



Novel homozygous mutations in *PATL2* lead to female infertility with oocyte maturation arrest

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Abstract

Purpose To identify the disease gene in 40 patients with female infertility due to oocyte maturation arrest.

Methods Genomic DNA was extracted from peripheral blood of 40 patients and their family members. Whole-exome sequencing was performed on the patients, and the *PATL2* mutations were identified and confirmed by Sanger sequencing. Harmfulness of the mutations was analyzed by SIFT, Polyphen-2, Mutation Taster, and M-CAP software, and we used western immunoblotting analysis to check the effect of mutations on *PATL2* protein expression in vitro.

Results Two novel missense mutations c.1528C>A (p.Pro510Thr) and c.1376C>A (p.Ser459Tyr) in *PATL2* were identified in three patients (7.5%) from two consanguineous families in our cohort. We found that mutations in *PATL2* resulted in variable oocyte phenotypes, including GV arrest, MI arrest, and morphologic abnormalities. Western immunoblotting analysis showed that the expression levels of the two novel mutant *PATL2* proteins decreased significantly.

Conclusions We identified two novel *PATL2* mutations that caused oocyte maturation arrest and abnormal morphology, and variable phenotypes in patients.

Keywords *PATL2* · Female infertility · Oocyte maturation arrest · GV arrest

Introduction

In 1978, the first IVF baby was born in Oldham General Hospital [1], and assisted reproductive technology has been widely used ever since in the treatment of infertility. Infertility is usually used to describe as a couple who cannot become

pregnant after 12 months of regular unprotected sexual intercourse and affects approximately 15% of all couples [2, 3]. Oocyte maturation arrest is of the principal causes of primary female infertility, including GV arrest, MI arrest, MII arrest, and mixed arrest [1]. Genetic mutations constitute one of the factors in oocyte maturation arrest, although enzyme and hormonal changes can also cause maturation arrest in oocytes. Recently, it was reported that *ZP1* mutations are responsible for female infertility due to a missing zona pellucida [4, 5]. *TUBB8* mutations cause female infertility due to arrest at metaphase I, fertilization, or early embryonic development [6]. *PATL2* mutations as a cause of female infertility are characterized by GV arrest, mixed arrest, and/or morphologic abnormalities [7–10]. Mutations in *WEE2* cause female infertility and fertilization failure [11]. *PANX1* channelopathies are responsible for human oocyte death [12]. However, the genetic etiology of most patients with oocyte maturation arrest remains largely unknown.

PATL2 is a mRNA-binding protein specifically expressed in immature oocytes that inhibits the post-transcriptional translation process in cells; and as the oocyte matures, the expression of *PATL2* gradually disappears. The amount of

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PATL2 was greatly impaired by *PATL2* mutations in patients with oocyte maturation arrest [8, 9], and overexpression of a *PATL2* ortholog (also named as P100) in *Xenopus* oocytes also repressed mRNA translation and resulted in maturation arrest [13]. These results indicate that temporal control of *PATL2* expression levels is critical for the normal maturation of oocytes.

Herein, we analyzed 40 unrelated Chinese patients with oocyte maturation arrest and found two novel homozygous mutations, c.1528C>A (p.Pro510Thr) and c.1376C>A (p.Ser459Tyr), in *PATL2* in three patients (7.5%). Noticeably, the phenotypes of two patients from the same family carrying the same mutation (p.Pro510Thr) were different. In vitro evidence also showed that the two novel mutations in *PATL2* decreased *PATL2* protein content. This present study provides additional evidence that *PATL2* is very important in oocyte maturation, expanding the current mutational spectrum.

Materials and methods

Study subjects

Forty individuals with primary infertility due to oocyte maturation arrest from 36 families were recruited from the Reproductive Medicine Center, Tongji Hospital, Huazhong University of Science and Technology. Peripheral blood from affected individuals and their family members were collected to extract genomic DNA using standard methods.

Evaluation of oocyte phenotypes

After obtaining oocytes from the affected individuals, we performed oocyte phenotype analysis under a light microscope to evaluate oocyte morphology and the degree of maturity. We characterized oocytes with a complete germinal vesicle (GV) to be at the GV stage, and oocytes that contained no GV or polar body to be at the metaphase I (MI) stage, and oocytes with the first polar body extruded were at metaphase II (MII) stage. Oocytes in GV and MI stages were characterized as immature [8].

Mutation analysis

We performed whole-exome capture (Agilent) and sequencing (NovaSeq 6000, Illumina) in affected individuals, and the sequencing coverage rate and target mean depth were 98.77% and 166.65, respectively. We mapped the raw FASTQ files to the human reference sequence (NCBI Genome build GRCh37), and SNP and InDel were searched using software such as SAMtools and GATK, and then annotated with ANNOVAR software to determine the genetic information, functional information, and harmfulness of the mutation site.

The conservation of the affected amino acid residues of the *PATL2* protein was analyzed among multiple species using MEGA software; the ExAC and 1000 Genomes databases were used to search for the frequency of the corresponding mutation, and we analyzed the harmfulness of mutations by using Sorting Intolerant From Tolerant (SIFT, <http://sift.bii.a-star.edu.sg/>), Polymorphism Phenotyping (Polyphen-2, <http://genetics.bwh.harvard.edu/pph2/>), Mutation Taster (<http://www.mutaiontaster.org/>), and Mendelian Clinically Applicable Pathogenicity (M-CAP, <http://bejerano.stanford.edu/MCAP>). We amplified all exons and exon-intron boundaries of *PATL2* by PCR using reference primers [9]. PCR products were purified using a Gel Extraction Kit (Beijing CoWin Biotech Co., Ltd., China), and then Sanger sequencing was carried out using an ABI PRISM 3500 Genetic Analyzer (Applied Biosystems, Foster City, CA) for all exons and exon-intron boundaries of *PATL2*.

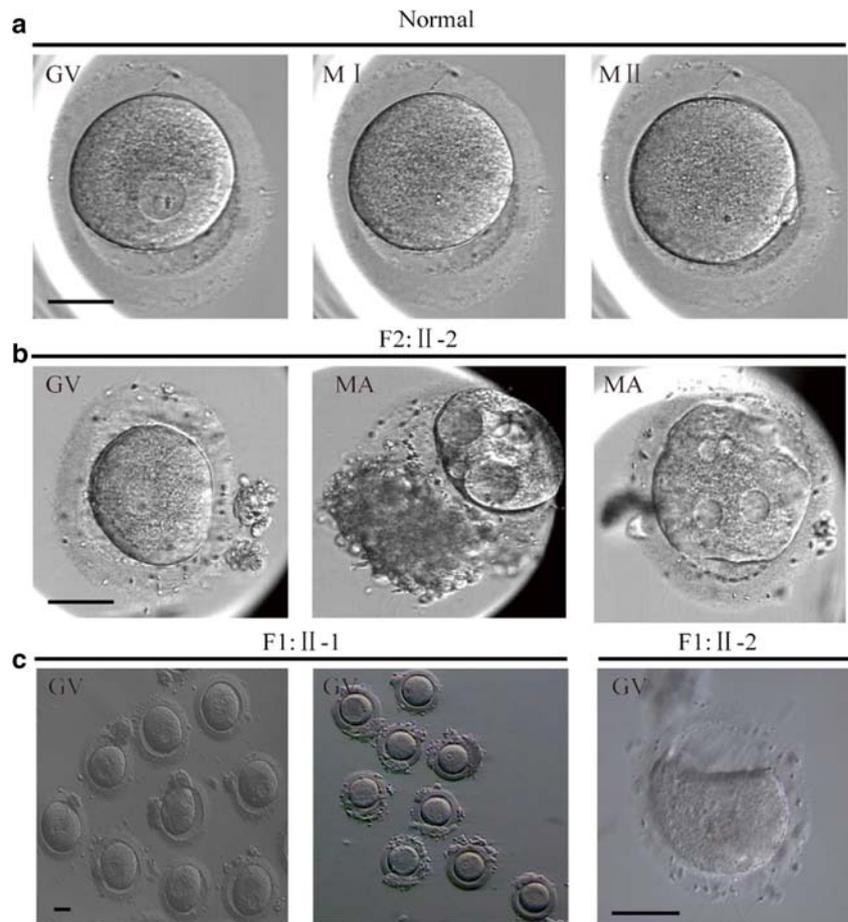
Expression constructs

The wild-type *PATL2* cDNA (a gift from Qing Sang at Fudan University) was inserted into the pEGFP-C1 vector for transient expression in HEK293T cells. The P510T and S459Y mutant plasmids were generated using the Mut Express II Fast Mutagenesis Kit V2 (Vazyme Biotech Co., Ltd) according to the manufacturer's protocol. All expression constructs were confirmed by Sanger DNA sequencing.

Western blotting analysis

The P510T, S459Y mutant, and wild-type *PATL2* expression plasmids were transiently transfected into HEK293T cells using Lipofectamine 2000 (Invitrogen, USA) to evaluate the effects of the mutations on *PATL2* protein expression. Thirty-six hours after transfection, total proteins were extracted from cell lysates by grinding in a protease inhibitor cocktail (Roche, Germany), and separated by 10% SDS/PAGE gels in a running buffer of Tris, glycine, and SDS. We transferred proteins onto a PVDF membrane (Merck KGaA, Germany). Membranes were blocked in 5% skim milk and washed 3 times in Tris-buffered saline-Tween 20 (TBS-T). The membranes were incubated with mouse anti-GFP-Tag primary antibodies (AB clonal, China) at a 1:2000 dilution overnight at 4 °C. The membranes were then washed in TBS-T and incubated with goat anti-mouse IgG HRP-linked secondary antibodies (Beijing CoWin Biotech Co., Ltd., China) at a dilution of 1:10000. We then captured the results using a ChemiDoc XRS+ System (Bio-Rad, USA) and scanned the gray values of the protein band with Quantity One software, using GAPDH as an internal control to quantify *PATL2* expression. We repeated this experiment 8 times. The *P* values were detected using one-way ANOVA with a multiple-comparison test with 95% confidence.

Fig. 1 Phenotypes of oocytes from patients and fertile control. **a** Morphology of GV, MI, and MII oocytes from a fertile control individual. **b** Oocytes arrested at the GV stage and morphologic abnormalities from II-2 (F2). **c** GV stage oocytes from II-1 and II-2 (F1). Scale bar, 50 μm. F2, Family2; F1, Family1; GV, Germinal Vesicle; MI, Metaphase I; MII, Metaphase II; MA, morphology abnormality



Subcellular localization in HEK293T cells and real-time quantitative PCR

The P510T, S459Y mutant, and wild-type EGFP-tagged PATL2 expression constructs were transiently transfected in HEK293T cells, and after 36 h, the cells were fixed in 4% formaldehyde for 10 min at room temperature. The nuclei of cells were stained with DAPI for 10 min at room temperature and washed in phosphate-buffered saline (PBS). We ultimately

captured images using a confocal microscope FV1000 (Olympus, Japan).

Total RNA was extracted using the RNAiso Plus kit (TaKaRa, China), followed by reverse-transcription with a HiScript 1st Strand cDNA Synthesis Kit (Vazyme, China), and we used ChamQ Universal SYBR qPCR Master Mix (Vazyme, China) to perform real-time quantitative fluorescence PCR. GAPDH was used as an internal control to quantify the expression of PATL2 mRNA according to the $2^{-\Delta\Delta Ct}$ method.

Table 1 Oocyte characteristics of three patients

	Age (years)	Duration of infertility (years)	IVF cycles						
			Date	Oocytes retrieved (n)	GV (n)	MI (n)	MII (n)	MA (n)	Fertilized oocytes (n)
Family 1 (II-1)	39	15	2008. 11	42	37	1	0	4	0
			2009. 3	29	25	1	0	3	0
Family 1 (II-2)	37	13	2018. 3	9	4	4	0	1	0
			2018. 8	4	3	0	0	1	0
			2018. 10	5	1	4	0	0	0
Family 2 (II-2)	30	2	2019. 5	7	2	0	0	5	0

GV, germinal vesicle; MI, metaphase I; MII, metaphase II; MA, morphology abnormalities

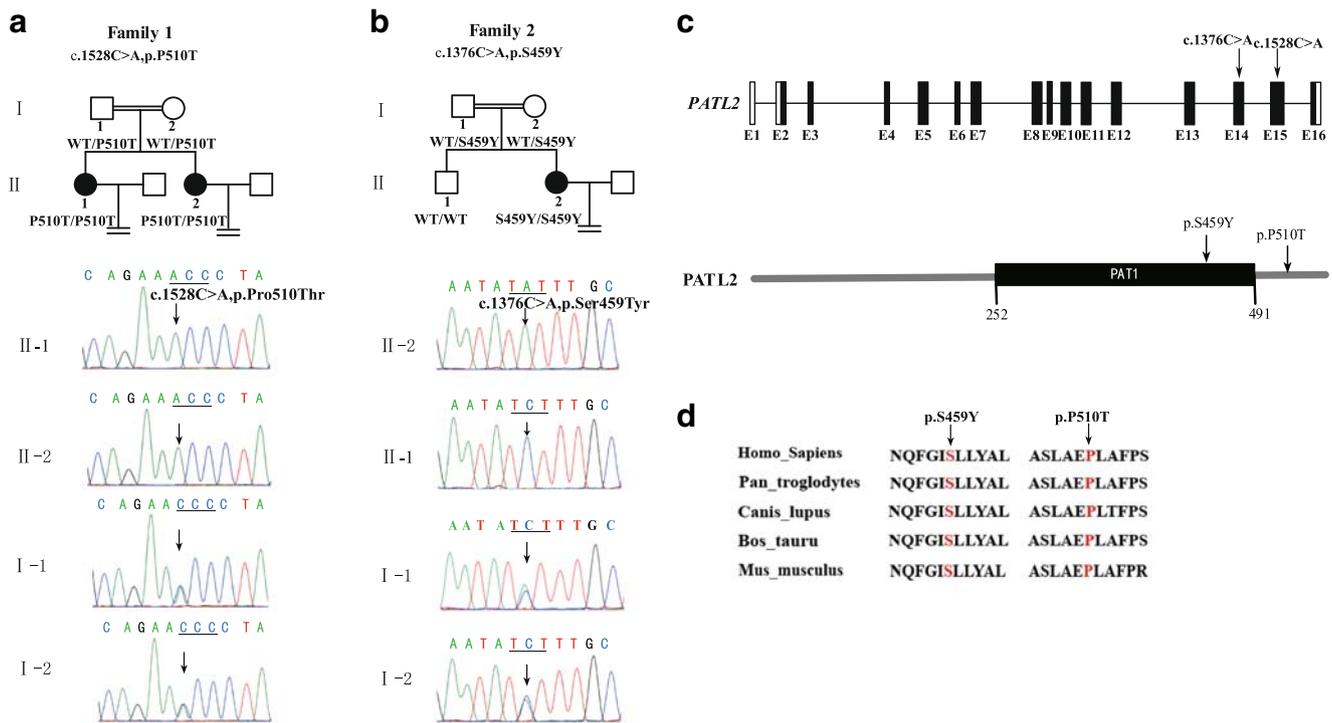


Fig. 2 Identification of mutations in *PATL2*. The patients in family1 (a) and family2 (b) carried 2 different missense mutations: c.1528C>T (p.P510T) and c.1376C>A (p.S459Y), respectively. Black circles represent patients. c Location of 2 novel homozygous missense

mutations in the *PATL2* gene and protein. We predicted the domain of the *PATL2* protein using SMART software. d The conservation of P510 and S459 among multiple species

Ethical approval

All participants in the study signed informed consent to participate in our investigation, and all studies on human subjects were approved by the Ethics Committee of Huazhong University of Science and Technology.

Results

Clinical phenotypes of patients

In consanguineous family 1 (F1), there were two sisters (II-1 and II-2, currently 39 and 37 years old, respectively) who both

have primary infertility. Affected individual II-1 had a 15-year history of primary infertility and underwent two failed IVF cycles, with 71 oocytes retrieved: 62 were arrested at the GV stage and the remainder at MI stage, with large vacuoles, and signs of degeneration. All oocytes were immature even after 48 h in vitro. The woman's baseline LH and FSH concentrations were 2.09 IU/L and 5.34 IU/L, respectively. Her sister (II-2) had a 13-year history of primary infertility, undergoing three failed IVF cycles, with 18 oocytes retrieved: eight were arrested at the GV stage, eight at the MI stage, and the remainder showed morphologic abnormalities. Mature oocytes were not obtained in extended culture (Fig. 1c).

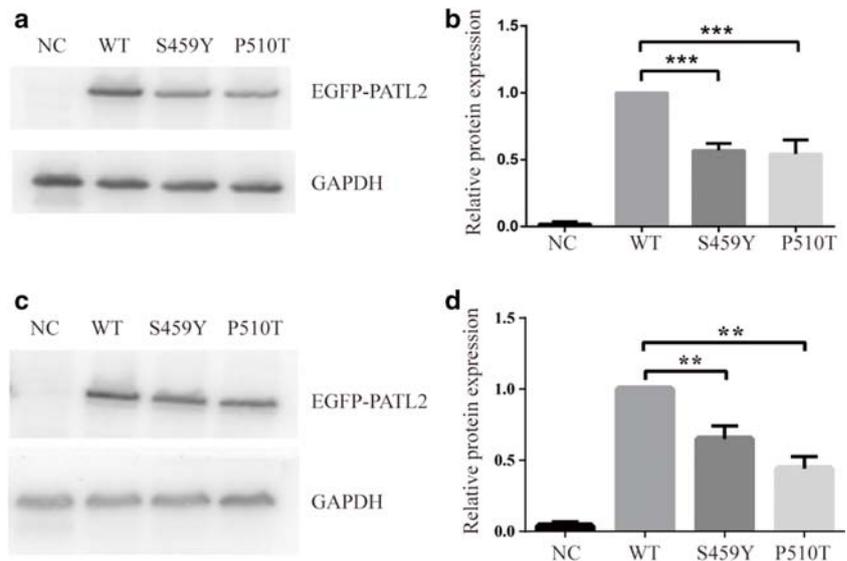
In consanguineous family 2 (F2), patient II-2 was a 30-year-old woman with a 2-year history of primary infertility.

Table 2 Summary of *PATL2* mutation analysis in two consanguineous families

	Chromosome 15	Mutation	Exon	Mutation type	ExAc allele frequency	SIFT ^a	Polyphen-2 ^a	Mutation Taster ^a	M-CAP ^a
Family 1 (II-1 and II-2)	44958675	c.1528C>T p.P510T	15	Missense	Not found	D	P	D	D
Family 2 (II-2)	44959391	c.1376C>A p.S459Y	14	Missense	Not found	D	P	D	D

^a Analysis of the harmfulness of mutations by using Sorting Intolerant From Tolerant (SIFT), Polymorphism Phenotyping (Polyphen-2), Mutation Taster, and Mendelian Clinically Applicable Pathogenicity (M-CAP). D, damaging; P, probably damaging

Fig. 3 Expression level of *PATL2* protein in vitro. Western immunoblotting analysis showed the expression levels of WT and mutant *PATL2* protein in HEK293T cells (a) and COS-7 cells (c). The relative expression levels of WT, P510T, and S459Y *PATL2* protein in HEK293T (b) and COS-7 cells (d). *** $P < 0.0001$, ** $P < 0.001$, $n = 8$ (b) and $n = 3$ (d). NC, negative control



In May 2019, she underwent 1 IVF cycle, and seven oocytes were retrieved: two were arrested at the GV stage and five showed morphologic abnormalities (Fig. 1b). The oocytes were cultured in vitro for 48 h without maturation (Table 1).

All three patients manifested regular menstrual cyclicality did not possess Nessler’s cysts and showed a normal karyotype (46, XX), and the respective husbands exhibited normal seminal parameters. All patients’ case data were from the Reproductive Medicine Center, Tongji Hospital, Huazhong University of Science and Technology.

Identification of *PATL2* mutations

We performed whole-exome sequencing in the patients from the two consanguineous families described above. As the pattern of inheritance is recessive in patients from consanguineous families, the infertile condition will be caused by homozygous mutations in the disease gene. We applied stringent screening criteria according to mutation types, allele frequency (< 1%) and gene function [4, 8]; only found a homozygous mutation in a known disease gene *PATL2* in three patients.

There were no mutations identified in any other disease genes related to female infertility or oocyte development.

We found a novel homozygous missense mutation (c.1528C>T; p.P510T) in *PATL2* in two patients (II-1 and II-2) in consanguineous F1, with genotype and phenotype co-segregated in F1 (Fig. 2a). This mutation was located at the C-terminal of the *PATL2* protein (Fig. 2c) and may affect protein stability.

In consanguineous F2, we identified another novel homozygous missense mutation in *PATL2* (c.1376C>A; p.S459Y) using whole-exome sequencing, and this was confirmed by Sanger sequencing (Fig. 2b). We did not find mutations in any other known disease gene related to female infertility, nor did we find mutations in other genes that are known to be involved in oocyte development. S459 is located in the PAT1 domain (Fig. 2c) involved in RNA binding, and the mutation might affect this binding. The patient’s mother and grandmother (not shown in the study) are heterozygous for the mutation. P510 and S459 are also known to be highly conserved among multiple species (Fig. 2d). The allele frequencies of two mutational sites were not found in the ExAc or 1000 Genomes databases. The SIFT, Polyphen-2, Mutation

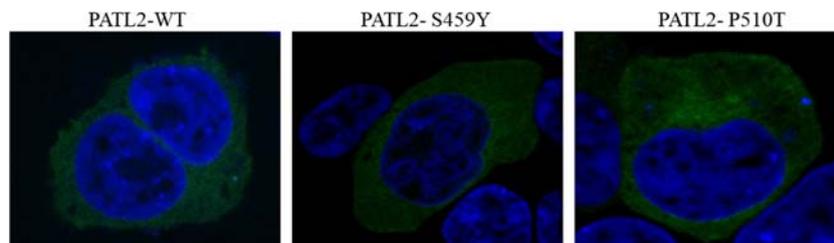


Fig. 4 The subcellular localization patterns of *PATL2* protein. PEGFP-C1-*PATL2* (WT, P510T, and S459Y) plasmids were transfected into HEK293T cells. After 36 h, cells were fixed in 4% formaldehyde, and then the nuclei of the cells were stained with DAPI (blue color)

Taster, and M-CAP predictions indicated that these two mutations were harmful (Table 2).

Expression level of PATL2 protein and subcellular localization in HEK293T cells

To assess whether the two novel mutations affected the expression of PATL2 protein in vitro, the P510T, S459Y mutant, and wild-type EGFP-tagged PATL2 expression constructs were transiently expressed in HEK293T and COS-7 cells. When we evaluated the expression of the protein by western blotting analysis (Fig. 3a and c), we showed that P510T and S459Y mutations in *PATL2* significantly decreased the expression of PATL2 protein (Fig. 3b and d). By RT-PCR, we also found that there was no significant difference in mutation levels of *PATL2* mRNA compared to WT *PATL2* in transfected HEK293T cells (36 h) (Fig. 5). Therefore, the mutation in P510T and S459Y did not affect mRNA, while affecting the level of PATL2 protein expression. There was no difference in subcellular localization patterns of the WT and *PATL2* mutation, which were both widely distributed in the cytoplasm of transfected HEK293T cells (Fig. 4).

Discussion

In the present study, we identified two novel homozygous missense mutations (P510T and S459Y) in the *PATL2* gene, in three patients from two consanguineous families that exhibited oocyte maturation arrest. P510 and S459 are highly conserved among multiple species. Chen et al. reported that the *PATL2* heterozygous mutations L189R and Y217N resulted in significant attenuation in the expression of PATL2 protein in oocytes [8]. These authors also demonstrated that the I318T mutation resulted in significantly diminished expression of PATL2 protein in cultured cell lines [8], most likely due to decreased stability of the PATL2 protein, resulting in its degradation. In our study, S459Y and P510T mutations in *PATL2* (similar to that for I318T) likely led to PATL2 protein degradation due to reduced stability of the protein, leading to a reduced level of PATL2 expression [8], and ultimately resulting in oocyte maturation arrest. S459Y and P510T mutations in *PATL2*, however, did not affect the levels of *PATL2* mRNA or the subcellular localization patterns of the PATL2 protein (Figs. 4 and 5). We therefore speculate that the main mechanism of mutations in the *PATL2* gene reduces the level of expression protein PATL2. Our three patients demonstrated significant differences in phenotypes, which might be explained by phenotypic heterogeneity.

A *PATL2* ortholog (also called *P100*) is specifically expressed in immature *Xenopus* oocytes, and gradually disappears during oocyte maturation [13]. Overexpression of P100 in *Xenopus* oocytes inhibited the accumulation of c-Mos and

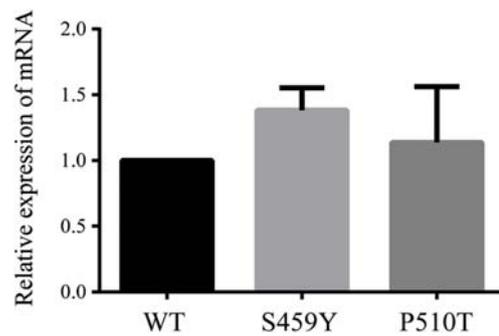


Fig. 5 The relative expression levels of *PATL2* mRNA. Real-time quantitative fluorescence PCR was performed to detect the relative expression levels of WT, S459Y, and P510T *PATL2* mRNAs 36-h post-transfection in HEK293T cells

cyclin B1 (which are involved in cell cycle regulation), and led to oocyte maturation arrest [13]. Female *PATL2* knock-out mice were fertile but fertility was significantly reduced; GV stage oocytes were significantly smaller than those from wild-type mice, and significant morphologic abnormalities were also observed in MII oocytes [14]. RNA-seq indicated a significant down-regulation of gene expression associated with oocyte maturation, including *CDC25a* and *Sohlh2*, in *PATL2*-deficient mouse oocytes [14]. Human *PATL2* (similar to *P100*) was also abundantly expressed in immature human oocytes, and some *PATL2* mutations in patients with oocyte maturation arrest resulted in decreased amounts of PATL2 protein [8]. The precise regulation of *PATL2* expression levels is important to oocyte maturation. For example, in the present study, the P510T and S459Y mutations decreased PATL2 protein expression in vitro potentially leading to a cascade of abnormal expression of genes involved in the normal maturation of oocytes resulting in arrest of oocyte maturation. However, the exact molecular mechanism whereby a *PATL2* mutation causes oocyte maturation arrest remains largely unknown and must be investigated further in the future.

To our knowledge, there are only five extant publications reported that describe mutations in *PATL2* causing female infertility with oocyte maturation arrest [7–10, 14]. Sixty-eight percent of the disease-causing mutations in *PATL2* are concentrated in the PAT1 domain (amino acids [aa] 252–491) of the *PATL2* protein, responsible for mRNA binding; 32% of mutations exist in the N-terminal region (aa 1–252), and no mutations have been reported at the C-terminus (aa 491–543) (Fig. 2c). Two novel mutations were reported in our study, one of which was located in the PAT1 domain and the other mutation (P510T) is the first mutation reported at the C-terminus. Although many genes have been reported to be involved in oocyte maturation arrest in mice and *Xenopus*, there are no reports of homologous mutations in human genes (including *Cdc25b*, *Pde3a*, *CDK1*, *MLH1*, *MEI1*, *CKS2*, *LFNG*, and *CCNB3*) [15–22]. Additionally, we did not find genetic causes for the remaining 92.5% of patients in our cohort, as there are

very likely other novel disease-causing genes involved in female infertility.

In conclusion, we identified two novel mutations in the *PATL2* gene and found that patients who carried the same *PATL2* mutation (P510T) also showed different phenotype: GV arrest (F1, II-1), and GV arrest and MI arrest (F1, II-2). We expect that our work will prove to be very useful in the diagnosis of certain infertile conditions, and to provide a basis for future treatment.

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Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

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