

Familial MND and genetic testing

What you should know

- About 10% of MND is 'familial', which means there is or has been more than one MND affected person in a family
- Learning about the genetics of MND, genetic testing, gene mutations, clinical trials and other MND research can help to better inform people affected by familial MND
- Understanding of the genetic mutations related to MND has increased over time, and is accelerating due to advances in technology and collaboration between researchers
- In Australia, recent research has found that the C9orf72, SOD1 and other MND-related gene mutations are present in 60.8% of all people with familial MND
- MND Associations, neurologists and genetic counsellors can help provide information and guidance on the genetics of MND

Genetics and MND

About 10% of MND is 'familial' which means that there is or has been more than one affected person in a family¹. The remaining 90% of people with MND are the only affected person in their family and are said to have 'sporadic' MND².

People with familial MND have the disorder because of a mutation in a gene³. A mutation is an error in the genetic code which causes a gene to work abnormally. People with genetic mutations can pass these onto their children. If a person has an MND-related genetic mutation each of their children has a 50/50 chance of inheriting the MND-related genetic mutation⁴.

People who inherit an MND-related genetic mutation have a high, but as yet uncertain, chance of developing MND during their lifetime. However, not all people with an MND-related genetic mutation will develop MND. Other triggers may be needed for the disease to actually begin.

The age at which symptoms of MND appear in people with an MND-related genetic mutation varies greatly⁵. It can be as early as the 20s and as late as the 80s. As well, the age of onset can vary considerably within a family, even though the mutation carried by family members is the same. The average age of onset of familial MND is around 45 years⁶.

Mutations in the genes that cause MND are also found in some people who have sporadic MND⁷. The number of people with sporadic MND who also have an MND-related gene mutation is not known.

Discovery of MND-related genetic mutations

Most people with MND have the Amyotrophic Lateral Sclerosis (ALS) form of the disease. A gene defect has been identified in around 60-70% of ALS families, the main ones in Australia being C9orf72, SOD1, TARDBP, FUS, OPTN, and UBQLN2⁸.

The Most Common Genetic Mutations

Year	Discovery	Relevant Facts and Insights
1993	The first genetic mutation related to MND was discovered in the superoxide dismutase 1 gene (SOD1).	Evidence suggests 13.7% of familial MND is caused by mutations in the SOD1 gene.
2008	Mutations in the TAR DNA binding protein (TDP-43) gene code were found to cause TDP-43 to become toxic, causing MND in a	Researchers are yet to find out how and why TDP-43 behaves abnormally to cause MND.

small percentage of MND families.		
2009	A gene mutation that causes a rare inherited form of MND, FUS (Fused in Sarcoma) was discovered.	Researchers have found that genetic mutations of FUS are a cause of MND for a small number of familial forms of MND and account for between 3% - 5% of MND families.
2011	The discovery of mutations in the C9orf72 gene was announced	Mutations in the C9orf72 gene have since been found in about 40% of all families with familial MND. C9orf72 is also found in 5% to 10% of sporadic MND.

In recent times the pace of gene mutation discovery has accelerated due to advancements in technology and a concerted international collaborative approach with many mutations that affect small cohorts of people with MND now identified.

Although there are still some MND families in which the faulty gene has not yet been identified, C9orf72, SOD1 and other MND-related gene mutations discovered in recent years now account for 60.8% of all people with familial MND in Australia^{9,10,11}.

Other more recent gene discoveries include NEK1, C21orf2, TBK1 and TUBA4A⁸.

Current research

Researchers continue in their quest to find the mutations in other genes that cause familial MND in the families in which the genetic cause has yet to be identified. The rate of gene discovery in ALS is doubling every 4 years¹².

Researchers are carrying out further studies to:

- understand how the known genetic faults cause MND
- work out how many of those with a faulty gene will actually go on to develop MND later in life
- identify mutations in other genes which may cause familial MND
- understand how genetic faults may also cause sporadic MND
- discover ways of preventing and treating familial and sporadic MND and trial potential therapies that target specific genetic mutations such as SOD1 and C9orf72

Relevance of the discovery of gene mutations that cause MND

It is now possible to test for the presence of mutations in the SOD1, TDP43, FUS and C9orf72 and other recently identified genes in a person diagnosed with familial MND¹³. Other family members can also be tested to determine if they have the same mutation that caused MND in their relative. For example, adult children or brothers and sisters of an affected person can be tested.

Unborn children can be tested to determine if they have inherited the mutation known in the family.

Pre-implantation genetic diagnosis (PGD), an advanced screening technique, can be used in conjunction with IVF to determine whether an embryo has inherited the familial MND gene. This screening technique has the potential to stop MND in future generations of that family.

Research will increase our understanding of the mechanism by which these mutations cause MND. Research may lead to treatments which can prevent or delay the onset of MND in someone with an MND-related genetic mutation. It is possible that research into MND caused by genetic mutations will also contribute to our understanding of the causes of other types of MND.

Some issues associated with testing for MND gene mutations

Some reasons people have given for **wanting to know** if they have an MND-related genetic mutation:

Health and Wellbeing	Family	Work and finances
<p>I am the sort of person who wants to know as much as possible about myself and my future and find it hard to live with uncertainty.</p> <p>To enable me to plan my life.</p>	<p>To help with decisions about marriage and having a family.</p> <p>To provide information of importance to my children.</p>	<p>If I do not have the gene, the information may help when I apply for jobs, life insurance, superannuation or when taking on long-term financial commitments.</p>

Some reasons people have given for **not wanting to know** if they have an MND-related genetic mutation

Health and Wellbeing	Family	Work and finances
<p>I can accept living with uncertainty and will be able to plan my life without knowledge of my genetic status.</p> <p>I do not think I would cope with knowing that I have the gene and will have an increased risk of developing MND.</p> <p>I am always free to change my mind and can take the test in the future if, for example, a treatment becomes available that can prevent MND.</p>	<p>I would not change my plans regarding marriage and having a family, whatever the test result.</p> <p>Relationships with my family, friends and workmates may change if I am shown to have the gene.</p>	<p>If I have a genetic mutation, the information may limit my life opportunities for example, in relation to career choices, life insurance, superannuation and financial matters.</p>

Frequently Asked Questions

How is the test performed?

Testing is offered as part of a formal program providing the information, counselling and support a person might need when trying to decide whether to have the test and after the result has been provided. The test is usually done on genetic material (DNA) obtained from a blood sample.

Some specialist MND Multidisciplinary Clinics undertake genetic testing as part of their research program. There may be a Medicare rebate available for testing for the presence of gene mutations that cause MND and some genetic services may provide subsidized or free testing for several MND-related genes.

Testing must be voluntary. While each person will consider the views of family, friends and researchers, the final decision must be taken by the individual concerned. It would be inappropriate for someone to take the test because of pressure from another person to do so. Any decision by a patient or consumer to undertake a genetic test should include time to consider the implications of having the test including the potential implications of genetic testing for individuals considering purchasing personal insurance products.

Can children be tested?

Children under 18 years of age should not be tested. Anyone having this test must be able to give informed consent. They need to understand and accept the testing process and the implications of the test result. This is a test which can give an indication of a person's future health and the results can have a significant effect on various aspects of life. The right of parents to have information about their child does not outweigh the child's right to make a personal choice about whether or not to be tested.

Can DNA be stored?

DNA can be stored frozen, so blood from people with the disorder can be collected now and used in the future to help other family members when further genetic mutations are discovered.

Can I give a blood specimen for research, but without getting the result?

Researchers are keen to receive blood samples from people with a family history of MND, particularly if testing for the known mutations has proved to be negative in that family. If you would like to support research in this way, please contact your local MND Association for more information.

Will the test result be kept confidential?

The result will not be released to others without the formal consent of the person tested. Currently, there is also a temporary suspension on the use of genetic test results as part of an insurance application up to the value of \$500,000 (for death and total permanent disability), \$200,000 for trauma and \$4,000 a month for income protection. The suspension will end on 30 June 2024. After the suspension ends, you will have an obligation to disclose your own genetic test results to insurers when applying for life insurance products and this may impact your ability to obtain personal insurance products, or increase the premium paid. Non-disclosure of genetic test results may invalidate your insurance policy.

Who can provide support for those taking the test?

Family, close friends or other trusted people close to the individual can provide emotional support, as can health professionals such as doctors, (clinical geneticists, neurologists, psychiatrists, general practitioners), MND Associations, psychologists, counsellors (including genetic counsellors) and social workers.

Who can help with IVF and genetic testing?

Genetic counsellors can provide information and support for people who have an MND-related genetic mutation and are planning to start a family, as can health professionals such as doctors, (clinical geneticists, neurologists, psychiatrists, general practitioners) psychologists and MND Associations. Pre-implantation genetic diagnosis (PGD) involves screening IVF generated embryos for genetic conditions prior to embryo transfer with only unaffected embryos transferred to the uterus.

IVF clinics can provide information on PGD and on where this specialist screening is available. They can also provide information on the associated costs and the Medicare rebates available. [Genea](#) (a provider for infertility, IVF and other assisted conception treatment) offers a PGD financial assistance program to those able to demonstrate financial need.

MND Associations – what role do they play?

- Provide guidance and advice for people with MND, families and health professionals
- Produce and disseminate information
- Fundraise and advocate for MND research
- Advocate for clinical programs developed in accordance with Australian medical and research guidelines, and for access to genetic services, counselling and support
- Promote the sharing of knowledge and experience as research advances and clinical testing programs expand

More information

Support and services

- Genetic counselling clinics operate across Australia. The Centre for Genetics Education ph. 02 9462 9599 maintains a national list at genetics.edu.au
- Information on temporary suspension of genetic test results for insurance applications: genetics.edu.au/health-professionals/genomic-videos/implications-for-life-insurance
- IVF and pre-implantation genetic diagnosis (PGD): IVF Australia ph. 1800 111 483
- PGD assistance program: Genea ph. 1300 361 795 or visit the website at genea.com.au
- Online support network MND Genies (member-only Facebook group for people who have MND related genetic mutation, but do not have MND): mndnsw.asn.au/what-we-do/groups/1299-mnd-genies.html
- MND Decision Making Tools: Online tools for helping people with MND make decisions for their care and quality of life mnddecisiontools.com

Updates, facts and insights

- Project Mine: An international research collaboration helping find many genetic mutations projectmine.com
- Human Genetics Society of Australia Position Statement 2018 PS01 Genetic Testing and Personal Insurance Products in Australia: hgasa.org.au/documents/item/20

For more information about familial MND contact:

- the neurologist who is treating, or treated, the person in your family with MND
- your local MND Association www.mndaust.asn.au/state-mnd-associations

References

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To find out about motor neurone disease and other fact sheets in this series contact the MND Association in your state or territory ph. 1800 777 175 or visit www.mndaustralia.org.au

This fact sheet was reviewed by: Prof Ian Blair Faculty of Medicine, Health and Human Sciences, Macquarie University