Mendelian inheritance and the most common genetic diseases

Cornelia Schubert, MD, University of Goettingen, Dept. Human Genetics

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Mendelian Inheritance

Gregor Mendel demonstrated in ~1850-1870 that the inheritance of certain traits follows particular laws. He described by his experiments the autosomal recessive and autosomal dominant inheritance.

http://mendel.imp.ac.at/mendeljsp/biography/biography.jsp

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**Autosomal dominant inheritance**

**Definition:**
- Affected gene locus is located on an autosomal chromosome.
- Dominant inheritance is given, if the present of a heterozygous mutation causes a phenotype.

**Haploinsufficiency:**
- The reduced dosage of the wildtype allele is not enough for the normal gene function.

**Gain-of-function:**
- The gene product of the mutated allele gains a new, abnormal function.

**Dominant-negative effect:**
- The mutated allele (misshapen protein) acts with the gene product of the wildtype allele and disturbs its function.
autosomal dominant inheritance

• Disease-spectrum in carriers of homozygous dominant mutation is broad: from identical phenotype as in heterozygous carrier to severe course/lethal
autosomal dominant inheritance

recurrence risk: 50%, vertical transmission, both sexes are similarly affected.

\[ AA = \text{dominant allele (mut)} \]
\[ a = \text{recessive allele (wt)} \]

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Autosomal dominant inheritance

- Currently, in human so far ~3700 autosomal dominant diseases are known.
- Incidence of autosomal dominant diseases: 7 in 1,000.
- Wide range of phenotypic spectrum.
- In case of a more mild phenotype, the mutation is mostly inherited by one of the parents.
- In affected person with a more severe phenotype, the mutation occurred mostly spontaneously.
- Examples of frequent autosomal dominant diseases:
  - Neurological diseases (ataxias, paraplegia, dystonia, inherited dementia).
  - Familial cancer syndromes (breast, colon, endocrinologically).
  - Cardiomyopathy (hypertrophic).
  - Skeletal dysplasia.
autosomal dominant inheritance

simple dominant (complete dominant):
the phenotype of the dominant allele will be expressed,
the phenotype of the recessive allele will be suppressed

\[ \begin{array}{ccc}
A & a \\
a & Aa & a \\
a & Aa & aa \\
a & Aa & aa \\
\end{array} \]

\[ = \text{affected} \]

A = dominant allele (mut)
a = recessive allele (wt)
**Autosomal Dominant Inheritance**

**Intermediate Dominant (Incomplete Dominant):**

Heterozygous genotype creates an intermediate phenotype (mixed traits)

**Example:** Flowering color

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Aa</td>
<td>Aa</td>
</tr>
<tr>
<td>a</td>
<td>Aa</td>
<td>Aa</td>
</tr>
</tbody>
</table>

- **A** = Dominant allele (mut)
- **a** = Recessive allele (wt)
**Autosomal dominant inheritance**

**Codominant inheritance:**
both alleles are dominant and lead to a phenotype,
in the presence of both alleles (heterozygosity), traits of each phenotype is present separately

**Example: Blood groups**

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>AA</td>
<td>AB</td>
</tr>
<tr>
<td>B</td>
<td>AB</td>
<td>BB</td>
</tr>
</tbody>
</table>

A = dominant allele (mut)
a = dominant allele (wt)
Simple autosomal dominant inheritance with complete dominance
autosomal dominant inheritance with reduced penetrance
autosomal dominant inheritance

with variable expression
The further transmission of spontaneous mutations depends on the severity of the phenotype and the reproductive fitness.
A gonadal mosaicism has to be considered if the same autosomal dominant mutation occurs in more than one offspring and causes a severe phenotype with nearly complete penetrance.
**Autosomal recessive inheritance**

**Definition:**
- Mutations are located on an autosomal chromosome (gene).
- A phenotype/disease is present if both alleles are mutated.
- In recessive genes, one wildtype allele is enough for a sufficient gene function.
Autosomal recessive inheritance

- Mutations are homozygous or compound-heterozygous.
- Carrier of heterozygous mutations are clinically unaffected.
- Parents of an affected child are usually healthy and are carriers of a heterozygous mutation.
- The risk for a healthy person to be a genetic carrier of a recessive disease is 1:10 to 1:200 (carrier frequency of normal population).
autosomal recessive inheritance

recurrence risk: 25%, horizontal transmission, both sexes are similarly affected

A = dominant allele (wt)
a = recessive allele (mut)

genotype: 1:2:1
phenotype: 1:3

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Autosomal recessive inheritance

- Currently, in humans so far ~4000 autosomal recessive diseases are known.
- Incidence of autosomal recessive diseases: 2.5 in 1,000 newborns.
- Wide range of phenotypic spectrum.
- Examples of frequent autosomal recessive diseases:
  - Metabolic disorders (enzyme defects) often with no external malformations:
    - Cystic fibrosis (incidence 1:2,500)
    - Hemochromatosis (incidence 1:400)
    - Phenylketonuria (1:5,000)
    - Spinal muscular atrophy (1:10,000)
autosomal recessive inheritance

The offspring of an affected person are in 100% genetic carrier of disease!

Healthy siblings of an affected person are in 2/3 genetic carrier of disease!
Risk for an autosomal recessive disease in non-consanguine couple

Heterozygous frequency: 1:100
Risk for an autosomal recessive disease in non-consanguine couple

\[(1 \times 1/2) \times (1/100 \times 1/2) = 1/400 = 0.25\%

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autosomal recessive inheritance
pedigree of a consanguine family
Risk for an autosomal recessive disease?
Autosomal recessive inheritance

Pedigree of a consanguine family

Risk for an autosomal recessive disease?

\[(\frac{1}{2} \times \frac{1}{2}) \times (\frac{1}{8} \times \frac{1}{2}) = \frac{1}{32} = \sim 3\%\]
Consanguine families and isolate ethnic groups (Jewish people or Amish people) are on a higher risk for recessive disease. Consanguine families are on a ~3 to 20 fold higher risk for autosomal recessive disease in comparing to non-consanguine-couples.
X-chromosomal recessive inheritance

• the mutations are recessive and they are located in X-chromosomal genes
• men are hemizygous for X chromosomal genes > they present symptoms
• women are diploid for X chromosomal genes > they are without symptoms
• usually the transmission of X chromosomal disease occurred by healthy women (carrier)
X-chromosomally recessive inheritance

Examples for X-chromosomal disease:

- Hemophilia A and B (1:10,000-25,000)
- Color blindness (1:500-2,000)
- Muscular dystrophy type Duchenne or Becker (1:3,000)
- Fragile X syndrome (1:4,000-6,000)
## X-chromosomal recessive inheritance

<table>
<thead>
<tr>
<th></th>
<th>Female carrier &amp; unaffected man</th>
<th>Healthy woman &amp; affected man</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Y</td>
<td>YY</td>
<td>Y</td>
</tr>
<tr>
<td>X</td>
<td>XX</td>
<td>Xx</td>
</tr>
<tr>
<td>xY</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Affected man &amp; female carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>x</td>
<td>Xx</td>
</tr>
<tr>
<td>Y</td>
<td>XY</td>
</tr>
<tr>
<td>xY</td>
<td>XY</td>
</tr>
</tbody>
</table>

X = dominant allele  
X = recessive allele

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