Researchers get a closer look at how the Huntington's gene works

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Huntington's disease is caused by a mutation in the Huntington's disease gene, but it has long been a mystery why some people with the exact same mutation get the disease more severely and earlier than others. A closer look at the DNA around the Huntington's disease (HD) gene offers researchers a new understanding of how the gene is controlled and how this affects the disease. These findings set the stage for new treatments to delay or prevent the onset of this devastating brain disease.

Huntington's disease is a genetic disorder that gets passed down in families, but symptoms generally don't appear until later in life. It affects the brain and gradually worsens, causing problems with coordination and movement, mental decline and psychiatric issues. While every person has two copies of each gene - one on each chromosome - a single mutation in one copy of the HD gene means the person will suffer from the disease.

The HD gene is controlled by surrounding regions of DNA that function to turn the gene on and off. Dr. Blair Leavitt, professor in UBC's Department of Medical Genetics, and his colleagues took a closer look at this part of the genetic code. They identified critical regions where proteins, called transcription factors, can bind to the DNA and control the function of the HD gene. Changes in these DNA regions can play both good and bad roles in the disease. In some cases, the DNA changes increase the severity of the disease and speed up the onset and in other cases it protects the person by delaying the onset of the disease.

"The gene for Huntington's was discovered over twenty years ago but there is very little known about how the expression of this important gene is controlled," said Leavitt, who is also a scientist with the Centre for Molecular Medicine and Therapeutics. "This study helps us understand how small genetic differences in the DNA surrounding the HD gene can both delay and accelerate the disease."

Researchers found that when the DNA change is found on a normal chromosome with no HD mutation, it turns off the expression of the good gene and allows the mutant gene to predominate, speeding up the onset of the disease. If the DNA change is found on a chromosome with the HD mutation, it turns off the bad gene and offers individuals some protection from the disease.

According to Leavitt, these findings provide critical evidence to support the development of new drugs that decrease the expression of the mutant HD gene, an approach called gene silencing. Leavitt is already involved in the testing of one gene silencing treatment that shows great promise, and will begin the first human trial of this therapy for HD later this year.

The study was published today in *Nature Neuroscience*.

More information: A SNP in the HTT promoter alters NF-kB binding and is a bidirectional genetic modifier of Huntington disease, *Nature Neuroscience*, DOI: 10.1038/nn.4014

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