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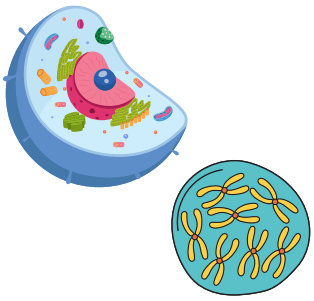
UNDERSTANDING A GENETIC LAB REPORT

Reading a genetic lab report can be overwhelming with its scientific terms and details. To make it easier, we've created this guide to help you understand the basics of genetics and common terms in your report. But remember, we at CUL3 Support & Awareness are not scientists—we're family members just like you. This is by no means comprehensive, but rather provides a simplified overview meant to help navigate reports with a bit more confidence.

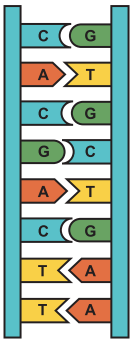
ALWAYS seek the guidance of a genetic counselor or your healthcare provider to fully understand your results and their implications.

GENETICS BASICS



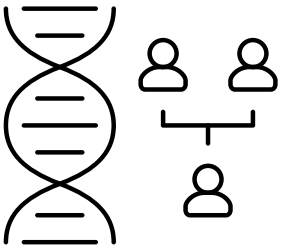
CELLS: The tiny building blocks of the body. Everything—from your skin and muscles to your brain and blood—is made of cells—trillions of them. Your cells need instructions to create who you are. Inside almost every cell is a nucleus, which acts as the control center. Inside the nucleus, you'll find DNA, which carries the instructions for how the body works. A small amount of DNA is also found in the mitochondria, the parts of the cell that produce energy. Nearly every cell in a person's body has the same DNA.

DNA (deoxyribonucleic acid): DNA makes up your body's instruction manual; it tells your cells how to grow and work. The "language" used to write your instruction manual is a code made up of four chemical bases—A, T, C, G. These are ordered (or "sequenced") almost like words in your instruction manual. These are called **nucleotides**.



GENOME: All of the DNA in your body.

EXOME: All of the exons in a genome.

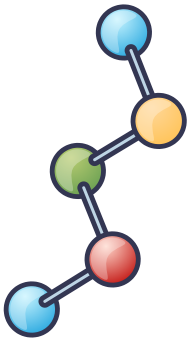


GENE: A section of DNA. Some genes give instructions to make proteins ("coding"), which are needed for the body to function, while others do not code for proteins. Humans typically have two copies of each gene—one from each parent—called alleles. Scientists name each gene uniquely to keep track of them, and since full names can be long, they often use short combinations of letters and numbers (like 'CUL3').

CHROMOSOMES: Like a package of DNA. A chromosome contains a single, long piece of DNA with many different genes. Humans have 22 pairs of numbered chromosomes (autosomes) and one pair of sex chromosomes (XX or XY), for a total of 46.

- Of note, the CUL3 gene is found on chromosome 2.

PROTEINS: The workers of the body—they help build, repair, and regulate everything from muscles to digestion to immune function. Each gene contains instructions for making a specific protein. If a gene has a change in its instructions, it can affect how a protein works, which may lead to a health condition.



- Of note, CUL3 is the gene where the body stores the information to build the protein called cullin-3. Cullin-3 is involved in the body's system for breaking down and recycling proteins. This makes it important in several developmental processes in the body.

AMINO ACID: The building blocks of proteins. The body uses 20 different amino acids to make thousands of unique proteins.

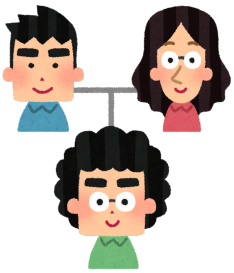
EXONS: The parts of a gene that contains the instructions for making a protein.

INTRONS: The parts of a gene that do not contain information to make proteins, but may play other roles in controlling how and when a gene works.

DNA SEQUENCING: A laboratory method used to determine the order of the bases within the DNA. This looks for changes that may affect how the body works.

VARIANT/MUTATION: A change in a gene's instructions is called a variant. Some variants don't cause any problems, while others can affect how the body functions.

INHERITANCE: How genetic traits and conditions are passed down from parents to children.



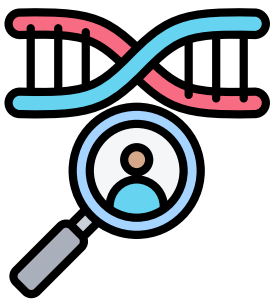
- DOMINANT: A change in one copy of a gene is enough to cause a condition.
- RECESSIVE: A person must inherit two changed copies of a gene (one from each parent) to have the condition.
- X-LINKED: The gene change is on the X chromosome and may affect males and females differently.

READING A GENETIC LAB REPORT

The following breaks down the parts of a typical genetic lab report and defines some of the common terms you may come across. Keep in mind that not all reports are structured the same or include the exact information presented here. Additionally, this list is not exhaustive, and your results should always be interpreted in the proper context with a healthcare provider.

INDICATION FOR TESTING

This section explains why the genetic test was ordered. It may describe symptoms or clinical features (also known as phenotype), family history, or a suspected condition that led to the testing.



PHENOTYPE: An individual's observable traits or characteristics, which are influenced by both genetic makeup (genotype) and environment. These include appearance, development, and behavior.

GENOTYPE: An individual's genetic makeup.

TEST PERFORMED

This section describes the specific genetic test used to analyze the DNA. Different tests are used depending on what information is being sought. The type of test performed affects the level of detail and the type of genetic variants that can be detected.

PROBAND: The first person in a family to undergo genetic testing for a particular condition. They are the individual through whom a genetic disorder is first identified in a family, and their results may guide testing and evaluation for relatives.

WHOLE GENOME SEQUENCING (WGS): A test that looks at nearly all of a person's DNA to find genetic changes that may explain health concerns.

WHOLE EXOME SEQUENCING (WES): A test that focuses on parts of the DNA that provide instructions for making protein (i.e., exons). These areas are where genetic changes that cause health concerns are most often found.

TARGETED TESTING: A type of testing that looks for a specific variant in a gene. This may be done if there is only one variant that causes a medical condition, or if a specific variant has been found in a family member and might have been inherited. The latter is called familial variant testing.

MULTIGENE PANEL: A type of testing that looks at a specific list of genes that could be related to a patient's health concerns. This type of testing may be done if there are multiple possible medical conditions that could explain a patient's health concerns.

SINGLE GENE ANALYSIS: A type of testing that focuses on just one gene. This may be done if a patient's health concerns strongly suggest a medical condition caused by changes in that one gene.

TRIO ANALYSIS: A type of testing often performed with whole genome or whole exome sequencing that includes the testing of the patient in addition to both parents (or other family members) at the same time.

MOLECULAR GENETIC RESULT

This section details the specific genetic variant(s) identified during testing, typically presented in a table format. It usually includes the gene name, the exact DNA change, the associated genetic condition, the mode of inheritance, zygosity, whether the variant was inherited or occurred spontaneously, and its classification based on clinical significance.

INTERPRETATION SUMMARY

This section summarizes the testing that was performed, the genetic variant that was identified, and the clinical diagnosis or condition it may be associated with.

VARIANT (MUTATION): A change in a gene. You can think of a variant as a spelling error in the instructions a gene contains. We all have variants in our DNA that make us unique, and most of them are harmless. Some variants, however, may cause health concerns. Historically, the term “mutation” was used, but now the term “variant” is preferred.

ZYGOSITY: The two copies of each gene that a person has—one from their mother and one from their father—are called alleles. Zygosity describes whether these two alleles are the same (homozygous) or different (heterozygous).

- HOMOZYGOUS: Both copies have the same genetic change.
- HETEROZYGOUS: One copy has a genetic change, and the other copy does not.

INHERITED VARIANT: A variant that is passed down from a parent to their child. This means that the parent and child both have the same genetic change.

DE NOVO VARIANT: A variant that was not passed down from either parent.

PATHOGENIC/LIKELY PATHOGENIC VARIANT: A genetic change known to or very likely to cause health concerns.

VARIANT OF UNCERTAIN SIGNIFICANCE (VUS): A genetic change that is not completely understood yet. It might be harmless (benign) or it might cause health issues (pathogenic), but more information is needed to know for sure.

BENIGN/LIKELY BENIGN VARIANT: A genetic change that is known not to cause health concerns.

AUTOSOMAL DOMINANT: A pattern of inheritance where having one copy of a gene with a pathogenic variant is sufficient to cause a genetic condition.

AUTOSOMAL RECESSIVE: A pattern of inheritance where both copies of a gene require a pathogenic variant to cause a genetic condition.

VARIANT DETAILS

This section provides more detailed information about the genetic variants found during testing. This may include the health condition(s) associated with the variant, its frequency in the general population, and the reasoning behind its classification. It will likely also distinguish between primary, secondary, and incidental findings,

POPULATION FREQUENCY: How common a variant is estimated to be in the population. If a variant has a very low population frequency, or has never been reported before, it may increase the chance the variant may cause health concerns. If the variant is considered very common in the population, this may reduce the chance it causes health concerns.

PRIMARY FINDINGS: Genetic changes that are related to the reason for testing. These findings often explain the cause for a person's health concerns.

SECONDARY FINDINGS: Genetic changes that may affect a person's health or medical care, but are not the primary reason for testing. These could include findings related to 'reportable variants in medically actionable genes', which are genetic variants known to have important implications for health, even if they are not directly related to the condition for which the test was initially ordered.

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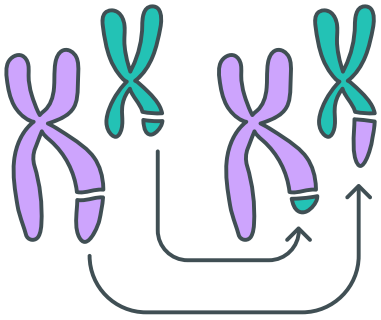
TYPES OF VARIANTS

A quick reminder:

- The information in our DNA is stored as a code made up of four chemical bases known as adenine (A), guanine (G), cytosine (C), and thymine (T).
- Changes to the sequence of these bases are called variants. Some changes might have no effect, while others can impact our health by affecting the function of important proteins.



There are several different types of variants that may be described in a genetic lab report. These may include (but are not limited to):

- SUBSTITUTION: When there is a substitution of one base for another-leading to the substitution of one amino acid for another(e.g., a change in a single "letter" such as switching an A to a G). MISSENSE, NONSENSE, and SILENT can all be substitution variants.
- INSERTION: When one or more extra bases are added.
- DELETION: When one or more bases are removed.
- FRAMESHIFT: When a base(s) is inserted or deleted, shifting the way the gene is read. INSERTIONS, DELETIONS, and DUPLICATIONS can all be frameshift variants.
- SPLICE SITE: When a change occurs at the boundary of an exon and an intron.

Genetic variants are associated with loss of function or gain of function depending on how they affect the gene's activity:

- LOSS-OF-FUNCTION: A change that reduces or stops the gene from working properly.
- GAIN-OF-FUNCTION: A change that makes a gene work too much or in a new way.

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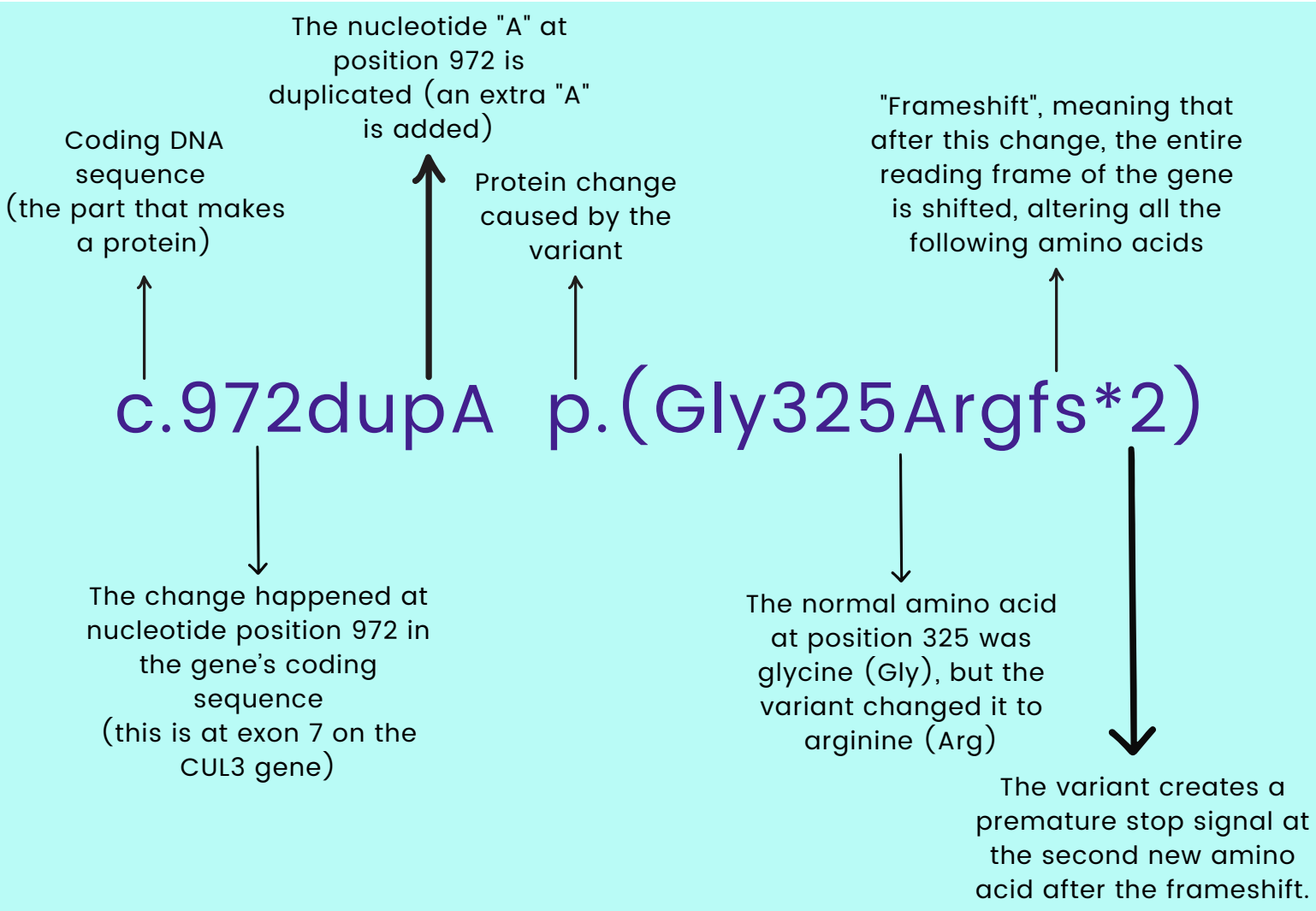
EXAMPLE VARIANT

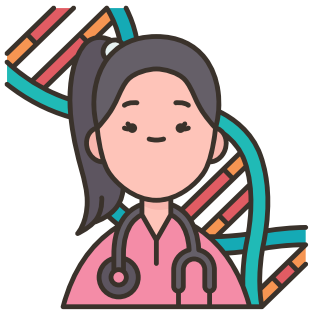
Here is an example of pathogenic genetic variant in the CUL3 gene and a breakdown of its components. NOTE: This is just one example—individuals will have different genetic variants—including in the CUL3 gene. This is to help you better understand the parts of a sequence variant that you may see.

The following is a frameshift variant caused by a duplication, which changes the reading of the genetic code. Instead of making a full, functional protein, the cell produces a truncated (shortened) version that is likely nonfunctional because it is cut off too early. Since CUL3 is important for protein regulation in cells, changes like this are likely to lead to health issues (i.e., CUL3-related neurodevelopmental disorder). This is considered a loss-of-function variant.



RECOMMENDATIONS

This section suggests next steps such as having a healthcare provider interpret the results in the context of clinical findings findings and seeking genetic counseling. May also note limitations of the testing.



CLINICAL CORRELATION: When a healthcare provider interprets how genetic test results relate to a person's symptoms or medical history. It helps to understand the significance of the results in the context of a person's overall health.

GENETIC COUNSELING: Service where a trained genetic counselor helps individuals and families understand genetic test results, their implications for health, and the potential risks for other family members.

MOSAICISM: A condition in which cells within the same person have a different genetic makeup. This condition can affect any type of cell, including blood cells, skin cells, and egg and sperm cells.

GERMLINE MOSAICISM: When a genetic change happens in the egg or sperm cells, but not in other cells of the body. A person with germline mosaicism typically won't show symptoms of the condition, but they may pass the genetic variant on to their children, who could be affected.

METHODOLOGY USED

This section provides detailed information about the specific type of genetic testing performed. It describes the techniques and technologies used to analyze the genetic material, as well as key details like the sensitivity of the test (how well it can detect genetic changes) and limitations.
This section is very technical and scientifically detailed, making it more suited for healthcare providers.

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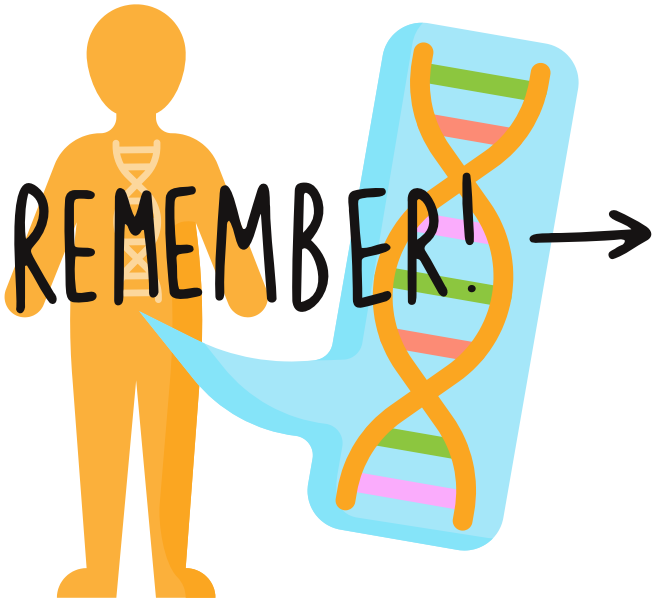
QUESTIONS TO ASK YOUR HEALTHCARE PROVIDER

Here are some questions that might be helpful to consider when discussing genetic test results with your healthcare provider:

1. What does this result mean for my / my child's health?
2. Is this genetic change inherited or new?
3. Does any additional genetic testing need to be done for myself / my child?
4. Are there any other family members that should consider testing?
5. What steps should we take next?
6. If for my child, can I get a medical note for their school and/or other healthcare providers?
7. Is there a plan for genetics follow-up?



Genetics is just one piece of the puzzle. Your or your child's genetic test results represent only one facet of overall health and identity. Other genes, along with environmental factors, also play a significant role in shaping who we are.

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FOR MORE INFORMATION

To learn more about the basics of genetics, we recommend the following resources:

MedlinePlus: Genetics
https://medlineplus.gov/genetics/

National Human Genome Research Institute: About Genomics
https://www.genome.gov/about-genomics

CDC: Genomics and Your Health
https://www.cdc.gov/genomics-and-health/index.html

American Society of Human Genetics: Discover Genetics
https://www.ashg.org/discover-genetics/

Your Genome
https://www.yourgenome.org/

Genetics for dummies
Kratz, R. F., & Spock, L. J. (2023). Genetics for dummies (4th ed.). John Wiley & Sons, Inc.

For Kids:

American Museum of Natural History
https://www.amnh.org/explore/ology/genetics/what-is-genetics

Brittanica Kids
https://kids.britannica.com/kids/article/genetics/353170