Overview of MND research

The purpose of this information sheet is to give you an overview of motor neurone disease (MND) research.

We only fund research of the highest scientific excellence and greatest relevance to MND. If you would like to find out more about the research funded by the Association, as well as current opportunities to get involved, view our ‘What’s happening in MND research?’ newsletter via www.mndassociation.org/whats happeninginmndresearch.

Further information is available on our website (www.mndassociation.org/research) and research information sheets. These can be downloaded from our website or ordered from MND Connect on 08457 626262 or mndconnect@mndassociation.org.

To view the latest news on MND research, please visit our blog at www.mndresearch.wordpress.com, where you can subscribe to receive email alerts.

You can also follow us on Twitter @mndresearch. Alternatively, contact the Research Development team for the latest news on 01604 611 880 or research@mndassociation.org.

<table>
<thead>
<tr>
<th>Contents:</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is MND?</td>
<td>2</td>
</tr>
<tr>
<td>What causes MND?</td>
<td>4</td>
</tr>
<tr>
<td>a) Genetics</td>
<td>4</td>
</tr>
<tr>
<td>b) Lifestyle and environment</td>
<td>5</td>
</tr>
<tr>
<td>c) Cellular mechanisms</td>
<td>6</td>
</tr>
<tr>
<td>MND Association research</td>
<td>7</td>
</tr>
<tr>
<td>The International Symposium on ALS/MND</td>
<td>7</td>
</tr>
<tr>
<td>Care and support</td>
<td>8</td>
</tr>
<tr>
<td>Useful resources</td>
<td>8</td>
</tr>
</tbody>
</table>
What is MND?

MND is an umbrella term covering a number of progressive degenerative conditions involving the selective degeneration of motor neurones.

MND can affect adults at any age, but it most commonly appears in people in their 50s or 60s. Motor neurones are the nerve cells along which the brain sends instructions, in the form of electrical impulses, to the muscles. They form the link between a person thinking about moving, as well as the movement itself.

There are two types of motor neurone:

- **Upper motor neurones**, which have long, thin processes connecting the brain to the spine
- **Lower motor neurones**, which connect the upper motor neurones in the spine to the muscles of the body.

The ‘wiring’ is more complicated than this, however, the process of making the muscles work essentially involves these two types of neurones forming a ‘chain of command’ from the brain to the muscles.

In MND the motor neurones lose the ability to communicate the message from the brain to the muscle.

MND represents a breakdown in this line of communication. This results in progressive paralysis of muscles and, because paralysed muscles cannot exercise, they tend to decrease in mass (atrophy). This is why muscle wasting is a common symptom of MND.

In most cases of MND, degeneration of both the upper and lower motor neurones occurs. This condition is called **amyotrophic lateral sclerosis** (ALS). When the muscles involved in speech and swallowing are solely affected, this is known as **progressive bulbar palsy**.
There are also less common forms of MND, in which a more selective degeneration of either the upper motor neurones (such as primary lateral sclerosis) or lower motor neurones (such as progressive muscular atrophy) is observed.

Up to half of the people living with MND may also experience difficulties with learning, language and concentration. This is generally known as cognitive change.

Recent research has found a link between a family history of MND and a family history of frontotemporal dementia (FTD). Frontotemporal dementia is an increasingly recognized form of dementia, with different signs and symptoms to the more common Alzheimer’s Disease.

**More information:**
Care information sheet 23: Cognitive impairment in MND: Information for Carers
Living with MND guide

*For further information about cognitive change and how different types of MND may affect people please see our Care and Support section towards the end of this information sheet*
What causes MND?

Understanding the causes and mechanisms of motor neurone degeneration is essential to allow the development of treatments. Only by understanding what goes wrong in MND can scientists know how to design and where to target drugs and other therapies.

What do we know so far?

The majority of cases of MND are thought to be caused by a number of underlying contributory factors. These include subtle genetic, environmental and lifestyle influences as illustrated below. It is important to note that these factors must all coincide to trigger the disease. Using a mathematical model, research in 2014 has suggested that it takes 6 steps (or factors) to trigger the disease.

a) Genetics

For approximately 5-10% of people living with MND, the cause of the disease is primarily due to a mistake within the genes. However, for the majority of cases of MND, genes are thought to play a more subtle role. They may increase a person’s susceptibility to developing the disease or even play a role in slowing down the progression. Genetic research is currently underway across the world to learn more about the causes of MND.

The instructions for the way our bodies develop and function are provided by genes, which we inherit from our parents. In Approximately 5-10% of cases, MND is directly caused by a genetic mistake. This mistake can be passed down from parent to child, so the disease appears in the different generations of a family. This is known as familial, or inherited MND.

For the majority of cases, the disease appears for no apparent reason and is not passed on to future generations (sometimes known as sporadic MND). Researchers have not yet established what causes this type of MND. Normal genetic variations may make people more susceptible, but on their own do not cause the disease. In these cases, MND is thought to result from a combination of subtle genetic, environmental and lifestyle factors.

Researchers believe that discovering the genetic causes of inherited MND will lead to a better understanding of what is going wrong in all forms of MND. As they are clinically indistinguishable scientists believe that the mechanisms underlying both types of disease might be similar.

So far, a number of genes have been identified that can cause inherited MND including genes called SOD1, TDP-43, FUS, VCP, C9ORF72, SQSTM1, Profilin 1, MATR3 and TUBA4A.

More information:
Research information sheet B: Inherited MND
Read the blog on the 6 steps: https://mndresearch.wordpress.com/tag/six-steps/
b) Lifestyle and environment

Exposure to environmental factors that might contribute to the development of MND has been extensively studied over the years. This research is known as epidemiology.

These studies have identified possible links with prior exposure to mechanical and/or electrical trauma, military service, smoking, agricultural, high levels of physical activity chemicals and a variety of heavy metals. However, it is important to note that these are only ‘suspected’ contributory risk factors and the evidence obtained in these studies has often been circumstantial or conflicting with no clear conclusions.

It is not known how environmental and lifestyle factors could increase the risk of MND. One possible explanation is that they have a cumulative effect in weakening nerve cells, making them more susceptible to degeneration. Another explanation is that these factors interact with specific genes, triggering the disease through gene-environment interactions.

A number of possible environmental factors have been linked to MND. Some are protective and some may increase the risk of developing MND. These have been listed below along with further information:

- **Diet:**
  Studies into the impact of diet on the risk of developing MND found that people who ate a healthier diet, with fruit and vegetables, were less likely to develop the disease. The findings of such studies apply only to the risk of developing MND, not its treatment, and often examine just one of the many factors that may ‘tip the balance’ towards somebody getting the disease.

- **Professional sportsmen:**
  Research in 2008 identified that professional Italian football (soccer) players develop MND more often than the general population. However, other professional sportsmen appear to be at no greater risk, such as cyclists and basketball players. It is important to note that this research has not been confirmed in other countries (including the UK).

- **Physical activity/Exercise:**
  Research funded by the MND Association in 2013 reported a link between increased physical activity and MND in predisposed individuals. The researchers plan to look further into the genetic make-up of these individuals in order to identify the genetic factors involved. Please note that physical activity alone is not responsible for causing MND, other contributory factors are needed to ‘tip the balance’ in predisposed individuals.

More information:
Visit our website: www.mndassociation.org/whyme or read the blog article on physical activity: http://mndresearch.wordpress.com/tag/physical-activity-and-mnd/
c) Cellular mechanisms

Within motor neurones there are a number of possible mechanisms that may cause degeneration. These include:

Faulty scaffolding: Cellular ‘scaffolding’ called the cytoskeleton ensures that the shape and structure of motor neurones, and other cells, is maintained. If the structure is not held, it could cause the cell to degenerate.

Editors on strike: ‘Editors’ copy, tidy and transport short sections of code, known as RNA, to produce instructions that can then be used to build proteins. If this process becomes faulty, then the production of proteins could be adversely affected and cause MND.

Disruption to chemical communication networks: Electrical messages are transmitted from one motor neurone to the next via the release of a chemical messenger in the gap between them. For many motor neurones this chemical messenger is glutamate, but at high concentrations glutamate can be toxic.

Transport disruption: Motor neurones are large cells, the largest of which can be up to a metre long. It is important that their transport systems for moving nutrients, waste and components from one end to the other work well.

Aggregation: Abnormal clumps (aggregates) of protein molecules are found inside motor neurones affected by MND and may disrupt their normal functioning.

Build up of toxic waste: Oxygen free radicals are toxic chemicals formed as a normal by-product of processes within the cell. They are normally mopped up by antioxidants. However, research suggests that in MND, the motor neurones’ own antioxidant defence pathways may be suppressed leading to a toxic build-up of waste.

Power failure: All cells contain tiny ‘batteries’ called mitochondria, which are responsible for producing energy for the cell and also play other key roles in maintaining the cell’s normal function. The mitochondria in motor neurones from people with MND appear abnormal.

Lack of nerve nourishing factors: There is some evidence that motor neurones become more susceptible to MND because of the lack of nutrients. One form of motor neurone nutrients are a group of chemicals called neurotrophic factors, literally meaning ‘nerve nourishing factors’.

Problem neighbours: Motor neurones are surrounded by cells called glia, which normally provide the neurones with support and nourishment. However, researchers have now come to realise that glial cells, such as oligodendrocytes, can in fact contribute to motor neurone degeneration. These cells may lose their supportive properties and can even become toxic.
MND Association research

We fund and promote research that leads to new understanding and treatments, and brings us closer to a cure for MND.

We are a leader in the funding and promotion of cutting-edge MND research both within the UK and across the world.

We are currently committed to funding over 50 research projects across five key themes:

- Identifying the causes
- Developing models of MND
- Identifying markers of disease progression
- Developing treatments
- Improving healthcare and disease management.

More information:
Research Information Sheet E: Research we fund

The International Symposium on ALS/MND

The International Symposium on ALS/MND is the largest medical and scientific conference specific to MND and is the premier event in the MND research calendar for discussion on the latest advances in research and clinical management.

Each year, we organize the three day event, which attracts over 800 delegates, representing the energy and dynamism of the global MND research community.

“The symposium is an extremely important event in the Association’s calendar, and having seen it for myself, I now understand better the very important role it plays in the world of MND research.”

– Sally Light, Chief Executive of the MND Association

The 26th International Symposium on ALS/MND will be held in Orlando, USA from 11 - 13 December 2015.

More information:
Visit our website: www.mndassociation.org/symposium and our MND Research blog: www.mndresearch.wordpress.com
Care and Support

If you would like to discuss MND research, get copies of recent blog posts, or if you have any other questions, you can contact our Research Development team on 01604 611880 or research@mndassociation.org.

Alternatively you can contact our helpline to discuss any of these issues further please contact MND Connect on 0808 802 6262 or mndconnect@mndassociation.org

More information is available online on the Association’s website at:
www.mndassociation.org/research

Useful resources

MND Research blog is continuously updated with the latest MND research news throughout the year. From the International Symposium on ALS/MND to research in the news, the MND Research blog keeps you up to date by demystifying the science and explaining what it really means for people living with MND.

Website: www.mndresearch.wordpress.com
Twitter: www.twitter.com/mndresearch
Request copies by contacting the Research Development team (details above)

What's happening in MND research? is a quarterly research-specific newsletter that focuses on the latest MND research. The newsletter also contains Association research project updates, conference news and current opportunities to get involved

Website: www.mndassociation.org/whatshappeninginmndresearch
Request copies by contacting the Research Development team (details above)

Research information sheets: Our research information sheets cover a range of different topics, such as the research we fund, clinical trials, stem cells and unproven treatments, in more detail.

Website: www.mndassociation.org/researchsheets
Request copies by contacting MND Connect or the Research Development team (details above)