Letter to the Editor

Exome sequencing reveals a novel ANO10 mutation in a Japanese patient with autosomal recessive spinocerebellar ataxia

To the Editor:

Spinocerebellar ataxia autosomal recessive type 10 (SCAR10, OMIM 613728) is caused by the mutation of ANO10 (1). The clinical phenotype was characterized by ataxia, hyper-reflexia, normal plantar reflex, downbeat nystagmus and lower motor neuron involvement.

Here, we report a novel ANO10 mutation in a patient with autosomal recessive spinocerebellar ataxia (ARSCA), using exome sequencing. The research procedure was approved by the Ethics Committee of Hiroshima University. All of the examinations were performed after obtaining informed consent from the patient. Control exomes were obtained from patients undergoing exome analysis for diseases other than SCA.

A Japanese patient with cerebellar ataxia born to consanguineous parents had a homozygous nonsense ANO10 (c.609C>G, p.Y203X) mutation. The identified mutation was validated with conventional Sanger sequencing. This mutation was not detected in our control exomes. A 58-year-old man had presented with loss of consciousness at age 42 and was treated with 800 mg of sodium valproate (further information could not be obtained). He had noticed a tendency to fall at age 46 and dysarthria at age 54. However, he continued to satisfactorily function at work. At age of 58, he presented with saccadic eye movement, hyper-reflexia, decreased vibration sense and constipation. Muscle atrophy, nystagmus and tortuosity of the conjunctival vessels were not observed. Electromyography was normal. His Mini-Mental State Examination score was 29. Brain magnetic resonance imaging (MRI) showed mild cerebellar atrophy, and brain stem was slightly atrophic at age 57 (Fig. 1). Single photon emission computed tomography showed a decrease in cerebellar flow.

Previously reported SCAR10 cases have originated from the Netherlands, Serbia and France (1, 2), and this is the first case reported outside Europe. In contrast to our case, previous reported cases also presented muscle atrophy, nystagmus, tortuosity of the conjunctival vessels and intellectual deficit. In addition, in our case, decreased vibration sense and constipation were detected and the age of onset was relatively late. These characteristics should be considered when diagnosing SCAR10. Previously, homozygous missense mutation, homozygous frame-shift mutation and compound heterozygous mutations were reported. Although our case had homozygous nonsense mutation, function of ANO10 protein might be partially retained. ANO10 is expressed at a high level in adults, and ANO10 gene is thought to encode a calcium-activated chloride channel (1). Additionally, an association between the ion channel and epilepsy has been demonstrated. Whether the loss of consciousness in this patient at middle age was due to an abnormality of ANO10 function is unknown. Chamova et al. reported that a brain MRI showed diffuse T2/FLAIR hyperintense and T1 hypointense zones in the cerebellar hemispheres, consistent with gliosis (2). Although our case did not show these features, further follow-up is needed.

ARSCAs are heterogeneous, complex, disabling inherited neurodegenerative diseases that manifest primarily in children and young adults (3). In contrast to autosomal dominant SCAs, which are typically caused by abnormal CAG expansions, most cases of ARSCAs are caused by single-nucleotide changes in all of the surrounding exons, making it much more difficult to screen for the disease with conventional sequencing methods. However, the recent development of new sequencing techniques allows the screening of most exons at one time.
As autosomal recessive disorders appear sporadic when the family size is small, family histories should be carefully recorded. It is also difficult to anticipate the casual gene based on the clinical presentation, particularly in ARSCAs. In these heterogeneous ataxic diseases, exome sequencing is useful for screening causal genes. The prognosis differs according to the subtype of SCA (4) and to the types of mutation even in the same gene (5), the identification of the SCA mutation type is important.

In conclusion, we detected a new ANO10 mutation in a patient with ARSCA by using an exome sequencing technique. Next-generation sequencing can aid in the diagnosis of autosomal recessive SCAs that have been difficult to investigate using conventional methods and will extend the clinical knowledge of these diseases. We believe that more attention should be given to ARSCAs.

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References

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