Mendelian Genetic Disorders

Martin Alexander Kennedy, *University of Otago, Christchurch, New Zealand*

Introductory article

Article Contents

Mendelian disorders occur in families with a pattern that reflects the inheritance of a single causative gene. Studies of families with conditions such as cystic fibrosis, Huntington disease and fragile X syndrome reveal a variety of inheritance patterns that reflect the nature of the underlying gene and the causative genetic lesion.

Mendelian Genetics

Mendel

In 1865 Gregor Mendel published his celebrated observations on the hybridization of pea plants. By describing the principles governing transmission of 'characters' that determined the colour and shape of peas, Mendel unwittingly laid the foundation for a coherent study of inherited human disease. From rigorous observation and mathematical analysis of pea hybridization data, Mendel deduced that if a plant is hybrid for a given character, it will produce pollen and eggs for both forms of that character, and in equal proportion. No blending or dilution of characters occurred in the offspring, but rather one or other form of each character appears in the offspring. The other form of the character may be hidden, but these 'recessive' characters may emerge in subsequent generations. These early genetics experiments, confirmed and rediscovered independently in 1900 by Carl Correns, Hugo de Vries and Erich Tschermak, demonstrated that the units of inheritance (now known as genes) are independent of one another and each is transmitted separately from parent to offspring.

The chromosomal basis of inheritance

Chromosomes are complex structures that package DNA in an orderly and consistent arrangement within the nucleus of the cell. A protein scaffold forms the basis of the chromosome, and on this is arranged the enormously long thread of DNA, intricately packaged by the action of DNA-binding proteins known as histones. The ends of the chromosome, or telomeres, are specialized structures that stabilize the DNA and prevent its degradation. Chromosomes also possess a centromere, usually visible as a constriction, that is the site at which spindle fibres bind and draw apart the paired chromosomes during cell division.

Before the end of the nineteenth century, microscopic analysis of a variety of cells led to the description of chromosomes and their behaviour in cell division. The chromosomes seemed an ideal vehicle for transmission of genetic information as described by Mendel, and by the beginning of the twentieth century this link had been established. By 1902 Walter Sutton and Theodor Boveri had independently outlined the chromosomal theory of mendelian inheritance, providing a mechanistic basis for the concepts of inheritance and setting the scene for development of cytogenetics ('cell genetics'). Cytogenetic analysis of plants and animals was an active area of research during the first half of the twentieth century, but cytogenetic methods were not applied to humans until the mid-1950s when the correct diploid number of 46 chromosomes was established.

Human genetics – from gene to genome

The first application of Mendel's ideas to human inheritance is attributed to the British physician Archibald Garrod, who in 1902 published his observations on the disease alkaptonuria. Garrod made the link between Mendel's work and a specific medical condition, deducing that alkaptonuria was inherited in a recessive manner in the families he studied. Garrod is regarded as the father of human biochemical genetics, and his ideas about inborn errors of metabolism and genetic influences on the more common diseases founded an investigative science that is a vital part of modern medicine.

By studying the inheritance of characters in the fruitfly *Drosophila*, T. H. Morgan and colleagues determined that genes are not completely independent as Mendel had thought, but that they tend to be inherited in groups. They observed that genes in the same chromosome are often transmitted together as a group, but that this was not always so and that 'crossing over' between chromosomes could occur to disrupt these linkage groups.

In 1911 E. B. Wilson mapped the colour blindness gene to the X-chromosome, and over the next 40 years about 36 X-linked traits or disorders were identified. Although some human genetic linkage groups were developed, it was not until 1968 that an autosomal assignment was made in humans (the Duffy blood group locus). Introduction of somatic cell techniques, and then molecular genetics, began to accelerate gene mapping soon after that. By the

late 1980s, a proposal to establish the entire DNA sequence of the human genome was gaining favour, and a draft of the entire 3×10^9 bp sequence was established in the year 2000. The twentieth century, then, neatly encapsulates all of the critical steps in development of human genetics. We have moved from a very basic understanding of the rules of heredity through to the completed sequence of the human genome, the ultimate gene map, in the space of 100 years.

A brief history of key events contributing to an understanding of mendelian genetic disorders is presented in **Table 1**.

Principles of Mendelian Analysis

Mendel's careful observations of pea hybridization experiments led to two key principles based on simple statistical rules (**Table 2**). These laws describe the inheritance of different forms (alleles) of each gene in all sexually reproducing organisms, and are as applicable to humans as to pea plants.

We now understand the biological principles that underpin these laws. Mendel's characters, or genes, are encoded in DNA molecules that are packaged into chromosomes. Somatic cells have two pairs of chromosomes (diploid), and these separate during meiosis such that gametes end up with only a single chromosome (haploid). This process, and the occurrence of genetic recombination during meiosis, are the mechanisms of inheritance now encapsulated in Mendel's law of segregation and law of independent assortment.

Mendel described the behaviour of characters as either dominant or recessive. A dominant character is one that is expressed in the heterozygote (an individual that inherits two different alleles of a gene). A recessive character is one that only manifests when an individual is homozygous (inherits the same two alleles of a gene). Again, a molecular understanding of biology allows us to understand why some traits are dominant and others are recessive. For example, a gene that encodes a dysfunctional protein (as in cystic fibrosis) may lead to a recessive phenotype if the remaining allele produces sufficient functional protein to compensate for the dysfunctional allele. Alternatively, a dysfunctional protein could 'poison' the protein complex or other cellular structure in which it normally operates (as in some haemoglobin diseases) and thus exert a dominant phenotype. Many traits can show partial dominance, or even codominance, contributing equally to the phenotype (as for ABO bloodgroups). It is curious, and perhaps fortunate, that all of the traits studied by Mendel showed clear dominance or recessiveness.

Pedigree Analysis

Before considering the principles of mendelian analysis in medicine it is important to recognize that Mendel chose almost ideal traits to examine. Only a small proportion of human traits and diseases have clear inheritance patterns like the texture and colour of the peas Mendel examined. Furthermore, humans are not amenable to breeding experimentation in the way that plants or animals are. In human genetic analysis we are often dealing with information about likely inheritance patterns that is incomplete or even incorrect, diseases and traits that may be exhibited at greater or lesser severity in different family members, and a range of potentially sensitive ethical, cultural and social issues that impact on the study of inherited disease.

Principles

The key to understanding mendelian inheritance in humans is to gather detailed family information, and where possible to ascertain accurately which individuals in the family are afflicted with the condition and which are not. The more extensive the pedigree data, the more likely a mendelian pattern of inheritance will be evident. The mode of inheritance of a condition will be much more apparent in a multigeneration, extended family tree than in cases where only a small number of members are known. Identification of the genes underlying many mendelian conditions by linkage mapping and reverse genetics often depends on spectacularly large and informative pedigrees, that contain multiple affected and unaffected individuals spread across several generations. The best way of recording family information is to construct a family tree using a standard set of symbols to indicate the clinical state of individuals and their relationship to one another (**Figure 1**).

The occurrence of a disease in a family may occur in several main patterns or modes. These are grouped according to whether the trait is sex specific (generally X-linked) or not (autosomal). Autosomal dominant disorders occur in both males and females, often affecting many individuals throughout the pedigree (**Figure 2a**). Affected individuals are heterozygous for the gene – in other words, inheritance of one copy of the affected gene is sufficient to cause disease. The risk of transmission of such a condition from affected individuals is 50%. This is the most common pattern of inheritance observed for mendelian disorders. Another common mode of inheritance is autosomal recessive, which occurs when two healthy individuals are carriers for the same recessive gene (**Figure 2b**). Most autosomal recessive genes are rare, and carriers usually will have no family history. The conditions often only occur within the children from one relationship. The risk of transmission of the disorder is 25%, and half of the unaffected offspring will be carriers for the gene. Consanguinity (relatedness between parents) is a risk

Table 1 Key events in the research history of mendelian genetic disorders

Year	Event
1865	Mendel's publication of the paper 'Versuche über Pflanzen-Hybriden' (Experiments in Plant Hybridization)
1900	Mendel's work independently rediscovered by Correns, De Vries and Tschermak
1902	Garrod published his work on alkaptonuria and introduced Mendel's concepts to human biology
1902	Sutton and Boveri proposed the chromosome theory of Mendelism
circa 1909	Johansson proposed the term 'gene'
1910	Morgan's experiments with fruitflies revealed that some genetically determined traits are sex linked and confirmed that genes determining these traits reside on chromosomes
1911	von Dungern and Hirschfield proved that human ABO blood types are inherited
1911	Wilson assigned the colour blindness gene to the human X-chromosome
1944	Experiments with pneumococcus bacteria by Avery, MacLeod and McCarty proved that DNA is the hereditary material
1949	Pauling and colleagues described the molecular basis of sickle cell anaemia
1953	Structure of the DNA molecule determined by Watson and Crick
1956	Correct human diploid chromosome number of 46 established by Tjio and Levan, and Ford and Hamerton
1968	First autosomal location of a gene described by Donahue, for Duffy blood group locus
1970	Development of somatic cell methods allowed chromosomal mapping of numerous human genes
1973	Cohen and Boyer carried out the first recombinant DNA experiment
1975	Edwin Southern developed the Southern blot for visualizing gene fragments
1976	First prenatal DNA diagnosis of sickle cell anaemia
1977	Different methods for DNA sequencing established by Sanger, and Maxam and Gilbert
1983	Genetic marker for Huntington disease identified on chromosome 4 by Gusella and colleagues
1985	Development of polymerase chain reaction by Mullis and colleagues
1986	Isolation of gene for chronic granulomatous disease based on chromosomal position alone (positional cloning)
1987	First linkage map of human chromosomes developed
1989	Cystic fibrosis gene (*CFTR*) isolated
1990	Formal launch of the international Human Genome Project
1991	Identification of the unstable trinucleotide repeat mutation responsible for fragile X syndrome
1992	Detailed linkage map of the human genome published
1993	Detailed physical map of the human genome published
1993	Huntington disease gene isolated by an international research consortium
1995	A human genome 'directory' of expressed sequence tags (ESTs) developed
1996	Detailed human gene map published (16 000 genes)
1996	Genome sequence of the yeast *Saccharomyces cerevisiae* completed
1998	Genome sequence of the worm *Caenorhabditis elegans* completed
1999	First DNA sequence of a human chromosome (22)
2000	Genome sequence of the fruitfly *Drosophila melanogaster* completed
2000	Draft sequence of human genome completed

Table 2 Mendel's laws of inheritance

Law of segregation	The reproductive cells of hybrids randomly transmit either one or the other of paired parental characters to their offspring. The characters (or genes, as we now know them) are unchanged during passage through each generation
Law of independence	When individuals with different alleles of more than one gene are crossed, alleles of each gene are assorted into the offspring (segregated) independently of the others. This law applies only when there is no linkage between the genes

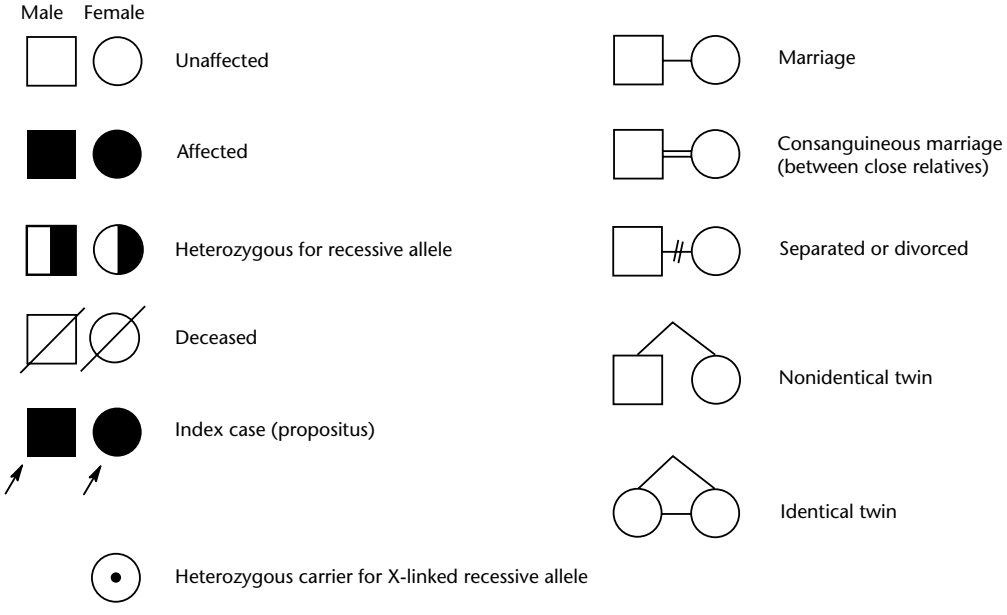

Figure 1 Pedigree symbols. A subset of symbols commonly used to illustrate a family tree, incorporating clinical details and the nature of specific relationships.

factor for autosomal recessive illness because both parents are more likely to carry the same rare recessive alleles, inherited from a common ancestor. It is salient to note that all individuals probably carry a large number of rare recessive alleles as a result of the natural genetic diversity present within the human population.

X-linked recessive conditions generally occur only in males (**Figure 2c**). Females are carriers, because their second X-chromosome provides a normal allele, but males who inherit the recessive gene on their sole X-chromosome will be affected. Occasionally females will show a degree of affectedness. Female carriers will transmit the gene to all of their sons (because they inherit only their mother's X-chromosome) and to half their daughters. Affected males will transmit the gene to all their daughters, all of whom will therefore be carriers. Sons of affected males receive only their father's Y-chromosome and will not inherit the disease.

Very rare examples exist of inheritance in X-linked dominant (e.g. incontinentia pigmenti) and Y-linked fashions. Furthermore, a number of (non-mendelian) inherited conditions are attributed to mutations in mitochondrial DNA, and these often show maternal inheritance that reflects the inheritance pattern of mitochondria (human eggs but not sperm contribute mitochondria to the embryo).

Accurate clinical investigation and careful description of the symptoms of affected family members is an important part of investigations aimed at discerning a condition with genetic origins. The complexities and variety of genetic disorders has led to the development of medical genetics as a specialized area of medicine, one in which the focus is on

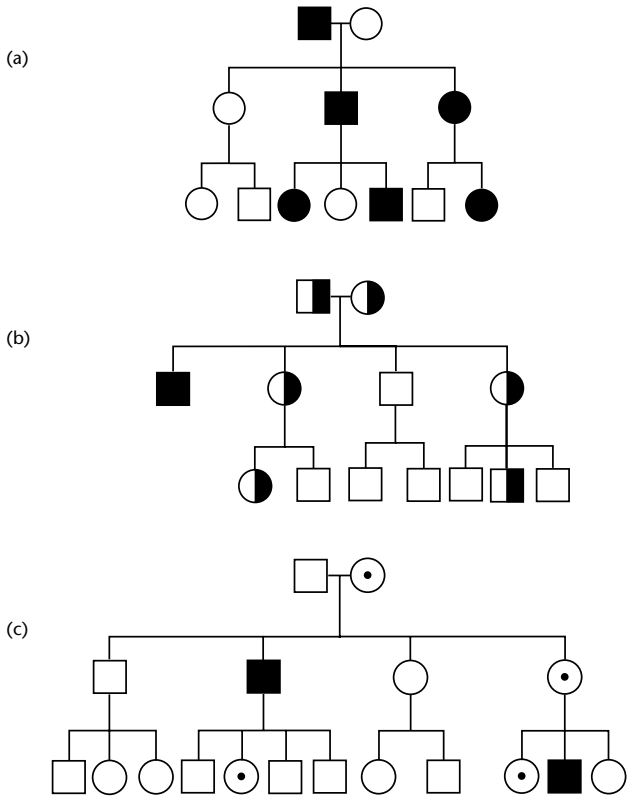

Figure 2 Inheritance patterns of mendelian disorders: (a) autosomal recessive, (b) autosomal dominant, (c) X-linked recessive.

prevention or avoidance of disease. A key aspect of medical genetics is the provision of accurate, up to date guidance for families by way of genetic counselling. In most centres, graduate trained genetic counsellors interact with family members to construct pedigrees and provide counselling in conjunction with the clinically trained medical geneticist, although it is not uncommon for these roles to be combined.

Examples of Human Mendelian Traits

Mendelian genetic disorders contribute very significantly to human suffering. Some 2–5% of newborns are affected by genetic disorders or congenital malformations, and these conditions are a major cause of death during childhood. About one third of admissions to paediatric hospital wards and about 10% of all adult hospital admissions are attributed to mendelian disorders. Many of these diseases are chronic in nature, making them a significant financial burden on healthcare systems, and exacting a substantial emotional toll on families and caregivers.

In addition to those inherited disorders that exhibit a mendelian pattern of inheritance, many common disorders have a strong genetic component. These disorders are referred to as complex, polygenic or multifactorial conditions, and they result from the combined action of multiple genes and environmental factors. Coronary heart disease, diabetes, asthma, bipolar disorder (manic depression) and depression are examples of polygenic illnesses. Because multiple independently segregating genes make variable contributions to such conditions, often in conjunction with environmental factors, such diseases do not occur in mendelian patterns.

It is important to stress that 'disease genes' are defective or variant genes that normally perform some important life function. It is the loss of this normal function or acquisition of a new and abnormal function that manifests as a disease phenotype, and leads to the common description of such genes as 'disease genes'. In addition to outright mutations, many genes also exist in more than one variant form, with subtle DNA sequence differences. Mutations are generally defined as variants that occur in the population with a frequency of less than 1%, and polymorphisms as those variants that occur at a frequency of greater than 1%. The distinction between the mutant allele (or disease gene) and a normal variant is not always clear, and appearance of disease symptoms in individuals with certain variant alleles can result from the combined influence of other genetic or environmental factors.

Normal variants

The human phenotype is a pastiche of interacting traits that have mixed contributions of genetic and environmental determinants. Although awareness of genetic disease is heightened because of the medical impact of such conditions, many traits that do not cause disease exhibit mendelian inheritance. **Table 3** lists normal variants that show mendelian inheritance.

Gilbert syndrome is generally a relatively benign condition that can lead to mild jaundice. Its inclusion in this table highlights the sometimes blurred distinction between normal variants and disease. Often, normal variants will become medically relevant given certain combinations of environmental and other genetic factors – such as the mutation of CCR5 that confers resistance to HIV infection.

Diseases

Online Mendelian Inheritance in Man (OMIM), an authoritative database of inherited human conditions, identifies some 4000 mendelian disorders. Some of the better known conditions are listed in **Table 4**. Frequencies given in this table are very approximate, and can vary markedly depending on ethnicity. Where the illness is

Table 3 Common normal variants with Mendelian inheritance

Variant	Inheritance mode	Population allele frequencies	Nature of underlying gene
ABO blood groups	A and B are inherited as codominant traits; O is recessive to both	Three allelic variants of one gene, present at about 30%, 10% and 60% for A, B and O respectively	A glycosyltransferase that modifies a red blood cell surface antigen
Dizygotic twinning	Autosomal dominant with low penetrance	4–30%	Unknown
Resistance to human immunodeficiency virus (HIV) infection	Recessive	5–13% (Caucasian)	CCR5 chemokine receptor
Ability to taste phenylthiocarbamide	Autosomal dominant	70%	Unknown
Gilbert syndrome (hyperbilirubinaemia I)	Autosomal dominant	5%	UDP glucuronosyltransferase

predominant in a particular ethnic group, this is indicated. Although birth frequencies are cited here, for some conditions the intervention of carrier screening and prenatal DNA diagnosis is reducing these frequencies significantly. Examples of successful reductions in genetic disease through this approach are Tay–Sachs in the Jewish community and β-thalassaemia in some Mediterranean areas.

Recurrence Risks

Understanding the nature and mode of inheritance of a genetic condition is crucial in estimating the recurrence risk of that condition in a family. Determining the mode of transmission depends on an accurate diagnosis and the careful ascertainment of affected family members.

Unfortunately, several factors can conspire to render diagnosis of a genetic disease difficult. Many mendelian conditions are genetically heterogeneous, that is they may have similar manifestations due to entirely different genetic causes. This means that even when a condition is accurately diagnosed, the mode of inheritance operating in a given family may not be immediately clear. Additional complexity derives from the variable expressivity (severity) of many traits, and incomplete penetrance (failure of the mutant gene to cause a disease phenotype). A proportion of inherited diseases do not manifest before a certain age, and this age of onset can often be variable, further confounding attempts to establish inheritance patterns. Occasionally, new mutations that give rise to disease can occur. These *de novo* mutations cause sporadic cases of disease, and the risk of future cases in the same family is negligible (although individuals so affected may pass the mutation on to their offspring). Further complexity can derive from the nature of the underlying mutation. The unstable trinucleotide repeat mutations found in fragile X syndrome, Huntington disease and several other inherited neurological disorders illustrate this problem.

With autosomal dominant traits, the risk for each child of an affected parent is 1 in 2, provided the disorder is highly penetrant. However, many dominant traits show variable penetrance, and the age of onset can influence occurrence of the disease (as with Huntington disease). This kind of conditional information about a particular disease can be combined with pedigree data to calculate recurrence risks using the probability calculations known as Baye's theorem.

For autosomal recessive traits, the probability of an affected (homozygous) child, when both parents are carriers for a given trait or condition, is 25%. Healthy siblings of carrier parents have a 67% risk of being carriers (not 75%, as homozygous mutant state can be excluded in a healthy individual). The chance of an unaffected sibling subsequently giving rise to an affected child will be related to the frequency of that gene in the general population.

In X-linked pedigrees, sons of female carriers are at 50% risk of being affected (assuming high penetrance) and daughters are at 50% risk of being carriers. Because males can transmit only their single X-chromosome to daughters, all daughters of affected males will be obligate carriers (100% risk). Sons of affected males receive their father's Y-chromosome, and therefore have a risk equivalent to the population risk of the disorder. The assessment of nonobligate female carriers presents a problem in such families. Occasionally, biochemical tests will be available for carrier detection, but these are rarely unequivocal because of random X-inactivation in female cells. In these circumstances, Baye's theorum may be applied to gain a better estimate of risk.

Assessment of recurrence risks for couples who have given birth to a child affected with a mendelian disorder is

Table 4 Common mendelian disorders

	Approximate frequency per 100 000 births	Gene name	Nature of underlying gene product
Autosomal recessive disorders			
β-Thalassaemia	400 (some Mediterranean areas, prior to screening programmes)	*HBB*	β-Globin
Haemochromatosis	250	*HFE*	Major histocompatibility complex class I protein involved in iron metabolism
Gaucher disease (type I)	250 (Ashkenazi Jews)	*GBA*	Glucocerebrosidase
Cystic fibrosis	50	*CFTR*	Epithelial chloride channel
Sickle cell disease	40 (Blacks)	*HBB*	β-Globin
Tay–Sachs disease	30 (Ashkenazi Jews)	*HEXA*	Hexosaminidase A
Phenylketonuria	12	*PAH*	Phenylalanine hydrolyase, an enzyme involved in phenylalanine metabolism
Autosomal dominant disorders			
Familial hypercholesterolaemia	200	*LDLR*	Low density lipoprotein receptor
Adult polycystic kidney disease	100	*PKD1*	Polycystin
Huntington disease	50	*HD*	Huntingtin
Neurofibromatosis type I	30	*NF1*	NF1 tumour suppressor gene
Myotonic dystrophy	12	*DM*	Myotonin
Tuberous sclerosis	10	*TSC1*	Tuberin
Achondroplasia	2	*FGFR3*	Fibroblast growth factor receptor
X-linked disorders[a]			
Fragile X syndrome	40	*FMR1*	RNA-binding protein
Duchenne muscular dystrophy	30	*DMD*	Dystrophin
Haemophilia A	10	*F8C*	Blood coagulation factor VIII
Lesch–Nyhan syndrome	10	*HPRT1*	Hypoxanthine guanine ribosyltransferase 1
Adrenoleukodystrophy	5	*ALDP*	A membrane transporter molecule located in the peroxisome

[a]Frequency given per 100 000 male births.

increasingly aided by access to a growing range of DNA tests. As well as guiding diagnosis and allowing identification of carriers, DNA tests can often be applied prenatally or presymptomatically (for late-onset disease). The completion of the human genome project and development of new methods for mass screening of DNA sequences (such as DNA microarrays) offer considerable promise for the enhanced application of DNA tests in the diagnosis and risk assessment of many mendelian disorders.

Further Reading

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