

### Parkinson Disease—Neurological conditions 3

#### **Important points**

- Parkinson disease (PD) is the second most common adult onset neurological condition with three major symptoms: tremor, stiffness of the muscles and slowed movements
- PD may be grouped into different forms according to age when symptoms start: late-onset (after age 50), young-onset (before age 50) and juvenile onset (before age 20)
- In the majority of cases, PD is said to be 'sporadic' ie. it occurs for no known reason and there is no family history of PD (no other affected family members)
- There is likely to be a combination of genetic and environmental causes
- Several early-and juvenile-onset forms of PD have been identified as involving inherited faulty genes with different patterns of inheritance in families
- In one form, the pattern is autosomal recessive inheritance. Therefore, both parents must carry the faulty gene involved and each child has a 25% chance of inheriting both faulty gene copies and developing the condition
- In another form of PD, the pattern is autosomal dominant inheritance in families. Therefore, parents, children and siblings have a 50% chance of carrying the faulty gene involved and are at increased risk for developing this form of PD and have an inherited predisposition. They may, however, never develop the condition if as yet unknown risk factors are also not present
- In Australia, genetic testing for PD is only available after specialised neurological review. This is still in the research phase and needs to be done in the context of genetic counselling.

#### Parkinson disease (PD)

**Parkinson disease (PD)** is the second most common neurological condition after Alzheimer disease (see Genetics Fact Sheet 45). It is estimated to affect about 100,000 people living in Australia.

The average age when PD is diagnosed is around 65 years. There are different forms of PD according to the age of onset of symptoms:

- Late-onset PD: Onset is after 50 years of age and it affects more than 1% of 55 year-old individuals and more than 3% of those over 75 years of age
- Young-onset PD (also known as early-onset PD): Onset before 50 years of age
- Juvenile-onset PD: Onset before 20 years of age

#### What are the features of Parkinson disease?

The symptoms of PD are due to a progressive degeneration of a group of nerve cells within the centre of the brain. Nerve cells use the chemical *dopamine* as their 'neurotransmitter' to send signals to other nerve cells.

As the nerve cells degenerate and stop working properly, dopamine does not reach the areas of the brain important for motor function or muscular movement. The condition is slowly progressive and may not become incapacitating for many years.

Three major symptoms of PD that result are the development of tremors, stiffness of the muscles (*rigidity*) and slowed movements (*bradykinesia*). These symptoms are also associated with disturbances in balance and gait or walking manner, particularly as PD progresses.

The symptoms may be isolated or be a combination of several. They usually start on one side of the body and after a period of several years will then involve the other side of the body. A proportion of individuals with PD may also develop symptoms associated with *dementia* in the course of the disease (the eventual decline of intellectual functions such as thinking, memory and reasoning).

'Parkinsonism' is a clinical description of tremor, muscle rigidity and slowed movement, which may also develop secondary to other conditions or on exposure to certain drugs. It is not the same as PD, but PD is the most common disease causing Parkinsonism.

#### What causes Parkinson disease?

In the majority of cases, PD is said to be 'sporadic' ie. it occurs for no known reason and there is no family history of PD (no other affected family members).

There is evidence to show that PD may have genetic and/ or environmental causes. Even where the contribution by changes in one or more gene(s) has been identified or implied, the environmental factors which trigger the inherited predisposition are still unknown.

In some cases there is a family history of PD. This can occur:

- Just by chance because the condition is common in older people
- Because family members are exposed to the same environmental factors
- Because a predisposition to PD due to a faulty gene(s) runs in the family, although this is rare

#### Where there is an identified genetic contribution to Parkinson disease, what is the pattern of inheritance?

The cells of the body contain the genes or set of instructions for the cell to make all the necessary proteins (chemicals) for our bodies to grow and work normally (see Genetics Fact Sheet 1).

A gene that contains a variation in the information that stops it working properly is described as faulty. The variation that makes the gene faulty is called a *mutation*. The information contained in the faulty gene, and its product, is impaired (see Genetics Fact Sheets 4 & 5).

A number of different genes have been identified in which variations are associated with PD. Some of these have been identified as being involved in juvenile and early-onset forms of PD. The *parkin* and  $\alpha$ -synuclein genes are discussed later in more detail as examples. Other genes identified as being important in inherited forms of PD include *DJ1*, *PINK1* and *LRRK2*.

#### (a) The parkin gene

In some families, variations in a gene called *parkin* that make the gene faulty have been identified as predisposing to juvenile-onset forms of the condition. Two factors influence the pattern of inheritance of this faulty gene.



1. The *parkin* gene is located on chromosome 6, an autosome (one of the numbered chromosomes)

Health

2. The effect of the variation in the gene is 'recessive' or hidden by the presence of the working copy of the gene (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance of the faulty gene predisposing to this juvenile-onset form of PD in families is therefore described as *autosomal recessive inheritance* (see Genetics Fact Sheet 8).

If both copies of the *parkin* gene are faulty, a person will develop symptoms of PD in their lifetime.

In *Figures 46.1* and *46.2* which illustrate the pattern of inheritance, the faulty *parkin* gene is represented by 'r'; the working copy by 'R'. There are four possibilities *in every pregnancy* for the combinations of genes passed from the parents.

As shown in *Figure 46.1*, for *a couple whom are both carriers* of the faulty *parkin* gene, in every pregnancy there is:

• A 1 chance in 4 (25%) that they will have a child who will develop PD over their lifetime. Unless both parents are carriers of the faulty gene, the child will not be at increased risk for developing PD

As shown in *Figure 46.2*, where **only one parent is a carrier** of the faulty *parkin* gene, in every pregnancy there is:

- It is unlikely that the couple will have a child who will develop PD
- 1 chance in 2 (ie 2 chances in 4) or 50% chance that the baby will be an unaffected genetic carrier of PD, just like his/her parents

#### (b) The alpha-synuclein ( $\alpha$ -synuclein) gene

In some families, variations in a gene called  $\alpha$ -synuclein that make the gene faulty have also been found to predispose to PD.

The  $\alpha$ -synuclein gene codes for important proteins in the brain called  $\alpha$ -synuclein proteins. When the gene is faulty, the  $\alpha$ -synuclein proteins form 'clumps' or aggregates in the brain cells, causing the symptoms of PD. Two factors influence the pattern of inheritance of the faulty  $\alpha$ -synuclein gene copy.

- 1. The  $\alpha$ -synuclein gene is located on chromosome 4, an autosome (one of the numbered chromosome
- 2. The effect of the variation in the  $\alpha$ -synuclein gene copy is 'dominant' over the information in the working copy of the gene on the partner chromosome 4 (see Genetics Fact Sheets 1, 4 & 5)

The pattern of inheritance of the faulty  $\alpha$ -synuclein gene copy in families where this predisposes to PD is therefore described as **autosomal dominant inheritance** (see Genetics Fact Sheet 9).

As shown in *Figure 46.3*, where one of the parents has PD, or will develop PD due to having the faulty  $\alpha$ -synuclein gene copy, **in** every pregnancy, each child has:

- A 1 chance in 2 (50%) of having inherited the faulty gene copy from that parent
- An equal chance (50%) of not having inherited it. Children who have not inherited the faulty gene copy are not at risk of developing PD. Importantly, these children cannot pass the faulty gene copy on to their own children

In *Figure 46.3* the autosomal dominant faulty gene copy causing PD is represented by 'D'; the working copy by 'd'. While the father is shown as the parent carrying the faulty PD gene copy, the same situation would arise if it was the mother. PD usually affects men and women equally.



**Figure 46.1:** Autosomal recessive inheritance where both parents are carriers of the faulty parkin gene. The faulty parkin gene copy is represented by 'r'; the working copy by 'R'.



**Figure 46.2:** Autosomal recessive inheritance where only one parent is a carrier of the faulty parkin gene. The faulty parkin gene copy is represented by 'r'; the working copy by 'R'.

Genetics

## Parkinson Disease—Neurological conditions 3



**Figure 46.3:** Autosomal dominant inheritance when one parent either has PD or has the faulty  $\alpha$ -synuclein gene copy. The faulty  $\alpha$ -synuclein gene copy is represented by 'D'; the working copy by 'd'.

# What does understanding the faulty genes involved in PD mean for people with a family history of the condition?

Having a family history of PD does not currently alter methods of treatment and diagnosis of PD. There is, however, ongoing research in these areas, potentially leading to new treatments being developed.

# Can a person determine if they have inherited the faulty gene for PD?

In Australia, genetic testing for PD is only available after specialised neurological review.

Clinical genetic testing programs are offered in conjunction with genetic counselling (see Genetics Fact Sheet 3). It is strongly recommended that all the advantages and disadvantages and limitations of having the predictive test be considered before having testing.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 4, 5, 8, 9, 17C, 18, 45

