遗传性耳聋的产前诊断与遗传咨询

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【摘要】 目的 耳聋是临床上常见的出生缺陷之一,大多数耳聋患儿家长对于耳聋的遗传检测及产前诊断持积极态度。**方法** 对 117 例非综合征型感音神经性耳聋患儿家庭进行耳聋基因检测,辅以恰当的遗传咨询,并为有再生育需求的家庭提供产前基因诊断。**结果** 通过基因检测为 57 例患儿找到明确致聋基因突变,并将致聋位点及遗传模式在每个患儿家庭中进行分析验证。接受详细的遗传咨询后,53 对携带常染色体隐性遗传致聋突变的夫妇选择产前基因诊断。出生后听力评估结果与产前诊断结果相符。**结论** 本临床研究中,94.6%携带常染色体隐性遗传致聋基因突变的夫妇选择接受产前基因诊断,提示绝大多数耳聋患儿的家长对于耳聋的遗传检测及产前诊断持积极态度,认为产前基因检测有助于家长从心理、经济、医疗等角度提前做好准备。

【关键词】 耳聋;产前诊断;遗传咨询
【中图分类号】 R714.55 **【文献标识码】** A

【Abstract】 Objective Genetic counseling and prenatal diagnosis are very necessary to detect hereditary hearing loss, especially in high-risk families. Prenatal diagnosis gives parents the chance to prepare psychologically, financially and medically for the probable health and educational needs of the affected neonates. **Method** 117 unrelated families with children affected with non-syndromic sensorineural hearing loss were enrolled in the study and received genetic analysis with microarray and DNA sequencing technologies. Genetic counseling was provided to each participating families, and prenatal diagnosis was given to those at risk and would like to know their fetuses' genotypes and probable hearing statuses. **Results** 57 cases in the present study were diagnosed with confirmed pathogenic mutations and clear inheritance patterns. After receiving genetic counseling, 53 carrier couples with pathogenic mutations chose to proceed prenatal diagnosis, the results of which were in accordance with the pregnancy outcomes. Infants prenatally detected to be monoallelic mutation carriers and those harbored neither deafness-causing mutations form their parents passed newborn hearing screening and six month follow-ups, while neonates prenatally detected to be carriers of diallelic or compound heterozygous mutations developed hearing loss after birth. **Conclusions** With appropriate genetic counseling and support services provided, the genetic testing and the prenatal diagnosis of hearing loss were valued by carrier couples for the information provided for future family planning and probably the preparation for the health and educational needs of the affected neonates.

【Key words】 hearing loss; genetic counseling; prenatal diagnosis

耳聋是临床上常见的出生缺陷之一,每 1000 名活产儿中便有 1~3 名新生聋儿[1,2]。在未全面开展早期听力检测计划前,患儿听力缺失多在 1.5~3 岁间被发现,但已错过了学语的重要时期[1,3]。由于幼儿期大脑可塑性的改变,在这一重要时期未获得充分的听觉刺激及语言接触的孩童将面临包括语言获取、认知发展、社会心理发展及社会交往能力等多方面的障碍[4-6]。据报道,绝大多数耳聋患儿的家长

DOI: 10.13470/j.cnki.cjpd.2015.04.009
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对于耳聋的遗传检测及产前诊断持积极态度[7-9]。产前基因检测有助于患儿家长及早从心理、经济、医疗等角度为受累患儿做好医疗及特殊教育的准备。在这个过程中,恰当的遗传咨询十分重要[10]。遗传咨询的内容需包括疾病的性质、突变携带的意义、遗传模式及再发风险等。

1 材料与方法

1.1 基本资料 本临床研究将 117 个曾生育非综合征型感音神经性耳聋患儿的家庭纳入研究范围,入组家庭均为在广东省妇幼保健院医学遗传中心门诊寻求耳聋基因诊断和遗传咨询的耳聋患儿家庭。研究方法和研究对象入组标准经广东省妇幼保健院伦理委员会审核通过。在受检者(监护人)充分知情同意情况下,签署知情同意书。临床上对入组家庭进行病史收集及体格检查,包括详细的过往病史、耳聋家族史、听力学检查情况、发病年龄及诱因、感染史、氨基糖苷类药物接触史等。

1.2 研究方法 采集耳聋患儿及其父母的外周血,提取基因组 DNA。通过晶芯™9 项遗传性耳聋基因检测试剂盒进行突变热点的初筛,对于检出单等位基因致聋突变的患儿,进行相应基因及可能相互作用复合致聋的相关基因的序列分析;对于初筛未检出致聋突变的患儿,进行 *GJB2* 基因、*SLC26A4* 基因、线粒体 12*S rRNA* 等耳聋基因的编码区序列测定及分析。对患儿父母进行相应致聋基因序列分析,以验证致聋基因突变并进行遗传分析。

综合分析耳聋患儿的临床表现及基因检测结果,为每个入组家庭提供详细的遗传咨询及生活指导[10,12-14],包括聋病性质、致聋因素、遗传模式、干预方式等。对于有再生育需求的家庭,提供再发风险分析及生育指导,包括胚胎植入前诊断、接受捐赠配子、产前基因诊断等。对于准备接受耳聋产前诊断的家庭,在遗传咨询中需包含胎儿取材术的手术流程、技术风险、检测局限性等内容[15]。

对于选择接受耳聋基因产前诊断的家庭,在夫妻双方充分知情同意情况下,经超声介导行绒毛穿刺术或羊膜腔穿刺术取得胎儿样本,进行产前基因检测[16]。胎儿样本采集过程经广东省妇幼保健院伦理委员会审核通过。为避免手术过程中母体细胞对羊水、绒毛等胎儿样本造成污染[17,18],影响产前基因检测结果,我们通过荧光定量 PCR 检测 13、18、21 号染色体上的 13 个微卫星多态标记以鉴别污染。

2 结 果

经基因检测,发现本临床研究所收集的 117 例非综合征型感音神经性耳聋患儿中,62 例携带常染色体隐性遗传致聋突变位点,其中 56 例携带双等位基因致聋突变或复合杂合突变,6 例仅检出单等位基因致聋位点,致聋位点及遗传模式在每个患儿家庭中经分析、验证。接受详细的遗传咨询后,53 对携带致聋突变的夫妇选择接受产前基因诊断。如表 1 所示,10 例胎儿未携带致聋突变、32 例携带单等位基因致聋突变位点、11 例携带双等位基因致聋突变或复合杂合突变。根据耳聋基因产前诊断的结果,为各家庭提供相应的遗传咨询及生活指导。出生后听力评估结果与产前诊断结果相符。此外,3 对携带常染色体隐性遗传致聋突变的夫妇经充分知情同意后选择不进行耳聋基因产前诊断,其中一对夫妇生育听力缺失患儿,我们为其提供早期诊断、干预及援助信息。

表 1 曾生育耳聋患儿且已明确夫妇均携带常染色体隐性遗传致聋基因突变的家庭行产前诊断的结果

家系编号	突变基因	先症者基因型	母亲基因型	父亲基因型	胎儿基因型
F1	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C
F2	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C
F3	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C	Wild type
F4	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C	Homozygous c. 235 del C
F5	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C	Wild type
F6	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C	Wild type
F7	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C
F8	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C

续表 1

家系编号	突变基因	先症者基因型	母亲基因型	父亲基因型	胎儿基因型
F9	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C	Wild type
F10	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C	Homozygous c. 235 del C
F11	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C
F12	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 235 del C	Not know (refuse prenatal diagnosis)
F13	*GJB2*	Heterozygous c. 235 del C, c. 299_300 del AT	Heterozygous c. 235 del C	Heterozygous c. 299_300 del AT	Heterozygous c. 235 del C
F14	*GJB2*	Heterozygous c. 235 del C, c. 299_300 del AT	Heterozygous c. 299_300 del AT	Heterozygous c. 235 del C	Heterozygous c. 299_300 del AT
F15	*GJB2*	Heterozygous c. 235 del C, c. 512 ins AACG	Heterozygous c. 512 ins AACG	Heterozygous c. 235 del C	Heterozygous c. 235 del C
	GJB2	Heterozygous c. 176_191 del 16bp, c. 235 del C	Heterozygous c. 176_191 del 16bp	Heterozygous c. 235 del C	Heterozygous c. 176_191 del 16 bp
F16	*GJB2*	Heterozygous c. 235 del C, c. 512 ins AACG	Heterozygous c. 235 del C	Heterozygous c. 512 ins AACG	Heterozygous c. 235 del C
F17	*GJB2*	Heterozygous c. 235 del C, c. 299_300 del AT	Heterozygous c. 235 del C	Heterozygous c. 299_300 del AT	Heterozygous c. 235 del C, c. 299_300 del AT
F18	*GJB2*	Heterozygous c. 109 G>A, c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 109 G>A	Heterozygous c. 109 G>A
F19	*GJB2*	Heterozygous c. 109 G>A, c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 109 G>A	Heterozygous c. 109 G>A, c. 235 del C
F20	*GJB2*	Heterozygous c. 109 G>A, c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 109 G>A	Heterozygous c. 109 G>A
F21	*GJB2*	Heterozygous c. 109 G>A, c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 109 G>A	Wild type
F22	*GJB2*	Homozygous c. 235 del C	Heterozygous c. 235 del C, c. 109 G>A	Heterozygous c. 235 del C	Heterozygous c. 109 G>A
F23	*GJB2*	Heterozygous c. 109 G>A, c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 109 G>A	Heterozygous c. 109 G>A, c. 235 del C
F24	*GJB2*	Heterozygous c. 109 G>A, c. 235 del C	Heterozygous c. 109 G>A	Heterozygous c. 235 del C	Heterozygous c. 109 G>A
F25	*GJB2*	Homozygous c. 109 G>A	Heterozygous c. 109 G>A	Heterozygous c. 109 G>A	Homozygous c. 109 G>A
F26	*GJB2*	Heterozygous c. 109 G>A, c. c. 250 G>A	Heterozygous c. 109 G>A	Heterozygous c. 250 G>A	Heterozygous c. 250 G>A
F27	*GJB2*	Heterozygous c. 235 del C, c. 299_300 del AT	Heterozygous c. 299_300 del AT	Heterozygous c. 235 del C	Heterozygous c. 235 del C
F28	*GJB2*	Heterozygous c. 109 G>A, c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 109 G>A	Heterozygous c. 109 G>A
F29	*GJB2*	Heterozygous c. 109 G>A, c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 109 G>A	Heterozygous c. 109 G>A
F30	*GJB2*	Heterozygous c. 176_191 del 16 bp, c. 235 del C	Heterozygous c. 176_191 del 16bp	Heterozygous c. 235 del C	Heterozygous c. 176_191 del 16 bp, c. 235 del C
F31	*GJB2*	Heterozygous c. 109 G>A, c. 299_300 del AT	Heterozygous c. 299_300 del AT	Heterozygous c. 109 G>A	Heterozygous c. 299_300 del A
F32	*GJB2*	Heterozygous c. 176_191 del 16 bp, c. 235 del C	Heterozygous c. 176_191 del 16bp	Heterozygous c. 235 del C	Heterozygous c. 176_191 del 16 bp
F33	*GJB2*	Heterozygous c. 109 G>A, c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 109 G>A	Heterozygous c. 235 del C
F34	*GJB2*	Heterozygous c. 109 G>A, c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 109 G>A	Heterozygous c. 109 G>A, c. 235 del C
F35	*GJB2*	Heterozygous c. 109 G>A, c. 176_191 del 16 bp	Heterozygous c. 176_191 del 16 bp	Heterozygous c. 109 G>A	Heterozygous c. 109 G>A
F36	*GJB2*	Heterozygous c. 109 G>A, c. 235 del C	Heterozygous c. 235 del C	Heterozygous c. 109 G>A	Not know (refuse prenatal diagnosis)
F37	*GJB2*	Homozygous c. 109 G>A	Heterozygous c. 109 G>A	Heterozygous c. 109 G>A	Wild type
	SLC26A4	Heterozygous c. 1229 C>T	Wild type	Heterozygous c. 1229 C>T	Wild type
F38	*SLC26A4*	Homozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G
	GJB2	Heterozygous c. 299_300 del AT	Wild type	Heterozygous c. 299_300 del AT	Heterozygous c. 299_300 del AT

续表 1

家系编号	突变基因	先症者基因型	母亲基因型	父亲基因型	胎儿基因型
F39	*SLC26A4*	Heterozygous c. 919-2 A>G, c. 1229 C>T	Heterozygous c. 1229 C>T	Heterozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G
	GJB2	Heterozygous c. 109 G>A	Heterozygous c. 109 G>A	Wild type	Wild type
F40	*SLC26A4*	Homozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G	Wild type
	GJB2	Heterozygous c. 109 G>A	Wild type	Heterozygous c. 109 G>A	Wild type
F41	*SLC26A4*	Heterozygous c. 919-2 A>G, c. 2168A>G	Heterozygous c. 2168 A>G	Heterozygous c. 919-2 A>G	Wild type
F42	*SLC26A4*	Heterozygous c. 919-2 A>G, c. 1536-1538 delAG	Heterozygous c. 1536-1538 delAG	Heterozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G, c. 1536-1538 delAG
F43	*SLC26A4*	Heterozygous c. 754 T>C, c. 2168A>G	Heterozygous 2168 A>G	Heterozygous c. 754 T>C	Wild type
F44	*SLC26A4*	Heterozygous C. 1343 C>T, c. 2086 C >T	Heterozygous C. 1343 C>T	Heterozygous c. 2086 C >T	Heterozygous C. 1343 C>T
F45	*SLC26A4*	Heterozygous c. 754 T>C, c. 2086 C >T	Heterozygous c. 754 T>C	Heterozygous c. 2086 C >T	Heterozygous c. 754 T>C
F46	*SLC26A4*	Heterozygous C. 1343 C>T, 2168 A>G	Heterozygous 2168 A>G	Heterozygous C. 1343 C>T	Heterozygous C. 1343 C>T
F47	*SLC26A4*	Heterozygous c. 919-2 A>G, c. 1548 ins C	Heterozygous c. 919-2 A>G	Heterozygous c. 1548 ins C	Heterozygous c. 919-2 A>G
F48	*SLC26A4*	Heterozygous c. 754 T>C, c. 2168A>G	Heterozygous c. 2168 A>G	Heterozygous c. 754 T>C	Heterozygous c. 2168 A>G
F49	*SLC26A4*	Heterozygous c. 754 T>C, c. 919-2 A>G	Heterozygous c. 919-2 A>G	Heterozygous c. 754 T>C	Heterozygous c. 754 T>C, c. 919-2 A>G
F50	*SLC26A4*	Heterozygous c. 754 T>C, c. 919-2 A>G	Heterozygous c. 754 T>C	Heterozygous c. 919-2 A>G	Heterozygous c. 754 T>C, c. 919-2 A>G
F51	*SLC26A4*	Homozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G
F52	*SLC26A4*	Heterozygous c. 754 T>C, c. 919-2 A>G	Heterozygous c. 919-2 A>G	Heterozygous c. 754 T>C	Heterozygous c. 754 T>C, c. 919-2 A>G
F53	*SLC26A4*	Heterozygous c. 919-2 A>G, c. 1486 C>T	Heterozygous c. 919-2 A>G	Heterozygous c. 1486 C>T	Wild type
F54	*SLC26A4*	Heterozygous c. 2086 C >T, c. 1548 ins C	Heterozygous c. 2086 C >T	Heterozygous c. 1548 ins C	Heterozygous c. 2086 C >T
F55	*SLC26A4*	Homozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G	Heterozygous c. 919-2 A>G
F56	*SLC26A4*	Heterozygous c. 754 T>C, c. 919-2 A>G	Heterozygous c. 919-2 A>G	Heterozygous c. 754 T>C	Not know (refuse prenatal diagnosis)

此外,一位耳聋患儿经检测发现携带线粒体 DNA 12S rRNA 1555A>G 同质性突变。该患儿自一岁半因肺炎接受常规剂量庆大霉素治疗后出现重度感音神经性耳聋。鉴于线粒体 DNA 12S rRNA 1555A>G 突变是氨基糖苷类药物遗传易感性的重要机制[19]且遵循母系遗传模式,我们为该患儿的母系亲属提供了详细的用药指导。

3 讨　论

在遗传检测过程中,客观、恰当的遗传咨询十分重要。一般来说,遗传咨询需包括检测前咨询与检测后咨询部分[10]。耳聋基因检测前的遗传咨询需涉及聋病性质、致聋因素、遗传方式、检测手段及各种检测方法的优势、劣势、风险等。检测后咨询需在检测前咨询的基础上对检测结果进行分析与解释,并对检测结果所产生的心理影响做出评估,必要时为病患家庭提供心理疏导机构信息。

本临床研究中,94.6%携带常染色体隐性遗传致聋基因突变的夫妇选择接受产前基因诊断,提示大多数耳聋患儿的家长对于耳聋的遗传检测及产前诊断持积极态度,认为产前基因检测有助于家长从心理、经济、医疗等角度提前做好准备。对于产前诊断结果及患病胎儿去留的态度则受多方面因素影响,包括伦理道德标准、宗教信仰、文化程度、经济条件以及管理相关领域的法律法规。

此外,本临床研究中的 117 例耳聋患儿均出生

于听力正常的家庭,其中 103 例无耳聋家族史。鉴于耳聋是临床上最常见的出生缺陷,每 1000 名活产儿中便有 1～3 名新生聋儿,而 90%～95%的耳聋患儿出生于听力正常的家庭[20],明确正常听力人群耳聋基因的携带率与突变谱对于耳聋防控具有重要意义。

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(收稿日期:2015-09-07)

编辑:宋文颖