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BRIEF COMMUNICATION

Compound heterozygous variants in *MOGS* inducing congenital disorders of glycosylation (CDG) IIb

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Abstract

This study is to present two Chinese siblings who were diagnosed with congenital disorders of glycosylation (CDG) IIb because of mannosyl-oligosaccharide glucosidase (MOGS) deficiency. The siblings visited our hospital due to "pulmonary infection". Facial dysmorphism including long eyelashes, blepharophimosis, depressed nasal bridge, and high palate was noted. Head MRI of the elder sister showed increased signals on T1W1, bilateral frontal gyrus stenosis, and thin corpus callosum. Both cases presented progressive hepatomegaly and elevated hepatic enzymes. Low immunoglobulin was discovered in the siblings. Compound heterozygous variants of NM_006302:c.1239_1267dup,p.Asp414Leufs*17, c.544 G > A,p.Gly182Arg, and c.1698C > A,p.Asp566Glu in *MOGS* were identified. Structural modeling demonstrated that the mutations were pathogenic to MOGS. Our study enriched the genetic and phenotypic spectrum of MOGS-CDG, and for children with facial dysmorphism, postnatal dyspnea, seizures, motor developmental delay, hypotonia, and immunological or gastrointestinal dysfunction, this disease should be highly suspected.

Introduction

Congenital disorders of glycosylation (CDG) are a group of genetic diseases due to defects in synthesis, processing, or transport of glycoconjugates [1]. CDG could be divided into two groups: Group I refer to limitations that alter the synthesis and transfer of precursor oligosaccharide, while Group II affect subsequent processing steps [2]. CDG are highly heterogeneous and could influence multiple organs in varying degrees [3, 4]. Mannosyl-oligosaccharide glucosidase (MOGS) is firstly defined to be associated with the occurrence of CDG IIb (OMIM:606056) [5], which is also known as MOGS-CDG. To date, a total of four individuals with MOGS-CDG are reported [5–8]. We herein present two siblings with MOGS-CDG so as to expand the clinical and genetic spectrum of this disease.

Case presentation

This study was approved by the ethics committee of Anhui Provincial Children's Hospital. Informed consent was received from the parents prior to the study. The elder sister initially presented at 4 months and 21 days of age with hypopnea on May 2015 (Table 1, Supplementary 1A). Sensory neural hearing was revealed. Her liver was palpable 3.0 cm under the subcostal margin. Bilateral inguinal hernia was noted. Blood biochemistry examination results indicated metabolic disorders, low blood sugar, electrolyte disturbance, and impaired liver and myocardial function. Food intolerance test was positive. Thyroid ultrasound detection result was normal, however, thyroid function test revealed central hypothyroidism. Anterior pituitary showed an increased signal on T1W1 by head MRI (Fig. 1a–c).

The younger sister was admitted on Feb 2018 when she was 3 months old. Slightly narrowed forehead, short

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Table 1 Clinical characteristics of patients reported to have MOGS-CDG

Phenotypes	Previously reported	Elder sister	Younger sister	Frequency
MOGS mutation	4/4	+	+	6/6
Prenatal problem	2/4	ND	+	3/6
Perinatal problem	1/4	+	+	3/6
Dysmorphic features	4/4	+	+	6/6
Recurrent infection	2/4	+	+	4/6
Immunological abnormalities	4/4	+	+	6/6
Respiratory difficulty	2/4	+	+	4/6
Gastrointestinal	4/4	+	+	6/6
Abnormal central nervous system	4/4	+	+	6/6
Ophthalmological	4/4	ND	ND	4/6
Hearing abnormality	4/4	+	−	5/6
Abnormal heart structure	1/4	+	+	3/6
Genitalia dysplasia	3/4	−	−	3/6
Skeletal abnormality	3/4	−	+	4/6
Abnormal endocrine function	1/4	+	−	2/6
Outcome (died)	2/4	+	+	4/6

ND not determined

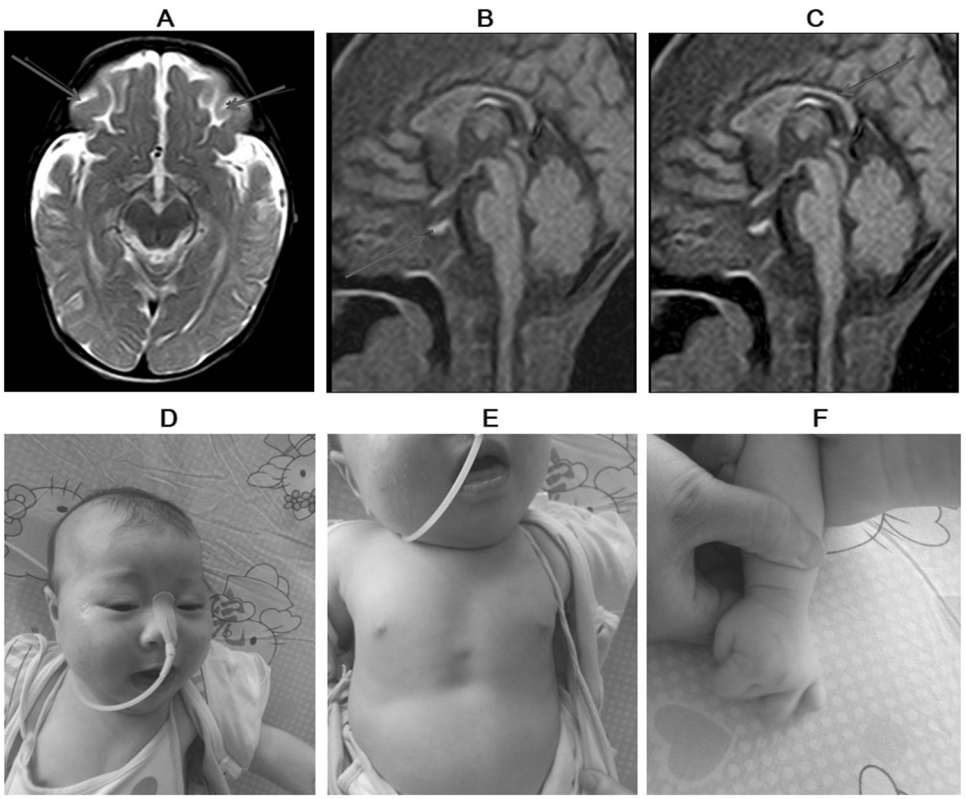

Fig. 1 Clinical features in two siblings diagnosed as congenital disorders of glycosylation (CDG) II due to mutations in *MOGS*. Head MRI of the elder sister showed bilateral frontal gyrus stenosis and lateral fissure space widening (**a**), an increased signal of anterior pituitary on T1W1 (**b**), and thin corpus callosum (**c**). Facial dysmorphism (**c**), mild pectus excavatum (**d**), and hand clenching (**e**) were found in the younger sister

palpebral fissure, wide nasal bridge, light hair, and high palate were noted (Fig. 1d). The girl was with mild pectus excavatum (Fig. 1e). Abnormal hand clenching posture was found (Fig. 1f). Auscultation revealed increased pulmonic second heart sound, II degree systolic murmur, and crackles in her lungs bilaterally. Like her elder sister, hepatomegaly, positive food intolerance detection, and positive CMV-IgM/IgG and EBV-IgG were identified. Lactic acid accompanied by non-carboxylic-dicarboxylic acid was detected by urinary genetic screening. Genetic and metabolic testing

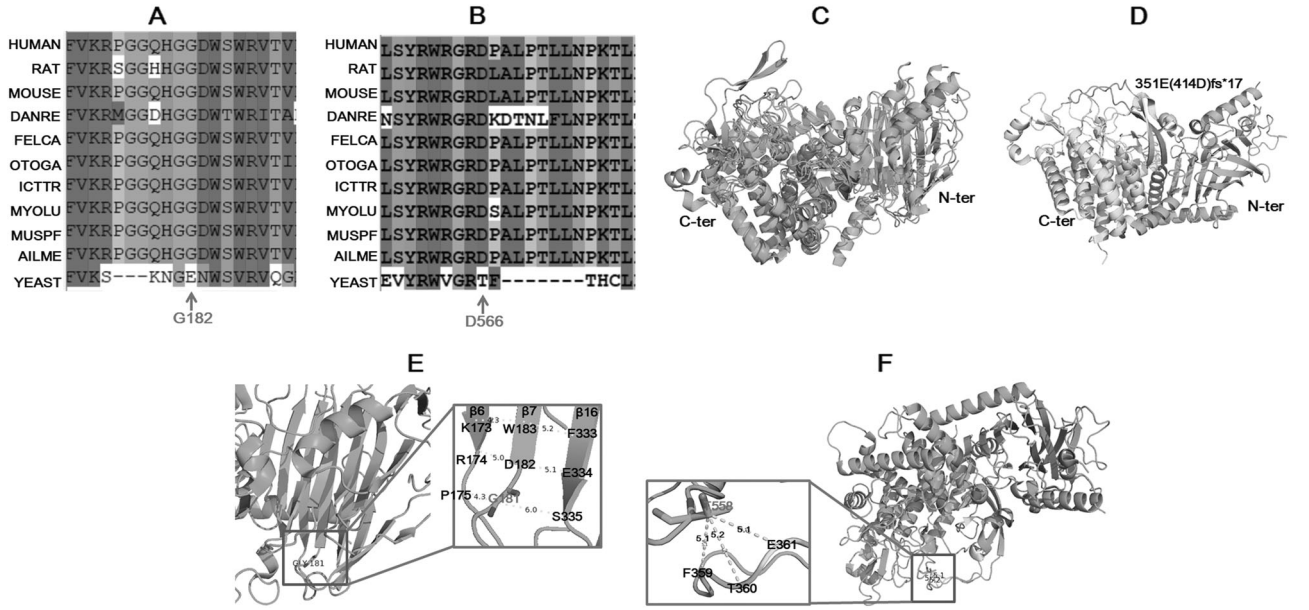

Fig. 2 Amino acids alignment and structural modeling indicated that the variants might be pathogenic. Amino acids alignment **a**, **b** showed that the point mutation sites were conserved among species. HUMAN: *Homo sapiens*; RAT: *Rattus norvegicus*; MOUSE: *Mus musculus*; DANRE: *Zebrafish*; FELCA: *Felis catus*; OTOGA: *Otolemur garnettii*; ICTTR: *Ictidomys tridecemlineatus*; MYOLU: *Myotis lucifugus*; MUSPF: *Mustela putorius furo*; AILME: *Ailuropoda melanoleuca*; YEAST: *Saccharomyces cerevisiae*. Structural alignment (cyan: 4j5t; green: 5mhf) demonstrated that MOGS structures were conserved (**c**). The frameshift mutation could lead to the deletion of almost the whole C terminal domain (**d**, yellow). The c.544 G > A,p.Gly182Arg variant could influence the local structure of three planes, which further disturb the N terminal structure (**e**). The c.1698C > A,p.Asp566Glu might influence the local structure of the binding pocket and thereby affects the combination of enzyme to its substrates (**f**). The binding pockets "site A" and "site B" of *Saccharomyces cerevisiae* CWH41 were colored in red and yellow, respectively

demonstrated that C18:1 increased, while tyrosine and C8/C10 decreased, arguing liver dysfunction. Ultrasonic cardiogram test illustrated atrial septal defect. No glycome testing like transferrin isoelectric focusing was performed. Amino acid-based infant formula via nasal feeding, plus oral levothyroxine tablets were given to the siblings; unfortunately, follow-up showed that they died at 9 months and 10 months, respectively.

Whole-exome sequencing (WES) was performed as described previously [9]. Finally, compound heterozygous variants of NM_006302 were identified: c.1239_ 1267dup, p.Asp414Leufs*17, c.544 G > A,p.Gly182Arg, and c.1698C > A,p.Asp566Glu in *MOGS*d. Provean, SIFT, Polyphen2_HDIV, Polyphen2_HVAR, M-CAP, and REVEL scores for the missense, and for paternal variants c.544 G > A,p.Gly182 Arg and c.1698C > A,p.Asp566Glu were −7.3, 0.0, 1.0, 1.0, 0.044, and 0.512 and −2.67, 0.055, 1.0, 0.998, 0.024, and 0.329, respectively. ACMG hazard ratings [10] for these variants were PVS1 + PM2, PM1 + PM2 + PM3+PP3, and PM + PM2 + PM3+PP3; all met the standard of "likely pathogenic". Sanger sequencing validated the variants (Supplementary 1B-D). Accordingly, the siblings were diagnosed as MOGS-CDG.

The point mutation sites are relatively conserved among different species (Fig. 2a, b). No MOGS structure of *Homo sapiens* has been resolved; therefore, structures of *Mus musculus* MOGS (Q80UM7) and *Saccharomyces cerevisiae* CWH41 (P53008) were downloaded from PDB (http://www.rcsb.org/) for structural modeling, as they have 85% and 32%, respectively, sequence identities to that of *Homo sapiens*. The root mean square (RMS) of *Mus musculus* (PDB: 5mhf, chain A) to *Saccharomyces cerevisiae* (PDB: 4j5t) is 1.454, indicating that the two structures are highly conserved (Fig. 2c). *Human* MOGS 414D is aligned to 351E of *Saccharomyces cerevisiae* CWH41. As shown in Fig. 2d, the frameshift mutation could lead to pre-termination and harbor a protein without almost the C terminus including the active sites [11]. *Human* MOGS G182 is aligned to G181 of *Mus musculus* MOGS. G181 is in close proximity to β7, which is parallel to β6 and β16 (Fig. 2e). β6, β7, and β16 present a parallel state (about 4.0–6.0 Å), showing high rigidity. The side chain of arginine is much longer than that of glycine; therefore, G182R variant could influence the local structure and further disturb the N terminal structure. *Human* MOGS D566 is aligned to T558 of *Saccharomyces cerevisiae* CWH41 (PDB: 4j5t). T558 is adjacent to E361 of the binding pocket "site B" [11], and the T558E variant might influence the local structure (Fig. 2f) and thereby affect combination of the enzyme to its substrates.

Discussion

Four mutations in *MOGS* have been reported [8], and three variants were detected in this study; as a consequence, we enriched the genetic and phenotypic spectrum of this rare disease. Children with facial dysmorphism, postnatal dyspnea, seizures, motor developmental delay, hypotonia, and immunological or gastrointestinal dysfunction should be highly suspected.

The frameshift mutation could harbor a premature protein without almost the C terminus, including the active sites [11]; therefore this variant is pathogenic. Sequence alignment and structural modeling showed that MOGS is highly conserved among different species; accordingly, the point mutations are possible to induce the occurrence of CDG IIb. As strcutural modeling is only in silico analysis, further functional studies are needed to investigate the possibility of pathogeny.

Glycosylation of proteins and lipids is ubiquitous, hence, CDG are characterized by multiple system dysfunction [7]. Despite their different races and nationalities, common facial features, such as light hair, long eyelashes, blepharophimosis, depressed nasal bridge, and high palate [5–8], in the reported and our patients were found. Central nervous system features like seizures, hypotonia, and thin corpus callosum were identified previously [5–8]. For the siblings, seizure was not found; however, motor developmental delay was noted. Head MRI of the elder sister was consistent with the previous reports [5–8]. Protein glycosylation plays an important role in formation of the central nervous system, which is involved in adhesion, migration, synaptogenesis, and conduction of nerve cells [12]. Glycosylation disorder may affect the migration and synaptic formation of neurons during brain development, hence leading to motor retardation [12]. In addition to the phenotypes reported in the previous four cases, hypothyroidism, congenital aryngomalacia, congenital laryngeal malformation, congenital glottic stenosis, food allergy, and gastroesophageal reflux were noted in this study. However, no phenotypes of genital dysplasia and chronic constipation were found in the siblings, which might be due to the high heterogeneity of CDG.

Both the cases presented progressive hepatomegaly and elevated hepatic enzymes, but without improvement after hepatoprotective drug administration, which was similar to the reported case [8]. Protein synthesis and secretion in hepatocytes are vigorous; therefore, immature protein synthesis and transport in the liver and biliary tract might be caused by glycosylation disorders, which further result in liver cell damage in children.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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