Autosomal Dominant and Autosomal Recessive Disorders

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Introduction

• Reminders on how to read a pedigree
• Concepts in autosomal dominant inheritance
• Autosomal dominant disorders
• Concepts in autosomal recessive inheritance
• Autosomal recessive disorders
Symbols in Pedigrees
Lecture 3

Mammalian X-chromosome inactivation

Mammalian males and females have one and two X chromosomes respectively. One would expect that X-linked genes should produce twice as much gene product in females compared to males. Yet when one measures gene product from X-linked genes in males and females they are equivalent. This phenomenon, known as dosage compensation, means that the activity of X-linked genes is either down regulated in females or up-regulated in males. The former proves to be the case: X-chromosome inactivation in females is the mechanism behind dosage compensation.

In females, one of the X chromosomes in each cell is inactivated. This is observed cytologically. One of the X-chromosomes in females appears highly condensed. This inactivated chromosome is called a Barr-body.

The inactivation of one of the two X-chromosomes means that males and females each have one active X chromosome per cell.

X-chromosome inactivation is random. For a given cell in the developing organism there is an equal probability of the female or the male derived X-chromosome being inactivated.

Given X-chromosome inactivation functions normally in the following individuals, why are they phenotypically abnormal?

- XXX individuals have 2 Barr Bodies leaving one active X
- XXXX individuals have 3 Barr Bodies leaving one active X
- XXY individual have one Barr Body leaving one active X (Klinefelter’s syndrome)
- X0 individuals have no Barr Bodies leaving one active X (Turner’s syndrome)

The answer to this is not completely understood, but part of the explanation for the abnormal phenotypes is that the entire active is not inactivated during Barr Body formation. The short end of the X-chromosome appears to remain active in the Barr Body. Consequently an X0 individual is not genetically equivalent to an XX individual.

Mendelian genetics in humans: Autosomal and Sex-linked patterns of inheritance

Obviously examining inheritance patterns in humans is much more difficult than in Drosophila because defined crosses cannot be constructed. In addition humans produce at most a few offspring rather than the hundreds produced in experimental genetic organisms such as Drosophila. Therefore the basic methods of human genetics are observational rather than experimental and require the analysis of matings that have already taken place rather than the design and execution of crosses to directly test a hypothesis.

To understand inheritance patterns in humans genetics often follow a trait for several generations to infer its mode of inheritance. For this purpose the geneticist constructs family trees or pedigrees.

Pedigrees trace the inheritance pattern of a particular trait through many generations. Pedigrees enable geneticists to determine whether a familial trait is genetically determined and its mode of inheritance (dominant/recessive, autosomal/sex-linked).

Pedigrees use the following set of standardized symbols:

- Male

- Female

- Mating

- Mating between relatives

- Offspring listed in birth order. Roman numbers symbolize generations. Arabic numbers symbolize birth order within generation.

- Monozygotic twins

- Dizygotic twins

- Offspring of unknown sex

- Aborted or stillborn offspring

- Deceased offspring

- Affected individual

- Propositus (male) or proposita (female); first case in family that was identified.

- Heterozygous

- X-linked carrier

- Indicates date of death

- Questionable whether individual has trait
Autosomal Dominant Inheritance

• Individuals have at least one affected parent
• Affected individuals have 50% chance of transmitting the dominant trait
• There are affected individuals in every generation in large families and transmission is vertical in pedigree.
• The frequency of males and females being affected is similar
• Two affected individuals may have unaffected offsprings.
Familial Hypercholesterolemia

- Autosomal Dominant
- Prevalence 1 in 500 in UK
- High cholesterol levels - specifically LDL
- Formation of xanthomas (fatty deposits)
- Treatment towards conventional cholesterol management usually does not work efficiently because of the mutations
- May lead to cardiovascular disease at early age
Familial Hypercholesterolemia

• Mutations in
  – LDLR on chr 19
  – ApoB on chr2 (mostly R3500Q)
  – PCSK9 on chr 1

• Mutations mostly result in either reduced LDL receptors and efficiency or LDL receptor ligands

• Thus the rate of LDL conversion is slowed resulting with the phenotype
Pedigree 1. An idealized pedigree of a family with hypercholesterolemia, an autosomal dominant disease where the heterozygote has a reduced number of functional low density lipoprotein receptors.
Each child  Possibilities  

○  ○  = Homozygous: very few or no LDL receptors; most die very young

○  ○  = Heterozygous: half normal number of LDL receptors; high cholesterol and risk early adult death

○  ○  = Same as above

○  ○  = Two normal alleles: normal LDL receptors
Huntington’s Disease

- Neurodegenerative disorder
- Cognition problems
- Lack of coordination
- Jerky body movements and decline in mental abilities
- Physical abilities gradually worsen
- Dementia, physical injury due to falls
Huntington’s Disease

- Triplet repeat disorder
- Prevelance 1 in 10,000 in the world
- HTT gene on chr 4
- HTT contains CAG repeats
- CAG repeats over 28 are unstable during replication
- CAG repeat expansion results in Huntington’s Disease
<table>
<thead>
<tr>
<th>Repeat count</th>
<th>Classification</th>
<th>Disease status</th>
<th>Risk to offspring</th>
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<tbody>
<tr>
<td>&lt;26</td>
<td>Normal</td>
<td>Will not be affected</td>
<td>None</td>
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<tr>
<td>27–35</td>
<td>Intermediate</td>
<td>Will not be affected</td>
<td>Elevated but &lt;&lt;50%</td>
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<tr>
<td>36–39</td>
<td>Reduced Penetrance</td>
<td>May or may not be affected</td>
<td>50%</td>
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<tr>
<td>40+</td>
<td>Full Penetrance</td>
<td>Will be affected</td>
<td>50%</td>
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<tr>
<td>60&lt;</td>
<td>Full penetrance</td>
<td>Will be affected severely</td>
<td>50%</td>
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</table>

Huntington’s Disease
Huntington’s Disease

• Genetic anticipation
  – symptoms of a **genetic** disorder become apparent at an earlier age as it is passed on to the next generation. e.g Huntington’s Disease

• The symptoms progress faster in every generation in families with Huntington’s Disease because of genetic anticipation
Variable Expressivity vs Incomplete Penetrance

- Each individual with a autosomal dominant trait may express all of the symptoms, or only a few. This is called **variable expressivity**.
- The individual with an autosomal dominant trait either expresses the disease phenotype or he/she doesn't. This is called **incomplete penetrance**.
- Variable expressivity and incomplete penetrance are only associated with autosomal dominant inheritance. These concepts are not relevant when autosomal recessive traits are considered.
Pedigree 2. An idealized pedigree demonstrating the effects of incomplete penetrance.
Autosomal Recessive Inheritance

• Males and females are affected
• Affected individuals may not have affected parents. However both parents must be carriers or affected for an individual to be affected
• There is 25% chance of being affected if the parents are carriers
• The risk of being carrier should be accounted in autosomal recessive traits
• People with the condition are usually in one sibship in one generation
• Consanguity increases the risk because of shared alleles in the family
Cystic Fibrosis

• Progressive damage to respiratory system and chronic digestive system problems
• The features and severity is highly variable among patients depending on the mutations
• Great variety of mutations
• Inherited in an autosomal recessive manner
• Treatment in different ways: mutation specific treatments are available
# All mutations and their classes

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<tr>
<th>Current name</th>
<th>New name</th>
<th>Class</th>
<th>N</th>
<th>(%)</th>
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<td>p.Gly551Asp</td>
<td>III</td>
<td>466</td>
<td>(5.6)</td>
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<tr>
<td>R117H</td>
<td>p.Arg117His</td>
<td>IV</td>
<td>336</td>
<td>(4.1)</td>
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<tr>
<td>G542X</td>
<td>p.Gly542X</td>
<td>I</td>
<td>295</td>
<td>(3.6)</td>
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<tr>
<td>621+1G-&gt;T</td>
<td>c.489+1G&gt;T</td>
<td>I</td>
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<td>(2.3)</td>
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<td>All mutations</td>
<td>New name</td>
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<td>N</td>
<td>(%)</td>
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</table>
Cystic Fibrosis Mutations and Their Functional Effects

Normal Quantity and Function
- No mutation
  - No effect

Quantity of the functional CFTR is at the cell surface is affected
- Little to no functional CFTR
  - **Class I:** premature stop codon or alteration of critical RNA results in full length CFTR synthesis failure
  - **Class II:** improper folding results in defective cellular processing and delivery of CFTR protein to cell surface

Function of CFTR is at the cell surface is affected
- Some functional CFTR
  - **Class V:** Often due to errors in RNA splicing that lead to reduced or variable quantity of functional CFTR
  - **Class VI:** Causes increased cell surface turnover and degradation of CFTR

- **Class III:** Structural defect in CFTR channels results in reduced passage of ions through the channel

- **Class IV:** Causes a defect in regulation that impairs opening of the CFTR chloride channel
Treatment

• Often with antibiotics to tackle the excess amount of bacteria in the lungs
• Physiotherapy to open up lungs
• Bronchiodilators
• Mutation specific treatment
  – Ivacaftor for p.Gly551Asp
  – Gentamicin for p.Phe508del and other class I mutations
Tay Sachs Disease

- Autosomal recessive
- Progressive neurodegenerative disease
- Build up undigested fat in brain cells
- Usually fatal by age 2 or 3
- Presented by intellectual disability, paralysis, dementia and blindness
- HEXA gene mutations
- 78 mutations across the gene causing TSD (mostly base substitutions)
Tay Sachs Disease

- Insufficient activity of hexosaminidase A, a vital enzyme found in lysosomes
- Glycolipids cannot be broken down
- Diagnosis with enzyme assay
- There is no cure for the disease
- Prevention through prenatal diagnosis, preimplantation genetics and mate selection reduces the incidence of the disease
Tay Sachs Disease Family
Familial Mediterranean Fever

• Autosomal recessive and autosomal dominant forms
• MEFV gene at 16p13.3
• Some mutations result in autosomal dominant inheritance whereas others (mostly) result in autosomal recessive inheritance. This is due to haploinsufficiency.
• Dominant form is milder compared with recessive form of the disease
Familial Mediterranean Fever

- Recurrent attacks of fever
- Inflammation and pain
- Amyloidosis with renal failure
- Disease presents early in life, often childhood
- It is a manageable disease
- Use of cholchecine reduces painful attacks, amyloidosis in FMF
Pedigree 4
Summary

• Autosomal dominant vs autosomal recessive inheritance patterns are different
• Variable expressivity, incomplete penetrance and haploinsufficiency are considered in autosomal dominant inheritance
• Carrier status should be considered in autosomal recessive inheritance
• Disease severity does not depend on recessiveness or dominance
• The risk of passing disease is different in different inheritance patterns