Information on genome-wide genetic testing

Array Comparative Genomic Hybridization (array CGH)
Single Nucleotide Polymorphism array (SNP array)
Massive Parallel Sequencing (MPS)

Information leaflet for non experts

Version 2/20151125
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UZ Brussel : B.U.N.143201524795
CHU Saint-Luc : JMM/PdP/CB2015/09/14

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INTRODUCTION

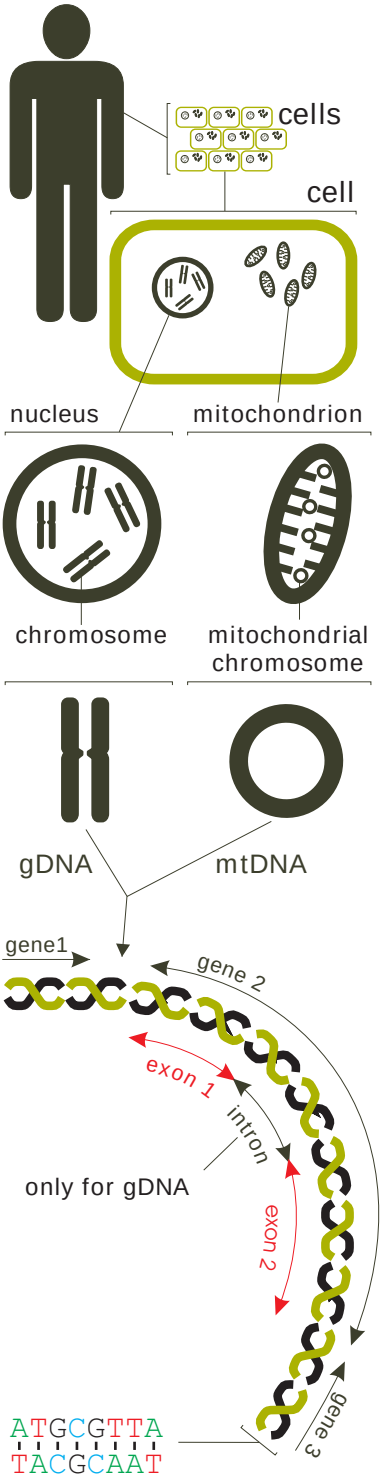
WHAT IS A GENE, WHAT IS A GENOME, WHAT IS AN EXOME?

Each human being is constituted out of lots and lots of tiny parts that we call “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” made of only four different units that we call “nucleotides”, or “bases”. We can compare our DNA to a very long word made of only 4 different letters: A, T, G and C. It is the order (or succession or sequence) of those 4 bases that makes the genetic information.
Different names are given to different aspects or parts of our DNA.

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).

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 messages 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 30.000 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.

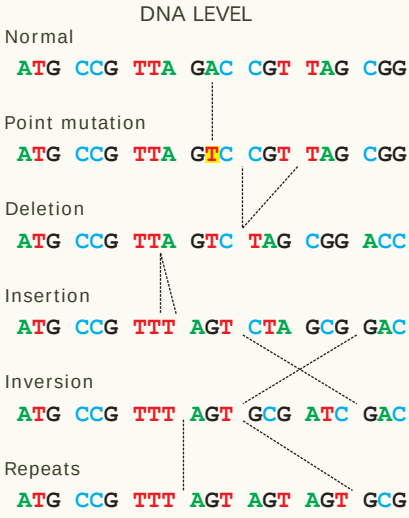
MITOCHONDRIA can be considered as the energy factories of the cells. Mitochondria have their own DNA, which is approximately 16.500 bases long, and thus much smaller than the genome or exome. Nevertheless, errors in the mitochondrial DNA can give rise to complex disorders, which can vary from muscle to liver or brain abnormalities.

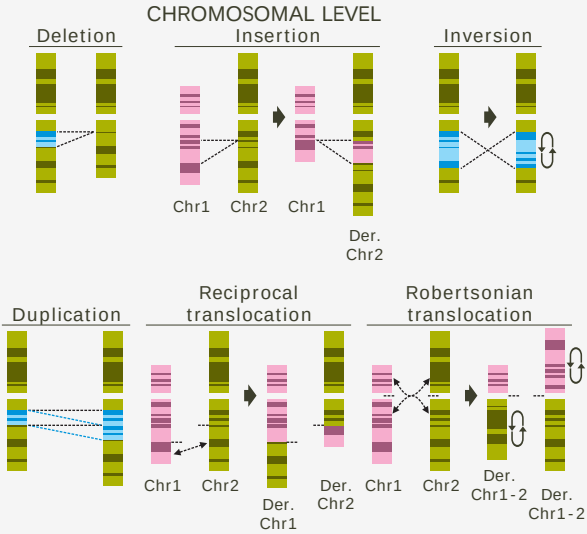
WHICH TYPES OF GENOMIC ALTERATIONS EXIST?

Each of us has a long list of DNA "words" that differ lightly from other people, and makes us all unique. It also happens that those variations in the correct succession of the letters A, C, G and T lead to genetic diseases.

Different types of anomalies can be identified:

- One of the A, T, G, C 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 (duplication).
- Small or bigger part can appear in the wrong place (insertion) or be turned around in a chromosome (inversion).
- Chromosomal parts can be exchanged between two different chromosomes (translocation).
- Small parts can be repeated an abnormal number of time (repeats)





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 to those of a control person. It can identify variations in the “quantity” of DNA. It can show when a small part is missing (a deletion) and when a small part is added somewhere (a duplication). 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, a CGH array would compare your shelf to a 'control shelf' and check if all your books (or genes) are present. It can then say if a book (or sometimes even part of it) is missing, or if a book 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.

Such deletions or duplications of small chromosomal fragments can have different consequences. Some are frequent and harmless, others can be responsible for genetic diseases, or cause malformations and/or intellectual problems. Some can promote the appearance of learning difficulties, or intellectual problems, but not in every individual, and can be inherited from a normal parent. It is not known for most of the deletions and duplications whether they are normal variants or disease-causing changes.

DNA LEVEL	nucleus	mitochondrion
Point variation	-	-
Deletion	-	-
Insertion	-	-
Inversion	-	-
Repeats	-	-
Homozygous regions (UPD/LOH)	-	/
CHROMOSOMAL LEVEL		
Deletion	+	-
Insertion	+	-
Inversion	-	-
Duplication	+	-
Translocation - balanced	-	/
Translocation - unbalanced	+	/
Aneuploidy	+	/

+ : detectable
~ : occasionally detectable
- : not detectable
/ : not applicable

SINGLE NUCLEOTIDE POLYMORPHISM ARRAY (SNP ARRAY)

A SNP array has several similarities with the CGH array, but instead of detecting a deletion or duplication of (larger) chromosomal parts, a SNP array detects (very small) single base variations (also called SNPs).

A SNP array can identify deletions or duplications like CGH array, but it can also trace the transmission of small parts of chromosomes in a family.

DNA LEVEL	nucleus	mitochondrion
Point variaton	~	-
Deletion	~	-
Insertion	-	-
Inversion	-	-
Repeats	-	-
Homozygous regions (UPD/LOH)	+	/
CHROMOSOMAL LEVEL		
Deletion	+	-
Insertion	+	-
Inversion	-	-
Duplication	+	-
Translocation - balanced	-	/
Translocation - unbalanced	+	/
Aneuploidy	+	/

+ : detectable
~ : occasionally detectable
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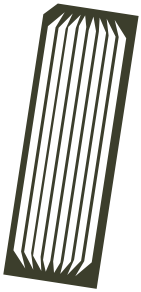
SINGLE GENE ANALYSIS

When it is known that a specific disease is often caused by mutations in a certain gene, that gene can be analysed first. In the shelf allegory, a single gene analysis would take every chapter of a single book and check for spelling mistakes.

DNA LEVEL	nucleus	mitochondrion
Point variaton	+	+/~
Deletion	+	+/~
Insertion	+	+/~
Inversion	~	~
Repeats	~	~
Homozygous regions (UPD/LOH)	~	/
CHROMOSOMAL LEVEL		
Not applicable		

MASSIVE PARALLEL SEQUENCING



Massive Parallel Sequencing (MPS) technology allows us to study not a single gene at a time, but 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 simultaneously at a set of genes (this is called a gene panel), or at all the genes (this is called an exome), or even all the genome. In the shelf allegory, MPS will take chapters from a set of books (panels) or of all the books (exomes) and analyse these at the same time. Bioinformatic tools are needed to analyse the large amount of information released by this kind of test.

DNA LEVEL	nucleus	mitochondrion
Point variaton	+	+
Deletion	+	+
Insertion	+	+
Inversion	+	+
Repeats	~	~
Homozygous regions (UPD/LOH)	+	+
CHROMOSOMAL LEVEL		
Deletion	+	+
Insertion	+	+
Inversion	+	+
Duplication	+	+
Translocation - balanced	~	/
Translocation - unbalanced	+	/
Aneuploidy	+	/

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FUNCTIONAL ANALYSIS

This type of analysis is not part of routine lab procedures. Yet, it might be necessary to analyse the consequences of the variations that are identified. This is only possible through dedicated 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.
- One or several anomalies are found that COULD explain your problems, but need additional research, or 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. 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?

Although the law of confidentiality still applies, given the complexity of the analysis of genomic data, we may have to share your results with another expert in the field in a coded (de-identified) or anonymised way to better interpret them, and/or to increase our general knowledge on data analysis.

WHAT ARE THE LIMITATIONS AND RISKS?

Due to the complexity of genome wide tests and their bioinformatic analysis, they also have their limitations: not all genetic variations can be picked up.
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 findings.

HOW DO WE COMMUNICATE TEST RESULTS?

Once the test results are available, you will be invited to the certified university genetic centre 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, we minimally need the following items:

- A blood sample (10ml ETDA tube) of you and preferentially your 1st degree relatives (e.g. parents and/or siblings).
- That your parents consent to the analysis, and sign the informed consent.
- To validate some results in a research setting, other samples, such as skin biopsy, may be asked later, upon your consent.

GENERAL

WHAT ARE THE COSTS?

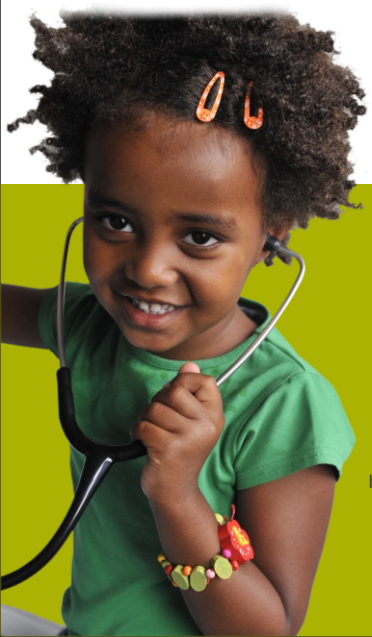
Genome-wide tests are expensive. However, some of these tests and the genetic counselling are reimbursed by the national health care system (for Belgium RIZIV/INAMI) in such a way that only a limited fee needs to be contributed by you. Expenses related to genome-wide tests performed in a research setting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

You require 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.



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