New Mutations in Neurological Disorders

Title:

An SCA14 family with a novel *PRKCG* mutation

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Spinocerebellar ataxia type 14 (SCA14) is an autosomal dominant neurodegenerative condition characterized by cerebellar ataxia (OMIM #605361) [1-3]. SCA14 families have been reported in many countries including Japan [3]. Although involuntary movements, cognitive dysfunction, depression, and extrapyramidal signs are observed in some SCA14 patients, cerebellar ataxia is the predominant symptom. SCA14 is caused by a mutation in the protein kinase C gamma (***PRKCG***) gene **(RefSeq nm_002739)**. Here, we present a Japanese family with SCA14 caused by a novel ***PRKCG*** mutation.

Case 1 is a 33 year old man (proband), who developed an unsteady gait at 20 years old and deteriorated progressively. He presented to our outpatient clinic at 33 years old. His past history was negative for alcoholism and epilepsy. A neurological examination showed mild cerebellar dysarthria, bilateral gaze nystagmus, ocular overshoot, saccadic pursuit eye movements, cerebellar ataxia of the limbs and trunk, and bilateral equivocal Babinski signs. His gait was ataxic, and tandem

walking was impossible. Involuntary movements were not observed. His muscle tones, limb reflexes, sensory perceptions, autonomic systems, and cognitive function were normal. Brain MRI showed severe atrophy of the cerebellum (Fig. 1A,B).

Case 2 is the 59 year old mother of Case 1. Initially, she just accompanied her son (Case 1) to our hospital, and she was not aware of her symptoms. However, a neurological examination disclosed slight cerebellar dysarthria, saccadic pursuit eye movements, limb and truncal ataxia, and an unstable ataxic gait.

Case 1 and 2 were diagnosed clinically as autosomal dominant cortical cerebellar atrophy. Genetic analysis showed a novel ***PRKCG*** heterozygous mutation (c.**302** A>G, p.H101R) in exon 4 (Fig. 1C). This mutation was not found in the 1000 Genomes Project or the Human Genetic Variation Database, but **was considered pathogenic** by MutationTaster, PROVEAN, and PolyPhen-2. Previously identified mutations of the SCA14 gene converge on exon 4 encoding the C1 domain.

This domain is a binding site for Ca^{2+} and diacylglycerol, which enhance PRKCG enzyme activity and are essential for signal transduction [4]. Therefore, the novel mutation may affect cerebellar function and lead to SCA14.

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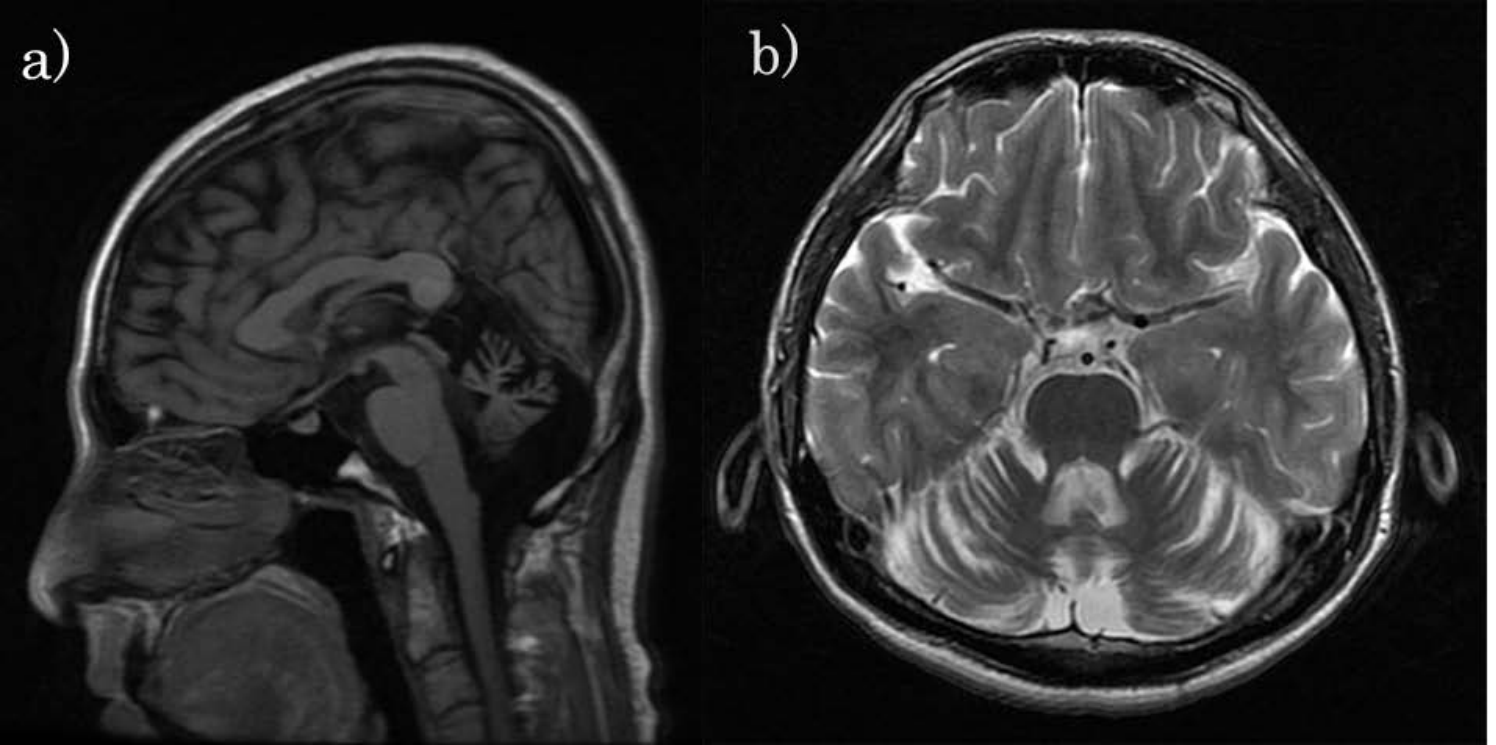
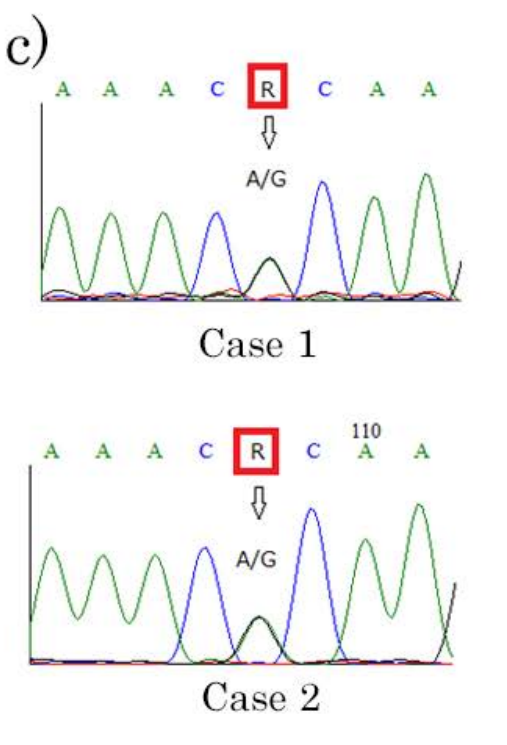
Legends of Figure 1

A and B: Brain MRI of Case 1 (A, T1-weighted image sagittal view, TR=1,966 ms, TE= 21 ms; B, T2-weighted image axial view, TR=4,000 ms, TE= 90 ms). Pure cerebellar atrophy was observed. C: Electropherogram of a heterozygous ***PRKCG*** c.302 A>G (p.H101R) mutation of both patients.


a)
b)


c)
A A A C R C A A
A/G
Case 1
A A A C R C A A
110
A/G
Case 2