Second MND gene mutation in one year signifies rapid research progress

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A collaborative research project involving Professor Christopher Shaw of the Institute of Psychiatry, King's College London (KCL), Dr Tom Kwiatkowski at Massachusetts General Hospital (MGH) and Professor Robert H Brown at University of Massachusetts, has revealed that mutations in a gene called FUS (fused in sarcoma) cause familial Motor Neuron Disease (also known as Amyotrophic Lateral Sclerosis). This is the second gene to be discovered for ALS in just one year and is an important step towards understanding disease mechanisms. The research was published on line in two back-to-back papers in the journal *Science* today.

Professor Christopher Shaw, senior author of the KCL paper, explained: "The new gene, called FUS, is a very important clue as to what causes motor neurons to degenerate. It links in with TDP-43, which is deposited in motor neurons in 90% of all people with MND.

"The genetic pieces of the jigsaw puzzle are beginning to fit together leading us in new and exciting directions of research. There are also major implications for diagnosis and treatment.

"We are very excited about this latest discovery and the collaboration between the Boston and London research groups has been crucial in this breakthrough. It is only by understanding the fundamental disease mechanisms that we will find a cure."

This latest discovery will not only help doctors to counsel those families at risk of MND but crucially aid researchers to develop better models of disease. The gene FUS is shown to be related to the TDP-43 gene found by Professor Shaw's team last year. Thanks to this development scientists now have two more genes with which to map out the origins of this dreadful disease and develop drugs to combat it.

Research Progress

For nearly a decade, researchers at KCL and MGH have been hunting a gene that they knew must lie on the 16th chromosome. Following up on a lead from Kwiatkowski and Brown at MGH, Shaw's team identified a FUS mutation in their chromosome 16 linked family and subsequently found that 4% of all families had FUS mutations. These were only detected in those with the inherited form of MND, which accounts for 10% of all cases.

This is the fourth MND-causing gene to be identified after 20 years of genetic research. The first gene, called SOD1, was discovered in 1993, the second ANG is a growth factor for nerve cells discovered in 2006. The new protein FUS has a very similar role to the third gene TDP-43, mutations in which were first described by Professor Shaw's group in 2008.

This latest discovery has been made possible by the longstanding collaboration between researchers and co-funding by research organisations, including the ALS Association in the US and the MND Association in the UK.

Commenting on this latest discovery, Dr Belinda Cupid, Research Manager at the MND Association said: "This is the second MND-causing gene to be identified in less than 12 months, a reflection of the accelerating pace of research around the world.

"Not only will it open up an entirely new avenue of scientific investigation, it will also allow researchers to compare the different known causes of MND and start to home in on the main biochemical events that cause motor neurones to die. This understanding will lead to new approaches to defeat this cruel disease."

The FUS Gene

The FUS protein, made by the FUS gene, normally carries out multiple functions within motor neurones. These include regulating how gene messages are created, modified, and transported in order to make proteins which are the building blocks of all cells.

The mutations were identified by detailed gene sequencing in families with an inherited form of the disease linked to Chromosone 16. Usually the FUS protein works in the cell's nucleus, but the mutation causes the protein to be abnormally located in the cell, outside the nucleus and it forms large aggregates within motor neurons in people carrying the mutations. More work is now needed to determine how the FUS and TDP-43 cause MND.

The condition

MND is the name given to a group of related diseases affecting people in different ways. ALS is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord and is the most common form of MND. There is currently no cure for this condition and around 5,000 people in the UK at any one time are affected. Life expectancy for most people with MND is two to five years, and around half will die within 14 months of diagnosis. Up to 10% of cases of MND are the inherited and known as familial MND.

More information: The paper Mutations in FUS, an RNA Processing Protein, Cause Familial Amyotrophic Lateral Sclerosis Type 6 is published on line in the journal Science. Authors were Caroline Vance, Boris Rogelj, Tibor Hortobágy, Kurt J. De Vos, Agnes Lumi Nishimura, Jemeen Sreedharan, Xun Hu, Bradley Smith, Deborah Ruddy, Paul Wright, Jeban Ganesalingam, Kelly L. Williams, Vineeta Tripathi, Safa Al-Saraj, Ammar Al-Chalabi, P. Nigel Leigh, Ian P. Blair, Garth Nicholson, Jackie de Belleroche, Jean-Marc Gallo, Christopher C. Miller, Christopher E. Shaw.

Source: King's College London