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◇临床医学研究◇

胚胎植入前单基因遗传学检测在遗传性癫痫家系中的应用

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摘要 **目的** 探讨胚胎植入前单基因遗传学检测(PGT-M)在遗传性癫痫家系中的临床应用价值。**方法** 基于全外显子组测序(WES)及家系共分离分析,对2例单基因遗传性癫痫家系(*PCDH19* c.1031C>G及*LGI1* c.856T>G)进行致病性评估,并实施PGT-M技术,建立临床路径模型,并追踪助孕结局。**结果** 家系1(*PCDH19*杂合可能致病变异)经2个周期促排卵活检13枚囊胚,筛选出3枚未受累整倍体胚胎(23.1%),第3次冻胚移植后成功分娩1个健康男婴,产前诊断确认胎儿未携带*PCDH19*致病变异。家系2(*LGI1*杂合意义未明变异)活检14枚囊胚,筛选2枚未受累整倍体胚胎(14.3%),首次移植未孕,第2次解冻移植后早期妊娠中。**结论** PGT-M可精准阻断单基因遗传性癫痫致病变异传递,为遗传性癫痫家系提供有效的生殖干预策略。

关键词 遗传性癫痫;全外显子组测序;*PCDH19*基因;*LGI1*基因;胚胎植入前单基因遗传学检测;家系研究

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全球约9 000种罕见病中,80%为单基因缺陷所致,综合发病率高达1%(http://www.omim.org/statistics/entry)。通过辅助生殖技术实施一级预防,可源头防控单基因遗传病,降低出生缺陷。遗传性癫痫系由单基因突变、染色体异常等引发的癫痫综合征,以反复神经元异常放电为特征,常伴神经发育障碍,具有家族聚集性或明确致病变异。Dravet综合征(Dravet syndrome, DS)作为典型代表,多由*SCN1A*基因突变(70%~80%)引起,表现为婴儿期难治性癫痫及认知衰退[1]。*PCDH19*基因(Xq22.1)是DS的第二大致病基因,以X连锁特殊遗传模式为主:女性杂合子表现为婴儿期癫痫伴智力障碍,而男性半合子通常不发病,但嵌合体男性偶见癫痫表型,具体机制未明[2-3]。*LGI1*基因变异可导致脑白质异常和癫痫表型[4],与家族性颞叶癫痫密切相关。该研究针对*PCDH19*及*LGI1*变异遗传性癫痫家系,系统解析其遗传特征与分子机制,并探讨胚胎植入前单基因遗传学检测(preimplantation genetic testing for monogenic disorders, PGT-M)的临床应用路径,为遗传性癫痫的精准阻断提供依据。

1 材料与方法

1.1 病例资料 本研究选择就诊于安徽医科大学第一附属医院生殖中心的遗传性癫痫家系为研究对象。本研究得到了安徽医科大学第一附属医院临床研究伦理委员会的批准[批号:(2023)伦理生第(20230216)号、(2023)伦理生第(20230710)号],临床资料的使用获得了患者的知情同意。家系1:男方,29岁。女方,28岁,因"男方*PCDH19*基因c.1031 C>G可能致病变异携带者(半合子,突变率49%)"于2023年7月至安徽医科大学第一附属医院生殖医学中心行PGT-M助孕治疗。男方同卵双胞胎哥哥生育2个遗传性癫痫患儿(图1A家系图);第一孩,足月顺产,女孩,出生后4个月无诱因下抽搐发作,出生后6个月再次抽搐发作夭折,未做基因检测;第二孩,足月剖宫产,女孩,出生后15个月反复抽搐发作,患儿脑电图异常,头颅MRI未见异常,心脏彩超提示心包腔少量积液,左心室假腱索,室间隔点状强回声,患儿染色体核型及拷贝数均正常,线粒体基因检测未见异常,患儿家系全外显子组测序(whole-exome sequencing, WES)检测到患儿*PCDH19*基因存在c.1031 C>G杂合变异(表1),依据美国医学遗传学与基因组学学会(American college of medical genetics and genomics, ACMG)指

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南，变异评级为可能致病变异，与早发性婴儿癫痫性脑病 9 型相关，系 DS 亚型之一。该变异来源于患儿父亲，患儿父亲该变异位点为嵌合型，患儿母亲该位点野生型，系 X 连锁特殊遗传模式。现男方本人基因检测：*PCDH19* 基因 c. 1031 C > G 可能致病变异（半合子，嵌合型，突变率 49%），男方及男方哥哥均无癫痫病史，亦无行为/精神异常等表型。家系 2：男方，29 岁。女方，35 岁，因“男方 *LGI1* 基因 c. 856 T > G 意义未明杂合变异（variant of uncertain significance，VUS）”于 2023 年 10 月至安徽医科大学第一附属医院生殖医学中心行 PGT-M 助孕治疗。男方 13 岁无诱因下首次发作性抽搐，2019 年发作性抽搐频率增多，2022 年 2 月头部 MRI：左侧海马信号稍增高，左杏仁核、海马、海马旁回信号增高，侧副沟皮层增厚。脑电图显示：异常脑电 I 型，慢波活动增多，弥漫性、中线区著。2022 年 3 月行左颞前叶及内侧结构切除术，术后癫痫发作频率明显降低，目前口服丙戊酸镁、卡马西平等。男方 WES 提示 *LGI1* 基因 c. 856 T > G 杂合变异，ACMG 评级为：VUS，位点验证提示男方母亲、男方舅舅、男方表弟均携带该杂合变异，并且均有癫痫病史；男方父亲、男方妹妹及 2 个姨妈，均不携带该变异位点，亦无相关临床表型（表 1），符合家系共分离（图 1B 家系图）。*LGI1* 基因变异相关疾病为：家族性颞叶癫痫 1 型相关，这是一种颞叶内局部病灶引起的反复发作性癫痫，遗传模式为常染色体显性遗传。

1.2 诊断与遗传咨询 结合病史、家族史及相关辅助检查结果，家系 1 诊断为：男方 *PCDH19* 基因 c. 1031 C > G 可能致病变异携带者（半合子，嵌合型）。

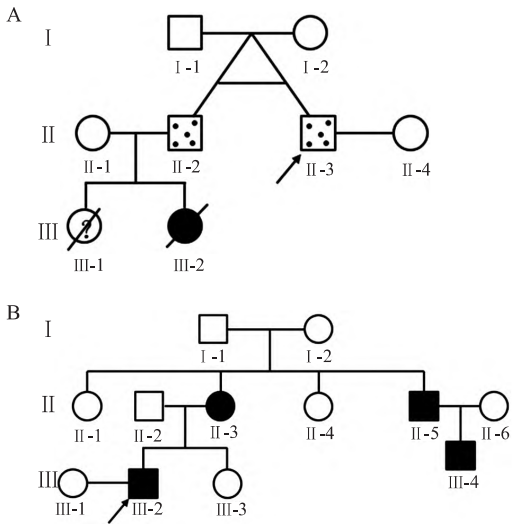

图 1 家系 1 图（A）和家系 2 图（B）

Fig. 1 Charts of Family 1 (A) and Family 2 (B)

该家族成员的遗传咨询：*PCDH19* 基因相关的 DS 的遗传模式为一种特殊的 X 连锁遗传，家系成员中携带 *PCDH19* 基因突变的杂合子女性发病；家系成员中携带 *PCDH19* 基因突变的半合子男性不发病，其女性子代均发病，男性子代均正常；而家系成员中携带 *PCDH19* 基因突变的半合子嵌合体男性可发病，也可不发病，但其女性子代可能发病，男性子代均正常。家系 2 诊断为男方 *LGI1* 基因 c. 856 T > G VUS 杂合变异，该家族成员的遗传咨询完全符合常染色体显性遗传规律，即子代中 50% 患病，50% 正常，男女患病概率均等。在涉及 VUS 的病例中，若实施 PGT-M，需建立标准化决策流程：首先由多学科团队（multidisciplinary team，MDT）综合评估变异的潜

表 1 家系成员基因检测结果

Tab. 1 Genetic testing results of family members

Family members	Chr.	Gene	Exon	Variant	Amino acid change	Genotype	Inheritance pattern
Ⅱ-4 of Family 1	ChrX	*PCDH19*	Ex1	Normal			
Ⅱ-3 of Family 1	ChrX	*PCDH19*	Ex1	c. 1031 C > G	p. Pro344Arg	Hemi (mosaicism)	XL
Ⅱ-2 of Family 1	ChrX	*PCDH19*	Ex1	c. 1031 C > G	p. Pro344Arg	Hemi (mosaicism)	XL
Ⅱ-1 of Family 1	ChrX	*PCDH19*	Ex1	Normal			
Ⅲ-2 of Family 1	ChrX	*PCDH19*	Ex1	c. 1031 C > G	p. Pro344Arg	Het	XL
Ⅲ-1 of Family 2	Chr10	*LGI1*	Ex8	Normal			
Ⅲ-2 of Family 2	Chr10	*LGI1*	Ex8	c. 856 T > G	p. Cys286Gly	Het	AD
Ⅱ-3 of Family 2	Chr10	*LGI1*	Ex8	c. 856 T > G	p. Cys286Gly	Het	AD
Ⅱ-2 of Family 2	Chr10	*LGI1*	Ex8	Normal			
Ⅱ-5 of Family 2	Chr10	*LGI1*	Ex8	c. 856 T > G	p. Cys286Gly	Het	AD
Ⅲ-4 of Family 2	Chr10	*LGI1*	Ex8	c. 856 T > G	p. Cys286Gly	Het	AD
Ⅲ-3 of Family 2	Chr10	*LGI1*	Ex8	Normal			
Ⅱ-1 of Family 2	Chr10	*LGI1*	Ex8	Normal			
Ⅱ-4 of Family 2	Chr10	*LGI1*	Ex8	Normal			

在致病性、临床相关性及检测可行性，随后提交伦理委员会审查并获得批准，以确保诊疗方案的科学严谨性和伦理合规性，从而降低因 VUS 不确定性带来的临床决策风险。对于基因诊断明确的高危家庭，可选择产前诊断、植入前遗传学诊断、供精或者抱养等生育方式。为避免妊娠遗传病患儿流产或引产给男女双方带来痛苦，通过充分的知情同意后，两对夫妇均决定在本中心行 PGT-M 助孕。

2 结果

2.1 家系 1 辅助生殖结局 家系 1 经 2 个周期控制性超促排卵(controlled ovarian hyperstimulation，COH)治疗，活检 13 枚囊胚，第 2 周期筛选出 3 枚未受累整倍体囊胚(23.1%)，第 3 次冻胚移植后成功妊娠。孕 20 周产前诊断，羊水核型 46，XN；羊水染色体微阵列分析(chromosomal microarray analysis，CMA)未见明确致病或者可疑致病变异；羊水 *PCDH19* 基因验证未检出 c.1031 C>G 位点。各项产检均正常，2025 年 5 月 21 日剖宫产 1 个健康男婴(家系 1 第 2 周期胚胎检测结果见表 2)。

表 2 家系 1 第 2 个 COH 周期胚胎检测结果

Tab.2 Embryo testing results of the second COH cycle in family 1

Embryo ID	Embryo grading	Haplotype	PGT-M	PGT-A
2	4BB(D6)	M1	Normal	-22
3	4BA(D6)	M1/F0	pathogenic	N/A
4	4AA(D5)	M0	Normal	Mosaic(Trisomy 9 mosaicism, 30%)
5	4BB(D5)	M0	Normal	22
6	**4BB(D5)**	**M0**	Normal	**Balanced; Euploid**
7	**4BB(D5)**	**M1**	Normal	**Balanced; Euploid**
8	4AA(D5)	M1/F0	pathogenic	N/A
10	4BB(D6)	M1/F0	pathogenic	N/A
12	4BC(D5)	M0/F0	pathogenic	N/A
13	**4BB(D5)**	**M1**	Normal	**Balanced; Euploid**

M0, M1: Maternal chromosomes; F0: Paternal at-risk chromosome; Results interpretation: Embryos-3, Embryos-8, Embryos-10, Embryos-12: Inherited the paternal F0 chromosome, sanger sequencing and high-throughput sequencing results were both normal, but the normal results do not exclude allele dropout (ADO); Embryos-6, Embryos-7, Embryos-13: Combined PGT-A analysis indicates no inheritance of the paternal at-risk chromosome (F0); Embryos-1, Embryos-9, Embryos-11: Arrested at pre-blastocyst stage, no biopsy performed and discarded.

2.2 家系 2 辅助生殖结局 家系 2 经 2 个周期 COH 治疗，活检 14 枚囊胚，筛选 2 枚未受累整倍体囊胚(14.3%)，首次移植未孕，第 2 次解冻移植后，现处于早期妊娠中。

3 讨论

PCDH19 基因(Xq22.1)编码原钙黏附蛋白 19，通过钙依赖性同源二聚化调控神经环路同步化[5]。本案例发现的 *PCDH19* c.1031C>G(p.Ala344Gly)变异位于 EC6 结构域，能够破坏钙离子结合位点(D386/E388)稳定性，导致二聚化能力下降(REVEL 评分 0.89)，根据 ACMG 指南分类为“可能致病”[6]。*PCDH19* 基因变异相关遗传性癫痫的 X 连锁特殊遗传模式由“细胞干扰”假说来解释：在健康男性和健康女性体内只表达野生型的 *PCDH19* 蛋白，男性半合子体内只表达突变型的 *PCDH19* 蛋白，相同的蛋白可以彼此黏附，因此表型均正常。*PCDH19* 基因突变的女性杂合子或男性嵌合体，因体内同时表达突变型和野生型 2 种不同的 *PCDH19* 蛋白，2 种细胞群共存造成的组织镶嵌性改变了正常的细胞与细胞之间的相互作用，导致临床症状的出现而致病[7]。但本案例中男性嵌合体(外周血嵌合率 49%)并未表现出癫痫症状，机制涉及：① 组织特异性嵌合分布：突变细胞富集于外周血 $CD34^+$ 祖细胞(51%)，而脑神经元前体突变率仅 3%[8]；② 表观代偿：X 染色体失活偏移(XCI>85%)及 H3K27me3 修饰沉默突变等位基因[9]；③ 同源基因代偿：*PCDH17* 表达上调 2.3 倍($P=0.007$)，部分替代 *PCDH19* 功能[10]。

LGI1 基因作为癫痫相关的重要遗传因子，有研究[4,11]表明，*LGI1* 编码的分泌蛋白通过与少突胶质细胞膜上的 OPALIN 受体结合，调控少突胶质细胞分化及髓鞘形成，其功能缺失可导致脑白质异常和癫痫表型。*LGI1* 突变(如新发现的 *LGI1*_D51G 和截短变异 c.1174C>T)被发现与家族性颞叶癫痫相关，患者临床表型较轻且对丙戊酸钠治疗反应良好[12]。这些发现不仅深化了对 *LGI1* 在神经发育和疾病中多功能性的理解，还为遗传性疾病阻断提供了理论依据。

PGT-M 常用于在胚胎植入子宫前检测其是否携带特定的单基因遗传病致病变异，帮助有单基因遗传病风险的夫妇筛选出不携带致病变异的胚胎，避免将疾病遗传给子代，适用于常染色体显性、隐性或 X 连锁遗传病的预防[13-15]。本案例优先移植男性胚胎易引发伦理争议，根据《人类辅助生殖技术管理办法》(2021 修订版)第 14 条及《中国医师协会生殖医学伦理指南》(2022 版)，严重 X 连锁致残性疾病允许胚胎性别选择，但需经伦理委员会审

批[16]。同时,孕中期通过产前诊断多项技术验证确保子代健康。

本研究通过 PGT-M 技术对 2 个罕见遗传性癫痫家系进行胚胎遗传学筛选,有效预防致病性变异向子代的垂直传递,系统构建了“分子诊断 - 胚胎选择 - 产前质控”的全链条管理体系。案例表明:针对 X 连锁嵌合突变和常染色体的 VUS 变异,需整合多学科联合、动态风险评估及多维度伦理框架,实现技术获益与社会价值的平衡。本案例为遗传性癫痫的生殖干预提供了可推广的“精准医学范式”。

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Application of preimplantation genetic testing for monogenic disorders in families with hereditary epilepsy

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Abstract ***Objective*** To evaluate the clinical efficacy of preimplantation genetic testing for monogenic disorders

(PGT-M) in families with hereditary epilepsy. ***Methods*** Whole-exome sequencing (WES) and familial co-segregation analysis were performed to validate the pathogenicity of variants (*PCDH19* c.1031C>G and *LGI1* c.856T>G) in two monogenic epilepsy families. A clinical PGT-M pathway was implemented, and reproductive outcomes were tracked. ***Results*** In Family 1 (*PCDH19* likely pathogenic variant), 13 blastocysts were biopsied over two ovarian stimulation cycles, yielding 3 unaffected euploid embryos (23.1%). After the third frozen embryo transfer, a healthy male infant was successfully delivered. Prenatal diagnosis confirmed that the fetus did not carry the pathogenic variant *PCDH19*. Family 2 (*LGI1* variant of uncertain significance, VUS) screened 14 blastocysts, identifying 2 unaffected euploid embryos (14.3%), with the first transfer unsuccessful. A clinical pregnancy was currently ongoing following the second frozen-thawed embryo transfer (FET). ***Conclusion*** PGT-M can precisely block the vertical transmission of monogenic epileptic pathogenic variants, offering an effective reproductive intervention strategy for families with hereditary epilepsy.

Key words hereditary epilepsy; whole-exome sequencing; *PCDH19* gene; *LGI1* gene; preimplantation genetic testing for monogenic disorders; pedigree study

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of microglia by lipopolysaccharide (LPS) and the inhibitory effect of Biochanin A (Bio A) on microglia activation. ***Methods*** The MTT method was used to select the optimal concentrations for LPS, CORT and Bio A on BV2 cells; BV2 cells were divided into 5 groups: Control group, CORT (50 nmol/L) group, LPS (1 μg/mL) group, LPS (1 μg/mL) + CORT (50 nmol/L) group, and LPS (1 μg/mL) + CORT (50 nmol/L) + Bio A (5 μmol/L) group; Except for the control group, each group was first incubated with CORT (50 nmol/L) for 2 h, and then each group was co-incubated with the corresponding concentrations of LPS (1 μg/mL) and BioA (5 μmol/L) for 36 h; DCFH-DA probe method was used to detect reactive oxygen species (ROS) content; Western blot was used to detect the protein expression levels of inflammatory cytokines, 5-hydroxytryptamine(5-HTT), glucocorticoid receptor (GR), mineralocorticoid receptor (MR), NOD-like receptor family pyrin domain containing 3 (NLRP3), apoptosis-associated speck-like protein containing a CARD (ASC) and cysteine-aspartic protease 1 (Caspase-1). ***Results*** Compared with the CORT (50 nmol/L) and LPS (1 μg/mL) groups, cells in the CORT (50 nmol/L) + LPS (1 μg/mL) group showed increased cell viability, higher levels of ROS, and increased levels of inflammatory cytokines, NLRP3, ASC, and Caspase-1 protein expression ($P<0.05$); Compared with the CORT (50 nmol/L) + LPS (1 μg/mL) group, the CORT (50 nmol/L) + LPS (1 μg/mL) + Bio A (5 μmol/L) group showed decreased cell viability, decreased levels of ROS, and decreased protein expression of inflammatory cytokines, NLRP3, ASC and Caspase-1 proteins ($P<0.05$). ***Conclusion*** A low dose of CORT pretreatment reinforces LPS-induced BV2 cell activation; Bio A inhibits CORT-pretreated LPS-induced BV2 cell activation. The mechanism of which may be related to the inhibition of NLRP3 inflammasome activation.

Key words corticosterone; lipopolysaccharide; microglia; biochanin A; reactive oxygen species; NLRP3 inflammasome

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