GENES AND CHROMOSOMES

PART 4 – GENETIC ANOMALIES AND DISORDERS

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Genetic disorders are caused by anomalies in genes or chromosomes. These can range from a small alteration in a single gene to the addition or deletion of entire chromosomes.

CHROMOSOME DISORDERS
Chromosomal anomalies account for a large proportion of spontaneous pregnancy loss and childhood disability. They may be due to the presence of an extra chromosome, or a missing or broken chromosome, and occur when eggs or sperm are forming. Chromosome anomalies are present in at least 10% of sperm cells and 25% of mature egg cells; 15–20% of pregnancies end in spontaneous miscarriage and, of these, 50% have a chromosome anomaly (Turnpenny and Ellard, 2007).

If a zygote forms from a chromosomally abnormal egg or sperm cell, and survives, the chromosome error can perpetuate each time the cells divide. Thus, as the embryo grows, the added or missing genetic information can translate into a wide range of abnormal body structures or functions. Some of the most common conditions involving chromosome anomalies result from gaining or losing an extra sex chromosome, or may involve the non-sex chromosomes, the autosomes (chromosomes 1–22).

AUTOSOMAL DISORDERS

Down’s syndrome
The chance of conceiving a child with a chromosomal inheritance error increases with the mother’s age, as is the case with Down’s syndrome. The condition is due to the presence of an extra chromosome (21), and is also known as trisomy 21.

Although the vast majority of individuals with Down’s syndrome have three copies of the entire chromosome (and all of the genes it contains), some individuals have smaller chromosome portions triplicated (due to a translocation). Such portions contain the Down’s Syndrome Critical Region (DSCR) and it is believed that these extra genes are responsible for the major features of this disease.

The most common clinical feature of Down’s syndrome in the newborn period is severe hypotonia (low muscle tone). Others include congenital cardiac abnormalities, brachycephaly (a disproportionately wide head) and the presence of single palmar creases (Fig 1) found in 50% of people with the syndrome, compared with 2–3% of the general population. Severe cardiac anomaly leads to early death in 15–20% of people with Down’s syndrome, otherwise the average life expectancy is 50–60 years.

Down’s syndrome can exist in a mosaic form (1–2% of cases), and children with this form will be less severely affected.

DiGeorge syndrome
This results from a micro-deletion of part of chromosome 22 and affects one in 4,000 births in the UK. Since several genes are lost it can cause a variety of problems:
- Heart malformations;
- Failure of parathyroid glands to develop;
- Thymic hyperplasia;
- Schizophrenia-like episodes in adult life (Turnpenny and Ellard, 2007).

Williams syndrome
This affects approximately one in 20,000 births. Individuals have part of chromosome 7 missing which contains the gene coding for the production of elastin. This affects blood vessels, muscles and ligaments. Its features include an ‘elfin-like’ face, and a degree of learning disability with problems in coordination, balance and joint movement.

Children with Williams syndrome are often of a low birth weight and will show a delay in attaining developmental milestones. Other typical problems include hypercalcaemia and a hoarseness of voice, associated with the missing elastin gene impacting on the connective tissue of the vocal cords (Morris et al, 1993). Another feature is hyperacusis – an aversion to loud and unexpected sounds.

SEX CHROMOSOME DISORDERS

Klinefelters syndrome
Klinefelters syndrome is due to the presence of an extra X chromosome resulting in an individual with 47 (XXY) chromosomes. Young boys with Klinefelters may have clumsiness or mild learning disabilities. Adult males tend to have long lower limbs, and are taller than...
average. Around 30% have moderately severe gynaecomastia (enlarged breasts) (Fig 2a), and affected males are infertile.

**Turner syndrome**

Turner syndrome is the presence of only one X chromosome (45, X) in females. At birth, many babies with Turner syndrome look normal, while some have puffy extremities (lymphoedema) or neck webbing.

The main medical problems associated with Turner syndrome are short stature and non-functioning ovaries. Other clinical presentations may include a low hairline, droopy eyelids and an absence of female sexual characteristics (Fig 2b). However, the majority of girls and women with Turner syndrome lead normal and healthy lives.

**SINGLE-GENE DISORDERS**

Over 10,000 single-gene disorders have been identified, affecting 1–2% of the population. Although mutational changes in DNA are central to the evolution of the diverse species of plant and animal life, in highly evolved species, such as man, many mutations are harmful.

Most mutations are due to copying errors as DNA is copied repeatedly when cells divide, giving plenty of opportunities for mistakes or mutations. These can cause errors in amino acid sequence, creating partially or completely non-functional proteins. More serious mutations involve the addition or deletion of a single nucleotide or sequence of nucleotides.

The other major cause of mutational changes in DNA is environmental, such as cigarette smoke or ultraviolet light, which can damage the DNA in cells exposed to them.

**Cystic fibrosis**

It is estimated that one in 25 people carry the recessive defective gene (on autosomal chromosome 7) for cystic fibrosis (CF). If two carriers have a baby, there is a 25% risk of it having CF. Incidence of CF in Western Europe is approximately one in 2,000 (Turnpenny and Ellard, 2007). The faulty gene causing CF codes for the production of a protein which controls movement of salt and water in and out of cells. This results in too much salt and too little water passing into cells and body secretions. Secretions become thick and sticky, clogging up airways and passageways, making them ineffective and prone to infection. Most commonly, chronic lung disease leads to heart failure.

Thick mucus also blocks the pancreatic ducts (in 85% of patients), obstructing the release of pancreatic enzymes needed for digestion. This results in malabsorption and production of large, bulky, fatty stools.

At present, life expectancy of people with CF is 30–40 years.

**Huntington’s disease**

Also known as Huntington’s chorea, this affects one in 18,000 people in the UK. It is caused by a mutation of a dominant gene on chromosome 4, which codes for a protein called Huntington. Due to its pattern of autosomal dominance, an affected parent has a 50% chance of having an affected child. The condition leads to the slow, progressive death of cells within the central nervous system. Symptoms usually appear between the ages of 30 and 50, although in 5–10% of cases they occur before the age of 20. Early signs include clumsiness, lack of concentration, memory lapses and uncontrollable muscular movements. Later, severe involuntary movements and speech and swallowing difficulties develop. Weight loss is common and, in the latter stages of the disease, full nursing care is needed.

**SEX-LINKED DISORDERS**

These are caused by a mutation on the sex chromosomes (X-linked or Y-linked). The most common are X-linked recessive conditions, where females are carriers and there is a 50% chance male offspring will be affected. Such is the case for disorders such as colour blindness, or the haemophilias.

**MULTI-FACTORIAL INHERITANCE**

Many common conditions are caused by a combination of inherited genetic mutations and other factors, such as environmental components. These include diabetes, rheumatoid arthritis and coronary heart disease. Developments in genetics and bioinformatics, alongside large population studies, have made it more possible to dissect out the genetic component of many complex diseases (Montague et al, 2005), and assess an individual’s risk of acquiring a disease.

**REFERENCES**

