Important points

- Multifactorial inheritance refers to the pattern of inheritance of common health problems and rarer conditions caused by a combination of both genetic and other factors that may include internal factors such as ageing and exposure to external environmental factors such as diet, lifestyle, and exposure to chemicals or other toxins
- Multifactorial conditions have in common that they do not always develop despite the suggested presence of a faulty gene(s)
- The inherited faulty gene(s) make the person at increased risk for developing the condition (predisposed or susceptible) but unless other factors are present, the condition may never develop at all
- It may be possible to determine if family members are at risk for a particular multifactorial condition by examining their family health history and discussing it with their doctor
- Having one or more blood relatives who have been affected by a condition, particularly at a younger than expected age, is an indication that family members may be at risk of also developing that condition or passing it on to the next generation
- Knowing that a person is at increased risk can lead to the use of early detection tests and preventative strategies. (See Genetics Fact Sheet 9)
- For a **very few conditions**, triggers have been identified, for example lack of the vitamin folate in the developing baby's environment is linked to the chance that the baby will have a neural tube defect such as spina bifida. Supplementation of a woman's diet with folate in pre-pregnancy and in early pregnancy can significantly reduce the chance of a baby born with this condition. Such a preventative approach is only possible for those few conditions where the environmental trigger, or some of the triggers, have been identified
- Research is continuing to better understand the process that lead to a build-up of faulty genes in a person's body over their lifetime, causing the condition to develop. For those who are at increased risk for conditions due to an inherited predisposition, this may provide the means by which the condition is avoided altogether

Understanding the patterns of inheritance of genetic conditions in families is becoming increasingly complex (See Genetics Fact Sheet 2).

Complex patterns of inheritance

As shown in *Figure 11.1*, the contribution from inherited genetic information to conditions that affect a person's growth, development and health is variable and ranges from conditions that:

- Are directly due to changes, present from birth, in the genetic information either in one or more of the 20,000 or so genes located in the nucleus (see Genetics Fact Sheet 1)
  - There are four 'traditional' patterns of inheritance that apply to the inheritance of the faulty gene(s) involved (see Genetics Fact Sheets 8, 9 & 10)
  - Risk for the development of these genetic conditions in current or future family members can generally be estimated
  - Other unknown factors impact on the severity, or age of onset of the expression of their symptoms as often there is variability even between family members
- Are due to external factors in the person's physical and chemical environment and where genetic factors are not involved; eg. due to shared exposure to the same environmental factor such as poor quality air or water or poor nutrition
- Tend to 'run in the family' and an inherited faulty gene appears to be involved, but the patterns of inheritance are less predictable than expected. In these conditions the person's genetic make-up makes them susceptible (predisposed) to develop the condition but other factors need to be present for the condition to develop at all

Risk estimation for these genetic conditions to develop for blood relatives, is complex.

Complex patterns of inheritance also result from:

- The faulty gene is not present in all the egg or sperm cells
- Faulty mitochondrial genes (See Genetics Fact Sheet 12)
- The parent has a mixture of faulty and working gene copies (Mosaicism) in the egg or sperm cells (See Genetics Fact Sheet 13).

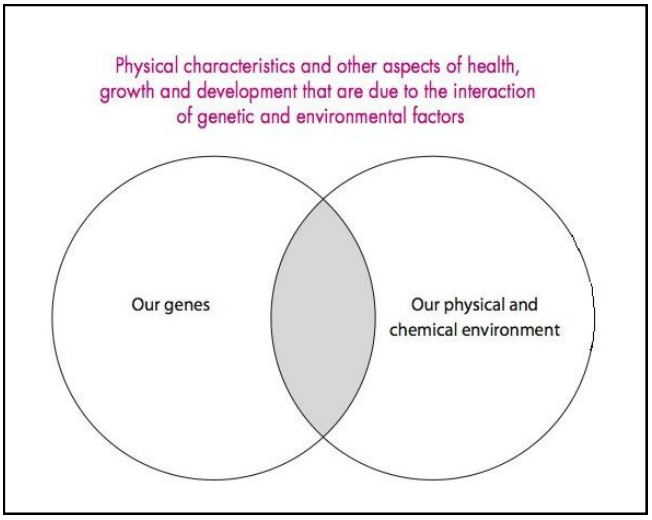

Figure 11.1: *A diagrammatic representation of the interaction between genetic and environmental factors.*

This Fact Sheet discusses conditions arising from the interaction of inherited changes in one or more genes with other factors in their internal or external environment.

A pattern of multifactorial inheritance

Multifactorial inheritance refers to the pattern of inheritance, of certain conditions due to a combination of both genetic and other factors that may include internal factors such as ageing, and exposure to external environmental factors such as diet, lifestyle, and exposure to chemicals or other toxins *(Table 11.1).*

Common health problems include some forms of cancer, some forms of cardiac disease, diabetes and mental illness such as schizophrenia and manic depression (see Genetics Fact Sheets: 47 -51, 53-56, 57 & 58).

These conditions have in common that they do not always develop despite the suggested presence of a faulty gene: the 'penetrance' of the condition is not complete.

- For example, not all women who have inherited a faulty breast cancer gene will develop breast cancer. The faulty gene is not completely `penetrant'.

The reason for this 'incomplete penetrance' of the condition is most likely due to the interaction between the information in the faulty gene with the information in one or more other genes and with other 'environmental' factors including physical and chemical elements as well as ageing

Table 11.l: *The conditions listed are some of the health problems in which genetics plays a role*

Birth Defects: cleft palate/lip, neural tube defects such as spina bifida	**Cancer**: bowel, breast, ovarian, bowel, melanoma and prostate
Cardiovascular conditions: high blood pressure, some causes of heart disease, high cholesterol	**Metabolic**: diabetes
Neurological/psychiatric conditions: Alzheimer disease in later life, schizophrenia, bipolar disorder	**Muscular/skeletal**: arthritis, rheumatic disorders, osteoporosis
Skin conditions: psoriasis, moles, eczema	**Respiratory**: asthma, allergies, emphysema

How can a person determine if they or their blood relatives are at risk for developing a multifactorial condition?

It may be possible to determine if blood relatives are at risk for developing a particular multifactorial condition by examining their family health history and discussing it with their doctor.

- A person's family health history can be an indication that a condition due to a faulty gene is running in the family (See http://www.genetics.edu.au/Genetic-conditions-support-groups/Your-Family-Health-History
- Having one or more blood relatives who have been affected by a condition, particularly at a younger than expected age, is an indication that family members may be at risk of also developing that condition or passing it on to the next generation
- This can lead to the use of early detection tests and preventative strategies. Triggering factors, if known, can be avoided

Recent advances in technology have also made it possible to determine, in some cases for some multifactorial conditions, if an individual has inherited a particular faulty gene that has predisposed him/her to a condition ie. they are at increased risk for a condition such as those listed in *Table 11.1* (also see Genetics Fact Sheet 21).

The inheritance of the predisposing faulty gene involved will follow a traditional pattern of inheritance.

- In the majority of cases, the pattern is autosomal dominant inheritance (See Genetics Fact Sheet 9) eg. inherited predisposition to breast and ovarian cancer (see Genetics Fact Sheet 48)
- This pattern is often suggested by the family history but inheriting the faulty gene simply makes a woman predisposed or at increased risk of developing breast cancer and ovarian cancer
- Despite inheriting a faulty gene, breast or ovarian cancer will not develop unless other genes are made faulty over the woman's lifetime

Possible triggers for other genes to become faulty include factors in our internal and external environments as well as the impact of ageing.

The variability of these genetic and environmental factors influence the number of blood relatives who develop the condition, affecting the 'penetrance' of the condition in the family

- Often fewer family members have the condition than would be expected according to traditional patterns of inheritance

A condition that runs in the family may be due to shared exposure to the same environmental factor such as poor quality air or water or poor nutrition; eg. having a number of family members who smoke can lead to exposure to toxins from passive smoking with its established health impact.

- In some cases, exposure to an environmental factor will be the only reason for a condition to run in a family; ie. genetic factors may not be involved at all

The estimation of the risk for developing a particular multifactorial condition in a family is dependent on a number of factors. These include:

- Whether there is a significant contribution by the inherited genetic information to the condition
- How closely related the person is to an affected relative
- Whether there are many affected family members
- In some cases, how early the symptoms of the condition first occurred

It is not currently feasible to screen everyone for every faulty gene and the number of conditions for which genetic testing is available is limited. Looking at their family health history in consultation with their doctor will therefore remain the most important tool in determining if a person is at risk for developing particular genetic conditions.

Discussion of an individual's family health tree with their doctor or a genetic counsellor can lead to an estimation of the particular risk for a condition that is present in the family.

Can some genetic conditions due to multifactorial inheritance be prevented?

As multifactorial conditions involve an inherited predisposition with an environmental trigger, an obvious preventive approach is to modify the known triggers in those individuals who are susceptible due to their family history.

For **a very few conditions**, these triggers have been identified.

- Lack of the vitamin folate in the developing baby's environment has been linked to the chance that the baby will have a neural tube defect such as spina bifida. Supplementation by folate in women pre-pregnancy and in early pregnancy can significantly reduce the number of babies born with this condition (see Genetic Fact Sheets 19 & 59)
- High dietary cholesterol is a factor in increased risk for cardiovascular disease (see Genetics Fact Sheet 54) and obesity has also been linked to increased risk for diabetes type 2 (see Genetics Fact Sheet 57) with exercise as an effective intervention

This approach is only possible for those few conditions where the environmental trigger, or some of the triggers, have been identified.

Understanding the process of the interaction between genetic predisposition and developing a condition

It is clear that for many common and rare conditions such as those listed in *Table 11.1,* simply inheriting one or more faulty genes associated with a particular condition is not enough for that condition to develop. The person's inherited genetic information may make them susceptible (predisposed) to the condition but if other steps do not occur during their life then the condition will never develop.

The field of cancer genetics has provided some clues as to how the pathway works for some cancers to develop and this may be the model for other multifactorial conditions.

Knudson's `2-Hit Hypothesis'

In 1971, Alfred Knudson, a scientist, hypothesised that there was a relationship between inherited and new or sporadic cancers (not inherited). Knudson was aware that cancers arose because of genetic variations, and that these caused the genes critical for controlling cell growth and the division of cells to become faulty. Another way of looking at it is that these are normal 'cancer protection' genes that become faulty and can no longer do their usual job in the body (*Figure 11.2* and Genetics Fact Sheet 47).

The example of retinoblastoma Dr Knudson proposed that the first cell of a rare tumour that developed in the eyes of children (*retinoblastoma)* underwent two different `hits' that changed the information in both copies of a gene so that both gene copies were faulty (mutations).

Everyone has a gene (called the RB gene) that contains the information for the cells to produce a protein whose role is to prevent tumour growth (*tumour suppressor* protein) in the nerve -rich layers that line the back of the eyes *(retina).* In retinoblastoma a malignant tumour develops when both copies of the RB gene become faulty so that the tumour in the retina is not prevented.

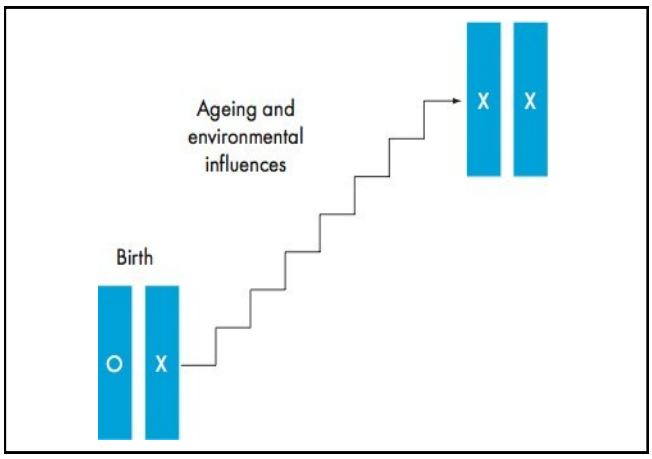

Figure 11.2: *The child inherits one of the RB gene copies already faulty. A change occurs in the other copy of the RB gene (the second 'hit') so now both RB gene copies are faulty and can no longer prevent the cancer developing in the retina*

RB occurs most commonly in children under the age of three and may be inherited or sporadic. He noted that RB could result from tumours (primary tumours) occurring in both eyes (*bilateral*) or only in one eye (*unilateral*), but the sporadic (non-inherited) forms of RB were always unilateral.

Most individuals with bilateral retinoblastomas had the familial form.

In other words, if two or more primary tumours occurred in the same person, it was more likely that all of the cells of the body had received the first 'hit' making the RB gene copy faulty at the time of conception. The child inherited one faulty copy of the RB gene and one working copy from each parent.

- As shown in *Figure 11.2*, the child is born with one of their RB gene copies faulty and then, over the first few years of their life, the other partner gene copy is also made faulty by some other unknown factor
- It was also very unlikely that each of these tumours arose independently at the same time due to independent chance 'hits' in the same gene out of the 20,000 or so genes in the human cells

Remarkably, this hypothesis was proposed in the early 1970s but it was not until 1987 that the identification of the retinoblastoma gene occurred and completely confirmed Knudson's hypothesis.

Knudson's theory is thought to not only apply to the development of inherited cancer in children, but to be one of the systems leading to other cancers that develop in later life. (See Fact Sheets 47).

It is likely that other complex conditions will be due to genetic and environmental interactions that lead to changes in the genetic information building up over the person's lifetime.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 2, 8, 9, 10, 12, 13, 19, 21, 47, 48, 49, 50, 51, 53, 54, 55, 56, 57, 58, 59