四川大学学报（医学版） 2024，55（3）：559－565
J Sichuan Univ（Med Sci） doi: 10.12182/20240560207

在线全文

范科尼贫血通路*FANCM*基因纯合突变导致早发性卵巢功能不全的致病机制*

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【摘要】 目的 探究范科尼贫血（Fanconi anemia, FA）通路中的*FANCM*（FA complementation group M）基因及其突变在早发性卵巢功能不全（premature ovarian insufficiency, POI）发生中的致病机制。**方法** 对1例POI患者进行了全外显子组测序，并通过Sanger测序对突变位点进行验证。构建含有野生型和突变型*FANCM*基因的质粒，分别转染至293T细胞中，转染野生型人类 *FANCM*质粒、突变型人类*FANCM* 质粒、pEGFP-C1空载体质粒的293T细胞分别命名为EGFP *FANCM*-WT组、EGFP *FANCM*-MUT组和EGFP组。对于截短蛋白的验证，3组质粒转染48 h后提取细胞蛋白，使用GFP抗体进行验证。对于DNA损伤修复影响的研究，免疫荧光实验在EGFP *FANCM*-WT组、EGFP *FANCM*-MUT组293T细胞质粒转染48 h后进行，以研究该突变是否会影响FANCM定位于染色质的能力；利用丝裂霉素C（mitomycin C, MMC）在体外诱导EGFP *FANCM*-WT组、EGFP *FANCM*-MUT组293T细胞链间交联（interstrand crosslinks, ICLs）损伤的形成，然后使用γ-H2AX抗体验证其对ICLs损伤修复的影响。**结果** 在1例近亲婚配家系的POI患者中，我们发现了*FANCM*基因c.1152-1155del:p.Leu386Valfs*10的纯合突变。Western blot结果表明，该突变导致截短的FANCM蛋白产生。在丝裂霉素C处理后，与EGFP *FANCM*-WT组相比，EGFP *FANCM*-MUT组293T细胞中γ-H2AX水平升高（$P<0.01$）。免疫荧光结果提示，突变FANCM蛋白的细胞定位只存在于细胞质，在细胞核中缺失，突变的FANCM定位于染色质的能力受损。**结论** *FANCM*基因c.1152-1155del:p.Leu386Valfs*10纯合突变导致截短的FANCM蛋白产生，并且影响FANCM蛋白在细胞核的定位，抑制其应对DNA损伤修复的能力，从而引起女性不孕。

【关键词】 *FANCM*基因 突变 早发性卵巢功能不全 DNA损伤

Homozygous Variant of *FANCM* of the Fanconi Anemia Pathway Causes Premature Ovarian Insufficiency: Investigation of the Pathogenic Mechanism

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【Abstract】 Objective Infertility affects approximately one-sixth of the people of childbearing age worldwide, causing not only economic burdens of treatment for families with fertility problems but also psychological stress for patients and presenting challenges to societal and economic development. Premature ovarian insufficiency (POI) refers to the loss of ovarian function in women before the age of 40 due to the depletion of follicles or decreased quality of remaining follicles, constituting a significant cause of female infertility. In recent years, with the help of the rapid development in genetic sequencing technology, it has been demonstrated that genetic factors play a crucial role in the onset of POI. Among the population suffering from POI, genetic studies have revealed that genes involved in processes such as meiosis, DNA damage repair, and mitosis account for approximately 37.4% of all pathogenic and potentially pathogenic genes identified. FA complementation group M (*FANCM*) is a group of genes involved in the damage repair of DNA interstrand crosslinks (ICLs), including *FANCA*-*FANCW*. Abnormalities in the *FANCM* genes are associated with female infertility and *FANCM* gene knockout mice also exhibit phenotypes similar to those of POI. During the genetic screening of POI patients, this study identified a suspicious variant in *FANCM*. This study aims to explore the pathogenic mechanisms of the *FANCM* genes of the FA pathway and their variants in the development of POI. We hope to help shed light on potential diagnostic and therapeutic strategies for the affected individuals. **Methods** One POI patient was included in the study. The inclusion criteria for POI patients were as follows: women under 40 years old exhibiting two or

* 国家自然科学基金（No. 82001516）和吴阶平医学基金会临床科研专项资助基金（No. 320.6750.2022-06-45）资助
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出版日期：2024-05-20

more instances of basal serum follicle-stimulating hormone levels>25 IU/L (with a minimum interval of 4 weeks inbetween tests), alongside clinical symptoms of menstrual disorders, normal chromosomal karyotype analysis results, and exclusion of other known diseases that can lead to ovarian dysfunction. We conducted whole-exome sequencing for the POI patient and identified pathogenic genes by classifying variants according to the standards and guidelines established by the American College of Medical Genetics and Genomics (ACMG). Subsequently, the identified variants were validated through Sanger sequencing and subjected to bioinformatics analysis. Plasmids containing wild-type and mutant *FANCM* genes were constructed and introduced into 293T cells. The 293T cells transfected with wild-type and mutant human *FANCM* plasmids and pEGFP-C1 empty vector plasmids were designated as the EGFP *FANCM-WT* group, the EGFP *FANCM-MUT* group, and the EGFP group, respectively. To validate the production of truncated proteins, cell proteins were extracted 48 hours post-transfection from the three groups and confirmed using GFP antibody. In order to investigate the impact on DNA damage repair, immunofluorescence experiments were conducted 48 hours post-transfection in the EGFP *FANCM*-WT group and the EGFP *FANCM*-MUT group to examine whether the variant affected FANCM's ability to localize on chromatin. Mitomycin C was used to induce ICLs damage *in vitro* in both the EGFP *FANCM-WT* group and the EGFP *FANCM-MUT* group, which was followed by verification of its effect on ICLs damage repair using γ-H2AX antibody. **Results** In a POI patient from a consanguineous family, we identified a homozygous variant in the *FANCM* gene, c.1152-1155del:p.Leu386Valfs*10. The patient presented with primary infertility, experiencing irregular menstruation since menarche at the age of 16. Hormonal evaluation revealed an FSH level of 26.79 IU/L and an anti-Müllerian hormone (AMH) level of 0.07 ng/mL. Vaginal ultrasound indicated unsatisfactory visualization of the ovaries on both sides and uterine dysplasia. The patient's parents were a consanguineous couple, with the mother having regular menstrual cycles. The patient had two sisters, one of whom passed away due to osteosarcoma, while the other exhibited irregular menstruation, had been diagnosed with ovarian insufficiency, and remained childless. Bioinformatics analysis revealed a deletion of four nucleotides (c.1152-1155del) in the exon 6 of the patient's *FANCM* gene. This variant resulted in a frameshift at codon 386, introducing a premature stop codon at codon 396, which ultimately led to the production of a truncated protein consisting of 395 amino acids. *In vitro* experiments demonstrated that this variant led to the production of a truncated FANCM protein of approximately 43 kDa and caused a defect in its nuclear localization, with the protein being present only in the cytoplasm. Following treatment with mitomycin C, there was a significant increase in γ-H2AX levels in 293T cells transfected with the mutant plasmid (P<0.01), indicating a statistically significant impairment of DNA damage repair capability caused by this variant. **Conclusions** The homozygous variant in the *FANCM* gene, c.1152-1155del:p.Leu386Valfs*10, results in the production of a truncated FANCM protein. This truncation leads to the loss of its interaction site with the MHF1-MHF2 complex, preventing its entry into the nucleus and the subsequent recognition of DNA damage. Consequently, the localization of the FA core complex on chromatin is disrupted, impeding the normal activation of the FA pathway and reducing the cell's ability to repair damaged ICLs. By disrupting the rapid proliferation and meiotic division processes of primordial germ cells, the reserve of oocytes is depleted, thereby triggering premature ovarian insufficiency in females.

【Key words】 *FANCM* Mutation Premature ovarian insufficiency DNA damage

早发性卵巢功能不全(premature ovarian insufficiency, POI)指女性40岁之前出现的卵巢功能丧失,由卵泡数量耗竭或残存卵泡质量下降引起。POI是导致女性不孕的重要原因,不仅对女性的身心健康造成巨大伤害,还会对家庭和社会产生不利影响。随着婚育观念的改变,POI的发病率逐渐上升,约为1%~3.7%,存在种族和地区差异[1]。POI是一种异质性疾病,其病因多样,包括遗传性、免疫性、感染性、医源性、代谢性、社会环境性、心理因素性及不明原因等。随着高通量测序技术的快速发展,越来越多的基因被发现与POI有关。最近的两项大型队列研究均指出,参与DNA损伤修复的基因构成了POI致病基因家族中的一个重要成员[2-3]。由于卵巢功能下降是不可逆的,在POI的早期阶段,患者尚能通过自然受孕或通过辅助生殖技术受孕,对POI患者进行早期识别和早期干预显得尤为重要。

范科尼贫血(Fanconi anemia, FA)是一种遗传性疾病,其主要特征是骨髓衰竭,患者对白血病和鳞状细胞癌等恶性肿瘤具有易感性[4]。该疾病由*FA*基因失活引起,在患者中,大约一半的女性患者和几乎所有的男性患者均表现出生育力受损的现象[5]。目前已确认的FA基因家族成员有22个,FANCM蛋白是FA通路的一个重要成员,曾被称为FAAP250或KIAA1596,具有ATP依赖的DNA转位酶活性,是FANCD2泛素化所必需的[6]。本研究拟通过全外显子测序的技术筛查早发性卵巢功能不全的致病基

因, 通过功能实验探讨相关基因及突变具体的致病机制。

1　资料与方法

1.1　对象资料、材料和主要仪器

1.1.1　临床样本

本研究所用患者血样标本来源于安徽医科大学第一附属医院。该患者符合POI纳入标准: ①年龄<40岁的女性; ②有两次或两次以上基础血清卵泡刺激素>25 IU/L(两次检查间隔至少为4周), 伴有月经紊乱的临床症状; ③染色体核型分析结果正常且排除其他已知可引起卵巢功能下降的疾病。本研究已经通过安徽医科大学伦理委员会批准(批准号20200113), 且受试者已签署知情同意书。

1.1.2　细胞系

人胚肾细胞(293T)购自上海富衡生物科技公司。

1.1.3　主要试剂与仪器

主要试剂: 胎牛血清、高糖DMEM培养基、1×PBS及青霉素-链霉素溶液购自中国南京森贝伽生物科技有限公司; 0.25%胰酶消化液、Lipofectamine™3000转染试剂盒及Opti-MEM培养基购自美国Invitrogen; QuickBlock™免疫染色封闭液、DAPI染色液、Western blot一抗稀释液、RIPA裂解液、磷酸酶抑制剂混合物A、蛋白酶体抑制剂PMSF、双色SDS-PAGE蛋白上样缓冲液购自中国碧云天生物技术有限公司; BIOG小量高纯去内毒素质粒提取试剂盒购自中国常州百代生物科技有限公司; ECL化学发光显色液购自中国兰杰柯科技公司; 预染蛋白Marker购自美国ThermoFisher公司; 胰蛋白胨、酵母提取物购自英国OXOID公司; 丝裂霉素C购自美国Sigma-Aldrich公司; 抗γ-H2AX抗体购自美国Cell Signaling Technology; 抗β-Actin抗体购自中国北京中杉金桥生物技术公司, 抗GFP抗体购自美国Immunoway公司; 和辣根过氧化物酶偶联的山羊抗小鼠/兔IgG抗体购自中国江苏亲科生物研究中心。

主要仪器: 核酸蛋白分析仪和二氧化碳恒温细胞培养箱购自美国Thermo Fisher公司; 恒温培养振荡器购自上海智城分析仪器制造有限公司; 细胞超声破碎仪购买自中国宁波新芝生物有限公司; 快速蛋白印迹显色仪购自中国上海天能生命科学有限公司; 超高分辨率激光共聚焦显微镜购自德国蔡司集团。

1.2　方法

1.2.1　全外显子测序和Sanger测序

患者血样分装冻存于−80 ℃, 送检进行全外显子测序。使用Agilent公司的液相芯片捕获系统, 对样本的全外显子区域DNA进行富集, 在Illumina平台进行测序。有效测序数据通过BWA和Samblaster与参考基因组(human_B37/hg19)进行比对, 随后用SAMtools对SNP、InDel及CNV位点进行识别, 并使用ANNOVAR软件进行注释。根据美国医学遗传学与基因组学学会(American College of Medical Genetics and Genomics, ACMG)制定的标准和指南对突变进行分类。筛选出的致病突变用Sanger测序进行验证。

1.2.2　细胞培养

293T细胞培养条件为: 高糖DMEM培养基(含体积分数为10%胎牛血清和体积分数为1%青霉素-链霉素溶液)。细胞置于37 ℃、体积分数5%CO_2的培养箱中培养。

1.2.3　重组质粒构建

①含有野生型和突变型人类*FANCM* cDNA的质粒由深圳华大基因股份有限公司合成, 构建的质粒载体为pEGFP-C1。*FANCM*的编码序列(coding sequence, CDS)位于EGFP的下游, EGFP表达并可产生预期的融合蛋白, 可使用抗GFP的抗体进行认证。质粒构建成功后使用Sanger测序进行验证。②将所得的菌液20 μL加入5 mL含卡那霉素的LB(Luria-Bertani)培养基, 置于震荡培养箱, 37 ℃, 200 r/min, 培养14 h。

1.2.4　质粒提取和转染

质粒提取步骤按照百代生物BIOG小量高纯去内毒素质粒提取试剂盒说明书进行。进行DNA浓度测定后, 待接种细胞长至70%融合度时, 按照Lipofectamine™3000转染试剂盒说明书进行转染, 最后将DNA-脂质体复合物加入293T细胞中, 转染质粒的终浓度约1.25 μg/mL。转染野生型人类 *FANCM*质粒、突变型人类 *FANCM*质粒、pEGFP-C1空载体质粒的293T细胞分别命名为EGFP *FANCM*-WT组、EGFP *FANCM*-MUT组和EGFP组。对于截短蛋白的验证, 质粒转染48 h后提取细胞蛋白, 使用GFP抗体进行验证。对于DNA损伤修复影响的研究, 免疫荧光实验在质粒转染48 h后进行, 以研究该突变是否会影响FANCM定位于染色质的能力; 利用丝裂霉素C(MMC, mitomycin C)在体外诱导链间交联(interstrand crosslinks, ICLs)损伤的形成, 然后使用γ-H2AX抗体验证其对ICLs损伤修复的影响。具体方法见1.2.5 ~ 1.2.6。

1.2.5　Western blot

使用新鲜配制的裂解液对细胞进行冰上裂解, 收集裂解液使用细胞超声破碎仪120 W, 15 s进行超声破碎。收集裂解液上清, 加入适量5×蛋白上样缓冲液, 100 ℃金属浴5 min使蛋白变性后, 保存于−80 ℃。提取的蛋白样品使用SDS-PAGE凝胶电泳进行分离, 然后转移至

PVDF膜上。将PVDF膜在5%脱脂牛奶中封闭，与特异性一抗γ-H2AX(1∶1 000)、GFP(1∶1 000)、内参β-actin(1∶ 1000)在4 ℃孵育过夜。第2天，将膜清洗后与二抗一起孵育1 h，清洗后用ECL化学发光显影液进行观察。最后，采用Image J软件进行灰度值计算。以目的条带灰度值与内参条带灰度值的比值，为目的条带蛋白的相对表达量。

1.2.6 *FANCM*突变对DNA损伤修复能力的影响的检测

使用免疫荧光检测突变对FANCM蛋白的定位和表达产生的影响。取EGFP *FANCM*-WT组、EGFP *FANCM*-MUT组293T细胞，转染48 h后弃去培养基。使用PBS清洗，然后在室温下使用体积分数4%多聚甲醛固定30 min。再次使用PBS清洗，使用QuickBlock™免疫染色封闭液(Beyotime)在37 ℃慢摇床上进行封闭，时长为10 min。加入DAPI染液室温染细胞核5 min。将样品置于激光共聚焦显微镜下观察细胞，并保存图像信息。另取EGFP *FANCM*-WT组、EGFP *FANCM*-MUT组293T细胞，质粒转染24 h后添加终浓度为2 μg/mL的丝裂霉素C(MMC, mitomycin C)，作用24 h后提取细胞蛋白，通过Western blot检测细胞中的γ-H2AX蛋白相对表达量(具体方法见1.2.5)，评估细胞的DNA损伤修复功能是否受到影响。

2 结果

2.1 POI患者的临床信息

患者(Ⅱ-1)为已婚汉族女性，33岁时因不孕症就诊于我院，身高165 cm，体质量57 kg。实验室性激素检查结果显示卵泡刺激素为26.79 IU/L(间隔4周以后复查为30.14 IU/L)，黄体生成素为9.81 IU/L，雌二醇为65 pmol/L，抗米勒管激素(anti-Müllerian hormone, AMH)为0.07 ng/mL。经阴道超声检查显示双侧卵巢未满意探及，子宫发育不良。患者自16岁月经初潮以来月经开始不规则，周期为3～4个月，经量偏少。24岁时在外院被诊断为卵巢功能低下，间断接受过中药及激素替代治疗。患者父母为近亲婚配，母亲月经正常。患者有两个妹妹，其中一个因骨肉瘤去世，另一个月经不规律，被诊断为卵巢功能低下，未生育。患者家系图及Sanger测序验证结果如图1A、图1B所示。

2.2 *FANCM*突变对蛋白表达的影响

生物信息学分析提示患者*FANCM*基因第6号外显子

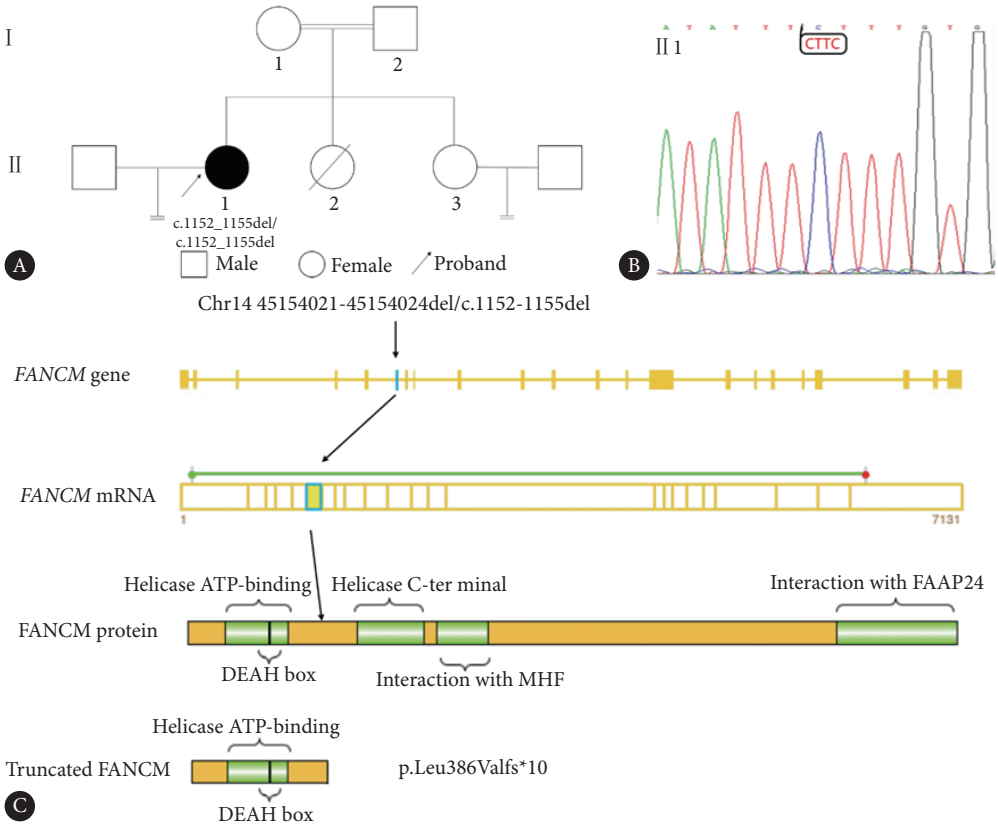

图 1 *FANCM*突变的鉴定

Fig 1 Identification of the *FANCM* variant

A, The pedigree of the patient. B, Sanger sequencing of the patient. C, Gene and protein structure schematic diagram of the *FANCM* c.1152-1155del variant. The variant caused a frameshift at codon 386, and a stop codon was introduced at codon 396, resulting in a predicted truncated protein of 395aa.

上存在4个核苷酸的缺失(c.1152-1155del)。这一突变导致第386个密码子处发生移码,并在第396个密码子处引入一个终止密码子,最终导致产生一个395个氨基酸的截短蛋白(p.Leu386Valfs*10)(图1C)。在过表达EGFP-*FANCM*-MUT的293T细胞中,可以检测到相对分子质量约为70×10^3的融合截短蛋白(来自*FANCM*-MUT的43×10^3加上来自EGFP的27×10^3);在过表达EGFP-*FANCM*-WT质粒的293T细胞中检测到相对分子质量约260×10^3的完整EGFP-FANCM蛋白(来自*FANCM*-WT的233×10^3加上来自EGFP的27×10^3)(图2A)。这些结果表明*FANCM*的纯合突变c.1152-1155del产生提前终止的密码子,形成截短的FANCM蛋白。

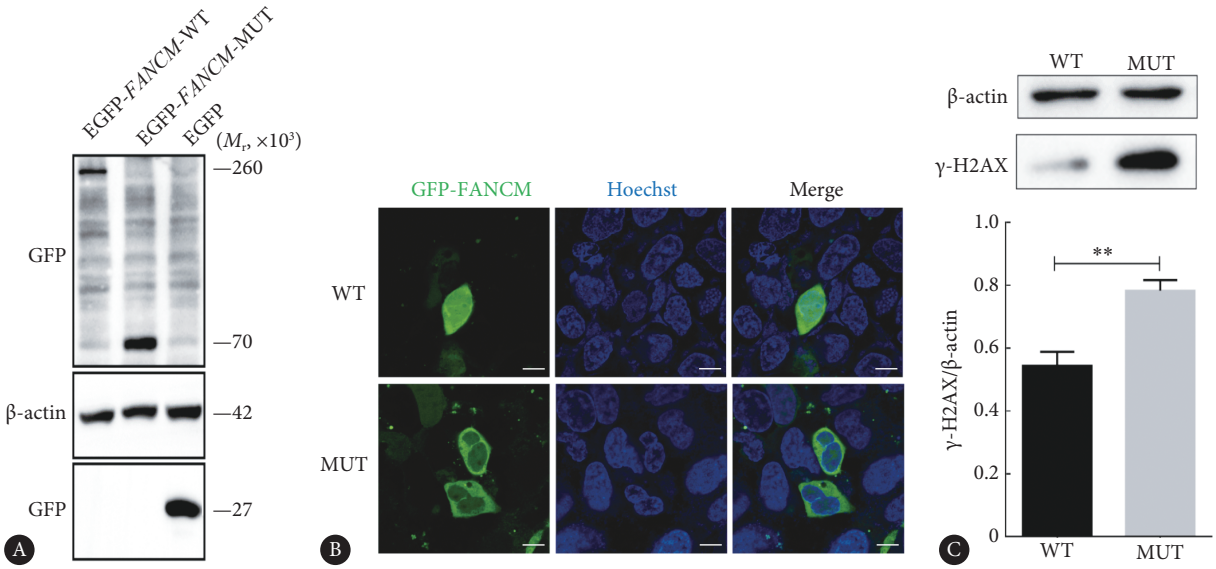

图 2　*FANCM*突变对蛋白功能的影响

Fig 2　Effect of the *FANCM* variant on the function of the protein

293T cells transfected with EGFP *FANCM*-WT, EGFP *FANCM*-MUT, and EGFP plasmid were named EGFP *FANCM*-WT group (WT group), EGFP *FANCM*-MUT group (MUT group), and EGFP group, respectively. A, EGFP *FANCM*-MUT produces a fusion protein of 70×10^3, the size of which corresponds to the predicted size of truncated FANCM (43×10^3) fusing into EGFP (27×10^3). B, Immunofluorescence localization of FANCM. FANCM was observed in the nuclei of the WT group, but was absent in the nuclei of MUT group. The scale bar represents 10 μm. C, Quantification of γ-H2AX in the WT group and the MUT group after MMC treatment. n=3. $^{**}P$<0.01. Statistical analysis was performed using t-test in SPSS. Error bars denote SD.

2.3　*FANCM*突变对DNA损伤修复能力的影响

免疫荧光检测结果显示野生型FANCM蛋白主要定位于细胞核,而突变型FANCM蛋白在细胞核中的表达受到影响,主要分布在细胞质中(图2B)。Western blot检测结果提示与过表达野生型FANCM的细胞相比,过表达突变型FANCM的细胞在MMC处理24 h后显示出更高水平的DNA损伤,差异有统计学意义(图2C),表明该突变会使细胞应对DNA损伤的修复能力受损。

3　讨论

卵子发育的过程中有两个重要时期,一个是原始生殖细胞(primordial germ cells, PGCs)的快速增殖期,另一个是卵母细胞发育成熟的减数分裂期[7]。PGCs的快速增殖会产生高复制和高转录,由此产生大量的转录-复制冲突(transcription-replication conflicts, TRCs),高频的TRC会激活FA通路。一旦FA通路失活,基因组不稳定性就会增加,进而影响卵母细胞的储备[8]。在第一次减数分裂过程中,只有当同源染色体正确排列在赤道板上时,它们才能正确分离。为了实现这种排列,同源染色体必须通过交叉(crossovers, CO)进行连接。有研究指出,FANCM有助于限制哺乳动物减数分裂的交叉数量形成,使其被严格控制在一个狭窄的范围内,此外,FANCM的同源物在减数分裂过程中通过与Mus81依赖的pro-CO途径竞争来促进非交叉的形成[9-10]。同时*FANCM*缺陷小鼠性腺中PGCs的增殖减少,并且减数分裂的DSB(双链断裂, double strand break)修复异常,进而导致性腺功能减退[11]。

FANCM蛋白属于DNA解旋酶/易位酶家族成员,是在对FA核心复合物进行质谱分析时发现的一种相对分子质量250×10^3的多肽[6]。它与古细菌的Hef以及酵母菌的Mph1 同源,在处理被干扰的复制叉和重组中间体时发挥作用[12],这些蛋白同属于超家族2解旋酶(superfamily 2 helicase, SF2)家族成员[13]。与其他家族成员的不同之处在于,FANCM缺少C端的ERCC4样核酸酶结构域,保留了

一个串联的螺旋-发夹-螺旋(HhH)2结构域,缺少作为核酸酶切割DNA的能力,但保留了与FA相关蛋白FAAP24形成异质二聚体的能力[14]。

在本研究中,我们在一个汉族近亲婚配家系中发现了*FANCM*的纯合移码突变:c.1152-1155del,p.Leu386Valfs*10。考虑到患者的家族史,其有一位妹妹因为恶性肿瘤去世,另一位妹妹也存在卵巢功能低下的情况,我们推测患者的父母可能是该突变的杂合携带者。目前关于*FANCM*基因突变引起女性不孕症的研究偏少,仅有1例涉及2名患有POI的芬兰姐妹,她们携带的*FANCM*纯合突变导致了截短蛋白p.Gln1701*的产生[15]。为了验证本研究所发现的突变是否会引起截短蛋白的产生,我们将*FANCM*-MUT的CDS序列插入EGFP的下游,EGFP表达并产生相对分子质量约为70×10^3的截短蛋白,证明该突变会引起截短蛋白的产生。有研究表明FANCM是FA核心复合物定位于染色质所必需的,在FANCM缺失的细胞中,FAAP24和其他FA核心复合物蛋白在染色质上的定位存在缺陷[16]。为了研究该突变是否会影响FANCM定位于染色质的能力,我们对转染野生型和突变型*FANCM*质粒的细胞进行免疫荧光检测,结果提示野生型FANCM蛋白主要定位于细胞核,而突变型FANCM蛋白则主要集中在细胞质,在细胞核中缺失,说明突变的FANCM定位于染色质的能力受损,这可能是其引起FA相关蛋白在细胞核定位缺陷的原因。

*FANCM*缺陷的小鼠及女性POI患者均呈现性腺功能低下的表型,这些研究主要聚焦于性腺的组织学检查和体细胞对MMC的敏感性,而没有研究其对ICLs损伤修复的影响。为了研究*FANCM*突变对ICLs损伤修复的影响,我们使用MMC对体外细胞诱导ICLs损伤,通过检测细胞中的γ-H2AX水平来评估细胞的DNA损伤修复功能是否受到影响。实验结果提示,*FANCM*突变削弱了细胞应对DNA损伤的修复能力。既往有研究表明,MHF1-MHF2复合体和FANCM-F片段(FANCM 661~800)之间会形成DNA结合位点,MHF-FANCM-F结构的改变会影响FANCM在体内的定位[17]。根据这一发现我们推测FANCM蛋白的截短使其缺失与MHF1-MHF2复合体的相互作用部位,无法进入细胞核,无法识别DNA损伤。这导致FA核心复合物在染色质上的定位受到影响,FA通路无法正常激活,使细胞对ICLs损伤的修复能力减弱。卵母细胞储备因此遭到破坏,从而引发女性POI。因此,我们推测本研究中的*FANCM*突变是本研究中POI患者的可能致病基因。然而,本研究也存在局限性,体外细胞实验不能完全模拟体内环境,携带相同*FANCM*突变的小鼠模型能够更好地探索该突变的致病机制,会在后续的工作中进一步展开。

综上所述,我们报道了第一例汉族女性的*FANCM*突变引起POI的病例。先前的研究已经指出DNA损伤修复基因与POI之间存在遗传联系[2-3],对于FANCM蛋白而言,其在卵母细胞发育过程的PGCs快速增殖,DNA损伤修复以及减数分裂中均发挥作用。鉴于FA基因失活可能导致范科尼贫血,并增加癌症易感性,对于由*FA*基因突变引起的POI患者长期随访显得尤为重要。已有多个FA相关基因敲除小鼠模型表现出卵巢功能不全的表型,同时也多次报道与FA相关的基因突变引起POI的病例,因此在临床工作中应考虑其他*FA*基因突变与POI的可能关联。对于*FA*基因突变引起的POI患者除了进行癌症风险的长期监测,还建议尽早婚育,因为此类患者在疾病早期可能还有部分卵巢功能残留;对于卵巢功能已衰竭的患者则建议尽早行辅助生殖技术受孕及卵子捐赠。

* * *

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Author Contribution WEN Xingxing is responsible for conceptualization, formal analysis, investigation, methodology, visualization, and writing--original draft. CHAI Menghan is responsible for data curation, formal analysis, and validation. ZHANG Qiannan is responsible for investigation, methodology, and validation. ZOU Huijuan is responsible for methodology, project administration, and resources. ZHANG Zhiguo and CAO Yunxia are responsible for funding acquisition, resources, supervision, and writing--review and editing. CHEN Beili is responsible for funding acquisition, project administration, resources, supervision, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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Declaration of Conflicting Interests All authors declare no competing interests.

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（2024 – 01 – 23收稿, 2024 – 04 – 28修回）

编辑　吕　熙