NOTE

Primary ovarian insufficiency in a female with phosphomannomutase-2 gene (*PMM2*) mutations for congenital disorder of glycosylation

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Abstract. Primary ovarian insufficiency (POI) is a highly heterogeneous condition, and its underlying causes remain to be clarified in a large fraction of patients. Congenital disorders of glycosylation (CDG) are multisystem diseases caused by mutations of a number of genes involved in N-glycosylation or O-glycosylation, and the most frequent form is PMM2-CDG (alias, CDG-Ia) resulting from biallelic mutations in *PMM2* encoding phosphomannomutase-2 involved in N-glycosylation. Here, we examined a 46,XX Japanese female with syndromic POI accompanied by an undetectable level of serum anti-Müllerian hormone (AMH). Whole exome sequencing identified biallelic pathogenic mutations of *PMM2* (a novel c.34G>C:p.(Asp12His) of maternal origin and a recurrent c.310C>G:p.(Leu104Val) of paternal origin) (NM_000303.3), and N-glycosylation studies detected asialotransferrin and disialotransferrin characteristic of PMM2-CDG, in addition to normally glycosylated tetrasialotransferrin. Clinical assessment showed cerebellar hypotrophy, which is a fairly characteristic and highly prevalent feature in PMM2-CDG, together with multiple non-specific features reported in PMM2-CDG such as characteristic face, intellectual disability, skeletal abnormalities, and low blood antithrombin III value. These results including the undetectable level of serum AMH, in conjunction with previously reported findings suggestive of the critical role of glycosylation in oocyte development and function, imply that PMM2-CDG almost invariably leads to POI primarily because of the defective oogenesis and/or oocyte-dependent early folliculogenesis rather than the compromised bioactivity of FSH/LH with defective glycosylation. Thus, it is recommended to examine *PMM2* in patients with syndromic POI, especially in those with cerebellar ataxia/hypotrophy.

Key words: Primary ovarian insufficiency, Congenital disorder of glycosylation, Phosphomannomutase-2

PRIMARY OVARIAN INSUFFICIENCY (POI) is defined as primary or secondary amenorrhea with hypergonadotropic (FSH ≥ 40 IU/L) hypogonadism in women under 40 years of age [1, 2]. It occurs as a non-syndromic form or as a syndromic form associated with

extragenital features [1, 2]. The underlying causes of POI are variable, including autoimmune, chromosomal, and gene abnormalities [1, 2]. Recently, multiple causative genes for POI have been identified by advanced molecular technologies such as next generation sequencing [2], although underlying causes still remain to be clarified in a large fraction of patients.

Congenital disorders of glycosylation (CDG) are multisystem diseases caused by mutations of a number of genes involved in N-glycosylation or O-glycosylation [3]. N-glycans are linked to the amide group of asparagine, whereas O-glycans are linked to the hydroxyl group of serine or threonine. The most frequent form is PMM2-CDG (alias, CDG-Ia) resulting from biallelic mutations in *PMM2* encoding phosphomannomutase-2 involved in N-glycosylation [4-6]. *PMM2* consists of

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Abbreviations: AMH, anti-Müllerian hormone; CDG, congenital disorders of glycosylation; ESI-MS, electrospray ionization mass spectrometry; MRI, magnetic resonance imaging; PMM2, phosphomannomutase-2; POI, primary ovarian insufficiency; and WES, whole exome sequencing.

eight exons and encodes 246 amino acids, and PMM2 catalyzes the isomerization of mannose 6-phosphate to mannose 1-phosphate [4]. PMM2-CDG is associated with a wide range of clinical features, including characteristic face, growth failure, intellectual disability, cerebellar hypotrophy, retinitis pigmentosa, peripheral neuropathy, skeletal abnormalities, and coagulation abnormalities [5, 6]. Notably, PMM2-CDG is also almost invariably accompanied by POI [5, 6]. However, underlying mechanism(s) leading to POI remains largely unknown.

Here, we report a female with syndromic POI in whom *PMM2* mutations were identified by whole exome sequencing (WES), and discuss the underlying mechanism(s) leading to POI.

Case Presentation

This Japanese female was born at 38 weeks of gestation, with a birth length of 45.5 cm (−1.5 SD) and a birth weight of 2.69 kg (−0.6 SD). She showed hypotonia and failure to thrive in infancy, and began to walk without support at 2 6/12 years of age. She had status epilepticus with abnormal electroencephalograms at 6 3/12 years of age. Thus, she was treated with sodium valproate until electroencephalograms became apparently normal at 15 years of age. She manifested moderate intellectual disability, and was enrolled in a special junior school for such children. Her stature remained between −1 SD and −2 SD until 10 years of age.

At 11 10/12 years of age, she was found to lack pubertal growth spurt and secondary sexual development when she came to our hospital due to common cold. She became short for her age with a height of 130.2 cm (−2.9 SD) and a weight of 25.6 kg (−1.9 SD). Her breast development was at Tanner stage 1, and her external genitalia were infantile. Physical examination at that time showed hypertelorism, asymmetric eye fissures, left internal strabismus, thin upper lips, well developed mandible, retracted nipples, kyphoscoliosis, and elongated slender fingers. There were no Turner-like external somatic features such as webbed neck and cubitus valgus. She exhibited ataxic gait and poor fine movement, but had no involuntary movement. Her visual, acoustic, and olfactory acuities were apparently normal. Endocrine studies showed severe hypergonadotropic hypogonadism, mild hyperprolactinemia, moderate hyperthyroglobulinemia, and apparently normal blood GH/IGF-1, ACTH/cortisol, TSH/T4, and glucose/HbA1c/insulin values (Table 1). Chromosome analysis showed a 46,XX karyotype. Her bone age was 8 10/12 years. Brain magnetic resonance imaging (MRI) delineated cerebellar hypotrophy (Fig. 1A), and abdominal MRI showed rudimentary uterus and

failed to detect ovaries (Fig. 1B). Estrogen replacement therapy enlarged the uterine size, and subsequent cyclic estrogen-progestin therapy successfully induced menses from 15 9/12 years of age. She also manifested mild antibody-negative hypothyroidism accompanied by overt hyperthyroglobulinemia and mild goiter with cystic masses from late teens (Table 1), and received *l*-thyroxin (25 µg/day) from 19 7/12 years of age. At 23 8/12 years of age shortly after the diagnosis of PMM2-CDG, we screened for clinical findings reported in PMM2-CDG [5, 6], revealing a low blood antithrombin III value of 51% (reference range, 80–130%). We also found an unmeasurable level of blood anti-Müllerian hormone (AMH) (Table 1). At that time, she measured 152.5 cm (−1.1 SD) and weighed 47.5 kg (−0.7 SD).

The 65-year-old father and the 62-year-old mother were non-consanguineous and healthy. The mother had menarche at 12 years of age (reference data, 9.75–14.75 years) followed by regular menses until 46 years of age, and had menopause at 47 years of age (45–56 years). The mother did not have a history of other pregnancies or fetal abortions.

Molecular Studies

This study was approved by the Institutional Review Board Committee at Hamamatsu University School of Medicine, and was performed using leukocyte genomic DNA samples of the patient and the parents after obtaining written informed consent. WES was carried out by the previously described methods [7], using Human GRCh37/h19 as the reference genome. In short, WES was performed with SureSelect Human All Exon V6 (Agilent Technologies), and captured libraries were sequenced by NextSeq 500 (Illumina) with 150 bp paired-end reads.

Consequently, we identified compound heterozygous missense mutations of *PMM2*, *i.e.*, c.34G>C:p.(Asp12His) of maternal origin and c.310C>G:p.(Leu104Val) of paternal origin (NM_000303.3) (Table 2). These mutations were confirmed by Sanger sequencing (Fig. 2A). They were almost completely absent from the public and in-house databases shown in Table 2, and were assessed to have high pathogenicity by several methods shown in Table 2. According to the ACMG Standards and Guidelines, the p.(Asp12His) was evaluated as “likely pathogenic” (positive for PM1, PM2, PM3, PP2, PP3, and PP4), and the p.(Leu104Val) was assessed as “pathogenic” (positive for PS1, PM1, PM2, PP2, PP3, PP4, and PP5) (for details, see Richards *et al.* [8]). While WES also identified several rare variants (minor allele frequencies of ≤0.01 in the public and in-house databases utilized in this study) under the assumption of Mendelian

Table 1 Blood endocrine data of this patient

	Patient		Reference value [§]	
	Basal*	Peak [†]	Basal	Peak
<11 10/12 years of age>				
GH (ng/mL)	0.19	11.8	<3.0	>6.0
ACTH (pg/mL)	58	88	22.0 ± 16.8	>50
Cortisol (μg/dL)	16.3	19.9	3.0–12.0	
LH (mIU/mL)	19.3	112.5	0.1–0.4 [¶]	1.6–4.8 [¶]
FSH (mIU/mL)	105.3	180.3	2.1–6.1 [¶]	14.5–21.9 [¶]
TSH (μU/mL)	4.1	16.7	0.62–3.36	10–35
Prolactin (ng/mL)	22.8	140.8	1.2–12.9	<70
Glucose (mg/dL)	80	60	60–100	
Insulin (IRI) (μU/mL)	2		2–10	
HbA1c (%)	5.3		4.6–6.2	
IGF-I (ng/mL)	145 [‡]		155–588	
Estradiol (pg/mL)	<2.5		0–63	
Free T ₄ (ng/dL)	1.14		0.98–1.90	
Tg (ng/mL)	104.5		10–30	
Anti-TPO-antibody	Negative		Negative	
Anti-Tg-antibody	Negative		Negative	
<19 1/12 years of age>				
TSH (μU/mL)	1.68		0.62–3.36	
Free T ₄ (ng/dL)	<u>0.88</u>		0.98–1.90	
Tg (ng/mL)	466.4		10–30	
<23 8/12 years of age>				
AMH (ng/mL)	<u><0.01</u>		2.00–12.50	

Abbreviations: IRI, immunoreactive insulin; Tg, thyroglobulin; TPO, thyroid peroxidase; and AMH, anti-Müllerian hormone.

The data above and below the reference values are boldfaced and underlined, respectively.

* Basal values obtained at 9:00 am in a fasting condition.

[†] The highest or lowest values during a triple tolerance test (insulin 0.1 U/kg, GnRH 100 μg/m², and TRH 300 μg/m² bolus i.v.; blood sampling: 0, 30, 60, 90, and 120 min).

[‡] Although the IGF-I value is lower than the age-matched female reference range, it appears to be normal for prepubertal girls.

[§] Age- and sex-matched Japanese reference values.

[¶] Reference ranges in prepubertal girls.

inheritance with complete penetrance (Table 2), there was no data in support of the relevance of such variants to the phenotypic development of this patient, in terms of pathogenicity and known phenotype.

N-glycosylation Studies

The N-glycosylation status of transferrin was examined by the electrospray ionization mass spectrometry (ESI-MS) analysis, as described previously [9]. In brief, transferrin was purified from serum by immunoaffinity with rabbit polyclonal antibody against human transferrin, and was subjected to liquid chromatography-ESI-MS using a reversed-phase (C4) minicolumn and an

API4500 quadrupole mass spectrometer (Sciex). The obtained mass spectrum of multiply-charged ions was transformed into a single-charge spectrum using a Promass protein deconvolution software (ThermoFisher Scientific).

Consequently, asialotransferrin and disialotransferrin compatible with PMM2-CDG were identified in this patient, together with the normally glycosylated tetrasialotransferrin (Fig. 2B). Such aberrant transferrins were barely detected in a control subject, while tetrasialotransferrin was clearly delineated.

Fig. 1 MRI findings.

- A. Brain MRI showing cerebellar hypotrophy.
 B. Pelvic MRI delineating a rudimentary uterus and an apparent lack of recognizable ovaries. B, bladder; R, rectum; and V, vagina.

Discussion

The present study indicates that this patient had PMM2-CDG. Indeed, molecular studies identified biallelic mutations in *PMM2* which were extremely rare in the general populations and were assessed to be pathogenic. While the p.(Asp12His) has not been reported previously, the p.(Leu104Val) has been shown to be a hypomorphic mutation by the previous functional study [10]. Furthermore, N-glycosylation studies revealed asialotransferrin and disialotransferrin compatible with an impaired biosynthesis of lipid-linked oligosaccharide in PMM2-CDG [9]. The presence of normally glycosylated tetrasialotransferrin would reflect the residual activity of the mutant PMM2 proteins, because complete lack of PMM2 function has been assumed to be lethal [4]. Consistent with such genetic and biochemical findings, this patient exhibited multiple clinical features reported in PMM2-CDG, such as characteristic face, intellectual disability, cerebellar hypotrophy, skeletal abnormalities, and coagulation abnormalities.

This patient also had POI which is almost invariably present in pubertal to adult females with PMM2-CDG [5, 6]. POI in PMM2-CDG has been assumed to be due to apparently hypergonadotropic but functionally hypogonadotropic hypogonadism because of compromised bioactivity of FSH/LH (especially FSH) with glycosylation defects [11, 12]. However, FSH bioactivity has been shown to remain at a low-normal range in PMM2-CDG [11, 13]. Furthermore, since AMH was undetectable in this patient, this suggests the occurrence of folliculogenic

failure at an early stage before the FSH-independent development of AMH-producing preantral and small antral follicles rather than the FSH-dependent subsequent development of non-AMH-producing antral and preovulatory follicles [14]. Indeed, serum AMH values remain grossly normal or rather increased in patients with hypogonadotropic hypogonadism [15, 16]. In this regard, it is notable that a critical role of glycosylation in oocyte development and function has been suggested: (1) *PMM2* is strongly expressed in the cytoplasm of oocytes in a human fetus aborted at 25 weeks of gestation [17]; (2) many proteins expressed in oocytes and involved in ovarian development and function such as BMP15 and GDF9 are glycosylated [18, 19]; (3) mice lacking *Clgakt1* (core 1 synthase, glycoprotein-N-acetylgalactosamine 3- β -galactosyltransferase 1) and *Mgat1* (α -1,3-mannosyl-glycoprotein 2- β -N-acetylglucosaminyltransferase) exhibit POI because of deficiency of core 1-derived O-glycans and complex N-glycans in oocytes [20]; and (4) oocyte-specific deletion of *Mgat1* leads to defective preovulatory follicles in mice [21]. Collectively, it is inferred that *PMM2* mutations and resultant N-glycosylation defects lead to syndromic POI primarily by affecting oogenesis and/or oocyte-dependent early folliculogenesis rather than by impairing gonadotropin functions.

Although ovaries were undetected by MRI in this patient, it is unlikely that *PMM2* mutations cause ovarian agenesis. Ovarian (gonadal) agenesis is caused by impaired formation of an indifferent gonad common to both sexes, in contrast to subsequent male-specific testis development with hormone-producing somatic cells or female-specific ovarian development with meiotic oocytes [22]. Since androgen-dependent male sex differentiation is preserved in PMM2-CDG [5, 6], this suggests the development of an indifferent gonad (at least somatic portion of the indifferent gonad) and subsequent hormone-producing testis formation in male patients with PMM2-CDG. Thus, it is inferred that this patient had rudimentary streak-like dysgenetic ovaries rather than ovarian agenesis, although ovarian regression may be possible [13]. In this context, since pubertal to adult males with PMM2-CDG have small testes (usually ≤ 5 mL) indicative of spermatogenic failure [11, 12], this may imply that *PMM2* is involved in meiosis common to both sexes.

The mother with the heterozygous *PMM2* mutation had no clinical finding suggestive of ovarian dysfunction. Consistent with this, there is no report describing ovarian dysfunction in females heterozygous for *PMM2* mutations, although no description might not necessarily indicate lack of ovarian dysfunction in such females. It is likely, therefore, that *PMM2* heterozygosity permits normal ovarian function.

Table 2 Rare variants extracted from whole exome sequencing under the assumption of Mendelian inheritance with complete penetrance in the trio analysis

Gene (Chromosome) Variant (GenBank)	De novo variants				Compound heterozygous variants				Homozygous variant	
	C4orf48 (Chr. 4)	LTK (Chr. 15)	FAM227B (Chr. 15)	FAM227B (Chr. 15)	FAM227B (Chr. 15)	PMM2 (Chr. 16)	PMM2 (Chr. 16)	PMM2 (Chr. 16)	LGALS3BP (Chr. 17)	
Variant (GenBank)	NM_001168243.1 c.146_148del p.(Pro49del)	NM_002344.6 c.2587C>T p.(Arg863Cys)	NM_152647.3 c.1137delG p.(Glu379Aspfs*15)	NM_152647.3 c.405+3A>G	NM_152647.3 c.34G>C	NM_000303.3 c.310C>G	NM_000303.3 c.310C>G	NM_000303.3 p.(Leu104Val)	NM_005567.4 c.879C>T p.(=)	Biparental
Inheritance	De novo	De novo	Maternal	Paternal	Maternal	Paternal	Maternal	Paternal		
<Frequency>										
gnomeAD East Asia	0.0000	0.0000	0.0015	0.0049	0.0000	0.0000	0.0000	0.0000	0.0021	
HGVD	0.0000	0.0000	0.0004	0.0025	0.0000	0.0000	0.0000	0.0000	0.0068	
8.3KJPN	0.0000	0.0000	0.0003	0.0014	0.0001	0.0000	0.0000	0.0000	0.0057	
In-house (n = 218)	0.0000	0.0000	0.0000	0.0023	0.0000	0.0000	0.0000	0.0000	0.0069	
<Pathogenicity>										
CADD	Not predicted	1% most deleterious	Not predicted	1% most deleterious	1% most deleterious	1% most deleterious	1% most deleterious	1% most deleterious	Non-deleterious	
PHRED score	Not predicted	22.4	Not predicted	21.6	33.0	25.1	25.1	25.1	4.5	
PolyPhen-2 Hum Var	Not predicted	Benign	Not predicted	Not predicted	Probably damaging	Probably damaging	Probably damaging	Probably damaging	Not predicted	
Score	Not predicted	0.232	Not predicted	Not predicted	0.993	0.995	0.995	0.995	Not predicted	
SIFT	Not predicted	Damaging	Not predicted	Not predicted	Damaging	Damaging	Damaging	Damaging	Tolerated	
Score	Not predicted	0.039	Not predicted	Not predicted	0.000	0.001	0.001	0.001	0.707	
MutationTaster	Polymorphism	Polymorphism	Disease causing	Not predicted	Disease causing	Disease causing	Disease causing	Disease causing	Polymorphism	
Score	1.000	0.922	1.000	Not predicted	1.000	1.000	1.000	1.000	1.000	
<Phenotype>										
OMIM	Unknown	Unknown	Unknown	Unknown	CGD-Ia	CGD-Ia	CGD-Ia	CGD-Ia	Unknown	

Shown are non-synonymous rare variants with minor allele frequencies of ≤ 0.01 in all the public and in-house databases employed.

The URLs utilized are as follows; *in silico* analyses were performed by using the default parameters.

- 1) GenBank: <https://www.ncbi.nlm.nih.gov/genbank>.
- 2) gnomAD (Genome Aggregation Database): <http://gnomad.broadinstitute.org/>.
- 3) HGVD (Human Genetic Variation Database): <http://www.hgvd.genome.med.kyoto-u.ac.jp/>.
- 4) 8.3KJPN (Whole-genome sequences of 8,380 healthy Japanese individuals and construction of the highly accurate Japanese population reference panel): <https://ijgvd.megabank.tohoku.ac.jp/>.
- 5) CADD (Combined Annotation-Dependent Depletion): <http://cadd.gs.washington.edu/> (Current version: 1.6, GRCh37/hg19); PHRED scores of $>10-20$ are regarded as deleterious, and those of >20 indicates the 1% most deleterious.
- 6) Polyphen-2 Hum Var: <http://genetics.bwh.harvard.edu/pph2/> (Current version: 2.2.2, GRCh37/hg19); HumVar scores were evaluated as 0.000 (most probably benign) to 1.000 (most probably damaging).
- 7) SIFT (Sorting Intolerant From Tolerant): <http://sift.jcvi.org/> (Current version: Mar 2013; GRCh37/Ensembl 66); Scores of ≤ 0.05 and those >0.05 are assessed as damaging and tolerated, respectively.
- 8) MutationTaster: <http://www.mutationtaster.org/> (MutationTaster2, GRCh37/Ensembl 69); Alterations are classified as disease causing or polymorphisms, and the high scores of ~ 1.00 indicate the high probability of disease-causing variant or polymorphism.
- 9) OMIM: <https://www.ncbi.nlm.nih.gov/omim>.

Fig. 2 The results of molecular and N-glycosylation studies.

A. Electrochromatograms showing biallelic *PMM2* mutations. The primers for c.34G>C on exon 1 are: forward, 5'-AACGGAGTCCCCTCTCT-3'; and reverse, 5'-AGAGTTCTTCAGCCCCGTCT-3'. The primers for c.310C>G on exon 4 are: forward, 5'-GACCTGGGTTTGCTATGAA-3'; and reverse, 5'-ACTGAACCCTGCTGTGAACC-3'.

B. ESI-MS findings (deconvoluted spectrum) showing N-glycosylation status of transferrin.

PMM2-CDG is occasionally associated with several endocrine features other than POI, such as hypothyroidism, hyperprolactinemia, hypocortisolism, and hypoglycemia [5, 6, 11, 12, 23]. In this regard, this patient manifested antibody-negative mild hypothyroidism in the presence of overt hyperthyroglobulinemia and normal serum TSH level. Since thyroglobulin is heavily N-glycosylated [24], *PMM2* mutations may compromise thyroglobulin functions, leading to hypothyroidism in patients with high susceptibility to hypothyroidism. In this context, hyperthyroglobulinemia may suggest compensatory phenomenon against reduced thyroglobulin functions, and normal serum TSH level would be explained by the mild degree of hypothyroidism. This patient also exhibited mild hyperprolactinemia. Since her thyroid function was normal at the time of prolactin measurement, it is unlikely that hyperprolactinemia is due to increased TRH secretion resulting from hypothyroidism. Thus, our data would support the notion that the decreased dopamine action may underlie the development of hyperprolactinemia in a certain fraction of patients [11].

In summary, we revealed *PMM2*-CDG in a female with syndromic POI. The results, in conjunction with the previous findings [1], imply that *PMM2* constitutes an important gene for syndromic POI. In this regard, while many clinical features such as characteristic face, growth

failure, and intellectual disability are non-specific, cerebellar ataxia is a fairly characteristic and highly prevalent feature in *PMM2*-CDG [5, 6]. Thus, it is recommended to examine *PMM2* in patients with syndromic POI, especially those with cerebellar ataxia/hypotrophy. In addition, since homozygous *PMM2* p.Gly186Arg mutation with a relatively high residual activity has been identified in sisters with apparently non-syndromic POI [17], *PMM2* may also be worth examining in patients with non-syndromic POI. Further studies will permit to clarify the relevance of *PMM2*-CDG to the development of syndromic and non-syndromic POI.

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Disclosure

The authors declare no conflict of interest.

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