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Short Communication

Novel mutation of *COG5* in a Taiwanese girl with congenital disorders of glycosylation manifesting as developmental delay

Yu-Chi Wang [a,b], Dau-Ming Niu [a,b], Li-Zhen Chen [a], Yun-Ru Chen [a,1], Chia-Feng Yang [a,b,*,1]

[a] Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan
[b] School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

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ABSTRACT

We are documenting the case of An 11-year-old girl who has been followed up at our out-patient clinic since birth with clinical presentations including intrauterine growth restriction, recurrent periodic fever in infancy, hypotonia, global developmental delay, liver function impairment with cirrhotic changes, and clinodactyly. Congenital abnormalities were suspected but a series of examinations including brain MRI, liver biopsy and muscle biopsy yielded insignificant findings. Whole genome sequencing (WGS) was conducted and revealed three novel mutations (c2T > G, c1826T > C, c.556–560delAGTAAinsCT) of the *COG5* gene. A diagnosis of COG5-congenital disorders of glycosylation (COG5-CDG, or CDG IIi), with neurologic presentation was established. Sanger sequencing in the patient and her parents confirmed the compound heterozygous mutation. Upon literature review, we identified the patient as the first case of COG5-CDG in Taiwan. Our study enhances the clarity of the correlation between the mutative genes and the presentation of COG5-CDG.

1. Introduction

In humans, glycosylation of proteins through the Endoplasmic Reticulum (ER) and Golgi apparatus is a crucial post-translational modification. This process where sugar and lipids attach to proteins thereby forming glycoproteins, plays a vital role in cell metabolism. Congenital Disorders of Glycosylation (CDG) encompass a spectrum of heterogenous diseases, in which abnormalities can occur at various stages of glycosylation [1]. One example of the numerous tethering complexes implicated in some CDG cases is The Conserved Oligomeric Golgi (COG) complex, consisting of eight subunits (COG1, COG2, etc.), which functions in the retrograde trafficking of Golgi components and plays a role in the localization of Golgi glycotransferase [2]. COG deficiency leads to glycosylation defects, resulting in multi-organ abnormalities and clinical symptomsamong patients. Our study presents the case of an 11-year-old girl with diffuse hypotonia, liver impairment and developmental delay who was diagnosed with COG5-CDG through Whole Genome Sequencing.

2. Method

The girl's medical records, family history and clinical presentations were collected comprehensively. We obtained the patient's blood sample for DNA extraction and analysis. After library preparation, KAPA HyperPrep Kits was used for hybridization and capture. Illumina NovaSeq6000 instrument was used for DNA fragments amplification and sequencing. We trimmed Low-quality bases (Q < 30) and aligned sequence data with DRAGEN (SW:05.021.595.3.7.5). Variant sites were searched based on human reference genome hg38 and annotated using the Variant Effect Predictor (v101) and Jannovar (0.35). The Human Phenotype Ontology and Online Mendelian Inheritance in Man (OMIM) databases were searched to identify genes associated with the patient's phenotypes. We used Clinvar and the common variant database (dbSNP version 150 and Taiwan BioBank) to filter out common diseases. Softwares, such as SIFT and PolyPhen-2 were used to predict protein structure changes. The variants were interpreted following the ACMG/AMP 2015 guidelines. Aditionally, we conducted a trio study with Sanger sequencing for the patient and her parents. The study was conducted following the acquisition of parental informed consent forms, accompanied by a comprehensive explanation of the study's objectives

* Corresponding author at: Department of Pediatrics, Taipei Veterans General Hospital, No.201, Sec. 2, Shipai Rd. Beitou Dist., Taipei 11217, Taiwan.
E-mail address: pum_chia@yahoo.com.tw (C.-F. Yang).
[1] Contributed equally: Yun-Ru Chen and Chia-Feng Yang

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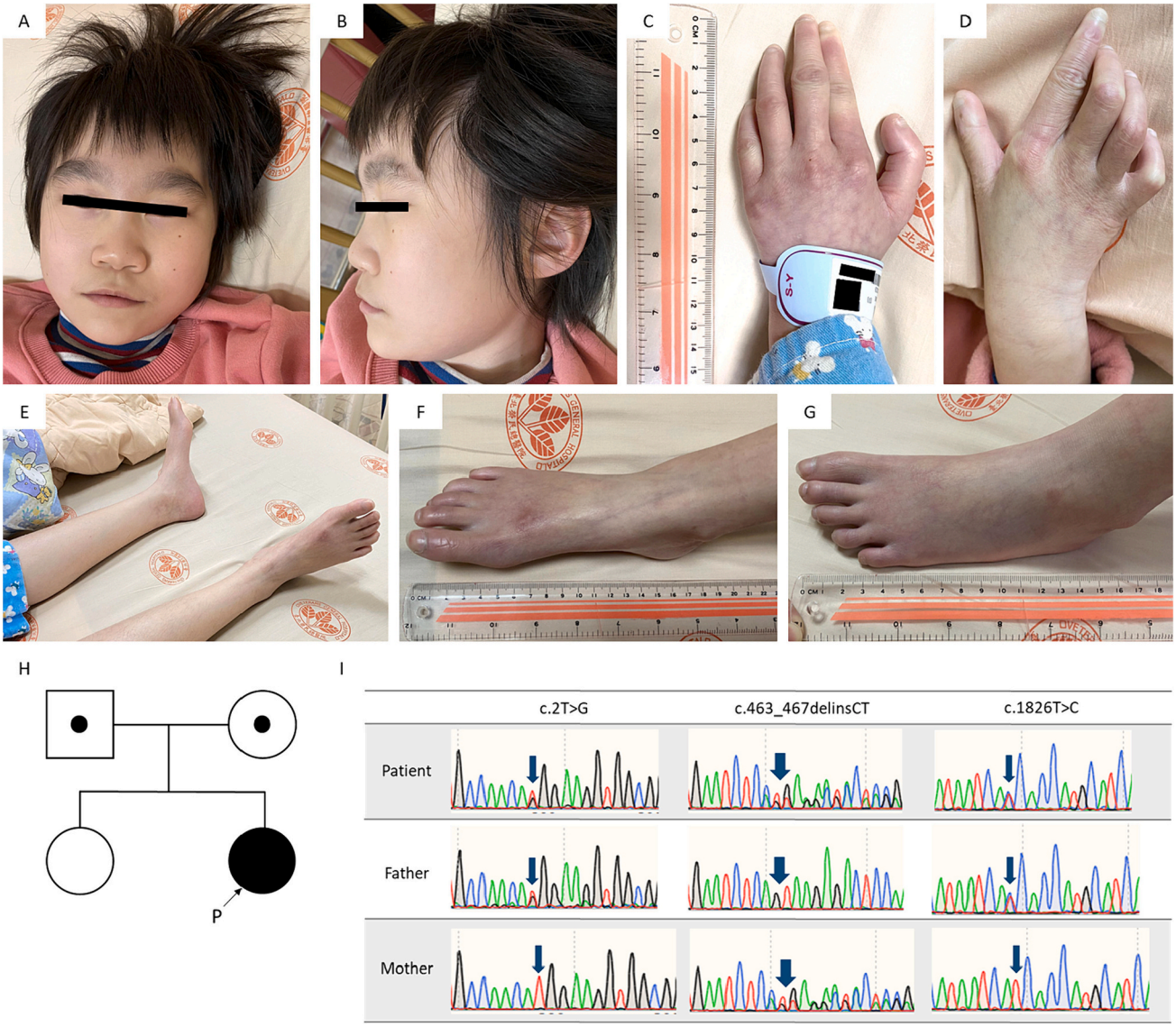

Fig. 1. Photos of the patient and analysis of the genetic data
A. Front photograph of the patient.
B. Left side photograph of the patient.
C. Left hand photograph of the patient.
D. Right hand photograph of the patient.
E. Photograph of the patient's feet.
F. Right foot photograph of the patient.
G. Left foot photograph of the patient.
H. Pedigree of the patient.
I. Sanger sequencing of the patient and her parents.

and procedures. All collected information was de-identified. The corresponding author has complete access to all the data and assumes the ultimate responsibility for the decision to submit the data for publication. The study was supported by the Ministry of Science and Technology, Taiwan [Grant Number: 112–2628-B-075-002]; Taipei Veterans General Hospital [Grant Number: V112C-046]. The research protocol was approved by the Taipei Veterans General Hospital (TVGH) Institutional Review Board (TVGH-2018-09-006 A), a full explanation of the study aims and procedures was provided, and informed consent was obtained from parents.

3. Results

The patient's medical records revealed a birth history of intrauterine growth restriction (IUGR). She presented to our out-patient department at 14 months old due to recurrent fever without a definite infectious focus. The fever, reaching up to 39 degrees Celsius, occurred three times in one week without associated symptoms. Physical examination revealed livedo reticularis on all four limbs, diffuse hypotonia, especially weakness in the upper limbs, clinodactyly of both hands (Fig. 1C&D) and mild inverted nipples. Laboratory analysis showed elevated liver enzymes (ALT 100 U/L, reference values [r.v.] are 0–32.0 U/L). General hypotonia and developmental delay were noticed since birth. She couldn't hold her head up until 9 months old and could barely sit unassisted by 11 months of age. Therapists was consulted and the Bayley Scales of Infant Development Index reported scores below 70. A pediatric infectious disease specialist was consulted but no specific pathogens were found. Abdominal sonogram images showed coarsening

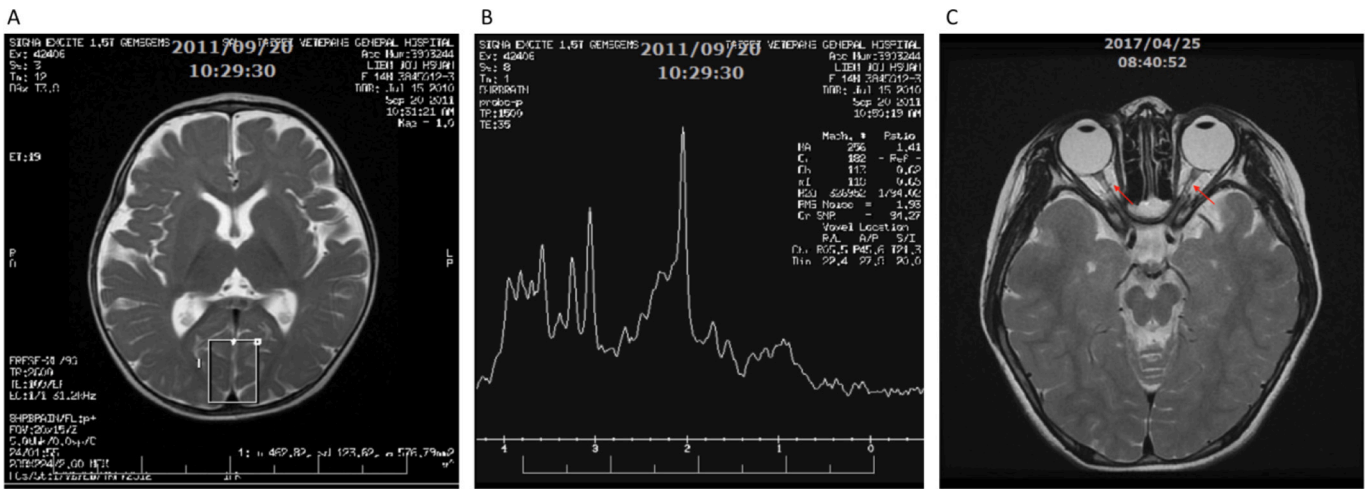

Fig. 2. Magnetic Resonance Imaging of Brain of the patient.
A&B. Magnetic Resonance Spectroscopy done when the patient was 14 months old showed some degree of demyelinating process in the white matter and presence of gliosis could not be excluded.
C. Magnetic Resonance Imaging of Brain followed up when the patient was 6 years and 9 months old showed bilateral smaller optic tracts, indicating congenital hypoplasia.

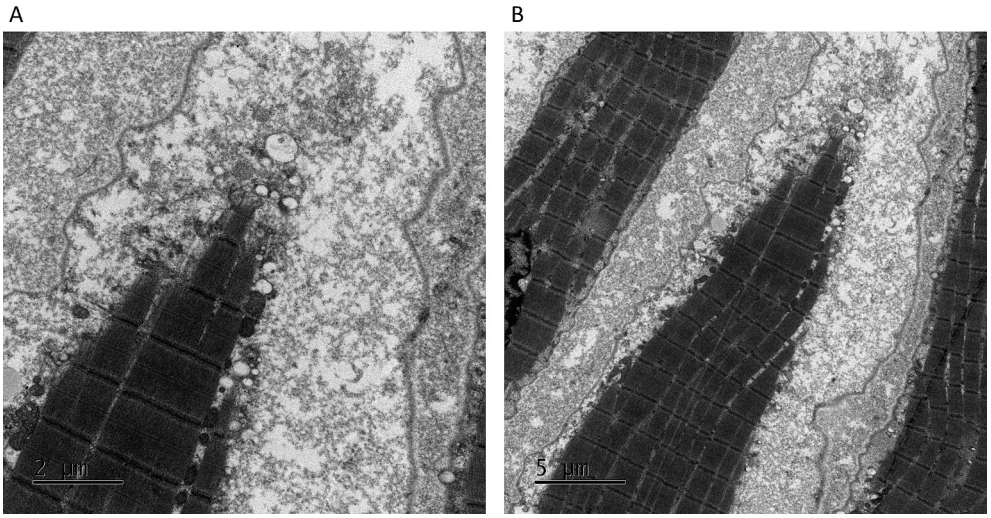

Fig. 3. Electron microscopic images of the patient's muscle biopsy.
A&B. Muscle biopsy done when the patient was 16 months old, showed the vesicles full of glycogens aggregate in the cytoplasm of the skeletal muscle cells.

echogenicity of the liver. Magnetic Resonance Imaging (MRI) of the brain indicated a normal degree of myelination and no abnormal signal changes were identified in the brain parenchyma. From these results, a demyelinating process in the white matter and gliosis could not be excluded (Fig. 2A&B). Suspicious of congenital disorders of glycosylation, a serum transferrin isoelectric focusing (IEF) test was performed, but it reported a negative result. Muscle biopsy for hypotonia showed focal mild pooling of glycogen (Fig. 3). Gaucher disease was suspected but serum glucocerebrosidase levels were within normal range.

During the patient's preschool years, her liver enzymes remained mildly elevated (ALT 61 U/L, AST 101 U/L). Abdominal sonograms continued to show coarsening echogenicity of liver parenchyma. Liver biopsy confirmed cirrhosis when the patient was 4-years and 8 months old. Ursodeoxycholic acid was prescribed, and the liver enzymes gradually normalized. Ophthalmology assessments reported strabismus, pallor optic disc and suspected optic neuropathy. Brain MRI revealed bilateral smaller optic tracts, indicating congenital hypoplasia (Fig. 2C). Developmentally, the patient exhibited slow movements in walking and jogging. Her oral responses during conversation were sluggish but the content was appropriate. According to the patient's father, she maintained a nearly normal social life with peers at school. The family history did not reveal any relevant findings, except the father also had strabismus but did not present with hypotonia, developmental delay, liver function impairment or other disabilities.

In 2021 on the fifth of August, WGS was conducted, and three mutative alleles were identified on the gene *COG5*. Firstly, a point mutation in NM_001161520.2:c2T > G caused a start-loss mutation, classified as a pathogenic variant in Clinvar database and ACMG/AMP 2015 guideline. Secondly, another base change (NM_001161520.2:c1826T > C) was found, which was reported uncertain significance. Thirdly, an inframe deletion and insertion (NM_001161520.2:c.463_467delAGTAAinsCT) was observed, leading to a frameshift mutation categorized as pathogenic in Clinvar database and likely-pathogenic in ACMG/AMP 2015 guideline. Sanger sequencing of the *COG5* gene was conducted on the patient and her parents. The mother's test results disclosed the patient inherited the inframe deletion and insertion variant (NM_001161520.2:c.463_467delAGTAAinsCT) from maternal origin. On the other hand, the other 2 mutations,

NM_001161520.2:c1826T > C and NM_001161520.2:c2T > G, were inherited from the patient's father (Fig. 1H&I). These compound heterozygous variants were identified and can attribute to the phenotype of COG5-CDG.

4. Discussion

To the best of our knowledge, our study describes the first case of COG5-CDG in Taiwan with the discovery of three novel mutations. Traditionally, based on the different pathologic pathway, CDG is categorized into 2 different types. CDG-I results from defects in the assembly of the dolichol-pyrophosphate-linked oligosaccharide chain, while CDG-II involves errors in the modification and trafficking of the protein-bound oligosaccharide chain [3]. Nowadays, >160 mutative genes have been found to be associated with CDG, allowing each type of CDG to be defined and named after specific genes. In our patient, the genetic defects are located in the *COG5* gene, which encodes COG5, one of the eight subunits comprising the COG complex. The COG complex functions as bridging the coat protein complex I (COPI) vesicles and Golgi membranes. Dysfunctional COG results in the abnormal distribution of SNARE proteins, Golgin and other enzymes and complexes participating in the process of glycosylation [4]. Any mutation leading to COG dysfunction can cause CDG. As summarized by Leslie et al. (Frontiers in Neuroscience, 2015), there are CDG with defects of COG1, 2, 4, 5, 6, 7, 8 causing variable abnormalities in morphology, neurology, motor function, ophthalmology and hepatic function.

The most severe cases, as reported by Rymen et al. [5], exhibit severe global developmental delay, spastic quadriplegia, scoliosis and neurogenic bladder. In their study, all six patients diagnosed with COG5-CDG presented with global developmental delay, hypotonia, consistent with our patient's clinical symptoms in variable severity. One of the six patients is a Chinese girl who was described by C.W. Fung [6]. The girl's mutation variants on *COG5* were c.556–560delAGTAAinsCT (from maternal origin) and c.1856 T > C (p.I619T) (from paternal origin), which are very similar with our patient. She shared nearly identical clinical symptoms with our patient, including hypotonia, global developmental delay, fixed flexion contracture of all fingers, liver nodules with impaired function, mild thrombocytopenia and splenomegaly. Another case described by Wang et al. [7], also presented similar symptoms. In our patient, the variant c.1826 T > C was found to have an incidence of 2.66% based on the Clinvar database and ACMG 2015 guidelines and was reported as benign and uncertain clinical significance. It seems that the variant c.463_467delAGTAAinsCT plays a more crucial role in the pathogenic process, along with the known pathogenic variant c.2 T > G in our patient.

There remain limitations to our study. According to medical records, the patient's blood sample had been sent to a laboratory outside of our hospital for the examination of Isoelectrofocusing (IEF) of serum transferrin >10 years ago. Traditionally, serum IEF is a crucial tool used to differentiate CDG-I between CDG-II when a patient is suspected of having CDG. The test was reported negative at that time, resulting in a delayed diagnosis. After 10 years of follow-up and with advancements in Next Generational Sequencing, the patient was finally diagnosed by means of WGS.

5. Conclusion

Our study describes a case of COG5-CDG characterized by mild neurodevelopmental symptoms diagnosed through WGS. The mutative variants c.556–560delAGTAAinsCT and c.2 T > G appear to play crucial roles in the pathogenesis of COG5-CDG. Further investigation is necessary in the future to explore potential treatments for patients with CDG.

CRediT authorship contribution statement

Yu-Chi Wang: Data curation, Writing – original draft, Writing – review & editing, Formal analysis, Visualization. **Dau-Ming Niu:** Investigation, Methodology, Resources, Supervision, Conceptualization. **Li-Zhen Chen:** Data curation, Visualization, Writing – review & editing, Formal analysis. **Yun-Ru Chen:** Formal analysis, Methodology, Visualization, Writing – original draft, Software. **Chia-Feng Yang:** Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Writing – review & editing.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to eliminate possible grammatical or spelling errors. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

There are no conflicts of interest to disclose.

Data availability

In order to protect patient's personal privacy, research data would remain confidential and would not be shared.

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