Genetics of Turner syndrome

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NCMG Clinical Genetic Services

- 4 Consultants
- 3 generic genetic counsellors
- 3 cancer specialist genetic counsellors
- 3 specialist genetic counsellors; Cardiac, CF and NF
- 1 medical registrar
- Genetics clinics in Dublin, Cork, Limerick and Galway
What is Clinical Genetics?

1. Diagnosis

   Clinical or laboratory Dx of genetic condition

   Estimation of risks to patient

   Estimation of risks to relatives

2. Advice

   Communicate information about condition and its consequences for the whole family
What is Clinical Genetics?

3. Support
   - To patient
   - To family
   - Non-directive counselling

4. Register of Genetic Disorders
   - Follow-up of appropriate individuals
   - Dissemination of new information

5. Research
Genetic counselling is a communication process that deals with the human problems associated with the occurrence, or the risk of recurrence, of a genetic disorder in a family.

ASHG 1975
3 Elements of genetic counselling

1) Comprehension of medical facts about a disorder, including diagnosis, natural history, and available management

2) Appreciation of the contribution of heredity to the disorder, and the chance of recurrence in relatives

3) Explore the impact of the genetic elements of a disorder both on individuals and on their family
Gene

• An inherited element which gives a person a particular trait

• A stretch of DNA which codes for a particular protein

• We all have 30,000 to 40,000 genes

• Genes are present in every cell in our body

• A person has 2 copies (a pair) of each gene, one from each parent
Chromosomes, DNA, and Genes

Cell → Nucleus → Chromosomes → Gene → Protein
A mutation is a change in the normal base pair sequence.

Commonly used to define DNA sequence changes that alter protein function.
The human chromosome number is 46
(44 autosomes and 2 sex chromosomes)
46 chromosomes is the diploid number
23 chromosomes is the haploid number
**HGBS OF CHROMOSOME PREPARATION**

1. **5 ml of venous blood**
2. **Separate off red cells**
3. **Add culture medium to white cell suspension**
4. **Incubate 3 days at 37°C**
5. **Colchicine added**
6. **Separate off white cells**
7. **Hypotonic saline added**
8. **Cells spread onto slide by dropping**
9. **Stained**
10. **Cells fixed**
11. **Photographed**

**KARYOTYPE**
Idiogram Karyotype

*Image courtesy of Vysis, Inc., Downers Grove, Illinois*
Normal Female - 46,XX
Meiosis and Fertilization

CHROMOSOME REPLICATION

MEIOSIS I

MEIOSIS II

GAMETES (Sex Cells)

FERTILIZATION

23 chromosomes

ZYGOTE

BLASTOCYST

Greenwood Genetic Center
Nondisjunction

Meiosis

Nondisjunction

Gametes

Trisomy 47 chromosomes

Monosomy 45 chromosomes

Zygotes

Normal cell division

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Turner Syndrome Karyotype
45,X
Monosomy X - Turner Syndrome 45,X

Gamete With 23 Chromosomes

Gamete With 22 Chromosomes

EMBRYO

MONOSOMY
When Turner’s Syndrome may be diagnosed

• Before birth
  – baby with excess fluid (hydrops)
  - Incidentally

• At Birth
  - Excess fluid (lymphoedema)
  - congenital heart disease (aortic problems)
  - incidentally

• As child
  - Short stature
  - Delayed Puberty
Medical Follow Up

- Cardiac Disease – not just as newborn
- Kidney scan – if normal at birth may be no need to repeat
- Check for underactive thyroid as teenager/adult
- Endocrinology follow up
  - Growth hormone use
  - Oestrogen replacement from puberty
Clinical Features

• Consistent Features
  short stature
  Ovarian dysgenesis (failure to develop)
  Primary amenorrhoea (absent periods)
  infertility

• Variable Features
  Webbed Neck
  Peripheral lymphoedema (swollen feet and hands)
  Coarctation (narrowing) of descending aorta

• IQ normal
Clinical Genetics

New genetic event in the girl with Turner’s

Likelihood of another affected child for parents is under 1%

No implication for unaffected sisters’ children

Very few women with Turner’s ovulate

Pregnancy in women with Turner’s can be achieved using donor eggs

Women with Turners’ may also adopt children
Other genetic forms of Turner’s syndrome

• >50% of Turner’s 45,X in all cells

• <30% have 46 chromosomes, with one normal X, but a second X which is missing a significant amount of genes
e.g. 46,XX,del(X)(q21-q27)

• <20% have mosaic Turner’s 46,XX/45,X
Mosaic Turner’s

- Some cells in the body have 46,XX (usual female pattern)
- Some cells in the body have 45,X (Turner's pattern)

- Can be a milder form, with greater final height, and sometimes ovarian function

- Mosaic pattern in blood does not reflect pattern in other tissues
Other genetic forms of Turner’s syndrome

- Ring X chromosome
- 46,X, r(X)
- Turner’s syndrome with usual clinical features
- Learning disability frequent in ring X Turner’s but not in usual form of Turner’s
Why don’t men get Turner Syndrome?

Men
One X chromosome in every cell

Women
one X chromosome active in any cell
One X chromosome is inactivated early in embryogenesis randomly in each cell

X-inactivation aka Lyonisation
Effect of Diagnosis

• Internet and conflicting information

• When to tell and who?

• How to tell?
The impact of words

• Some words have an inherent negative connotation; e.g.,
  • Risk
  • Faulty genes
  • Abnormal genes

Use of more neutral words are favoured; e.g.,
  • Chance/ likelihood
  • Altered genes
X inactivation is incomplete

On every X chromosome – several regions which “escape” X inactivation

Xp22.3 & Xq21– pseudoautosomal regions

Girl get Turners, partly because they lack two copies of pseudoautosomal region of the X chromosome
How do genes actually work?