INFORMATION ON GENOME-WIDE GENETIC TESTING

WHAT IS A GENE, WHAT IS A GENOME, WHAT IS AN EXOME?

Each human being is constituted of millions of "cells".
Each of our cells contains ***genetic information***. Genetic information is necessary to guide the development of the baby in the mother's belly, to allow every part of the body to function well. *Genetic information* is transmitted to us by our parents, and we will transmit this information to our children.
Genetic information is made of DNA.

DNA is a long molecule, composed of four different kind of building blocks called *nucleotides (Adenine (A), Guanine (G), Cytosine (C) and Thymine (T))*. It is the order of those 4 bases that **makes the genetic information**.

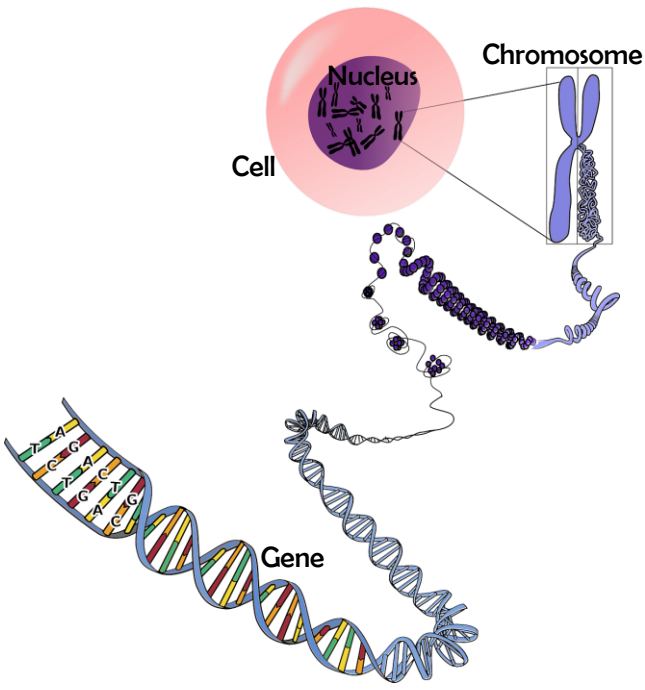
Different names are given to different aspects or parts of our DNA:

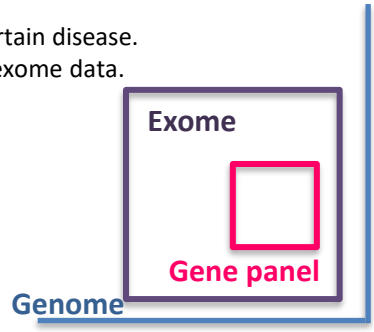
Genome is the name given to the entire DNA content in the nucleus. We have two copies of the genome, (one received from our mother, one from our father). Each copy is made of 3 000 000 000 of A, C, G or T letters.

Gene is the name given to a small part of the genome, which contains the information to build "proteins". Proteins are components of our body, but also messengers that our body uses to communicate from one organ to another or from one cell to another inside of an organ (such as the brain), or to guide the development of the fetus. Genes are composed of **exons** (which contain the crucial information to build the proteins) and introns (which are not part of the proteins). We have about 20 000 genes in our genome.

Exome is the name given to the subset of our genome, composed of all the exons of our genes. Although the exome is approximately only 1% of the human genome, the cause of most of the known genetic diseases are lying in it.

Gene panel analysis is a "targeted" analysis of genes known to be involved with a certain disease.
The term ***in-silico*** means the filtering of a list of genes decided by computer on the exome data.





Chromosome is the name given to the DNA when it is packed in small "stick"-like structures that are visible under the microscope. We have 2 pairs of 23 chromosomes (so 46 in total). We receive 23 chromosomes from our mother, and 23 chromosomes from our father. Two of the 46 chromosomes are special, the chromosome X and Y, because they make us a boy (XY) or a girl (XX).

Mitochondria can be considered as the energy factories of the cells. Mitochondria have their own DNA, which is approximately 16 500 bases long, and thus much smaller than the genome or exome. Nevertheless, errors in the mitochondrial DNA can give rise to complex disorders, which can vary from muscle to liver to brain abnormalities.

WHICH TYPE OF GENOMIC ALTERATIONS EXIST?

Our genomic and mitochondrial DNA contain **variations**, which determines the looks (phenotype) of a person (e.g. color of the eyes and hair), but also whether this person is more susceptible to some diseases or is affected or a carrier of a genetic condition.

Different types of anomalies can be identified:

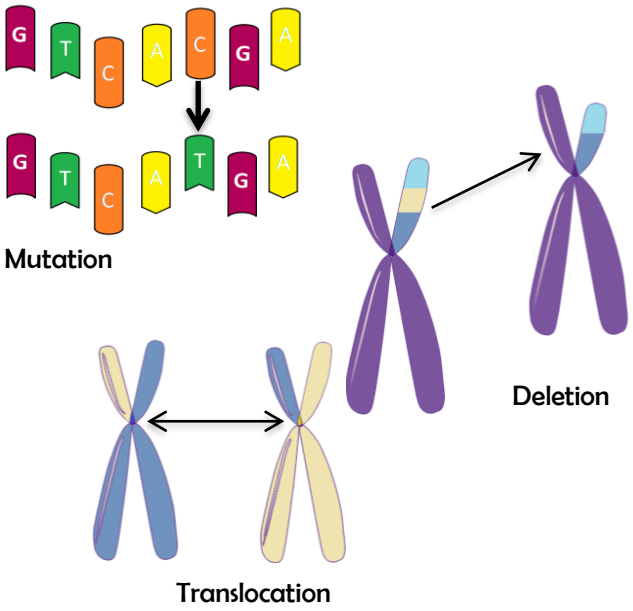
One or few of the A, G, C , T letter can be changed into another: it is called a "**point mutation**".

Small or bigger parts may have disappeared: it is called a "**deletion**", or be doubled: it is called a "**duplication**".

Small or bigger part can move to the wrong place: it is called an "**insertion**", or be turned around in a chromosome: it is called an "**inversion**".

Chromosomal parts can be exchanged between two different chromosomes: it is called a "**translocation**".

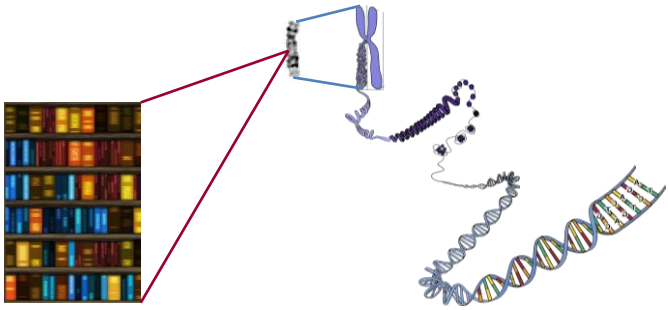
Small parts can be repeated an abnormal number of time: it is called " a **repeats** disorder".



HOW CAN WE EXPLORE OUR GENOMIC OR MITOCHONDRIAL DNA?

Various techniques have been developed that are able to find certain abnormalities, but no single technique can find them all.

***Comparative genomic hybridization array (CGH array)**:*
CGH array allows the comparison of small chromosomal parts of the patient towards those of a control person. CGH array can identify variations in the "quantity" of DNA, such as deletion, or duplication, of at least a certain size, known as structural variants or "**SVs**". Such SVs can have different consequences. Some are frequent and harmless (they are often called copy-number variants or "CNVs"), others can be responsible of genetic diseases, cause malformations and/or intellectual problems. Some SVs can be inherited from a normal parent. Most SVs are still of unknown clinical significance.
CGH array cannot detect changes in the order of the bases (the spelling of our DNA molecule).



If all of your genome would be represented by a shelf full of books, CGH array can tell if a book (or sometime even part of it) is missing, or if a book (or a part of it) is doubled. It will not, however, be able to tell if a book, a page or a word is in the wrong place, or if it contains spelling mistakes.

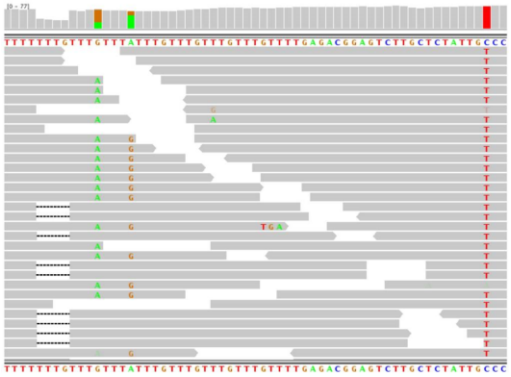
Single nucleotide polymorphism array (SNP array)
A SNP array can identify deletions or duplications like a CGH array, but, as it is based on another technology, which consists of detecting lot of single base variations (called SNPs), frequently found in the human species, all along the 46 chromosomes, it can also trace the transmission of small parts of chromosomes in a family (called "genetic linkage study").

Single gene analysis
When it is known that a specific disease is (often) caused by mutations in a certain gene, that gene can be sequenced and analyzed first.

In the bookshelf allegory, a single gene analysis would take every chapter of a single book and check for spelling mistakes.

Massive parallel sequencing

Massive Parallel Sequencing (MPS) technology (also called Next Generation Sequencing, NGS) allows us to study many genes together. This is useful when one out of several genes might be responsible for the disease.



In this case the MPS technology greatly accelerates the genetic diagnosis. MPS can look at once at a set of genes (this is called a gene panel, or at all the protein-coding genes (this is called an exome), or even at all the genome (whole genome sequencing, WGS). Bioinformatics' tools are needed to analyze the enormous amount of information released by this kind of test.

In the shelf allegory, MPS will take chapters from a set of books (panels) or from all the books (exomes) and analyze these at the same time.

Functional analysis

This type of analysis is not part of routine lab procedures. Yet, it might be necessary to analyze the consequences of the variations that are identified. This is only possible via dedicated (long) research projects. This can be done in many ways.

WHAT KIND OF RESULTS CAN BE EXPECTED?

The result is normal. This does not completely rule out the possibility of a genetic disorder.

One or several anomalies are found that explain your problems. This opens the possibility of genetic actionability.

One or several anomalies are found that COULD explain your problems, but need additional clinical work-up, or looking for the anomaly in other members of the family. This often asks for further testing.

It can also happen that an anomaly is found in a gene, which is not related to your problems, but which can cause another disease. These so-called *incidental or secondary findings* can occasionally be identified and can - with your prior consent - be reported to you, if there is a clear advantage for you.

HOW DO WE MANAGE YOUR TEST RESULTS?

Your genetic results will be interpreted by dedicated persons in the lab (technicians, biologists, medical doctors). They will then be returned to you through your own doctor, or through genetic counseling.

The application of new MPS sequencing technologies allows identifying hundreds or thousands of variations in each individual. Knowing which variation is disease causing, and which is not, is sometimes difficult. This situation brought scientists all over the world to recognize the need to share genomic and phenotypic data to get better insight into the consequences of those, sometimes very rare, variations. Many genetic diseases are caused by a severe alteration in one single gene (monogenic). Some other conditions depend on the accumulation of several variations to occur (oligogenic). The accumulation and sharing of genomic data allow broadening our comprehension of disease mechanisms, by comparing lots of variations in lots of individuals. You will be invited, while singing the informed consent document, to decide whether you agree or not that your results are shared in such a way. Be assured that your data will be pseudonymised, and that collaborations or research projects will be submitted to relevant ethical committees approval.

WHAT ARE THE LIMITATIONS & RISKS?

Due to the complexity of genome wide tests and their bioinformatics analysis, they also have their limitations: not all genetic variations can be picked up, and not all genetic variations are clinically understood. In summary, these tests are useful if we find a pathogenic variant that explain the disorder, but these genomic tests do *not rule out* the possibility of a genetic disorder if we do not find a pathogenic explanation.

Be aware that these tests can result in secondary findings (not related to the disorder). You can opt in or out to be informed about these secondary findings.

HOW DO WE COMMUNICATE TEST RESULTS?

Once the test results are available, you will be invited to the certified university genetic center for a genetic counseling to discuss the test results and their possible impact on your life and that of your family.

WHAT DO WE NEED FROM YOU?

To start with a CGH or SNP array, or MPS technology, we need minimally the following items:
- A blood sample (10ml ETDA tube) of you and preferentially your 1st degree relatives (e.g. parents and/or siblings).
- That you (or your parents if you are a minor) consent to the analysis, and sign the informed consent.

To validate some results in a research setting, other samples, such as further blood sampling or biopsies, may be asked later, upon your consent.

WHAT ARE THE COSTS?

Genome-wide tests are expensive. However, some of these tests and the genetic counseling are reimbursed by the national health care system (for Belgium RIZIV/INAMI) in such a way that only a limited fee needs to be contributed by you. Expenses related to genome-wide tests performed in a research setting will be supported financially for by the investigator's research grants.

IS FOLLOW-UP POSSIBLE?

Genetics is a fast evolving domain, with regular new discoveries on gene and protein function, and the impact of specific variants/mutations. In case of inconclusive results at the time of the availability of the first test results, it is possible that we re-analyze the data at a later stage in a scientific context to re-evaluate your results when more and updated data resources are available.

QUESTIONS?

Do you want to receive additional information on genome wide testing after reading this information leaflet?
Do you feel unsure about the informed consent and the use of your test results?
Would you just like to exchange opinions or ideas?
You are welcome to discuss your questions with your referring medical doctor or you can make an appointment for a genetic consultation.

CONTACT:

This information document has been jointly created by the ULB and VUB Genetics Centers, and De Duve Institute at UCL. This version was approved by the Ethics Committees of Hôpital Erasme and HUDERF in 2016.