

Welsh-Finnish link pinpoints important new familial motor neuron disease gene

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Families suffering from a history of motor neuron disease have helped an international scientific team locate a new gene linked to the incurable disease.

The investigators studied a large group of Finnish patients and a family from Gwent, South Wales who have lost many relatives to early onset motor neuron disease (MND) and the neurodegenerative disease fronto-temporal dementia, also known as Pick's disease. The team, including scientists from Cardiff University, The University of Manchester and UCL (University College London), discovered that both the Gwent family and the Finnish patients share a changed genetic segment on the short arm of chromosome 9.

Five thousand people in the UK have MND, and well known sufferers have included David Niven and Don Revie. The disease has recently been diagnosed in the South African rugby player Joost van der Westhuizen. The disease is progressive and fatal, with an average survival from onset of symptoms between two and five years.

Motor neuron scientists have been studying chromosome 9 for some years but until now have not been able to pinpoint the gene that causes the disease. The [new discovery](#) identifies the critical gene change as an expanded sequence of DNA repeats. Unaffected people carry up to 20 DNA repeats in a gene called C9orf72 whereas affected patients with motor neuron disease may carry hundreds of repeats. The gene change affects a gene segment outside of the normal protein coding portion of

the gene (affecting non-coding RNA).

The role of this DNA expansion is currently unknown but it probably disrupts multiple mechanisms in [motor nerve cells](#) (motor neurons), leading to their premature failure and motor neuron cell death. The new discovery will lead to new blood tests for families with a history of this condition, and, potentially, to new avenues for treating the [incurable disease](#).

The [genetic variation](#) was difficult to identify because it lies outside the protein coding regions that are normally studied in human genetic work. Although this variation was identified first in Finnish and Welsh patients it appears to occur in many different populations and accounts for the disease in up to one third of patients with a family history of motor neuron disease.

The Motor Neurone Disease Association and the ALS (Amyotrophic Lateral Sclerosis) Association funded the study, together with the Medical Research Council and the Wellcome Trust.

Dr Huw Morris, based at the MRC Centre for Neuropsychiatric Genetics, Cardiff University and the Royal Gwent Hospital, said: "This work is the culmination of many years work by doctors and scientists studying this condition and it is due in large part to the courage and tenacity of many patients facing motor neuron disease, particularly the Gwent kindred and the Finnish cohort. Although this work is the end of our long hunt for this gene, it is the beginning of our search for therapies based on this discovery that can stop this brutal disease in its tracks."

Professor John Hardy, based at the UCL Institute of Neurology, commented: "This is a very exciting finding which not only explains a significant proportion of motor neuron disease and frontal dementia but also puts RNA biology at the centre of the disease causation"

Professor Stuart Pickering-Brown, from The University of Manchester, added: "This is the most common genetic cause of motor neuron disease and frontotemporal dementia identified to date and opens up important new avenues of research."

The international collaboration was led by Bryan Traynor of the National Institutes of Health in the USA with colleagues from Cardiff University, UCL, The University of Manchester, Amsterdam and Finland. Their findings have just been published in the leading international journal *Neuron*. The same finding was independently made by a group at Mayo Clinic, Jacksonville, Florida, led by Dr Rosa Rademakers and published in the same journal.

Dr Brian Dickie, director of research development at the Motor Neurone Disease Association, said: "Discoveries in genetics are driving the ever-increasing momentum of motor neuron disease research. Chromosome 9 has been a prime suspect in motor neuron disease for some time but pinning down the precise genetic factor involved had proved elusive. The discovery of this rogue gene has the potential to significantly advance our understanding of [motor neuron disease](#), helping scientists to home in on the pivotal cellular changes underlying all forms of the disease."

Provided by Cardiff University

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