XomeDx*Xpress*: Rapid Whole Exome Sequencing

Description:

XomeDx*Xpress*, or rapid whole exome sequencing (WES), can be used to identify the underlying molecular basis of a genetic disorder in an affected individual. The XomeDx*Xpress* test is different from other types of genetic diagnostic tests in terms of the number of genes that are sequenced simultaneously. The XomeDx*Xpress* test targets the protein-coding regions of the human genome, which represents ~20,000 genes and accounts for approximately ~2% of all human genetic material.[1] These targeted regions of an individual's genes, called exons, are captured and sequenced using massively parallel sequencing. An individual's sequence is then compared to published reference sequences, other individuals from the affected individual's family, and control individuals to identify causal variants that could explain the disorder in the affected patient.

The XomeDx*Xpress* test is whole exome sequencing with an expedited turnaround time (TAT) of approximately 2 weeks. A verbal result is given within 7 calendar days after the start of testing. International clients will receive an email status update at 7 days. The verbal result will include pathogenic and/or expected pathogenic variants in known disease-causing genes (Human Genome Mutation Database genes). A written report including all clinically relevant, confirmed variants will be reported within approximately 2 weeks after the start of testing. Because of the rapid TAT, blood samples on the proband and both biological parents must be submitted at the same time, along with clinical information. XomeDx*Xpress* is best suited for patients whose medical management may be altered by having a rapid molecular diagnosis. This test requires approval by GeneDx; please email Xpress@GeneDx.com to discuss prior to sending in samples.

Result Reporting:

Whole exome sequence analysis is performed on the proband and parental samples, and/or additional relatives as needed, when submitted together for analysis. A single XomeDx or XomeDxPlus report will be issued on the affected individual in the family. A separate report will not be issued for unaffected parents or other unaffected family members who may also have submitted a specimen for the purpose of allowing better interpretation of the results from the affected individual. If additional reports are requested for other affected family members, additional fees will apply.

The XomeDx or XomeDxPlus report issued for the affected individual in the family will contain variations in genes previously implicated in a human disease similar to the affected individual or in genes hypothesized to be related to the cause of the disease (candidate genes), based upon the function, tissue of expression, and phenotype of model organisms with alterations in

the gene. Variants in candidate genes may also be reported based on internal data, such as observations of previous XomeDx cases with similar phenotypes and types of variations in the same gene.

ACMG Secondary Findings:

The American College of Medical Genetics and Genomics (ACMG) recommends that secondary findings, known and/or expected pathogenic variants, identified in a specific subset of genes associated with medically actionable, inherited disorders be reported for all probands undergoing whole exome sequencing. Please refer to the latest version of the ACMG Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing Report for complete details of the genes and associated genetic disorders. Secondary findings will be included for all XomeDx and XomeDxPlus reports, unless a family opts-out of receiving this information on the Informed Consent and Authorization Form as part of the XomeDx Test Requisition Form. The status for any secondary finding(s) reported for the affected individual will be provided for all relatives tested by XomeDx or XomeDxPlus; GeneDx does not conduct an independent evaluation of secondary findings in relatives. Relatives have the ability to opt-out of receiving secondary findings. Secondary findings will be confirmed by an alternate test method.

XomeDx*Xpress* Test method:

An affected individual's clinical records and prior genetic testing results will be reviewed prior to analysis. Using genomic DNA from the submitted specimen(s), the exonic regions and flanking splice junctions of the genome are sequenced by massively parallel (NextGen) sequencing on an Illumina sequencing system with 100bp or greater paired-end reads. Reads are aligned to human genome build GRCh37/UCSC hg19, and analyzed for sequence variants using a custom-developed analysis tool (Xome Analyzer). Capillary sequencing or another appropriate method is used to confirm all potentially pathogenic variants identified in the individual and parental samples. Sequence alterations are reported according to the Human Genome Variation Society (HGVS) nomenclature guidelines.

Limitations:

The XomeDx*Xpress* test attempts to evaluate the most important regions of the majority of the ~20,000 genes in the human genome. However, it is not technically possible to capture and sequence the entire exome at present. It is anticipated that approximately 95% of the targeted region of an affected individual's exome will be assessed with the XomeDx*Xpress* test at 10x coverage, while >98% of the target region will be covered at a minimum of 1x. There may be some genes or portions of genes that are not amenable to capture, sequencing, and alignment. Additionally, certain types of sequence variations are difficult to identify using whole exome sequencing; however, GeneDx can utilize other types of diagnostic tests in conjunction

with the XomeDx*Xpress* test to increase the likelihood of identifying a disease-causing variant in an affected individual's exome.

The scientific knowledge available about the function of all genes in the human genome is incomplete at this time. It is possible that the XomeDx*Xpress* test may identify the presence of a variant in the exome sequence of an affected individual, but that we will not recognize it as the cause of their disease due to insufficient knowledge about the gene and its function. Even if the XomeDx*Xpress* test identifies the underlying genetic cause of a disorder in an affected individual, it is possible that such a diagnosis will not permit an accurate prediction of the prognosis or severity of the disease. While there is a possibility that identifying the genetic cause may help direct management and treatment of the disease, it is also possible that this knowledge will not change management or treatment.

References:

1. Bamshad et al. (2011) Nature Reviews Genetics. 12:745-755.