

Family genetics: The future???

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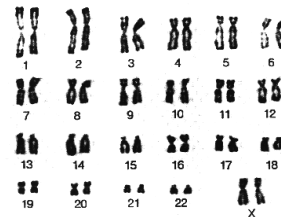


Learning objectives

- Understand how genetic problems may affect successful conception
- Consider the possible conditions and ethical considerations of counselling a healthy couple planning to conceive.
- Understand the modern technologies of genetic testing
- Understand the possibilities for non-invasive prenatal testing
- Understand the methodology of PGD and it's applicability.



The traditional genetics



The new genetics

- Real time quantitative PCR for individual genes and chromosomes
- Array CGH (Comparative genomic hybridisation)
- Single nucleotide polymorphisms (SNP)
- Next generation sequencing



Genetics and reproduction in early 2015

- Genetic contribution to reproductive problems
 - Maternal side
 - Paternal side
 - Translocations
 - Miscarriage testing
- Routine testing as part of pre-conceptional care
- Genetic testing in pregnancy
- Preimplantation genetic diagnosis

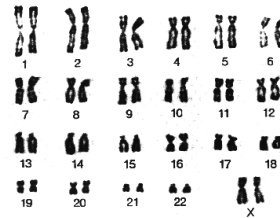


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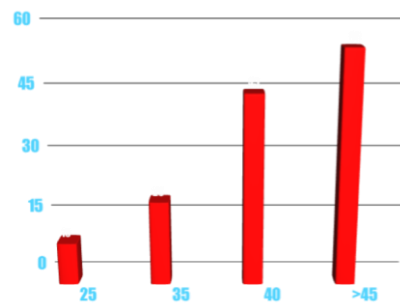
Maternal reproduction and chromosomes



Down syndrome and maternal age

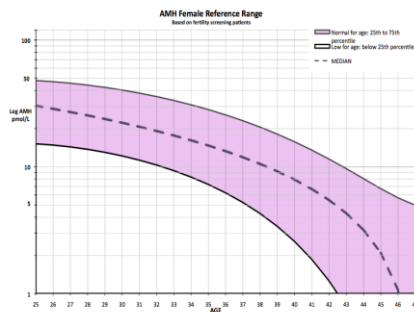
Maternal Age	Risk for trisomy 21 (Down syndrome)	Risk for all trisomies
20	1 in 1,667	1 in 526
25	1 in 1,250	1 in 476
30	1 in 952	1 in 384
35	1 in 385	1 in 192
40	1 in 106	1 in 66
45	1 in 30	1 in 21
49	1 in 11	1 in 8

Miscarriage rate & maternal age



Dew et al 1998

Ovarian reserve

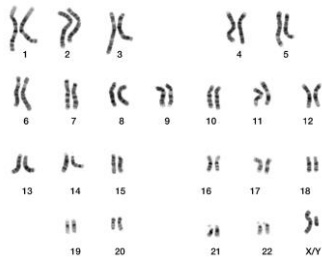


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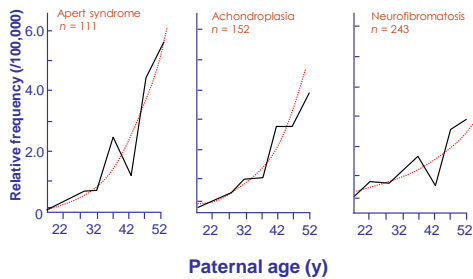
Paternal reproduction and chromosomes



Genetic disorders of male reproduction

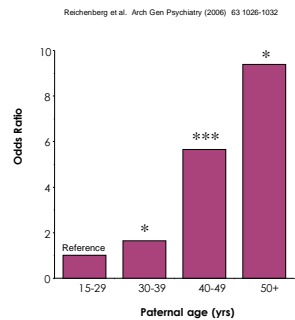
- Klinefelters syndrome
- Cystic fibrosis mutations
- Y-chromosome gene-deletions

Relative frequency of affected children of normal parents



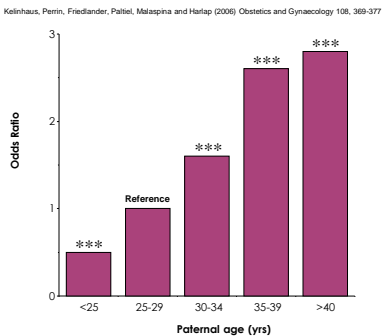
Aitken et al., 2014

Impact of paternal age on Autism



Aitken et al., 2014

Impact of paternal age on miscarriage



Aitken et al., 2014


Excessive Sperm DNA Fragmentation

- Can be assessed clinically by carrying out SCSA or TUNEL on a semen sample
- Gives an indication of overall level of damage to DNA in sperm cells
- Excessive damage linked to infertility and recurrent miscarriage
- Mostly thought to be due to oxidative damage from locally-produced free oxygen radicals



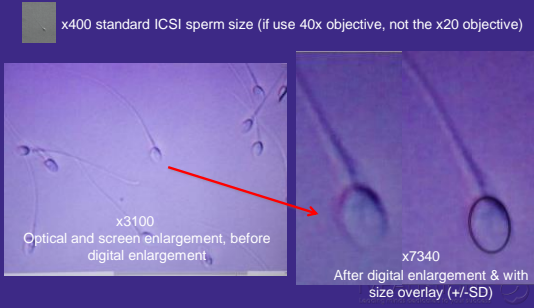
Treatment of abnormal DNA fragmentation in sperm

- Simple anti-oxidants (Menevit, Men's Performance Multi)
 - Readily available
 - Evidence of efficacy limited
- Frequent ejaculation at fertile time
 - Thought to limit the exposure to endogenous oxygen radicals
- Obtaining sperm direct from the testis
- Selection of sperm for ICSI through digital high magnification




Digital High Mag IMSI – Sperm Selection

x400 standard ICSI sperm size (if use 40x objective, not the x20 objective)

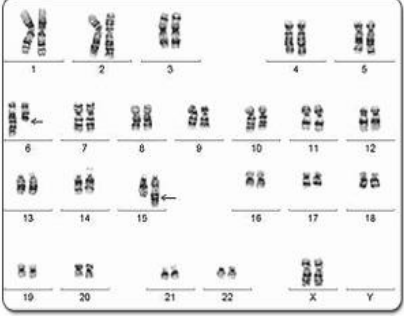


Genetics and reproduction in early 2015

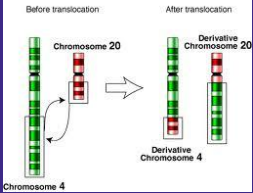
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Balanced translocation



Translocations




- Associated with reproductive problems
- Can be linked to livebirth of child with problems
- What to do?



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Investigation for genetic causes of recurrent miscarriage

- Karyotypes in both partners
- Sperm DNA fragmentation
- AMH level
- Karyotype products of conception where possible



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Pre-conceptual genetic testing in healthy families?

The present:

Discussion of:

- Cystic Fibrosis
- Fragile X
- Spinal muscular atrophy (SMA)
- Haemoglobinopathy
- Autosomal recessive for (Ashkenazi) Jewish background

Pre-conceptual genetic testing in healthy families?

The future???

The screenshot shows the CD Genomics website. The main heading is 'Risk Forecast of Disease'. Below it, there is a sub-heading 'CD-Genomics proprietary GeneFlow™ offers genetic testing portfolio which is based on a technology that assesses a complex but specific set of alleles on the human genome - Risk-Susceptible Allelic Variants (RSAs) - that determine an individual's likelihood of disease. A person's genetic susceptibility to disease is a complex interplay of many genes and environmental factors. By assessing your carrier status for mutations linked to 30 common disease susceptibility, we'll give you and your family insights to help you prepare for the future.' The website also includes a navigation menu with options like Home, Health, Sequencing, Microarray, Custom Libraries, Bioinformatics, Genotyping, Aptamers, and Platforms. There is also a 'Contact us to order' section with contact information for IVF Primary Road in Perth.

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Prenatal testing for genetic disorders

Prenatal testing

- 1970s – amniocentesis >35years
- 1980s – chorionic villus sampling
- 1990s - nuchal translucency screening
- 2000 - nuchal translucency plus biochemistry



Current prenatal testing

The diagram shows an ultrasound transducer on the left and a cross-section of a pregnant woman on the right. A needle is shown entering the amniotic fluid to collect a sample. Labels include 'Ultrasound transducer', 'Amniotic fluid', and 'Fetus'.

Non-invasive prenatal testing

	Maternal Sequence	Fetal Sequence
SNP	G•C	G•C
	C•G	C•G
	T•A	C•G
	A•T	A•T

A SNP (Single-Nucleotide Polymorphism) is a DNA sequence variation occurring when a single nucleotide — A, T, C or G — in the genome is changed, which is part of the natural genetic variation within a population.

How does Natera non-invasively examine fetal DNA?

Blood Draw → **SNP Targeted Sequencing** → **Analysis** → **Accurate Reporting**

The process involves a blood draw at 9 weeks gestation, followed by centrifugation and sequencing of the plasma and buffy coat. The resulting data is analyzed using the NATUS algorithm to distinguish fetal DNA from maternal DNA. A report is then generated for chromosomes 21, 18, 13, X, Y, and 16, including risk scores and chromosome-specific accuracies.

Non-invasive prenatal testing

- Requires minimum amount of fetal DNA in circulation
- Usually present after 9 weeks gestation
- Can assess commonest 5 abnormalities + sex
- 2 week turn around
- Not MBS listed —cost \$400-900

Where does NIPT fit in routine antenatal care?

Where does NIPT fit in routine antenatal care?

High risk?

Low risk?

The diagram shows a 'nuchal translucency measurement' ultrasound image on the left. A red arrow points to the 'panorama prenatal test' logo. A red arrow then points to a diagram of the amniocentesis procedure, indicating that NIPT is used to assess high-risk pregnancies.

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Preimplantation Genetic Diagnosis



Preimplantation Genetic Diagnosis



Test the cells
Replace only the unaffected embryos



Preimplantation genetic diagnosis methods

Chromosome structures

- FISH
- Array CGH

Single genes

- Real-time PCR
- Karyomapping

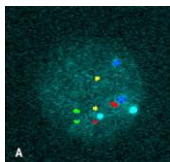
Everything

- Next generation sequencing



Testing for chromosomal problems

FISH



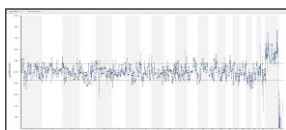
Array CGH

Test DNA
Amplified
Labelled

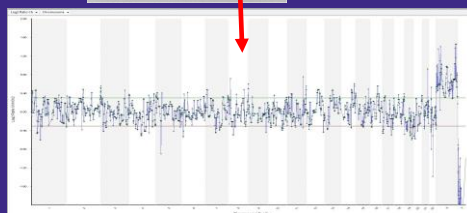
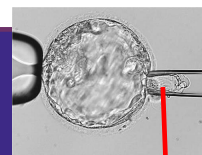
Reference DNA
Labelled

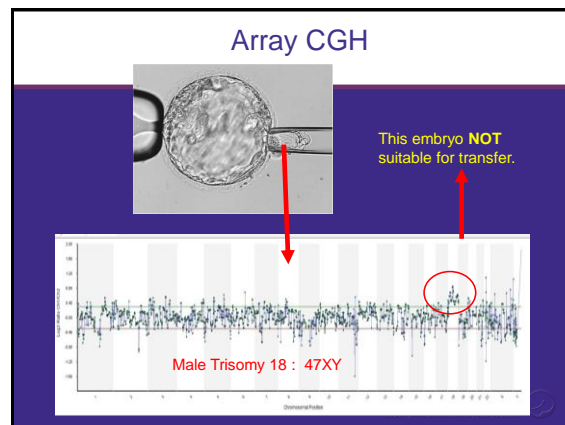
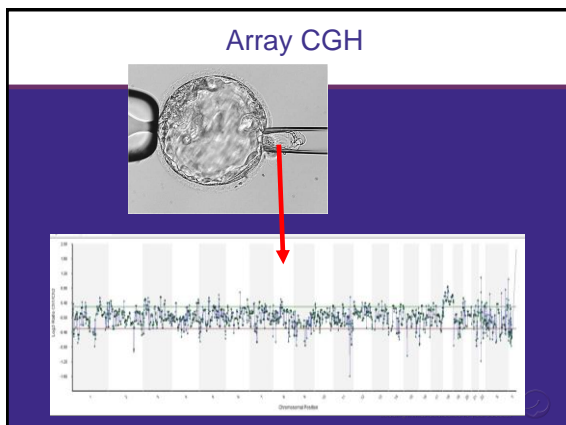
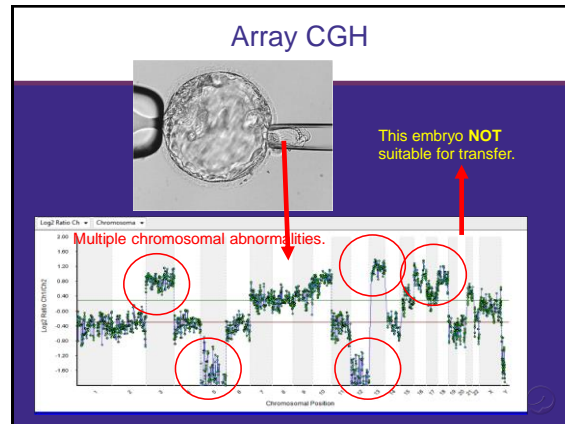
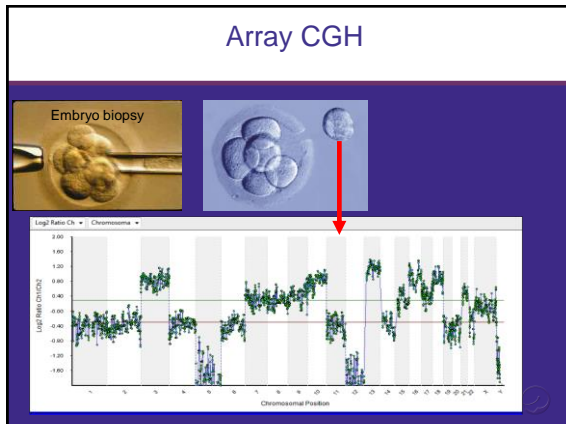
Hybridised

Automated analysis



Array CGH





- ### PGD for known single gene disorders
- Past: sequencing the mutation.
 - Effective but needs extensive preparation.
 - Can take six months to prepare
 - Current: Karyomapping
 - Based on SNP variation (DNA fingerprinting).
 - Uses automatic algorithms to pick from which parent, the sequence has come
 - Immediate
 - Will, eventually, be able to test multiple sites
-

- ### So what's the role of PGD in 2015?
- Testing for known single gene disorders
 - Identifying health embryos where there's a translocation
 - Preventing miscarriage?
 - Improving success rates for IVF?
 - Others?????
-

What does the future hold?



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- Cheaper and easier tools to assess health



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- More worry



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- Cheaper and easier tools to assess health
- IVF will still be less fun than spontaneous conception (a lot less!)
- “Designer babies” ??? – Not the big issue
- Exponential growth in testing for future possibilities
- More worry
- Longer consultations...

