

children to have decreased over time. It appears likely that this decrease is in response to the introduction of legislation encouraging the use of unleaded petrol, the general lowering of paint-lead concentration over the decades and community awareness.

3.2 Genetic factors

Genetic factors play an important role in human health and disease. An individual's genetic make-up (genome) sets the main features and boundaries within which life is to be experienced. It also provides the blueprint for how the human body interacts with the environment. In addition, the genome is programmed to protect its own molecular structure and to repair any damage caused to it by environmental agents.

Human health also depends on the genetics of other life forms, especially organisms that infect humans. Therefore, human health should be seen as the result of our environment (including the genetics of other life forms), our genes, and the interaction between the two.

The spectrum of genetic diseases

Genetic factors contribute to diseases at various levels and in many different ways (Khoury 1996). A study in British Columbia, Canada, suggests that prior to age 25, more than 5% of all live-born individuals will be affected by a disease that primarily has a genetic component (Baird et al. 1988). Separate estimates put the proportion at about 10% when measured for recurrent genetic diseases over the whole lifetime (UNEP & ICPEMC 1992).

Broadly, three major types of genetic diseases/disorders are identified. (For explanation of various genetic terms and a description of the organisation of the human genetic material, see Box 3.2.) These are:

- single gene (monogenic) disorders, genetic defects that result from an alteration or a change (mutation) in the structure of the gene and can be traced through families and clearly defined;
- chromosomal abnormalities, caused by structural changes in the chromosomes or the gain or loss of whole chromosomes (or parts of chromosomes), some of which can be related to specific clinical syndromes; and
- multifactorial diseases, which seem to have a strong genetic component but are expressed following interaction of genes with environmental factors such as diet, chemical exposure and lifestyle.

About 2% of the population will have a monogenic problem or condition, with some of the problems showing up at birth and others showing up later in life. Common examples of monogenic disorders are muscular dystrophy, cystic fibrosis and haemophilia. Limited data are available to generate reliable estimates of the prevalence of these problems in Australia.

The incidence of chromosomal abnormalities or malformations among live-born infants is estimated to be at least 0.5%. In addition to well-defined clinical syndromes, e.g. Down syndrome, chromosomal abnormalities also account for more than 20% of spontaneous abortions (Riccardi 1977). Chromosomal abnormalities represented 13% of all notified

Box 3.2: Human genetic organisation

It is estimated that each human cell has at least 70,000 different types of genes. Genes, whose main function is to code for various proteins, are regions of deoxyribonucleic acid (DNA) that operate as units of heredity. The total set of genes and its organisation is called a genome.

The genetic information is stored in the ordered sequence of four types of nucleotides (building blocks of nucleic acids) that are linked together to form DNA molecules. There are some 6 billion nucleotides in each human cell. This extensive information system is packaged up into 46 chromosomes (23 pairs) within the nucleus of the cell, with genes situated at specific sites or loci on the chromosomes.

For every pair of chromosomes, one chromosome comes from one parent and the second from the other parent. These paired chromosomes are separated again at the time of formation of sperm and ova.

While broadly similar in underlying structure, i.e. the ordered sequence of their nucleotides, individual genes on each member of a pair of chromosomes may exist in alternative forms, called alleles. Examples of this variation are alleles of the ABO gene, located on Chromosome 9, that lead to the formation of A, B and O blood groups.

This existence of many different forms of the same gene in the population – although an individual may carry no more than two alleles for any one gene – in concert with various chromosomal combinations (possible from a set of 23 pairs of chromosomes) is the source of much genetic variation. In addition, maternally inherited genetic information contained in mitochondria, components of cells that are important in various cellular activities, adds to the genetic complexity.

An international effort, the Human Genome Project, is currently under way to map the location of each gene on the chromosomes along with their nucleotide sequence in order to understand the function of various genes (Box 3.3, page 140).

Genetic terms

Cell: Cells are basic structural units of organisms, made up of various membranes, organelles and cytoplasm. The genetic material (DNA) is contained within the nucleus of the cell as well as its mitochondria.

Chromosome: A very long strand of DNA supported by proteins. In each human cell, except the egg and sperm cells, there are 46 chromosomes (arranged in 23 pairs, with one member of a pair inherited from one parent) that vary in size and structure.

Chromosomal abnormalities: An anomaly resulting from a change in the number or structure of the chromosomes. Chromosomal anomalies may occur either during the production of the egg or sperm, or at conception, and may even transmit (or be inherited) over generations.

DNA (deoxyribonucleic acid): The molecule in which genetic information is stored; composed of two complementary chains of nucleotides (its basic unit) wound in a double helix.

Gene: The basic unit of heredity; a sequence of nucleotides that codes for a peptide chain (assembled into proteins), along with other intermediary genetic molecules such as ribonucleic acid (RNA).

Box 3.3: The Human Genome Project

Initiated in the United States in 1988 – the project is now an international research effort – the Human Genome Project (HGP) plans to generate genetic maps of all human chromosomes by 2005 (Trent 1999). This includes the location of various genes on the chromosomes and determination of their ordered nucleotide sequence.

Several useful outcomes with relevance to human health are expected from the project, including:

- *knowledge about the structure of various genes and their function;*
- *improved diagnosis and predictive testing for genetic disorders; and*
- *new treatments for genetic disorders, including gene therapy.*

Before the advent of HGP, only 4–6% of all human genes had been identified and their function partially described. These genes could at best be used as markers of various diseases. Availability of new molecular techniques, and a concerted international effort, has now ensured that the full sequence of the human genome, covering more than 70,000 genes, will soon become available (Foote 1999).

There have been many spin-offs from the HGP already, including the development of:

- *new technologies for microtesting, e.g. automated DNA testing of relatively small samples of tissue or blood, with a variety of forensic, diagnostic, screening and biological applications; and*
- *sophisticated methods to link vast arrays of data, originally developed to determine locational relationships between different genes, which may prove highly suitable for linking various administrative collections.*

congenital malformations in Australia in 1996, with an incidence rate of about 228 per 100,000 live births (Table 3.1) (AIHW NPSU: Hurst et al. 1999). In addition to chromosomal abnormalities, genetic contribution to congenital malformations such as spina bifida, congenital heart disease, and cleft lip/cleft palate is also high (Weatherall 1993).

The health impact of various genetic disorders mentioned above is small compared with their role in common diseases, several of which are multifactorial in origin. High blood pressure, asthma, diabetes and schizophrenia, common chronic diseases whose population impacts are known to be linked to environmental and lifestyle factors, also have large genetic components (Schull & Hanis 1990). However, the involvement of many genes in these diseases, each with an additive effect, makes it difficult to quantify the extent of the genetic contribution (Nora et al. 1991).

In addition to the diseases that result from the abnormal functioning of the genes that people have inherited from their parents, many genetic diseases result from abnormalities of the genetic machinery of cells that manages genetic and cellular processes (UNEP & ICPEMC 1992). Many forms of cancer which result from acquired abnormalities of the genetic machinery in body cells are prime examples of such changes. With the exception of a few rare childhood forms, cancer is now considered to result from mutations acquired during the lifetime. These changes affect only the body

cells, and are not passed on unless they affect the DNA of the egg or sperm. However, it appears that we may inherit genes that make us more likely to develop a particular cancer following their mutation in body cells (Weatherall 1993).

Table 3.1: Notifications of chromosomal malformations, 1996

ICD-9 code	Chromosomal abnormality	Number	Incidence (per 100,000 births)
758.0	Trisomy 21 (Down syndrome)	312	121
758.1	Trisomy 13 (Patau's syndrome)	25	10
758.2	Trisomy 18 (Edward's syndrome)	56	22
758.3	Autosomal deletion	46	18
758.5	Other autosomal anomalies	76	30
758.6	Turner's syndrome	28	11
758.7	Klinefelter's syndrome	17	07
758.8	Sex chromosome anomalies	25	10
758.9	Unspecified	2	1
758	Total	587	228

Note: All States and Territories notify fetuses and infants with major congenital malformations, including chromosomal abnormalities, to the AIHW National Perinatal Statistics Unit which provides a national monitoring system.

Source: AIHW NPSU: Hurst et al. 1999.

Genetic resistance to disease

Examples of genetic diseases given above reflect mutational changes in the genome that can damage health. However, not all mutations are harmful. Generally, along with other mechanisms, mutations lead to the generation of significant genetic diversity that is essential to our survival as a species.

The wide range of human leukocyte antigens (HLA), sentries that help differentiate self from non-self (see immunological health in chapter 2 for immune mechanisms), are good examples of this type of variation. The HLA diversity ensures that there is enough variation among individuals in a population to resist new diseases.

Other forms of genetic resistance to disease include our innate ability to counter various infections and environmental hazards. Genetic traits such as sickle cell haemoglobin and ovalocytosis, which resist infection by the malarial parasite *Plasmodium* or stunt its growth inside the cell, are good examples of innate genetic resistance. However, individuals differ markedly in their ability to resist infection (Wakelin 1988), and this changes with age (Anderson & May 1991). Other environmental hazards are also handled variously by individuals using many different genetic mechanisms.

The genetic preparedness of the human host to resist disease is also influenced by the genetic ability of the invading organism to bypass the resistance mechanisms. Quite often, human parasites evolve in step with the disease-resistance mechanisms of the host. Host-parasite interactions therefore present a fascinating example of how environmental interactions between species influence health and disease processes. Undoubtedly, many of the genetic traits we observe today, in either host or parasite, are results of this co-evolution.

A variety of determinants, however, may influence our inherent resistance to disease (Table 3.2). These include age, nutrition and socioeconomic factors. Variation in the capacity and mechanism for DNA repair may also lead to differences in the survival of harmful mutations. The genetic complexity of the invading organisms, as mentioned earlier, is another important factor.

However, this variation in response to infectious and other environmental agents depends on the degree of exposure. If the exposure is high, such as a highly virulent strain of a virus, then a large proportion of the population may be overwhelmed by the exposure irrespective of genetic resistance.

Table 3.2: Factors influencing genetic susceptibility to disease

Factor	Mechanisms and outcomes
Age	Older people are more vulnerable to disease than younger people because of the decline in their ability to handle environmental damage to DNA and the accumulation of harmful mutations over time.
Nutrition	Diet can have a major influence on DNA mutation and cancer promotion. Some dietary factors may lead to certain genetic changes that in turn lead to cancers.
Socioeconomic factors	No direct relationship has been identified between socioeconomic factors and increases in genetic risks. However, poor diet, inadequate health care, infectious diseases, and exposure to environmental agents such as tobacco smoke can increase an individual's susceptibility to agents that cause genetic change.
Genetic complexity of parasites	Several parasitic organisms have evolved to circumvent the defence mechanisms of the human host, e.g. drug resistance, the ability to mutate at a faster rate, increased virulence and other evading mechanisms.
Degree of exposure	There is an upper limit to the ability of organisms to survive in a hostile environment. For example, extensive exposure to agents such as sunlight increases risks of skin cancer and may override all DNA repair capacities.
DNA repair mechanisms	Damaged capacity to repair DNA may allow new mutations to survive. This repair capacity varies between individuals and between different tissues of the same individual.
Evolutionary maladaptations	Several genetic traits such as sickle cell haemoglobin and thalassemias have evolved to help individuals and populations adapt to their environment. However, when the affected individuals live in other environments, the disadvantages may outweigh any special advantage.

Note: Based on list given in UNEP & ICPEMC (1992).

Prevention of genetic diseases

A common perception is that, since the genetic inheritance of an individual or a population is unchangeable, its outcomes cannot be significantly altered. However, the latest advances in genetic testing may remedy this problem partly through disease prevention. A series of tests for prenatal screening of chromosomal abnormalities and some single-gene disorders is now available. A variety of gene therapy techniques has also been developed to manipulate naturally occurring genes and introduce them into the body to combat disease. Also, given the role of genetic factors in influencing an individual's response to various diseases, gene technology has the potential to contribute to the prevention of these diseases by identifying those most at risk.