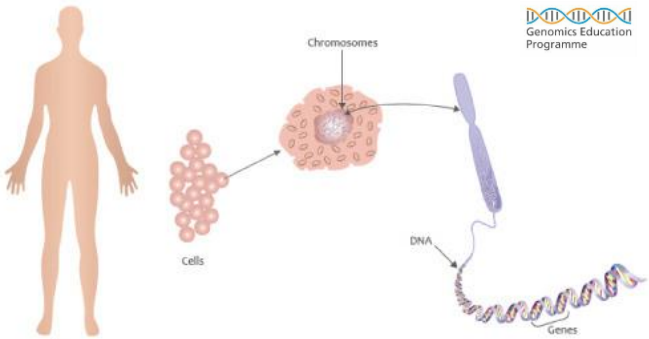
A guide to…

A Genetic Test Report

NHS East of England
NHS Genomic Medicine Centre

Introduction

Genetic disorders are caused by rare changes in the DNA sequence of a person's genome that cause particular genes not to function properly. To communicate specifically how a patient's DNA is different, and where that change is located in the genome, the international scientific community has agreed a system of coordinates for describing genetic changes. This system enables all biomedical professionals to refer to a particular change, or "variant", in the same way, so that information about genetic variants can be shared. This leaflet aims to explain the terminology used in genetic test reports as, at first glance, it can be confusing. Resources to find additional information about specific genes and variants are also included.



Genes are the instructions for building our bodies and making them work. Each person has ~20,000 genes. Genes are encoded in the DNA of the chromosomes in each cell. There are two copies of each gene, one inherited from each parent (except in males, who only have one copy of the genes that lie on the X and Y chromosomes).

Explanation of report

Report Summary: The summary tells you whether or not any potentially meaningful changes have been detected in the genes that were analysed. It will also state whether the change is present in one or both of the copies of the patient's gene. If no meaningful change was detected, i.e. the genetic test was "negative", it does not necessarily mean that there isn't a meaningful change present in the patient's DNA, just that the laboratory did not find one using the test that was performed (*see overleaf).
Please read this information sheet thoroughly.

Gene: A genetic test can analyse from one to over a thousand genes, depending on the symptoms of the patient. The genes that were analysed will have been selected on the basis of their known link to the patient's symptoms. **It is important to clinically assess how well a gene in the report could explain the symptoms of each individual patient.** More information about the genetic disorders caused by particular genes can be found on the following websites:
Genetic Home Reference: https://ghr.nlm.nih.gov/
GeneReviews:
https://www.ncbi.nlm.nih.gov/books/NBK1116/

Variant: The patient's DNA sequence is compared to a reference sequence for the gene(s) that is being analysed. Any differences between the patient's DNA sequence and the reference sequence are known as "variants". Everyone's DNA is different, but most variants do not alter the function of genes. After detecting such variants, the laboratory must interpret them to decide whether each variant is likely to be meaningful, i.e. to affect the function of the gene(s) being analysed, or whether it is just normal genetic variation in the population.

How likely is it that a gene change is linked with a genetic condition?

Classification of variants: The laboratory interprets the variants that are found and classifies them into one of five categories. It is important to understand that this classification relies on the information that is currently available on the variant and that if new information becomes available in time, the classification of the variant may change.

Pathogenic: it is known that this variant affects the function of the gene and that it can cause a genetic disorder (Class 5).
Likely Pathogenic: it is probable that this variant affects the function of the gene and it is likely that it can cause a genetic disorder (Class 4).
Variant of Uncertain Significance (VUS): there is currently not enough information to know whether this variant can cause a genetic disorder or not (Class 3). Further information may become available in time. It may be helpful to test for this variant in other family members to help with the interpretation.
Unlikely Pathogenic/Likely Benign: it is probable that this variant is just part of normal genetic variation in the population and is unlikely to cause a genetic disorder (Class 2). Such variants are generally not included in genetic test reports.
Not Pathogenic/Benign: it is known that this variant is just part of normal genetic variation in the population and does not cause a genetic disorder (Class 1). Such variants are generally not included in genetic test reports.

Information on how variants are classified:
https://www.acmg.net/docs/Standards_Guidelines_for_the_Interpretation_of_Sequence_Variants.pdf

Continued overleaf ►

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…continued

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Genetic terminology

Co-ordinates of a Variant: The exact location, or "address", of a variant in the DNA sequence of the human genome is given by co-ordinates on the genetic test report. The location of a variant can be described in several ways:

A co-ordinate beginning with "g." or "ChrN:" or "N:" (where N is the chromosome number) describes the location of the variant in the whole genome sequence.

A co-ordinate beginning with "c." describes the location of the variant in the coding DNA sequence of the particular gene in which it was detected.

A co-ordinate beginning with "p." describes the change that results from the variant in the protein coded for by that gene.

A number that starts with "LRG", "ENST", "NM_" or "GRCh" refers to the sequence that is being used as a reference to derive the co-ordinates.

Using the co-ordinates of the variant, it is possible to look up whether any information is known about that particular genetic variant in various databases. Good places to start are:
Decipher: https://decipher.sanger.ac.uk/
ClinVar: https://www.ncbi.nlm.nih.gov/clinvar/

Homozygous/heterozygous/hemizygous: These words indicate whether a variant is present in one or both of the copies of the patient's gene:

Homozygous: the same variant was detected in both copies of the patient's gene

Heterozygous: the variant is only present in one copy of the patient's gene

Hemizygous: the patient only has one copy of the gene and that copy contains the variant

Dominant genetic disorders are caused by a pathogenic variant in **one** copy of the gene.

Recessive genetic disorders require a pathogenic variant to be present in **both** copies of the gene. This can be due to a homozygous variant, or due to two different heterozygous variants if each is present in a different copy of the gene. Sometimes the laboratory will request samples from the patient's parents in order to clarify whether the two changes are in the same or different copies of the patient's gene. A person can be a **"carrier"** for a recessive genetic disorder if they have a pathogenic variant in only one copy of their gene.

X-linked genetic disorders are caused by a pathogenic variant in a gene on the X chromosome. These conditions generally affect males rather than females since males only have one X chromosome. Females may have a milder version of the condition or be unaffected **"carriers"** of the disorder.

*Reasons that a genetic test can be "negative":

- **The patient DOES NOT have a meaningful variant in the gene(s) that were tested**

However, there may be **other genes** that can cause the patient's disorder that have not been examined because:
- they weren't included in the test, or
- they are not yet known to cause a genetic disorder.

- **The patient DOES have a meaningful variant(s) in the gene(s) that were tested**

But it **could not be detected** by the test method that was used (please refer to guidelines for testing particular genes/disorders and the reported analytical sensitivity of the test).

Questions not answered by this information sheet?

Please contact Clinical Genetics where there is an On Call service for health professionals and patients Mon-Fri during office hours: 01223 216 446

More information:
NHS: http://www.nhs.uk/Conditions/Genetics/Pages/Introduction.aspx EuroGentest: http://www.eurogentest.org/index.php?id=622