

TDP-43 and motor neurone disease

For some years, it has been known that TDP-43 protein accumulates in spinal cord neurones of patients with motor neurone disease (MND). These aggregates are not seen in the familial SOD1 form of motor neurone disease but are present in all sporadic MND patients. It was not known whether the accumulation of this protein is a normal repair process or whether aggregated protein causes the death of these neurones.

At the end of 2006, we found mutations in the *TDP-43* gene (which is the DNA code for the TDP-43 protein) in a single Australian family with multiple affected members who had English relatives. No mutations were found in the normal, non-affected members of the family. As is usual in motor neurone disease, we only had a few samples from living affected individuals to study in Australia, so we asked the family to contact their relatives in England. They found there were some living members of the family affected with MND. We therefore asked the English family to contact our MND research collaborators Professor Chris Shaw and Dr Sreedharan at King's College Hospital, London, to give blood samples for research. The results from the English branch of the family, added to our evidence that the mutation was only found in affected individuals, thus proving that this gene, when mutant, can cause motor neurone disease.

Our evidence that the abnormal (mutant) gene can cause the disease makes it likely that the accumulation of TDP-43 seen in the common sporadic cases of motor neurone disease may also be causing motor neurone disease. If this proves to be true, then TDP-43 will be a target for drug development. The search will be on for drugs that can reduce TDP-43 accumulation. There are now many research groups throughout the world interested in TDP-43, so it is likely that this research will progress rapidly. If a drug can be found which normalises TDP-43 in patients, then trials in animal models will be done. If successful, human trials will follow.

So, in summary, our breakthrough has been a pointer to the way ahead. How long it will take for this to translate into a motor neurone disease drug treatment is a guess. It is possible that an effective treatment could happen this year or in decades.

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