Family stories:
to illustrate inheritance and the impact on families

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Overview

With respect to inherited cardiac conditions

- Simple modes of inheritance (Mendelian)
- Complex modes of inheritance (non-Mendelian)
- Other complicating factors in genetics, dealing with families
  - Technical aspects
  - Counselling/ethical issues
Inherited cardiac conditions
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- congenital heart disease
- familial hypercholesterolaemia
- aortopathies
- channelopathies
- cardiomyopathies
Genetics of ICCs

- Genetics of ICCs particularly interesting/challenging
  - Overlap with non-genetic cardiac conditions
  - Heterogenous
  - Type of gene mutations: often subtle, difficult to interpret

- Consequence of ICC = sudden death
  - Anxiety, counselling issues

- Ethical issues - the genetic blueprint - family secrets
Genetics of ICCs

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• Ethical issues-the genetic blueprint - family secrets
Inherited genetic diseases

• Any disease involving your genes, including:
  – single gene disorders (monogenic)
  – multifactorial disorders (polygenic + non-genetic)
  – chromosomal disorders

• Understanding how these various disorders are inherited allows you to predict risk to relatives
Genes and chromosomes

Chromosomes shown with this X shape during cell division—sister chromatids still attached
Inheritance: genes and chromosomes

- We inherit one copy of each chromosome from each parent
- => 22 pairs of autosomes
- => 1 pair of sex chromosomes
- Homologous pairs
Inheritance: genes and chromosomes

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• Genome = the entire genetic information of an individual
• Haploid = containing one copy of each chromosome
Pedigrees

- A family tree
- Why are they important?
  - To visualise patterns of inheritance
  - To record related symptoms among family members to refine the diagnosis
  - To help calculate risk in other family members
    - informs testing, surveillance, management, treatment
  - Provides a record which can be updated with new information
Pedigrees

- https://www.futurelearn.com/courses/diabetes-genomic-medicine/0/steps/10049
Pedigrees

- male
- female
- sex unknown
- unaffected
- affected
- carriers
- deceased
- consanguineous marriage
- twins
- identical twins
Inheritance

- ICCs caused primarily by changes in genes

- Some recognisable chromosomal conditions in cardiology clinics
  - Turner syndrome
  - DiGeorge syndrome (22q11 deletion)
  - Microdeletions and microduplications – detected by new technologies
Chromosomal deletion

aCGH

Genes and chromosomes
Genes and chromosomes
MENDELIAN INHERITANCE PATTERNS
Simple inheritance

- Mendelian inheritance

- Single gene characteristics /traits inherited in a predictable way
  - Autosomal dominant
  - Autosomal recessive
  - X-linked (recessive or dominant)

- Autosomal carried on an autosome (chromosomes 1-22)
- X-linked carried on the X chromosome
- Alleles different forms of the same gene
- Dominant trait is present when only one mutant allele is present (heterozygous)
- Recessive trait is present when both alleles are mutated (homozygous)
Simple inheritance

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Genetic disease

INHERITANCE
Autosomal dominant inheritance

Typical characteristics

- 50% risk in offspring
- Males and females equally affected
- Affected individuals (usually) have an affected parent
- Tends to occur in every generation

Disease locus
Autosomal dominant inheritance

- The most common/important inheritance pattern in ICCs

- Sometimes a clear AD inheritance pattern masked, which can make accurate counselling difficult

- “Masking” can occur due to
  - reduced penetrance
    - disease seems to “skip” a generation
    - heterozygous but no clinical phenotype
    - age related penetrance-not apparent until already passed on

- Variable expressivity
  - individuals show only some, or variable symptoms
Disclosure – impact on family

• In some situations, disclosure and dealing with a life-threatening situation brought families closer together due to improved communication:

• “I think [our family] got closer .. we check up on each other all the time.”

• “It’s been really kind of sweet, because of this information, like I don’t even really know [my half-brother] that well, but this information has kind of bonded us... We have kind of been connected and we have been in touch on Facebook with him and his wife...”

Vavolizza et al. J Genet Couns. 2015 August ; 24(4): 608–615
Disclosing Genetic Information to Family Members about Inherited Cardiac Arrhythmias: An Obligation or a Choice?
Disclosure – impact on family

• On the other hand, several participants reported disclosure further separated their family due to feelings of animosity and blame, bringing about social tensions and ill effects within the family unit:

• “It totally changed our lives. It put a very, very big strain on our family. They always say that life-threatening things bring you closer together, I felt it threw our family apart.”

• “[My brother-in-law] said something to me six months later like ‘Well, you know I am just, I am so scared I just wish I had never known this’... he was kind of angry at me, that’s what it seemed like.”

Vavolizza et al. J Genet Couns. 2015 August ; 24(4): 608–615
Disclosing Genetic Information to Family Members about Inherited Cardiac Arrhythmias: An Obligation or a Choice?
Most ICCs

Most Aortopathies (Marfan; Loeys Dietz)
- Reasonably high penetrance/Variable expressivity

Most Cardiomyopathies/channelopathies
- Lower penetrance
- Less variable (in terms of expressivity)

Beware of digenic (and polygenic)
Autosomal recessive inheritance

**Typical characteristics**

- 25% risk in offspring
- Males and females equally affected
- Usually no previous family history
- Most commonly affects siblings
- More common in consanguineous families
Impact of genetic tests for family 2

• Enable prenatal tests
• Enable Preimplantation genetic diagnosis (PGD)

• Ethical and counselling issues
• Formal legal framework (HFEA)
AR ICCs

• Some forms of CPVT
  – CASQ2
  – TRDN

• Some forms of LQT (Jervell Lange Nielson)

• Some forms of DCM
  – Carvajal syndrome with woolly hair, DSP mutations
  – May be especially important in infantile DCM

• Some forms of ARVC
  – Naxos disease with palmoplantar keratoderma

• Some forms of Aortopathy (GLUT10, SLC2A10)
Family 3

- Emery Dreifuss
- Muscle weakness
  - Scapulo-humeroperoneal
- Contractures (elbow, Achilles, neck flexor)
- Cardiac involvement:
  - Atrial fibrillation, flutter and standstill, supraventricular and ventricular arrhythmias, AV and BB blocks
  - Dilated or hypertrophic cardiomyopathy

- Heterogenous
  - *EMD* (XL)
  - *FHL1* (XL)
  - *FLMNA* (AD)
X-linked inheritance

Typical characteristics

- No male-to-male transmission
- Predominantly affects males
- Females less severely affected
XL ICCs

- Cardiomyopathy – usually dilated
  - Emery Dreifuss (*EMD*)
  - Dystrophin related (Becker; Duchenne)
  - Barth syndrome

- Cardiomyopathy – usually hypertrophic
  - Fabry
  - *FHL1*

- Women can manifest—particularly important DYSTROPHIN, and in FABRY’s where the cardiac phenotype may be the only manifestation
NON-MENDELIAN INHERITANCE PATTERNS
Digenic

- Diseases caused by co-inheritance of mutations at two distinct genetic loci (i.e., in two different genes)

- Relatively common in ICCs which are genetically heterogenous
Loeys Dietz

- AD disorder
- Genetically heterogenous

**Table 1 LDS classification**

<table>
<thead>
<tr>
<th>LDS type (proposed)</th>
<th>Gene symbol</th>
<th>Other disorders reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDS 1</td>
<td>TGFBR1</td>
<td>TAAD (previously, LDS 1a, 1b, 2a, 2b)</td>
</tr>
<tr>
<td>LDS 2</td>
<td>TGFBR2</td>
<td>TAAD, MFS2 (previously LDS 1a, 1b, 2a, 2b)</td>
</tr>
<tr>
<td>LDS 3</td>
<td>SMAD3</td>
<td>Aneurysms-osteoarthritis syndrome</td>
</tr>
<tr>
<td>LDS 4</td>
<td>TGFBR2</td>
<td>Aneurysm, aortic and cerebral, with arterial tortuosity and skeletal manifestations</td>
</tr>
</tbody>
</table>

LDS, Loeys–Dietz syndrome; MFS2, Marfan syndrome type 2; TAAD, thoracic aortic aneurysm and dissection; TGFBR, transforming growth factor-β receptor.

Would you perform a predictive test on the 2 year old child in family 4?
• Would you perform a predictive test on the 2 year old child?
• Considerations include
• Is it medically indicated? If not, wait till mature enough to be involved in test decision
• Future insurance/employment issues
• Right of the child to decline predictive test
Digenic

- Common in inherited cardiac conditions
  - ARVC 4-47% (Xu 2010, Bao 2013, Rigato 2013, Bhonsalelet 2015, Groenweg 2015)
  - LQT 4-10% (Shwartz 03, Westenskow 04, Tester 2005, Itoh 2010)
  - HCM app 5% (Oxford)
  - DCM uncertain

- Often associated with earlier onset and/or more severe phenotype
Polygenic inheritance

Disease / phenotype threshold

Common variant association analysis (SNP array)

Rare variant association analysis (WES/WGS)

Accumulation of susceptibility variants

Disease susceptibility

Mendelian
Near-Mendelian
Oligogenic

LQTS, CPVT, HCM
BrS, ERS, DCM

• Mutations SCN5A in 15-30%
• Also associated with mutations in many other genes:
  – GPD1L, CACNA1C, CACNB2, SCN1B, KCNE3
• SCN5A mutations discovered by candidate gene approach, and only very limited linkage data
SCN5A

- Several families where SCN5A pathogenic mutation identified; but, some individuals testing negative for familial mutation have Brugada
In 5/13 families there were 8 individuals with phenotype to suggest affected, but genotype negative including 3 with spontaneous type 1 ECG

For Brugada you can't rely on gene testing alone to determine who is at risk
Multifactorial inheritance

• Interaction between genetic and environmental factors
• Cluster in families but incidence in close family members is <5%

Most ICCs

- Cystic fibrosis
- Duchenne muscular dystrophy
- Schizophrenia
- Coronary heart disease
- Diabetes
- Scurvy
- Tuberculosis

Most ICCs
Mitochondrial HCM
A Homoplasmic Mitochondrial Transfer Ribonucleic Acid Mutation as a Cause of Maternally Inherited Hypertrophic Cardiomyopathy

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Newcastle upon Tyne, United Kingdom; New York, New York; and Rome, Italy

OBJECTIVES The purpose of this study was to understand the clinical and molecular features of familial hypertrophic cardiomyopathy (HCM) in which a mitochondrial abnormality was strongly suspected.

BACKGROUND Defects of the mitochondrial genome are responsible for a heterogeneous group of clinical...
Impact for family 5

- All intervening relatives will have this mutation
- All will be at risk of HCM
- 100% risk to their children, though non-penetrance described (reasons for this not yet known)
Impact for family 5

Method one: Embryo repair

Step 1
Parents’ embryo
- Unhealthy mitochondria
- Parents’ nucleus

Donor embryo
- Healthy mitochondria
- Donor’s nucleus

Step 2
- Parents’ nucleus removed
- Donor’s nucleus removed and destroyed

Step 3
- Parents’ nucleus now in donor embryo

Source: HFEA
Mosaicism
Mosaicisim

- Presence of two or more cell lines with different genetic or chromosomal constitutions within a single individual or tissue
- Somatic mosaicism—arises post-fertilisation
- Germline mosaicism—affecting only gamete producing cells; leads to sporadic disease with a second affected sibling

Germline: cells that produce the gametes (sperm/egg)
Somatic: all other cells of the body except the gametes
Mosaicism
First description of germline mosaicism in familial hypertrophic cardiomyopathy

Jean-François Forissier, Pascale Richard, Sylvain Briault, Céline Ledeuil, Olivier Dubourg, Bernard Charbonnier, Lucie Carrier, Claude Moraine, Gisèle Bonne, Michel Komajda, Kitty Schwartz, Bernard Hainque
Summary

• Inherited cardiac conditions are high risk conditions which can result in sudden death
• Treatments are available
• Understanding the mode of inheritance is important for calculating risk to relatives, and enabling personalised management
• ICCs can be associated with all inheritance patterns: autosomal dominant /recessive; X-linked recessive; mitochondrial
Summary

• Autosomal dominant inheritance is the most common for ICCs
  – can show reduced penetrance, variable expressivity
  – can be due to new mutations or associated with mosaicism
  – digenic/polygenic and environmental influences have a particularly important role in pathogenesis of ICCs

........hope for new technologies and bioinformatics to fully understand the impact of these on clinical phenotypes and penetrance