MND Australia
International Research Update

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March 2015

Getting personal: the future of medical research

The majority of people with MND report no previous family history of the disease and the main line of thinking is that multiple factors, both genetic and environmental, contribute to the development of this sporadic MND (sMND). This is also the case for many other human diseases, and their study has entered a new and unprecedented molecular era with the availability of DNA sequence data. Techniques used to measure changes in everything from the DNA sequence itself to the actual expression of genes and the levels and activity of the proteins they encode continue to be developed. These developments are leading the way to the personalisation of treatment, catering to the individual's specific biological dysfunction.

Measuring gene activity to understand MND

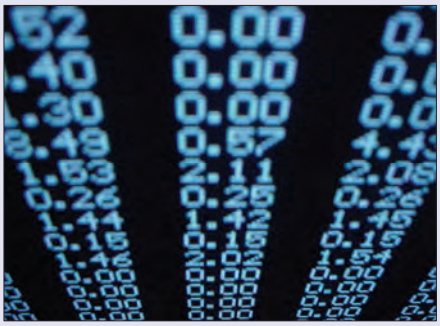
Every one of our genes is like a chapter in our very own biological manual, unique to each of us and holding all the information needed for our cells to grow and function. DNA is the language that encodes this information for storage, but before it can be read and used to make up the proteins of our cells it must first be translated into RNA. The amount of RNA copied for each gene varies from cell to cell and changes dramatically if our cells are stressed or diseased. Thus an important new technique for deciphering the genes involved in disease involves quantifying the entire population of RNA molecules present in a certain cell type (the transcriptome), comparing between the diseased and non-diseased cells.

Numerous transcriptome studies on MND have been carried out and published in recent years, however they have been limited in sample size, calling for the need for further studies of larger scale to confirm the results. To address this issue, Eleonora Aronica and her colleagues in Amsterdam, the Netherlands and Catania, Italy carried out the largest and most comprehensive transcriptome study yet reported. They analysed the RNA profiles across the entire genome in samples taken from the motor cortex of the brain from a large number of people with sporadic MND (who had previously been well-described clinically and neuropathologically) and also healthy individuals as controls. They then grouped the samples together based on similarities in the number of copies of RNA for each gene, with more RNA copies indicating the gene to be more active.

The researchers found that gene activity was different between sMND and controls, and that sMND samples could be divided based on distinct differences in gene deregulation. These findings show the power of gene activity analysis in discerning the genes and pathways involved in disease. Importantly, the findings also highlight the diversity between different cases of sMND, the need for personalisation of treatment and understanding of changes at the level of the cell's system rather than individual genes and molecules in isolation.

Going genome scale - handling the explosion of data

In this accelerated era of disease research and the increasing scale of genetic studies comes the equally large challenge of dealing with the volume of data that comes out. Accordingly, several methods have now been developed and are in widespread use to gain biological meaning from this data.



Cluster analysis is an umbrella term referring to several methods by which genes are clustered based on similarities in their expression patterns, or their levels of activity. Genes involved in the same pathways or that share similar functions can be identified this way. This is important for disease research as it facilitates identification of the genes and pathways that are deregulated in the disease. This is the first step to understanding how to treat the disease, as the genes, proteins and pathways involved can be targeted with specific drugs to try and alleviate their detrimental effects.

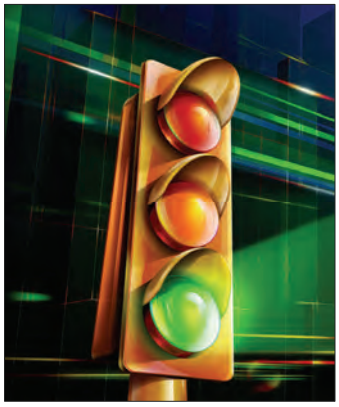
MND Research Shorts

- *Supporting the notion that multiple genetic factors lead to MND development, collaborating researchers across the US sequenced 17 known MND genes in about 400 people with MND and found that a significant proportion carried genetic mutations in multiple genes. Interestingly, the age of symptom onset in each case correlated with the specific combination of genes involved.*
- *Researchers in Ljubljana, Slovenia, have uncovered differences in the 3D DNA structure of the C9ORF72 mutation that is responsible for a major proportion of inherited MND cases. This structural variation will be an important consideration in further studies of the role of C9ORF72 in MND.*
- *Collaborators in Portugal and Germany have confirmed the finding by other groups that spinal cord levels of phosphorylated neurofilament heavy chain (pNFH) could be a useful biomarker for MND. They detected increased pNFH levels in people with MND that correlated with the rate of disease progression. Additionally they discovered changes in the pattern of carbohydrate modification of proteins that may also prove to be a valuable MND biomarker.*
- *Researchers in Shanghai, China, have shed light on how accumulation of the protein FUS in motor neurones may disrupt normal energy metabolism and protein break-down. They found that as the protein builds up, it disrupts the way in which the neurone would normally break it down. This research may help in the development of pharmacological interventions.*

Helping a nerve growth factor to slow degeneration

There is substantial evidence to indicate that glial cell derived neurotrophic factor (GDNF), a protein involved in the growth and maintenance of neurones, has a potent therapeutic effect on spinal motor neurones. Several studies have already demonstrated that GDNF production can be increased through activation of, mGlu3, a protein that sits on the surface of neurones and helps control the entry and exit of molecules to the cell. Investigating this potential further, Giuseppe Battaglia and his fellow researchers in Pozzilli and Rome, Italy, used a mouse SOD1-MND model to study the therapeutic effect of the drug LY379268, an activator of mGlu3. Continuous treatment with this drug enhanced levels of GDNF in the spinal cord, and reduced spinal motor neurone degeneration. This group's findings raise the possibility of incorporating drugs that specifically enhance mGlu3 receptor activity into the treatment plan for MND patients to slow down neuronal degeneration.

Controlling over-excitation through traffic control



Motor neurone degeneration in MND is attributed to several mechanisms, one of which is the toxicity induced in neurones by increased exposure to the neurotransmitter, glutamate, which over-excites the cells (excitotoxicity). Like other neurotransmitters, glutamate has its own protein transporter that carries it for release into the synapse, the tiny gap between communicating neurones. The trafficking of the transporters themselves is important for regulating the levels of neurotransmitters and thus crucial for normal nervous system function. In the last 15 years several studies have shown that the cellular mechanisms of endo- and exocytosis have an important role in regulating this trafficking. These are the cell's import and export pathways, controlling the substances that enter and leave the cell according to the cell's needs and the messages sent to the cell from its surrounding environment. Marco Milanese and his colleagues in Genoa, Italy, studied the impact of this import and export on the trafficking of two glutamate transporters, GAT-1 and GlyT-1/2, in the spinal cord of SOD1-MND mice. They found that exocytosis was working in over-drive, with excessive export of the two transporters, causing excessive release of glutamate into the synapse. It remains to be investigated further whether targeting the exocytosis-mediated release of glutamate pharmacologically proves to be a feasible way to reduce excitotoxicity and prevent motor neurone degeneration.

A small molecule with a big impact

With the variety of disease mechanisms believed to be involved in MND, clearly it would be ideal to combat several of these mechanisms at once, without causing any disturbances to normal cell function. Recently, small molecules of the vasoactive intestinal peptide (VIP) family have been shown to have anti-inflammatory protective effects during spinal cord injury, showing promise for targeting the neuroinflammation that occurs in MND. In Brussels, Belgium, Stéphanie Goursaud and others have been investigating the therapeutic benefits of SNV, a modified VIP, in a rat SOD1-MND model.

Just like the waves a small droplet makes upon hitting a pool of water, this small molecule makes a big impact. SNV delayed the onset of motor dysfunction and extended survival through reducing the aberrant activation of neuronal support cells, decreasing levels of pro-inflammatory molecules, and increasing levels of anti-inflammatory molecules as well as GDNF and two other beneficial neurotrophic factors. Continued study of SNV to confirm these findings and characterise any other biological effects it may elicit should prove a promising road to follow in the hunt for effective MND treatment.

Finding the culprits that lead TDP-43 astray

The RNA-binding protein TDP-43 is well-known to be a key player in MND. In the neurones of MND patients it has been shown to become "lost", straying from its home in the nucleus to instead loiter in the cytoplasm. How TDP-43 loses its way and why this is related to motor neurone dysfunction is an intense research focus as it may reveal a central event in the development of MND. Following a previous finding of the beneficial effects of reduced activity of an important protein called AMPK which is involved in energy regulation, Yu-Ju Liu and a team of researchers in Taipei, Taiwan, investigated its effect on TDP-43 behaviour and motor neurone function. In spinal cord motor neurones of MND patients they found abnormal activation of AMPK that was correlated with changes in the location of TDP-43. Supporting this result, treatment of an AMPK activator in cell culture and mouse MND models caused TDP-43 shift from the nucleus to the cytoplasm, and the use of agents that suppress AMPK activity rescued TDP-43, restoring it to its location in the nucleus. The pathway in which AMPK is involved and deciphering the mechanism by which it leads TDP-43 astray will no doubt be under further investigation following these intriguing results.