Huntington's research results in treatment advance

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Treatment of Huntington's disease may become more targeted and individualised as a result of research at the University of Auckland's Centre for Brain Research.

Scientists have for decades strived to understand why Huntington's disease, which is caused by a single gene mutation, can produce such variable symptoms. Post-doctoral researcher, Dr Eric Kim with his supervisor, Distinguished Professor Richard Faull, have found that different Huntington's disease symptoms are characterised by cell loss in different functional regions of the brain, suggesting a possible direction for developing targeted therapies.

In patients with severe motor and movement disorders, there was significant cell loss only in the motor cortex, (a region that regulates movement). In patients with severe behavioural and mood affected disorders, they found the opposite – that there was significant cell loss in the limbic cortex, (a region which regulate mood and behaviour), and not in the motor cortex.

"This is direct evidence to show the structural or anatomical origins of the symptom variability in Huntington's disease, and shows why some people manifest with different symptom profiles in Huntington's disease," says Dr Kim, who was involved in this work over the past four years. "It also showed us that every individual Huntington's disease patient is slightly different in the way their symptoms show up in the brain."

"Even studies on a pair of identical twins that share the same genetic background, show different symptom profiles," he says.

The study team used tissue from the Centre's Human Brain Bank and characterised 13 Huntington's disease patients and compared it to 15 normal control brains at the cellular level.

It's already known from previous research over the past two decades that Huntington's disease is caused by a single gene mutation that produces a mutant protein which forms aggregates within the neurons. The formation of these aggregates is known to cause an array of molecular changes that ultimately results in overt clinical symptoms associated with Huntington's disease.

Although it is caused by a single gene, there are major variations in the symptoms of Huntington's disease. The pattern of symptoms exhibited by each individual can differ considerably and present as varying degrees of jerky movements, mood and behavioural changes, and cognitive decline such as memory loss.

Recent investigations have focused on what the defective gene does to various structures in the brain and understanding the relationship between changes in the brain and the variable symptom profiles in Huntington's disease.

Analyses of post-mortem human Huntington's disease tissue suggest that variation in clinical symptoms is strongly associated with degeneration in two major regions of the brain, the striatum of the basal ganglia and the cerebral cortex.

The brain mass at the base of the brain – the basal ganglia – has strong connections with the lining of the outer layer of the brain – the cerebral cortex, says Dr Kim. The cerebral cortex initiates signals that are

interpreted by the basal ganglia.

"There are already well validated studies that the cerebral cortex and the basal ganglia are severely affected in Huntington's disease," he says. "That work is done using magnetic resonance imaging (MRI) with researchers from Boston at the forefront of that research."

The brains of Huntington's disease patients show severe atrophy in both the basal ganglia and the cerebral cortex.

As MRIs can show the region of the brain affected, but not what is happening at the cellular level, another approach was needed to find the different cell types involved in each of the disease processes.

"We decided to characterise 13 Huntington's disease patient cases and compare them to 15 normal control cases," says Dr Kim. "We focussed our study on the motor cortex for movement symptoms and the limbic cortex for mood and behavioural symptoms."

The study team worked with psychologists, Dr Lynette Tippett and Virginia Hogg from the University's Department of Psychology, who did clinical data analysis on the clinical symptom profiles for each case.

"We divided the patient group between those who had mainly behavioural symptoms and those with predominantly motor symptoms, and found that there were major differences in terms of cell loss in the motor cortex and limbic cortex, " he says. "There, a major cell loss in the motor cortex was only observed in the patient group with predominant motor symptoms and a major cell loss in the limbic cortex was only observed in the patient group with mainly behavioural symptoms."

"This suggests that our own recent detailed quantitative study in the post-mortem human Huntington's disease brain has complemented and

expanded the neuroimaging studies by providing a cellular basis of symptom variability in Huntington's disease," says Dr Kim. At present, there are several treatment strategies for Huntington's disease under study. These include cell transplants, gene therapy, and approved drugs to manage or alleviate the symptoms.

"We now believe our research shows that individualised symptoms need targeted treatments."

The research formed part of Dr Kim's doctorate that he has followed up in his post-doctoral research studies.

The research was published in a highly rated clinical neurology journal, the *Annals of Neurology*. It was supported by a grant from the Health Research Council of New Zealand, Neurological Foundation of New Zealand and the Auckland Medical Research Foundation.

Notes

Huntington's disease (HD) is an inherited brain disorder that causes cells in specific parts of the brain to die resulting in impairment of both mental capability and physical control.

Huntington's disease is a genetic disorder that afflicts about one in every 10,000 people. About one in every 1,000 people is affected by HD whether at risk, as a caregiver, a family member or a friend.

The HD gene is dominant, so that each child born to a parent with Huntington disease has a 50 per cent chance of sharing the same fate.

Provided by University of Auckland