variantyx
For Clinicians

Variantyx Unity™ Test

Detecting structural variants using whole genome sequencing

Variantyx Unity™ test comprehensively reports genome-wide pathogenic and likely pathogenic structural variants.

How does Variantyx define structural variants?

Structural variants are gross deletions (losses) or duplications (gains) of DNA that are greater than 50bp in size. Structural variants include small copy number variants (CNVs) that are often referred to as del/dup events and which are commonly accepted to range in size from a single exon to a full gene. Structural variants also include larger CNVs, including inversions, translocations and complex rearrangements, that have typically been detected by traditional cytogenetic methods.

Insertions and/or deletions (indels) less than 50bp in size are considered to be small sequence changes. The methods that Variantyx uses to detect these small sequence changes are discussed in a separate document.

What role do structural variants play in genetic disease?

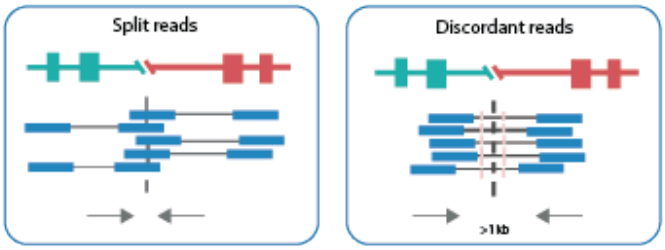
Structural variants have been shown to cause mendelian disorders such as Charcot-Marie-Tooth disease (duplication of the PMP22 gene) and Williams syndrome (deletion of the q11.23 region of chromosome 7). They've also been shown to contribute to complex disorders such as autism and schizophrenia. Although pathogenic structural variants are less commonly identified than pathogenic small sequence changes, recent studies of neurodevelopmental delay patients estimate that causal inherited or de novo structural variants account for ~15% of cases. With standard exome sequencing approaches, these genetic changes can be missed.

How does Variantyx detect structural variants?

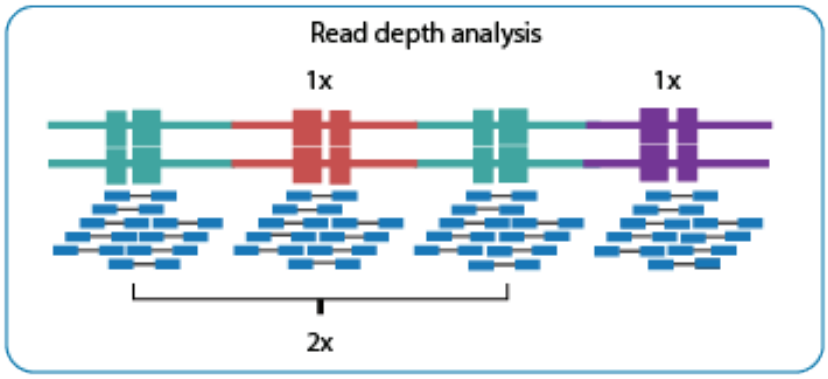
Variantyx uses whole genome sequencing (WGS) technology to provide comprehensive coverage of the entire genome. To analyze structural variants, two distinct analysis strategies are used: breakpoint analysis and read depth analysis.

Breakpoint analysis takes advantage of two types of reads: split reads and discordant reads. Under normal circumstances, a given paired sequence read will align to a single region of the genome. But for split and discordant reads, the paired read aligns to two distinct regions of the genome with little or no overlap. In the case of split reads, the breakpoint occurs within one of the reads and can be identified to the resolution of a single base pair. In the case of discordant reads, the breakpoint occurs in the insert between the reads, resulting in an unexpected span size or inconsistent orientation. Both are indicative of structural variation.

Read depth analysis takes advantage of the expectation of consistent coverage across the genome. Regions with unexpected levels of coverage – both significantly higher (>=2X) and significantly lower (<=.5X) – are indicative of structural variation.



These three distinct signals are detected by Variantyx's computer algorithms, subjected to relevant QC parameters and then combined to produce structural variant calls that are reviewed for possible pathogenicity. In most cases, the exact genomic coordinates of the structural variant can be determined.



Advantages of Variantyx Unity™ structural variant 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 structural variant detection is present. Variantyx's custom-built, validated computer algorithms analyze the data, identifying structural variants across the full spectrum from small and large indels to small CNVs to large CNVs. Those structural variants interpreted as pathogenic or likely pathogenic are included in the Variantyx Unity™ clinical report alongside any other relevant variants.