

# Part 2

Diagnostic perspective  
in general practice

# 19

## Genetic disorders

People love to oversimplify genetics, saying we have a ‘gene for cancer’ or a ‘gene for diabetes’. But the fact is, genes determine only so much. Identical twins are identical genomes, yet one may develop juvenile diabetes and the other typically doesn’t. Understanding the role of genes should help pinpoint environmental factors...The genome is a history book showing the entire 6 billion-member human species traces back 7000 generations to a tiny founding population of some 60 000 people. Our species has only a modest amount of genetic variation—the DNA of any two humans is 99.9% identical.

Eric Lander, the Human Genome Project, 3 July 2000<sup>1</sup>

The family doctor has an important role to play in the exciting and rapidly expanding world of medical genetics. The role includes routine diagnosis, early detection, and community and ethical guidance. Virtually all of the three billion nucleotides of the human genome have been sequenced and the knowledge of their organisation into the known 30 000–35 000 (possibly 100 000) functional units or genes continues to become more sophisticated.<sup>2</sup>

The genome project has commenced mapping out ‘single nucleotide polymorphisms’ (SNPs) as signposts throughout the genome to assist in locating disease-associated genes and studying variations between individuals.<sup>3</sup> Any two unrelated individuals differ by one base per every thousand or so—these as SNPs—and it is believed that SNPs are the cause of the most common genetic disorders. If we carry the wrong set of SNPs, we can be predisposed to various diseases.

Genetic testing is now freely available for most common hereditary disorders, such as the *HFE* genes for haemochromatosis, presymptomatic DNA tests are available for the hereditary neurological disorders, such as Huntington’s disease, and predictive DNA testing is available for some forms of hereditary cancer, such as breast and colon cancer, and in the future for cardiovascular disease and diabetes.<sup>4</sup> Also in the future, pharmacogenetics, which predicts genetically determined responses to pharmaceuticals, will greatly assist rational prescribing, and gene therapy is a futuristic treatment modality.

A summary of the prevalence of genetic disease is present in Table 19.1.<sup>5</sup>

**Table 19.1** Prevalence of genetic disease (after Kingston)<sup>5</sup>

Type of genetic disease	Estimated prevalence per 1000 population
Single gene	
Autosomal dominant	2–10
Autosomal recessive	2
X-linked recessive	1–2
Chromosomal abnormalities	6–7
Common disorders with appreciable genetic component	7–10
Congenital malformations	20
<b>Total</b>	<b>38–51</b>

### Key facts and checkpoints

- All people carry a small number of recessive genes, which are carried asymptotically.
- The background risk that any couple will bear a child with a birth defect is about 4%. This risk is doubled for a first cousin (consanguineous) couple.<sup>6</sup> Although the majority of cancers are not inherited, some people carry inherited genetic mutations for certain cancers, notably breast and ovarian (linked), colorectal and others on a lesser scale, such as prostate and melanoma.

- General practitioners should look out for a family history of cancer, including the number of people with cancer on both sides of the family and the age and onset of primary cancers.
- A general practitioner caring for 1000 patients would expect to have 15–17 patients with a hereditary cancer predisposition.
- As genetic testing becomes more accessible it is prudent to be aware of the psychological consequences to patients of predictive or presymptomatic testing.
- Prenatal screening and testing of genetic disorders is also a reality, especially for Down syndrome, foetal abnormalities and the haemoglobinopathies. Once again, careful selection, screening and counselling is important.
- Genetic services and familial cancer clinics provide an excellent service for referral, especially for counselling expertise and advice about appropriate services and genetic testing.
- Gene therapy, which is the genetic modification of cells to produce a therapeutic effect, is a promising futuristic treatment for inherited or acquired genetic disorders. Basically, it involves using a vector such as a virus to deliver a therapeutic gene to the target cells.

### Selected terminology

*Allele* One of two different genes that occupy corresponding positions (loci) on paired (homologous) chromosomes (from the Greek *allelon*, of one another).

*Haploid* Normal state of genetics, containing one set of chromosomes ( $n$ ).

*Diploid* Normal state of somatic cells, containing two haploid sets of chromosomes ( $2n$ ).

*Anuploid* Chromosomal number that is not an exact multiple of the haploid set (e.g.  $2n - 1$  or  $2n + 1$ ).

*Translocation* An exchange of chromosomal material between two non-homologous chromosomes.

*Phenotype* The physical characteristics of a person (symptoms and signs) that reflect his or her genetic make-up and environmental influence.

*Genotype* The genetic make-up, that is, the information content inscribed on the DNA present in every cell of the body.

*Gene* The total DNA carried by the reproductive cell.

*Genome* All the DNA in an organism, including its genes.

*Chromosomes* The carriers on which the genes are carried from generation to generation.

*Dominant* A trait or characteristic expressed in the offspring who are heterozygous for a particular gene.

*Recessive* A trait expressed in offspring who are homozygous for the gene (not heterozygous).

*Mutation* A spontaneous alteration in the nucleoside sequence of DNA.

*Penetrance* An expression of the frequency of appearance of a phenotype in the presence of one or more mutant alleles.

*Multifactorial inheritance* Characteristics resulting from a combination of more than one gene plus the influence of the environment.

*Polymorphism* Genetic characteristics with more than one common form in the population.

*Oncogenes* Genes with the potential to trigger cancer.

*Consanguinity* Where a couple shares one or more common ancestors.

*First-degree relatives* Mother, father, sisters, brothers, daughters and sons.

*Second-degree relatives* Grandparents, uncles, aunts, half-brothers, half-sisters, nieces, nephews and grandchildren.

*Single nucleotide polymorphisms (SNPs)* Base pairs of nucleotides that differ between individuals.

## The spectrum of genetic disorders

The list of inherited disorders continues to grow as evidence supports intuition that certain conditions are hereditary. It is important for the family doctor to be aware of this potential. We are familiar with the more common classic disorders, such as cystic fibrosis, thalassaemia, Down syndrome and haemochromatosis, but it is incumbent on us to be conversant with the

genetic basis of diseases such as cancer, particularly breast, ovarian and bowel cancer, in addition to the childhood chromosomal abnormalities and various inborn errors of metabolism.

A quick checklist from a non-exhaustive list includes the following genetic disorders (AD = autosomal dominant; AR = autosomal recessive; XL = sex linked):

- alcohol/drug dependence
- cancer—breast, ovary, colon (big three), stomach, endometrium, melanoma, prostate, Burkitt's lymphoma, Wilm's tumour, acute myeloid leukaemia, chronic myeloid leukaemia, retinoblastoma
- cardiovascular—familial hypercholesterolaemia (AD), hypertension, acute myocardial infarction
- chromosomal abnormalities (childhood expression syndromes)—Down, fragile X, Prader-Willi, Turner's, Noonan, Rett, Williams, Angelman, Apert's, tuberous sclerosis (AD)
- congenital malformations—cleft lip/palate, spina bifida, congenital heart defects, tracheo-oesophageal fistula (TOF), foetal alcohol syndrome
- cystic fibrosis (AR)
- deafness (AR)
- endocrine: diabetes type I and II (AD), congenital adrenal hyperplasia (AR)
- eye disorders—blindness, retinitis pigmentosa (XL), colour-blindness (XL)
- gastrointestinal—Peutz-Jegher's syndrome (AD), coeliac disease (AR)
- gynaecological: PCOS
- Haematological: haemophilia A and B (XL), sickle-cell disease (AR), spherocytosis (AD), thalassaemia (AR), glucose-6-phosphate dehydrogenase deficiency (XL), von Willebrand's disease (AD)
- inborn errors of metabolism:
  - lipids—hyperlipidaemias,  $\alpha$ -lipoprotein deficiency (Tangier disease, AR)
  - carbohydrates—glycogen storage disease (AR), galactosaemia (AR)
  - amino acids—Fanconi syndrome, homocystinuria (AR), phenylketonuria (AR), alkaptonuria (AR)
  - others: Gaucher's disease (AR), Tay-Sachs disease (AR), acute intermittent porphyria (AD), Wilson's disease (AR)
- kidney—adult polycystic kidney disease (AD)
- musculature—muscular dystrophy (e.g. Duchenne, XL; facioscapulohumeral, AD; myotonic dystrophy, AD)
- neurological—Huntington's (AD), essential tremor (AD), familial Alzheimer's (AD), epilepsy, familial periodic paralysis, Friedreich's ataxia, neurofibromatosis I and II (AD), Wilson's disease (AD), familial motor neurone disease, familial prion dementias
- psychiatric—schizophrenia, bipolar disorder, Tourette syndrome (AD)
- respiratory—chronic obstructive pulmonary disease,  $\alpha_1$ -antitrypsin deficiency (AR), asthma, allergies
- sex chromosome abnormalities (syndromes)—Klinefelter's XXY, Turner's XO, triple X (XXX), XX male
- skeletal—short stature, osteoarthritis, Marfan's syndrome (AD), achondroplasia (AD), osteogenesis imperfecta (some AD), progeria (AR)
- skin and hair—psoriasis, atopic dermatitis, dysplastic naevi, albinism, epidermolysis bullosa (some forms AD), frontal baldness (men), X-linked hypohidrotic ectodermal dysplasia

## The genogram

The genogram is a valuable pedigree chart that usually covers three generations of a family tree. It is a simple and disciplined means of gathering data about an individual couple or family, especially for inheritance patterns. The data has to be gathered with tact and care. A useful strategy is to encourage patients to develop their own family genogram using charts as templates.

An example including the use of symbols is shown in Figure 19.1.



Fig. 19.1 A genogram showing the symbols used

## Specific important genetic disorders

### *Haemochromatosis*

Hereditary haemochromatosis (HHC) is the most common serious genetic disorder in our population.

DxT: fatigue + polyuria and polydipsia + tanned skin = bronze diabetes

It is a common condition in which the total body iron concentration is increased to 20–60 g (normal 4 g). The excess iron is deposited in and damages several organs:

- liver—cirrhosis (one-third develop a hepatoma)
- pancreas—‘bronze’ diabetes
- skin—bronze or leaden grey colour
- heart—restrictive cardiomyopathy
- pituitary—hypogonadism, impotence
- joints—arthralgia (especially hands), chondrocalcinosis

It may be primary (hereditary, AR) or secondary (e.g. chronic haemolysis, increased dietary iron, multiple transfusions).

#### Genetic profile<sup>6</sup>

Being an autosomal recessive disorder, the patient must inherit two abnormal (mutated) copies of the gene (see Fig. 19.2). It is a problem mainly affecting Anglo-Saxons usually from middle age onwards. About 1 in 10 people are silent carriers of one mutated gene, while 1 in 200 are homozygous and are at risk of developing haemochromatosis. These people can have it to a variable extent (the penetrance factor), and some are asymptomatic while others have a serious problem. It is rare for symptoms to manifest before the third decade.

The two identified specific mutations in the *HFE* gene are C282Y and H63D:

- homozygous C282Y—high risk for HHC
- homozygous H63D—unlikely to develop clinical HHC
- heterozygous C282Y or H63D—milder form of HHC

The key diagnostic sensitive marker is serum transferrin saturation; serum iron levels are not a good indicator while elevated ferritin levels are not diagnostic of HHC.

#### Symptoms

May have extreme lethargy, polyuria and polydipsia, arthralgia, and loss of libido.

#### Signs

Look for hepatomegaly, very tanned skin, cardiac arrhythmias.

#### Diagnosis

- Increased serum transferrin saturation.
- Increased serum ferritin level > 1000 µg/L.
- CT or MRI—increased iron deposition in liver.
- Liver biopsy (if liver function test enzymes are abnormal or ferritin > 1000 µg/L).
- Genetic studies: *HFE* gene—a C282Y and/or H63D mutation.
- Screen first-degree relatives (serum ferritin levels and serum transferrin saturation).
- *Note:* Full blood count (FBE) and erythrocyte sedimentation rate are normal.

#### Management

- Weekly venesection 500 mL (250 mg iron) until serum iron levels are normal (may take at least 2 years), then every 3–4 months to keep serum ferritin level < 100 µg/L (usually 40–80 µg/L) and iron levels normal.
- Normal diet.
- Life expectancy is normal if treated before cirrhosis or diabetes develops.

### *Thalassaemia*

The thalassaemias, the most common human single-gene disorders in the world, are a group of hereditary disorders characterised by a defect in the synthesis of one or more of the globin chains ( $\alpha$  or  $\beta$ )—there are two of each ( $\alpha_2$ ,  $\beta_2$ ). This causes defective haemoglobin synthesis leading to hypochromic microcytic anaemia.  $\alpha$ -Thalassaemia is usually seen in people of Asian origin while  $\beta$ -thalassaemia is in certain ethnic groups from the Mediterranean, the Middle East, South-East Asia and the Indian subcontinent.

DxT: pallor + jaundice + hepatosplenomegaly = thalassaemia major

#### Genetics<sup>6</sup>

$\alpha$ -Thalassaemia is usually due to the deletion of one or more of the four genes for  $\alpha$ -globin, the severity depending on the number of genes

deleted: deletion of all four genes— $\alpha$ -thalassaemia (hydrops foetalis); of three genes—haemoglobin H disease, which results in lifelong anaemia of mild-to-moderate degree; of one or two genes—a symptomless carrier.

### *$\beta$ -Thalassaemia*

In  $\beta$ -thalassaemia, the  $\beta$ -chains are produced in decreased quantity rather than having large deletions. People who have two mutations (one in each  $\beta$ -globin gene) have  $\beta$ -thalassaemia major. That is, the two types are:

- $\beta$ -thalassaemia minor—a single mutation (heterozygous), the carrier or trait state
- $\beta$ -thalassaemia major—two mutations (homozygous), the disorder

Both thalassaemias are inherited in an autosomal recessive pattern, which is illustrated in Figure 19.2. If both parents are carriers, there is a 1 in 4 chance that their child will have the disorder.

### Clinical

Thalassaemia minor is clinically asymptomatic and does not need treatment apart from counselling.

Patients with thalassaemia major present with symptoms of severe anaemia (haemolytic anaemia). Children with thalassaemia major are lethargic and inactive, show a failure to thrive or to grow normally and delayed puberty, hepatosplenomegaly and jaundice. Signs usually appear after 6 months and death from cardiac failure is common between ages 20 to 30 years.

### Diagnosis

- FBE: in most carriers the mean corpuscular haemoglobin/mean corpuscular volume is low but can be normal. There is usually mild hypochromic microcytic anaemia but this is severe with the homozygous type.
- Haemoglobin electrophoresis: measures relative amounts of normal adult haemoglobin (HbA) and other variants (e.g. HbA<sub>2</sub>, HbF). This will detect most carriers.
- Serum ferritin level: helps distinguish from iron deficiency.
- DNA analysis: for mutation detection (mainly used to detect carriers).

### Treatment for thalassaemia major

Treatment is based on a regular blood transfusion schedule for anaemia, with as few as possible to avoid iron overload. Folate supplementation and

a low iron diet are advisable. Excess iron is removed by iron chelation (e.g. deferoxamine). Allogenic bone marrow transplantation has been used with success.<sup>7</sup> Splenectomy is appropriate.

## Cystic fibrosis

Cystic fibrosis is the result of a defect in an ion channel protein, the cystic fibrosis transmembrane receptor, which is found in the membranes of cells lining the exocrine ducts. The defect affects the normal transport of chloride ions, leading to a decreased sodium and water transfer, thus causing viscid secretions that affect the lungs, pancreas and gut.

DxT: failure to thrive + chronic cough + loose bowel actions = cystic fibrosis

### Genetics

- The most common AR paediatric illness.
- About 1 in 2500 Caucasians affected.
- About 1 in 20–25 are carriers.
- A mutation ( $\delta$ -F508) of chromosome 7 is the main one. This deletes a single phenylalanine residue from a 1480-amino-acid chain.

### Clinical features

- General: malaise, failure to thrive, exercise intolerance.
- Chronic respiratory problems: cough, recurrent pneumonia, bronchiectasis, sinus tenderness, nasal polyps.
- Gastrointestinal: malabsorption, pale bulky stools, jaundice (pancreatic effect), meconium ileus (10% of newborn babies).
- Infertility in males (atrophy of vas deferens).
- Pancreatic insufficiency.
- Early mortality but improving survival rates (mean age now 31 years).

### Investigations

- Screening for immunoreactive trypsin in newborns detects 75%.
- Sweat test for elevated chloride and sodium levels.
- DNA testing for carriers identifies only the most common mutations (70–75%).

### Treatment

- Early diagnosis and multidisciplinary team care are important.