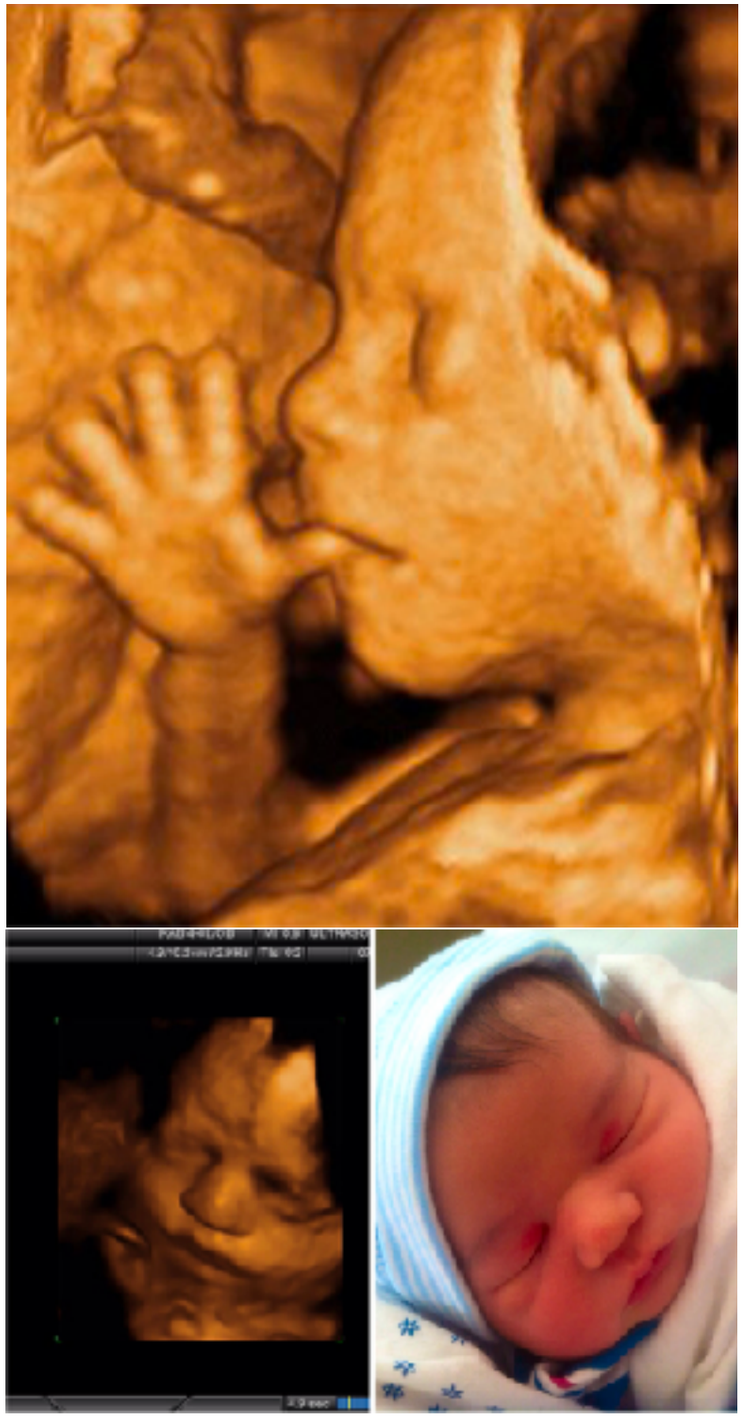
常见胎儿超声异常的遗传性诊断

先天性心脏病　　神经系统异常　超声软指标异常

北京协和医院妇产科 蒋宇林

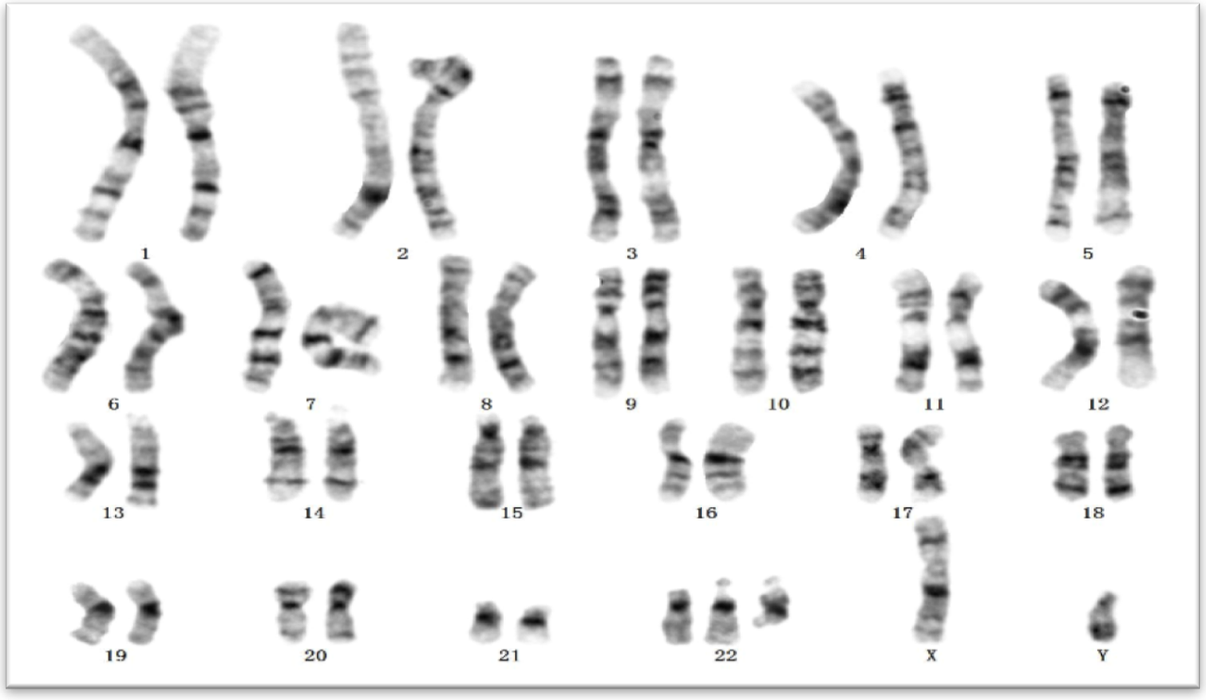
产前超声技术的迅猛发展

- 近年来超声技术的发展非常迅猛
- 胎儿超声的分辨率不断提高
- 胎儿超声产科诊断和产前诊断的重要工具
- 胎儿MRI作为新的胎儿影像手段，进展也十分迅速
- 越来越多的胎儿超声异常征象在产前被诊断出来
- 这对于产前咨询和诊断带来了显著的挑战
- 单纯胎儿结构畸形 — 遗传综合征的一部分表现?



病例-从超声异常到遗传诊断

- 贾XX，32岁，G1P0
- 孕12周NT测定1.2mm
- 中孕期唐氏筛查低危
- 孕22周胎儿系统超声提示双侧脑室增宽1.2mm，双肾回声增强
- 23周我院行羊水穿刺，送检核型分析及microarray（染色体芯片）

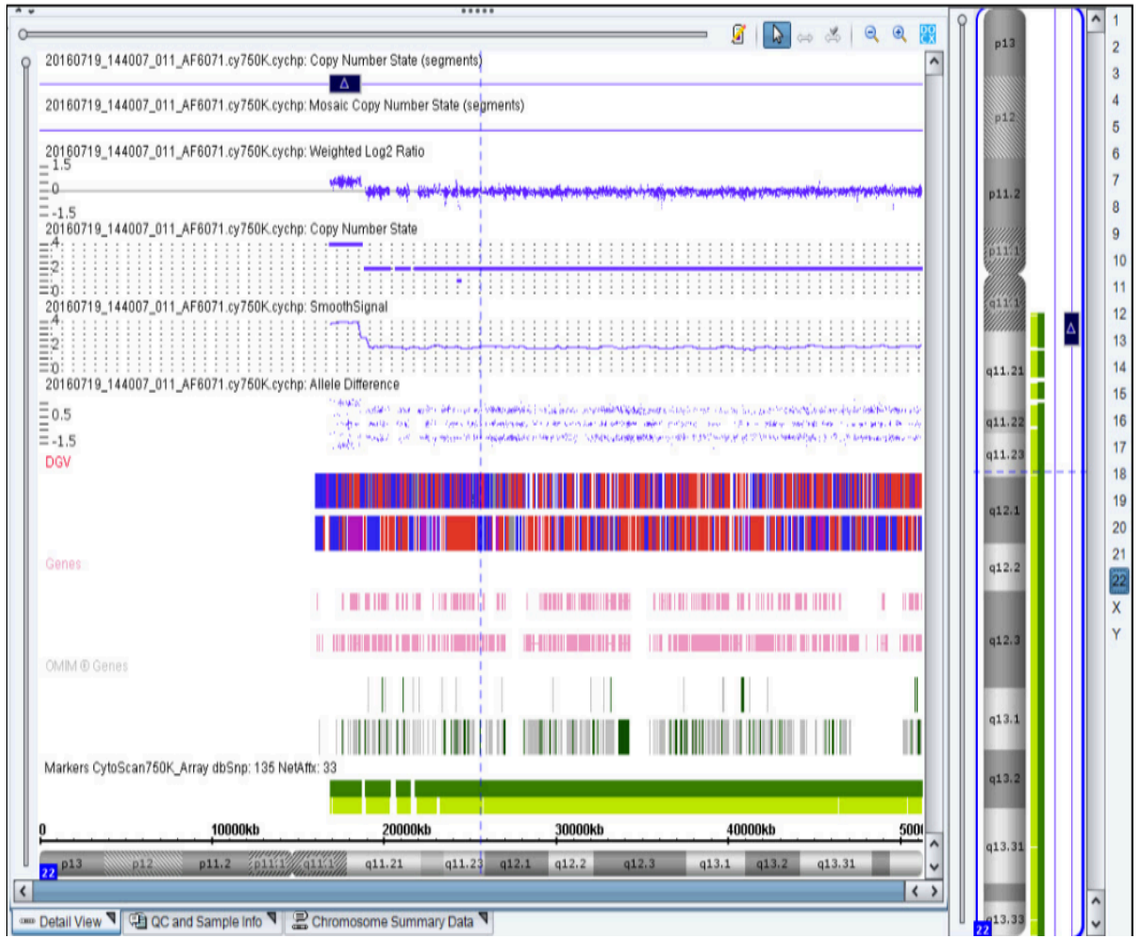


47，XY，+mar，del（22）？

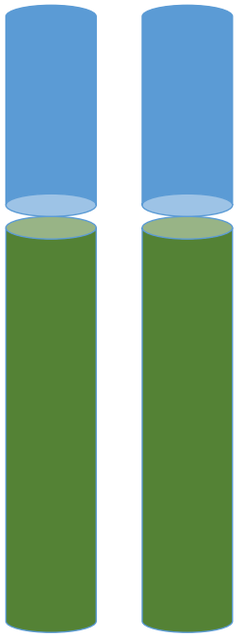
病例-microarray结果

arr[hg19] Yq11.23(26,527,669-27,456,495)x0,
22q11.1q11.21(16,888,899-18,649,190)x4

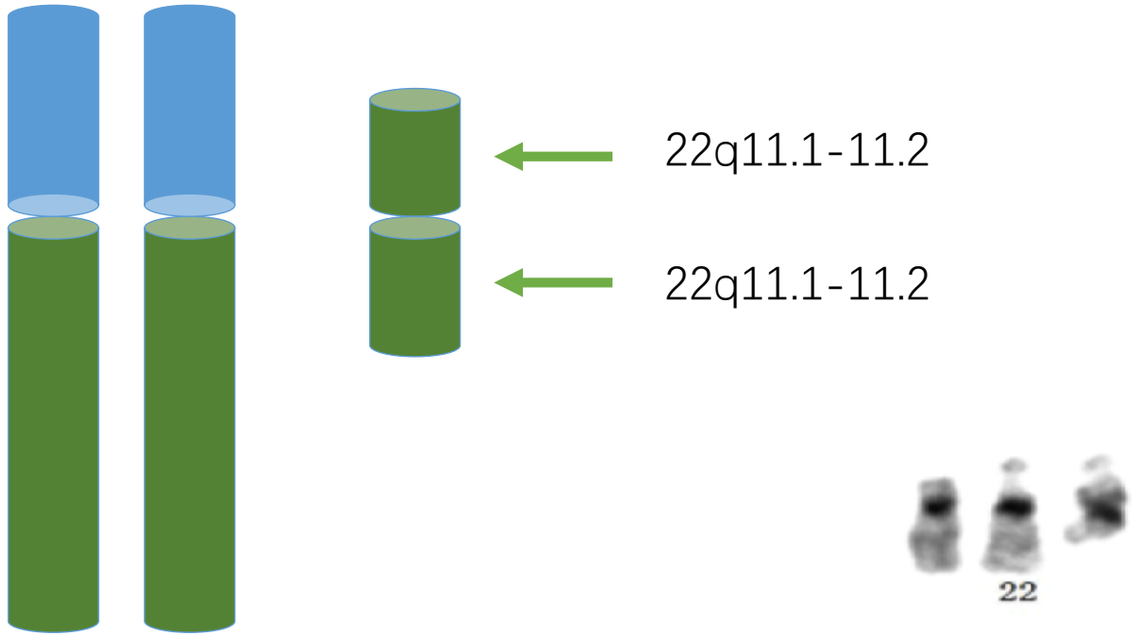
- Microarray芯片检测结果显示胎儿Y染色体Yq11.23区段存在928.8Kb片段的缺失。位于AZFc区域,内含DAZ2,DAZ3等3个OMIM基因,包含了sY587和部分sY255位点. 含有DAZ1/DAZ2,DAZ3/DAZ4的Y染色体长臂AZFc区段的缺失是男性无/寡精,不育的原因之一。
- 胎儿22号染色体22q11.1q11.21区段存在1.76Mb的2次重复, 内含XKR, CECR1, CECR2, ATP6V1E1,MICAL,PEX2,TUBA8等 11个OMIM基因，涉及Cat eye syndrome (CES) 猫眼综合征的关键区域。CECR1,CECR2 和ATPV1E1 等OMIM基因是CES 猫眼综合征的候选基因.
- 夫妇双方的染色体核型分析及microarray是正常的



胎儿发生了什么？



正常人的22号染色体



该胎儿的22号染色体组成

病例：最终诊断

- 胎儿诊断结果：47,XN,idic(22)(q11.2),+22
- 胎儿含有一条额外的由两条22号染色体断裂点位于22q11.2对接而形成的含有双份22号短臂，着丝粒，部分长臂的异常双着丝粒等臂染色体，为猫眼综合症患者
- 绝大多数CES猫眼综合征的患者含有一条额外的包含2份以上候选基因位点片段的22 号染色体部分长臂的idic(22)(q11.2)标记染色体而导致以上基因片段的4倍体性
- 其临床特征是虹膜缺损伴有肛门闭锁/瘘；其他临床异常表现随患者的额外的22号染色体长臂等臂标记染色体所包含重复片段的大小而有不同程度的异常, 包括智力发育低下， 胎儿生长发育迟缓, 先天的下斜睑裂, 眼, 耳, 鼻等面部, 头部异常和心脏,肾脏发育畸形等异常

病例 — 从新生儿的结构畸形到遗传诊断

5岁男孩，智力和体格发育迟缓，幼年时做过心脏室缺修补术，怀疑是某种染色体病

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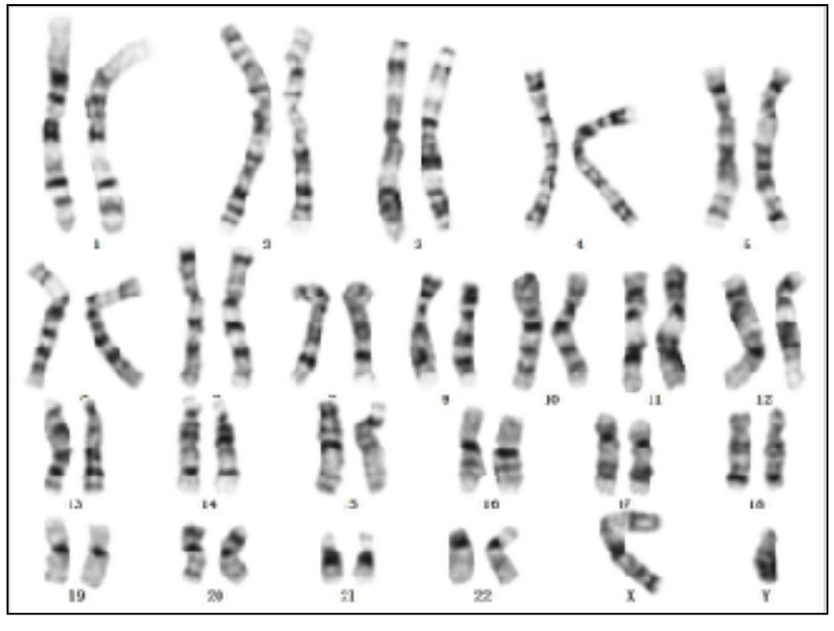

46，XY

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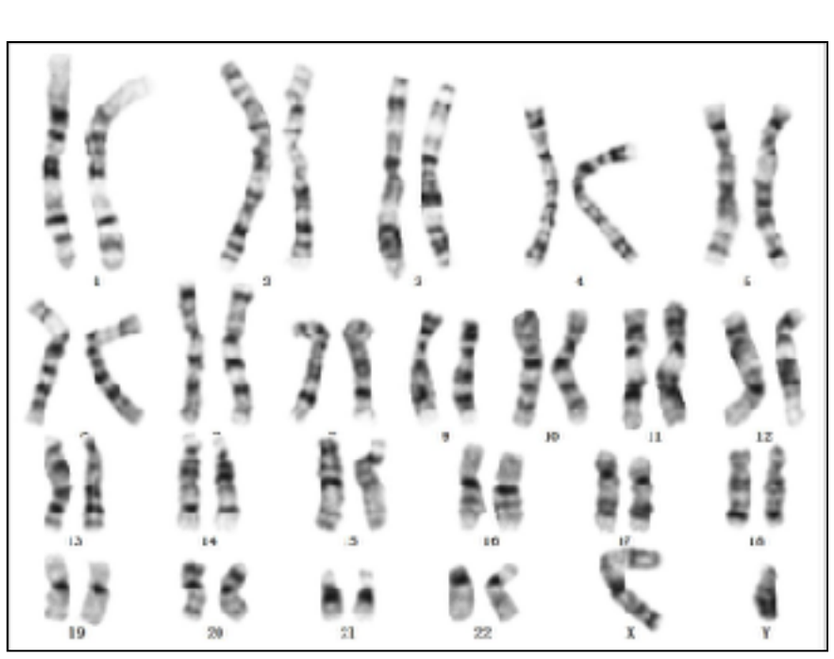
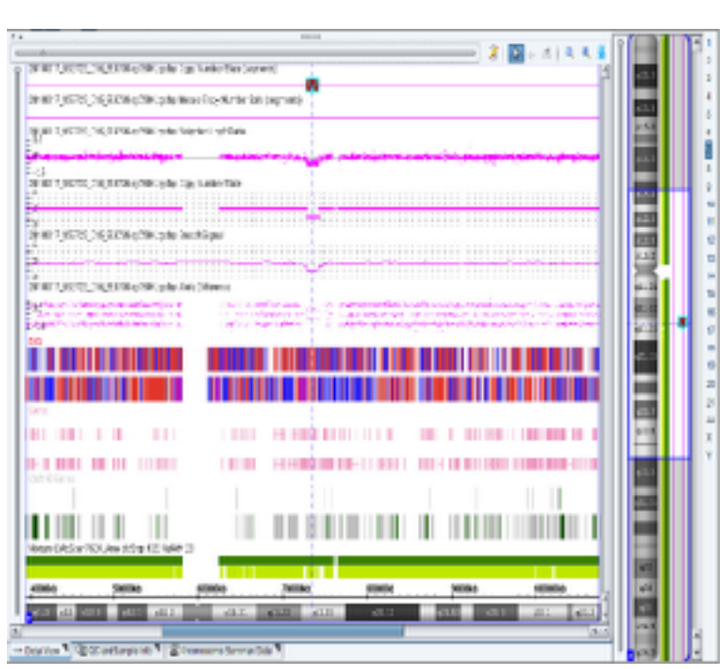


46，XY



7q11.23(72,749,941-74,154,209)缺失1.4M

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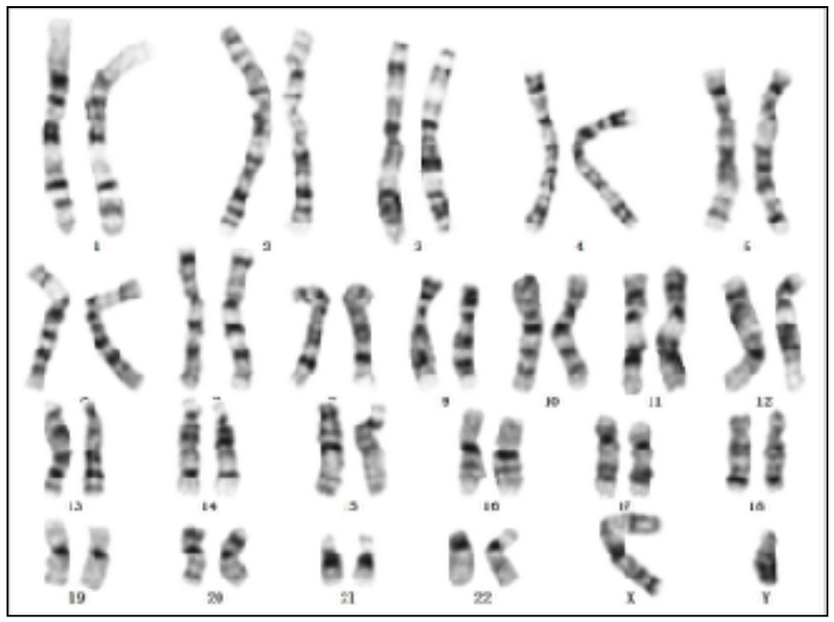
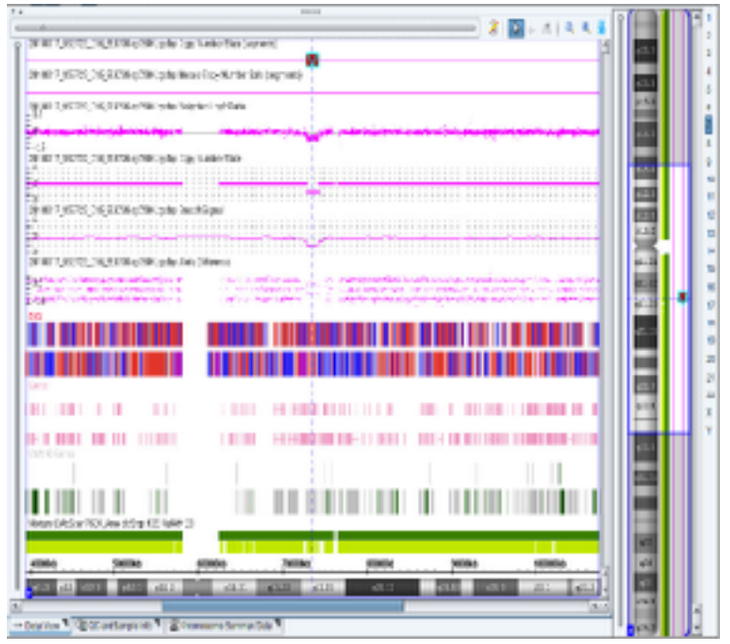
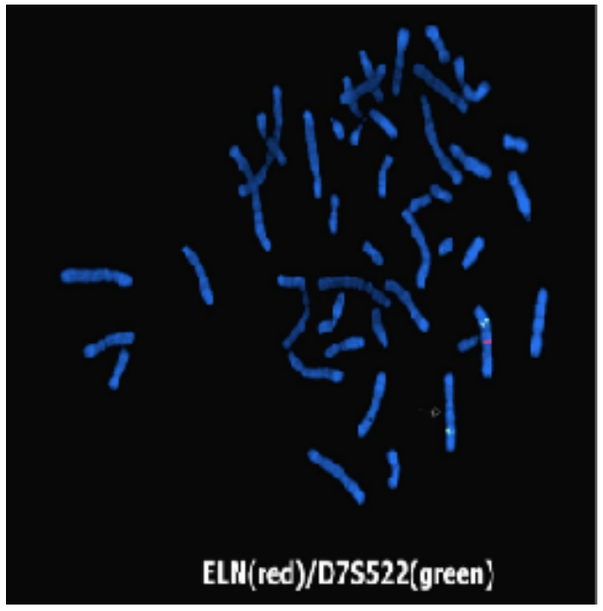


46，XY



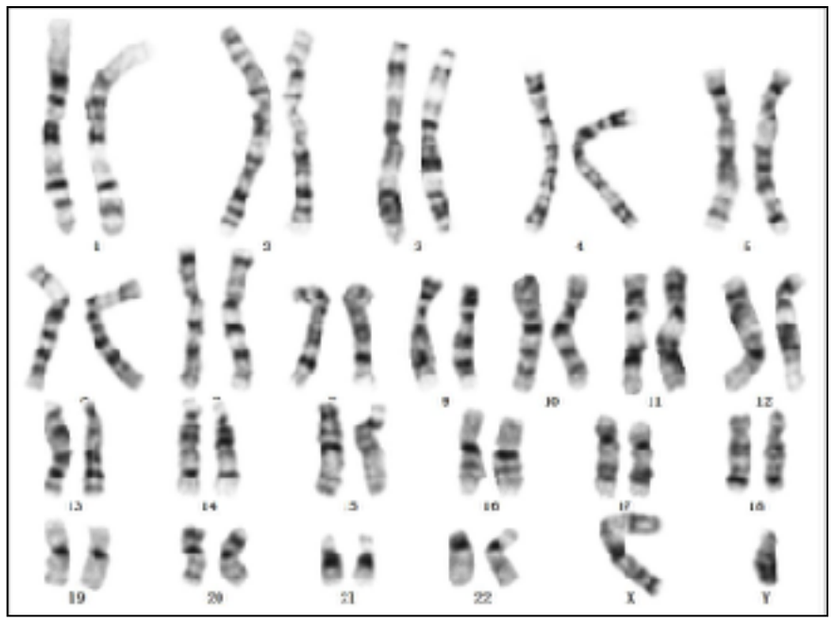
7q11.23(72,749,941-74,154,209)缺失1.4M



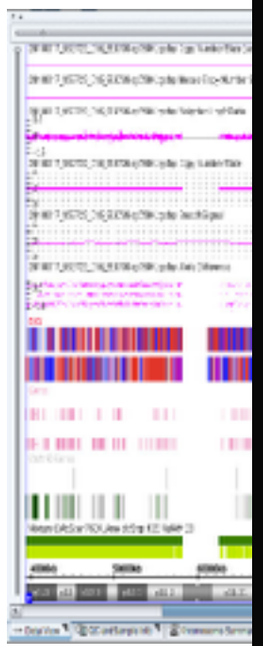
ish del(7)(q11.23q11.23)(ELN-)

病例 — 从新生儿的结构畸形到遗传诊断

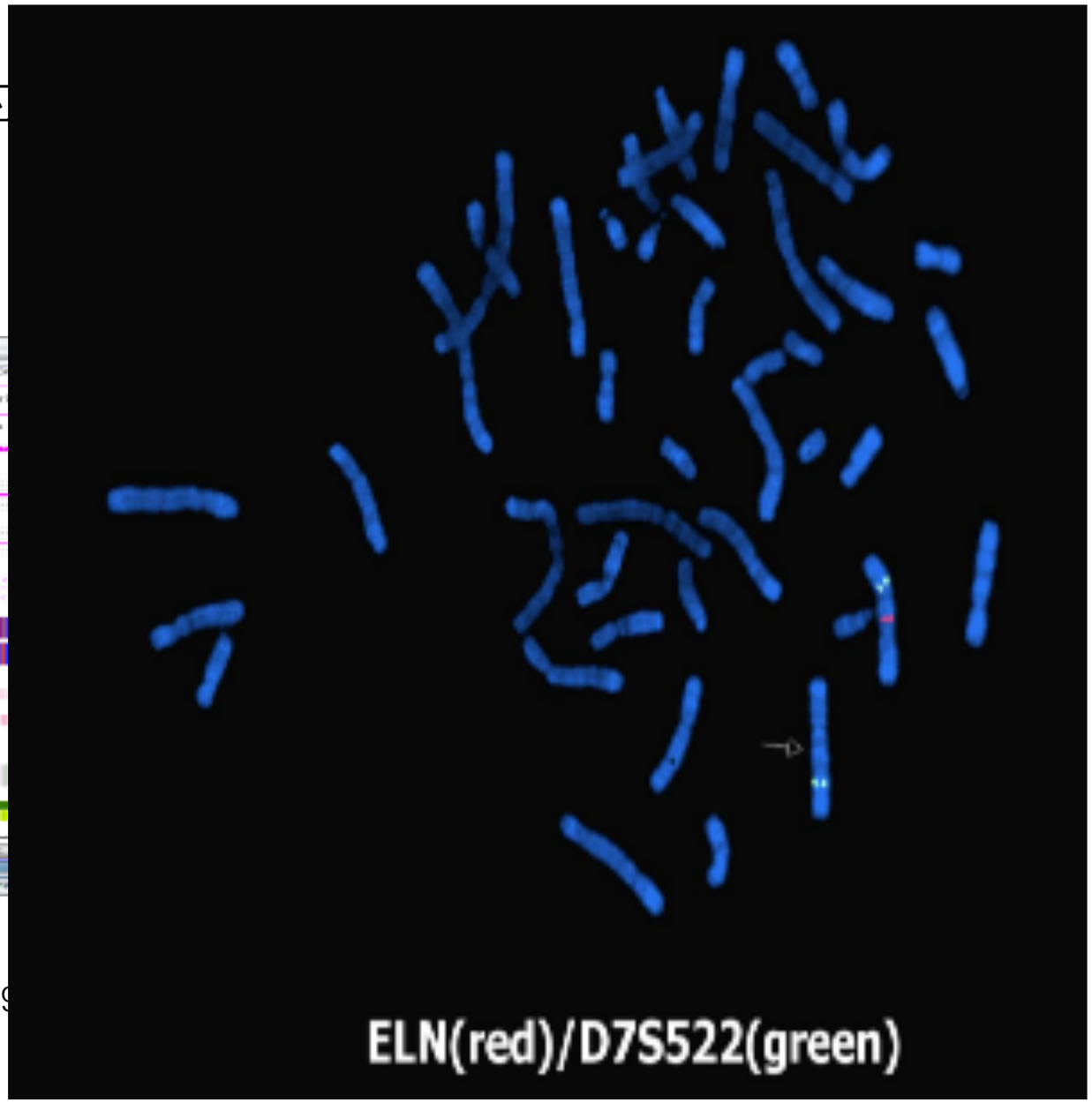
5岁男孩，智力和体格发育迟缓，幼年时



46，XY



7q11.23(72,749



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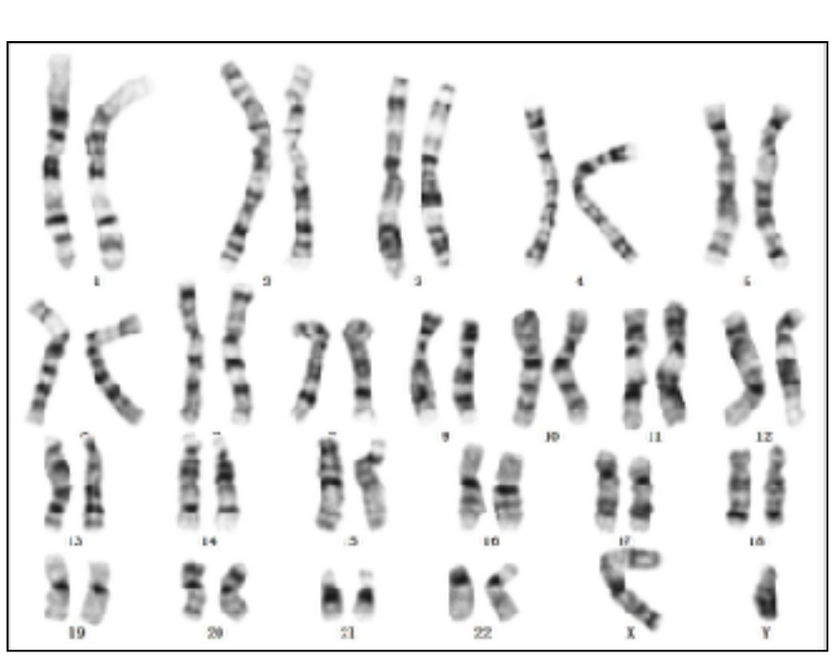
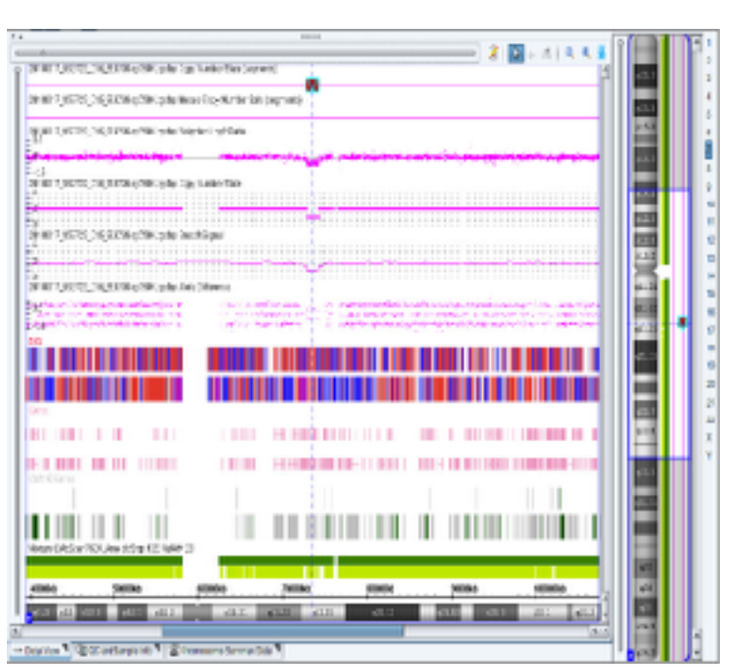
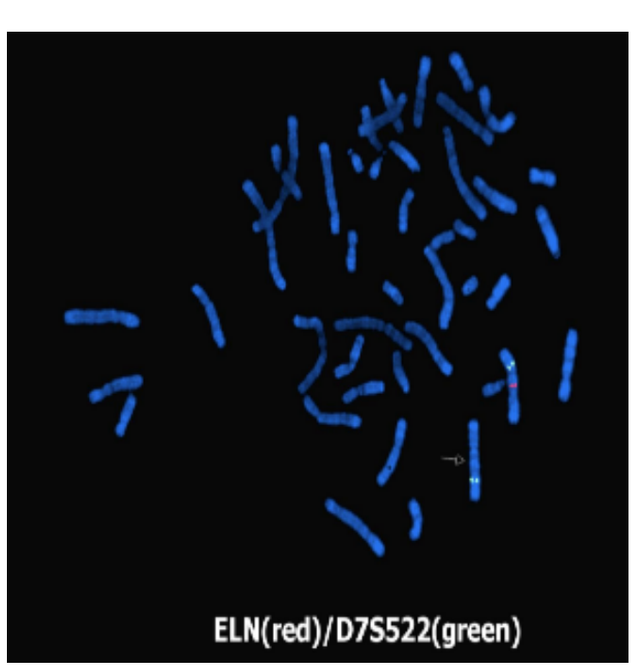


46，XY



7q11.23(72,749,941-74,154,209)缺失1.4M



ish del(7)(q11.23q11.23)(ELN-)

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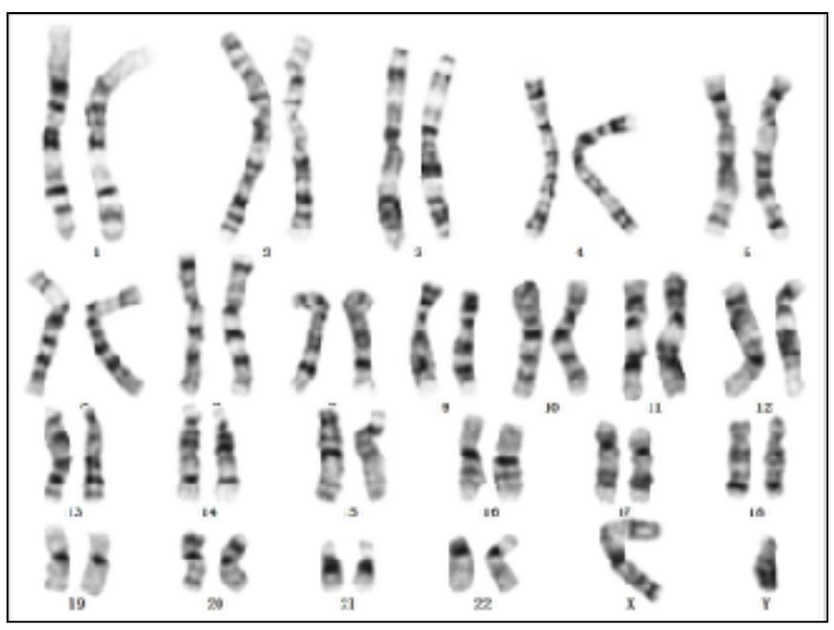
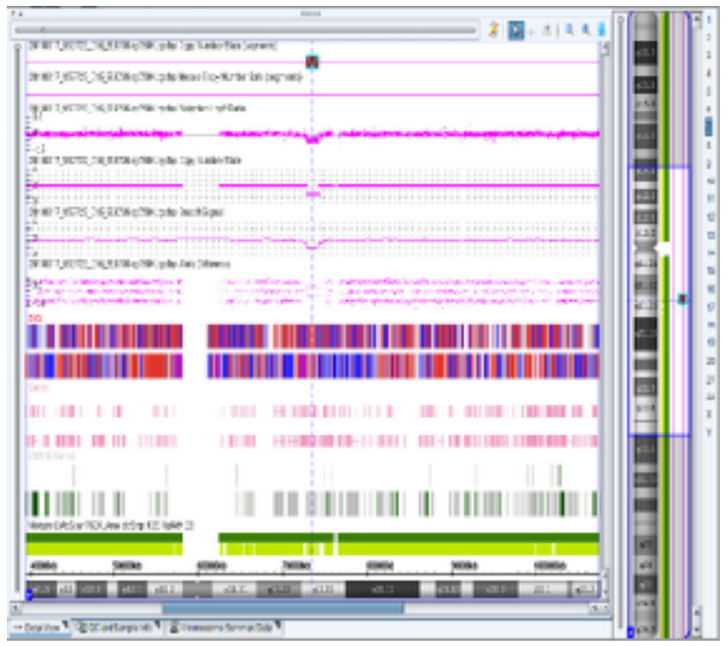
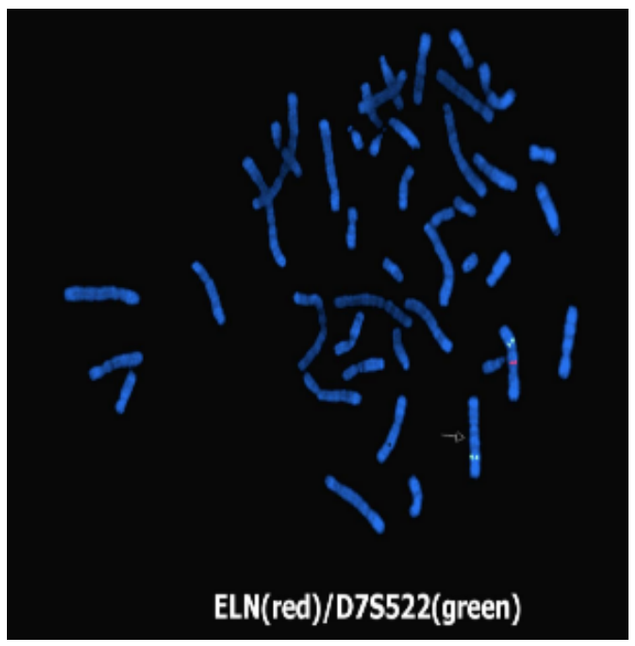
46,XY.ish del(7)(q11.23q11.23)(ELN-)dn　　Williams-Beuren综合征







46，XY　　7q11.23(72,749,941-74,154,209)缺失1.4M　　ish del(7)(q11.23q11.23)(ELN-)

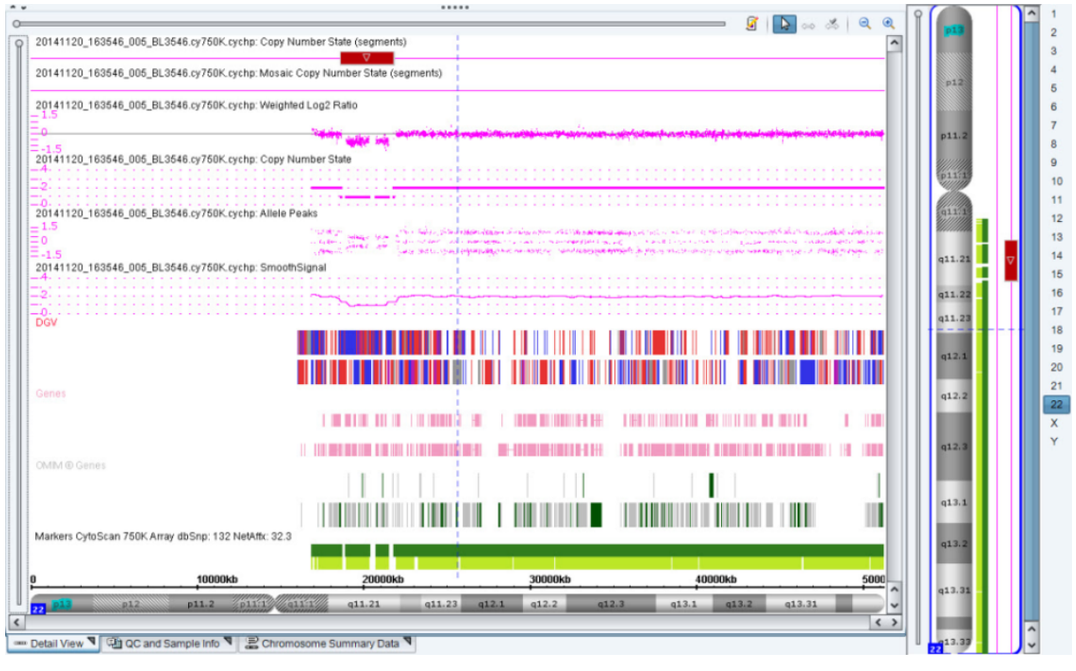
Williams-Beuren综合征(WBS)-7q11.23

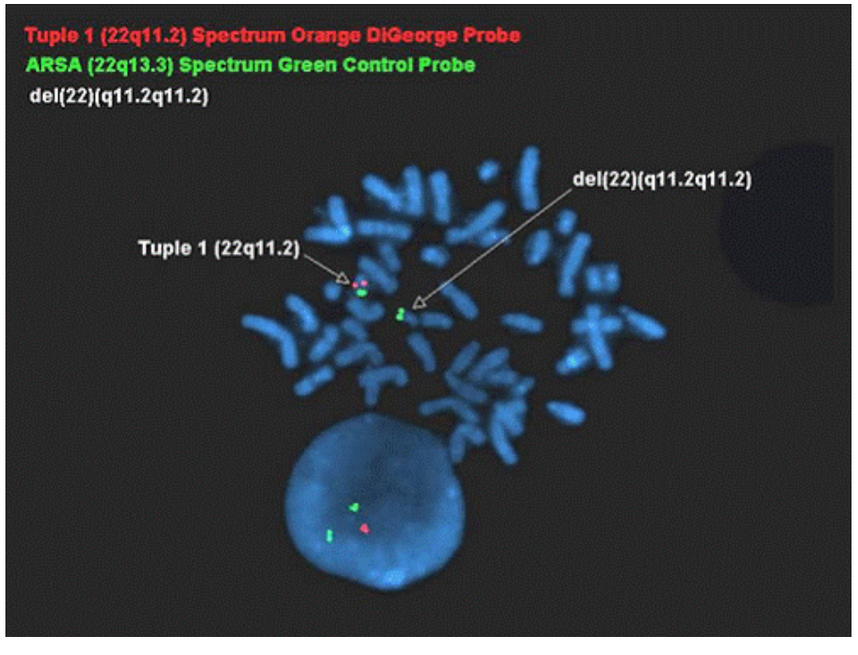
- 产前临床表现:IUGR
- 产后临床表现:
  - 70%伴有心血管畸形（主动脉流出道狭窄），特殊面容（嘴唇厚，鼻孔前倾，长人中）、智力迟滞、发育迟缓、特殊性格，皮肤早熟等
  - 婴儿期常有腹痛发作，高血钙表现
  - 有突出的社交性，表现为喜欢外出，交流过度频繁，待人过份友好和善
  - 中枢神经系统和骨骼肌肉系统的发育迟缓
- 该综合征不能被常规或高分辨核型分析发现

J Med Genet, 2003;40:526-530
Arch Dis Child 1999;81:198-200
Arq Bras Cardiol,2003;81(5):468-73
Am J Human Genet,1999;64,000
J Med Genet 2007;44:2 136-143

病例

- 孕24周产前超声提示胎儿心脏流出道异常，行脐带血穿刺
- 芯片及FISH检测结果：22q11.21 3.1Mb的缺失

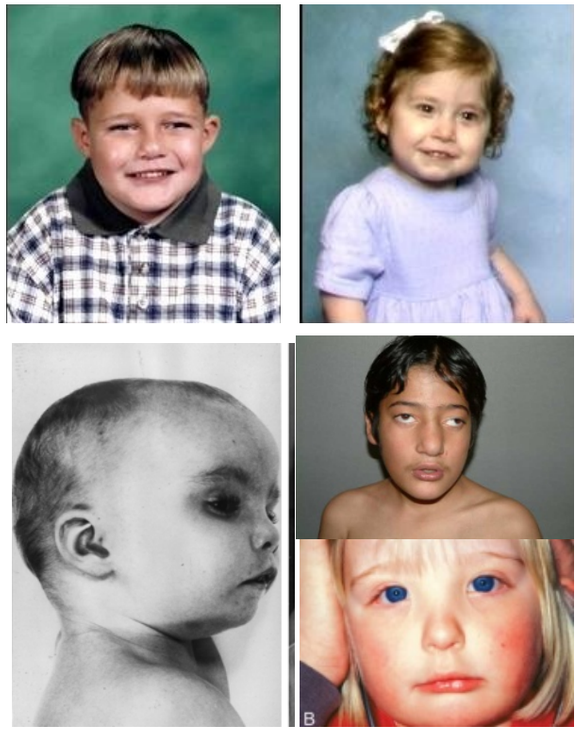




22q11.2微缺失综合征（ DiGeorge 综合征）

DiGeorge 综合征(DGS)

- DiGeorge I:22q11.2/ DiGeorge II:10p14



- 最常见的微缺失综合征
- 活产婴儿发生率1/4000-5000
- 1.5~3.0 Mb 的缺失
- 30%可通过细胞遗传学诊断技术发现
- 产前临床表现: 先天性心脏病、腭裂等
- 产后临床表现:

85%合并心脏畸形（流出道畸形）、胸腺发育不全、低钙血症、部分存在学习困难、进食困难、听力损伤及骨骼畸形、免疫缺陷、癫痫等

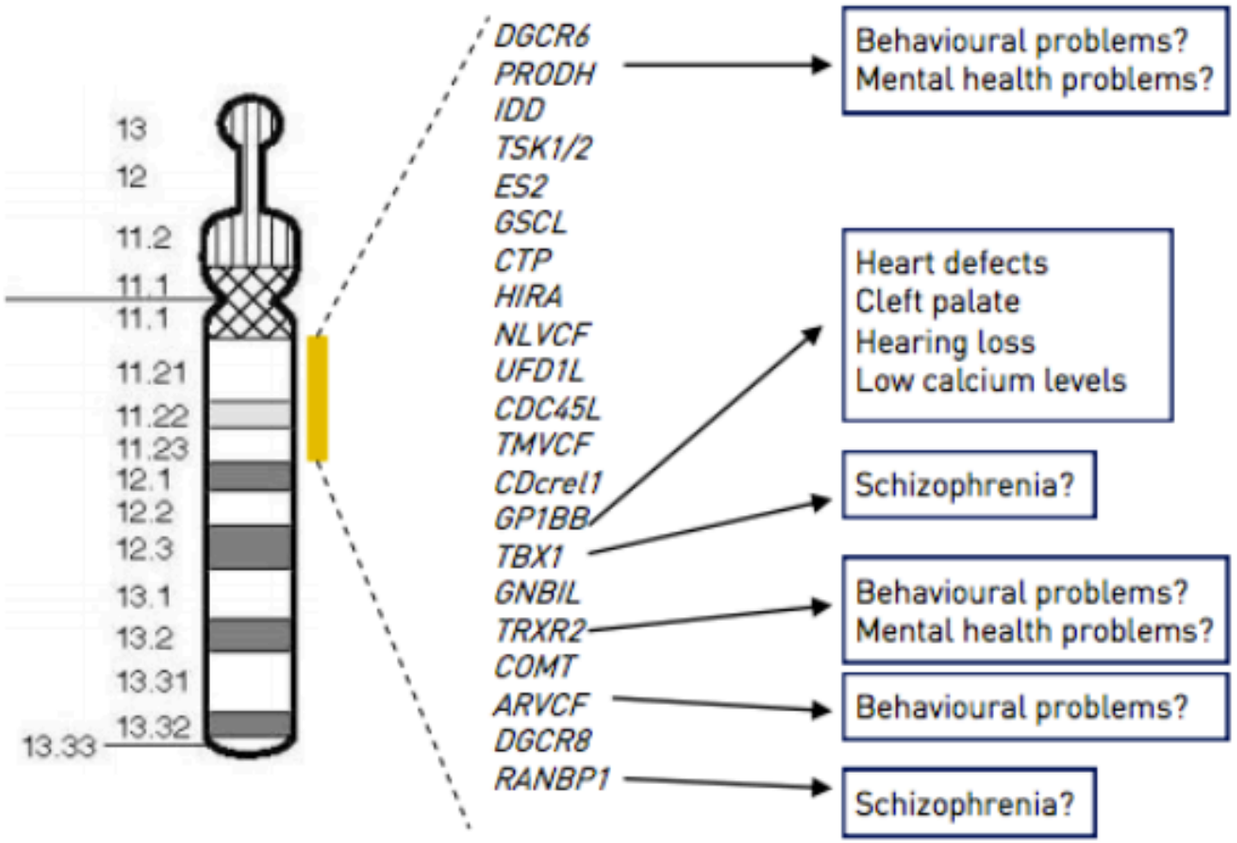
Br J Ophthalmol 2002;86:1312–1321

J Med Genet 2000;37:33–37

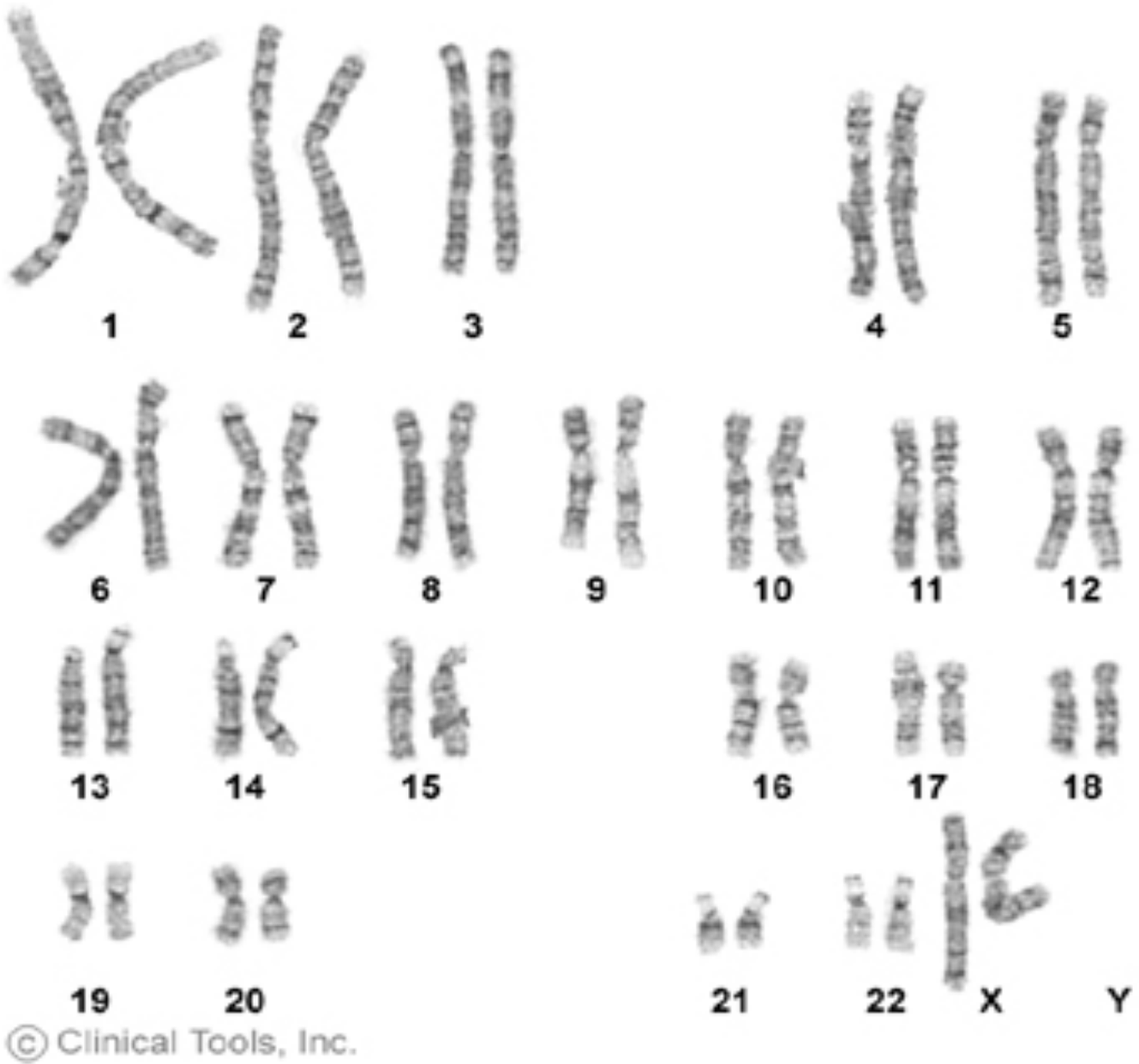
Am. J. Hum. Genet. 1999;64:659–667

22q11.2微缺失综合征

- 先天性心脏病
- 颚弓异常导致的鼻音重
- 特殊面容
- 低钙血症，常导致抽搐
- 喂养困难
- 语言能力下降
- 学习和认知能力下降



胎儿超声异常的传统遗传诊断技术 – 核型分析



优点

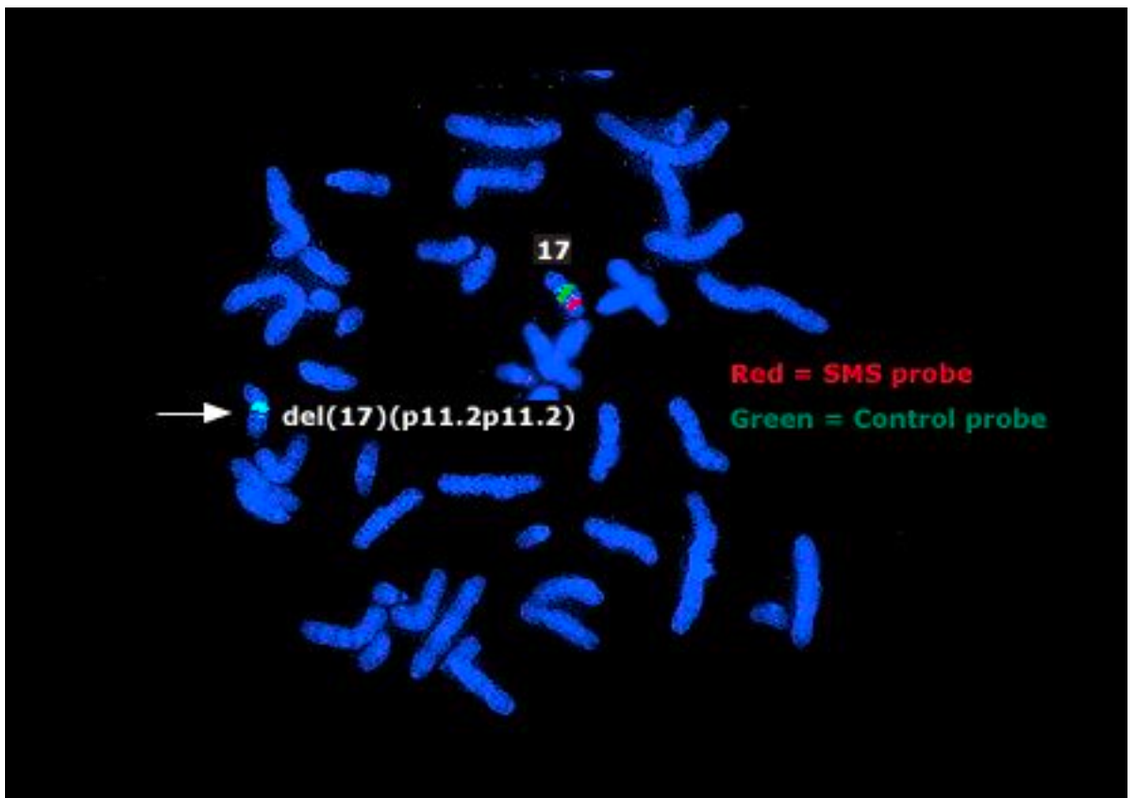
- ✓ 单细胞
- ✓ 直观形态
- ✓ 诊断金标准

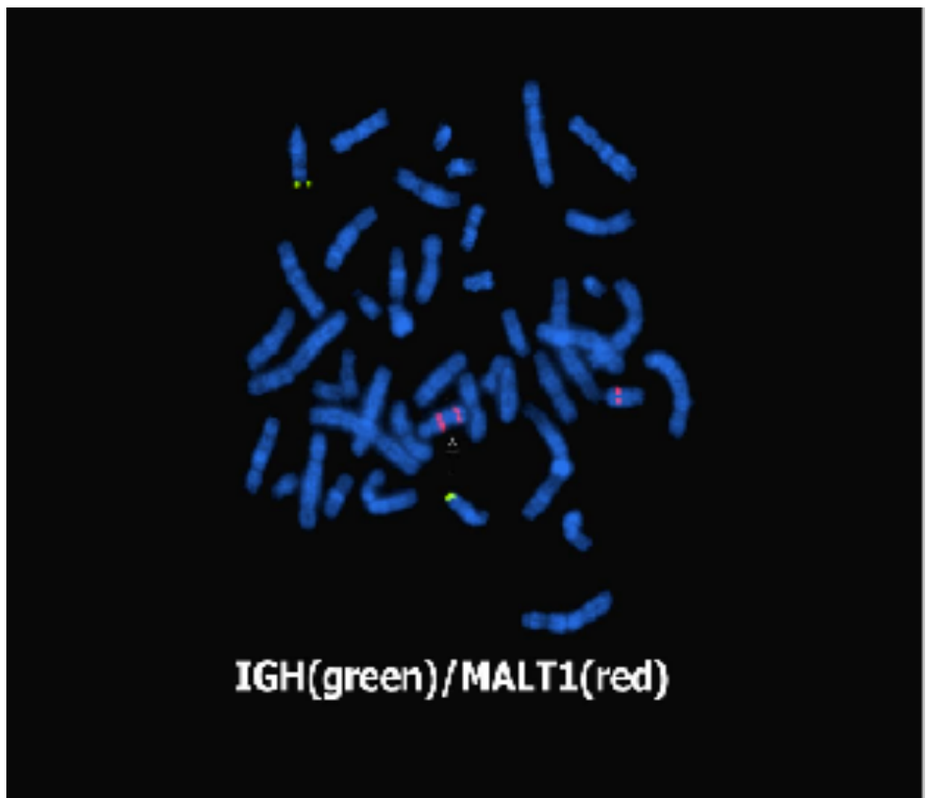
缺点

- ❖ 需要细胞培养
- ❖ 有丝分裂细胞
- ❖ 分辨率低: 5-10Mb
- ❖ 要求经验
- ❖ 费时

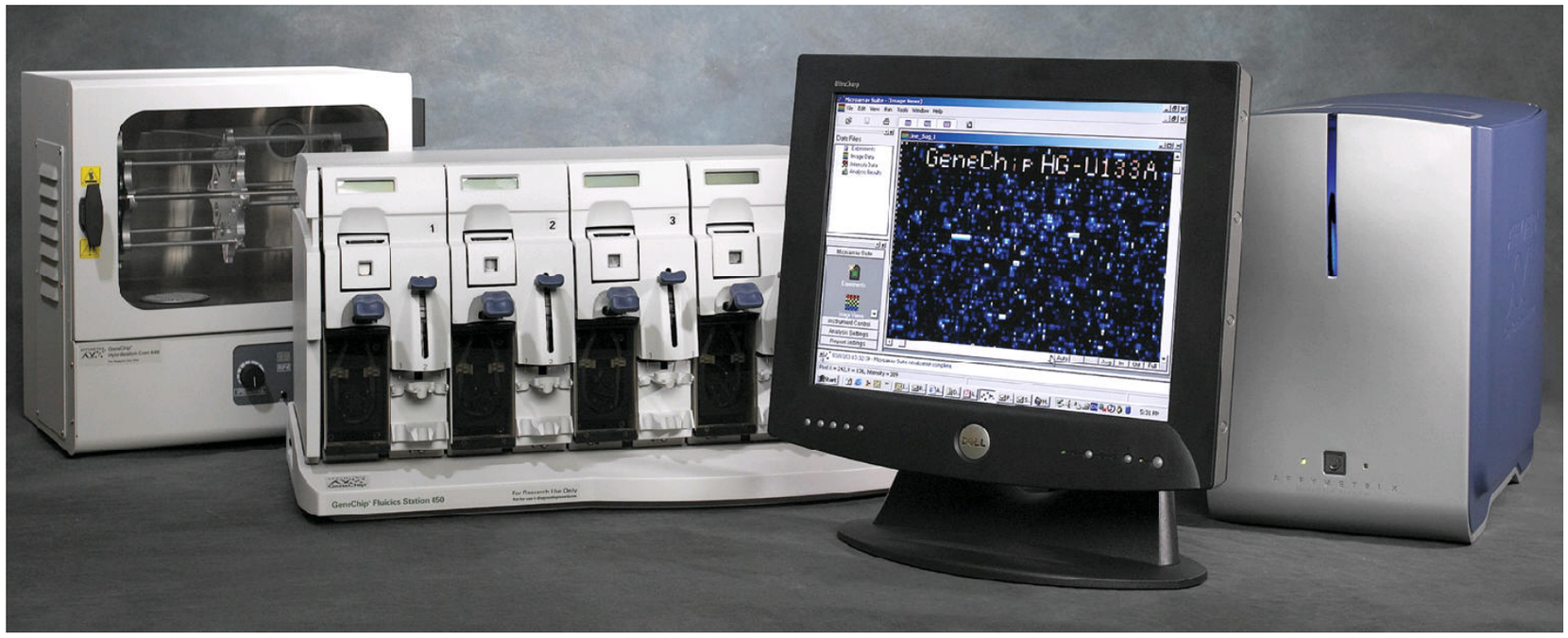
诊断产前超声异常的主要技术手段：荧光原位杂交技术（FISH）

- 根据可能的染色体缺失重复片段位点，选择特异的探针进行杂交，荧光显微镜下进行显色判断
- 特异性强，诊断明确，操作快捷
- 需要有明确的诊断方向，不适合“大撒网式”的诊断，多用于验证性的检测

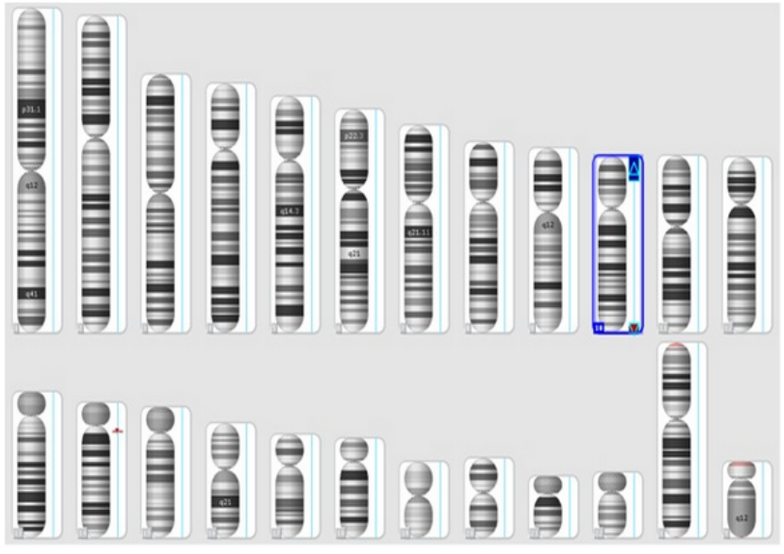




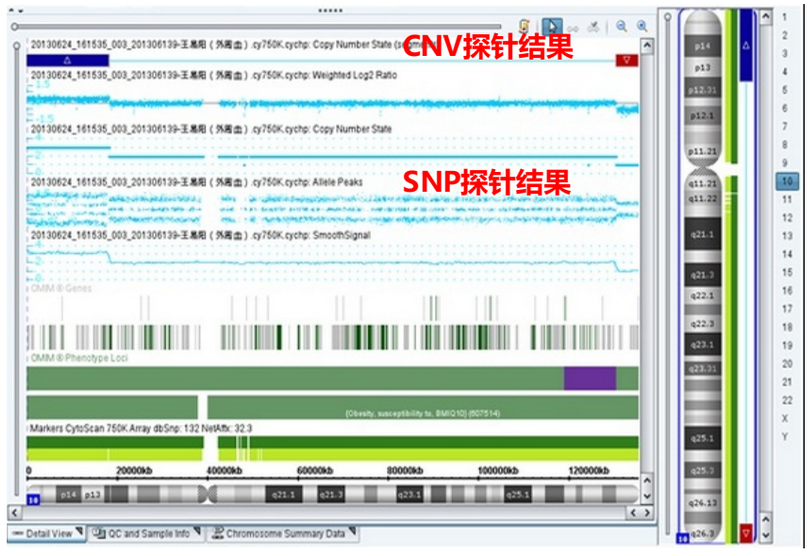
诊断产前超声异常的主要技术手段：全基因组染色体芯片技术（microarray）



全染色体组模拟核型图



异常染色体详图



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Chromosomal Microarray versus Karyotyping for Prenatal Diagnosis

Ronald J. Wapner, M.D., Christa Lese Martin, Ph.D., Brynn Levy, M.Sc.(Med.), Ph.D., Blake C. Ballif, Ph.D., Christine M. Eng, M.D., Julia M. Zachary, Melissa Savage, M.S., Lawrence D. Platt, M.D., Daniel Saltzman, M.D., William A. Grobman, M.D., M.B.A., Susan Klugman, M.D., Thomas Scholl, Ph.D., Joe Leigh Simpson, M.D., Kimberly McCall, B.S., Vimla S. Aggarwal, M.B., B.S., Brian Bunke, B.S., Odelia Nahum, M.Sc., Ankita Patel, Ph.D., Allen N. Lamb, Ph.D., Elizabeth A. Thom, Ph.D., Arthur L. Beaudet, M.D., David H. Ledbetter, Ph.D., Lisa G. Shaffer, Ph.D., and Laird Jackson, M.D.

ABSTRACT

BACKGROUND

Chromosomal microarray analysis has emerged as a primary diagnostic tool for the evaluation of developmental delay and structural malformations in children. We aimed to evaluate the accuracy, efficacy, and incremental yield of chromosomal microarray analysis as compared with karyotyping for routine prenatal diagnosis.

METHODS

Samples from women undergoing prenatal diagnosis at 29 centers were sent to a central karyotyping laboratory. Each sample was split in two; standard karyotyping was performed on one portion and the other was sent to one of four laboratories for chromosomal microarray.

RESULTS

We enrolled a total of 4406 women. Indications for prenatal diagnosis were advanced maternal age (46.6%), abnormal result on Down's syndrome screening (18.8%), structural anomalies on ultrasonography (25.2%), and other indications (9.4%). In 4340 (98.8%) of the fetal samples, microarray analysis was successful; 87.9% of samples could be used without tissue culture. Microarray analysis of the 4282 nonmosaic samples identified all the aneuploidies and unbalanced rearrangements identified on karyotyping but did not identify balanced translocations and fetal triploidy. In samples with a normal karyotype, microarray analysis revealed clinically relevant deletions or duplications in 6.0% with a structural anomaly and in 1.7% of those whose indications were advanced maternal age or positive screening results.

CONCLUSIONS

In the context of prenatal diagnostic testing, chromosomal microarray analysis identified additional, clinically significant cytogenetic information as compared with karyotyping and was equally efficacious in identifying aneuploidies and unbalanced rearrangements but did not identify balanced translocations and triploidies. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and others; ClinicalTrials.gov number, NCT01279733.)

From the Departments of Obstetrics and Gynecology (R.J.W., M.S.) and Pathology and Cell Biology (B.L., V.S.A., O.N.), Columbia University Medical Center, Carnegie Hill Imaging for Women (D.S.), and Montefiore Medical Center/Albert Einstein College of Medicine (S.K.) — all in New York; the Department of Human Genetics, Emory University School of Medicine, Atlanta (C.L.M., B.B., D.H.L.); Signature Genomic Laboratories, Spokane, WA (B.C.B., A.N.L., L.G.S.); the Department of Molecular and Human Genetics, Baylor College of Medicine, Houston (C.M.E., A.P., A.L.B.); George Washington University Biostatistics Center, Rockville, MD (J.M.Z., E.A.T.); Center for Fetal Medicine and Women's Ultrasound, Los Angeles (L.D.P.); Feinberg School of Medicine, Northwestern University, Chicago (W.A.G.); Integrated Genetics, Westborough, MA (T.S.), and Santa Fe, NM (K.M.); Florida International University, Miami (J.L.S.); and Drexel University College of Medicine, Philadelphia (L.J.). Address reprint requests to Dr. Wapner at Columbia University Medical Center, Department of Obstetrics and Gynecology, 622 W. 168th St, PH16-66, New York, NY 10032, or at rw2191@mail.cumc.columbia.edu.

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Table 3. Frequency and Clinical Interpretation of Microdeletions and Duplications on Chromosomal Microarray in the 3822 Samples with a Normal Karyotype, According to Indication for Prenatal Testing.

Indication for Prenatal Diagnosis	Normal Karyotype	Common Benign	Pathogenic	Uncertain Clinical Significance (N=130)		Total Known Pathogenic and Potential for Clinical Significance*
				Likely to Be Benign	Potential for Clinical Significance	
	no.	*no. (%)*				*no. (%) [95% CI]†*
Any	3822	1234 (32.3)	35 (0.9)	69 (1.8)‡	61 (1.6)	96 (2.5) [2.1–3.1]
Advanced maternal age	1966	628 (31.9)	9 (0.5)	37 (1.9)	25 (1.3)	34 (1.7) [1.2–2.4]
Positive on Down's syndrome screening	729	247 (33.9)	3 (0.4)	13 (1.8)	9 (1.2)	12 (1.6) [0.9–2.9]
Anomaly on ultrasonography	755	247 (32.7)	21 (2.8)	16 (2.1)	24 (3.2)	45 (6.0) [4.5–7.9]
Other§	372	112 (30.1)	2 (0.5)	3 (0.8)	3 (0.8)	5 (1.3) [0.6–3.1]

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Microarray是诊断胎儿超声异常背后的染色体病的首要技术

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2016年美国妇产科学会指南

核型分析或microarray可以适用于任何一例产前诊断的病例

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal-Fetal Medicine

(Published Electronically Ahead of Print on March 1, 2016)

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

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(Replaces Practice Bulletin Number 88, December 20
(See also Practice Bulletin Number 163, *Screening for Fetal Aneuplo*

Prenatal Diagnostic Testing for Genetic Disorders

Prenatal genetic diagnostic testing is intended to determine, with as much certainty as possible, whether a specific genetic disorder or condition is present in the fetus. In contrast, prenatal genetic screening is designed to assess whether a patient is at increased risk of having a fetus affected by a genetic disorder. Originally, prenatal genetic testing focused primarily on Down syndrome (trisomy 21), but now it is able to detect a broad range of genetic disorders. Although it is

mutation that causes the disease. Karyotype or microarray analysis should be offered in every case, although performing karyotype or microarray may not be necessary in a low-risk patient. Also, routine measurement of amniotic fluid alpha fetoprotein to screen for neural tube defects may not be necessary in all cases when amniocentesis is performed for other indications and the ultrasound examination is normal with good visualization of the fetal spine and head (Table 1).

In patients with a major fetal structural abnormality found on ultrasound examination, CVS or amniocentesis with chromosomal microarray should be offered (10). If a structural abnormality is strongly suggestive of a particular aneuploidy in the fetus (eg, duodenal atresia or an atrioventricular heart defect, which are characteristic

Microarray检测应该用于所有胎儿超声有异常结果的产前诊断病例

ithout FISH
ay analysis.
g offspring
with trisomy 13, 18, or 21 based on abnormal serum screening or cell-free DNA testing, amniocentesis with FISH plus karyotype or with karyotype alone should be offered. Additionally, chromosomal microarray analysis should be available to women undergoing invasive

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二代测序技术在产前超声遗传诊断领域的应用

- NIPT
- CNV－seq
- 靶向基因panel
- 全外显子测序
- 全基因组测序

全外显子测序主要用于以下临床情况

- 临床高度怀疑是一种罕见孟德尔遗传单基因病
- 已经除外了染色体病或临床常见的单基因病
- 涉及多个候选基因，基因panel检测的费用非常昂贵
- 受试者往往为儿童，产前超声异常的适应症正在探索

先天性心脏病

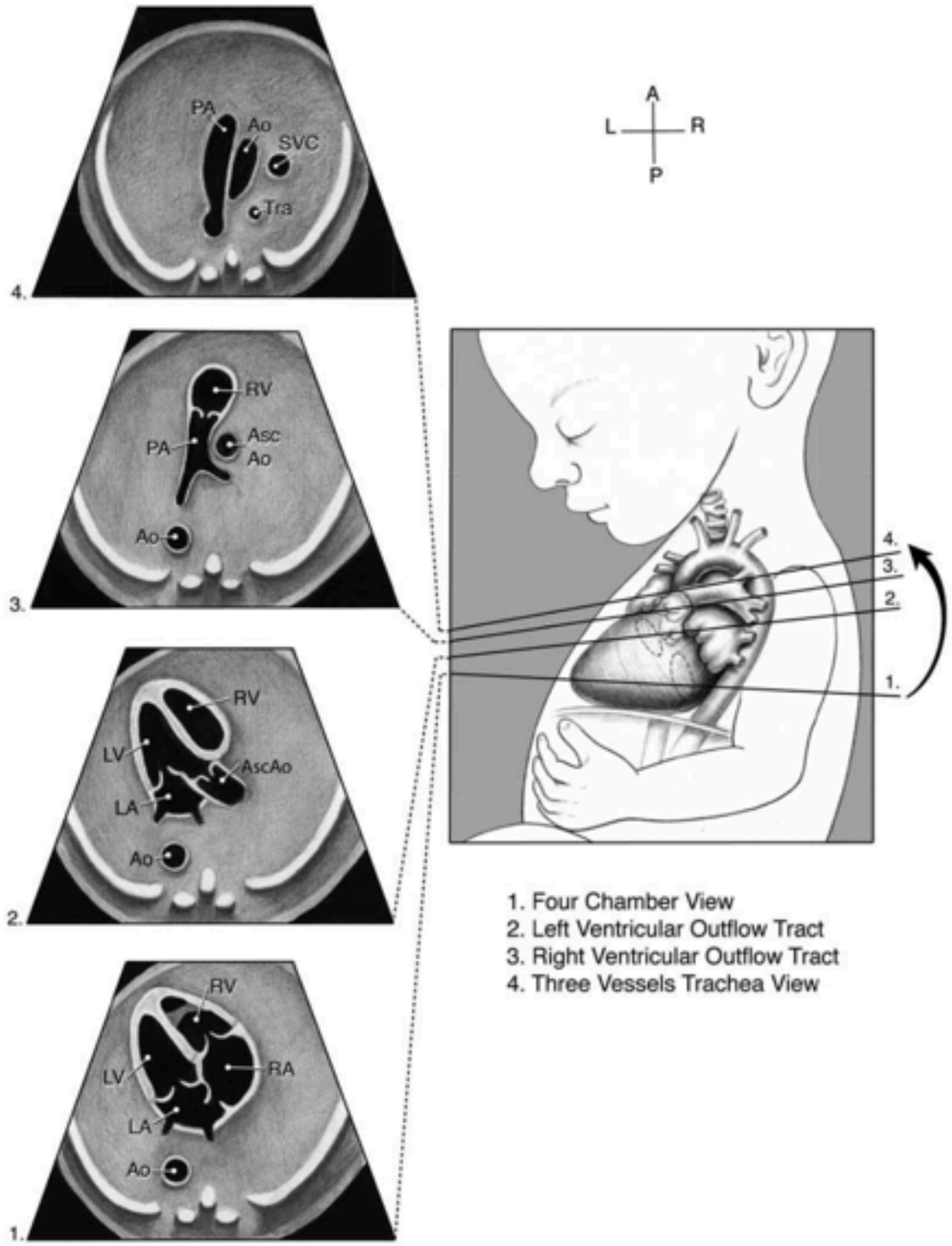
- 最常见的出生缺陷类型
  - 严重的先心病类型 2-3‰
  - 中度以上的先心病类型 6‰
- 也是新生儿死亡的重要原因
- 引起先天性心脏病的原因有遗传基因、表观遗传学和环境因素

筛查孕周

- 最适合的筛查孕周是18-22周
- 一些心脏问题直到孕期中晚期才会出现
- 包括心律失常，心肌病，心力衰竭，瓣膜病以及心脏肿瘤等
- 也有较少的情况是孕期无法检出的
- 包括轻微的房间隔缺损，瓣膜病变，冠状动脉异常等

基础胎儿心脏评估

- 三个重要切面
  - 4腔心切面
  - 左 / 右室流出道切面
  - 三血管平面



高级胎儿心脏评估 （UCG）— 什么情况需要做

- 母亲糖尿病或妊娠早期诊断糖尿病
- 母亲患苯丙酮尿症（未控制）
- 母亲有自身抗体SSA / SSB阳性
- 母亲使用心脏致畸药物（孕期使用沙利度胺，ACEI，维A酸，NSAIDs）
- 母亲妊娠早期风疹感染
- 母亲感染并胎儿怀疑有心肌炎（四腔心平面有肌力收缩不良或有积液）
- IVF-ET妊娠
- 胎儿的一级亲属患有先天性心脏病
- 胎儿的一级或二级亲属患有与先天性心脏病有关的遗传综合征或孟德尔遗传病
- 基础超声怀疑胎儿心脏畸形
- 胎儿存在心外畸形的情况
- 胎儿染色体检测提示异常（包括微缺失重复综合征）
- 胎儿心律失常
- NT检测大于本孕周的95%（3mm）
- 单绒双羊双胎
- 胎儿水肿或积液

Donofrio MT et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association *Circulation*. 2014;129:2183-2242

心外的系统评估很重要

- 如果胎儿存在心脏的畸形，心外的畸形评估很重要
- 不同人群的心外畸形比例不同，一般为20%-40%
- 心脏畸形常常是遗传综合征的一部分表型
- 全面掌握胎儿各系统的异常表型对于遗传综合征的识别很有帮助

Table 4 Detection rate of associated extracardiac abnormalities in 379 fetuses with congenital heart defects, according to organ system

Organ system	%
Central nervous	71.7
Genitourinary	
Genital	25.0
Renal	75.0
Skeletal	52.3
Respiratory	38.1
Gastrointesinal	47.5
Craniofacial	35.7
Total	53.6

Song MS et al. Ultrasound Obstet Gynecol 2009; 33:552.

先天性心脏病的遗传学评估

- 染色体非整倍体异常
- 染色体微缺失微重复综合征
- 单基因病
  - 常染色体显性
  - 常染色体隐性
  - X连锁隐性
- 非综合征性的先心病基因

Selected genetic disorders associated with cardiovascular malformations

Syndrome	Cardiovascular anomaly
Genetic associations	
VATER/VACTERL association	Wide ranging (including VSD, TOF, TGA and others)
Chromosomal syndromes	
Down syndrome (trisomy 21)	AV canal defect, VSD, ASD, TOF, PDA, pulmonary hypertension
Edwards syndrome (trisomy 18)	ASD, VSD, PDA, PS, AS, COA, TOF, HLHS, pulmonary hypertension
Patau syndrome (trisomy 13)	ASD, VSD, TOF, PS, AS, COA, HLHS, DORV, pulmonary hypertension
Turner syndrome	Aortic valve abnormalities, COA, systemic and pulmonary venous abnormalities, VSD, HLHS, ASD, aortic dilation/rupture
Chromosomal deletion/microdeletion syndromes	
DiGeorge syndrome (22q11 deletion syndrome)	TOF, IAA and other aortic arch anomalies, truncus arteriosus, VSD
Williams syndrome	Pulmonary and aortic valve defects, ASD, VSD, coronary ostial stenosis, branch pulmonary artery stenosis, arteriopathy
Single gene syndromes – Autosomal dominant inheritance pattern	
Alagille syndrome	Peripheral pulmonary artery stenosis, ASD, VSD, TOF, COA
Albright hereditary osteodystrophy	Cardiomyopathy
Cardiofaciocutaneous syndrome	PS, ASD, VSD, HCM
CHARGE syndrome	VSD, ASD, TOF, DORV, PDA, PS, pulmonary vein anomalies
Costello syndrome	HCM, PS, ASD, VSD, atrial arrhythmias
Ehlers-Danlos syndrome (vascular type)	Rupture of large vessels
Holt-Oram syndrome	ASD, VSD, left-sided lesions, conotruncal defects, AV block
Leopard syndrome	PS, prolonged PR interval, ASD, VSD, HCM
Marfan syndrome	Aortic root dilation/aneurysmal dissection, AI, MVP
Myotonic dystrophy	Cardiomyopathy
Neurofibromatosis	COA, renal artery stenosis
Osler-Weber-Rendu disease	Multiple telangiectasis, pulmonary AVM
Treacher Collins syndrome	ASD, VSD, PDA
Tuberous sclerosis	Myocardial rhabdomyoma, WPW
Noonan syndrome	PS, ASD, AS, subaortic stenosis, HCM
Single gene syndromes – Autosomal recessive inheritance pattern	
Carpenter syndrome	PDA
Cutis laxa	Pulmonary hypertension
Ellis-van Creveld syndrome	ASD, AVSD
Friedreich ataxia	Cardiomyopathy
MPS type IH (Hurler syndrome)	AI, MR, premature CAD, cardiomyopathy
MPS type IS (Scheie syndrome)	Aortic valve disease
MPS type IV (Morquio syndrome)	Aortic valve disease
MPS type VI (Maroteaux-Lamy syndrome)	Aortic valve disease
Pompe disease (GSD type 2)	Cardiomyopathy
Pseudoxanthoma elasticum	Premature CAD, MVP
Smith-Lemli-Opitz syndrome	VSD, PDA, HLHS
Thrombocytopenia absent radii syndrome (TAR)	ASD, TOF
Single gene syndromes – X-linked inheritance pattern	
MPS II (Hunter syndrome)	Valvular disease, premature CAD, cardiomyopathy
Duchenne muscular dystrophy	Cardiomyopathy
Emery-Dreifuss muscular dystrophy	Cardiomyopathy
X-linked heterotaxy	Heterotaxy
Incontinentia pigmenti	PDA, hypertension
Genetic mutations associated with nonsyndromic congenital heart disease	
NKX2-5 mutation	ASD, VSD, TOF, HLHS
GATA4 mutation	ASD, VSD, TOF
TAB2 mutation	Valvular disease, VSD, TOF

染色体非整倍体与先天性心脏病

- 胎儿染色体非整倍体异常是第一个被发现与胎儿先天性心脏病相关的遗传综合征
- 主要是T21 / T18 / T13 / Turner综合征

Table 1 Chromosome abnormality syndromes associated with CHD

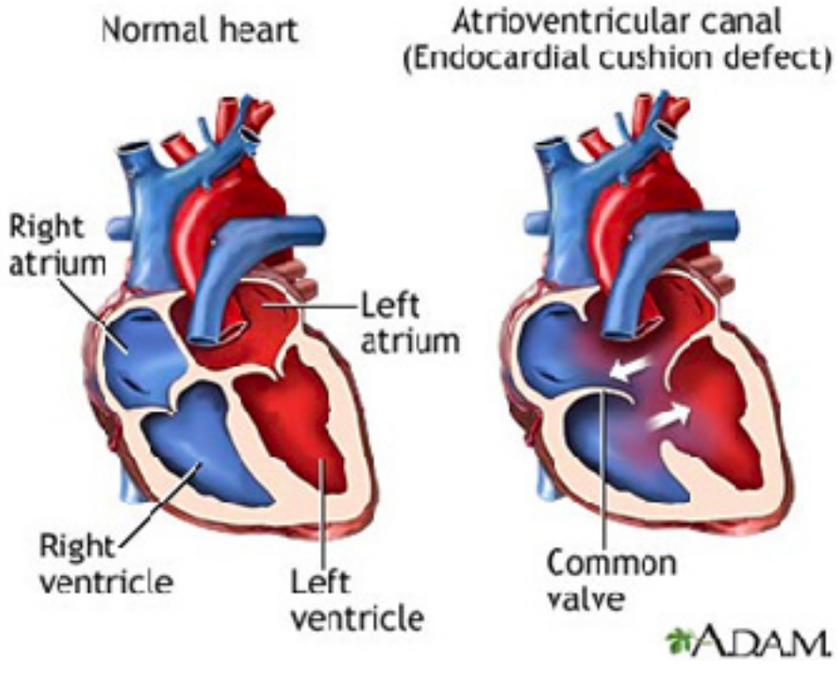
Syndrome	% CHD	CHD type
Chromosome aneuploidy		
Trisomy 21	44	AVSD (complete, partial), VSD, ASD, TOF
Trisomy 18	83	VSD, ASD, TOF, DORV, AVSD, CoA
Trisomy 13	51–64	Conotruncal CHD: TOF, DORV; VSD, ASD, AVSD; valvular anomalies
45X (Turner syndrome)	38	Left-sided cardiac structures: bicuspid aortic valve, AS, CoA, mitral valve anomalies, HLHS, aortic dilation, dissection
Chromosome deletion		
22q11.2 deletion syndrome (DiGeorge syndrome, velocardiofacial syndrome)	75–80	"Conotruncal anomalies": interrupted aortic arch type B, truncus arteriosus, TOF, TGA, perimembranous VSD, isolated aortic arch anomalies
7p11.23 microdeletion (Williams–Beuren syndrome)	82	Supravalvular aortic and pulmonary stenosis, peripheral pulmonary stenosis
1p36 deletion syndrome	35	VSD, ASD, TOF, CoA, PDA
11q23 deletion syndrome (Jacobsen syndrome)	56	VSD, left heart anomalies

AS aortic stenosis, *ASD* atrial septal defect, *AVSD* atrioventricular septal defect, *CHD* congenital heart defects, *CoA* coarctation of the aorta, *DORV* double outlet right ventricle, *HLHS* hypoplastic left heart syndrome, *PDA* patent ductus arteriosus, *TGA* transposition of the great arteries, *TOF* tetralogy of Fallot

21三体与先天性心脏病

- 21三体综合征是最常见的与CHD相关的遗传综合征
- 44%的唐氏综合征患儿存在先天性心脏病
- 其它超声表现
  - 四肢短小
  - 眼距宽
  - 发育迟缓
  - 松弛姿态
  - NT增厚
  - 多种超声软指标

21三体的心脏病表现	室间隔缺损	43%
	房间隔缺损	42%
	房室间隔缺损	39%



18三体与先天性心脏病

- 18三体的发病率较低，畸形更严重，存活时间更短
- 76-83%的18三体胎儿存在严重的CHD
- 往往有小头畸形，小下颌，发育迟缓，骨骼畸形，以及多个脏器的异常（神经系统，胃肠道，肾脏，心血管系统
- 最常见的心脏畸形是室间隔缺损

18三体的心脏异常表现
室间隔缺损
多瓣膜病变
房间隔缺损
Fallot四联症
右室双流出道
房室间隔缺损
主动脉缩窄
动脉导管未闭

13三体与先天性心脏病

- 51-64%的13三体存在CHD
- 其它超声表现为小头畸形，全前脑，唇腭裂，发育迟缓，肾脏畸形，骨骼畸形

13三体的心脏异常表现
圆锥动脉干发育相关畸形
室间隔缺损
多瓣膜病变
房间隔缺损
房室间隔缺损

Turner综合征与先天性心脏病

- 核型为45，X0，有时为不同程度的嵌合体
- 主要表现为女性外观，身材矮小，生殖腺发育差，不育
- 26%的Turner综合征合并有CHD，嵌合体较完全型发生率低
- 主要表现为左心的结构异常为主

Turner的心脏异常表现
主动脉瓣膜缩窄
二尖瓣异常
主动脉弓缩窄
主动脉弓离断
左室发育不良

从心脏表现预测胎儿染色体非整倍体

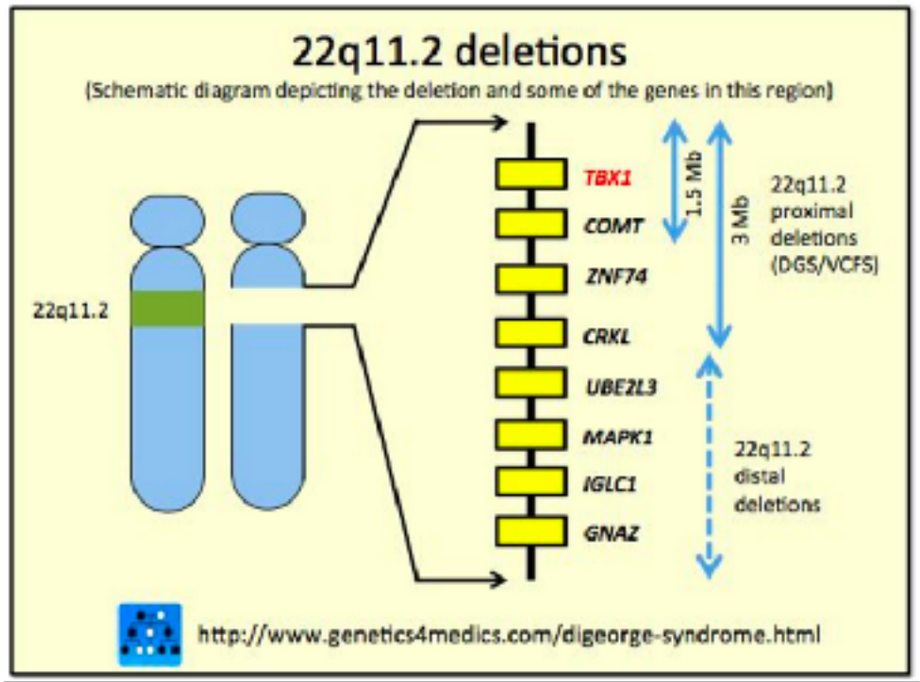
Table 10. Risk of Aneuploidy With Selected Cardiac Malformations

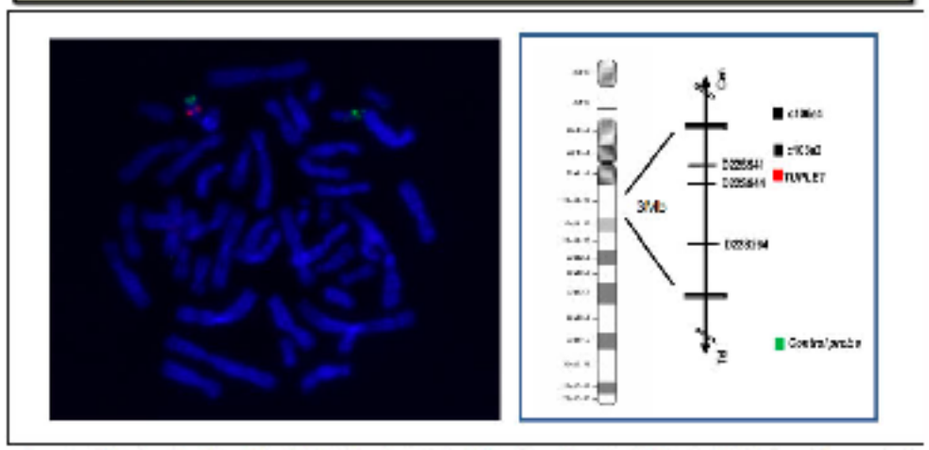
Lesion	Risk, %[113,360,380]
Atrioventricular septal defect	46–73
Coarctation/arch interruption	5–37
Double-outlet right ventricle/conotruncal malformations	6–43
Hypoplastic left heart syndrome	4–9
Heterotaxy/cardiosplenic syndromes	0
Pulmonic stenosis/atresia with intact septum	1–12
Transposition of great arteries	0
Tetralogy of Fallot	7–39
Truncus arteriosus	19–78
Tricuspid valve dysplasia (including Ebstein malformation)	4–16

Donofrio MT et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association *Circulation*. 2014;129:2183-2242

22q11.2微缺失 / 微重复综合征与先天性心脏病

- 又称为 DiGeorge 综合征, Velocardiofacial 腭心面综合征
- 最常见的微缺失微重复综合征，目前认为发病率接近1/1000
- 40%以上合并有先天性心脏病
- Microarray检测可发现22q11.2多种片段的缺失 / 重复
- 缺失引起的表型多样:
  - 腭咽部发育异常（50%），如腭裂、先天性腭咽闭合不全等
  - 特异面容，包括眶距过宽、眶下区扁平、睑裂较窄、鼻梁较挺，长脸等
  - 先天性心脏病（动脉干发育异常为主）如法洛四联症、主动脉断离、永存动脉干、室间隔缺损等
  - 低钙血症 / 甲状旁腺功能减退
  - 免疫功能低下
  - 精神、行为及认知能力的障碍（90%）
- 5-10%遗传自父母，有时父母患者的表现很轻微或正常
- 建议对于动脉干发育异常的胎儿进行相关FISH诊断
  - 15-30%以上的Fallot胎儿为22q11.2缺失综合征
  - 10%以上右位主动脉弓胎儿为22q11.2缺失综合征





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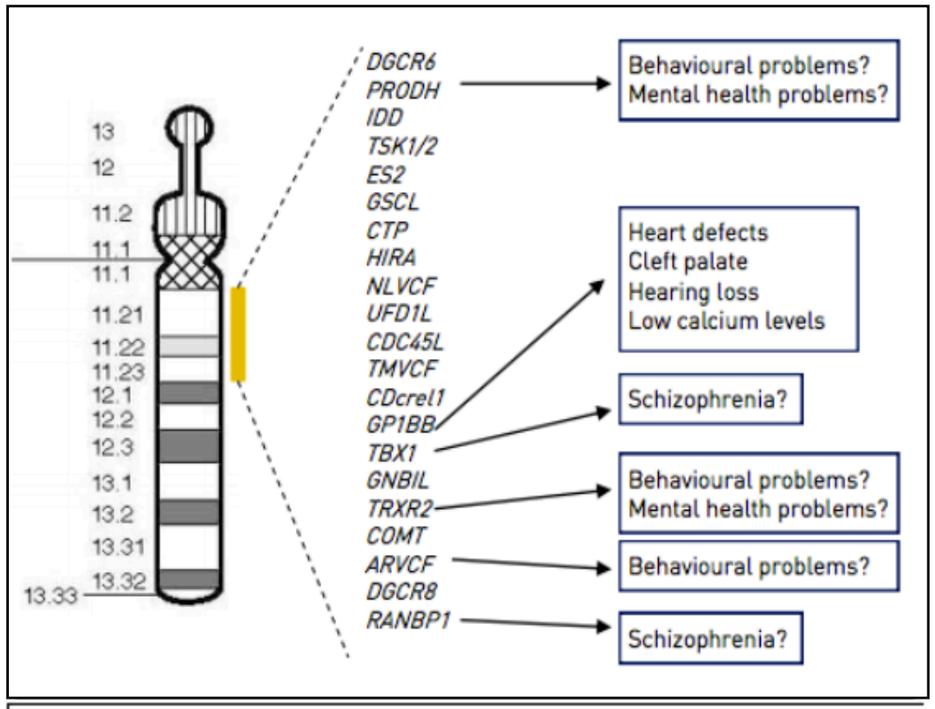
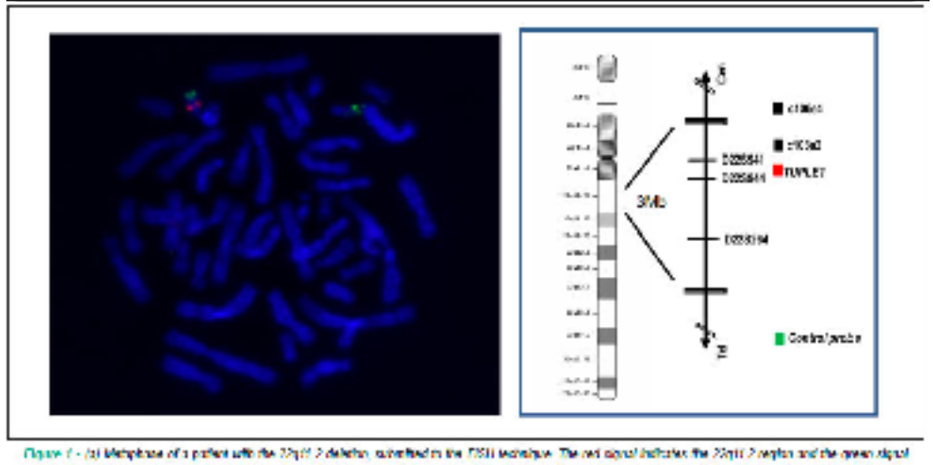
  - 精神、行为及认知能力的障碍（90%）
- 5-10%遗传自父母，有时父母患者的表现很轻微或正常
- 建议对于动脉干发育异常的胎儿进行相关FISH诊断
  - 15-30%以上的Fallot胎儿为22q11.2缺失综合征
  - 10%以上右位主动脉弓胎儿为22q11.2缺失综合征



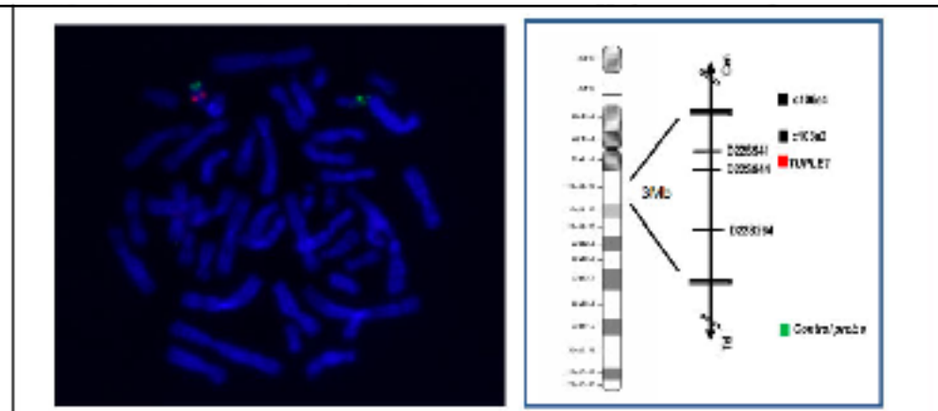


22q11.2微缺失 / 微重复综合征与先天性心脏病

- 又称为 DiGeorge 综合征, Velocardiofacial 腭心面综合征
- 最常见的微缺失微重复综合征，目前认为发病率接近1/1000
- 40%以上合并有先天性心脏病
- Microarray检测可发现22q11.2多种片段的缺失 / 重复
- 缺失引起的表型多样:
  - 腭咽部发育异常（50%），如腭裂、先天性腭咽闭合不全等
  - 特异面容，包括眶距过宽、眶下区扁平、睑裂较窄、鼻梁较挺，长脸等
  - 先天性心脏病（动脉干发育异常为主）如法洛四联症、主动脉断离、永存动脉干、室间隔缺损等
  - 低钙血症 / 甲状旁腺功能减退
  - 免疫功能低下
  - 精神、行为及认知能力的障碍（90%）
- 5-10%遗传自父母，有时父母患者的表现很轻微或正常
- 建议对于动脉干发育异常的胎儿进行相关FISH诊断
  - 15-30%以上的Fallot胎儿为22q11.2缺失综合征
  - 10%以上右位主动脉弓胎儿为22q11.2缺失综合征

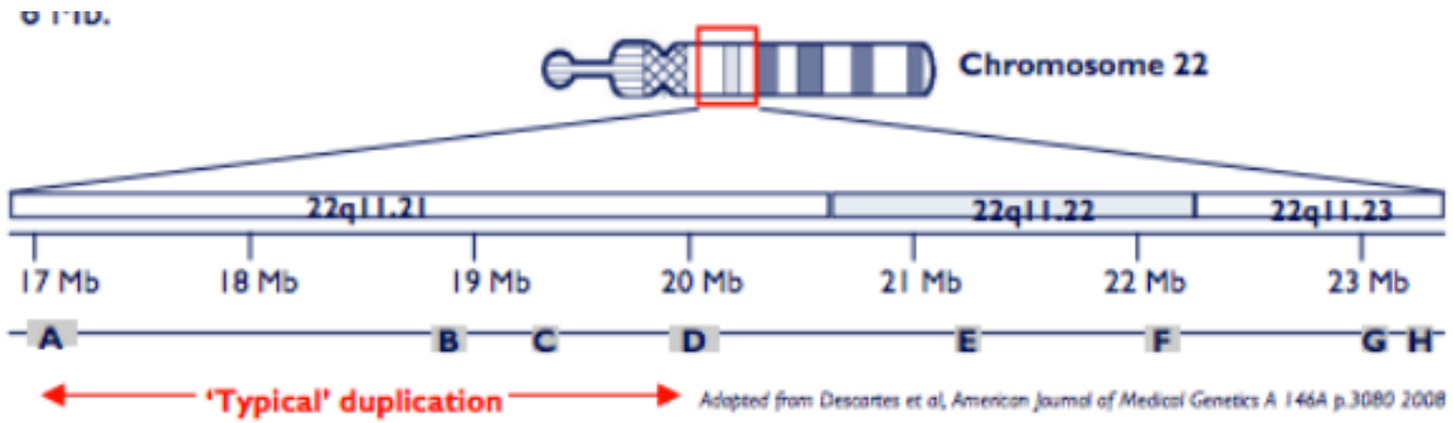
Table 11. Estimated 22q11 Deletion Frequency With Selected Cardiac Defects

Lesion	Estimated Frequency, %[113,361,380]
Interrupted aortic arch	50–90
Ventricular septal defect (overall)	10
Ventricular septal defect with aortic arch anomaly	45
Truncus arteriosus	35–40
Tetralogy of Fallot	8–35
Isolated aortic arch anomaly	25
Double-outlet right ventricle	<5
Transposition of the great arteries	<1



22q11.2微重复综合征

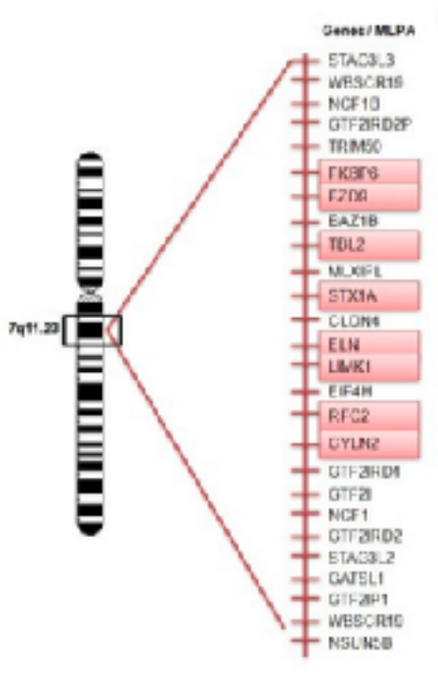
- 多种先天性心脏病
- 颚咽综合征
- 听力损害
- 体格发育迟滞
- 学习认知能力下降

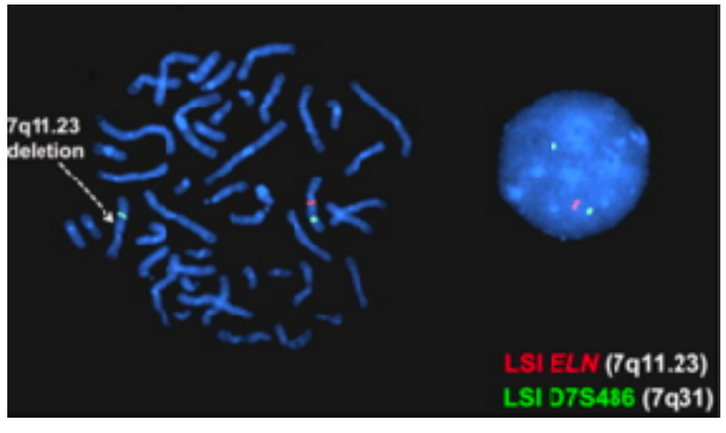


Williams–Beuren （7q11.23）综合征与先天性心脏病

- 常见的与先天性心脏病有关的微缺失综合征
- 与染色体7q11.23区域的缺失有关
- 82%存在胎儿先天性心脏异常
- 75%为流出道异常
- 有时单独与ELN基因突变有关

7q11.23缺失的心脏异常表现
主动脉流出道狭窄
二尖瓣脱垂
肺动脉缩窄
室间隔缺损





Williams-Beuren综合征(WBS)-7q11.23

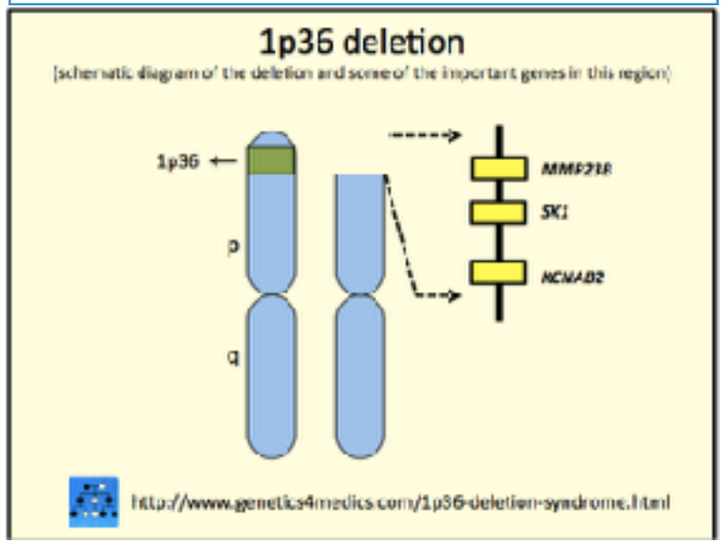
- 产前临床表现:IUGR
- 产后临床表现:
  - 70%伴有心血管畸形（主动脉流出道狭窄），特殊面容（嘴唇厚，鼻孔前倾，长人中）、智力迟滞、发育迟缓、特殊性格，皮肤早熟等
  - 婴儿期常有腹痛发作，高血钙表现
  - 有突出的社交性，表现为喜欢外出，交流过度频繁，待人过份友好和善
  - 中枢神经系统和骨骼肌肉系统的发育迟缓
- 该综合征不能被常规或高分辨核型分析发现

J Med Genet, 2003;40:526-530
Arch Dis Child 1999;81:198-200
Arq Bras Cardiol,2003;81(5):468-73
Am J Human Genet,1999;64,000
J Med Genet 2007;44:2 136-143

1p36微缺失综合征与先天性心脏病

- 第二常见的微缺失综合征，发生率1/5000
- 71%胎儿存在先天性心脏异常
- 其它异常包括特殊面容，听力丧失，神经认知功能异常，视力下降
- FISH / CMA检测能清楚的诊断

1p36缺失的心脏异常表现
室间隔缺损
房间隔缺损
Fallot四联征
主动脉缩窄
遗传性心肌病



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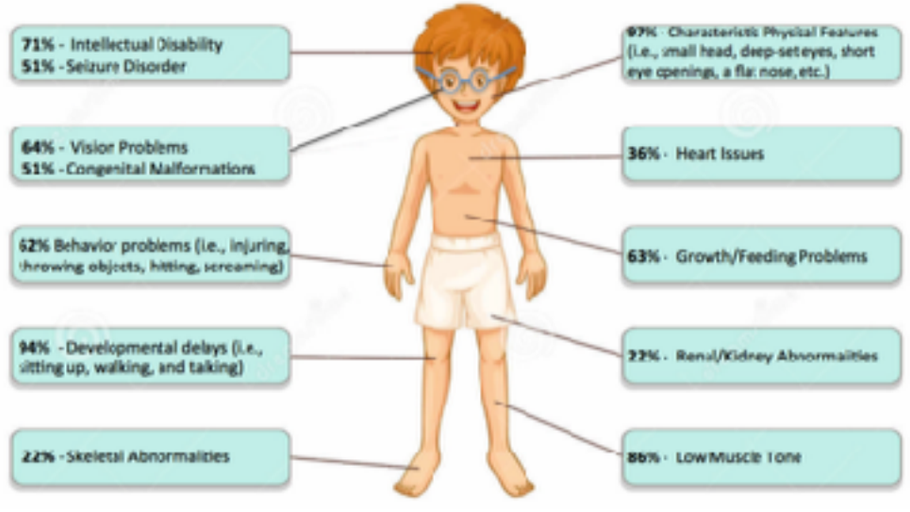
1p36缺失的心脏异常表现
室间隔缺损
房间隔缺损
Fallot四联征
主动脉缩窄
遗传性心肌病



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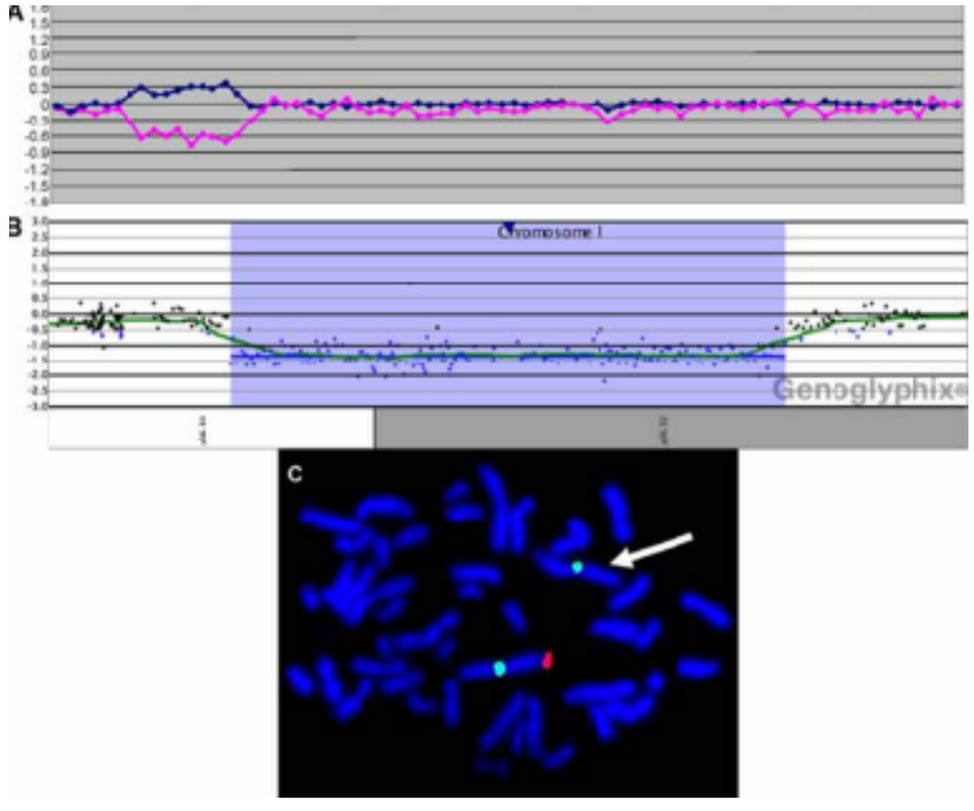
1p36缺失的心脏异常表现
室间隔缺损
房间隔缺损
Fallot四联征
主动脉缩窄
遗传性心肌病



常见单基因病与先天性心脏病

	OMIM number	Gene	References	Locus	Cardiac involvement
Alagille syndrome	118450	JAG1	Alagille et al. (1975)	20p12.2	Peripheral or valvular pulmonary stenosis, TOF, CoA
		NOTCH2	McDaniell et al.(2006)	1p12	
Holt–Oram	142900	TBX5	Holt and Oram (1960) Basson et al. (1997) Sletten and Pierpont (1995)	12q24.21	ASD, VSD, atrioventricular conduction delay, HLHS, TAPVR, TAC
Noonan syndrome	163950	PTPN11	Tartaglia et al. (2001)	12q24.13	Pulmonary valve stenosis—the most frequent, ASD, VSD, TOF, CoA, hypertrophic cardiomyopathy
	609942	KRAS	Schubbert et al. (2006)	12p12.1	
	610733	SOS1	Roberts et al. (2007)	2p22.1	
	611553	RAF1	Pandit et al. (2007)	3p25.2	
	613224	NRAS	Cirstea et al. (2010)	1p13.2	
	613706	BRAF	Sarkozy et al. (2009)	7q34	
	615355	RIT1	Aoki et al. (2013)	1q22	
	616559	SOS2		14q21.3	
	616564	LZTR1		22q11.21	
	605275	NS2		Not mapped	
LEOPARD syndrome	151100	PTPN11	Digilio et al. (2002)	12q24.13	Pulmonary stenosis, hypertrophic cardiomyopathy, conduction abnormalities
	611554	RAF1	Pandit et al. (2007)	3p25.2	
	164757	BRAF	Sarkozy et al. (2009)	7q34	
Costello syndrome	218040	HRAS	Aoki et al. (2005)	11p15.5	Pulmonary stenosis, cardiac hypertrophy, rhythm disturbances (atrial tachycardia)
Cardiofaciocutaneous syndrome	115150	BRAF	Rodriguez-Viciana et al. (2006)	7q34	Pulmonary stenosis, ASD, hypertrophic cardiomyopathy
	190070	KRAS	Niihori et al. (2006)	12p12.1	
	176872	MAP2K1	Schulz et al. (2008)	15q22.31	
	601263	MAP2K2	Rodriguez-Viciana et al. (2006)	19p13.3	
CHARGE syndrome	214800	CHD7	Bajpai et al. (2010)	8q12.2	TOF, DORV, aortic arch anomalies.
		SEMA3E	Lalani et al. (2004)	7q21.11	

常见单基因病与先天性心脏病

单基因相关综合征	主要表现
Alagille综合征	常染色体显性涉及多系统疾病，肝内胆管的减少缺失，存在与以下五项发现中的三项相关：CHD，骨骼，眼部表现，胆汁郁积和典型的面部特征，心脏表现外周或瓣膜性肺动脉狭窄，法洛四联症，主动脉缩窄
Holt-Oram综合征	肢体和拇指异常，以及心脏异常（75%），通常为房间隔缺损或室间隔缺损，房室传导延迟，左心发育不全综合征
Noonan综合征	心血管异常（80%）;其中60%患有CHD（肺动脉瓣狭窄最常见，房间隔缺损，室间隔缺损，法洛四联症，主动脉缩窄），20%患有肥厚型心肌病
CHARGE综合征	由CDH7基因中的杂合突变引起的。胆管闭锁，内耳畸形，视网膜以及心脏异常（最常见的是法洛四联征，其他包括右心室双出口，主动脉弓异常）

单独存在的心脏结构异常

- 占胎儿CHD的大多数
- 部分情况下与某个基因突变相关
- 并常常与多个基因相关

孤立性先心病的主要基因家族	
GATA转录因子	GATA4.GATA5，GATA6
Home-BOX转录因子	NKX2.5 NKX2.6
T-BOX转录因子	TBX1，TBX5，TBX20
其它	CITED2, ANKRD1, FOG2, ZIC3, HAND2

单独存在的心脏结构异常

- 占胎儿CHD的大多数
- 部分情况下与某个基因突变相关
- 并常常与多个基因相关

Table 3 Single-gene defects associated with non-syndromic CHD

Gene	OMIM number	Locus	CHD
GATA4	600576	8p23.1	VSD Zhang et al. (2008) TOF Tomita-Mitchell et al. (2007); Zhang et al. (2008) AVSD Rajagopal et al. (2012); Zhang et al. (2008) ASD Garg et al. (2003)
GATA5	611496	20q13.33	AVSD (Ackerman et al. 2012)
GATA6	601656	18q11.2	ASD Lin et al. (2010) AVSD Maitra et al. (2010) TOF Maitra et al. (2010); Lin et al. (2010) TAC Kodo et al. (2009)
NKX2.5	600584	5q35.1	ASD ± conduction delay Schott et al. (1998) and McElhinney et al.(2003) VSD Peng et al. (2010) and Wang et al. (2011) TOF Goldmuntz et al. (2001) and Rauch et al. (2010) TAC McElhinney et al. (2003) HLHS McElhinney et al. (2003) and Stallmeyer (2010)
NKX2.6	611770	8p21.2	TAC Heathcote et al. (2005) Conotruncal malformations Ta-Shma et al. (2014)
TBX1	602054	22q11.21	TOF Jerome and Papaioannou (2001)
TBX20	606061	7p14.2	ASD Kirk et al. (2007)
NODAL	601265	10q22.1	Heterotaxy Mohapatra et al. (2009)
GDF1	602880	19p13.11	TOF, TGA Karkera et al. (2007)
NOTCH1	190198	9q34.3	Aortic valve disease Garg et al. (2005)
JAG1	601920	20p12.2	TOF Eldadah et al. (2001)
ZFPM2	603693	8q23.1	TOF Pizzuti et al. (2003)
ELN	130160	7q11.23	Supravalvular aortic stenosis Ewart et al. (1994) and Micale et al. (2010)
GJA1	121014	6q22.31	AVSD, HLHS Dasgupta et al. (2001)
MED13L (PROSIT240)	608771	12q24.21	TGA Muncke et al. (2003)

单独存在的心脏结构异常

- 占胎儿CHD的大多数
- 部分情况下与某个基因突变相关
- 并常常与多个基因相关

Table 4 The most important genes involved in the etiology of CHD

CHD	Genes
ASD	*GATA4, NKX2.5, TBX5, TBX20, MYH6*
VSD	*GATA4, KKX2.5, TBX5, TBX20, TBX1*
AVSD	*PTPN11, KRAS, SOS1, RAF1, CRELD1*
PDA	*TFAP2B*
TAC	*TBX1*
TGA	*THRAP2, NKX2.5*
DORV	*THRAP2, NKX2.5*
TOF	*NKX2.5, JAG1, TBX1, NOTCH1, NOTCH2*
PS	*PTPN11, JAG1, NOTCH2*
BAV, AS	*NOTCH1*
HLHS	*NKX2.5, NOTCH1*

AS aortic stenosis, *ASD* atrial septal defect, *AVSD* atrioventricular septal defect, *BAV* bicuspid aortic valve, *CHD* congenital heart defects, *CoA* coarctation of the aorta, *DORV* double outlet right ventricle, *HLHS* hypoplastic left heart syndrome, *PDA* patent ductus arteriosus, *PS* pulmonary stenosis, *TAC* truncus arteriosus communis, *TGA* transposition of the great arteries, *TOF* tetralogy of Fallot

Table 3 Single-gene defects associated with non-syndromic CHD

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GATA5	611496	20q13.33	AVSD (Ackerman et al. 2012)
GATA6	601656	18q11.2	ASD Lin et al. (2010) AVSD Maitra et al. (2010) TOF Maitra et al. (2010); Lin et al. (2010) TAC Kodo et al. (2009)
NKX2.5	600584	5q35.1	ASD ± conduction delay Schott et al. (1998) and McElhinney et al.(2003) VSD Peng et al. (2010) and Wang et al. (2011) TOF Goldmuntz et al. (2001) and Rauch et al. (2010) TAC McElhinney et al. (2003) HLHS McElhinney et al. (2003) and Stallmeyer (2010)
NKX2.6	611770	8p21.2	TAC Heathcote et al. (2005) Conotruncal malformations Ta-Shma et al. (2014)
TBX1	602054	22q11.21	TOF Jerome and Papaioannou (2001)
TBX20	606061	7p14.2	ASD Kirk et al. (2007)
NODAL	601265	10q22.1	Heterotaxy Mohapatra et al. (2009)
GDF1	602880	19p13.11	TOF, TGA Karkera et al. (2007)
NOTCH1	190198	9q34.3	Aortic valve disease Garg et al. (2005)
JAG1	601920	20p12.2	TOF Eldadah et al. (2001)
ZFPM2	603693	8q23.1	TOF Pizzuti et al. (2003)
ELN	130160	7q11.23	Supravalvular aortic stenosis Ewart et al. (1994) and Micale et al. (2010)
GJA1	121014	6q22.31	AVSD, HLHS Dasgupta et al. (2001)
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单独存在的心脏结构异常与染色体片段改变

TABLE 1 | A summary of CNVs identified by CMA in non-syndromic CHDs reported in the literature.

Study	CNVs (limited list)	Confirmed or putative candidate genes for CHDs noted by authors (limited list)	CHD types in study	Other notes
Thienpont et al. (41)	4q34 deletion 5q35.1 deletion 9q34.3 deletion 22q11.2 duplication	*NKX2-5* *NOTCH1*	AS, TOF, CoA, VSD, truncus arteriosus, PS	
Erdogan et al. (36)	1q21.1 deletion 2p22.3 duplication 17p11.2 deletion 22q11.2 duplication	*GJA5* *LTBP1* *(See note in last column)* *TBX1, CRKL*	Any CHD: majority were VSD, TOF, PS, CoA, ASD, AS, HLHS, and AVSD	The 17p11.2 deletion is causative for Smith–Magenis syndrome. Features of this disorder were not appreciated until after the test result
Greenway et al. (42)	1q21.2 deletion and duplication 2p23.3 duplication 3p25.1 duplication 9q34.3 deletion 20p12.2 deletion[a] 22q11.2 deletion[a]	*GJA5, PRKAB2, CHD1L, BCL9* *ASXL2, KIF3C, RAB10* *PAF1* *NOTCH1* *JAG1* *TBX1, CRKL*	TOF	Study involved only subjects with TOF
Silversides et al. (40)	1q21.1 duplication 1q32.2 deletion 3p25.1 deletion 7q21.11 deletion 7p15.3 deletion 7p22.2 deletion 8p23.1 deletion[a] 8p23.3 duplication	*GJA5* *PLXNA2* *PAF1* *SEMA3E, SEMA3D* *DNAH11* *SNX8* *GATA4, ANGPT2* *ARHGEF10*	TOF	Study involved only subjects with TOF
Soemedi et al. (37)	1q21.1 duplication 4q34 deletion 5q14.1q14.3 duplication 5q35.3 duplication 8p23.1	*GJA5* *NAND2* *SSBP2, TMEM167A, VCAN, EDIL3* *CNOT6* *GATA4*	TOF, ASD, VSD, CoA, complex left-sided defect, TAPVR	Other rare CNVs identified with unconfirmed candidate genes associated with cardiac development; TOF overly represented
Fakhro et al. (43)	1q32.3 duplication 2p25.1 duplication 3p24.1-p23 deletion 3p24.1 duplication 7q36.1 deletion 8p23.1 deletion 9q34.11 duplication	*NEK2* *PCCK2* *TGFBR2, RBMS3, GADL1* *TGFBR2, GADL1* *GALNT11* *GATA4* *NUP188*	Heterotaxy with D-TGA; dextrocardia; VSD, ASD, PAPVR; malposed great arteries, CoA	Study involved CHDs with heterotaxy
Zhao et al. (44)	3q21.3 duplication 16q23.1 duplication 18q23 duplication 22q11.2 deletion[a]	*PLXNA1* *WWOX* *NFATC1* *TBX1, CRKL*	ASD, VSD, PDA, TOF, Ebstein anomaly, tricuspid incompetence	Study involved 100 Han Chinese subjects

AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CHD, congenital heart defect; CoA, coarctation of the aorta; D-TGA, dextro-transposition of the great arteries; HLHS, hypoplastic left heart syndrome; PAPVR, partial anomalous pulmonary venous return; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TAPVR, total anomalous pulmonary venous return; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

[a]It was unclear if these reports included patients with clinical diagnoses of syndromic disorders (i.e., DiGeorge syndrome for 22q11.2 deletion or Alagille syndrome for the 20p12.2 deletion). It could be that these reports were either unrecognized syndromes or individuals who were mildly affected.

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Array comparative genomic hybridization and fetal congenital heart defects: a systematic review and meta-analysis

F. A. R. JANSEN*, Y. J. BLUMENFELD†, A. FISHER‡, J. M. COBBEN§, A. O. ODIBO¶, A. BORRELL** and M. C. HAAK*

- 即使核型正常，排除22q11缺失，染色体芯片仍可提供7.0%有临床意义的信息
- 不明意义的拷贝数改变（VOUS） 占3.4%
- 存在心外畸形时，病理性染色体片段异常占 9.3% （生后报道为17~53%）
- 孤立性CHD，染色体异常片段改变占 3.4%，与生后相似，总体15-20%存在染色体异常*
- 作者建议所有心血管畸形产前诊断时进行aCGH检测，包括孤立的先天性心脏病

Paladini D et al. Prenatal diagnosis of congenital heart disease and fetal karyotyping. *Obstet Gynecol*. 1993;81(pt 1):679–682.

胎儿先天性心脏病与神经系统发育具有相关性

Ultrasound Obstet Gynecol 2017; 49: 287–288
Published online 27 November 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/uog.17324

isuog.org

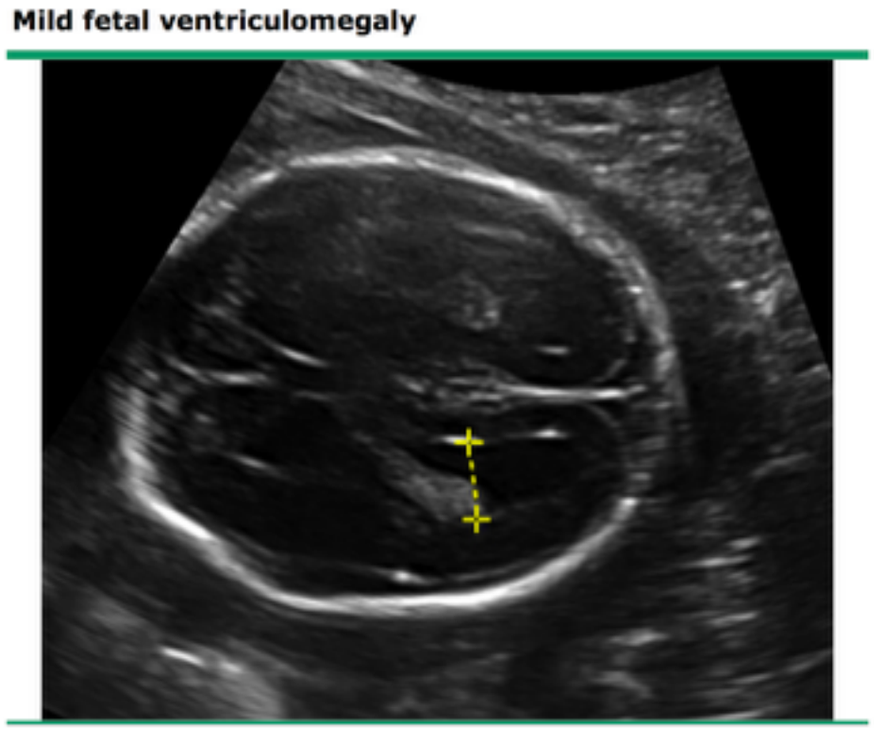
CONSENSUS STATEMENT

ISUOG consensus statement on current understanding of the association of neurodevelopmental delay and congenital heart disease: impact on prenatal counseling

如下叙述可能在咨询时有用：“..,大多数患有孤立性CHD的胎儿或新生儿预后良好，但也有证据提示某些患儿存在一定程度的NDD，在产前不能预测。这些障碍的严重程度存在个体差异，可能的发生率随着CHD类型的不同而不同，最高的是造成单室循环的畸形（某些研究可高达40%-45%），例如HLH。我们建议遗传学检查，包括array-CGH，以排除相关的、综合征型的CHD。”

侧脑室增宽

- 胎儿侧脑室增宽是一种常见的情况，占2%左右
- 常常与神经，运动 / 认知障碍有关
- 伴有 / 不伴有其它神经系统或各脏器异常
- 程度分类：
  - 10-15mm轻度 >15mm重度
  - 10-12mm轻度 12-15mm中度 16-重度
- 病因为特发性，染色体异常与遗传综合征，中脑导水管异常（发育，感染）



侧脑室增宽的遗传学诊断

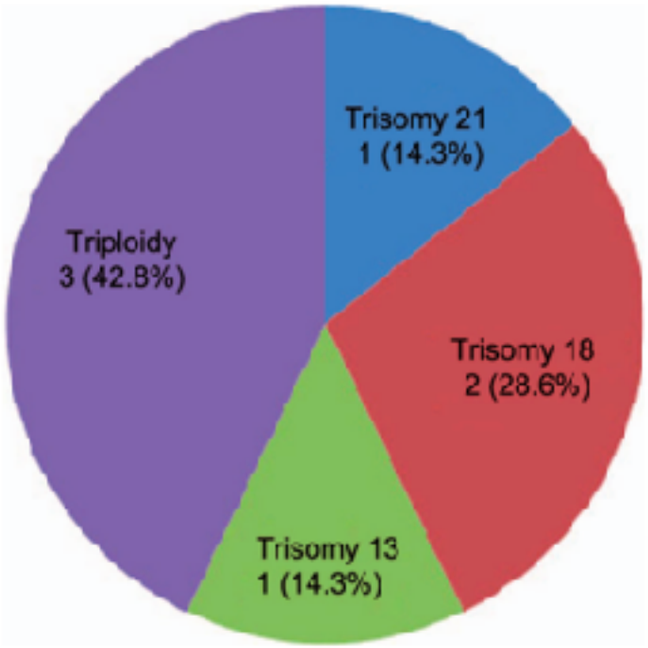


Figure 1. Distribution of the chromosome abnormalities with ventriculomegaly (*n*, %).

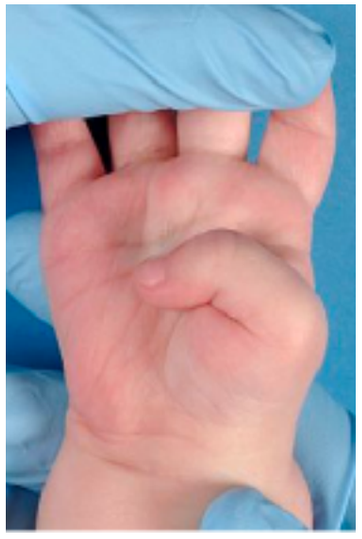
Table III. Chromosomal abnormality rates in the symmetric, asymmetric and unilateral VM groups, mild and severe ventriculomegaly groups associated by gender and anomaly type.

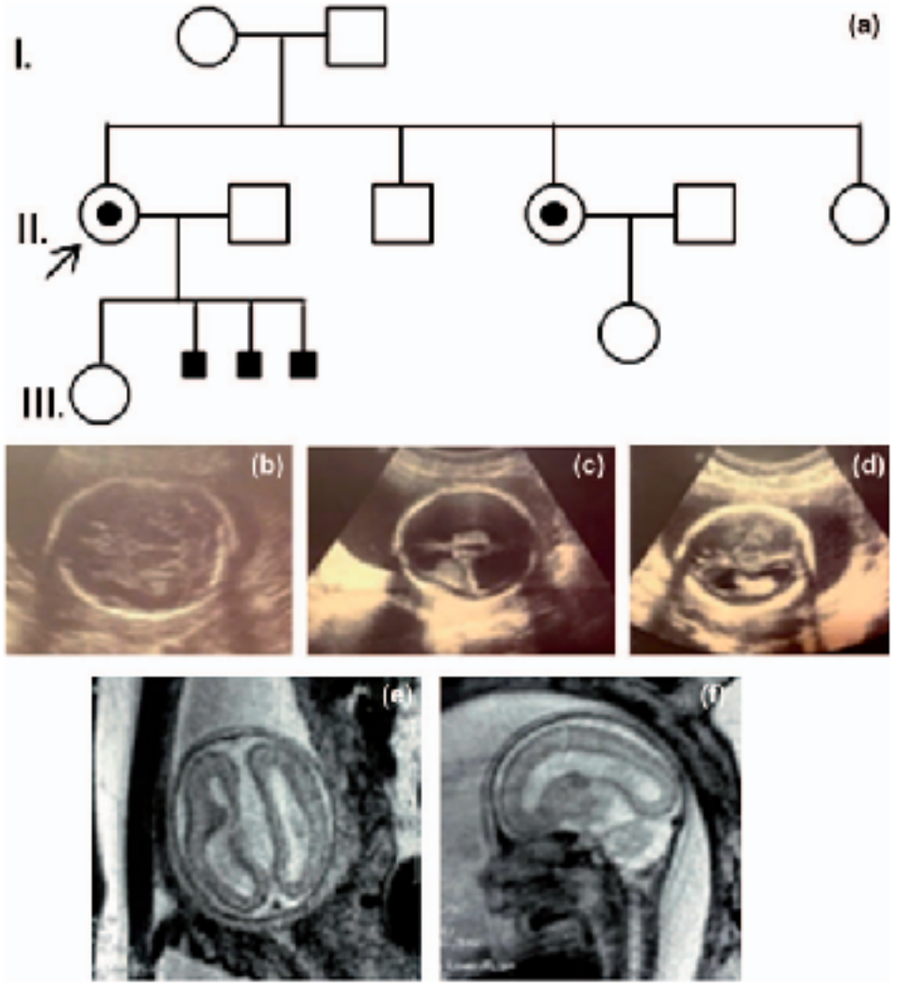
	Cases		Fetuses with chromosomal abnormalities (*n*)	Chromosomal abnormality rate	
	n	(%)		*n*	(%)
Symmetric and bilateral VM	119	85	6	6/119	5
Asymmetric VM	16	11.4	1	1/16	6.2
Unilateral VM	5	3.5	0	0/5	0
Mild VM	96	68.6	4	4/96	4.2
Severe VM	44	31.4	3	3/44	6.8
Male fetuses	65	46.4	1	1/65	1.5
Female fetuses	75	53.6	6	6/75	8
VM without any major anomaly*	54	38.6	5	5/54	9.3
VM accompanied with major anomaly†	86	61.4	2	2/86	2.3
Total	140	100	7	7/140	5

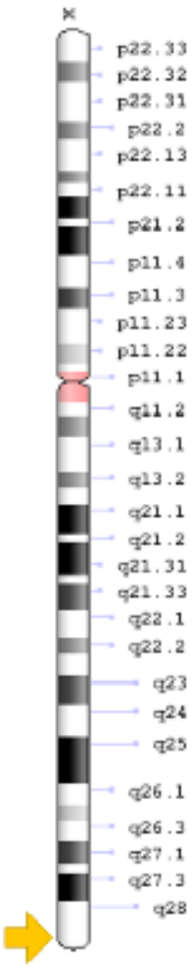
C. Gezer et al. Chromosome abnormality incidence in fetuses with cerebral ventriculomegaly Journal of Obstetrics and Gynaecology, July 2014; 34: 387–391

侧脑室增宽的遗传学诊断 - X连锁的遗传性脑积水

- L1CAM基因，定位于X染色体长臂末端
- 发生突变时，X-连锁隐性发病
- 遗传性脑积水伴有其它神经系统发育异常
- 进行诊断 / 筛查的指证
  - 性别（男性发病，女性携带）
  - 脑积水
  - 拇指内收
  - 中脑导水管狭窄
  - 胼胝体发育异常
  - 脑沟回发育异常

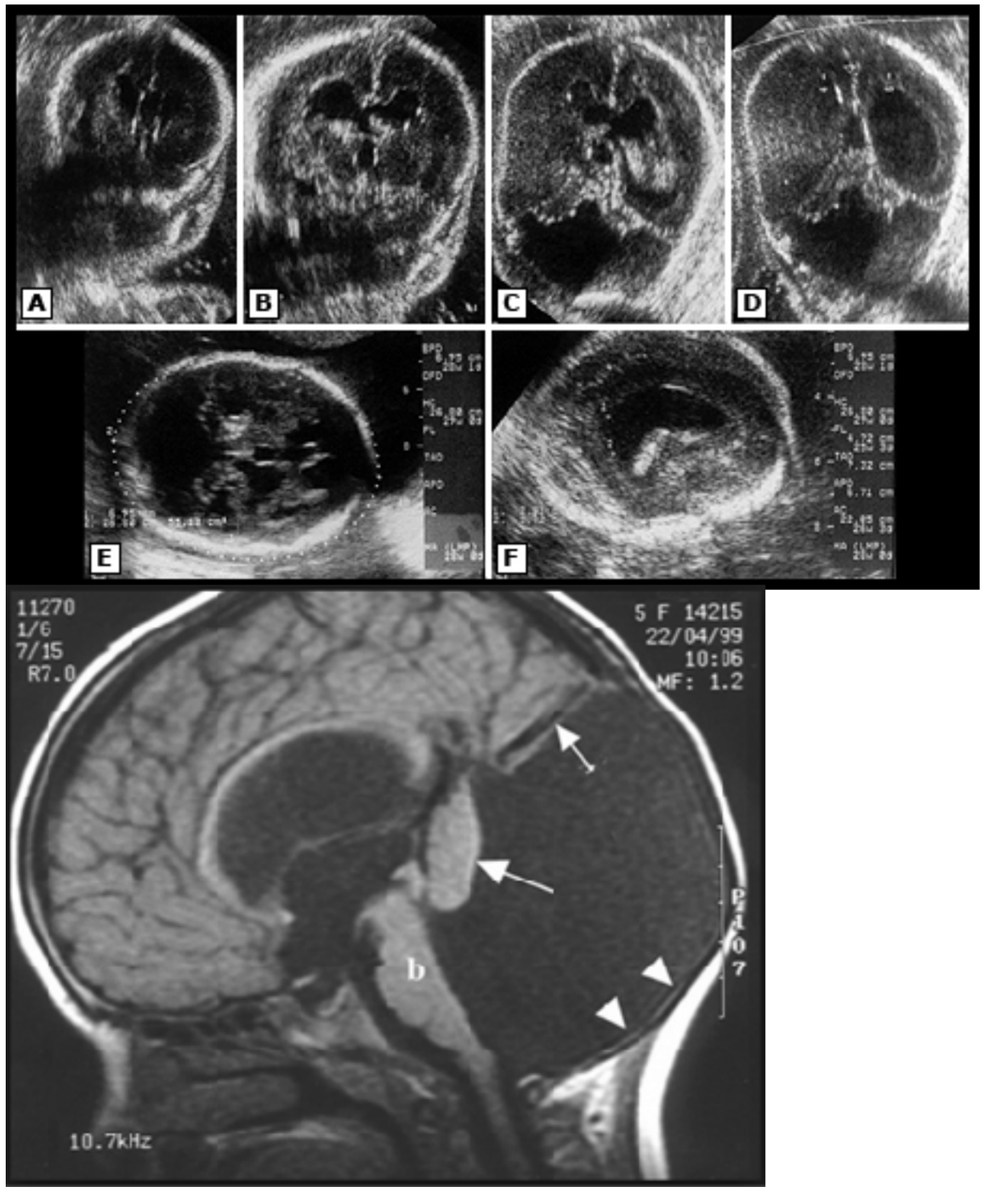






Dandy-Walker畸形

- 早孕期妊娠发生的第四脑室发育畸形
- 发生率1/30000（出生）
  - 第四脑室扩张
  - 颅后窝囊肿
  - 小脑蚓部发育不全或未发育
  - 小脑幕抬高
  - 合并第三脑室或侧脑室扩张



Dandy-Walker畸形与染色体异常

- 孤立的Dandy-walker畸形合并染色体异常的发生率16.3%（不同的染色体异常类型）
- 与Dandy-Walker畸形有关的基因：ZIC1, ZIC4, FOXC1, FGF17, LAMC1, and NID1

Table 3 Pooled proportions (PP) for outcomes in fetuses with isolated Dandy–Walker malformation assessed prenatally for additional anomalies

Outcome	*Studies* (n)	*Fetuses* (n/N)	I^2 (%)	*Raw (95% CI) (%)*	*PP (95% CI) (%)*
Chromosomal anomalies	11	9/60	0	15.00 (7.1–26.6)	16.32 (8.7–25.7)
Additional anomalies detected only at prenatal MRI	4	2/18	56.1	11.11 (1.4–34.7)	13.72 (0.2–42.6)
Additional anomalies detected only postnatally					
CNS anomalies	6	3/21	0	14.29 (3.1–36.3)	18.19 (6.2–34.6)
Extra-CNS anomalies	5	3/20	0	15.00 (3.2–37.9)	18.93 (6.3–36.2)
Discrepancy between pre- and postnatal diagnosis	6	7/33	54.9	21.21 (9.0–38.9)	28.18 (8.5–53.9)

ANDREA PORETTI et al. Cerebellar Hypoplasia: Differential Diagnosis and Diagnostic Approach DOI 10.1002/ajmg.c.31398

常见超声软指标的遗传学诊断

超声软指标	说明
颈后透明层增厚	单独作为指标筛查T21检出率78%左右，假阳性率4%，对多种染色体异常有检出意义
鼻骨缺失	检测准确较困难，人群差异大，联合检测检出率可达90%，假阳性率2.5%
肠管回声增强	存在于13-21%的唐氏综合征胎儿以及1-2%正常胎儿，羊膜腔出血也与之相关
肾盂扩张	存在于10-25%的唐氏综合征胎儿以及1-3%正常胎儿，单独存在时染色体异常占0.3-0.9%
长骨（股骨，肱骨）短缩	针对唐氏综合征，以肱骨短缩的预测值更好，长度小于第五百分位或弯曲需要重视
心内强回声灶	存在于21-28%的唐氏综合征胎儿以及亚洲人群30%正常胎儿，目前认为不增加染色体异常风险
脉络膜囊肿	存在于13-21%的18三体综合征胎儿以及1-3%正常胎儿，在低危人群中检出意义很小

超声多普勒频谱的遗传学诊断

超声软指标	说明
舒张末期血流反流	评估NT增厚，早发型生长受限的重要参考指标
静脉导管血流异常	不同核型类型发生静脉导管a波反流的比例为：正常（3%），T21 66%，T18 58%， T13 55%
三尖瓣血流反流	妊娠早期应用，目前认为在低危人群中的意义有限

对于NT检测增厚的孕妇

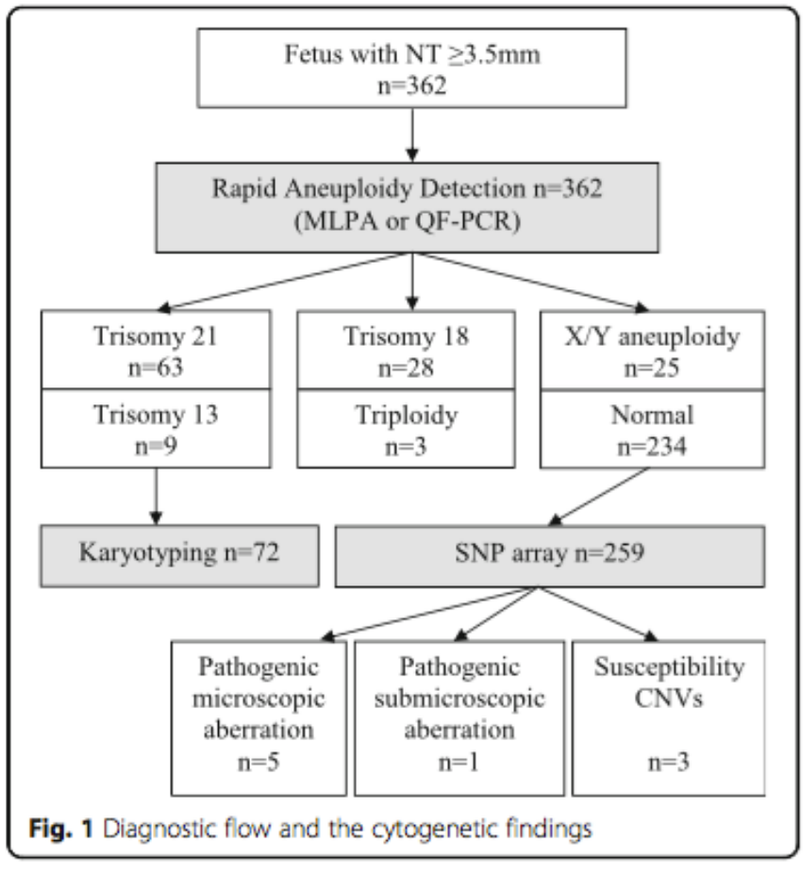


Fig. 1 Diagnostic flow and the cytogenetic findings

Table 1 Distribution of chromosomal abnormalities according to NT within the study population ($n = 362$)

NT in mm	Number of cases in the cohort (%)	Number of cases with chromosome aberrations (% within the category)
3.5–4.4	179 (49 %)	35 (19 %)
4.5–5.4	68 (19 %)	32 (47 %)
5.5–6.4	42 (11.6 %)	30 (71 %)
6.5–7.4	24 (6.6 %)	14 (58.3 %)
7.5–8.4	14 (3.9 %)	6 (43 %)
≥8.5	10 (2.8 %)	6 (60 %)
unknown (hygroma colli, where NT measurement was not specified)	25 (7 %)	14 (56 %)
Total	362	137 (38 %)

Srebniak et al. Molecular Cytogenetics (2016) 9:69

NT增厚的遗传学诊断

染色体异常类型	病例数	需要NIPT检测的检测类型	相应NIPT技术漏诊率
常染色体非整倍体		常规NIPT，同时有3例CPM有漏诊的可能	10%（37/362）
T21	63（17%）		
T18	28（7.7%）		
T13	9（2.5%）		
性染色体非整倍体		需要有扩展至性染色体异常筛查的NIPT方法	4%（14/362）
45，XO	20（5.5%）		
XXX	2（0.5%）		
XXY	1（0.3%）		
X/XY嵌合型	2（0.5%）		
三倍体	3（0.8%）	需要结合有SNP分析的NIPT方法	3%（11/362）
病理性的染色体片段异常	6（1.6%）	需要扩展至其他染色体检测的NIPT方法	2%（7/362）
染色体微缺失/重复	3（0.8%）	针对微缺失/微重复的NIPT筛查	
总计	137（38%）		

Srebniak et al. Molecular Cytogenetics (2016) 9:69

Society for Maternal-Fetal Medicine

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The role of ultrasound in women who undergo cell-free DNA screening

Society for Maternal-Fetal Medicine (SMFM) with the assistance of Mary E. Norton, MD; Joseph R. Biggio, MD; Jeffrey A. Kuller, MD; Sean C. Blackwell, MD

The introduction of cell-free DNA screening for aneuploidy into obstetric practice in 2011 revolutionized the strategies utilized for prenatal testing. The purpose of this document is to review the current data on the role of ultrasound in women who have undergone or are considering cell-free DNA screening. The following are Society for Maternal-Fetal Medicine recommendations: (1) in women who have already received a negative cell-free DNA screening result, ultrasound at 11–14 weeks of gestation solely for the purpose of nuchal translucency measurement (Current Procedural Terminology code 76813) is not recommended (GRADE 1B); (2) diagnostic testing should not be recommended to patients solely for the indication of an isolated soft marker in the setting of a negative cell-free DNA screen (GRADE 2B); (3) in women with an isolated soft marker that has no other clinical implications (ie, choroid plexus cyst or echogenic intracardiac focus) and a negative cell-free DNA screen, we recommend describing the finding as not clinically significant or as a normal variant (GRADE 2B); (4) in women with an isolated soft marker without other clinical implications (ie, choroid plexus cyst or echogenic intracardiac focus) and a negative first- or second-trimester screening result, we recommend describing the finding as not clinically significant or as a normal variant (GRADE 2B); (5) all women in whom a structural abnormality is identified by ultrasound should be offered diagnostic testing with chromosomal microarray (GRADE 1A); and (6) routine screening for microdeletions with cell-free DNA is not recommended (GRADE 1B).

Key words: aneuploidy assessment, aneuploidy screening, cell-free DNA screening, nuchal translucency measurement, serum markers, ultrasound

The introduction of cell-free DNA (cfDNA) screening for aneuploidy into obstetric practice in 2011 revolutionized the strategies utilized for prenatal testing. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) both recommend that all women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders.[1]

The most recent guidance addressing this issue suggests that traditional screening with serum markers and nuchal option for low-risk patients,[2,3] while in women at higher risk for common aneuploidies, cfDNA screening may be more accurate for detecting these aneuploidies. In addition, SMFM has stated that because of the ethics of patient autonomy, after appropriate genetic counseling regarding the benefits and limitations of cfDNA screening, this option should be available to women who request additional testing beyond what is currently recommended by professional societies.[4]

The number of different screening and testing options has

美国SFMF指南 2017

指南意见	证据级别
对于NIPT低风险的孕妇，不用再去做NT的检测	1B
NIPT低风险的孕妇，单独的软指标异常不用再去穿刺诊断	1B
NIPT或者早中孕期筛查低风险的孕妇，临床意义不强的超声单独软指标可判断为正常变异	2B
对于胎儿超声结构异常的孕妇，建议介入性诊断及CMA检测	1A
针对染色体微缺失微重复的NIPT筛查不推荐开展	1B

SOGC COMMITTEE OPINION

No. 254, September 2009 (Replaces No. 79, August 1999)

Evaluation of Prenatally Diagnosed Structural Congenital Anomalies

This committee opinion was prepared by the Genetics Committee and approved by the Executive of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHOR

Alain Gagnon, MD, Vancouver BC

guideline. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The evidence obtained was reviewed by the Genetics Committee of the Society of Obstetricians and Gynaecologists of

1. 当确定胎儿结构异常时，孕妇应及时与受过培训的遗传顾问及母体医学专家和/或医学遗传学家进行协商。 咨询应该是公正的，尊重患者的选择，文化，宗教信仰. (III-A)

2. 应告知患者18～20周的产前超声可以检测到大约60%的这种情况下的主要结构异常. (II-2A)

3. 当怀疑或确定胎儿结构异常时，应尽快转诊到三级超声单位以优化治疗选择. (II-2A)

4. 在持续的胎儿结构异常妊娠中，应重复超声检查（复查频率以异常的类型为准），以评估异常的发生，并尝试检测以前未确定的其他异常，因为这可能会影响咨询以及产科或围产期管理。 (II-2B)

5. 一旦胎儿结构异常通过二维超声识别，其他成像技术如胎儿超声心动图，3-D产科超声，超快胎儿MRI，偶尔的胎儿X射线和胎儿CT扫描（使用低剂量方案 ）在具体情况下可能会有所帮助。 (II-2A)

6. 在特定情况下应考虑父母的检查，具体取决于所鉴定的胎儿异常类型（例如潜在的显性遗传）。 (III-A)

7. 也可能需要进行亲代血液检测和侵入性产前检测以明确具有孤立或多重结构异常的胎儿的遗传学诊断. (II-2A)

8. 孕妇应以明确，关怀和及时的方式，并在确保隐私的情况下收到关于异常超声检查结果的信息。 应转诊给适当的儿科或外科亚专科专家，以提供关于异常情况及相关预后的更准确信息. (II-2 B)

9. 应告知父母，尽管胎儿核型正常，主要或次要胎儿结构异常（无论是孤立还是多重）可能是遗传综合征序列或关联的一部分. (III-A)

10. 如果可能需要提早出生或紧急的产后管理，则应考虑在能够提供适当新生儿护理的中心进行分娩. (III-A)

11. 当产前发现先天性结构异常时，全面的出生后新生儿评估对于未来怀孕的病因，预后和复发风险的诊断和咨询至关重要，特别是当病因尚未明确发现时。 (III-A)

12. 在终止妊娠，死胎或新生儿死亡的情况下，卫生专业人员应鼓励围产期或儿科病理学家进行完整的尸体解剖，以提供关于结构性胎儿异常或异常的诊断和病因的最大信息。 当完全尸体解剖被拒绝时，卫生专业人员应鼓励进行至少部分或外部的尸体解剖（包括X射线和照片）。 (III-A)

Thank you

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