Many of the genetic diseases reviewed here are monogenic, resulting from a single error in one gene of human DNA; however, the nature of the disease depends on the functions performed by the modified gene. At least 6000 monogenic disease are known, and the examples selected are based on prevalence and relevance to practical biomedical science.

### Ancient Evidence

- Some phylogenetic evidence shows that mutations for genetic diseases existed with the first human life on Earth some 200,000 years ago.
- Stone artwork shows an Egyptian Queen with a form of muscular dystrophy (1480 BC).
- DNA sequencing of dental bones from Egyptian mummies (ca 3200 BC) show mutations for sickle cell anaemia, while chemical analysis of their other bone deposits indicates alkaptonuria.
- Some genetic studies date the most common mutation for cystic fibrosis to Neolithic times at least 4500 BC.

### Some Early Observations

- Hippocrates (400 BC) recognised that some diseases are inborn.
- Prolonged bleeding in haemophilia during surgery, accident or in warfare must have been evident in ancient times.
- A 200AD ruling in the ‘Talmud’ by Rabbi Judaeus banned circumcision if a previous haemophiliac son died from the procedure.
- In 1000 AD, Arab physician Albucasis described the hereditary nature of haemophilia.
- The extreme skin photosensitivity of certain forms of Porphyria must have been recognised by early physicians.

### Seeing is believing: discovery of the cell, nucleus and chromosomes

Microscopes developed in late 16th century made study of fine structure of plants, insects and biological materials possible. The English natural philosopher Robert Hooke published his collected results in 1655 and used the term ‘cell’ in comparing pores of cork sections to cella (Latin: small room). The Dutch microscopist Antonie van Leeuwenhoek (1676–1719) drew images and observed single-celled organisms and the central ‘lumen’ of nucleated salmon red blood cells. This latter observation was confirmed in 1831 by Scottish botanist Robert Brown, who identified the opaque centres of orchid flower cells and coined the term ‘nucleus’ (Latin: kernel).

Theories for the function of cell were proposed by German scientists Matthias Schleiden and Theodor Swann (1839) and by Rudolf Virchow (1858). The collective theory identifies the cell as the basic unit of life, formed from pre existing cells by division. Animal fertilisation studies by August Weismann (1873) and Oscar Hertwig (1876) confirmed the role of the nucleus in inheritance and meiosis.

In the same year, Walther Flemming used aniline dyes to stain material he termed ‘chromatin’ and also studied cell division and the separation of thread-like structures in a process he named ‘mitosis’. In 1888 the stained thread-like structures were named ‘chromosomes’ by his colleague H von Waldeyer-Hartz.

In 1896 Paul Mayer developed his version of the classical haematoxylin and eosin (H&E) stain, used to highlight the nucleus and cytoplasm, respectively.

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Mendel, mutations and molecular mechanisms

In 1866, meticulous studies undertaken by Gregor Mendel of the physical characteristics of pea plants set rules of inheritance to predict expression of traits in future generations. Integrated with later chromosome theory of heredity, Mendel’s findings became founding principles of classical genetics.

Cytological approaches to genetics

- 1900: Mendel’s work was re-evaluated by Dutch botanist Hugo de Vries and found to apply to other plants, resulting in the concept of genes and mutations for spontaneous variants.
- 1903: US geneticist Walter Sutton studied grasshopper chromosomes and showed the equal distribution of parental chromosome sets in meiosis for parents to pass on genetic material. With German biologist Theodor Boveri, he proposed that genes located on chromosomes.
- 1911: Term gene used by Danish botanist Wilhelm Johannsen.
- 1913: Alfred Sturtevant produced the first genetic map for Drosophila.
- 1915: US geneticist Thomas Morgan undertook breeding studies on Drosophila and provided evidence that genes carried genetic information.

Biochemical approach to genetics

- 1908: Archibald Garrod’s concept of inborn errors of metabolism suggested that certain lifelong diseases were due to a reduced activity of an enzyme regulating a single metabolic step in alkaptonuria, cystinuria, essential pentosuria and albinism.
- 1929: US biochemist Phoebus Levene proposed nucleic acids as polymers of nucleotides, each composed of a five carbon sugar, phosphate group, and purine or pyrimidine bases.
- 1933: Belgian biochemist Jean Brachet showed that chromosomes contained DNA, and RNA produced in the nucleus moves to cytoplasm during cell protein synthesis.
- 1941: T.G. Goodwin isolated adenosine triphosphate (ATP) from a different enzyme. By 1941 they formulated their hypothesis that ATP was the energy currency of the cell.
- 1952: US biochemist Hans Krebs, the urea cycle (1932) and citric acid cycle (1937).

One gene-one enzyme hypothesis

- 1935: US geneticist George Beadle and Boris Ephrussi induced eye pigment mutation in Drosophila to demonstrate genetic control of eye pigment synthesis. Beadle, with Edward Tatum, induced mutations in Neurospora, studied requirements for specific vitamin metabolites in culture medium, traced to losses of single chemical reactions, each dependent on a different enzyme. By 1941 they formulated their hypothesis, which fitted Garrod’s concept of IEM.
- 1948: Quentin Gibson described recessive methaemoglobinaemia, the first enzyme defect in human disease. In 1952, Cori described glucose 6-phosphatase deficiency in type 1 glycogen storage disease.
- 1953: US zoologist James Watson and British physicist Francis Crick constructed a detailed 3D molecular model of DNA as the perfect fit with data from X-ray crystallography images created by biophysicists Rosalind Franklin, Raymond Gosling and Maurice Wilkins. This was a double helix, with two long complementary chains of nucleotides, going in reverse directions, with matching base pairs (A-T, G-C) interlocked at the centre of the double helix.
- 1961: Sydney Brenner, Francois Jacob, and Matthew Meselson found infection of E. coli with T4 phage takes over protein synthesis confirmed that mRNA carries information from nucleus to cytoplasm following transcription.
- 1964: Robert Holley discovered tRNA, which brings specific amino acids to the ribosome for assembly into polypeptides and proteins.
- 1965: Severo Ochoa developed methods to synthesise single-stranded mRNA used by Marshall Nirenberg in a cell-free system for protein synthesis to solve in 1961 the genetic code, with H Gobind Khorana’s group, as triplet base combinations coding for specific amino acids.

Molecular aspects of genetic disease

- 1995: With improved methods of DNA sequencing, US biochemist John Venter’s group sequenced the whole genome of Haemophilus influenzae using ‘shotgun’ sequencing to reduce segments for analysis.
- 2001: Venter working with Celera Genomics published the whole human genome using automated sequencing of three billion base pairs and 25,000 genes.

Types of mutation

Many mutations occur at more complex translational stages, with single base change (point mutation) resulting in altered protein composition, or the substitution may introduce a stop codon to reduce the length of polypeptide chain. Other mutations may add or lose more bases to cause a ribosomal coding frame-shift error.

DNA double helix (Nature Education 2013)

Genome sequencing

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Genetic resource (OMIM)

Victor McKusick (1921-2004), a US medical geneticist, published the first of 12 volumes of detailed genetic database information in 1966, online in 1985 and updated to hold records of over 26,000 human genetic diseases.

Transcription

RNA polymerase builds a complementary copy of one strand of DNA; this mRNA carries the coding sequence for specific proteins, moving to cytoplasmic ribosomes (the site of synthesis).

Translation

tRNA binds one end to specific amino acids and the other end to mRNA, with direction from RNA. The ribosome moves along the mRNA from the start codon to elongate the chain of amino acids, completing the protein at the stop codon. These processes may be observed using electron microscopy.

Lost in Translation: Landmarks in the Investigation of Some Common Genetic Diseases

Produced by the History Committee for Congress - 2015
Haemophilia & von Willebrand disease (VWD)

Haemophilia A & B are X-linked recessive traits with prolonged bleeding due to deficiencies in factor VIII and factor IX, respectively. Queen Victoria passed mutation for haemophilia B to son and, through daughters, to many royal families of Europe.

Haemophilia reported by US physician John Otto (1803) with family studies
- 1952: Factor IX, also known as Christmas factor described by Biggs and MacFarlane.
- 1953: Langdale developed activated partial thromboplastin time, modified to measure factor activity.
- Fresh-frozen plasma (FFP) and recombinant factors (1997) main treatment.

VWD described by Erik von Willebrand (1926), in Finland in child and family studies.
- 1950s: caused by deficiency of a glycoprotein, vW factor involved in platelet adhesion, activation and protective carrier of factor VIII.
- Tests devised for vW glycoprotein last few decades are antigen or activity assays of red cell-deficient enzymes and DNA mutation analysis for inherited bleeding disorder. Compound heterozygotes occur with other abnormal haemoglobins, notably HbS.

Porphyrias

Porphyrias - metabolites in biosynthesis of haem, acquired and inherited partial enzyme deficiencies, with a prevalence of ~1/1000. Porphyrias may accumulate in red cells, bone marrow, liver or skin and may produce light sensitive dermatitis, gastrointestinal & neuropathy or triggered by hormones, drugs or dietary restrictions.

Porphyria cutanea tarda

Porphyrias may accumulate in red cells, bone marrow, liver or skin and may produce light sensitive dermatitis, gastrointestinal & neuropathy or triggered by hormones, drugs or dietary restrictions.

Landmarks in the investigation of porphyria
- 1844: Chemical and spectral studies by Mulder and Ernst Hoppe-Seyler (1871).
- 1889: Hallmark red urine in acute porphyria reported by Stoikov.
- Hans Fischer studied porphyrin structure, synthesis and classification-identified uroporphyrin in urine (1913) and coproporphyrin in faecal extracts (1915).
- 1946: Haem synthesis pathway elucidated by Shemin and Rittenberg.
- Analytical techniques based on spectrofluorimetry or chromatography in red blood cells, plasma, urine and faeces, assays of red cell-deficient enzymes and DNA mutation analysis for diagnostic confirmation.

Two most common porphyrias are autosomal dominant with a prevalence of ~1/10000. Porphyria cutanea tarda with extreme photosensitive dermatitis or also acquired by excessive iron or alcohol, Hepatitis C or HIV and Acute intermittent porphyria with acute episodes of gastrointestinal & neuropathy or triggered by hormones, drugs or dietary restrictions.

Beta thalassaemia blood film

Sickle cell anaemia

Sickle cell anaemia (SC) is an autosomal recessive hereditary disorder caused by a single nucleotide substitution in the beta globin gene, leading to the production of a non-functional haemoglobin, HbS. This results in the sickling of red blood cells in response to hypoxic conditions, leading to microvascular occlusion and tissue damage.

Beta thalassaemia

Beta thalassaemia is a group of blood disorders characterized by a deficiency in the production of one of the two types of polypeptide chains of the globin component of haemoglobin. This imbalance leads to disorders of red cell morphology and function.

Thalassaemias

Thalassaemias are a diverse group of globally prevalent autosomal recessive conditions with reduction or absence of synthesis of one of two types of polypeptide chains of the globin component of haemoglobin. This imbalance leads to disorders of red cell morphology and function.

Heritage – haemophilia, haem and haemoglobin disorders

Haemoglobinopathies

Large group of diverse genetic disorders affecting chemical structure of one polypeptide chain of the globin component of haemoglobin, which may alter its physiological function.

Most common monogenic inherited diseases with over 300 haemoglobin variants, many without clinical symptoms (HbC, HbD, HbE may show mild haemolytic anaemia), Heterozygous HbS trait usually symptomless but homozygous HbSS has most serious clinical consequences. Compound heterozygotes (HbSC or HbSTh) show variable anaemia, require close management during infection.

Sickle cell anaemia

- 1910: First reported case by James Herrick/Emest. Iorns, with hallmark sickle-shaped red cells.
- 1930: Scrivener and Waugh showed sickling correlated with oxygen tension, and later that Hb polymerisation with RBC rigidity leads to vaso-occlusion, vascular disease and fragility haemolytic anaemia.
- 1949: Linus Pauling, using moving boundary electrophoresis, demonstrated HbS and proposed autosomal recessive inheritance.
- 1957: US biologist Vernon Ingram identified single amino acid substitution in polymerisation chain for combination of electrophoresis and chromatoigraphy.

Beta thalassaemia blood film

1965: Various forms of electrophoresis (eg paper) used in diagnosis.
- 1968: Sickling tube test with dithionite and saponin devised with electrophoresis confirmation.
- 1980s: HBB gene mapped to chromosome 11.


1990s: Automated HPLC used in newborn screening with confirmation by isoelectric focusing or capillary electrophoresis.

HbS and HbE

- 1925: First clinical report of BT in small group of children of Italian descent, by Thomas Cooley, with severe anaemia and failure to thrive.
- 1925: F Rietti showed similar findings with jaundice, splenomegaly and decreased RBC fragility.
- 1957-9: Studies by Pauling with Hb electrophoresis, and haemoglobin structure studies of Ingram and Perutz, established defect in globin polypeptide synthesis.
- 1959: Ingram with Stretton classified two forms, AT and BT, with reduced beta chains both result from various chromosomal mutations. Compound heterozygotes occur with other abnormal haemoglobins, notably HbS and HbE.

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2005: Automated HPLC used in newborn screening with confirmation by isoelectric focusing or capillary electrophoresis.
Cystic fibrosis (CF)

- 1934: Ivar Folling, a Norwegian physician, investigated two children with mental and physical disability, found excessive urine phenylketones and raised blood phenylalanine.
- 1953: George Jervis demonstrated deficiency of phenylalanine hydroxylase leads to accumulation of phenylalanine and metabolites neurotoxic to brain development.
- 1954: German physician Horst Bickel used low phenylalanine diet to improve clinical outcome.
- 1984: Locus for PKU gene detected chromosome 12, 1986 first mutation, now over 50 mutations.

Medium chain acyl-CoA dehydrogenase deficiency (MCADD)

- 1983: Cellular mechanism in CF-defects in transport of electrolytes in sweat gland and lung epithelium, latter producing sticky mucus vulnerable to bacterial infection.
- 1991: Defect identified as mutations in CF transmembrane regulator gene located on chromosome 7, notably a deletion mutation at position 508 of gene channel protein.

Phenylketonuria (PKU)

- 1968: Increased faecal albumin by US pathologist Dorothy Anderson, who developed assays to measure duodenal enzymes.
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- 1972: With technical difficulties, plasma LDL calculated by equation using total and HDL cholesterol and triglycerides results (Friedewald, 1972).
- 1991: Defect identified as mutations in CF transmembrane regulator gene located on chromosome 7, notably a deletion mutation at position 508 of gene channel protein.

Familial hypercholesterolaemia (FH)

- 1925: Studies by Norwegian pathologist Francis Harbitz and physician Carl Muller (1938) included role of raised blood cholesterol, proposed autosomal dominant inheritance.
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- 1955: Studies using ultracentrifugation and chromatography led to characterisation and classification of lipoproteins (Fredrickson, 1967), including low-density lipoprotein (LDL), which transports triglycerides and cholesterol to tissues, notably liver and adipose tissue.
- 1972: With technical difficulties, plasma LDL calculated by equation using total and HDL cholesterol and triglycerides results (Friedewald, 1972).
- 1991: Defect identified as mutations in CF transmembrane regulator gene located on chromosome 7, notably a deletion mutation at position 508 of gene channel protein.

UK National Newborn Screening Programme


- Following PKU, screening for sickle cell anaemia was added in 2005, followed by cystic fibrosis (2006) and MCADD (2008).
- 2015: Programme expanded to include homocystinuria, isovaleric acidaemia, maple syrup urine disease and glutaric aciduria type 1 using tandem mass spectrometry.