1998 to 2007. These samples have been collected following the ethical guidelines of India Council of Medical Research (ICMR) with prior consent of the patients. Screening has been carried out for repeat expansions at SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA12, SCA17, Friedreich's

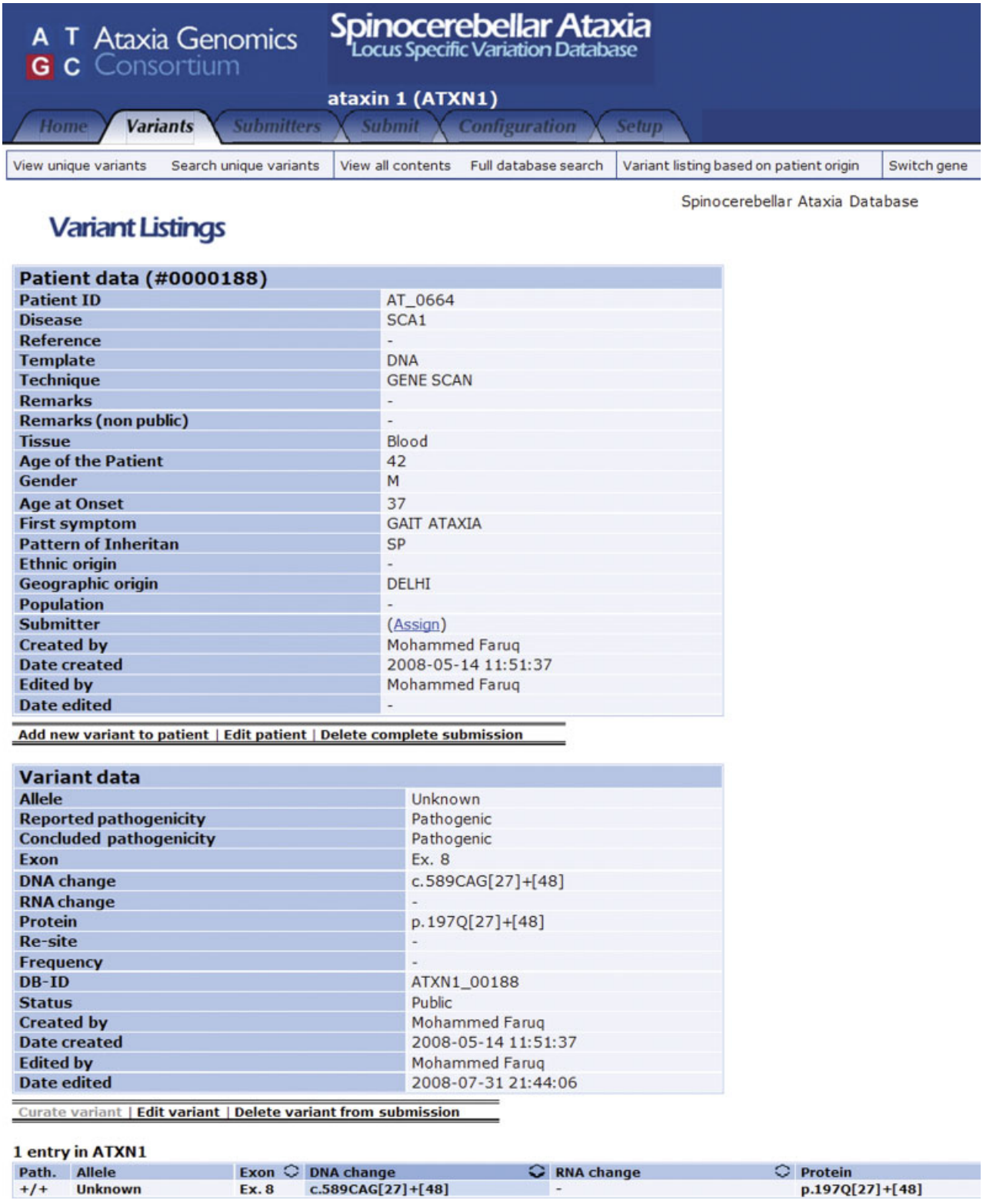

Figure 2. An example of a complete variant listing for an individual patient in SCA-LSVD. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

ataxia (FRDA), and DRPLA in patients and affected and unaffected family members. Repeat sizes were estimated by PCR amplification using fluorescently-labeled primers. The size of the fluorescently-labeled amplicon was determined by GeneScan analysis on an ABI Prism 3130xl Genetic Analyzer (Applied Biosystems [ABI], Foster City, CA). Sequencing was carried out using dideoxy chain terminator chemistry on an ABI Prism 3130 Automated Genetic Analyzer to confirm the repeat size and interruption pattern. The repeat-related data generated for all the probands in eight SCA genes, excluding SCA8 and SCA17, from 400 families is registered in the database. Since FRDA shares clinical features with SCA and is also associated with repeat expansion we have included variations at the FRDA locus in the database. In addition, related phenotypic information, e.g., age gender, age at onset, symptom at onset, mode of inheritance, and ethnic and geographic origin of the patient, for all 400 patients are available for future genotype–phenotype correlation analyses. Genotype data was compiled and transformed according to the HGVS Nomenclature guidelines for reporting genomic variations.

SCA-LSVD

The SCA-LSVD was developed based on the Leiden Open Variation Database (LOVD; Leiden University Medical Center, Leiden, the Netherlands), which is a commonly used tool for organizing locus-centric variation data [Fokkema et al., 2005]. The database is supported on the back end by a MySQL relational database management system. The resource is linked to various other gene databases, which would assist the user to accrue detailed information related to the gene. In addition, plug-ins have been created to export the data to a standard meta-tagged format to aid future integration of data with various resources. This would help the user to have a genome-centered and holistic view of the variation, which would be useful in providing biologically meaningful insights on the variation.

The database (Fig. 2) provides, at each SCA loci, information on gene name, chromosomal location link to the reference sequence, advance search option, variant submission link, and registration guidelines for a new submitter (http://miracle.igib.res.in/ataxia).

Analysis of the Variations in SCA-LSVD

SCA-LSVD currently contains information on genetic testing carried out for repeat-containing loci implicated in SCA pathogenesis in 400 probands of Indian origin. SCA2 is the most represented type, with a frequency of 16%, followed by SCA12 (12%), SCA1 (7%), SCA3 (3%), FRDA (4%), and SCA7 (1%). A total of 57% of both inherited and sporadic cases do not show identifiable expansion at any of the loci. So far we have not observed SCA6, SCA8, SCA17, or DRPLA in our cohort. In SCA1, SCA2, and SCA3, gait ataxia is the most common symptom at onset. For SCA12, hand tremor is the earliest feature of the disease but there are a few cases in which gait ataxia is the presenting symptom, a feature which has not been observed in previous studies [Bahl et al., 2005; Fujigasaki et al., 2001; Holmes et al., 1999; Srivastava et al., 2001].

Future Perspectives

At present, the SCA-LSVD houses data generated in-house. We intend to make it a central database for locus-specific variation information on SCA genes for community participation. We are in the process of curating variations on all ataxia-related genes. In addition, we are working toward making the data interoperable with various genomics databases and workflows, which would allow users to look at the variations from a genomics perspective. We have initiated this by porting the variations as a University of California, Santa Cruz (UCSC; http://genome.ucsc.edu) track and would in the future be integrating this database with other population variation resources such as the Haplotype Map of the Human Genome (International HapMap Project; www.hapmap.org) and the Indian Genome Variation Resources [Indian Genome Variation Consortium, 2008]. We aim to update this database with associated haplotypes in disease gene region, additional microphenotypic information in concordance with the international cooperative ataxia rating scale (ICARS), and data from other research groups working in ataxia. This would facilitate researchers in genotype-to-phenotype (G2P) studies and provide a helpful resource for tracing founder chromosomes and for discovery of novel mutations. SCA-LSVD would also allow cross-comparisons between different cohorts of SCA patients and help in understanding the molecular correlates of phenotypes in ataxia, a multilocus disease that converges to overlapping phenotypes, probably due to related molecular mechanisms.

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