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Autosomal recessive spinocerebellar ataxia 20: Report of a new patient and review of literature

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ABSTRACT

Inherited ataxias are an extremely heterogeneous group of disorders. Autosomal recessive spinocerebellar ataxia 20 (SCAR20) is a recently described disorder characterized by intellectual disability, ataxia, coarse facial features, progressive loss of Purkinje cells in the cerebellum and often hearing loss and skeletal abnormalities. Mutations in the gene *SNX14,* which plays an important role in autophagy, have been found to cause SCAR20. The unique clinical findings of progressive coarsening of facial features makes the clinical phenotype recognizable among the various hereditary ataxias. Here we report on a child with a novel missense mutation in the *SNX14* gene that appears to be debilitating for protein conformation, function and review the previously reported cases from 15 families.

1. Introduction

Autosomal recessive spinocerebellar ataxias are a clinically and genetically heterogeneous group of early-onset disorders associated with cerebellar atrophy or hypoplasia, imbalance and uncoordinated gait. Multisource population based studies have estimated their prevalence at an average 3.3 per 100,000 (Ruano et al., 2014). The common forms of recessive childhood ataxias include Friedreich ataxia, ataxia-telangiectasia, and ataxia oculomotor apraxia. The uncommon forms constitute a highly heterogeneous group of disorders with early onset ataxia as the predominant feature. Intellectual disability is present in more than 60% of these patients (Poretti et al., 2014). The precise molecular etiology has been elucidated in only a small number of these conditions.

Autosomal recessive spinocerebellar ataxia 20 (SCAR20 [MIM 616354]) is a recently described disorder characterized by early onset cerebellar atrophy or hypoplasia, severe ataxia, neurodegeneration due to Purkinje cell loss, coarse facial features, hypotonia, developmental delay and severe intellectual disability caused by loss of function mutations in *SNX14*, encoding for a sorting nexin (Akizu et al., 2015; Sousa et al., 2013; Thomas et al., 2014). The distinct dysmorphism associated with this syndrome makes it a clinically recognizable disorder. SCAR20 is part of an emerging group of conditions with underlying defect in the degradation of intracellular proteins and organelles termed macroautophagy (Ebrahimi-Fakhari et al., 2016).

In the present study we describe a consanguineous Indian family with one child affected with SCAR20. Using exome sequencing we delineated a homozygous missense mutation in *SNX14* coding region as its underlying molecular cause. We discuss our molecular and clinical findings in the light of the previous studies and review the currently known salient features of *SNX14*-linked spinocerebellar ataxia.

2. Clinical report

The proband was evaluated at 6 years and 9 months. She was born at term by lower segment cesarean section to a consanguineously married couple (Fig. 2A). She weighed 3.75 kg (normal) at birth. Global developmental delay was recognized in late infancy. She attained head control at 6 months of age and could crawl at 1

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year and 3 months. She is able to walk with support and has frequent falls. There is no speech till date but is able to comprehend simple commands. There is no history of seizures in her. Behavioral abnormalities particularly aggression were noted in her. At the time of examination her weight was 21 kg (normal), height was 110 cm (normal) and head circumference was 52 cm (normal). Small forehead, thick eyebrows with lateral flaring, telecanthus, broad bridge and base of nose, long philtrum, thick and everted vermillion of the lower lip with small and narrow chin were noted (Fig. 1A). Dental caries were present. She had increased facial and body hair (Fig. 1B and D). Both gait and truncal ataxia were present. Tone and deep tendon reflexes were normal. There were no contractures or laxity. The child has normal hearing. Rest of the systemic examination was unremarkable. Her skeletal radiographs and karyotype did not show any abnormality. Magnetic resonance imaging of the brain revealed cerebellar atrophy with normal brain stem structures (Fig. 1C).

2.1. Chromosomal microarray

Chromosomal microarray revealed no copy number changes. However, large regions of homozygosity were detected on chromosomes 1, 2, 3, 6, 7, 8, 9 and 10.

2.2. Exome sequencing

Genomic DNA was extracted from the whole blood using the standard phenol-chloroform method. Genomic capture was carried out with Illumina's Nextera Rapid Capture Exome Kit. Massively parallel sequencing was done using the NextSeq500 Sequencer (Illumina, Inc., San Diego, CA, USA.) in combination with the NextSeq™ 500 High Output Kit (2 × 150 bp). Raw sequencing reads were subjected to quality control and aligned to the GRCh37 (hg19) build of the human reference genome using bwa software with mem algorithm. The primary alignment files based on GATK best practices recommendation were used for variant calling using three different variant callers (GATK HaplotypeCaller, freebayes and samtools). Variants were annotated using Annovar and in-house *ad hoc* bioinformatics tools. Alignments were visually verified with the Integrative Genomics Viewer v.2.3 and Alamut v.2.4.5 (Interactive Biosoftware, Rouen, France). Variant prioritization was performed without bias with a cascade of filtering steps. A homozygous variant p.E370K (c.1108G > A, NM_153816.5) was identified in the proband in exon 12 of *SNX14*. The variant information is submitted to ClinVar database in NCBI (Submission ID: SUB2086432). It is not present in heterozygous or homozygous state in The Exome Aggregation Consortium (ExAc), 1000 Genomes and Varsome. It is also absent in exomes of 139 unrelated individuals from local population. Further,

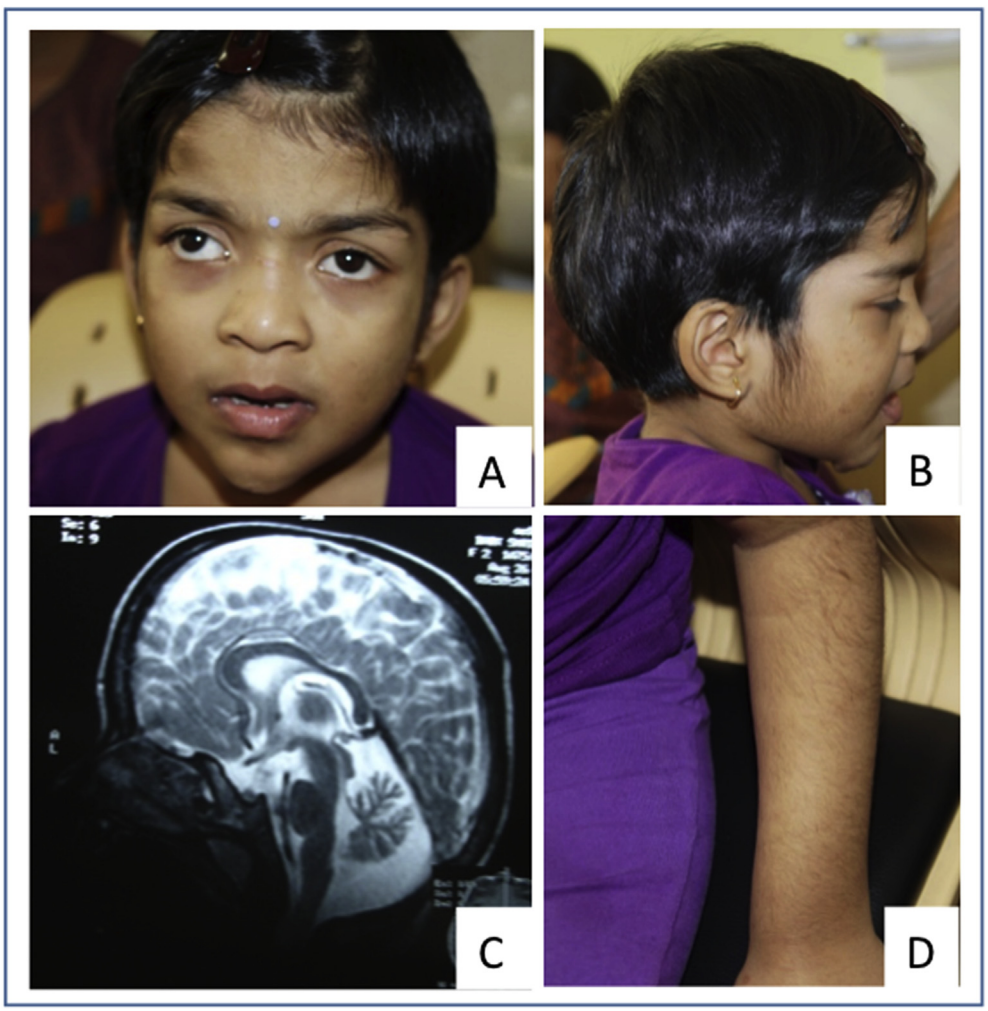

Fig. 1. Subject at age 6 years and nine months. Note the telecanthus, strabismus, puffy eyelids, long and deep philtrum, broad bridge and base of nose, thick vermillions of upper and lower lip, pointed chin (A) and increased facial and body hair (B,D). Magnetic resonance imaging of brain shows cerebellar atrophy with normal brainstem structures (C).

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