Whole genome sequencing (WGS) and whole exome sequencing (WES) are two of the most comprehensive genetic tests currently available. If you haven't already, you may wish to review some of the basics in Genetics 101 and gene sequencing, as that information will be very helpful background to have first.

Background

The entire genetic code in humans is called the human genome. Our genome is made up of about 20,000 individual genes, or instructions. Our bodies read and process that information, and use the instructions to make proteins. These proteins carry out different functions or jobs within the body. More specifically, each gene is made up of two alternating types of information called "exons" and "introns". Every gene contains multiple exons and multiple introns. When the body is processing a gene to make a protein, the introns are removed and it is mainly the exons that tell the body how to make the proteins. Most known genetic changes that cause human disease or health issues are found in exons. This is why the exons are considered the most important part of the genome, and why we used to refer to the introns as "junk DNA". We now know that the introns are not junk, but we are still learning how information in the introns is used and what role they play in human development and function.

What is WGS and WES? And how are the tests different?

Through the use of technology called next generation sequencing, we are now able to look at large amounts of DNA at one time. With this technology, we can look at the letter sequence of all of the genome's exons. This is called the exome, and it makes up only 1-2% of the genome. This testing is called whole exome sequencing (WES). In comparison, whole genome sequencing (WGS) is when we look at all of the letter sequence of the entire genome (introns and exons).

WES is more commonly used in patient care for multiple reasons. At this time, we are able to better understand how variations in the letter sequence of an exon impacts our health. Also, WES generally costs less, and we are able to analyze the data more quickly.

WGS is sometimes used in patient care, but is more commonly used in research. In addition to looking at both introns and exons, WGS is able to better identify copy number variations (parts of the genome that are repeated – the number of these repeats may vary from person to person), and may be a more effective test for certain parts of the genome.

What type of results may be found?

All of us have variations in our DNA; it is part of what makes each one of us unique. As part of WES and WGS, hundreds to thousands of variants (changes) in the letter sequence may be found. The testing laboratory will analyze these variants and only provide information on a small amount of them because a majority of these variants do not have clinical relevance (they are part of what makes us unique and are not thought to cause health problems). These variants are classified as "benign" or "likely benign."

For those who undergo WES or WGS to help identify a genetic cause for their complex medical history, the primary focus is generally on variations in genes that, after analysis and interpretation, are thought to be the underlying genetic cause for the that person's medical concerns. It is important to know that not all variants that are reported will be in a gene that is associated with known or well-described health issues. There is a potential of a variant being reported in a gene that we don't know much about yet (called candidate genes). The type of variants reported may be classified as "pathogenic" (known to cause or contribute to health concerns), "likely pathogenic" (strongly suspected to cause or contribute to health concerns), or "variant of uncertain significance" (it is unknown whether it causes or contributes to health concerns).

To help with the interpretation of these variants, the laboratory may use past medical history, family history, and previous test results. Also, family member's samples may be requested (such as DNA from parents) to help understand if the variant is likely to be affecting someone's health or not.

Please see our page on genetic testing results for more general information.

Secondary Findings

Because WES and WGS look at all of our genes, an individual may be found to have variant in a gene that causes a medical condition that is not related to why the testing was done. An individual may or may not already have symptoms of the condition. These type of results are called "secondary findings" or "incidental findings."

The American College of Medical Genetics (ACMG) published recommendations that testing laboratories should report secondary findings in genes that are associated with medical conditions with clear and immediate medical significance. ACMG provided a list of 59 genes that should be reported when a "pathogenic" or "likely pathogenic" variant is found. This list of genes includes conditions such as hereditary cancer syndromes (i.e. high risk for

cancer), conditions with significant heart disease risk, or others with known treatment or preventative recommendations.

Other secondary findings that may be reported by a laboratory include other known genetic disorders not associated with the individual's medical concerns that are not on the ACMG list, carrier status for recessive disorders, and pharmacogenetic variants.

The reporting of secondary findings are optional. When you undergo informed consent for WES or WGS, you should be given the option to either opt-in or opt-out of these types of results.

Are there potential risks to doing this testing?

The primary potential risk associated with this testing is that the results may reveal genetic information about the patient or other family members that is unexpected (unrelated to the reason the testing was done). For example, a result may reveal that a patient or family member is affected with a specific genetic condition that may or may not have treatment or preventative recommendations.

Also, because we often request samples from other family members, we may inadvertently determine non-paternity (the person who was thought to be the father is not actually the biological father), or that an individual's parents are related (called consanguinity).

Are there limitations to this testing?

Although both WES and WGS are becoming very important diagnostic tools in discovering the cause of rare disorders, there are limitations. These limitations can be somewhat different between WES and WGS. There are some parts of our genome that are difficult to sequence. This may be due to the specific letter sequence, or the location of the letter sequence in the gene. Some types of genetic changes cannot be found by these technologies.

What does it mean if my WES or WGS was "negative"?

A negative result does not rule out an underlying genetic cause for an individual's health concerns. Variants could be found in the DNA that were not reported because based on our knowledge at this time, they were not suspected to be associated with any health issues. Over time, we will likely learn more about these variations. In the future, you can request reanalysis of the data to see if additional information can be provided.

Additional Resources

Unique

Genetics Home Reference WGS and WES and secondary findings

Genetic and Rare Disease (GARD) Tips for an undiagnosed condition