variantyx
For Clinicians

Variantyx Unity™ Test

Detecting tandem repeat expansions using whole genome sequencing

Variantyx Unity™ detects and reports pathogenic tandem repeat expansions in selected, known pathogenic regions.

What are tandem repeat expansions?

Tandem repeats are short sequences of DNA, typically 1 to 6 nucleotides in length, that repeat consecutively. The number of repeats naturally vary from person to person, with the length sometimes expanding during transmission from parent to child. Most repeats do not have a discernable function, but some have the potential to become pathogenic when the number of repeats exceeds a locus-specific threshold.

What role do tandem repeat expansions play in genetic disease?

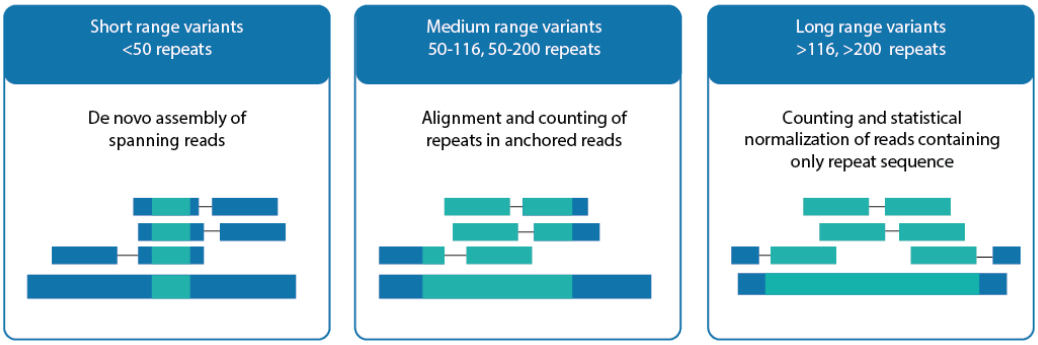
There are dozens of tandem repeat expansions that are known to be pathogenic. Some, like the CAG repeat expansion in the HTT gene, lead to late onset neurological disorders like Huntington disease. Others, like the CGG repeat expansion within the 5' UTR of the FMR1 gene which causes Fragile X syndrome, affect the individual early in life and are routinely tested for as part of the rare disease diagnostic odyssey.

At each pathogenic locus, alleles are classified as normal, premutation or full mutation based on the number of repeats with the ranges varying for each locus. For example, in the case of FMR1, alleles up to 44 repeats in length are considered normal. Alleles between 55 and 200 repeats in length are considered premutation and are at a high risk of having the number of repeats further expand into the full mutation range of >200 repeats when transmitted from a parent to child.

Until recently, detecting repeat expansions has required the use of PCR or southern blot analysis, usually employed to interrogate a single targeted gene. Panel and exome-based tests will miss these genetic changes.

How does Variantyx detect tandem repeats?

Variantyx uses whole genome sequencing (WGS) technology to provide comprehensive coverage of the entire genome. To analyze tandem repeat expansions in known pathogenic loci, three separate paired-end read strategies are used, all within a single assay.



The first strategy focuses on short range variants that are less than 50 repeats in length. Here de novo assembly of spanning reads is used as the full length of the repeat is contained within either R1 or R2, with uniquely mappable flanking sequences.

The second strategy focuses on medium range variants that range from 50 to 116 or 50 to 200 repeats in length, with the upper limit determined by whether the sequencing insert size is 350 bp or 550 bp. Here alignment and counting of repeats in anchored reads is used. With anchored reads, one member of the pair, either R1 or R2, contains only repeat sequence while the other member contains partial repeat sequence and partial uniquely mappable sequence.

The final strategy focuses on long range variants that are >116 or >200 repeats in length. Here counting and statistical normalization of reads containing only repeat sequence is used to estimate the repeat length.

Combing the three different methods, repeat length is calculated with good specificity up to the threshold that is determined by the sequencing insert size. Alleles with repeat lengths near or exceeding the threshold represent high-confidence estimates that are independently confirmed by an orthogonal technology.

What tandem repeats does Variantyx Unity™ detect?

We screen for more than 20 different repeat expansions. For the most up-to-date list of genes and diseases covered, please contact us at info@variantyx.com.

Advantages of Variantyx Unity™ tandem repeat analysis

With Variantyx Unity™ there is no need for a separate sample and separate assay.

Because WGS provides comprehensive coverage of the entire genome, all sequence data necessary for detection of tandem repeat expansions is present. Variantyx's custom-built, validated computer algorithms analyze the data, identifying repeat expansions for more than 20 different loci. Those alleles classified as premutation or full mutation are included in the Variantyx Unity™ clinical report alongside any other relevant variants.

Variantyx Inc.
1671 Worcester Road, Suite 300
Framingham MA 01701

Controlled document #: DCMMPRC630011
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Updated 01-10-19

Phone: 617 209 2090
Email: sales@variantyx.com
www.variantyx.com/clinicians