

NEW MND GENE FOUND

Found: One new familial MND gene! FUS.

A new gene has been identified as playing a role in families with familial MND. Dr Ian Blair's overview of the discovery of mutations in the FUS gene appears at the end of this review.

SPORADIC MND, IS IT ALL IN THE GENES?

Worlds largest genome-wide screen for genes linked to sporadic MND finds nothing... Yet!

The hunt is on all over the world for variations in people's genetic makeup that may increase risk of sporadic motor neurone disease. So far these ambitious scientists are mostly coming back empty-handed. This is likely due to the fact that, like snowflakes, each case of MND presents differently. This is the conclusion the authors of the largest genome-wide (a genome is a person's complete set of genes) association study to date; "A two-stage genome-wide association study of sporadic amyotrophic lateral sclerosis (also known as MND)", published in *Human Molecular Genetics*.

It appears that the variability present in MND, both clinically and genetically, means that researchers have their work cut out for them. But researchers have not given up hope, the International Consortium on Amyotrophic Lateral Sclerosis Genetics, sponsored by the ALS Association (ALSA; USA), is working to collect thousands of subjects by archiving and analysing genetic data in one large repository.

Researchers uncover gene thought to be associated with sporadic MND.

Dr. Robert Brown and his group at the University of Massachusetts have teamed up with researchers in London and Belgium to identify a gene whose normally occurring variations appear to determine the susceptibility to sporadic (non-familial) MND.

The gene, elongation protein 3 (ELP3), is a gene that influences RNA metabolism. RNA is the messenger molecule communicating the coded blueprint hidden in DNA and aids in the production of functional proteins.

Dr Brown's group are excited by the findings, and are busy testing the effects of this gene on different cell types and in mice. "In the longer term, our goal as always is to determine how we can use this information to develop treatments for MND" says Dr Brown. The findings have been published in *Human Molecular Genetics* in an article titled "Variants of the elongator protein 3 (ELP3) gene are associated with motor neuron degeneration".

NEW MUTANT SOD1 MND RESEARCH

SOD1 production line woes.

Like the automated machines on a production line producing cars, inside each and every cell is a complex production line that produces proteins.

It seems that the latest research coming out of a collaboration between the laboratories of Dr David Borchelt and Dr P. John Hart in the USA show that mutations in SOD1 that cause MND mean that the SOD1 doesn't come off the protein

production line looking like a shiny new 2009 model Holden. In fact, it probably is more likely to resemble a rusty old 1978 model that no longer goes. As you can imagine this is not a good sign for a newly produced protein. The researchers found plenty of problems with the mutated versions and suggest that these production problems may represent the difference between the regular and the mutant versions of the protein that may point the way to understanding how mutant SOD1 causes MND.

It seems that the protein is no longer able to efficiently bind to the atom of copper and zinc which are so important to its normal function. The mutant version may also be able to interact inappropriately with other components of the cell. The findings were published online on the 19th February in the journal *Biochemistry* under the title "Structural and Biophysical Properties of the Pathogenic SOD1 Variant H46R/H48Q".

Aging changes mutant SOD1 housekeeping

The study outlined above indicates that the mutant SOD1 proteins don't come off the production line ready to "drive away". There are plenty of problems with it. However, new research from Yale shows that cells can deal with this broken down piece of junk.

Just like NRMA roadside assistance each cell in our body has a system in place to either jump-start our proteins back into working order or to tow them to the scrap heap where they can be dismantled and used to build more proteins.

The findings were published in the January 26 issue of the *Proceedings of the National Academy of Sciences USA*. The study, done in mice, suggests that as we get older we are less able to deal with the broken down junk proteins. So what ends up happening is that piles of this junk accumulate in the cell. It would be like our streets filling up with broken down cars, we would not be able to use the roads properly. In the authors words "we conclude that motor neurons, initially "compensated" to maintain the misfolded protein in a soluble state, but become progressively unable to do so".

MND AND THE IMMUNE SYSTEM

Overactive immune signalling in MND?

A group of researchers, led by Dr Adam Czaplinski, in Basel, Switzerland have measured the levels of the immune systems signalling molecules in spinal fluid. The results were published online on February 19 in the *European Journal of Neurology*. The researchers found that in MND patients the immune systems signals are more overactive than in other patients studied. Like the Bat-signal calls Batman to come and fight Gotham's criminals, these signalling molecules attract the brains crime fighting immune cells "microglia" to an area of inflammation. These signals may even attract other immune cells from outside the brain.

As there are no "foreign invaders" for these immune cells to fight it is thought their job is to clean up the dying motor neurons and while doing this may harm other nearby neurons. The authors suggest that the information contained in their research may lead to diagnostic tools and treatment targets.

Immune cells “switch-on” before symptoms.

A group of researchers from the University of Verona has shown that the genes that control the immune system are switched on before symptoms appear in MND mice. The study published in the *Journal of Neuropathology and Experimental Neurology* reported shrinkage of upper motor neurones (running from the brain to the spinal cord) and the “switching on” of surrounding immune cells such as astrocytes and microglia. The work found alterations indicating that the entire motor circuit is affected in the animal model of MND and that changes in the microenvironment of neurones occur before clinical signs of disease. Lead author Dr Roman Kassa feels that this study validates the use of the mouse model of MND and hopes that it can be used to develop novel and effective treatments.

NEWS OF RECENT DRUG TRIALS

Thalidomide performs poorly in phase II clinical trial.

Thalidomide had shown great promise in a mouse model of MND but results in humans have been disappointing. It was thought that Thalidomide may have reduced the levels of immune signalling molecules in the brain. However, the study did not seem to find any significant decrease in the immune signals or any effect on the disease progression. In addition, it caused unwanted side effects.

In conclusion, “treatment of MND with thalidomide, does not appear to effectively modulate disease progression and can cause adverse effects” say the researchers. The work was published in *Amyotrophic Lateral Sclerosis* in January 2009.

Modafinil helping with tiredness in MND

A small group of 32 patients took part in a short trial (four weeks) to test whether the drug modafinil could help MND patients with tiredness. The results were positive. There was a much higher response to the drug than to the placebo. This study published in the journal *Muscle and Nerve* suggests that modafinil, which is used in MS, could also help people with MND with their fatigue. However, the researchers caution “before modafinil is widely recommended for use in clinical care of MND patients, a multisite placebo-controlled trial with a larger, more diverse sample is necessary”.

Stem cell implants into motor cortex, safe or not?

Researchers in Mexico have taken cells from the bone marrow of MND patients and injected them back in to their brains in an attempt to stimulate new neuronal growth. Their findings were published in the journal *Cytotherapy* on February 3 2009. The treatment is “a well-tolerated procedure” reports Dr Martinez and co-workers.

Although this result shows that this type of therapy is well tolerated in MND patients, it is too early to tell how effective it has been. While other researchers are trying to examine and understand the smallest details of the stem cells they intend to use, some groups are not. The current study used cells that could potentially grow up to become microglia or other immune cells. Many reports have shown that these types of immune cells are damaging to the MND brain. So although stem cell based therapies are very exciting, some caution must be taken.

DIET AND MND

Fruit and vegetables join the fight against MND.

To date there have not been many researchers tackling the question of whether there is a link between diet and MND. However, a team of researchers in Japan have attempted to do just that. Their work was published on February 11 2009 in the journal *Neuroepidemiology*. “We investigated the relationship between dietary intake of vegetables, fruit, and antioxidants and the risk of MND in Japan” reports Dr Okamoto and co-workers.

153 MND patients and 306 age- and gender-matched controls were asked about their diet. The researchers found that “a higher consumption of all fruits and vegetables was associated with a statistically significantly reduced risk of MND”.

This led the researchers to suggest that higher intake of fruit and vegetables gives protection against the onset of MND. This research must be viewed with caution, since there are many other lifestyle choices that may be associated with the level of fruit and vegetable intake. For example, people who eat more fruit and vegetables may also be more likely to participate in regular exercise and other healthy activities and thus, in general, be in better health.

Another new MND gene discovery (FUS) implicates a common mechanism underlying MND

Two reports published simultaneously in the journal *Science* on 27 February 2009 describe mutations that have been identified in the gene encoding fused in sarcoma (FUS). One study describes FUS mutations found in Australian and UK MND families; the other reports FUS mutations in North American MND families.

FUS mutations account for between 3% and 5% of MND families. As such, FUS is the second most common known cause of MND after SOD1. However, a substantial significance of this discovery lies in the functional similarity of the FUS protein with TDP-43, a protein previously shown to be abnormal in MND. Abnormal TDP-43 pathology is thought to be present in over 90% of all MND cases (sporadic and familial MND combined). In contrast, SOD1 pathology only accounts for about 2% of all MND cases. Until now, the known MND genes (including SOD1, TDP-43 and ANG) had diverse and seemingly unrelated functions. It has been difficult to identify a common defective mechanism underlying motor neurone degeneration. With the discovery of abnormal FUS in MND, a common defective mechanism

has been identified. Both FUS and TDP-43 are RNA binding proteins that are thought to process and transport RNA. They both normally reside in the nucleus of the cell. In the affected motor neurones of most MND patients, TDP-43 is shuttled out of the nucleus to the cytoplasm where it forms aggregates. This same process has been found to occur with FUS in MND patients who carry a FUS mutation. Research efforts can now focus on this common defective mechanism to better understand the disease biology and ultimately give insights into new therapies that target that defective process. Development of cell and animal models based upon mutant FUS should help accelerate the search for therapies.

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