

Patient name

I  voluntarily request Variantyx to analyze my DNA for expansion of the CAG repeat in the HTT gene and expansion of the CTG repeat in the JPH3 gene in order to determine if I am at increased risk of developing Huntington disease or Huntington disease-like 2 respectively.

Huntington disease (HD) and Huntington disease-like 2 (HDL2) are late-onset, neurodegenerative disorders characterized by chorea and dementia. Although sometimes they appear earlier or later, symptoms typically first appear in the 30's or 40's, progressively worsening over a period of 10-25 years. As the disease progresses, individuals develop a range of physical, cognitive and behavioral symptoms. These may include:

**Movement symptoms:** unsteady gait and/or balance, involuntary movements, muscle rigidity or contracture, slow eye movements, difficulty speaking or swallowing

**Cognitive symptoms:** difficulty learning new information, difficulty recalling words from memory, difficulty organizing or focusing on tasks, tendency to repeat actions or behaviors, decreased impulse control and/or awareness of one's behavior

**Behavioral symptoms:** insomnia, loss of energy, fatigue, withdrawal from social situations, feelings of sadness or apathy, irritability

HD and HDL2 are inherited in an autosomal dominant manner, which means that one copy of an expanded repeat will result in the disease. HD affects approximately 1 in 10,000 individuals. HDL2 affects fewer individuals.

I agree to participate in predictive testing for HD and HDL2. I understand that this is a very accurate test. False positives and false negatives can occur, but are very rare.

For HD, Variantyx will analyze the number of CAG repeats within the HTT gene located on chromosome 4. The size of the repeat determines the clinical presentation of HD. I understand that if a mutation is identified it cannot tell me when I will begin to experience symptoms of HD. I understand that diagnosis of HD can only be made through a neurological exam.

I understand that there are four possible outcomes of the HTT analysis:

**Normal:** A repeat size of < 27 is considered normal. I will be told that my CAG repeat size is within the normal range and that I am not at risk of developing HD.

**Premutation:** A repeat size of 27 to 35 is considered a premutation. I will be told that CAG repeats of premutation size are not usually associated with HD, but are considered to be unstable and could become expanded. If my repeat expands, it could cause HD in my child if it is transmitted. Each of my children has a 50% chance of inheriting this unstable allele from me, but the risk of expansion is unknown.

**Intermediate mutation:** A repeat size of 36 to 39 is considered intermediate. I will be told that CAG repeats of intermediate size are usually, but not always, associated with HD. Most individuals with an intermediate repeat will develop HD, but there are a few older individuals who carry an intermediate size repeat and show no symptoms. Each of my children has a 50% chance of inheriting this allele from me. There is a significant risk of expansion to the disease-causing range. If transmitted to my children there is a significant risk that they will develop HD.

**Full mutation:** A repeat size of > 39 is considered to be a disease-causing, full mutation. I will be told that a CAG repeat of this size always leads to development of HD. Each of my children has a 50% chance of inheriting this mutation from me and developing HD.

For HDL2, Variantyx will analyze the number of CTG repeats within the JPH3 gene located on chromosome 16. The size of the repeat determines the clinical presentation of HDL2. I understand that if a mutation is identified it cannot tell me when I will begin to experience symptoms of HDL2. I understand that diagnosis of HDL2 can only be made through a neurological exam.

I understand that there are three possible outcomes of the JPH3 analysis:

**Normal:** A repeat size of < 29 is considered normal. I will be told that my CTG repeat size is within the normal range and that I am not at risk of developing HDL2.

**Premutation or Intermediate mutation:** A repeat size of 29 to 40 is considered a premutation or intermediate mutation. I will be told that the scientific literature is not clear on whether CTG repeats of intermediate size are reduced penetrance alleles that result in very late onset of HDL2 or whether they are actually not sufficient to cause HDL2. CTG repeats of intermediate size are however considered to be unstable and could become expanded. If my repeat expands, it could cause HDL2 in my child if it is transmitted. Each of my children has a 50% chance of inheriting this unstable allele from me, but the risk of expansion is unknown. If scientific evidence eventually shows that CTG repeats of intermediate size are reduced penetrance alleles that result in very late onset of HDL2, each of my children has a 50% chance of developing very late onset HDL2.

**Full mutation:** A repeat size of > 40 is considered to be a disease-causing, full mutation. I will be told that a CTG repeat of this size always leads to development of HDL2. Each of my children has a 50% chance of inheriting this mutation from me and developing HDL2.

I understand that learning I carry an HTT or JPH3 repeat expansion can result in serious psychological consequences including feelings of depression, futility and despair. If a repeat expansion is identified, I agree to post-test counseling.

By signing this form, I acknowledge that I have decided to undertake this test after reading the above information. I have been given an opportunity to ask questions about the test, and any questions I had were answered to my satisfaction. I acknowledge that I have sufficient information and understanding to give this informed consent.

Patient (or legal guardian) signature

Date



Legal guardian first name

Legal guardian last name



Patient (or legal guardian) signature

Date

