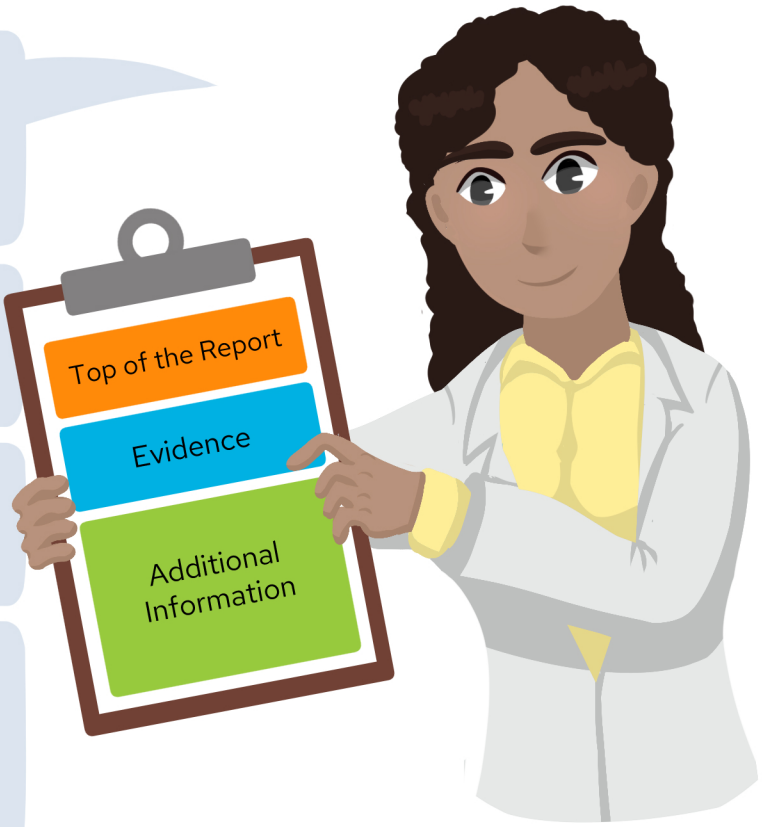
Visual Genomics Report

The genomics test will examine if there is a genetic cause for your patients condition. The report will have one of three outcomes.

A genetic cause:
Eg. Genetic diagnosis of polycystic kidney disease 1 (MIM#173900)

No cause:
A genetic cause for this individual's phenotype has not been identified

A variant that is of uncertain significance (VUS):
The result is uncertain because of a lack of evidence pertaining to one or more of the examined variants



If your patient has no cause found, there may still be options to do a re-analysis. This may include expanding the gene panel that was looked at or routine re-analysis in a few years.

This document was designed to help Doctors explain the content of a genomics report to their patients, with the assistance of the included illustrations.

If your patient desires more information, you can refer them to this Melbourne Genomics page

Plain language genomics report templates are available to download and edit here:

Melbourne Genomics Health Alliance

This resource was created as part of a **Melbourne Genomics project** and was created with **Alternative Contracting** in collaboration with the **UWA Comic Contracting Project** and **Coventry Comics**
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Top of the Report

The Variant

Your report will say:

Which test you have requested
eg. Clinical Exome singleton

Reason for Referral
eg. Persistent Microscopic Haematuria

Which genes have been looked at Gene List applied
eg. Haematuria Alport v1.0

The classification of the variant:

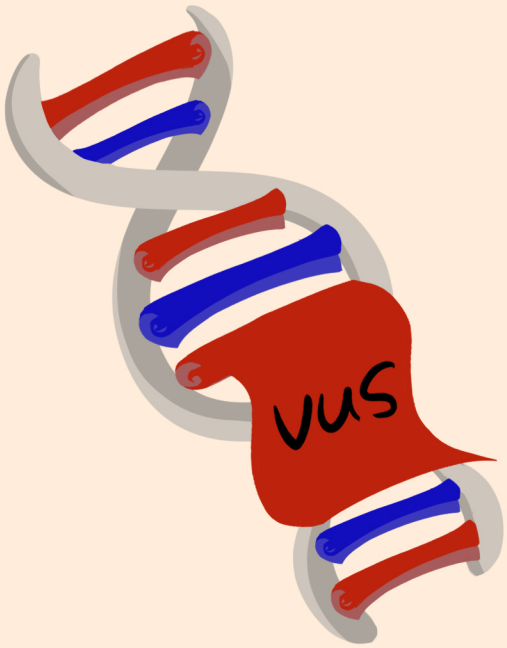
Unique identifier for record | Gene where variant occurs | Change to DNA sequence | Resultant change to protein

NM_12345(Gene):c123A>C; p.(Asn123Asp)
This variant is classified as_____

Classification of variant

If no diagnosis is found this information will help you decide if further testing is needed.

There are 5 possible classifications for a variant:



5. Pathogenic:
A cause of medical issues

4. Likely Pathogenic:
Likely the same except the databases contains too few example to be certain.

3. VUS:
a variant of uncertain significance

2. Likely benign:
Likely no negative effects.

1. Benign:
No known negative consequences.

Middle of the Report

The Evidence

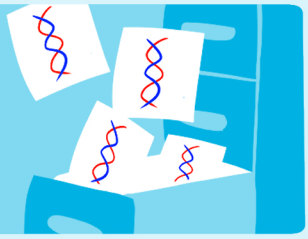
This part of the report discusses the evidence for the classification, and whether it has been previously reported.

It also examines the inheritance pattern, and the variants known impact.

Evidence in support of pathogenic classification:
- Variant is present in gnomAD (v2) <0.01 for a recessive condition (1 heterozygote. 0 homozygotes).
- Heterozygous variant detected *in trans* with a second pathogenic heterozygous variant (p.(Ile2331Lys)) in a recessive disease.

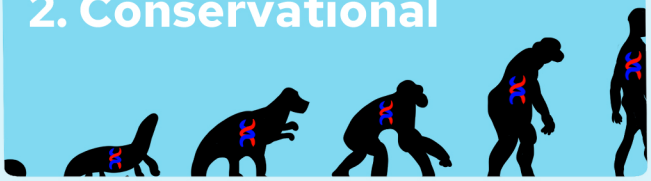
Evidence in support of benign classification:
- Missense variant consistently predicted to be tolerated by multiple *in silico* tools or not conserved in placental mammals with a minor amino acid change.

1. Population

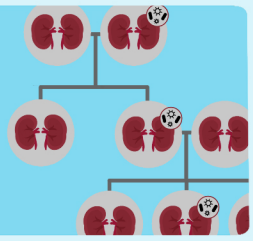


We will use the American College of Medical Genetics and Genomics standards and guidelines to help interpret the variants.

2. Conservational

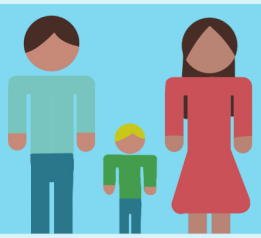


5. Segregation



3. Computational

6. De novo



4. Functional

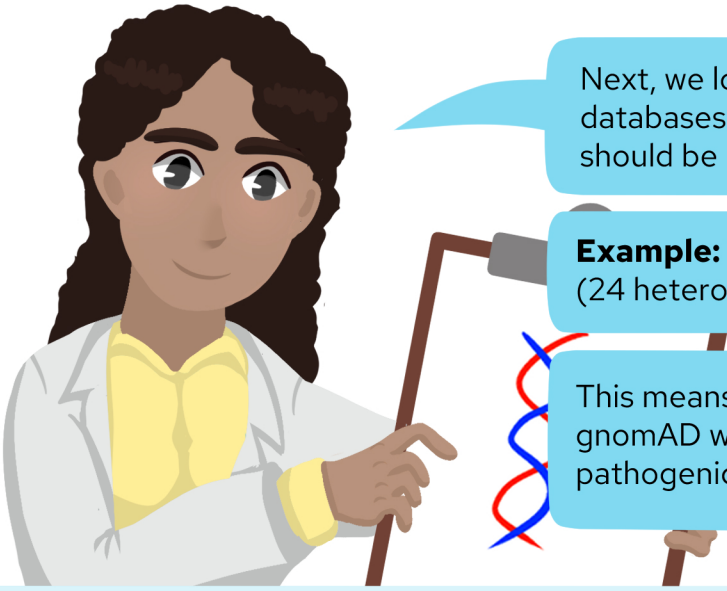
7. Allelic

1. Population

We look at the information gathered at a population level in large databases of genomic information.

First, we look to see if the variant is known to be associated with a particular disease, using 'disease' databases like **ClinVar** and **OMIM**.

Example: This variant has been reported many times as likely pathogenic and pathogenic. It has been reported in compound heterozygous individuals with milder renal disease and autosomal recessive polycystic kidney disease (ClinVar, PMID: 33532864, PMID: 15698423).

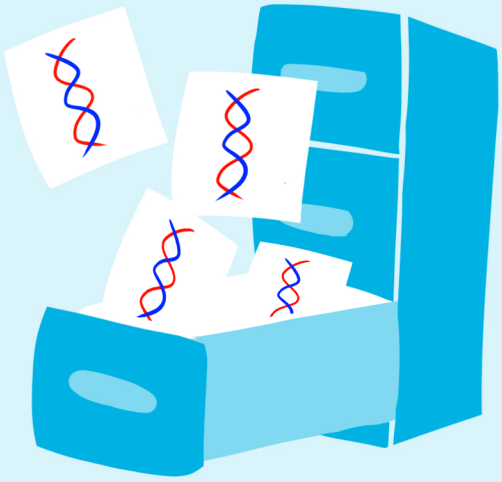


Next, we look at 'healthy' population data from databases like **GnomAd**. Disease causing variants should be rare in the general population.

Example: Variant is present in gnomAD(v2) < 0.01 (24 heterozygotes, 0 homozygotes).

This means that this variant is present <0.01% in gnomAD which is in favour of this variant being pathogenic.

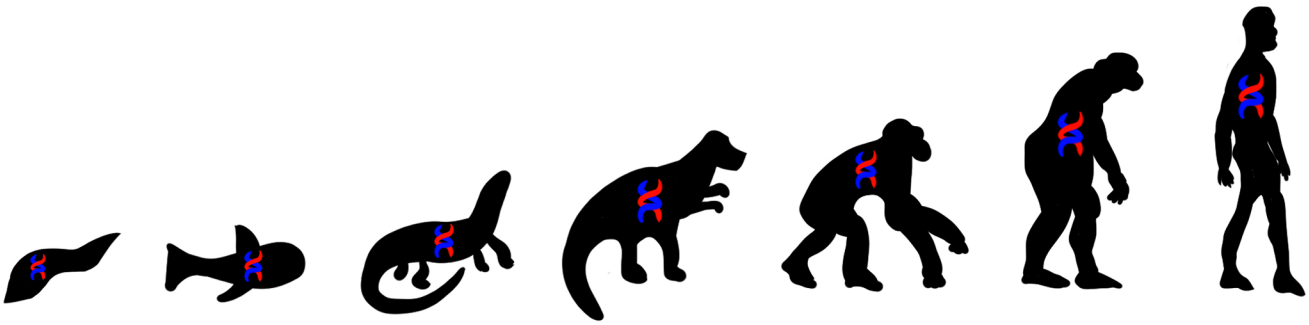
Not all ethnicities and populations are represented equally in these databases. This is important to bear in mind for your patients.



2. Conservational

The idea of conservation is the importance of where in the DNA the variant occurs. "Highly conserved" regions are sections of DNA that are the same across species and over a long period of time, and a variant here is more likely to be pathogenic.

The reports may mention scores like the GERP (Genomic Evolutionary Rate Profiling) or the Mutation Assessor score.



Example: *Missense variant consistently predicted to be tolerated by multiple in silico tools or not conserved in placental mammals with a minor amino acid change.*

This evidence is in support of a benign classification of a variant.

A **missense variant** is a genetic change where a single base pair is altered. Like changing a cooking recipe, it can have a neutral, beneficial or harmful effect.

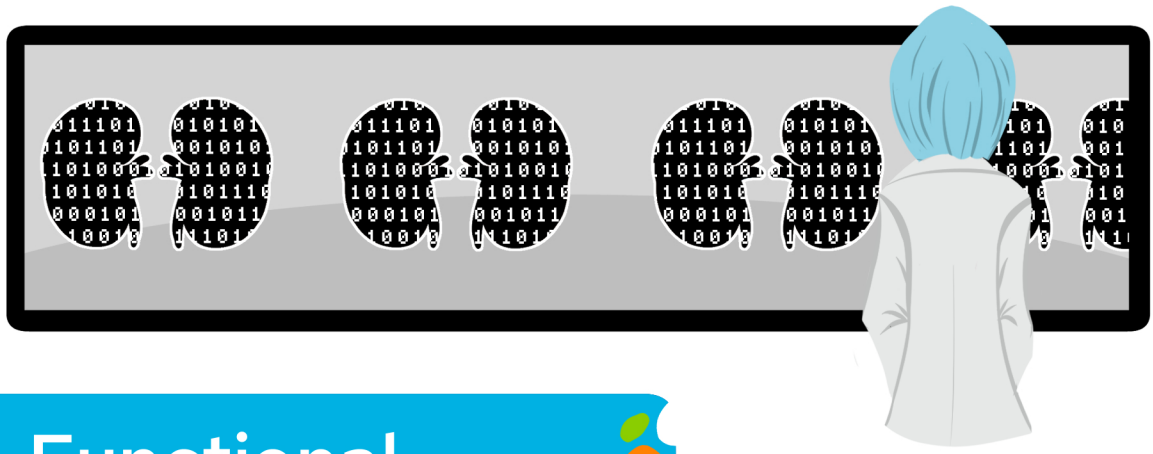
3. Computational

Because diseases can have complex causes, computer models can allow the creation of large virtual patient groups to better study the impact of the variant.

In silico (computer modelled) are used to determine the consequences of the variant by simulating the proteins created.

Example: Missense variant consistently predicted to be damaging by multiple in silico tools

You will see this referred to in relation to conservational and functional evidence.

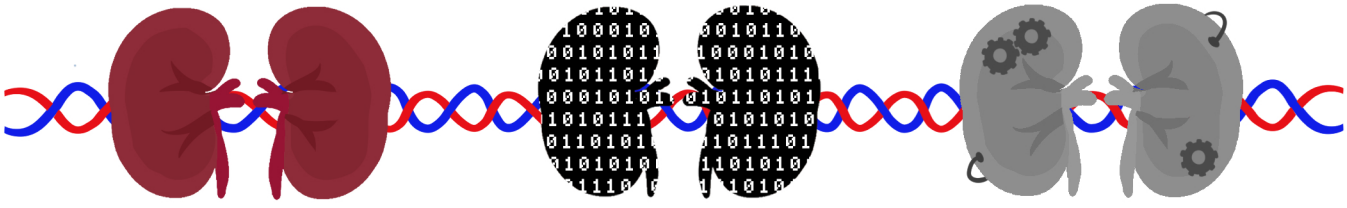


4. Functional

Functional tests are used to look at the impact of the variant in a lab setting. Animal models are often used and more recently newer tools such as organoids.

Example: *Loss of function is a known mechanism of disease for this gene*

This means that there is scientific evidence that supports this variant as pathogenic.



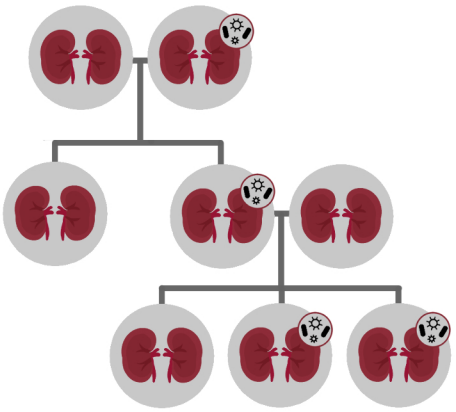
In silico tools are also used to predict the impact the variant could have on function.

Example: *Missense variant with conflicting in silico predictions*

In this case the in silico tool has not been able to support a benign or pathogenic determination

5. Segregation

Another useful step in understanding the pathogenicity of a variant is to look at segregation within the family. If other family members with the same condition have the same genetic variant, then it indicates that the variant is the cause.

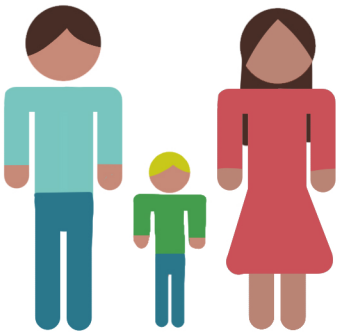


Example: This variant has strong evidence for segregation with disease. This variant has been shown to segregate in four affected pairs of siblings.

Beware that maternity and paternity need to be confirmed.

6. De Novo

De novo describes the first occurrence of disease. If the variant is known to have autosomal dominant inheritance, and both parents are unaffected, this is evidence that the variant is pathogenic.

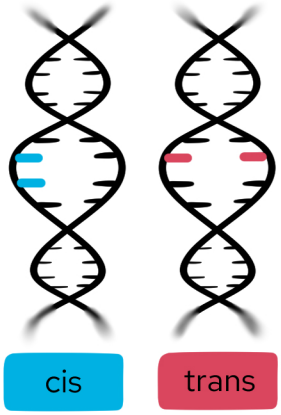


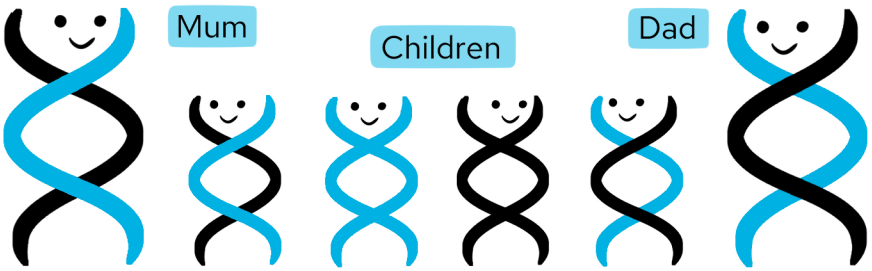
7. Allelic

Allelic data looks at the parents. If both are healthy carriers for a recessive condition, then this is supportive of pathogenicity. It means that the child is likely to have a variant on each copy - this is described as 'in trans'

If one parent carries both variants for a recessive condition on one copy of the gene (described as 'in cis') then their child is likely also a carrier.

If an affected parent for a dominant condition has the same change on one copy of the gene, then this is supportive of pathogenicity.





Bottom of the Report

Additional Information

The bottom of the report contains some additional information that will help to put your patient's results in context

Additional information:
- Loss of function is a known mechanism of disease in this gene and is associated with polycystic kidney disease 4, with or without hepatic disease (MIM#263200).
- This gene is associated with autosomal recessive disease.
- Variant in this gene are known to have variable expressivity. There is significant intrafamilial variation of severity (GeneReviews).

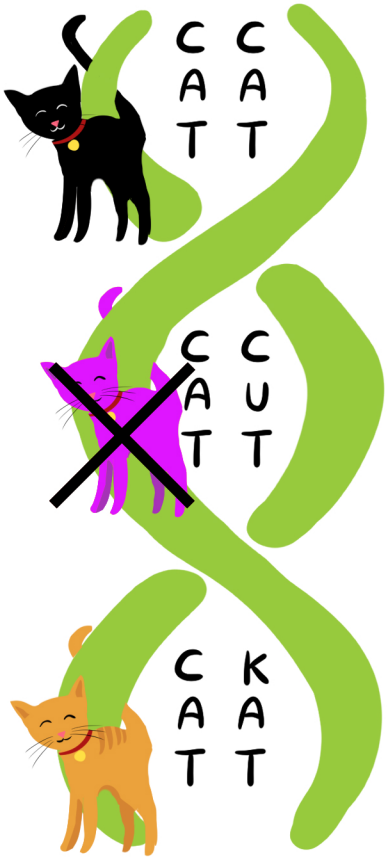
This may include:

Conditions that have previously been linked with this variant

Whether the variant can be passed down to children

How severe the variant potentially is

Any evidence of exactly how the variant can cause disease



You may have to remind your patient that there are no top marks in a DNA test.

Not all variants in our DNA are important, misspelling cat with a K instead of a C is less problematic than an U instead of the A.