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Noted tension headache, anxiety, and depression in a Chinese patient with spinocerebellar ataxia, autosomal recessive 10 caused by a novel anoctamin 10 mutation

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TO THE EDITOR

Spinocerebellar ataxia, autosomal recessive 10 (SCAR10) is a rare neurogenetic disease due to anoctamin 10 (*ANO10*) mutations.[1] Herein, we report a Chinese SCAR10 patient with a novel nonsense mutation site in *ANO10* gene and highlight several infrequent clinical manifestations.

The proband TYP (IV:2; Figure 1A) was a Chinese woman with a primary school diploma, who was born in a consanguineous family (Figure 1A). At age 33, TYP started to present with gradually aggravating slurred speech and vision, limb weakness, dizziness, and tension headache. Within half a year, she went through progressive gait instability and visible tremor when her hand approached the target, and her handwriting got bigger when writing. She experienced tonic–clonic seizures twice. She also complained of recent memory decline, depression and anxiety since age 34. Her headache worsened after treatment with buspirone.

At age 35, TYP was seen in the Memory Clinic of Huashan Hospital. A physical examination showed dysarthria, clumsy hands, intention tremor, dysmetria, finger–nose test (+), Romberg's test (+), drunken gait, binocular horizontal nystagmus, diplopia, bradykinesia, diminished myodynamia (5-), and hyperreflexia. Fasciculation, ankle clonus, pathologic reflex, bowel or bladder dysfunction, pes cavus, and tortuosity of the conjunctival vessels were absent.

She scored 24/30 in Mini-Mental State Examination (MMSE) and 3.7 in Informant Questionnaire on Cognitive Decline in The Elderly, indicating her mild cognitive impairment. Due to poor compliance of the patient, anxiety and depression rating scales were not performed. Electroencephalogram was normal. Magnetic resonance imaging of the brain indicated the presence of cerebellar atrophy (Figure 1B, C).

Sanger sequencing found that she had a homozygous mutation of *ANO10*, a nonsense mutation of c.1213_1215delTTA (p. L405del) (NM_018075). Her mother (III:5; Figure 1A) and her two brothers (IV:4, 5; Figure 1A) were heterozygous carriers (Figure 1D).

Her symptoms did not progress at the time of her visit at the age of 36. Physical examinations showed binocular horizontal nystagmus, finger–nose test (+, on the left more than on the right), Romberg's test (+/–), and difficulty walking in a straight line. She scored 24/30 in MMSE and 19/30 in the Montreal Cognitive Assessment-Basic version.

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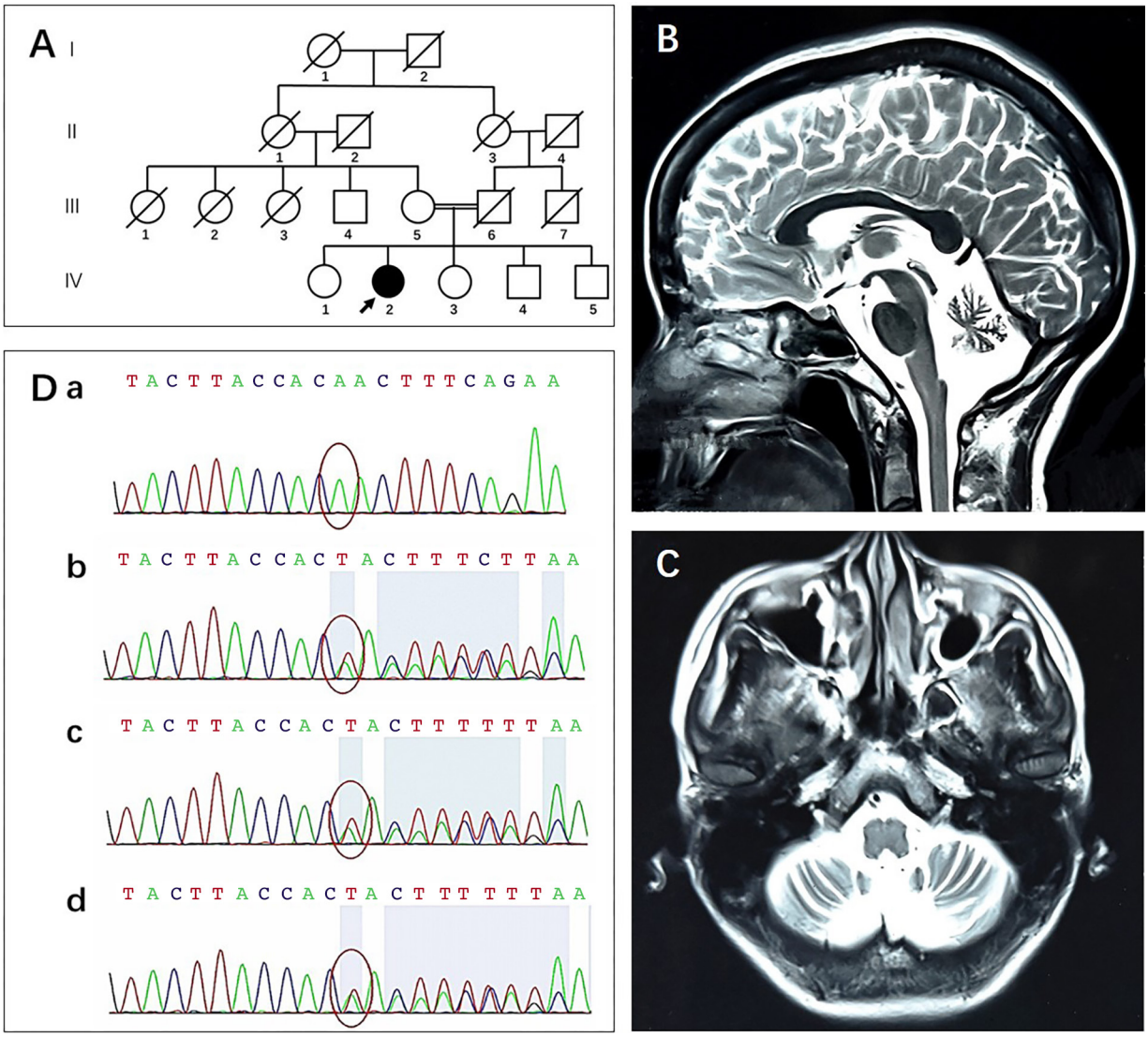

Figure 1: Pedigree, brain MRI, Sanger sequencing. (A) The proband (IV:2, arrow) was born to consanguineous parents (III:5 and III:6). (B and C) Brain MRI shows marked cerebellar atrophy. (D) Red circles indicate the site of mutation. Sanger sequencing confirmed that the proband (IV:2, a) was homozygous for the c.1213_1215delTTA (p. L405del) mutation of *ANO10* and her mother (III:5, b), 28-year-old brother (IV:4, c), and 24-year-old brother (IV:5, d) were heterozygous carriers. MRI: magnetic resonance imaging.

ANO10 spans 2734 bp and consists of 13 exons, 12 of which code 660 amino acid residues. Anoctamin 10, also known as transmembrane protein 16K (TMEM16K), is encoded by *ANO10*. TMEM16K is a member of TMEM16 protein family, in which all members are composed of eight transmembrane domains. TMEM16 proteins are involved in the process of ion transport, phospholipid scrambling, and regulation of other membrane proteins. Research showed that TMEM16K played a role in the process of inositol 1,4,5-triphate receptor 1(IP3R1)-mediated intracellular Ca^{2+} release and regulated Ca^{2+} signaling in Purkinje cells.[2] TMRM16K-knockout mice showed neuromuscular and motor impairment, in line with ataxic phenotypes in SCAR10 patients.[3] c.1213_1215delTTA is a novel deletion variant of *ANO10*, which could lead to the amino acid change of p. L405del. This mutation might contribute to dysregulation of calcium signaling within cerebellar Purkinje cells, which is the most characteristic pathologic mechanism underlying SCAs.[4] Further functional research is needed to reveal the precise mechanism of *ANO10* mutation.

SCAs are a large complex spectrum of inherited neurodegenerative disorders characterized by progressive cerebellar ataxia, extrapyramidal signs, peripheral neuropathy, sphincter disturbances, optic atrophy, ophthalmoplegia, cognitive impairment, and epilepsy. SCAs could be divided into autosomal dominant (SCAD) and autosomal recessive (SCAR) forms according to their inheritance mode. The clinical presentation of

both SCAD and SCAR is heterogeneous in symptoms, signs, age at onset, and disease worsening, depending on the specific mutation and subtype. According to the specific pathogenesis, SCAR could be divided into different subtypes, including Friedreich's ataxia, ataxia telangiectasia, and so on. About 40 subtypes of SCAD are further classified into three groups based on their clinical features.[5,6] Unlike its autosomal dominant counterparts, which typically originate from CAG trinucleotide repeat expansions in the respective genes, SCAR10 is caused by single-nucleotide changes in the surrounding exons of *ANO10*.[7] Overall, genetic screening is recommended for making a definite diagnosis of SCAR10.

SCAR10 is more common in Caucasians than Asians. Based on known cases, the age at onset of SCAR10 patients in China, including this case, ranges from 31 to 39 years. Our patient showed uncommon phenotypes like mild cognitive decline, tonic–clonic seizures, tension headache, depression, and anxiety. Among the other Chinese patients, while most had cognitive impairments, none of them had seizures.[8–10] What is worth noting is that our patient experienced tension headache at the outset, which aggravated after treatment with buspirone. Minnerop *et al.*[11] reported a patient with a homozygous c.132dupA mutation, who initially had tension headache and gradually progressed to ataxia. Her tension headache improved after medication with amitriptyline. Tension headache should be considered when diagnosing SCAR10.

In conclusion, we reported here a novel *ANO10* mutation in a Chinese SCAR10 patient and highlighted several clinical manifestations that improve our understanding of SCAR10 genetically and clinically.

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Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Medical Ethics Committee of Huashan Hospital, Fudan University, Shanghai, China (Approval No. 2011-288). Written informed consent was obtained from the proband and her family.

Conflict of Interest

None declared.

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