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光学基因组图谱技术在隐匿性复杂染色体平衡易位家系中的遗传学诊断应用

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[摘 要] 目的：对于有反复不良孕产史但常规核型分析未见异常者，其潜在的遗传学病因(如隐匿性染色体平衡易位)难以通过传统方法明确。这类复杂结构变异因分辨率限制常被漏诊，成为临床遗传学诊断的难点之一。本研究对有2次异常生育史的夫妇进行遗传学病因诊断及生育指导，旨在为光学基因组图谱(optical genome mapping，OGM)技术在生殖遗传领域的拓展应用提供依据。**方法：**收集于兰州大学第一医院生殖医学中心就诊、连续2次不良妊娠结局、寻求遗传学病因诊断的1对夫妇的临床资料，包括既往超声检查、染色体核型检查、拷贝数变异测序(copy number variation sequencing，CNV-seq)、荧光原位杂交(fluorescence in situ hybridization，FISH)技术结果。进一步采用OGM技术对夫妇双方外周血样本进行高分辨率全基因组结构变异分析，评估OGM在隐匿性染色体平衡易位，尤其是复杂结构变异诊断中的临床应用价值。**结果：**该夫妇2次妊娠胎儿的CNV-seq结果分别显示为del(4)(p16.3)，3.80 Mb及dup(4)(p16.3)，3.74 Mb合并del(22)(q13.31~q13.33)，4.64 Mb。夫妻双方外周血染色体核型分析均未见明显异常，提示可能为隐匿性染色体平衡易位携带者。OGM检测结果显示，男方携带涉及1、4、22号染色体的隐匿性复杂平衡易位，其断裂点位于与2次胎儿CNV-seq异常片段边界一致的区域内，证实男方为表型正常的复杂平衡易位携带者，2次胎儿的染色体异常均为其亲代减数分裂过程中衍生染色体不平衡分离所致。**结论：**OGM作为一种高分辨率、超长读长、自动化的新型非测序基因检测技术，在隐匿性平衡易位的检测方面相较于传统细胞遗传学技术更高效。

[关键词] 染色体结构变异；光学基因组图谱；隐匿性复杂染色体平衡易位；拷贝数变异测序；遗传咨询

Application of optical genome mapping technology in the genetic diagnosis of a family with a cryptic complex chromosomal balanced translocations

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ABSTRACT

Objective: For couples with recurrent adverse pregnancy outcomes but normal results on conventional karyotype analysis, the underlying genetic causes (such as cryptic chromosomal balanced translocations) are difficult to identify using traditional methods. These complex structure variations are often missed due to resolution limitations, posing a major challenge in clinical genetic diagnosis. This study aims to perform genetic etiological diagnosis and provide reproductive guidance for a couple with two abnormal reproductive histories, and to evaluate the application value of optical genome mapping (OGM) in the field of reproductive genetics.

Methods: Clinical data were collected from a couple who attended the Reproductive Medicine Center, First Hospital of Lanzhou University, with two consecutive adverse pregnancy outcomes and seeking genetic diagnosis. Previous results from ultrasonography, chromosomal karyotyping, copy number variation sequencing (CNV-seq), and fluorescence in situ hybridization (FISH) were reviewed. OGM was further performed on peripheral blood samples from both partners to conduct high-resolution, genome-wide structural variation analysis, in order to assess the clinical utility of OGM in detecting cryptic chromosomal balanced translocations, particularly complex structure variations.

Results: CNV-seq results from the 2 pregnancies showed del(4)(p16.3), 3.80 Mb, and dup (4) (p16.3), 3.74 Mb combined with del(22) (q13.31 − q13.33), 4.64 Mb, respectively. Conventional chromosomal karyotyping of peripheral blood from both parents revealed no obvious abnormalities, suggesting the possibility of a cryptic chromosomal balanced translocation carrier. OGM analysis demonstrated that the male partner carried a cryptic complex balanced translocation involving chromosomes 1, 4, and 22. The breakpoints were located in regions consistent with the boundaries of the abnormal CNV segments identified in both fetuses. These findings confirmed that the male partner was a phenotypically normal carrier of a complex balanced translocation, and that the chromosomal abnormalities in both fetuses resulted from unbalanced segregation of derivative chromosomes during parental meiosis.

Conclusion: As a novel non-sequencing-based genomic technology characterized by high resolution, ultra-long read length, and automation, OGM is more efficient than traditional cytogenetic techniques in detecting cryptic balanced translocations.

KEY WORDS chromosomal structure variation; optical genome mapping; cryptic chromosomal complex balanced translocation; copy number variation sequencing; genetic counseling

染色体病是严重危害人体健康的疾病之一，具有高发性、不可治性及社会成本高的特点，预防是其核心策略。显著提升异常胚胎的早期识别能力，为高风险家庭提供科学生育选择，推动技术创新与临床转化是生殖医学领域的重点。染色体结构变异(structure variations，SVs)指基因组中大规模的DNA序列变化，通常涉及大于50个碱基对的变异类型，包括拷贝数变异、插入、倒位、易位等[1]。SVs极可能导致出生缺陷、不孕不育、反复流产或胚胎发育异常，因此在生殖遗传学领域中备受关注。隐匿性平衡易位指易位片段小于5 Mb或易位的染色体区域带纹相似的平衡易位[2-3]，常不易被传统细胞遗传学

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技术(如染色体核型分析)发现，故需要更精准的技术来检测[4]。光学基因组图谱(optical genome mapping，OGM)技术利用荧光标记和成像分析大片段DNA的SVs，具有直接检测平衡性SVs(特别是精确定位断裂点)的能力[5]。目前OGM技术可检出的变异类型包括拷贝数变异、平衡性结构重排及大片段重复序列的扩张等，可一次性检测多种SVs和拷贝数变异，分辨率可达500 bp[6]。OGM技术的应用范围正逐渐扩大，目前在血液系统恶性肿瘤领域中的应用经验最为丰富。在生殖医学领域，尤其是针对不明原因生殖障碍患者，OGM日益成为进行染色体SVs筛查的重要工具，为精准诊断和生育干预提供了关键途径[7]。

本研究运用传统细胞遗传学方法及OGM技术对有2次异常生育史的夫妇进行遗传学病因诊断，总结该夫妇的诊疗过程，旨在为OGM在生殖遗传领域的拓展应用提供证据。

1 对象与方法

1.1 伦理声明

本研究已获得兰州大学第一医院伦理委员会批准(审批号：LDYYSZLLKH2025-08)，符合《赫尔辛基宣言》的要求，并已获得研究参与者的知情同意。

1.2 对象

回顾性分析于兰州大学第一医院生殖中心就诊、有2次不良孕产史、寻求遗传学病因诊断的1对夫妇的临床资料。男方33岁，女方35岁，双方否认近亲结婚及家族遗传病史。

1.3 方法

1.3.1 既往资料收集

收集既往2次孕产史的超声检查、染色体核型检查、拷贝数变异测序(copy number variation sequencing，CNV-seq)、荧光原位杂交(fluorescence in situ hybridization，FISH)结果。

1.3.2 OGM检测

2025年4月，夫妻双方至兰州大学第一医院生殖医学中心门诊进行遗传学咨询；为进一步明确病因，经双方知情同意后行OGM检测。从该夫妇外周血中分别分离超高分子量(ultra-high molecular weight，UHMW) gDNA；随后，用Bionano Prep DLS试剂盒(美国Bionano Genomics公司)对分离的UHMW gDNA进行荧光标记，将标记的UHMW gDNA加载到Saphyr芯片上并线性化；最后，在Saphyr仪器(美国Bionano Genomics公司)上成像。通过配套的生物信息学分析软件对原始图像数据进行自动化处理与分析。

2 结　果

2.1 胎儿1检查结果

2020年孕12周时，超声检查结果(图1)显示，胎儿颈项透明层(nuchal translucency，NT)增厚，鼻骨欠清。建议18~24周行羊水穿刺。孕18周时，通过FISH检测，对胎儿1的13、18、21、X和Y染色体进行检查，计数50个细胞，D18Z1、DXZ1、DYZ3、DLEU2及DSCR2探针信号数目未见异常(图2)。胎儿1的CNV-seq检测结果(图3)显示4号染色体p16.3处缺失3.80 Mb，遂引产。



图1　孕妇2020年孕12周时超声检查结果

Figure 1　Ultrasound results for the pregnant woman at 12 week of pregnancy in 2020

2.2 胎儿2检查结果

2021年孕12周时，超声检查结果(图4)显示，NT在正常范围内，鼻骨欠清。因孕妇有不良孕产史，于孕19周再次行羊水穿刺。孕19周CNV-seq检测结果(图5)显示，4号染色体p16.3处重复3.74 Mb，22号染色体q13.31~q13.33处缺失4.64 Mb，遂引产第2次。

2.3 夫妻双方染色体核型分析结果

夫妻双方外周血染色体核型分析均未见明显异常(图6)。

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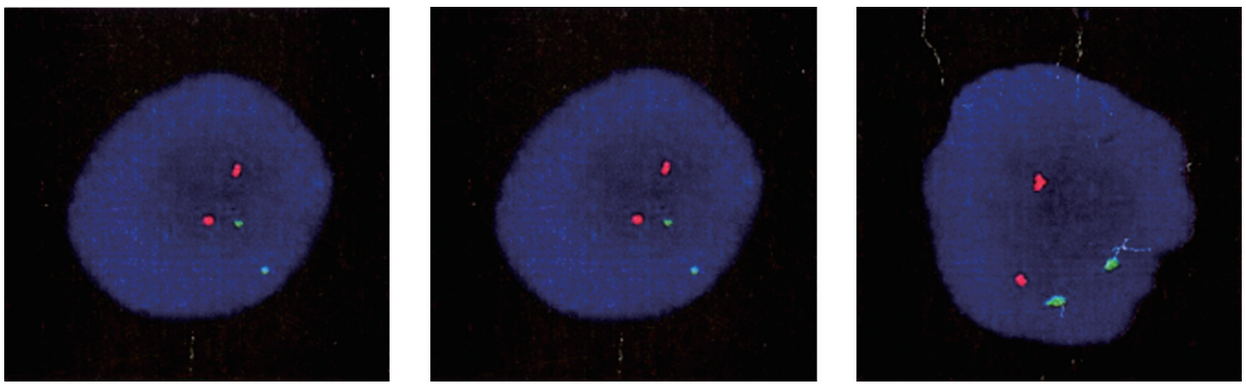


图2 孕妇2020年孕18周FISH检测结果(×1 000)

Figure 2 FISH test results for the pregnant woman at 18 weeks of pregnancy in 2020 (×1 000)

FISH: Fluorescence in situ hybridization.

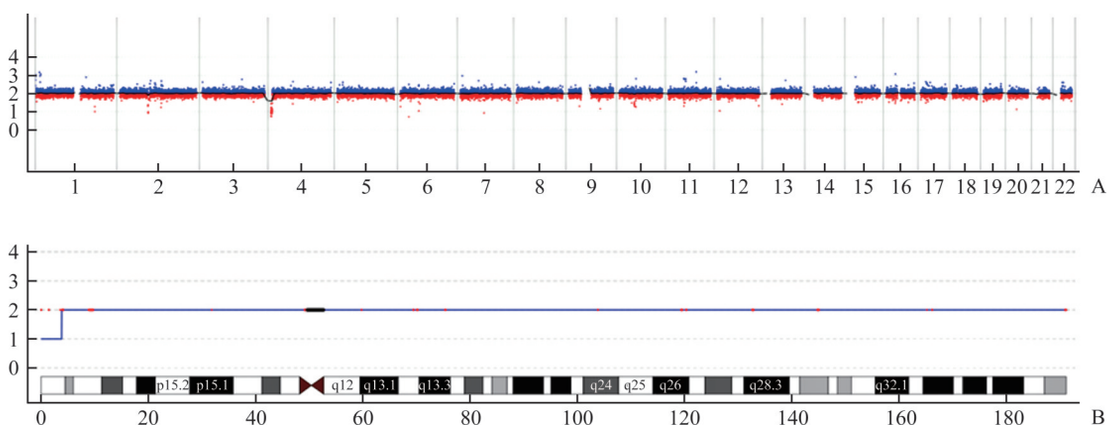


图3 胎儿1 CNV-seq检测结果

Figure 3 CNV-seq test results for the fetus 1

A: Whole genome test results. B: Fourth chromosome test results. CNV-seq: Copy number variation sequencing.

2.4 OGM结果

OGM检测结果(图7)显示女方无明显异常；男方结果为46，XY，t(1；4；22)(p36.33；p16.3；q13.31)。男方基因组存在复杂的染色体重排，经OGM单分子图谱组装及断点分析(图8)，确认男方携带涉及1、4、22号染色体的隐匿性复杂平衡易位，其断裂点位于与前2次胎儿CNV-seq异常片段边界重叠的区域内，证实男方为表型正常的复杂平衡易位携带者，2次胎儿的染色体异常均为其亲代减数分裂过程中衍生染色体不平衡分离所致。



图4 孕妇2021年孕12周超声结果示意图

Figure 4 Schematic diagram of ultrasound results for the pregnant woman at 12 week of pregnancy in 2021

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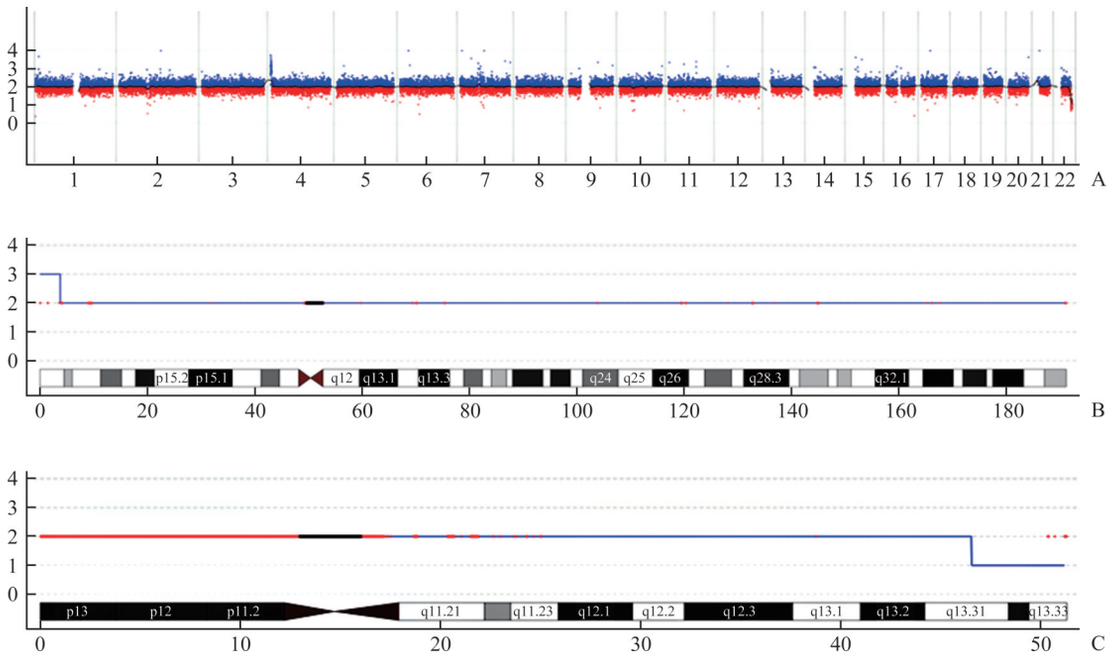


图5　胎儿2 CNV-seq检测结果

Figure 5　CNV-seq test results for the fetus 2

A: Whole genome test results. B: Fourth chromosome test results. C: Twenty-second chromosome test results.

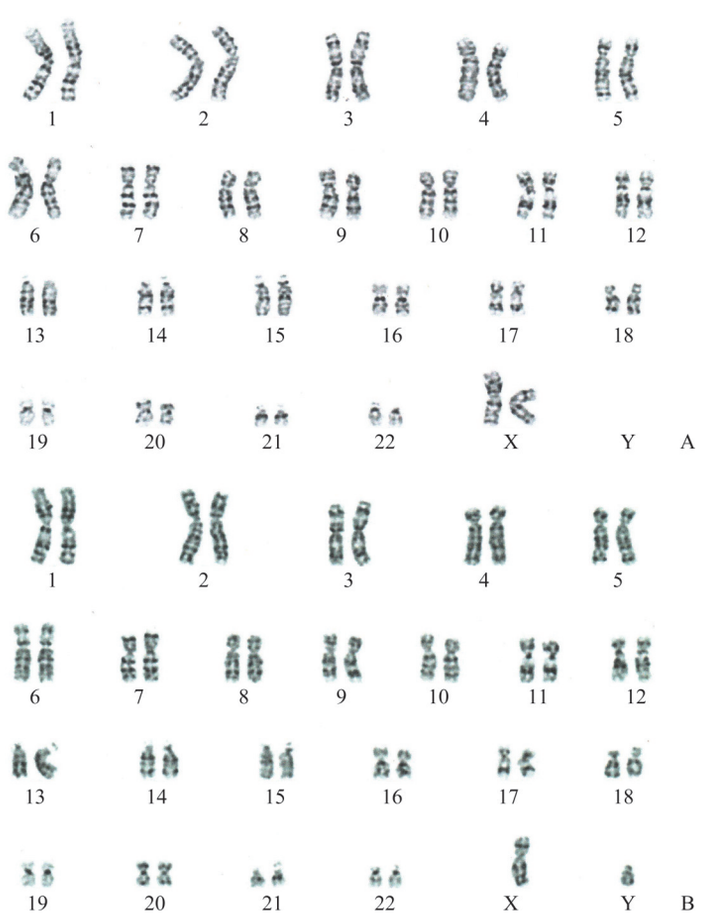


图6　女方(A)和男方(B)染色体核型分析结果

Figure 6　Results of karyotype analysis for both the female (A) and the male (B)

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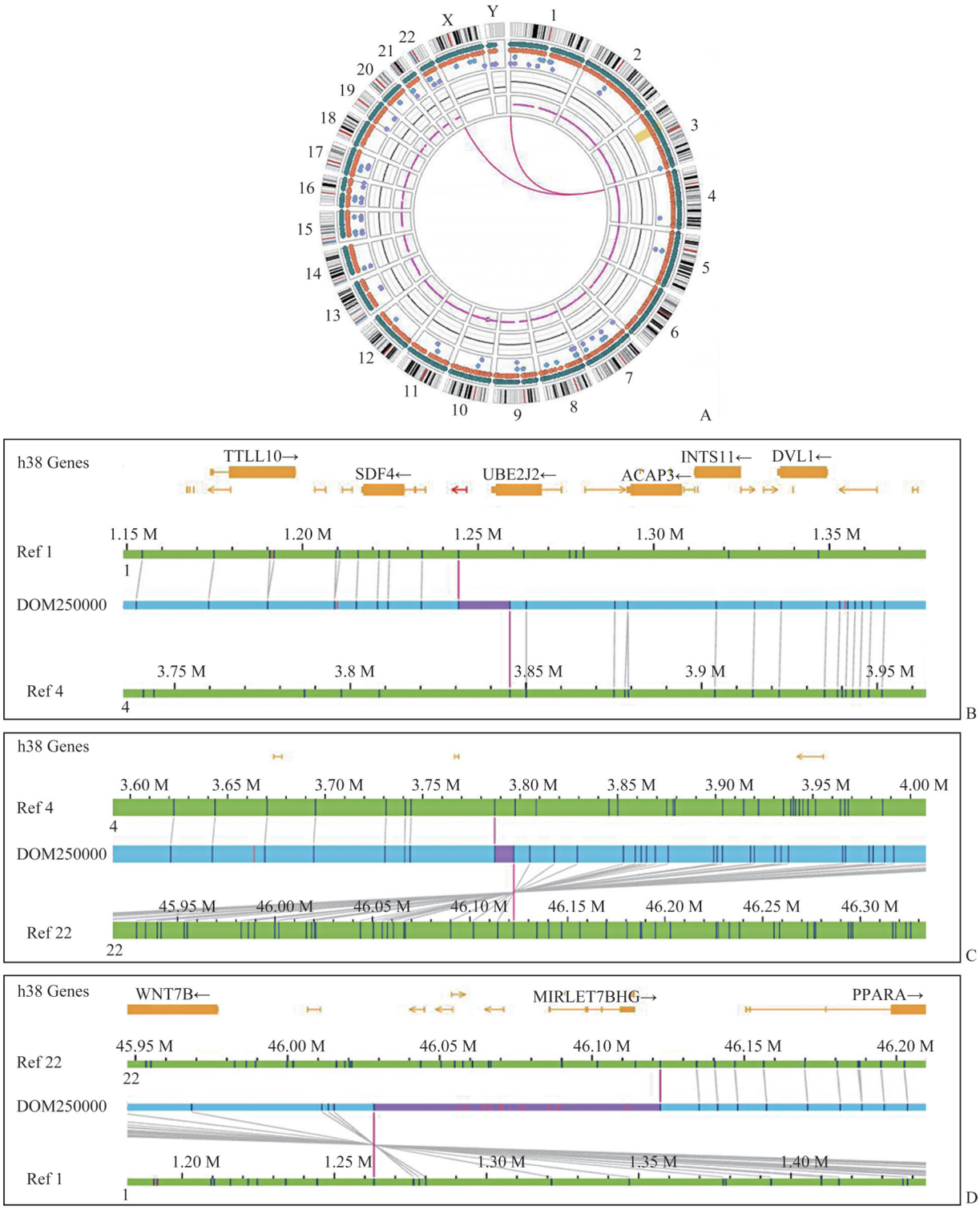


图7 男方隐匿性平衡易位的OGM检测结果

Figure 7 Detection results of the male's cryptic balanced translocation by OGM

OGM gene map showing the breakpoint positions and the interrupted gene information after aligning sample assembly fragments to the reference genome. A: OGM circular diagram. B: Diagram showing the translocation of the male's chromosome 1 p36.33 region and chromosome 4 p16.3 region. C: Diagram showing the translocation of the male's chromosome 4 p16.3 region and chromosome 22 q13.31 region. D: Diagram showing the translocation of the male's chromosome 1 p36.33 region and chromosome 22 q13.31 region. OGM: Optical genome mapping.

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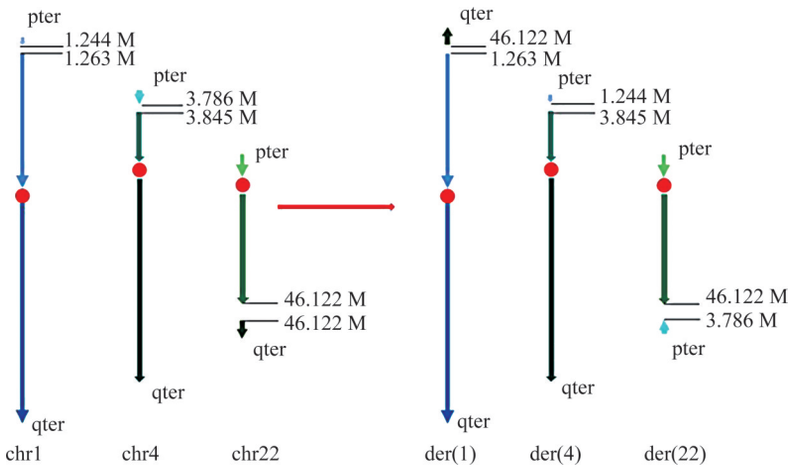


图8　男方1、4、22号染色体构建示意图

Figure 8　Diagram of chromosome construction for male chromosomes 1, 4, and 22

This patient exhibits 3 chromosomal breakpoints involving chromosomes 1, 4, and 22. A proximal breakpoint occurs near chr1:1,244,412, which is joined in a forward orientation to a breakpoint near chr4:3,845,422 on chromosome 4. Separately, a breakpoint near chr4:3,786,949 is fused in a reverse orientation to a breakpoint near chr22:46,122,412. Additionally, a breakpoint near chr1:1,263,035 is connected in a reverse orientation to the same chr22:46,122,412 locus.

3 讨　论

在生殖医学领域，染色体SVs包括易位、倒位、缺失、重复等，是导致不孕不育、反复流产和胚胎停育的重要遗传因素。虽然传统遗传学检测技术在产前诊断和遗传学检测中被广泛应用，但仍存在局限性。染色体核型分析作为金标准，可检测5~10 Mb的染色体变异，但对于片段小于10 Mb或易位的染色体区域带纹相似的易位容易漏诊[8]；FISH技术只能靶向验证特定易位或微缺失微重复，即只能检测所选探针所在位置的异常[9]；CNV-seq可检测>100 kb的基因组拷贝数变异，但是不能检测平衡易位。在胎儿1的病因分析中，FISH结果并未提示异常，但其CNV-seq结果提示4号染色体p16.3处缺失3.80 Mb，故在2021年自然怀孕时，虽超声提示NT正常，临床医师依旧建议行CNV-seq及染色体核型分析。夫妇双方染色体核型分析结果与胎儿1FISH结果一致，均未提示异常。因此，查明胎儿在2次CNV-seq检测中基因异常的源头成为亟待解决的问题。直至后续遗传咨询夫妻双方行OGM检测后才明确，胎儿基因异常为父源性隐匿性平衡易位所致。OGM结果不仅为该夫妻明确了病因，也为后续遗传学咨询中采用第3代试管婴儿技术进行移植助孕提供了有力支持。

目前，OGM技术已逐渐被应用于医学的多个领域。Shim等[10]在研究面肩肱型肌营养不良症(facioscapulohumeral muscular dystrophy，FSHD)时，对OGM及Southern印迹技术的测试时间及工作流程进行统计学分析，发现OGM需要的时间更短、精力更少，且同样准确可靠。在探究白血病基因组SVs过程中，研究[11]表明尽管OGM尚未被广泛采用为一线检测技术，但其高分辨率和独立于序列信息筛选整个基因组的能力使其展现出改进白血病诊断策略的巨大潜力。同时，OGM技术在生殖遗传方向中隐匿性平衡易位的检测优势也逐步被发现。研究[12]证实，OGM是核型分析、FISH和染色体微阵列分析(chromosomal microarray analysis，CMA)的可靠替代方法，可用于检测复杂染色体重排(complex chromosomal rearrangement，CCR)和隐性易位。在一项研究[13]中，除了chr 17、18和22之间的三向CCR外，仅使用OGM能发现chr 9和11之间小片段的隐性易位。一项病例报告[2]概述了OGM技术在检测染色体SVs中的应用及临床效用，提出OGM在识别隐匿性平衡易位方面具有先天优势，可以为患有不孕症等复杂疾病的夫妇提供精确的病因学诊断。由此可知，OGM作为一种高分辨率、超长读长、自动化的新型非测序基因检测技术，在隐匿性平衡易位研究中具有显著优势，可一次性检测全基因组范围内的结构和数目异常，包括染色体非整倍体、插入、缺失、重复、倒位、平衡易位及复杂SVs异常等，且OGM检测分辨率高至500 bp，对基因组SVs检测具

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有较高应用价值[14]。

虽然OGM有潜力作为产前诊断技术的前列[15]，但其局限性也不可忽略。相较于三代DNA测序技术，OGM不产生序列信息，无法直接获得碱基序列，而三代测序可获得具体的序列信息，这是OGM最根本的功能限制之一。OGM对于基因组中的特定复杂度区域检测灵敏度较低[16]，目前的基因组参考中仍然存在空白区域，着丝粒周围区域内的间隙会遗漏[17]，相较于三代测序有概率导致临床相关变异的漏诊。OGM无法精确到单碱基水平，发现的变异如果需要精确定位断裂点，往往需要借助三代测序进行验证和细化，例如当多个结构异常共存于同一对染色体时，OGM无法有效区分2个DNA断裂重接事件位于同一条染色体(顺式)或分别位于同源染色体(反式)[18]。在治疗成本方面，其直接检测费用高于传统临床技术，但亦有部分学者[19]认为1次OGM检测可能替代一系列繁琐的单项检测，缩短诊断周期，从而降低整体诊疗成本。

综上，OGM通过高分辨率线性基因组物理图谱，直接可视化染色体断裂重接事件，克服了传统技术的部分局限，但其临床应用仍不能完全替代核型分析等技术，需要与之配合使用，才能更高效地进行遗传病的诊断，从而改善妊娠结局。同时，规范的产前诊断和遗传咨询是指导优生优育的重要手段，对具有生育需求的夫妇应该加强其遗传学病因检测的意识，以此为再次妊娠制订更加科学的管理路径，从而降低我国遗传病的发生率。

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