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INFORMATION ON GENOME-WIDE GENETIC ANALYSIS

ULB Center of Human Genetics

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

Each human being is constituted out of lots and lots of tiny parts that we call "cells".
Each of our cells contains ***genetic information***. We receive one copy of this information from our mum and the other from our dad from the very beginning of our life in our mother's belly. And we will give half of this *genetic information* to our children.

Genetic information is necessary to guide the development of the baby in the mother's belly, to allow every part of the body to be well-formed and to function well throughout the life.

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 as if our DNA was like a long book composed of only 4 different letters: A, G,C, and T. **It is the order of those 4 letters that makes the *genetic information*.**

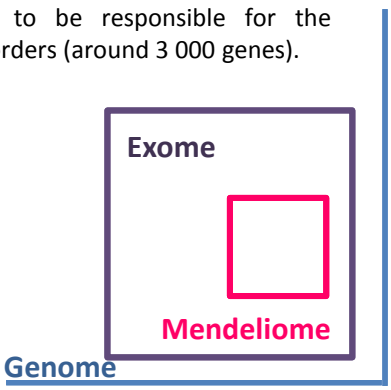
Different names are given to different aspects or parts of our DNA, and your doctor may use one or the other names.

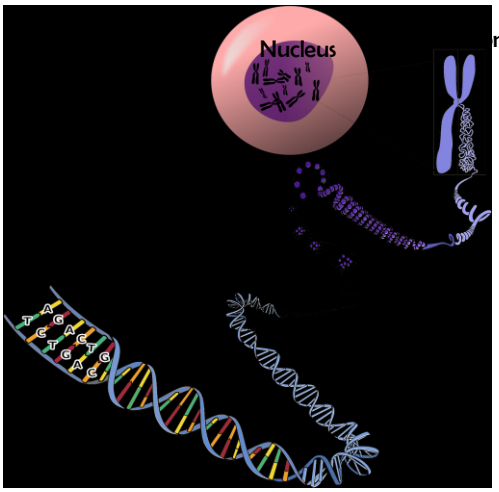
Genome is the name given to the entire DNA content in the nucleus. We have two copies of the genome, one received from our mother, one from our father. Each copy is made of 3 000 000 000 of A, C, G or T letters.

Gene is the name given to small parts of the genome. Genes act like sets of instructions guiding the development of the foetus, how we grow, how our body works. We have about 20 000 genes in our genome.

Exome is the name given to the subset of our genome composed of all the DNA book pages that correspond to our 20 000 genes.

Mendeliome is the name given to the subset of our exome, composed of all the genes that are currently known to be responsible for the genetic (rare) disorders (around 3 000 genes).





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 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 different kinds of **variations**. Some are "normal", they determine the way we look (e.g. colour of the eyes and hair), and make us unique. Others can stop a gene, or several genes to do its or their normal job. These variations can bring a genetic disease. Different types of anomalies can be identified (if you are interested look in the box below).

Knowing the difference between normal variations, and disease causing variations **is not always simple**. Most of the variation are yet of unknown significance.

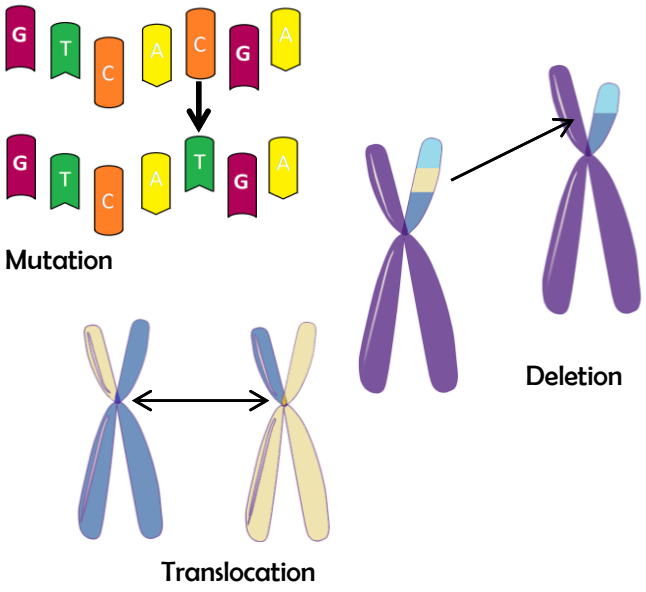
One or few of the A, T, G or C letters can be changed into another: it is called a "**point mutation**".

Small or bigger parts may have disappeared: it is called a "**deletion**", or been 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 times: 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 if there are abnormalities in a gene, or a set of genes, or a chromosome. No single technique can find them all at once. Some are designed to identify if there is some genes missing or in excess (like **CGH-array** – Comparative Genomic Hybridization, or **SNP-array**), others are designed to identify small changes in the order of the A, T, C, and G letters that can alter the instructions contained in a gene. This second type of analysis can look at one gene at a time (**single gene analysis**), or at lot of genes at a time (**massive parallel sequencing** of a panel of genes, the **mendeliome**, the **exome** or even the **whole genome**).

WHAT KIND OF RESULTS CAN BE EXPECTED?

It can happen that the analysis does not reveal any **pathologic anomaly**, and is considered a normal result. This does not completely rule out the possibility of a genetic disorder.

It can happen that the analysis does reveal one or several anomalies, and provides an **explanation** to your problems.

It can happen that the analysis does reveal one or several anomalies, and that this **COULD provide an explanation** to your problems, but that **further clinical work-up** is needed, or that we have to look for the anomaly in other members of the family.

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. We call this an ***incidental or secondary finding***. We will report and explain those results to you, **if** you (your parents) had given their prior consent, **and if** we are convinced that giving this result to you as a child may be useful for you (if we can start a treatment to avoid the disease to occur, or if visiting a doctor from time to time to make sure you are all right would be necessary).

HOW DO WE MANAGE YOUR TEST RESULTS?

Dedicated persons in the lab (technicians, biologists, medical doctors) will **interpret** your genetic results. These results will then be returned to you and your parents through your own doctor, or through genetic counselling.
When we analyse lots of genes at the same time, we find lots and lots of variations. As it is not easy to know which are harmless and which are disease causing, scientists all over the world started to **share their data** to **improve our knowledge** on those variations and their impact on health. Your parents will be invited, while signing the informed consent document, to decide whether they agree or not that your results are shared in such a way. Be assured that your data will be **de-identified** (which means that no one will know it is your DNA but your geneticist), and that collaborations or research projects will be submitted to relevant ethical committee's approval.

WHAT ARE THE LIMITATIONS & RISKS?

Both the technologies used, and their interpretation is complex. It is possible that a pathologic variation is missed for several reasons.
Be aware that these tests can result in secondary findings (not related to the disorder). You, and your parents, will choose whether you want to be informed about these findings.

HOW DO WE COMMUNICATE TEST RESULTS?

Once the test results are available, you, and you parents will be invited to the certified university Medical Genetics Center for a genetic counselling 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 (e.g., a mendeliome), we need at least 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/your parents consent to the analysis, and do sign the informed consent.

To validate some results in a clinical or a research setting, other exams, or other samples, such as another blood sample, a buccal swap or a biopsy (skin, muscle), may be asked later, upon your consent and the consent of your parents.

WHAT ARE THE COSTS?

Genome-wide tests are expensive. However, some of these tests and the genetic counselling 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 paid for by the investigator's research grants.

IS FOLLOW-UP POSSIBLE?

Genetics is a fast evolving domain, with regular new discoveries on genes and proteins 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-analyse 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?
Or 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 to discuss them with your geneticist.

NOTES

CONTACT:

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