TRACK-HD reveals changes in HD mutation carriers, empowering future trials

Follow-up data from TRACK-HD study proves that we have the tests we need to successfully run drug trials for HD

By Prof Anne Rosser | **December 05, 2011** | **Edited by Dr Jeff Carroll**

The results of a two-year study of HD mutation carriers, called TRACK-HD, have just been released. These results prove that a number of changes, including thinking ability and brain changes, occur early in people carrying the HD mutation. Most importantly, these changes are suitable for use as endpoints in future clinical trials for drugs to prevent or delay the onset of HD.

What is TRACK-HD and why is it important?

The longitudinal results of the TRACK-HD study were published today in Lancet Neurology. TRACK-HD is a study that involved people positive for the HD gene, but without symptoms ('premanifest') and people who were in the very early stages of the condition ('early manifest').

TRACK-HD is a study designed to observe changes over time in people carrying the HD mutation.

TRACK-HD followed (or 'tracked') individuals over a period of two years to see if it was possible to pick up subtle changes that occurred even before the disease had become manifest. These changes are referred to as 'biomarkers' and will be important for both clinical diagnosis and for running clinical trials of new treatments.

Why do we need biomarkers?

‘Biomarkers’ are biological measures that can be used to follow change in disease status. A wide range of measures can be considered, ranging from the levels of specific chemicals in blood or urine, to changes that can be measured on a brain scan, to scores in a memory and thinking test.

The important point about biomarkers is that they can be measured repeatedly, and can be given a value that allows us to compare between individuals, and also to follow the changes in an individual over time.

Without biomarkers, we have to measure change using clinical scales. This is the approach that has been used in most studies involving HD patients to date. Clinical scales rely on questionnaires, or a clinician’s observation of a patient’s symptoms.

Although clinical scales can be used for this purpose, they aren’t very reliable because they depend on the judgment of a clinician. For example, a doctor may have to rate the amount of movement problems a patient has. Anything that depends on human judgment tends to be rather variable.

In light of this variability, trials have had to include many more patients, which makes them more expensive and difficult to run. This problem is magnified if we want to run trials on premanifest people, as our clinical scales are very poor at measuring any change at all in this situation.

Because of these problems with clinical scales, high quality clinical trials with premanifest subjects will be very heavily dependent on identifying suitable biomarkers.

All HD-affected people would like to run trials to prevent or delay the onset of HD, but this would be very difficult or impossible to do using clinical scales as an outcome measure.

As well as being important for the future of clinical trials, biomarkers may be useful for doctors trying to diagnose the onset of disease in an individual who has had a predictive test. At the moment, the only way to do this is to follow someone in the clinic over a period of years to try to assess whether their condition is changing.

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How did TRACK-HD work?

TRACK-HD was funded by the CHDI foundation and started in January 2008. It enrolled 117 premanifest individuals, 116 people with early HD and 116 people without HD, for comparison. Because the assessments were complex and time-consuming there was a limit to how many patients could be assessed in an individual clinic, and so the study took place between several sites in Canada, France, the Netherlands and the UK.

Participants had a ‘baseline’ visit at the start of the study, another at the end of year one, and one at the end of year two.

The baseline visit for each patient occurred between January and August, 2008. PREDICT-HD is another study, coordinated from the University of Iowa, which uses complementary (and partially overlapping) assessment tools.

What were the measures used in TRACK-HD?

A variety of assessments were used that aimed to measure changes across a wide range of symptoms in HD, including involuntary movements, slowing and irregularity of movements, eye movements, memory and thinking tests, and assessment of behavior. The participants were also assessed using clinical scales already in routine use, as this allows a comparison to be made between the new findings and the measures we already use.

The assessments were designed to be as objective to remove as much human judgment as possible. For example, rather than relying on a physicians observations, the movement assessments used a sensor that could be held between the forefinger and thumb. The same type of device can be pushed with the tongue to test how constant the pressure is; while this sounds odd, it turns out to be an indirect measure of movement problems.

Rather than being written down and transcribed by hand, readings were made directly and stored electronically. Another example of the advanced technology in TRACK-HD is the use of sophisticated eye tracking equipment to measure the very rapid tiny movements made by the eyes.

In addition to the clinic tests, scans of the brain were performed to measure how the volume of certain brain structures changed, and blood was taken and stored.

What were the findings in TRACK-HD after two years?

Now we need to work on measurements sensitive enough to detect change and test drugs before symptoms begin

The study revealed a lot of changes in the early symptomatic HD group over time. The most sensitive was loss of brain volume, but there were also changes in the memory and thinking and movement tasks. There were also measurable changes in eye movements, but they require more development before they could be used in clinical trials. Few of the behavioral tests showed reliable changes, although a test of reduced motivation looks more promising and provides a basis for further work.

Not surprisingly, it was much harder to see changes in the premanifest group. Because there is a relationship between the number of CAG repeats in someone's mutant HD gene and the expected age of onset of HD symptoms, researchers can crudely predict whether someone is 'close to' or 'far from' expected onset of symptoms. When the premanifest subjects were divided this way, researchers could see more changes in the brain scans of the group predicted to be closer to onset.

Where does this leave us and where next?

Some data from TRACK-HD has been previously published, in particular, the 'cross-sectional' data, which was a comparison of the differences between the premanifest and early HD groups at their first visit to the clinic. The cross sectional data has been useful, but the data presented in this current publication is much more valuable, because it follows individuals over time.

This follow-up study specifically describes the clinical and brain scan changes in the group over the study period, but some of this data will continue to be analyzed and so we should expect further publications in the future. Of particular interest, the researchers are continuing to analyze the blood samples for chemical changes.

The TRACK-HD results are important in that they will allow doctors and scientists to select better tests for clinical trials. They will also facilitate much better estimates of the numbers of patients needed for these trials. Clinical trials are very expensive to run and also hold a certain amount of risk for participants, so, although it is important to make sure trials have sufficient patients to get an answer, it is also important not to include patients unnecessarily.

In addition, very large trials would tie up a lot of patients and would result in fewer trials being conducted overall. This is going to become an even more important issue as more drugs come along to be tested. TRACK-HD helps us understand exactly how many subjects we need for each trial.

There are some things that we don't know yet about the TRACK-HD data. In particular, we don't know whether it is possible to modify the observed changes with treatment. If we do find a drug that makes HD symptoms better, will it also modify the behavioral and brain

scan changes revealed by TRACK-HD? This is the gold-standard for defining a 'biomarker', which will enable subsequent trials to be run even more efficiently.

It is also not known whether changes in a specific biomarker are related to a change in how a person functions. We're less interested in biomarkers that change in response to a drug if that drug doesn't also make the patient any better. All of these are questions for the future, so we should expect more publications from the TRACK-HD team.

Dr Ed Wild, co-founder of HDBuzz, works closely with Sarah Tabrizi, the global head of the TRACK-HD study. Dr. Wild had no input into the writing or editing of this article. For more information about our disclosure policy see our FAQ...

GLOSSARY

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

manifest after HD diagnosis, or when symptoms are already showing

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