This fact sheet describes a condition known as Parkinson disease and includes the symptoms, causes, and any treatment or testing that is available.

In summary

- Parkinson disease (PD) is the second most common neurological condition in Australia, characterised by tremors, muscle rigidity, and slowed movements
- Most cases of PD are not inherited but occur because of a combination of genetic and environmental factors.
- Rare families have a faulty gene that causes PD and genetic testing is available in these cases.

WHAT IS PARKINSON DISEASE?

Parkinson Disease is a progressive neurological condition characterised by tremors, stiffness of the muscles (rigidity) and slowed movements (bradykinesia). It is estimated to affect 1 in 350 individuals in Australia, with approximately 70,000 -80,000 affected individuals, making it the second most common neurological condition after Alzheimer disease. Symptoms may be isolated, or be a combination of those most commonly observed. In addition a proportion of individuals with PD may also develop symptoms associated with dementia in the course of the disease with decline of intellectual functions such as thinking, memory, reasoning, and personality changes.

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

- **Late-onset**: Onset is after 50 years of age. This form is estimated to affected approximately 1% of 55 year-old individuals and more than 3% of those over 75 years of age.
- **Early-onset (also known as young-onset PD):** Onset before 50 years of age.
- **Juvenile-onset:** Onset before 20 years of age.

The younger onset forms of PD are very rare and may be more likely to be due to an inherited cause than the more common, late-onset form.

WHAT CAUSES PARKINSON DISEASE?

Neurons are a specialised type of cell in the brain and central nervous system. The symptoms of PD are due to the progressive degeneration of a particular group of neurons in a part of the brain known as the **substantia nigra**, which is in turn part of a larger group of neurons called the **basal ganglia** that co-ordinate movement.

It is poorly understood what causes these neurons to die off, however there are many theories that are currently being researched. An abnormal build -up of a protein known as **alpha-synuclein** which forms clumps in neurons called **Lewy bodies** is thought to contribute, however the mechanism of how and why these occur is still unknown.

The neurons in the substantia nigra have an important function – to produce a chemical called **dopamine**. This is a **neurotransmitter** that allows one neuron to send signals to other neurons. In PD, the loss of these neurons means that there is a loss of dopamine. The lack of this important chemical in the brain accounts for the symptoms of tremors, muscle rigidity, and slowness of movement that characterise the condition.

The genetic cause of PD is very complex, and in most cases it is not considered to be a genetic condition. It is rather thought to develop because of a combination of genetic and environmental factors.

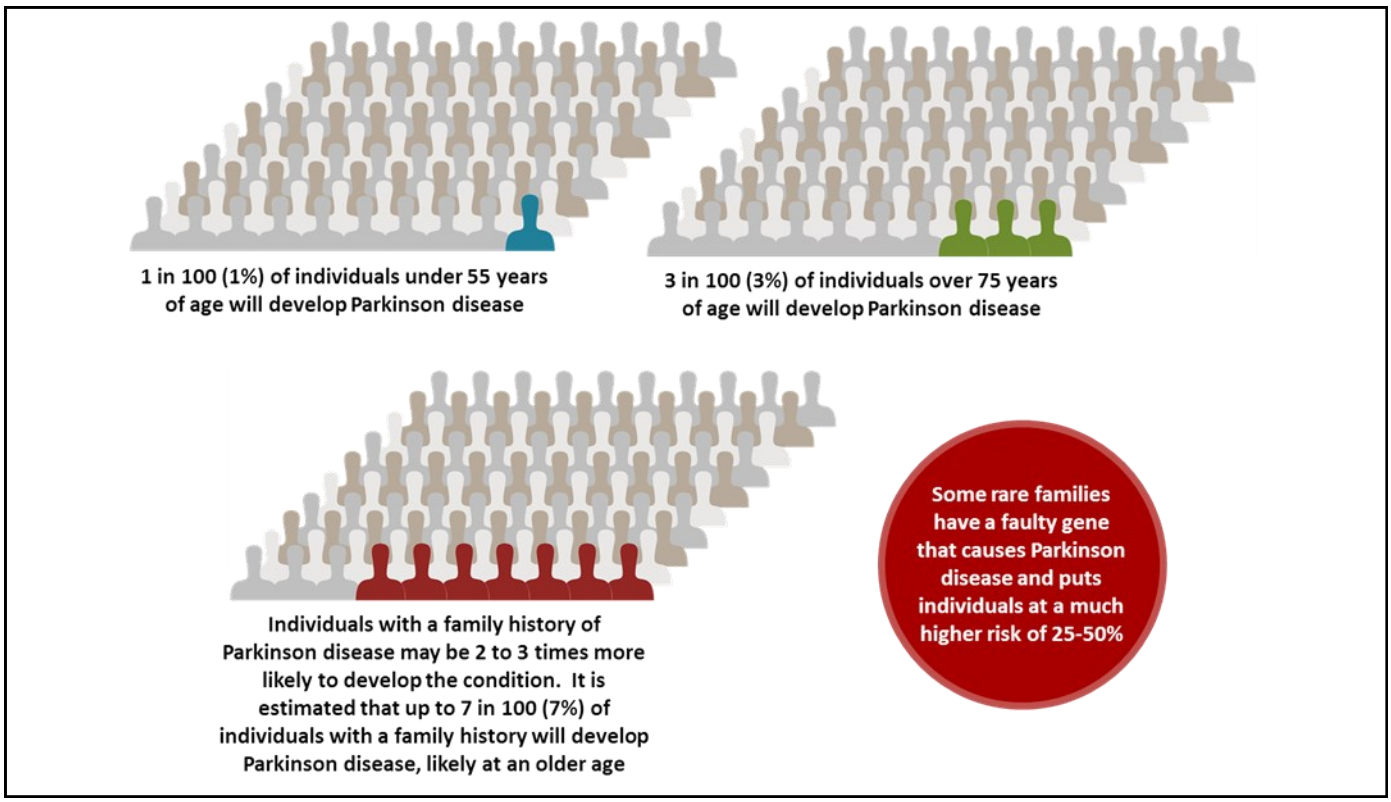

Figure 51.1: *Prevalence of PD. Only 1% of individuals less than 55 years of age in the general population will develop PD, increasing to 3% over the age of 75 years. Individuals with a family history may be 2 to 3 times more likely to develop PD and are estimated to have an up to 7% chance over their lifetime. Some rare families have a faulty gene and have a high chance of inheriting the condition.*

HOW IS PARKINSON DISEASE INHERITED?

In some families where there are multiple affected family members there may be an **inherited predisposition**, meaning that individuals in that family are more likely to develop PD but it is not a certainty that they will, with a combination of other genetic and environmental factors playing a role in whether the disease develops or not.

Our body is made up of millions of cells, and in each cell there are recipes, called genes, for structural components and chemicals necessary for the body to function. These genes are packaged onto strands called chromosomes.

Each body cell has 46 chromosomes arranged into 23 pairs. One copy of each pair is inherited from our mother and the other from our father. The first 22 chromosome pairs are numbered and are known as autosomal chromosomes. The 23rd pair is made up of the sex chromosomes called X and Y. Males have an X and a Y chromosome and females have two copies of the X chromosome.

Since all our chromosomes come in pairs, all our genes also come in pairs. Sometimes, a gene may have a variation in the instruction that causes the gene to no longer function properly. This variation is called a **mutation** or **pathogenic variant**, and means that the product for which the gene is a recipe, (usually a protein), is altered or absent.

Gene mutations may be inherited from a parent, or occur for the first time in an individual. Once you have a gene mutation however, it may be passed on to future generations. This is referred to as genetic inheritance.

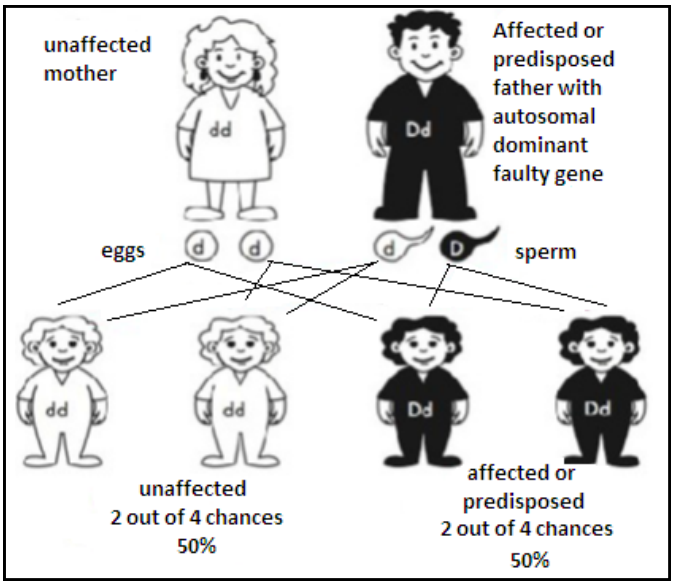

Figure 51.2: *Autosomal dominant inheritance when one parent carries the autosomal dominant faulty gene copy. The autosomal dominant faulty gene copy is represented by 'D'; the working copy of the gene by 'd'.*

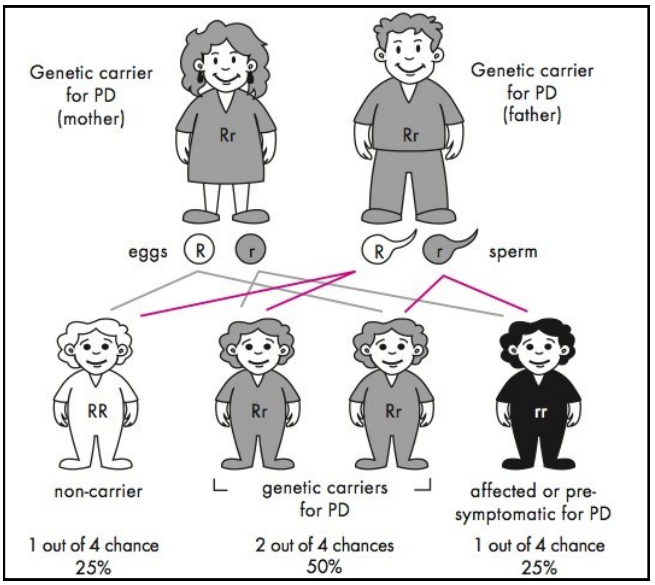

Figure 51.3: *Autosomal recessive inheritance where both parents are genetic carriers of the faulty gene. The faulty gene is represented by 'r'; the working copy by 'R'.*

It is thought that individuals with a family history of PD are about 2 to 3 times more likely than someone without a family history to develop the condition, but as PD is still fairly rare and affects mainly older individuals, the risk over an individual's lifetime increases to only 3-7% (Figure 51.1). The environmental factors that trigger PD are still unknown. There is some evidence that long term exposure to pesticides and similar environmental toxins may be a risk factor.

Rare families have a mutation in a gene that causes PD. ***LRRK2*** is one gene associated with late-onset, familial PD. Other genes cause early-onset or juvenile forms of PD and include ***PARK2***, which produces the protein **parkin,** and ***SNCA,*** which produces the protein **alpha-synuclein**. We do not yet understand how these genes lead to the symptoms of PD.

We can understand the inheritance of PD only in those rare families with a mutation in a gene associated with the condition. Depending on which gene is affected, the pattern of inheritance is different.

The two main modes of inheritance are autosomal dominant, which occurs for ***SCNA*** and ***LRRK2***, and autosomal recessive, which occurs for ***PARK2***.

Autosomal Dominant Inheritance

We each have two copies of every one of our genes, one inherited from our mother and the other from our father. When PD is due to a mutation in *SCNA* (alpha-synuclein) or in another gene that follows an autosomal dominant pattern of inheritance, a mutation in only one copy of the gene is needed to cause the disease despite the other copy working properly (Figure 51.2). This also applies to mutations in *LRRK2*, however these mutations demonstrate **reduced penetrance**, which means that not everyone who inherits the mutations will definitely develop PD.

The mutation gives an **inherited predisposition** and additional unknown inherited or environmental factors play a role in whether an individual will go on to have PD.

For every pregnancy in this situation there is:

- 50% chance that a child, either male or female, will inherit only working copies of a gene from their parents and be healthy
- 50% chance that they will inherit one copy of the faulty gene, and one working copy and be predisposed to developing the condition
- A mother or a father can pass on an autosomal dominant condition and both male and female children may be affected.

Autosomal Recessive Inheritance

When PD is due to a mutation in *PARK1* (*parkin*) or in another gene that follows an autosomal recessive pattern of inheritance, both parents are healthy carriers of the mutation and have one copy of their gene that is faulty (has the mutation) and one that is working. Their offspring will develop PD only if they inherit a faulty copy from both parents, meaning that they have no working copy of the gene (Figure 51.3).

For every pregnancy where a couple are both genetic carriers for PD there is:

- 1 chance in 4 (25% chance) that they will have a child who inherits both copies of the recessive gene mutation from his/her parents. In this case, no working gene product will be produced and their child will be affected by PD.
- 1 chance in 4 (25% chance) that their child will inherit both copies of the working gene and will be unaffected by PD and not a genetic carrier.
- 1 chance in 2 (2 chances in 4 or 50% chance) that their child will inherit the recessive gene mutation and the working copy of the gene from the parents and he/she will be an unaffected genetic carrier for PD, just like the parents.

If you are worried that you may be at an increased risk for PD because of your family history, you can discuss this with a genetic specialist who can determine the mode of inheritance – whether multifactorial, autosomal dominant, autosomal recessive, or something more complex – that is playing a role in your family and provide you with advice accordingly.

IS THERE ANY TESTING OR TREATMENT AVAILABLE FOR PARKINSON DISEASE?

Clinical Testing for Diagnosis of PD

For individuals who may be demonstrating symptoms of PD a neurological assessment is recommended to analyse these symptoms and look for the characteristic tremors, muscle rigidity, and slow movements seen in this condition. A range of brain imaging such as MRI or CT scans may be used to rule out other neurological conditions that could cause similar symptoms.

If a diagnosis of PD is strongly suspected, medication may be prescribed, and the response to this might help to clarify the diagnosis. Sometimes post-mortem examination can confirm a diagnosis in a deceased relative by looking for characteristic Lewy bodies in the basal ganglia area of the brain.

Genetic Testing

Where a familial form of PD is suspected, genetic testing can be used to confirm the diagnosis in the patient and provide options for testing of family members. The first step is a **mutation search** in an affected family member to try to identify the faulty gene. If the mutation is identified, predictive genetic testing can be offered to other family members who are at-risk. If a mutation cannot be found, no further genetic testing can be offered in the family.

Prenatal testing and PGD

For couples where the familial mutation is identified, testing may be available during a pregnancy to determine whether or not the baby has inherited the mutation. It may also be possible to undergo pre-implantation genetic diagnosis (PGD) on an embryo created using in vitro fertilisation (IVF). These options are best discussed and considered before pregnancy, when possible, in order to ensure all possible risks, benefits and outcomes are explored.

Treatment Options

There are a number of treatments available for PD which aim to replace the dopamine that is lost. These include **levodopa**, which is a synthetic form of dopamine, and **enzyme inhibitors**, which inhibit specific enzymes such as COMT and MAO-B that degrade dopamine. Surgical options are also available, known as **deep brain stimulation (DBS)**, which have been shown to reduce symptoms, however are not curative. Eligibility for this procedure should be discussed with your doctor.