# Through the eyes of a friend: changes in mood and behavior in early HD

**Companions of HD gene carriers are more likely to notice psychological changes in presymptomatic HD.**

**By Dr Leora Fox** | **December 02, 2015** | **Edited by Dr Jeff Carroll**

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The family and friends of individuals with HD often tell doctors that they began to notice changes in behavior long before a diagnosis was made. To better understand these early signs, researchers analyzed a psychological questionnaire filled out yearly for a decade by thousands of HD mutation carriers and their companions. The companions were more likely to perceive worsening symptoms over time.

## Understanding the early symptoms of HD

Huntington's Disease is inherited at conception, but for most carriers of the mutation, symptoms don't begin until middle age. Even though the HD mutation is toxic to brain cells called neurons, most mutation carriers spend several decades symptom-free. This means that the brain has a remarkable ability to withstand many years of exposure to the mutation.

*The input and support of trusted companions can be a great advantage.*

The period before major symptoms have developed is known as the *prodromal* phase of HD, when behaviors may begin to change gradually and subtly. Often, the very first symptoms noticed by HD patients or their families involve small alterations in thinking, mood, or disposition. These symptoms are real, but it's not possible for physicians to say that they're definitively due to someone carrying an HD mutation because many people who don't carry the mutation also experience these challenges.

What are these early symptoms like? Maybe a punctual person finds it more difficult to be on time for appointments, or a spouse notes that a good sleeper has become a bit restless. Since these early signs don't usually interfere with daily activities, medical research didn't focus there at first. Now, we are aware that investigating early changes is important, because they can inform when and how to begin treatment, especially when new drugs become available.

Recently, a group of researchers concentrated on understanding the psychiatric and behavioral difficulties that can occur in prodromal HD. The work is just one arm of a huge study that relies on thousands of HD-positive and unaffected volunteers. Over the course of a decade, participants and their companions filled out a questionnaire every year, evaluating the participant's psychological health. The study revealed some of the subtle psychological changes that can occur in pre-symptomatic HD, and showed that close companions were more likely to notice worsening symptoms than the HD mutation carriers themselves.

# PREDICT-HD: studying prodromal HD

The story behind this research actually began more than ten years ago, when researchers started recruiting for a huge study called PREDICT-HD. The overall goal of the work, which is ongoing, is to identify and understand the earliest signs of HD. HD mutation carriers and their families frequently report early behavioral changes, but diagnosis is usually based on movement symptoms that are more specific to HD.

To create standards for assessing patients and treating them with current and future therapies, clinicians need a clearer picture of what occurs during the years prior to the development of involuntary movements. This way, doctors can make decisions based on documented history from HD carriers around the world, rather than isolated anecdotes from just their own experience with patients.

Volunteers participating in PREDICT-HD came from all over the world, at 33 medical sites in six countries. Each person generously agreed to visit a study site for a whole day or two once a year, for up to 10 years. Participants were examined by clinicians, received brain scans, completed written evaluations, and donated blood samples.

Importantly, participants in the PREDICT-HD study had to have already undergone testing for the HD mutation – a person at risk for HD could only enroll if they knew their gene status. As a comparison, the researchers also included a group of control individuals from HD families who did not inherit the HD mutation. From the test tube to the clinic, the findings from PREDICT-HD are helping us to better understand the earliest changes experienced by HD mutation carriers.

# A yearly psychological pop-quiz

In the last decade there have been *hundreds* of publications about early HD based on data from PREDICT-HD volunteers. We'll zoom in on one study, which focused on prodromal psychiatric symptoms. Jane Paulsen, a clinical psychologist at the helm of the PREDICT-HD project, led the research team.

Every year, participants in the study completed a questionnaire about their psychological health. The test is used worldwide for many disorders, and it consists of 90 fill-in-the-bubble questions designed to measure a broad range of psychological problems. For example, a question might ask "In the past week, how much were you bothered by trouble concentrating?"

Respondents would rate each question on a scale of 0 (not at all) to 4 (extremely). Questions are designed to ask about feelings related to anxiety, depression, compulsions, interpersonal interactions, and many other categories.

Around 1300 participants took part in the study, both mutation carriers and controls, and most brought along a close companion to help assess their mental health using the same questionnaire. The companion was usually a live-in partner or spouse, but sometimes another family member or friend. The researchers were especially interested to see how mutation carriers' psychological scoring compared to individuals without HD, how their evaluations changed over an entire decade, and whether their companions' ratings matched their own.

# Assessing mental health in HD: at the beginning, over time, and via a friend

The authors of the study used different types of mathematical analyses to answer three main questions about prodromal HD:

*At the beginning of their participation in the study, were there already psychological differences between HD mutation carriers and unaffected individuals?*

> **"When behaviors and habits deteriorate slowly over long periods of time, the change is easier to see from an outside vantage point. "**

Yes. When they enrolled in PREDICT-HD, participants with the HD mutation rated themselves higher than control subjects on almost all aspects of the psychiatric questionnaire, including symptoms like anxiety, obsessive-compulsiveness, hostility, hyperawareness of physical illness or injury, and paranoia. Their companions also noticed these types of mental and mood changes, especially when their participating loved ones were closer to developing movement symptoms (such as those who were older, or had more severe mutations).

*Over time, from the beginning to the end of an HD mutation carrier's participation in the study, was there a noticeable change in their psychological health?*

Well, their companions noticed a change – but the mutation carriers didn't always agree. The majority of HD mutation carriers did not perceive their mental health to be getting worse over the years they participated in the study. However, their companions reported that certain psychological signs got worse, like anxiety, paranoia, and interpersonal distress.

*Was there an overall difference in how participants rated their own symptoms, versus how their companions rated their symptoms?*

Yes. The difference between the companions and the participants' ratings was especially striking in those predicted to have a higher likelihood of experiencing motor symptoms within a few years. Companions usually noticed more psychological distress in their loved ones than the HD mutation carriers did in their self-reports.

# The message

What is the meaning of these results? First, analyzing participants at baseline (the very beginning of the study) showed that early on in symptom progression, HD mutation carriers and their companions noticed subtle changes in their behavior and personalities compared to unaffected individuals.

This is important because it confirms on a much larger scale that mood and behavior symptoms are apparent early on to patients and their loved ones. These types of symptoms can increase in severity over time before movement symptoms occur, to an extent that was not previously appreciated. Gaining a better handle on the psychological health of people with presymptomatic HD could help shape how and when people receive a diagnosis, and when might be a good time to begin treating symptoms such as anxiety, depression, compulsions, or difficulty sleeping.

Second, HD mutation carriers and their loved ones may perceive *longitudinal* changes in behavior (those that occur over time) in different ways. While many participants with the HD mutation did not believe that their symptoms were getting worse, their companions definitely noticed increasing psychological problems or mental distress.

One explanation for this finding is that HD affects the complex circuitry of the brain in a way that hinders insight. This could be due to gradual damage in many connected parts of the brain that sync up to control self-awareness. Or it could simply be that when behaviors and habits deteriorate slowly over long periods of time, the change is easier to see from an outside vantage point. A person at risk for HD almost always completes their own health assessments, which may be part of the reason why the psychiatric symptoms have been difficult to link with disease progression.

# Considerations and conclusions

There are a couple of caveats to reflect on when we consider these results. The psychological questionnaire is very general, and it only asks about the previous *week* of the participant's life, so their answers might not always capture their feelings about the whole *year* since they last responded.

Another consideration is that all the participants and their companions were aware of their mutation status from the beginning to the end of the study. Getting tested is an extremely personal choice made by only a small fraction of those at risk for HD, and that knowledge could affect how a person and their friends and family perceive changes in behavior.

Nevertheless, PREDICT-HD is the largest and longest study that has ever been completed about the prodromal phase of HD, and there are many new results emerging from the data. The questionnaire responses show that there are a great variety of psychological and behavioral symptoms experienced by people with prodromal HD.

The results also imply that patients may not always be aware of how their symptoms change, confirming that the input and support of trusted companions can be a great advantage. Importantly, the combined data from thousands of helpful volunteers has turned individual anecdotes into solid data that will inform how we can better evaluate and treat the early symptoms of HD.

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*The authors have no conflicts of interest to declare.For more information about our disclosure policy see our FAQ...*

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**GLOSSARY**

**prodromal** prior to onset or diagnosis of movement symptoms
**neuron** Brain cells that store and transmit information

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