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Genetic counseling in perinatal medicine

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National Society of Genetic Counselors; Genetic Alliance. Washington (DC): Genetic Alliance; 2008.

Making Sense of Your Genes

a Guide to Genetic Counseling

Genetic counseling is a communication process, which aims to help individuals, couples and families understand and adapt to the medical, psychological, familial and reproductive implications of the genetic contribution to specific health conditions

(Resta, 2006)

Genetic counselors provide information and education about:

- Full range of prenatal tests that can be offered
- Conditions that are been tested for
- Options that will be available following a diagnosis
- They aim to facilitate informed decision-making at all stages of this process

Prenatal or preconceptional patient who is or will be:	
Finding	***Reason to consider consultation***
Age 35 years or older at the time of delivery (for a singleton pregnancy)	Discuss testing options for identifying an age-related chromosome anomaly
Age 33 years or older at the time of delivery (for a twin pregnancy)	Discuss testing options for identifying an age-related chromosome anomaly
A close blood relative of her partner (consanguineous union)	Review pedigree and assess degree of relatedness; discuss potential additional fetal risks and testing options before and/or after delivery
Prenatal or preconceptional patient who has:	
An abnormal first or second trimester maternal serum ± NT screening test	Discuss risks to pregnancy and testing options
Exposure to a teratogen or potentially teratogenic agent during gestation such as radiation, high-risk infections, drugs, medications, alcohol, etc.	Discuss risks to pregnancy and testing options and rule out significant fetal ± maternal risks
A fetal anomaly or multiple anomalies identified on ultrasound and/or through echocardiography	Discuss risks to pregnancy and testing options
A personal or family history of pregnancy complications known to be associated with genetic factors such as acute fatty liver of pregnancy	Rule out significant fetal risks ± maternal risks, including a metabolic disorder

Either member of the couple with:	
A positive carrier screening test for a genetic condition such as cystic fibrosis, thalassemia, sickle cell anemia, Tay-Sachs, etc.	Discuss additional testing strategies and inheritance
A personal history of stillbirths, previous child with hydrops, recurrent pregnancy losses (more than two), or a child with sudden infant death syndrome (SIDS)	Rule out a chromosomal, metabolic, or syndromic diagnosis that may be associated with an unexplained neonatal death or SIDS
A progressive neurologic condition known to be genetically determined such as a peripheral neuropathy, unexplained myopathy, progressive ataxia, early onset dementia, or a familial movement disorder	Discuss a potential diagnosis, the differential diagnosis, inheritance, and testing options
A statin-induced myopathy	Discuss a potential mitochondrial disorder, inheritance and testing options
Either member of the couple with a family or personal history of:	
A birth defect such as a cleft lip ± palate, spina bifida, or a congenital heart defect	Discuss recurrence risks and testing options; discuss folate supplementation, if appropriate, for subsequent pregnancies
A chromosomal abnormality such as a translocation, marker chromosome, or chromosomal mosaicism	Discuss risks to the fetus and testing options
Significant hearing or vision loss thought to be genetically determined	Discuss risks to the fetus and testing options
Mental retardation or autism	Discuss risks to the fetus and testing options

The human genome is comprised of:

- 6 billion DNA base pairs packaged into two sets of 23 chromosomes, one set inherited from each parent
- The DNA encodes approximately 27,000 genes
- Humans differ:
  - ✓ at the level of DNA sequence
  - ✓ can also differ in the number of copies of each gene

Prenatal genetic counseling

Prenatal diagnosis is an integral part of obstetric practice

- Prenatal diagnosis encompasses:

  - ✓ Pedigree analysis
  - ✓ Population screening
  - ✓ Fetal genetic risk assessment
  - ✓ Genetic counseling
  - ✓ Fetal diagnostic testing

Aneuploidy - Current screening timeline

Screening

Results

Diagnostic testing

Results

Informed reproductive decision

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POSITION STATEMENT

Position statement from the Aneuploidy Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis†

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Table 1 Model-predicted Down syndrome detection rate for a 3% false-positive rate and positive predictive value for various screening protocols

Protocol (completed weeks*)		DR (%)	OAPR 1:*n*
1a	PAPPA + free β (10), NT (12)	82	29
1b	PAPPA + hCG (10), NT (12)	80	29
1c	PAPPA + free β (12), NT (12)	80	29
1d	PAPPA + hCG (12), NT (12)	79	30
2a	AFP + free β + uE_3 + InhA (15–19)	64	36
2b	AFP + hCG + uE_3 + InhA (15–19)	60	39
3a	PAPPA + free β (10), NT (12), contingent AFP + free β + uE_3 + InhA (15–19)	90	26
3b	PAPPA + hCG (10), NT (12), contingent AFP + hCG + uE_3 + InhA (15–21)	88	27
3c	PAPPA + free β (10), NT (12), stepwise AFP + free β + uE_3 + InhA (15–21)	92	25
3d	PAPPA + hCG (10), NT (12), stepwise AFP + hCG + uE_3 + InhA (15–21)	91	26
4a	PAPPA (10), NT (12), AFP + free β + uE_3 + InhA (15–19)	91	26
4b	PAPPA (10), NT (12), AFP + hCG + uE_3 + InhA (15–19)	89	26
4c	PAPPA + free β (10), NT (12), AFP + free β + uE_3 + InhA (15–19)	93	25
4d	PAPPA + hCG (10), NT (12), AFP + hCG + uE_3 + InhA (15–19)	91	26
4e	PAPPA + free β (10), AFP + free β + uE_3 + InhA (15–19)	80	29
4f	PAPPA + hCG (10), AFP + hCG + uE_3 + InhA (15–19)	75	33

5a	PAPPA + free β (10), NT + NB (12)	91	26
5b	PAPPA + free β (10), NT (12), contingent NB	89	26
5c	PAPPA + free β (10), NT (12), contingent TR	88	27
5d	PAPPA + free β (10), NT (12), contingent DV	88	27
6a	AFP + free β + uE_3 + InhA + NF + NBL + PT (15–19)	90	26
6b	AFP + hCG + uE_3 + InhA + NF + NBL + PT (15–19)	89	27
7a	PAPPA + free β (10), NT (12), ANOMALY (18+)	88	27
7b	PAPPA + hCG (10), NT (12), ANOMALY (18+)	86	27
8a	ANOMALY (18+)	56	41
8b	AFP + freeβ + uE_3 + InhA (15–19), ANOMALY (18+)	80	29
8c	AFP + free β + uE_3 + InhA (15–19), contingent ANOMALY (18+)	77	30
9a	PAPPA + free β (10), NT (12), AFP + free β + uE_3 + InhA (15–19), ANOMALY (18+)	96	25
9b	PAPPA + hCG (10), NT (12), AFP + hCG + uE_3 + InhA (15–19), ANOMALY (18+)	95	25

DR – detection rate
FPR – false positive rate
OAPR - odds of being affected given a positive result

International Society for Prenatal Diagnosis, 2013

NIPT for Tr 21 – DR and FPR

Autor	DR	FPR	Bez rezultata
Palomaki, 2011 MPS	99%	0.2%	5,3%
Bianchi, 2012 MPS	100%	0%	3%
Norton, 2012 TS	100%	0.04%	4,6%
Nicolaides, 2012 TS	100%	0%	4,9%
Zimmermann, 2012 SNP	100%	0%	12,6%

cffDNA for Tr 13 and Tr 18

Autor	13		18		21	
	DR	FPR	DR	FPR	DR	FPR
Palomaki, 2011 MPS	92%	1,0%	100%	0,3%	99%	0,2%
Bianchi, 2012 MPS	79%	0%	99%	0%	100%	0%
Norton, 2012 TS			97.4%	0.07%	100%	0.04%
Nicolaides, 2012 TS			100%	0,1%	100%	0%
Zimmermann, 2012 SNP	100%	0%	100%	0%	100%	0%

Royal College of Obstetricians & Gynaecologists

Non-invasive Prenatal Testing for Chromosomal Abnormality using Maternal Plasma DNA

Scientific Impact Paper No. 15
March 2014

years and guidelines should already reflect this change in practice. Fetal sex determination for clinical indications in pregnancies at high sex-linked genetic risk is also established practice. Testing for aneuploidy and especially Down syndrome by maternal plasma MPS is now available commercially but while the test result is much more accurate than existing screening strategies, it is still not a diagnostic assay. Hence, the term 'non-invasive testing' is currently used.

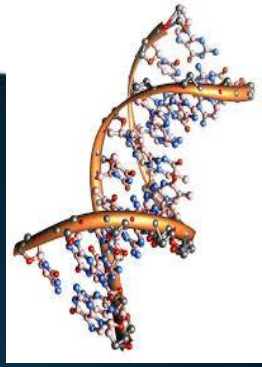
Detection of Down syndrome by maternal plasma DNA testing will alter the way that prenatal diagnosis and screening is delivered in the UK, both in the NHS and the private sector. It will have significant implications for some existing services such that clinical biochemistry serum screening laboratories and cytogenetic and molecular genetics laboratories can expect a fall in the number of samples. Since women are already accessing these tests, all obstetricians should have knowledge of the counselling issues involved. In addition, major NHS health policy decisions are required. In time, this technology is likely to become the primary screen for chromosomal abnormalities in pregnancy. This will enhance the information available to pregnant women while greatly reducing the loss of uncomplicated pregnancies as a result of miscarriage caused by unnecessary invasive procedures.

References

Indications for invasive testing

- Advanced maternal age (>35 years)
- Positive screening tests
- A prior history of a fetus with a chromosomal abnormality
- Parental reciprocal translocation or inversion
- Parent or previous child with a mosaic karyotype or marker chromosome, or a sex chromosome or autosome translocation
- Ultrasound identification of fetal structural anomalies
- Ultrasound markers for fetal infection, anemia, or other disorders
- To obtain material for biochemical or DNA studies

Prenatal genetic diagnosis – genetic material is sampled by invasive procedures



- *Cytogenetic*
- *Targeted molecular diagnostic testing*
- *Rapid aneuploidy testing*
- *Prenatal genomic microarray*

Cytogenetic analysis

karyotyping

- Enables the examination of numerical and structural abnormalities at a resolution of 5–10 Mb

Various molecular cytogenetic techniques

- FISH, QF-PCR, MLPA
- Used to overcome limitations of karyotyping
- Complement the detection of chromosomal abnormalities
- Methods are targeted to detect specific chromosomal abnormalities

Rapid analysis of the common aneuploidies

- QF-PCR
- Usually used to detect common numerical chromosome anomalies, such as trisomies 21, 13, 18, X and Y
- ‘Targeted’ approach capable only of assessing a limited number of loci

A list of the more common genetic conditions for which DNA-based prenatal diagnosis is available

TABLE 30-26 Common Conditions for Which Molecular Prenatal Diagnosis Is Available

Disorder	Mode of Inheritance	Prenatal Diagnosis
α_1-Antitrypsin deficiency	AR	Determine PiZZ allele. Not all homozygotes have liver involvement; pre-procedure genetic counseling critical.
α-Thalassemia	AR	α-Hemoglobin gene mutation (see text)
Adult polycystic kidney	AD	*PKD1* and *PKD2* gene mutations. In large families, linkage is possible in >90%. Gene mutation identifiable in ~50% of PKD1 and 75% of PKD2.
β-Thalassemia	AR	β-Hemoglobin gene mutation (see text)
Congenital adrenal hyperplasia	AR	*CYP21A2* gene mutations/deletions. Nine common mutations/deletions detect 90% to 95% of carriers. Sequencing available.
Cystic fibrosis	AR	*CFTR* gene mutation (see text)
Duchenne/Becker muscular dystrophy	XLR	Dystrophin gene mutation
Fragile X syndrome	XLR	CGG repeat number (see text)
Hemoglobinopathy (SS, SC)	AR	β-Chain gene mutation (see text)
Hemophilia A	XLR	Factor VIII gene inversion 45%, other gene mutations 45% (not available in all labs), linkage analysis in appropriate families.
Huntington disease	AD	CAG repeat length (PGD and non-informing PND possible to avoid disclosing presymptomatic parents' disease status)
Marfan syndrome	AD	Fibrillin *(FBN-1)* gene mutation. Linkage in large families. Approximately 70% have mutation identified (not always clinically available).
Myotonic dystrophy	AD	CTG expansion in the *DMPK* gene
Neurofibromatosis type 1	AD	*NF1* gene mutation identifiable in >95% of cases but requires sequencing. Linkage in appropriate families.
Phenylketonuria	AR	4 to 15 common mutations, 40% to 50% detection. Further mutation analysis, >99%
Spinal muscular atrophy	AR/AD	
Tay-Sachs disease	AR	Enzyme absence; gene mutation (see text)

AD, autosomal dominant; AR, autosomal recessive; PGD, preimplantation genetic diagnosis; PND, prenatal diagnosis; XLR, X-linked recessive.

Based on the incidence of the currently recognized microdeletion/microduplication syndromes and consequential imbalances

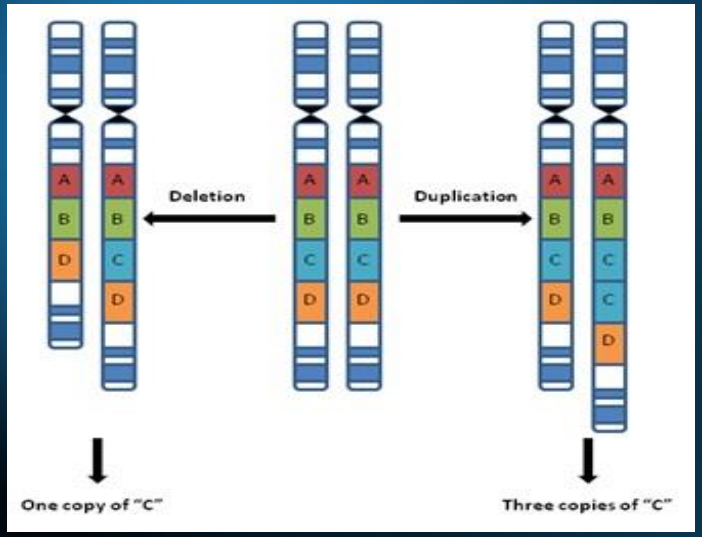
It is estimated that one out of 300 to 600 newborns would be affected with one of these conditions, undetected by karyotype

The incidence of a poor prognosis chromosome abnormality that would be undetected by rapid aneuploidy detection for chromosomes 13, 18 and 21 is approximately 1/1600 pregnancies

After ruling out a 13, 18 and 21 trisomy - a whole genome screen that could identify both the poor prognosis chromosome abnormalities as well as the recurrent microdeletion/microduplication syndromes

INVASIVE PRENATAL DIAGNOSIS

HOW FAR HAVE WE REACHED?



Large segments of DNA, different in size, can vary in copy-number

- ***Copy number variations (CNVs)***
- Genes that were thought to always occur in two copies per genome have now been found to sometimes be present in:
  - ✓ one
  - ✓ three
  - ✓ more than three copies
  - ✓ in a few rare instances the genes are missing altogether

- ***CNV can encompass genes leading to dosage imbalances***

Copy-number variations (CNVs)

- A form of structural variation - submicroscopic chromosomal deletions and/or duplications
- Typically defined as DNA segments 1kb (1000 base pairs) or larger in size (but typically less than 5 Mb, which is the cytogenetic level of resolution)
- Present in a different number of copies when compared to a reference (or standard) genome
- ***CNV can encompass genes leading to dosage imbalances***
- ***A difference in the copy number of a gene can increase or decrease the level of that gene's activity***

CNVs - microdeletions and microduplications

Origin:

- During production of the sperm or egg that gave rise to a particular individual
- Passed down for a few generations within a family

Technique of microarray comparative genomic hybridization (aCGH)

- The intensity of the hybridization of the labeled patient DNA is compared to a competitively hybridized differentially labeled control, representative of the normal genome
- By comparing the amount of hybridization, genomic imbalances can be identified in the patients DNA
- Thoroughly evaluated in the postnatal (adolescent and adult) population

Copy-number variations (CNVs)

- ***Apparently benign CNVs:***
  - Cause no ill effects on the individual(s) harboring them
  - Have been observed throughout the human genome in the general population
  - The database for the normal variation is growing all the time

BUT,

- Large and rare CNVs are disproportionately more often observed in postnatal patients with mental retardation, developmental delay, autism and schizophrenia
- These alterations may be more important in neurocognitive diseases than other forms of inherited mutations

Prenatal setting

There are no available concise guidelines establishing the chromosomal microarray analysis applications and platforms for a prenatal setting

Advantages over conventional G-band karyotyping

- Improved resolution - potentially higher detection rates of chromosomal variation
- Allows detection of smaller pathogenic chromosomal variants that are undetectable using standard cytogenetic analyses
- Fetal cells obtained by invasive prenatal procedures do not have to be cultured - results may be reported more quickly
- Testing can be customized
- Potentially amenable to automation and high-throughput analysis

Potential limitations

- Able to potentially detect ‘unbalanced chromosomal changes’

- ***Does not allow detection of:***
  - ✓ Balanced chromosomal rearrangements - no loss or gain of DNA; **But, i**n practice, many apparently balanced rearrangements detected by G-banding are not truly balanced at a DNA level
  - ✓ Low level of mosaicism - it would result in a relatively reduced difference in hybridization between the patient and the control
  - ✓ Triploidy
  - ✓ Imbalance within the patient’s DNA that do not have targets on the array platform

Most important current challenge of the application of CGH microarrays in the clinical setting

- Determining a copy number imbalance as:
  - de novo and likely to be causative,

    or

  - inherited and likely to be benign

Categorization of array data (CNVs) in clinical setting:

- CNVs likely to be benign – the majority (>99%) of benign CNVs are inherited and the vast majority of these are less than 500 kb
- CNVs likely to be pathogenic - CNVs that overlap critical regions of established microdeletion/ microduplication syndromes
- CNVs of unknown clinical significance - identification of novel, previously unreported chromosomal variants of unknown clinical significance (VOUS); difficulties in term of prenatal clinical management
- ***Development of CNV databases -*** effort to catalog and collate genomic and clinical information

CGH is robust, accurate and valuable in the prenatal setting

- A small advantage over karyotyping when employed for the prenatal population as a whole
- aCGH is a valuable tool for screening for chromosomal microdeletion and microduplication, particularly in fetuses with normal karyotypes and abnormal ultrasonographic reports (finding potentially pathological CNVs in 5 to 8.5% of cases)
- Particularly useful in a fetuses with karyotypic de novo balanced translocation or marker chromosomes

Limitation in prenatal setting

- Patients should be counseled and informed that VOUS do occur at a rate of approximately 1.4–2.1%

- Many of microdeletion/microduplication syndromes identified in the postnatal population may not have any obvious ultrasound finding, or the findings may be transitory

ACOG Committee Opinion No. 446: array comparative genomic hybridization in prenatal diagnosis (2009)

aCGH is useful when a fetal anomaly is found on ultrasound but is currently not a substitute for G-band karyotyping

The American College of Obstetricians and Gynecologists Committee on Genetics and Society for Maternal-Fetal Medicine Committee Opinion , Number 581, December 2013

The Use of Chromosomal Microarray Analysis in Prenatal Diagnosis

- In patients with a fetus with one or more major structural abnormalities identified on ultrasonographic examination and who are undergoing invasive prenatal diagnosis, chromosomal microarray analysis is recommended. This test replaces the need for fetal karyotype.
- In patients with a structurally normal fetus undergoing invasive prenatal diagnostic testing, either fetal karyotyping or a chromosomal microarray analysis can be performed.
- Most genetic mutations identified by chromosomal microarray analysis are not associated with increasing maternal age; therefore, the use of this test for prenatal diagnosis should not be restricted to women aged 35 years and older.
- In cases of intrauterine fetal demise or stillbirth when further cytogenetic analysis is desired, chromosomal microarray analysis on fetal tissue (ie, amniotic fluid, placenta, or products of conception) is recommended because of its increased likelihood of obtaining results and improved detection of causative abnormalities.

The American College of Obstetricians and Gynecologists Committee on Genetics and Society for Maternal-Fetal Medicine Committee Opinion , Number 581, December 2013

The Use of Chromosomal Microarray Analysis in Prenatal Diagnosis

- Limited data are available on the clinical utility of chromosomal microarray analysis to evaluate first-trimester and second-trimester pregnancy losses; therefore, this is not recommended at this time.

- Comprehensive patient pretest and posttest genetic counseling from qualified personnel such as a genetic counselor or geneticist regarding the benefits, limitations, and results of chromosomal microarray analysis is essential. Chromosomal microarray analysis should not be ordered without informed consent, which should be documented in the medical record and include discussion of the potential to identify findings of uncertain significance, nonpaternity, consanguinity, and adult-onset disease.

Future

- Given the procedure-related risks of conventional prenatal diagnosis, it would be ideal if genetic analysis of the fetus could be performed non-invasively
- The assessment of fetal sex, RhD status, monogenic diseases, fetal chromosomal aneuploidy
- The scene is now set for prenatal diagnosis to be performed non-invasively in the clinical setting within the next decade