How to read and understand your genetic test report

When you first receive a genetic test report, it can be overwhelming to figure out what all the numbers, letters, and terminology mean. You are not alone! If you have questions about your report, a genetic counselor is best suited to explain it to you. However, we know there are always more questions that arise afterward, so we hope this document will help you out!

What is Whole Exome Sequencing?

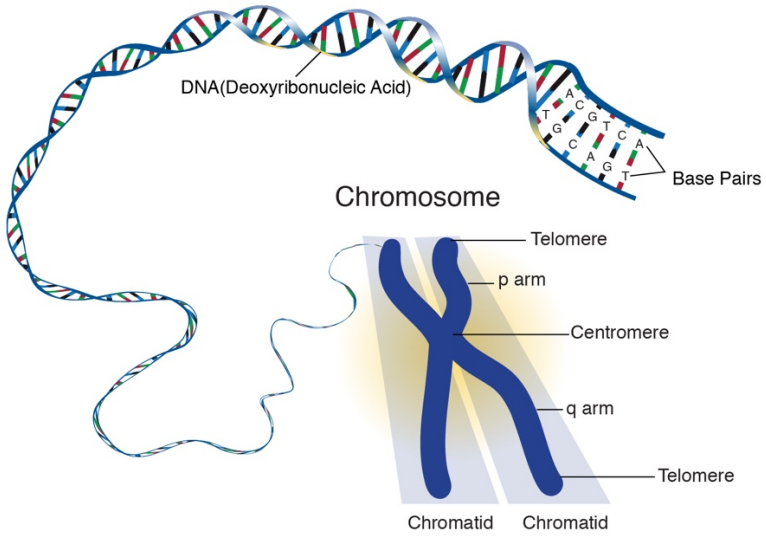
Genetic testing is the process of **sequencing** (or reading) our DNA to find **mutations** (or changes) that differ from what is common in the human population. **Whole Exome Sequencing** reads all of the **exons** to look for changes in our **genome (**all of our DNA) that might explain a specific **phenotype** (a symptom or set of symptoms). Our **genome** (all of our DNA) is separated into subunits called **genes**. Within these genes, there are even smaller subunits called **exons.** These exons contain the information for making proteins, which are the tools that cells use to do work. While exons account for only 1-2% of the genome, changes in exons have been linked to most genetic diseases, which is why we focus on them.

On our website, we will refer to a change in a gene as a **variant**, not a mutation. In the scientific literature, however, you will often see the word “mutation” used to describe a change.

Why is DNA important?

DNA, or deoxyribonucleic acid, contains all the information to make and maintain an entire organism. There are over 23,000 genes in the human genome and over 3 billion base pairs. On average, most genes have 3,000 nucleotides and 8.8 exons. The *CACNA1A* gene is a large gene with 300,000 nucleotides and 49 exons!

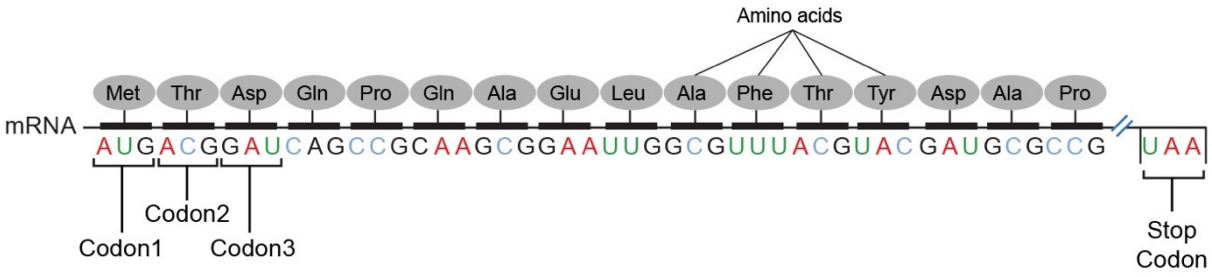
The information in our DNA comes in the form of four **nucleotides** (or **bases**): Adenine (A), Cytosine (C), Thymine (T), and Guanine (G). These nucleotides are strung together in pairs (A-T and C-G) to form units called **base pairs**. Each base pair forms the “rungs” of a ladder between two strands of DNA, creating the recognizable double helix structure. Further coiling of the double helix packs our genome into a larger but more compact structure called a **chromosome** (see figure on next page). Humans have 23 pairs of chromosomes: 22 numbered pairs (autosomes) and a pair of sex chromosomes (XX or XY). Each pair is made up of one chromosome from the mother and one from the father. Each gene has a specific location on a specific chromosome. For example, the *CACNA1A* gene is located on the small arm (p arm) of the 19th (autosomal) chromosome.



http://www.genome.gov/sites/default/files/tg/en/illustration/chromosome.jpg

What is the significance of variants?

When our genetic test reports a variant in a gene, what does that mean and how can it affect our body? Remember that proteins are the tools our cells use to get work done. How do we go from a gene to a protein? A gene is first transcribed or rewritten into **RNA (mRNA)**, an intermediate form of genetic information. The mRNA containing all the exons is used to build a protein through a process called translation. The specific information in the mRNA and exons comes in the form of **codons**, a sequence of three nucleotides that specifies an **amino acid** (shown below).

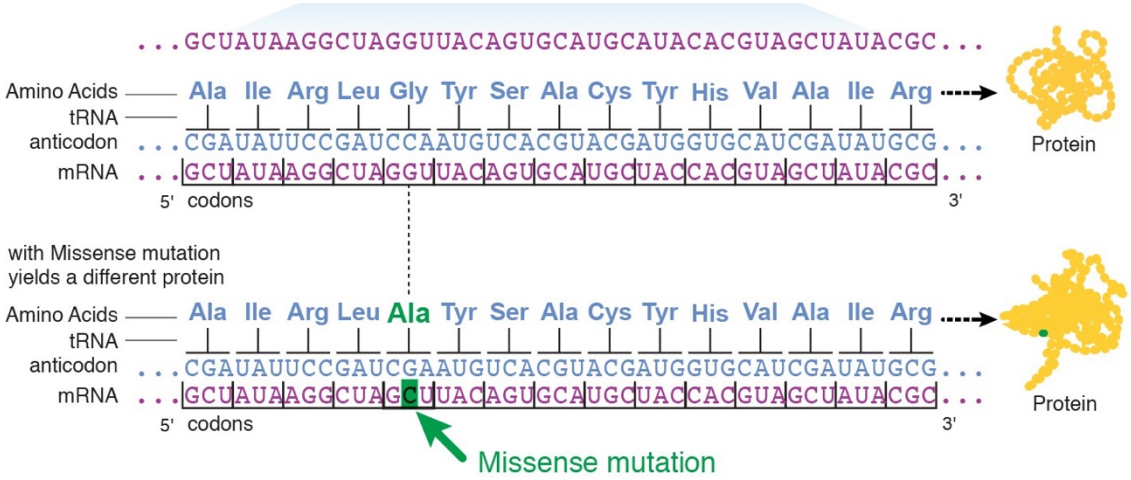


https://www.genome.gov/sites/default/files/tg/en/illustration/codon.jpg

Amino acids are the building blocks of proteins. The order of codons determines the correct sequence, or the order, of amino acids. There are 20 amino acids in our cells (see table below). Each one has a three-letter abbreviation and a single-letter abbreviation. In your genetic test report, you will see the change in both the DNA sequence and the amino acid sequence.

Name	3-letter	1-letter	Name	3-letter	1-letter
Alanine	Ala	A	Leucine	Leu	L
Arginine	Arg	R	Lysine	Lys	K
Asparagine	Asn	N	Methionine	Met	M
Aspartic Acid	Asp	D	Phenylalanine	Phe	F
Cysteine	Cys	C	Proline	Pro	P
Glutamine	Gln	E	Serine	Ser	S
Glutamic Acid	Glu	E	Threonine	Thr	T
Glycine	Gly	G	Tryptophan	Trp	W
Histidine	His	H	Tyrosine	Tyr	Y
Isoleucine	Ile	I	Valine	Val	V

So how does a variant affect a protein? The bottom line is that a variant in a codon can result in a different amino acid at a specific position in the protein. This matters because a protein's final 3-D structure is dependent on the correct sequence of amino acids. Furthermore, a protein's function, or what it does, is determined by its structure. Even if the variant only changes one amino acid (we call this a missense mutation shown below), the entire protein structure can still be altered! This can interfere with the protein's normal function and disrupt essential cellular processes that are necessary for growth and development. When proteins, like the Calcium Ion Channel, no longer function correctly in the parts of the brain that control movement, learning, memory, cognition, etc., it can lead to the symptoms we see with *CACNA1A* variants, such as ataxia, developmental delays, and/or seizures.



https://www.genome.gov/genetics-glossary/Missense-Mutation

Using what we just learned, how do we read a genetic test report?

Gene	Disease	Mode of Inheritance	Variant	Coding DNA	Zygosity	Inherited From	Classification
CACNA1A	*CACNA1A*-Related Disorder	Autosomal Dominant	p.V1393M	c.4177G>A	Heterozygous	Father (apparently Mosaic)	Pathogenic Variant

In this sample report, a change was discovered in the *CACNA1A* gene.

- The **Autosomal Dominant** mode of inheritance refers to the fact that a person only needs one copy of the variant in order for the symptoms/disease to manifest. This is called a **dominant** mutation. And the change occurred on an autosome (numbered chromosome).
    - NOTE: Sometimes two copies of a variant are required to see an effect. Those are referred to as **recessive** mutations. The known variants of CACNA1A typically present themselves in an **autosomal dominant** pattern.
- The specific amino acid change is **V1393M**, meaning the Valine (V), at position 1393 in the protein, was replaced by Methionine (M).
- The specific DNA change is **4177G>A**. This means that at nucleotide position 4177, the G was changed to an A, which changed the codon to one that specifies Methionine instead of Valine.
- The **heterozygous** zygosity means only one chromosome was detected to have the variant. In this case, the chromosome containing the variant was inherited from the father. **Mosaic** means the variant was not present in all of his cells.
- This variant has also been categorized as **pathogenic**, meaning there is clear data linking it to specific symptoms or a disease.

Gene	Disease	Mode of Inheritance	Variant	Coding DNA	Zygosity	Inherited From	Classification
CACNA1A	*CACNA1A*-Related Disorder	Autosomal Dominant	p.Asp1634Asn	c.4900G>A	Heterozygous	De novo	Likely pathogenic

In this sample report, a variant was also discovered in the *CACNA1A* gene.

- The amino acid change is **Asp1634Asn**. The Aspartic Acid (Asp) at position 1634 in the protein was replaced by an Asparagine (Asn).
- **4900G>A** means the nucleotide change occurred at the 4900th position, and the G was replaced by an A. The new codon specifies Asparagine instead of Aspartic Acid.
- The mode of inheritance is **autosomal dominant**, meaning only one copy of the variant is needed to see an effect. The **heterozygous** zygosity means only one of the chromosomes has the variant.
- The inheritance pattern was deemed "***de novo***" meaning the variant arose by itself as a new change that was not inherited from either parent.
- The variant is classified as **likely pathogenic** because there is some data linking it to specific symptoms or a disease.

If your genetic test report finds a change in the *CACNA1A* gene, does this mean you have a *CACNA1A*-related disorder?

This is something your genetic counselor will discuss with you. They will consider all the symptoms that have presented themselves and decide if a *CACNA1A*-related diagnosis is appropriate. Please keep in mind that the same variant in numerous people can also manifest itself

differently. Symptoms can be similar, but each person's body can uniquely process the variant, resulting in different outcomes. Genes also often work together with many other genes for our bodies to function properly. It is possible that variants in other genes will affect how the *CACNA1A* variant behaves.

Additional references:

https://www.ncbi.nlm.nih.gov/gene/773

https://medlineplus.gov/genetics/gene/cacna1a/#resources

https://www.genome.gov/

https://www.technologynetworks.com/applied-sciences/articles/essential-amino-acids-chart-abbreviations-and-structure-324357