

Scientists identify early predictors of disease progression which could speed Huntington's disease drug trials

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Scientists have identified a set of tests that could help identify whether and how Huntington's disease (HD) is progressing in groups of people who are not yet showing symptoms. The latest findings from the TRACK-HD study, published Online First in *The Lancet Neurology*, could be used to assess whether potential new treatments are slowing the disease up to 10 years before the development of noticeable symptoms.

"Currently, the effectiveness of a new drug is decided by its ability to treat symptoms. These new tests could be used in future preventative drug trials in individuals who are gene positive for HD but are not yet showing overt motor symptoms. These people have the most to gain by initiating treatment early to delay the start of these overt symptoms and give them a high quality of life for a longer period of time", explains lead author Sarah Tabrizi from University College London's Institute of Neurology.

The TRACK-HD investigators have previously reported a range of tests that could be used in [clinical trials](#) to assess the effectiveness of potential disease-modifying drugs in people who already show signs of the disease. But in individuals without noticeable symptoms there was little evidence of a decline in function over two years, limiting the ability to test [new drugs](#) early in the disease course.

HD is caused by the mutation of a single gene on chromosome 4, which

causes a part of the DNA (known as a CAG motif) to repeat many more times than it is supposed to. The length of the CAG repeat is known to be a major determinant of the age at which symptoms of the disease are likely to start, but its contribution to progression is unclear.

Here the TRACK-HD investigators extend the study to a third year with the aim of identifying some of the earliest [biological changes](#) in individuals with presymptomatic HD, giving additional power to predict how the disease may progress beyond that already expected from age and CAG length.

Over 3 years, baseline measures derived from brain imaging were the clearest markers of disease progression and future diagnosis, above and beyond the effect of age and CAG count, in gene carriers up to 20 years before they were expected to show symptoms.

In particular, the investigators suggest that measuring volume change in white matter and the caudate and putamen regions might be future endpoints for treatment trials.

In individuals up to 10 years away from developing symptoms, there was also significant deterioration in performance on a number of motor (movement) and cognitive (intellectual function) tasks compared with controls, and the frequency of apathy increased. Finger tapping was the most sensitive of the motor assessments, while the symbol digit modality test proved to be the most sensitive of the cognitive measures.

According to Tabrizi, "A new generation of drugs will be ready for human trials in the very near future. Diagnosis in HD is something of an artificial construct at onset of motor symptoms, and this study now gives us a number of other, more well-defined parameters that correlate with disease progression. Something that suggests we're moving towards a more biological, as opposed to physical, definition of [disease progression](#)

that reduces the importance of an 'onset event' is great news. By extending the reach of clinical trials to include individuals who are currently free of overt [symptoms](#) there is a realistic future possibility that treatments in the pipeline can significantly improve the [quality of life](#) for patients and families."

Writing in a linked Comment, Francis Walker from Wake Forest Medical School in the USA says that the [TRACK-HD investigators](#) have set the standard for observational studies in other neurodegenerative diseases, adding that, "Virtual roadmaps of disease in the minds of practitioners⁶ are good for care in the framework of the traditional patient encounter, but it takes substantial effort, teamwork, and genius to turn them into rigorous, quantifiable timelines that can be used to test efficacy in future therapeutic trials."

More information: [www.thelancet.com/journals/lan ... \(13\)70088-7/abstract](http://www.thelancet.com/journals/lan... (13)70088-7/abstract)

Commentary: [www.thelancet.com/journals/lan ... \(13\)70088-7/abstract](http://www.thelancet.com/journals/lan ... (13)70088-7/abstract)

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