

December 2011

Over the last three years I have had the pleasure of writing this report with the aim of creating a report that could translate the most recent MND research filled with scientific jargon into something that we can all understand. It has been a very exciting three years and we have covered some great leaps in scientific progress in the understanding of MND. When I first started writing this report it was common to see the phrase “we do not know what causes most familial cases of MND”. Since then mutations in the genes TDP-43, ELP3, FUS/TLS, ANG, OPTN, ATXN-2, VCP and UBQLN-2 have all been found to cause MND. Most recently two groups of scientists have reported that a new gene, C9ORF72, causes many cases of MND and FTD. This new gene has become the most common known cause of MND. We have also seen progress in understanding the biology of MND with uncovering of pathways in inflammatory processes, stress pathways, protein disposal and much more. In this, my last report before passing on the job, we will focus on this new genetic mutation and what this means for understanding MND, and as always we will look at some of the other MND research going on all around the world.

## A molecular stutter causes MND?

Stuttering is best known as an involuntary repetition of sounds that can cause a block in communication for the affected individual. It now appears that a molecular stutter or repetition of code is the newest cause of MND. What is likely the biggest MND news this year, and possibly this decade, is the discovery that mutations in the gene called C9ORF72 cause both MND and frontotemporal dementia (FTD). This is now the most common known cause of MND.

This breakthrough finding was published simultaneously by two large cohorts headed by Dr Bryan Traynor from the National Institutes of Health, Bethesda, USA and Dr Rosa Rademakers at the Mayo Clinic in Florida, USA.

Although this gives us a new gene to blame for many cases of MND there is very little known about the gene itself. Normally genes are named after something that tells us about what they do. In the case of this gene, C9ORF72, its name tells us how little we know about it. All we know is where it can be found – chromosome 9, gene 72. At the moment we have no idea what it does. What we do know is that the gene has a special kind of mutation called a hexanucleotide repeat. This is an increase in the number of repetitions or ‘stutters’ of a 6-letter sequence in the DNA code. This pattern is not found in a region of the gene that ends up being part of the final message or blueprint for protein production. So the question still remains how does this cause MND? This is a question that will be tested in the near future.

## What are hexanucleotide repeats?

DNA is a long molecule that can be represented by a code of ‘nucleotide bases’.

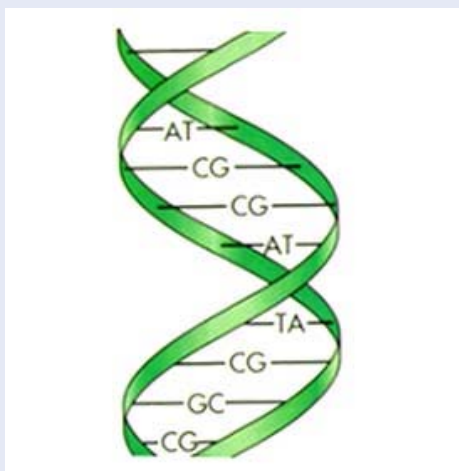
The number of nucleotide bases or letters in the code is estimated at around 2.9 billion.

Each gene has a specific code or sequence of nucleotide bases that can be represented by a series of letters.

A hexanucleotide repeat is a series of 6 bases that are repeated over and over.

These repeats are a normal part of our DNA. However, in some cases these repeats are increased from a normal 20 or so repeats to hundreds of repeats. This kind of increase is associated with diseases such as spinocerebellar ataxia.

The repeated pattern that is increased in the new MND gene C9ORF72 is GGGGCC.



## MND Research Shorts

- Researchers in Spain have found that injection of DNA that encodes a neurotrophic factor (GDNF) significantly delayed the onset of symptoms in MND mice prolonging life span.
- Scientists at the University of Rochester, USA have found that there is no relationship between prior exposure to magnetic fields and MND.
- Researchers in Italy have found antibodies against SOD1 are increased in some cases of slower progressing MND. This suggests that antibodies towards MND proteins are protective in MND.
- Work conducted in the Turin region in Italy has used PET imaging to study glucose metabolism in the brain. The study found that there was a huge increase in glucose metabolism in the MND brain.
- Researchers in Chicago, USA have discovered that mutations in the gene SQSTM1 are associated with MND. This provides more evidence that protein disposal mechanisms are associated with MND pathology.

### How does the hexanucleotide repeat cause MND?

A common element of MND pathology, regardless of the gene that is involved, is the accumulation of proteins into large junk piles called inclusions inside neurones. In many cases the protein made from the mutant gene is found in these junk piles of protein. Most protein inclusions in MND contain the protein TDP-43, known for its association with some forms of familial MND. Work conducted in the laboratory of Professor Chris Shaw in London has shown that in patients with hexanucleotide repeats in C9ORF72 some of the junk piles of protein do not have TDP-43 and some are in unusual locations in the cell. The researchers conclude that the C9ORF72 mutation may represent a subset of MND and that the mutation may cause a different set of proteins to end up in the junk piles.

### Release of synaptic signals in MND?

While the causes of most cases of sporadic MND are unknown, it has been hypothesised that there must be some genes that make people more susceptible to the disease than others. Researchers led by Dr Jan Veldink from the Netherlands have found that mutations in a gene (UNC13A), whose function is important in neurone signaling at the synapse, are associated with susceptibility to MND and a shorter disease duration. The synapse is the space between neurones through which messages can be passed; it is the main portal of communication in the brain. The findings of Dr Veldink suggests that dysfunctional release of signals from the synapse is associated with disease progression in MND. Similar results have been found in SOD1 familial MND where mutant SOD1, but not normal SOD1, binds to proteins that are associated with the synaptic signaling. The researchers, led by Dr Arima from Tokyo, Japan, suggest that this could mean that release of signals from the synapse could be directly affected by mutant SOD1.



If we think of the signaling between neurones like a tennis ball being thrown from one person to another, then it would be like having the ball covered in glue and making the ball sticky and hard to release. This means the message doesn't get through and causes problems with the neurones that could lead to cell death.

### Can an umbilical cord help fight MND?

It has been previously shown that while growing new motor neurones from stem cells is not feasible, creation of new non-neuronal cells in the spinal cords of MND patients could be beneficial. Dr Susanne Petri in Hannover, Germany has taken stem cells from umbilical cord blood and injected them into the spines of SOD1 MND mice. Injection of stem cells at early stages led to a drop in loss of motor neurones, better motor performance and increased lifespan. The researchers say that umbilical cord stem cells are neuroprotective and thus could potentially be used as a treatment in MND. This warrants further research for human disease.

### Evidence that algal toxin could cause MND?

There has long been a link to high levels of the algal toxin BMAA to a kind of MND with Parkinson's dementia complex in Guam.



However, there has not ever been any evidence that this toxin can actually cause neuronal death in animals let alone humans. A research team led by Dr Grace Zhai in Miami has tested the effects of ingesting the toxin on fruit flies. The scientists found that the flies that were treated with the toxin had shorter life spans, loss of motor function and memory and learning deficits. This provides the first evidence that BMAA can kill neurones, but it still remains to be shown that this toxin can actually cause a MND like disease.

### Drug delivery of copper protects MND mice

Copper is important to the function of the MND associated gene, SOD1. In fact, SOD1 is also known as copper/zinc SOD (superoxide dismutase). We know that for SOD1 to be at its most stable it requires both copper and zinc. With this in mind researchers in Melbourne led by Dr. Qiao-Xin Li have treated SOD1 MND mice with a drug that can deliver copper through the blood brain barrier. This treatment significantly preserved motor neurones and prolonged lifespan of the mice. This represents a potential new class of drugs that may be useful in treating human MND.

### From beer to MND?

Yeast has been used for hundreds of years to brew beer. Now it is being used in the fight against MND.

A research team headed by Dr. Aaron Gitler at the University of Pennsylvania has used the well-studied yeast to identify genes similar to MND associated TDP-43 and FUS in an attempt to identify potential candidates for new MND genes. The study identified the gene TAF15, which has a similar function to TDP-43.



### Clinical trial news

A drug that targets mitochondria, the centre for energy production in the cell, is being trialled for MND. The drug called dextramipexole has been developed specifically for MND and has been put on a fast track for approval by the FDA in the USA. It has been shown to be safe and well tolerated in MND patients and shows no adverse interactions with riluzole. Some patients were able to continue taking the drug after 26 months. Although the variation in the speed of disease progression often makes drug trials difficult to quantify, over the study period there was a statistically significant difference in decline between treatment groups as measured from baseline. These results are positive and support further testing of this drug.