A Mild Form of COG5 Defect Showing Early-Childhood-Onset Friedreich’s-Ataxia-Like Phenotypes with Isolated Cerebellar Atrophy

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INTRODUCTION

Hereditary cerebellar ataxias comprise a heterogeneous group of neurodegenerative, metabolic, and genetic disorders (1-4). They are classified based on their pattern of inheritance, and about 50 genes have been identified (1-4). Autosomal dominant cerebellar ataxias are typically observed in patients aged 20–50 years (1-3). During childhood, most of the hereditary cerebellar ataxias are autosomal recessive, X-linked, or mitochondrial (1-4). Autosomal recessive cerebellar ataxias are categorized into three subclasses according to age at onset and coexistence of cerebellar atrophy: ‘Friedreich’s-ataxia-like,’ ‘Friedreich’s-ataxia-like with cerebellar atrophy,’ and ‘early-onset ataxia with cerebellar atrophy (1,2).’ However, assessment of hereditary cerebellar ataxias is confusing, as there are many chemical studies and genes to consider (1-4).

The conserved oligomeric Golgi (COG) complex, which consists of 8 subunits, is an important membrane protein for maintaining the Golgi structure (5,6). It plays a critical role in retrograde vesicular trafficking in the Golgi apparatus (5,6). COG deficiency that is one of the subtypes of congenital disorders of glycosylation (CDG)-II, causes glycosylation defects and other posttranslational modifications of glycoproteins (5,6). In humans, mutations of the genes encoding the COG1 and COG4-COG8 subunits have been reported (5-15). Since the first report in 2009, five mutations of the gene encoding COG5 have been reported in seven patients (11-13). Since the first report in 2009, five mutations of the gene encoding COG5 have been reported in seven patients (11-13). Most of these patients had hypotonia, microcephaly, and developmental delay with or without short stature (11-13). Combined cerebellar atrophy was noted in two unrelated patients (11-13).

The present study identified a novel heterozygous deletion of COG5 in a family with three affected siblings presenting with early-childhood-onset Friedreich’s-ataxia-like phenotypes, isolated cerebellar atrophy, intellectual disability, and scoliosis. However, the patients exhibited normal growth and muscle tone differently from the previous severe cases with homozygous or com-
pound heterozygous mutations of COG5. This finding suggests that variations of COG5 need to be considered in patients with similar early-onset Friedreich’s-ataxia-like phenotypes and isolated cerebellar atrophy.

CASE DESCRIPTION

In January 2013, a girl was admitted to the hospital due to ataxic gait, scoliosis and intellectual disability. In her family, three female siblings including her (proband) showed Friedreich’s-ataxia-like phenotypes with isolated cerebellar atrophy (Fig. 1A). They were born at full term to unrelated healthy parents and their perinatal history was uneventful. Their ataxia was first detected below 2 years of age in all patients. Dysmetria, dysdiadochokinesia, and dysarthria were observed with decreased deep tendon reflex. Scoliosis was detected between 1 and 4 years of age, and developmental slowing was recognized after the first year. All affected patients had mild-to-moderate intellectual disability but had no regression. The height and head growths were normal. No hypotonia, seizures, abnormal movements, ophthalmologic problems, neuronal hearing loss, facial dysmorphism, skin lesions, or abnormalities in the internal organs were observed (Table 1). Brain magnetic resonance imaging (MRI) demonstrated isolated diffuse cerebellar atrophy with enlarged interfolial spaces in a normal-sized cerebellum, although the supratentorial structures of the brain appeared to be normal in

![Family Pedigree and Brain MRI](https://example.com/fig1)

**Fig. 1.** Family pedigree and brain MRI. (A) Family pedigree of the family with early-childhood-onset Friedreich’s-ataxia-like phenotype and isolated cerebellar atrophy. (B) Mid-sagittal T1-weighted brain MRI in patients III-3 and III-4 (proband) showing cerebellar atrophy with enlarged interfolial spaces in the cerebellum. No abnormalities in other parts of brain parenchyma were noted. MRI = magnetic resonance imaging.
all patients (Fig. 1B). Extensive chemical, metabolic, and molecular genetic studies were performed, including a test for the gene encoding frataxin. All other tests except for whole-exome sequencing (WES) failed to establish the causes in this family.

WES was performed for the three affected siblings and their mother using a TruSeq Exome Kit (Illumina Inc., San Diego, CA, USA) on a HiSeq2000 platform (Illumina Inc.). The blood sample from their father was not available. The obtained sequence reads were aligned to the human genome (hg19) using Bowtie 2. Allele frequencies of the known variants were confirmed from multiple databases, including the 1000 Genomes Project, the National Heart, Lung, and Blood Institute Exome Sequencing Project, the Single Nucleotide Polymorphism Database, and the Korean Single Nucleotide Polymorphism Database (400 Korean controls; http://nih.go.kr/NIH_NEW/main.jsp). To prioritize the variants, we established and tested our bioinformatics workflow (Fig. 2A). No potential variant was found under autosomal recessive or compound heterozygous models. Under autosomal dominant model, only one potential variant was left: the bioinformatics pipeline detected a novel heterozygous deletion in exon 12 of COG5 causing a frameshift and premature stop (c.1209delG, NM_181733.2; p.Met403IlefsX3, NP_859422.2). Sanger sequencing reverified the presence of the COG5 variation only in the patients (Fig. 2B).

To assess the expression of COG5, Western blotting of the COG5 protein was performed. The skin tissues from the affected proband and a healthy control were disrupted in liquid nitrogen with a mortar and pestle, and the proteins were extracted. Western blotting of COG5 proteins was performed using an anti-COG5 antibody (ab90301, Abcam, USA). Although a single band with a COG5 protein of about 90 kDa was detected by Western blotting of normal skin tissue as reported previously (11), two bands — one of the same size (about 90 kDa) and one smaller (about 40 kDa) — were detected in the affected proband. The intensity of the 90-kDa band in the affected proband appeared to be significantly decreased compared to that in the normal healthy control (Fig. 2C).

As there is no fundamental or curative treatment for COG5 defect, the patients were supportively treated for their scoliosis by an orthopedic surgeon.

**Ethics statement**

This study was approved by the Human Research Ethics Committee of Chonnam National University Hospital (IRB No. CNUH-2014-179). Informed consent to participate was obtained from the mother of the affected siblings. The biospecimens were provided by the Chonnam National University Hospital Biomedical Research Institute Biobank with informed consent, under Institutional Review Board-approved protocols.

**DISCUSSION**

Using the traditional classification, CDG can be subdivided into two types: CDG-I and CDG-II (5,6). CDG-I affects the addition of glycans to proteins and CDG-II affects processing of the protein-bound N-glycans (5,6). CDG-I results only in an N-glycosylation defect, while CDG-II causes a combined N- and O-glycosylation defect (5,6). CDG can be screened with isoelectric focusing of N- or O-glycosylated proteins such as serum transferrin or apolipoprotein CIII, respectively (5,6). However, isoelectric focusing is available only in some specialized clinical centers, usually takes a long time and its sensitivity and specificity are unreliable (6). Moreover, transferrin glycan analysis reveals a nonspecific pattern in most patients with the CDG-II, in contrast to those with the CDG-I (6). Due to this limitation of screening tests for CDG-II, Western blotting or genetic analysis

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**Table 1. Clinical features and radiologic findings of the patients**

| Features and findings | III-2 | III-3 | III-4 (proband) |
|-----------------------|-------|-------|-----------------|
| Gender                | Female| Female| Female          |
| Age, yr               | 25    | 18    | 14              |
| Progressive ataxia: age at detection, yr | <2   | <2   | 1–2            |
| Other neurologic signs| Data not available | Dysarthria, dysmetria, dysdiadochokinesia, decreased deep tendon reflex | Dysarthria, dysmetria, dysdiadochokinesia, decreased deep tendon reflex |
| Scoliosis: age at detection, yr | 2    | 4    | 1              |
| Involvement of other organs | No  | No   | No             |
| Echocardiography      | Data not available | Normal (at 10 yr) | Normal (at 13 yr) |
| Developmental slowing: age at onset, yr | <1   | <1   | <1             |
| Intellectual disability| Moderate| Mild | Mild           |
| Brain MRI             | Normal (at 2 yr) → diffuse isolated cerebellar atrophy (at 18 yr) | Diffuse isolated cerebellar atrophy (at 10 yr) | Diffuse isolated cerebellar atrophy (at 12 yr) |
| Spine MRI             | Data not available | Data not available | No abnormality in spinal cord (at 12 yr) |
| Array CGH*            | Data not available | Data not available | 46, XX, inv(9)(p12q13), arr[hg18] (1-22), X;21 |
| Test for FXN mutations| No abnormalities | Data not available |

MRI = magnetic resonance imaging, CGH = comparative genome hybridization, FXN = the gene encoding frataxin.

*Array CGH was performed with the Roche NimbleGen CGX-3 135K whole-genome array. *Pericentromic inversions of chromosome 9 have been reported in some normal populations.
of COG subunits in suspected patients with COG deficiency is recommended (5,6,8-10). WES can be an alternative useful diagnostic method in CDG-II or COG deficiency, as it can screen for diverse variants simultaneously and rapidly with only small amounts of blood. Deficiencies in COG subunits have been reported in patients with developmental delay, intellectual disability, growth failure, hypotonia, dysmorphic features, cerebral or cerebellar abnor-
malities, and feeding problems (5-15). The most commonly reported defective subunit in humans is COG7, followed by COG5 (5-8,11-13). Although the clinical features are not easy to delineate in small numbers of patients, the phenotypes appear to differ between the different defective subunits (5-15). Most patients with COG7 defects died below 1 year of age, and had severe intellectual disability, growth retardation, facial dysmorphism, hyperthermia, and congenital defects of multiple internal organs (5-8). However, the patients with the other COG subunit defects showed lower mortality rates (5,6,9-15).

All seven previously reported patients with COG5 mutations had hypotonia, developmental delay and intellectual disability (11-13). Six of them had moderate-to-severe intellectual disability; all six had microcephaly and five had short stature (11-13). Only one patient with mild intellectual disability exhibited normal head and height growth (13). Two patients presented with deafness and blindness and one of them had convulsions (13). Brain MRI findings were abnormal in two patients: the one patient had global cerebral and cerebellar atrophy (13), while the other patient had diffuse cerebellar and brainstem atrophy (11). Neurogenic bladder was present in two patients (13). Contracture was noted in one patient (12). Most of the patients with COG5 mutations were from consanguineous parents and had homozygous or compound heterozygous mutations (11-13).

Based on the previous diagnostic algorithm for childhood ataxia, recessive cerebellar ataxias were initially suspected in the family described herein, such as ataxia telangiectasia, infantele-onset spinocerebellar ataxia, or Friedreich’s ataxia (1-4). Prior to the WES study in this family, COG5 deficiency was difficult to suspect initially because the patients had no hypotonia, microcephaly, or short stature (5-15). The mild phenotypes in the present family might be due to the heterogeneous deletion involving only one allele, although a novel heterozygous deletion of COG5 (c.1209delG) resulted in a premature stop (p.Met-403IlefsX3) causing a smaller, aberrant COG5 protein and a reduction in normal COG5 expression. Isolated cerebellar atrophy in this report is also rare radiologic finding in either of COG5 deficiency or early-childhood-onset cerebellar atrophy (4,11,13). Associated cerebral abnormalities or abnormal signal changes in the cerebellum are reported frequently (4,11,13). Although this type of cerebellar ataxia is not common, COG5 mutational analysis need to be considered in suitable patients showing early-childhood-onset Friedreich’s-ataxia-like phenotypes and isolated cerebellar atrophy.

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DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceptualization: Kim YO. Data curation: Kim YO, Choi SM, Kim SK, Yoon W, Woo YJ. Formal analysis: Kim YO, Park C, Hong Y. Funding acquisition: Kim YO. Investigation: Kim YO, Yun M, Jeong JH, Park C, Hong Y. Writing - original draft: Kim YO. Writing - review & editing: Kim YO, Kim SK, Park C, Hong Y, Woo YJ.

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REFERENCES

1. Ashley CN, Hoang KD, Lynch DR, Perlman SL, Maria BL. Childhood ataxia: clinical features, pathogenesis, key unanswered questions, and future directions. J Child Neurol 2012; 27: 1095-120.
2. Fogel BL, Perlman S. Clinical features and molecular genetics of autosomal recessive cerebellar ataxias. Lancet Neurol 2007; 6: 245-57.
3. Brusse E, Maat-Kievit JA, van Swieten JC. Diagnosis and management of early- and late-onset cerebellar ataxia. Clin Genet 2007; 71: 12-24.
4. Poretti A, Wolf NJ, Bolshusaha E. Differential diagnosis of cerebellar atrophy in childhood. Eur J Paediatr Neurol 2008; 12: 155-67.
5. Zeevaert R, Foulquier F, Jaeken I, Matthijs G. Deficiencies in subunits of the Conserved Oligomeric Golgi (COG) complex define a novel group of Congenital Disorders of Glycosylation. Mol Genet Metab 2008; 93: 15-21.
6. Jaeken J. Congenital disorders of glycosylation (CDG): it’s (nearly) all in it! J Inherit Metab Dis 2011; 34: 853-8.
7. Wu X, Steet RA, Bohonov O, Bakker J, Newell J, Kröger M, Spaapen L, Kroeff S, Freeze HH. Mutation of the COG complex subunit gene COG7 causes a lethal congenital disorder. Nat Med 2004; 10: 518-23.
8. Morava E, Zeevaert R, Korsch E, Huijben K, Wopereis S, Matthijs G, Keymolken K, Lefebvre DJ, De Meirleir L, Wevers RA. A common mutation in the COG7 gene with a consistent phenotype including microcephaly, aducted thumbs, growth retardation, VSD and episodes of hyperthermia. Eur J Hum Genet 2007; 15: 638-45.
9. Foulquier F, Vasile E, Schollen E, Callewaert N, Raemaekers T, Quelhas D, Jaeken J, Mills P, Winchester B, Kröger M, et al. Conserved oligomeric Golgi complex subunit 1 deficiency reveals a previously uncharacterized con-
genital disorder of glycosylation type II. Proc Natl Acad Sci U S A 2006; 103: 3764-9.

10. Foulquier F, Ungar D, Reynders E, Zeevaert R, Mills P, Garcia-Silva MT, Briones P, Winchester B, Morelle W, Krieger M, et al. A new inborn error of glycosylation due to a Cog8 deficiency reveals a critical role for the Cog1-Cog8 interaction in COG complex formation. Hum Mol Genet 2007; 16: 717-30.

11. Paesold-Burda P, Maag C, Troxler H, Foulquier F, Kleinert P, Schnabel S, Baumgartner M, Hennet T. Deficiency in COG5 causes a moderate form of congenital disorders of glycosylation. Hum Mol Genet 2009; 18: 4350-6.

12. Fung CW, Matthijs G, Sturiale L, Garozzo D, Wong KY, Wong R, Wong V, Jaeken J. COG5-CDG with a mild neurohepatic presentation. JIMD Rep 2012; 3: 67-70.

13. Rymen D, Keldermans L, Race V, Régal L, Deconinck N, Dionisi-Vici C, Fung CW, Sturiale L, Rosnoberlet C, Foulquier F, et al. COG5-CDG: expanding the clinical spectrum. Orphanet J Rare Dis 2012; 7: 94.

14. Reynders E, Foulquier F, Leão Teles E, Quelhas D, Morelle W, Rabouille C, Annaert W, Matthijs G. Golgi function and dysfunction in the first COG4-deficient CDG type II patient. Hum Mol Genet 2009; 18: 3244-56.

15. Shaheen R, Ansari S, Alshammari MJ, Alkhalihi H, Alrukban H, Eyaid W, Alkuraya FS. A novel syndrome of hypohidrosis and intellectual disability is linked to COG6 deficiency. J Med Genet 2013; 50: 431-6.