Genetic diseases: cystic fibrosis, PKU and other common single gene defects

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Genetic diseases: cystic fibrosis, PKU and other common single gene defects.

**Learning objectives.** At the end of this lecture you should be able to:

- Recognise the inheritance patterns autosomal recessive and dominant, X-linked recessive.
- Define incomplete dominance, polygenic inheritance, and a congenital defect.
- Explain how the inheritance of different mitochondrial disorders can differ.
- Use collagen as an example of how different mutations in the same system cause different diseases.
- List the 10 most common single gene disorders, and list the genes that are tested for prenatally in Australia.
- Explain why the gene defect in phenylketonuria leads to the symptoms, and how it is treated.
- Describe cystic fibrosis, the role of the protein, prognosis, treatment and diagnosis.
- Describe primary hypothyroidism, its cause, treatment and prognosis.
- Discuss some the pros and cons of prenatal testing, using examples.
There are hundreds of distinct genetic diseases. Many have subtypes e.g. multiple porphyrias.
A comprehensive information source about human genetic disorders and variation: Online Mendelian inheritance in man http://www.omim.org/

About the human genome project web.ornl.gov/sci/techresources/Human_Genome/

For Research level information try www.ncbi.nlm.nih.gov/books/NBK1116/

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GeneReviews are expert-authored, peer-reviewed disease descriptions ("chapters") presented in a standardized format and focused on clinically relevant and medically actionable information on the diagnosis, management, and genetic counseling of patients and families with specific inherited conditions.

GeneReviews currently comprises 632 chapters.

Published exclusively online, each chapter is: (1) reviewed for accuracy by editors expert in clinical genetics, laboratory genetics, and genetic counseling; (2) peer-reviewed by internationally acknowledged subject experts; (3) updated by the author(s) in a formal comprehensive process every two to three years or as needed; and (4) revised by the author(s) or editorial staff whenever significant changes in clinically relevant information occur. Genetic counseling and testing terms used in GeneReviews are glossed and hyperlinked to additional information in the GeneReviews Illustrated Glossary. GeneReviews are indexed in PubMed.

GeneReviews by Title

1 2 3 9 15 16 21 22 46 A B C D E F G H I J K L M N O P R S T U V W X Y Z
Autosomal inheritance

- **Autosomal recessive**
  - Carrier father
  - Carrier mother

- **Probabilities:**
  - 75% cystic fibrosis not expressed
  - 25% cystic fibrosis

- **Genotypes:**
  - Father: Cc, cc
  - Mother: C, c

- **Offspring genotypes:**
  - CC, Cc, Cc, cc
**Phenotype:** physical appearance of the individual with regard to a trait

**Genotype:**

Two alleles for a trait

A capital letter symbolizes a dominant allele (W) like Widow’s peak.

A lower-case letter symbolizes a recessive allele (w).

Dominant does not mean frequent.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>WW</td>
<td>Homozygous dominant</td>
<td>Widow’s peak</td>
</tr>
<tr>
<td>Ww</td>
<td>Heterozygous</td>
<td>Widow’s peak</td>
</tr>
<tr>
<td>ww</td>
<td>Homozygous recessive</td>
<td>Straight hairline</td>
</tr>
</tbody>
</table>
Incomplete Dominance

A person with straight hair ($H_1H_1$)

A person with naturally curly hair ($H_2H_2$)

Heterozygous Parents ($H_1H_2$)

Key
- Straight hair
- Wavy hair
- Curly hair

Phenotypic Ratio
- 1: 1: 1

Offspring

Wavy hair - heterozygote
Mutations in more than 6 genes restrict the range of colours that stimulate cone-cells.

The most common is red-green colour blindness (OPN1LW and OPN1MW genes) and is X-linked recessive. In Australia Caucasian men have 8% incidence, Asian men have 5%, and women ~0.4%.

Blue-Yellow colour blindness is autosomal dominant.

X-linked recessive conditions include the following serious diseases:

- Hemophilia A,
- Duchenne muscular dystrophy,
- Lesch-Nyhan syndrome.
The Ishihara Colour Test
for red-green colour deficiencies.

Ishihara (University of Tokyo) first published his tests in 1917.

The numeral "74" should be clearly visible to viewers with normal colour vision. Viewers with dichromat or anomalous trichromat may read it as "21", and viewers with achromat may see nothing.

Images from Wikimedia commons.
Inheritance is not always what it seems

Male pattern baldness is often cited as an X-linked recessive trait, BUT…

… the famous American Adams family shows us otherwise.

Male pattern baldness is autosomal and sex-influenced
  - it acts like a dominant trait for men, and a recessive trait for women
Thalidomide was used in the 1950s -60s as a treatment for morning sickness in pregnancy. It was manufactured as a racemic mixture. Phacomelia caused by S - thalidomide. Developmental errors apparent at birth are CONGENITAL. Anomalies may or may not have a genetic basis.
Mitochondrial inheritance

The mitochondria require proteins encoded by both the mitochondrial genome and the nuclear genome.

- Disorders of energy – poor growth, developmental problems
- Disorders in energy-hungry tissues – seizures, vision and/or hearing loss
- Estimated ~1/4000 have mitochondrial diseases – progressive and no cure or treatment
- There are many many different subsets caused by mutations in different genes

Mitochondrial disease can be caused by mutations in the mitochondrial genome OR the mitochondrial genes in the nuclear genome.

Figure 14-53. Molecular Biology of the Cell (© Garland Science 2008)
Polygenic Inheritance – Skin Colour

Tyrosinase begins a cascade of pigment pathways and there are many heritable variations.
Albino / Albinism

- Single gene disorder

Tyrosinase defective

Images: Wikimedia commons

Tyrosinase initially makes DOPA = dihydroxyphenylalanine

**Melanin** is a polymer of structures derived from tyrosine involving the enzyme tyrosinase.
A genetic lack of tyrosinase = albinism
Collagen

Collagen is the most abundant of human proteins. Collagen is a family of structural proteins giving toughness and inextensibility to tendons and protection to organs (e.g. in skin). A matrix of collagen forms the scaffold for mineralisation to create bone and teeth.

The sequence of most collagens involves multiple repeats of the sequence -Gly-Pro-Ala-. Human skin protein is 33% glycine, 22.2% proline and 11% alanine.

Leather is collagen from animal hide.

Links between collagen fibres keep them in bundles.

Voet and Voet 3rd Ed. Figure 8-3 (Wiley, NY). Electron micrograph of collagen fibrils from skin.
Osteogenesis imperfecta

When glycine at position 748 mutates to cysteine (-CH$_2$-SH) the disruption to the collagen helix causes a kink and interferes with strand alignment because no other side chain fits into the small space at the centre of the collagen helix. A major symptom is brittle bones.

This disease has many different levels of severity, with 8 types (genes encoding collagen or enzymes that process collagen). Inheritance autosomal dominant or recessive. Frequency 1/20,000 births.


Ehlers Danlos Syndrome

Mutations in genes encoding collagen or the enzymes that process collagen proteins can cause Ehlers–Danlos syndrome.

Most forms of the condition are inherited as an **autosomal dominant**.

Incidence is around 1 in 10,000.

Patients need occupational and physical therapy. They have chronic pain, and are often misdiagnosed with depression or chronic fatigue.

The 10 most common single gene genetic disorders

More than 6,000 human diseases are caused by single gene disorders. Although individually they are rare, they occur in ~1.4% of the population as a whole and cause a high rate of morbidity and mortality.

Familial hypercholesterolemia 1 / 500
   – late onset high cholesterol, treated with statins
   Diagnosis by lipid levels and genetic screening

Sickle cell anaemia – higher frequency in African (1 / 500), Indian or Arabian descent
   Currently very rare in Australia

Polycystic kidney disease – 1 / 400 – 1 / 1000
   middle-aged onset, kidney failure, no cure

Cystic Fibrosis – 1 / 2500 in Caucasians
   More information in this lecture

Neurofibromatosis type I – 1/2500
   Causes small nerve ending tumours to grow on skin during adulthood

Tay-Sachs disease – 1 / 3000 – higher in some populations eg. Ashkenazi jews – some screening carried out on behalf of potential carriers
   progressive mental and physical retardation – death in early childhood

Produced: 24/03/2017
Marfan syndrome – 1 / 4000
  Disorder of connective tissue – long limbs and fingers and long face

Hereditary spherocytosis – 1 / 5000
  Change in shape of erythrocytes, which are then destroyed by the spleen

Duchenne Muscular Dystrophy – 1 / 7000 X-linked recessive (1 / 3500 boys)
  Muscle degeneration and premature death

Phenylketonuria – 1 / 12,000
  Defect in metabolism of phenylalanine. Mental retardation if not treated immediately
Prenatal testing

What do we test for?

- Phenylketonuria
- Cystic Fibrosis
- Galactosaemia (in some states)
- Primary congenital hypothyroidism
- Rare metabolic conditions
Phenylketonuria

PKU incidence ~1/10,000 – 1/14000 in Australia

Autosomal recessive

Carriers (Aa) = ~1 in 60

Aa x Aa have 1 in 4 children as aa genotype.

Check 1/60 x 1/60 x 1/4 = 1/14,400

1934 Dr. Asbjorn Folling of Norway identified PKU.

1953 Researchers in Birmingham developed a low-phenylalanine diet for the first treatment of PKU. If not treated within the first few weeks of life it can cause mental retardation, seizures, tremors and behavioral disorders.

1960 The Guthrie Test: A dried blood spot, from a heel prick, enabled mass screening of all newborns. A blood spot can be easily tested for phenylpyruvate and other metabolites.

Dr. Robert Guthrie (1916-1995) is acknowledged as the Father of Prevention.
Phenylketonuria (PKU) = lack of phenylalanine hydroxylase (in 99% of cases)

A build up of Phe that cannot be converted to Tyr drives this pathway

In PKU elevated phenylpyruvate damages the brain and inhibits tyrosinase the melanin making enzyme.

A phenylketone! Builds up in PKU.
Treatment:
- Monitoring by metabolic specialists and dieticians with paediatrician
- A strictly monitored low-protein diet with supplements (to provide tyrosine and essential amino acids)
- Compliance with this highly restrictive diet is essential for a PKU child to reach their maximum potential
- This diet is generally continued for life
- Blood phenylalanine levels are monitored
- Women with PKU need to continue restrictive diet if considering pregnancy
CFV operates a state-wide Contact & Support Network liaises with international organisations focused on CF care, support and research.

Cystic Fibrosis (CF) is the most common life-threatening genetic disorder in Australia with an incidence of 1 in 2,500 births (in Caucasians)

It is uncommon in Africans and Asians

CF primarily affects the respiratory system (lungs), digestive system (pancreas and sometimes liver) and reproductive system.

Prenatal testing and carrier testing are available from Genetic Health Services Victoria.
Cystic Fibrosis

CF causes a build up of mucous in the lungs which may lead to repeated chest infections. Lung damage may result, reducing lung function. Most people with CF have a persistent cough to clear away mucous secretions in the lungs.

Common clinical features:
• Frequent respiratory tract infections, later chronic sinopulmonary disease
• Malabsorption, failure to gain weight
• Mucus blockage in the small intestine (Meconium ileus – 5-10% of newborns)
• 98% of males are infertile (but not sterile – failure of the vas deferens to form, sperm may be immotile), and many females too
• Pancreatitis and/or possible liver cirrhosis (thickened secretions)
• Characteristic cystic fibrosis-related diabetes (characteristics of Type 1 and Type 2 diabetes)

Cardiorespiratory complications are the most common cause of death (~80%) in the US.

Treatment:
• Paediatrician and GP involved in monitoring of health, early treatment and prophylaxis for bacterial respiratory infections, physiotherapy, high calorie diet and pancreatic enzyme replacement
• Early treatment can slow the progress of CF
Cystic Fibrosis diagnosis

The Guthrie heel prick blood test is performed on all babies born in Victoria. CF is suggested by elevated immunoreactive trypsinogen (IRT) secreted by the pancreas. This detects about 90% of cases of CF.

Blood is further tested for Delta F508 and 11 other common CF mutations (in Victoria).
There are 1,900 known mutations for CFTR. Diagnosis of CF is supported by excessive NaCl in sweat.

CFTR: The CF Gene
- Located on Chromosome 7
- Product is the **Cystic Fibrosis Transmembrane conductance Regulator**, a chloride channel protein active in membranes of the lungs, liver, pancreas, intestines, reproductive tract, and skin.
- Normal allele is 250,000 base pairs long and contains 27 exons.
- Protein is 1480 amino acids long, Mr =168,173 Da.
Cystic Fibrosis Transmembrane conductance Regulator

Mucous blocks lung alveoli and pancreatic duct.

http://learn.genetics.utah.edu/content/disorders/whataregd/cf/
Primary congenital hypothyroidism

- Used to be called cretinism (term rarely used now)
- Thyroid hormone deficiency
- ~1/4000 births – severe deficiency

If untreated for several months, can lead to growth failure and permanent intellectual disability.

Signs and symptoms
- Can be initially asymptomatic or mild symptoms of lethargy and reduced interest in nursing
- Complete absence of thyroid gland causes umbilical hernia, large tongue (macroglossia), large anterior fontanel (gap between bones of skull)

https://commons.wikimedia.org/w/index.php?curid=1056927
Caused by:
- Failure of gland to develop
  - Genetic (multiple possible genes)
  - No identifiable cause (sporadic)
- Iodine deficiency (rare in developed world)

Diagnosis
- Heel prick identification of high levels of TSH (thyroid-stimulating hormone) or low levels of thyroxine ($T_4$)

Treatment
- Treatment should start within 1-2 weeks of life
- Daily dose of thyroxine, as a tablet
- Doses need to be checked throughout childhood growth

Prognosis
- Most children will develop normally when treated

Congenital hypothyroidism is the most common preventable cause of intellectual disability! “Few treatments in the practice of medicine provide as large a benefit for as small an effort.”
Prenatal testing

What do we test for?

• Phenylketonuria
• Cystic Fibrosis
• Galactosaemia (in some states)
• Primary congenital hypothyroidism
• Rare metabolic conditions