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604 例育龄期夫妇单基因遗传病携带者筛查的结果分析

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摘要 **目的** 了解安徽省育龄期人群单基因遗传病致病基因携带情况以及常见变异,探索建立安徽省携带者筛查临床应用网络与转诊模式,探讨在临床实施扩展性携带者筛查(ECS)的应用价值。**方法** 收集备孕或早孕期(≤13⁺6 周)表型正常无遗传病家族史的 604 例育龄人群样本。采用基于高通量测序结合特殊 PCR 分析技术,检测与 220 种疾病相关的致病变异,对阳性携带者的配偶进行相关基因检测。**结果** 截至 2023 年 5 月 16 日,收集到受检样本 604 例,检测出目标疾病携带者 340 例;检出致病变异检测阳性率为 56.29%;共检出致病变异 499 个,每名受检者携带 0~5 个变异;携带 1 种单基因隐性遗传病致病变异 216 例,占 35.76%,最为常见。携带 2 种单基因隐性遗传病致病变异 95 例,占 15.73%。截至目前已发报告夫妻 302 对,筛查中共发现高风险夫妇 7 对,高风险率为 2.32%。遗传模式为常染色体隐性的共 5 对(夫妻双方均携带同一致病基因),遗传模式为 X-连锁的共 2 对(女方携带 X-连锁致病基因)。**结论** 本研究获得了 604 例接受 ECS 检测的受检者目标疾病的总体携带和临床应用情况以及常见单基因遗传病致病基因的携带率,可以为安徽省携带者筛查临床应用网络与转诊模式的建立提供科学指导。

关键词 单基因遗传病;扩展性携带者筛查;高通量测序;遗传咨询;出生缺陷;产前诊断;二代测序技术
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单基因遗传病是指由一对等位基因或者一对同源染色体上的单个基因突变所导致的疾病。OMIM 数据库显示,目前单基因病超过 8 000 种,其中隐性遗传病约 1 300 多种。单基因病虽然相对少见,但综合发病率约 1/100,占出生缺陷的 22.2%,可致死、致畸、致残,缺乏有效的治疗手段或治疗费用昂贵。总而言之,单基因病在总体人群中的发病率并不低,多数单基因病不易诊断且病情严重,目前尚无有效的治疗措施,此类胎儿的出生通常会给患儿家庭以及社会带来沉重的心理及经济负担[1]。因此通过检测无症状人群的致病基因携带情况,采用合理的生育选择来有效地避免严重缺陷患儿的出生就显得尤为重要。扩展性携带者筛查(expanded carrier screening, ECS)以高通量测序技术为基础,可以不分种族或地理背景,一次性筛查十几种甚至上百种常染色体隐性或 X 染色体连锁隐性单基因病,是出生缺陷一级防控中不可缺少的环节[2]。该研究采集 302 对备孕或早孕期(≤13+6 周)的育龄期受试者夫妻双方 3~5 ml 血液样本,用高通量测序结合特殊 PCR 技术对本项目规定的基因列表中的 SNV、Indel 进行分析,从而完成对检出位点的变异注释和对 220 种以上目标筛查疾病的过滤筛查。

1 材料与方法

1.1 研究对象 回顾性分析 2022 年 6 月-2023 年 5 月来安徽医科大学第一附属医院产前诊断中心就诊的备孕或早孕期(≤13+6 周)的正常夫妇 302 对,共 604 例;夫妻双方均自愿参与且签署知情同意书,并接受随访。在 302 对夫妻中,女性平均年龄约为 31 岁,男性平均年龄约 32 岁;其中备孕及早孕的夫妻分别为 239 对和 63 对。处于早孕期且携带目标疾病的妻子共 34 例,平均年龄为 31 岁;未携带致病基因的早孕期妻子 29 例,平均年龄为 30 岁。

1.2 方法

1.2.1 检测平台 本科研项目为单基因遗传病携

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带者筛查检测,测序及分析工作根据科研项目进度安排分别在杭州博圣医学检验实验室与中国人民解放军总医院进行,采用高通量测序结合特殊 PCR 技术对不少于 220 种疾病进行筛查。

数据分析以 GRCh37(hg19)基因组版本为依据。对测序下机的原始数据进行目标区域覆盖度和测序质量评估,采用一系列生物信息学分析流程(pipelines),对本科研项目规定的基因列表中的 SNV、Indel、常规 CNV 及部分特殊 CNV 变异进行生物信息学分析和致病性分析。

对于变异分析的结果进行变异注释和过滤筛查,参照 ACMG 遗传变异分类标准及指南(PMID:25741868),并基于目前对基因的认知水平进行变异的致病性判读。最终在研究结果告知书中报告致病性等级为致病(pathogenic)和疑似致病(likely pathogenic)的变异。

1.2.2 纳入筛查疾病的选择标准 目前已明确发病机制的单基因疾病种类繁多,盲目增加携带者筛查的疾病种类只会加大临床遗传咨询的难度,同时给受检者带来负担。因此本研究为最大限度地发挥筛查的临床效果与减小受检者压力,制定了如下筛查疾病的选择标准:① 基因型 - 表型联系明确;② 目前临床上已有成熟的诊断标准;③ 携带率高,发病率高,且在生命早期发病;④ 疾病明确会影响患者认知及生活质量,需要医疗干预的。

1.2.3 检测技术 本研究采用液相杂交捕获结合二代测序(next generation sequencing, NGS)技术,对目标基因的外显子区域和附近区域进行捕获富集,再进行测序和生信分析,可以检测单碱基变异(single nucleotide variant, SNV)、缺失重复变异(indel variant),以及部分拷贝数变异(copy number variation, CNV)和特殊变异。液相杂交捕获结合二代测序技术可同时检测 220 种基因(不少于 220 种相关疾病,后期根据实施有改变)中的变异,探针设计区域覆盖目标基因全部外显子及侧翼区域,以及已报道的非编码区域致病和疑似致病变异位点。检测范围包括目标区域内的 SNV、10 bp 以内的 indel 变异。此外,通过特殊的探针设计和特殊生信算法,也可以检测部分基因的大片段缺失和重复变异,如 DMD、SMN1 和 HBA1/HBA2 等。通过该方法可以用较低的成本在大量的受检者样本中对数百个基因同时进行检测。

1.3 统计学处理 采用 SPSS 26.0 软件和 Excel 对所有数据进行处理,对受检者的年龄、携带致病变异个数及筛查出的单基因病频率进行比较分析,计数资料以频率(百分比)表示。对高风险夫妇年龄进行正态性检验分析其是否具有正态分布特质,经 S-W 检验可得 P 值均大于 0.05,服从正态分布。并使用均值和变异系数对高风险夫妇男女双方年龄进行离散程度和变异程度的比较,其中变异系数 C · V =(标准偏差 SD/平均值 Mean)×100%。高风险夫妇男女双方年龄变异系数均 <15%,数据分布均匀。

2 结果

2.1 总体携带情况 截至 2023 年 5 月 16 日,本研究受检样本共 604 例,检测出目标疾病携带者 340 例;检出致病变异检测阳性率为 56.29%;共检出致病变异 499 个,每名受检者携带 0 ~ 5 个变异;携带 1 种单基因隐性遗传病致病变异 216 例,占 35.76%,最为常见。携带 2 种单基因隐性遗传病致病变异 95 例,占 15.73%;携带 3 种单基因隐性遗传病致病变异 24 例,占 3.79%;携带 4 种单基因隐性遗传病致病变异 4 例,占 0.66%;携带 5 种单基因隐性遗传病致病变异 1 例,占 0.17%。平均每人携带 0.83 个致病变异,提示隐性单基因致病变异携带的普遍性。

本研究中,截至目前已发报告夫妻 302 对,经筛查发现高风险夫妻 7 对。其中遗传模式为常染色体隐性即夫妻双方均携带同一致病基因的共 5 对,遗传模式为 X-连锁即女方携带 X-连锁致病基因的共 2 对。在 5 对常染色体隐性遗传病高风险的夫妻中,有 3 对夫妻携带致病基因 GJB2,该基因突变可导致常染色体隐性耳聋 1A 型。GJB2 基因突变不仅是引起遗传性耳聋最常见的原因,而且由 GJB2 突变所引发的隐性耳聋疾病的异质性和表型可变程度很强。另外 2 对高风险夫妇则分别携带致病基因 NPC1 和 ACADM,与之相关联的疾病分别为尼曼-匹克病 C1 型和中链酰基辅酶 A 脱氢酶缺乏症,见表 1。

本研究受检样本共 604 例,检测出目标疾病携带者 340 例,其中检测出女性携带目标致病基因者 163 例,平均年龄 31 岁;男性携带目标致病基因者 177 例,平均年龄在 32 岁,男女比例约 1.09,检测出目标疾病携带者未见明显性别差异。

检测范围内共检出 111 种疾病,肝豆状核变性、Krabbe 病、线粒体 DNA 耗竭综合征、常染色体隐性耳聋 1A 型、苯丙氨酸羟化酶缺乏症等疾病携带率较高。常染色体隐性耳聋 1A 型、眼皮肤白化病、脊

髓性肌萎缩症及脆性 X 综合征等常见引起出生缺陷的疾病均有发现,详见表 2。ECS 作为多种疾病的联合筛查,能够避免常见罕见病的漏筛。

表 1 高风险夫妇携带致病基因情况

Tab. 1 Carriage of disease-causing genes in high-risk couples

Diseases	Pathogenic gene	Patterns of inheritance	Number of cases
Autosomal recessive deafness type 1A	GJB2	AR	3
Niemann-Pick disease type C1	NPC1	AR	1
Medium chain acyl coenzyme A dehydrogenase deficiency	ACADM	AR	1
Progressive pseudohypertrophic muscular dystrophy	DMD	XL	1
Glucose-6-phosphate dehydrogenase deficiency	G6PD	XL	1

2.2 检测出高风险夫妻及其后续遗传咨询情况

2.2.1 *高风险夫妇携带致病基因情况* 已发报告夫妻 302 对,筛查中共发现高风险夫妻 7 对,高风险率为 2.31%。遗传模式为常染色体隐性的共 5 对(夫妻双方均携带同一致病基因),遗传模式为 X-连锁的共 2 对(女方携带 X-连锁致病基因)。这 7 对高风险夫妻中女性受试者平均年龄为 31 岁,男性受试者平均年龄为 33 岁,携带致病基因的高风险夫妻年龄分布情况详见表 3,目前无明显证据表明携带致病基因的高风险率与年龄相关。本研究统计了 7 个高风险家系女性受试者与男性受试者携带的致病突变及关联疾病,其中常染色体隐性耳聋 1A 型致病基因 GJB2:c.109G>A(p.V37I)位点杂合突变出现较为频繁,见表 4。

2.2.2 *后续遗传咨询情况* 本研究中经筛查发现的 7 对高风险夫妻均在本院产前诊断中心接受遗传咨询,咨询医师告知受试者夫妇检测结果。后经本院电话随访得知,其中 1 对夫妻已妊娠,现孕周较小,暂未行产前诊断确认,待达到孕周后将行介入性产前诊断手术确认。另外 6 对夫妻暂未妊娠,但明确表示如妊娠将行产前诊断确认,具体随访情况可见表 4。

3 讨论

单基因病是出生缺陷的重要组成部分,约占出生缺陷的 22.2%,是继先天畸形后的出生缺陷的第二大重要组成因素。常见的单基因病如表 4 所示,多数致死、致畸,例如脊髓性肌萎缩症、戈谢病和肌营养不良等。最初的单基因病携带者筛查,往往是

表 2 604 例 ECS 受检者检出致病基因携带数前 25 种分布情况

Tab. 2 Distribution of the top 25 disease-causing gene detected in 604 ECS subjects

Diseases	Gene	Patterns of inheritance	Number of cases	Positivity rate(%)
Autosomal recessive deafness type 1A	GJB2	AR	67	11.09
Hepatolenticular degeneration	ATP7B	AR	23	3.81
Mitochondrial DNA depletion syndrome	POLG	AR	18	2.98
Krabbe disease	GALC	AR	17	2.81
Phenylalanine hydroxylase deficiency	PAH	AR	17	2.81
Neonatal-type citrullinemia type 2	SLC25A13	AR	17	2.81
Usher syndrome type 2A	USH2A	AR	15	2.48
Autosomal recessive deafness type 4 with enlarged vestibular aqueducts	SLC26A4	AR	14	2.32
Spinal Muscular Atrophy	SMN1	AR	14	2.32
Methylmalonic aciduria combined with homozygous hemi	MMACHC	AR	12	1.99
Cystinuria cb1C	SLC22A5	AR	11	1.82
Systemic primary carnitine deficiency	CYP21A2	AR	11	1.82
21-Lightening enzyme deficiency	TYR	AR	11	1.82
Oculocutaneous albinism	ALPL	AR	9	1.49
Hypophosphatasia in children	ALDH3A2	AR	9	1.49
Sjogren-Larsson syndrome	MMUT	AR	8	1.32
Methylmalonic aciduria mut	ACADS	AR	7	1.16
Short-chain coenzyme A dehydrogenase deficiency	GAA	AR	6	0.99
Glycogen storage disease type 2	ETFDH	AR	6	0.99
Glutaric acidemia type 2	PTS	AR	5	0.83
Tetrahydrobiopterin deficiency type A	CAPN3	AR	4	0.66
Autosomal recessive limb-girdle muscular dystrophy type 1	SLC26A2	AR	4	0.66
Multiple skeletal dysplasias type 4	CFTR	AR	4	0.66
Cystic fibrosis	PKHD1	AR	4	0.66
Polycystic kidney disease type 4 with or without polycystic liver disease	ABCG5	AR	4	0.66

表 3 携带致病基因的高风险夫妻年龄情况

Tab. 3 Age of high-risk couples carrying disease-causing genes

Subjects	Female subjects	Age	Male subjects	Age	Pregnancy
Genealogy1	Liu**	33	Wang**	34	Early pregnancy
Genealogy2	Wu**	30	Lian*	30	Prepare for pregnancy
Genealogy3	Cui**	33	Duan**	29	Prepare for pregnancy
Genealogy4	Wu**	34	Zhang**	35	Prepare for pregnancy
Genealogy5	Wang**	29	Zhou**	33	Prepare for pregnancy
Genealogy6	Wang*	29	Zeng**	29	Prepare for pregnancy
Genealogy7	Ren**	32	Yao*	42	Prepare for pregnancy
Average age	–	31	–	33	–
Variation coefficient(%)	–	6.6	–	13.9	–

表 4 高风险夫妻携带致病突变及关联疾病

Tab. 4 Carriage of disease-causing mutations and associated diseases in high-risk couples

Subjects	Female subjects	Male subjects	Related diseases	Follow-up
Genealogy1	NPC1:c. 1110_1113del (p. V371Gfs * 77) heterozygous	NPC1:c. 2728G > A (p. G910S) heterozygous	Niemann-Pick disease type C1	Pregnant, pending prenatal diagnosis
Genealogy2	GJB2:c. 235del(p. L79Cfs * 3) heterozygous	GJB2:c. 109G > A (p. V37I) heterozygous	Autosomal recessive deafness type 1A	Planned pregnancy, not yet pregnant
Genealogy3	GJB2:c. 95G > A(p. R32H) heterozygous	GJB2:c. 109G > A (p. V37I) heterozygous	Autosomal recessive deafness type 1A	Planned pregnancy, not yet pregnant
Genealogy4	G6PD:c. 1376G > T(p. R459L) heterozygous	/	Glucose-6-phosphate dehydrogenase deficiency	Planned pregnancy, not yet pregnant
Genealogy5	DMD: exon49-exon51del heterozygous	/	Progressive pseudohypertrophic muscular dystrophy	Planned pregnancy, not yet pregnant
Genealogy6	ACADM:c. 1085G > A (p. G362E) heterozygous	ACADM:c. 616C > T (p. R206C) heterozygous	Medium chain acyl coenzyme A dehydrogenase deficiency	Planned pregnancy, not yet pregnant
Genealogy7	GJB2:c. 109G > A (p. V37I) heterozygous	GJB2:c. 109G > A (p. V37I) heterozygous	Autosomal recessive deafness type 1A	Planned pregnancy, not yet pregnant

针对某一个种族或某一地域的高发性疾病,例如,蒋玉欢 等[3]对 5 584 例广东省随机婚配的男女在接受婚前医学检查时进行 α 与 β 地中海贫血的筛查。但是伴随着现代社会复杂的人口流动和地区交融,针对特定种族、人群或特定地域的单基因病携带者筛查已经不能满足社会需要。随着高通量测序技术的发展,越来越多的单基因遗传病的分子学致病机制被发现,扩大携带者筛查计划逐渐成为可能[4]。

近年随着高通量测序技术的蓬勃发展,遗传病携带者筛查的方式也不断发生改进,目前基于高通量测序结合特殊 PCR 分析技术检测,能够以较低的成本对数百种单基因遗传病进行携带者筛查,明确受检者致病基因携带情况以及常见变异,从而为优生优育提供精准的指导。高通量测序技术可以同时检测多个基因,这大大降低了 ECS 的成本,为安徽省多中心大规模单基因遗传病携带者筛查提供了基础。但是目前,由于我国针对遗传性疾病筛查的咨询能力不完善的现状,大众人群普遍对携带者筛查认知度低[5]。

本次安徽省单基因遗传病携带者筛查回顾性分析了备孕或早孕期(≤13 +6 周)表型正常无遗传病家族史的 604 例育龄人群的单基因遗传病致病基因携带情况以及常见变异。通过分析 ECS 目标疾病的总体携带和临床应用情况,为形成适合安徽省人群单基因病扩展性携带者筛查临床应用模式并推广应用打好基础。有遗传病家族史或生育过遗传性疾病孩子的正常夫妻需要谨慎纳入。应告知受检者 ECS 报告目前只包括致病性、可能致病性变异,且本项目不能代替其他遗传检测。

本次研究共纳入 220 种较为常见的单基因遗传病,截至 2023 年 5 月 16 日,安徽医科大学第一附属医院共报告受检样本 604 例,检测出目标疾病的携带者 340 例,检出致病变异检测阳性率为 56. 29%。在本次检测范围内共检出 111 种疾病,其中发病率排在第一位的疾病是常染色体隐性耳聋 1A 型,检出 67 例,阳性率 11. 09%。Krabbe 病、线粒体 DNA 耗竭综合征、肝豆状核变性、苯丙氨酸羟化酶缺乏症等疾病的总体携带率也不低。应用高通量测序技术对 604 例孕期或早孕期的正常夫妻进行 220 种单基因病的扩展性携带者筛查,首次初步明确安徽省的单基因病携带者频率,并对高风险受检者夫妇进行遗传咨询,以减少严重出生缺陷患儿的出现。本次筛查活动大大推动了安徽省地区单基因疾病携带者筛查的普及宣教,有利于携带者筛查在当地有序开展,切实提升筛查率,逐步改善群众对单基因遗传病筛查的认知。携带者筛查利用基因检测技术,识别携带致病基因的隐形群体,通过评估其后代患病的风险来减少患儿的出生,是降低出生缺陷率的关键性的一级预防措施[6]。安徽省育龄期人群单基因遗传病携带者筛查研究初步了解常见的 220 种单基因遗传病致病基因突变在安徽地区的携带率,为后续产前诊断咨询及出生缺陷防治工作提供指导依据,为遗传性疾病扩展性携带者筛查的临床应用及在安徽地区的推广打下基础。

国外关于各种遗传病的携带者筛查项目早已普遍开展,早在 1969 年一项针对犹太人家族性黑蒙性痴呆的携带者筛查,该项研究有效降低了家族性黑蒙性痴呆在犹太人群中的发病率[7]。此后世界各地先后开展了针对常染色体隐性耳聋 1A 型、脊髓性肌萎缩症及脆性 X 综合征等常见引起出生缺陷

的疾病的筛查。然而中国人群普遍对携带者筛查认知度低,因此针对中国人群的首次大规模的单基因病携带者筛查可以追溯到2005年,中国台湾地区对10万余例孕妇进行了SMA的筛查[8]。2021年,南京医科大学附属妇产医院开展SMA携带者筛查的宣教活动,在16 549例孕妇中只有5 776例孕妇自愿参加宣教活动,接受率仅达34.9%[9]。

因此,建立一套完善的安徽省单基因病携带者筛查的宣教、筛查、咨询、诊断与救助临床体系,将大大有利于携带者筛查在当地有序开展,切实提升筛查率,解决遗传咨询和产前诊断等难题,有效降低出生缺陷。本次针对安徽省的单基因遗传病携带者筛查为安徽省常见隐性单基因遗传病数据库和安徽省携带者筛查网络与转诊体系的建立提供了依据,同时也是安徽省单基因遗传病项目宣传和遗传咨询培训体系确立的关键性一步。

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Analysis of the results of screening for carriers of monogenic genetic diseases in 604 couples of childbearing age

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Abstract ***Objective*** To understand the carrying situation and common variation of pathogenic genes of single gene hereditary disease in childbearing age population in Anhui province, to explore the establishment of clinical application network and referral model of carrier screening in Anhui province, and to explore the application value of expansible carrier screening (expanded carrier screening, ECS) in clinic. ***Methods*** Samples were collected from 604 individuals of childbearing age, all exhibiting a normal phenotype and a family history of inherited dis-

ease. These samples were obtained during the first trimester or early stages of pregnancy (≤13 +6 weeks). Based on high-throughput sequencing and special PCR analysis techniques, pathogenic variants associated with 220 diseases were detected, and related genes were detected in the spouses of positive carriers. ***Results*** As of May 16, 2023, 604 tested samples had been collected, and 340 carriers of the target disease had been detected; The positive rate of pathogenic variation detection was 56.29%; A total of 499 pathogenic variants were detected, with each tested individual carrying 0 -5 variants; 216 cases, accounting for 35.76%, carried a single gene recessive disease pathogenic variation, which was the most common. There were 95 cases carrying two types of single gene recessive genetic disease pathogenic variation, accounting for 15.73%. As of now, 302 couples have been reported, and a total of 7 high-risk couples have been found through screening, with a high-risk rate of 2.32%. There are a total of 5 pairs with autosomal recessive genetic pattern (both spouses carry the same pathogenic gene), and 2 pairs with X-linked genetic pattern (the female carries the X-linked pathogenic gene). ***Conclusion*** In this study, we obtained the overall carrier and clinical application of target diseases as well as the carrier rates of causative genes of common single-gene genetic diseases in 604 subjects who underwent ECS testing, which could provide scientific guidance for the establishment of a clinical application network and referral model for carrier screening in Anhui Province.

Key words monogenic disease; expanded carrier screening; high throughput sequencing; genetic counseling; birth defects; prenatal diagnosis; second generation sequencing

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(ISS) and compare them with those of children with growth hormone deficiency (GHD) and normal children, and to explore the characteristics of ocular biological parameters in this group, so as to provide a reference for the screening of visual acuity and the safety of growth hormone therapy in children with ISS. ***Methods*** A total of 15 children aged 5 -14 years old with ISS were selected as the observation group, 32 children with GHD were selected as the control group, and 47 children of normal height who underwent routine visual acuity screening were selected as normal controls. The ocular biological parameters of children with ISS were studied. The differences of vision-related parameters between the above three groups were compared. The influencing factors affecting the visual development of children with ISS were analyzed. ***Results*** The axial ratio of ISS was significantly higher than that of the GHD group and normal children, and the intraocular pressure of the ISS group was significantly higher than that of the GHD group and normal children. There was no significant difference in axial length between the ISS group and the GHD group, as well as normal children ($P > 0.05$), but the axial length of the GHD group was significantly shorter than that of normal children. The corneal curvature of ISS was significantly greater than that of normal children. The axial rate ratio of the ISS group was positively correlated with the peak value and corneal curvature of growth hormone provocation test ($\beta = 1.052$, $P < 0.05$; $\beta = 0.004$, $P < 0.05$). ***Conclusion*** Children with ISS may have high intraocular pressure and high risk of myopia. Higher peak results of growth hormone provocation test and large corneal curvature may be the risk factors for myopia.

Key words idiopathic short stature; growth hormone deficiency; eye axis; axial ratio; intraocular pressure; corneal curvature

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