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Case Report

A patient with a GNAO1 mutation with decreased spontaneous movements, hypotonia, and dystonic features

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Abstract

We report on a 4-year-old girl with a *de novo GNAO1* mutation who had neurological findings, including decreased spontaneous movements, hypotonia, and dystonic features. She was referred to our hospital because of delayed psychomotor development. She showed hypotonia and decreased spontaneous movements. Voluntary movements of the limbs were more frequent in the lower extremities than in the upper extremities. Occasional dyskinetic features, such as awkward hand/foot posturing and grimacing, were seen during the voluntary movements. Serum metabolic screening, head magnetic resonance imaging, and electroencephalography were unremarkable. Whole-exome sequencing revealed a *de novo* mutation in the patient's *GNAO1* gene, c.709 G > A (p.E237K). We calculated the free-energy change using the FoldX Suite to evaluate the impact of the E237K mutation. The FoldX calculations showed an increased free-energy change in the active state of the GNAO1 protein, indicating that the E237K mutation destabilizes the active state complexes. No seizures, chorea, tremor, or myoclonia, which are frequently reported in patients with *GNAO1* mutations, were observed as of the last follow up. Our patient will improve the understanding of early neurological features in patients with *GNAO1* mutations.

Keywords: GNAO1; Decreased spontaneous movement; Dystonic features; Hypotonia

1. Introduction

The *GNAO1* gene encodes $G\alpha_o$ protein, which is most commonly expressed in the central nervous system. *GNAO1* mutations have been described in patients with epileptic encephalopathy, and some of these patients have had movement disorders, including chorea,

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dystonia, athetosis, and stereotypy [1–5]. Patients with marked movement disorders without epilepsy have also been reported [1,6–14]. Therefore, *GNAO1* mutations are thought to be associated with two distinct phenotypes: epilepsy-related and movement-disorder-related. Feug et al. investigated the genotype–phenotype correlation of *GNAO1* mutations and reported that loss-of-function mutations were associated with the epilepsy-related phenotype, whereas gain-of-function or normal-function mutations were found in patients with movement disorders [6]. We found a *de novo* missense mutation of *GNAO1* in a patient with decreased spontaneous movements, hypotonia, and dystonic features. Here, we report the clinical features and results of a computational analysis of a patient with a *GNAO1* mutation.

2. Patient report

The patient was a 4-year-old girl who was the first child of non-consanguineous healthy parents. Her perinatal course was uneventful. At the age of 6 months, she was referred to our hospital because of developmental delay. The physical examination showed no anomalies, whereas a neurological examination showed truncal hypotonia and reduced spontaneous movement. A diagnostic workup, including serum metabolic screening, electroencephalography, and head magnetic resonance imaging, showed no abnormalities. Array comparative genomic hybridization revealed no pathogenic copy number variants.

Her developmental milestones were markedly delayed. Head control was achieved at 6 months, roll over at 7 months, and sitting with support at 2.5 years. At the last follow up at 4 years and 10 months of age, she could not speak a word but could obey simple verbal directions. She is practicing walking with a walker (Fig. 1). Marked hypotonia and decreased spontaneous movements were remarkable at rest. She could maintain a sitting position but would readily lean backwards. When she was set in a certain posture, she maintained the posture for a while, even when it was uncomfortable (supplemental video 1). Voluntary movements of the limbs were more frequent in the lower extremities than in the upper extremities (Fig. 1 and supplemental video 1). There was a marked reduction in truncal movement when she attempted to touch an object using the lower extremities with her back on the floor or a backrest (Fig. 1 and supplemental video 1). Occasional dyskinetic features such as awkward hand/foot posturing and grimacing were seen during voluntary movement (Fig. 1). No chorea, tremor, or myoclonia was seen. She had

Fig. 1. Photographs of the patient. (A and B) The patient at 4 years, 8 months of age. There was marked hypotonia at rest (A). Truncal hypotonia and awkward hand posturing were observed when she practiced walking with a walker (B). (C and D) The patient at 2 years, 5 months of age. Voluntary movements of the limbs were more frequent in the lower extremities than in the upper extremities (C). The awkward feet posture was remarkable during voluntary lower limb movements (C). The reduction in truncal movement was remarkable when she attempted to touch an object using the lower extremities (D). Informed consent to use these photos was obtained from her parents.

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