# VARIANT CLASSIFICATION

### What do the different variant classifications mean?

Genetic mutations are classified into specific groups that describe how they will affect protein function and human health. These groups are categorized based on various factors, including their frequency in the healthy population and the type of mutation present. Classification typically involves assessing the available evidence from scientific literature, databases, and clinical studies to determine the variant's significance.

### Variant classifications:

Pathogenic: Variants classified as pathogenic are likely to cause or contribute to a genetic disorder.

Likely pathogenic: Variants classified as likely pathogenic are involved in the development of the associated condition based on available evidence. However, they may not always result in disease manifestation on their own and may require additional factors, such as environmental influences or other genetic variations, to trigger the development of the disease phenotype.

Variant of Uncertain Significance (VOUS/VUS): Variants classified as VOUS/VUS have uncertain significance and may or may not be associated with a genetic disorder. Further research or clinical evidence may be needed to determine their significance.

Likely benign: Variants classified as likely benign are unlikely to cause or contribute to a particular disease or disorder based on available evidence. This evidence may include the variant being present in healthy populations and frequency in the general population, and their predicted lack of impact on protein function or gene regulation. These variants will not appear on genetic reports.

Benign: Variants classified as benign are not known to be associated with any known health problems or diseases. These variants are typically found in healthy people. Databases such as gnomAD, a website listing variants in healthy people, typically list these types of variants. If your child's mutation is not found in this database in the gnomadAD variant section, it may mean it is not a benign mutation and can cause disease. (https://gnomad.broadinstitute.org/)

### What if my child's mutation is not in a database?

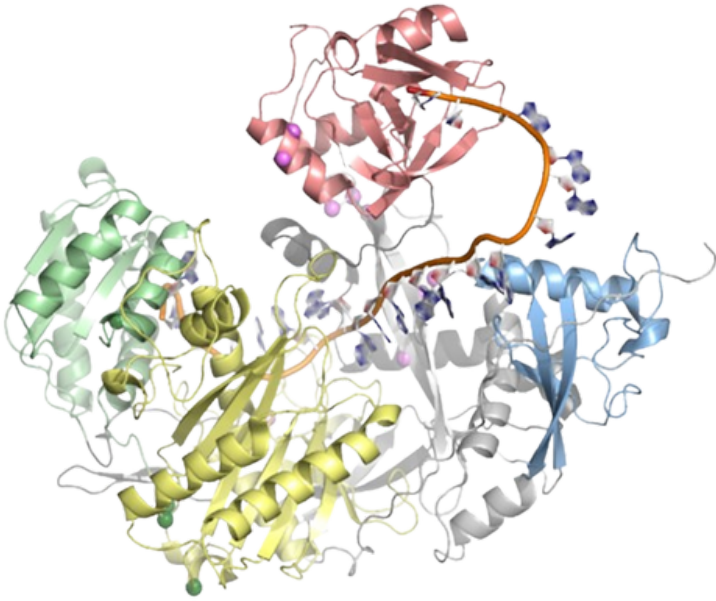
If a variant is not found in any database (either associated with healthy populations or unhealthy), it may indicate that the variant is rare or newly discovered. Further research or clinical evaluation may be needed to determine its significance and association with genetic disorders.

# Questions?

# Contact the AGO Alliance!

AGO Alliance
Balgriststrasse 82
CH - 8008 Zürich
Email:
contact@argonautes.ngo

AGO



***AGO Protein Adapted from:***
***10 Schalk A, et al.***
***J Med Genet 2021;0:1–10. doi:10.1136/jmedgenet-2021-107751***

# Argonaute Syndromes

# Understanding Your Child's Genetic Testing Report

# BASICS OF GENETICS

## What is a genetic disorder?

Genetic disorders are conditions caused by changes or mutations in a person's genes, which are located on chromosomes. These changes can affect how the body's cells work, leading to health problems.

## What does my child's report mean?

Your child's genetic report is a document that provides information about their genetic makeup after genetic testing. The report includes any variations or mutations that may be present in their genes and chromosomes. This report can help doctors understand the likely underlying cause of certain health issues or predict the likelihood of developing certain conditions in the future.

## What are genes and chromosomes?

Genes: Genes are like the instruction manual for our bodies. They are segments of DNA that contain the information needed to make proteins, which are essential for various functions in our cells. Changes or mutations in Argonaute genes can lead to Argonaute syndromes (AGO1-related syndrome, AGO2/Lessel-Kreienkamp syndrome).

Chromosomes: Chromosomes are structures found inside the nucleus of our cells that contain our genes. Humans typically have 46 chromosomes, arranged in 23 pairs. These chromosomes come in different sizes and carry different genes. Each chromosome has a longer side (known as the q arm) and a shorter side (known as the p arm). The AGO1 gene is located on chromosome 1p34.3 and AGO2 is located on chromosome 8q24.3, meaning that AGO1 is located on the p arm of chromosome 1, and AGO2 is located on the q arm of chromosome 8.

## Important Terms

Allele: Genes are organized in pairs on our chromosomes. Each pair consists of two alleles, one inherited from the child's mother and the other from the father. An allele represents a variant form of a gene, differing in sequence, and consequently, in the traits or characteristics it may encode. Mutations can arise, generating alternative alleles, alter the expression or function of the associated gene.

Protein: Proteins are created from the genes in our body. These molecules are essential for many functions in the body such as carrying messages between cells and repairing tissues. Argonaute proteins play a crucial role in controlling gene expression. They are involved in a process called RNA interference, where they help regulate which genes are turned on or off in our cells.

Amino acid: An amino acid is a fundamental organic molecule that serves as a building block of proteins and is encoded by a gene sequence. There are 20 essential amino acids that are commonly found in the body.

# GENETIC TESTING REPORTS

## I recieved my child's report... Now what?

The information on your child's genetic testing report can be overwhelming. It's always best to review the report with your child's genetic counselor or geneticist for more information. However, the information below can give you a head start.

DNA is composed of four nucleotide bases: adenine (A), guanine (G), cytosine (C), and tyrosine (T). When there is a mutation in a gene, these nucleotide bases are switched, deleted, or changed in certain spots along the gene on a specific chromosome. Since nucleotides encode amino acids, a change will affect the amino acid sequence of the protein. Argonaute syndromes involve missense mutations and deletions of nucleotides in the AGO1 and AGO2 genes that create Argonaute proteins.

Missense mutations: These are changes in a single nucleotide of DNA that result in a stop codon, or the substitution of one amino acid for another in the protein sequence.

Deletions: These are mutations where a section of DNA is lost or deleted, leading to a loss of genetic information and a shortened protein.

The table in your child's genetic testing report is a summary of what was found. An example of what this could look like is below.

| Gene | Associated Syndrome | Mode of Inheritance | Genotype/ Zygosity | Alteration | Classification |
|---|---|---|---|---|---|
| AGO1 (NM_01 2199.5) | AGO1-related neurodevelop -mental disorder | Autosomal Dominant | Heterozygous | c.569T>G (p.Leu190Arg) | Likely pathogenic |

Below are definitions of what is stated in these tables:

Gene: This section identifies the specific genes that have been analyzed and present with a mutation possibly relating to your child's phenotype. You may see a long number starting with "NM," which is known as the transcript. Genes have different versions of themselves, which do different functions in the body. The transcript you may see on the report is the version of the gene that is affected.

Associated syndrome: This section indicates the known disease/syndrome that is associated with the mutation detected.


Mode of inheritance: Argonaute syndromes are Autosomal Dominant conditions. This means a single copy of the mutated gene is sufficient to cause disease. Generally, these mutations occur de novo, meaning that the mutation is not inherited from either parent and occurred by chance. It's important to emphasize that neither a randomly occurring mutation nor a mutation that is unknowingly passed on are not your fault! Please know that you did nothing wrong. If your child would like to have children in the future, we suggest they obtain genetic counseling.

Genotype/Zygosity: All humans have two copies of each gene. These are called alleles. This section indicates whether your child has the same mutation in both alleles (homozygous) or only in one allele (heterozygous). In AGO1/AGO2, mutations are typically heterozygous.

Mutation/Alteration: This explains the change in the chromosome and gene that is present in your child. In addition, there is a corresponding change in the protein that is normally expressed by the AGO1/AGO2 genes. Please see the "Genetic Testing Reports" section for details. Note: Mutations are sometimes called variants.

Classification: This indicates the significance of a genetic variant and how likely it is to be associated with a known disorder. Examples include pathogenic, likely pathogenic, variants of uncertain significance, benign or likely benign. Please see the section on variant classification examples for more information.

The following are examples of the type of mutations that can be seen in Argonaute disorders. Please note that this is not a comprehensive list.

| Nucleic acid change | Protein change | Mutation found |
|---|---|---|
| c.577G>A | p.Gly193Arg | c.577G>A: This part indicates the change in the DNA sequence. In this case, a G (guanine) nucleotide at position 577 in the coding DNA sequence is replaced by an A (adenine) nucleotide.<br><br>p.Gly193Arg: This part describes the change in the protein sequence. The original amino acid at position 193 in the protein was glycine (Gly), but due to the DNA change, it is now arginine (Arg). |
| c.1070C>T | p.Thr357Met | c.1070C>T: Here, a C (cytosine) nucleotide at position 1070 in the coding DNA sequence is replaced by a T (thymine) nucleotide.<br><br>p.Thr357Met: This indicates the change in the protein sequence. The amino acid threonine (Thr) at position 357 in the protein has been replaced by methionine (Met) due to the DNA alteration. |
| c.539_541delTCT | Phe180del | c.539_541delTCT: In this variant, three nucleotides (TCT) at positions 539 to 541 are deleted from the coding DNA sequence.<br><br>p.Phe180del: This describes the corresponding change in the protein sequence. The deletion of these nucleotides results in the deletion of the amino acid phenylalanine (Phe) at position 180 in the protein. |