The 101 Genomes Marfan Project

of the Fondation 101 Génomes

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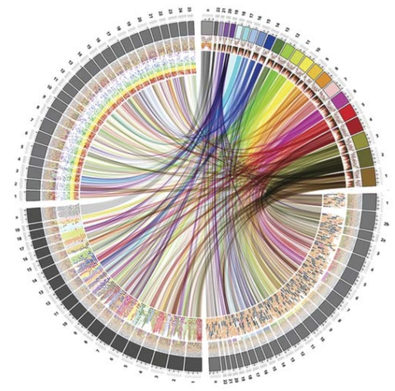

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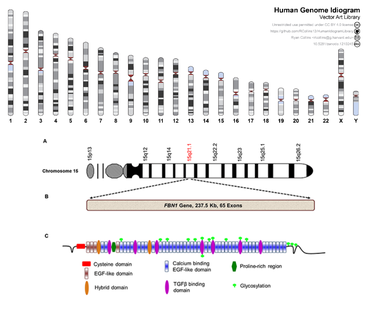
Objectives

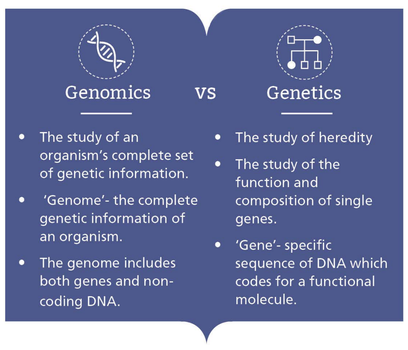
The 101 Genome Foundation (F101G) aims at creating a **bioinformatics tool** containing the **genomic and phenotypic cross data** of patients with **rare diseases** (like Heritable Thoracic Aortic Disease (HTAD)). This tool, accessible to scientists through **a secure computer platform**, will allow researchers to reach a better comprehension of variable phenotypic expressivity in rare diseases. Moreover, it provides the opportunity to identify the existence of possible modifier genes **that protect against (or aggravate)** the major damage caused by the primary mutation in rare diseases. Identification of possible **protective (or aggravating) modifier genes** could allow the development of treatments that replicate their protective effects in patients whose genes are not activated in the same way.

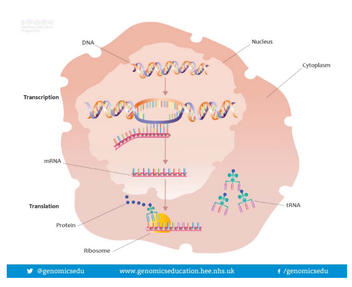
Origin

The idea to create F101G sparked after reading an interview with the Professor Hal Dietz in which he mentions that the crossing of genomic and phenotypic data could help to understand "*how natural genetic variants can protect some people from the consequences of a fibrillin-1 mutation*" and that, on this basis, scientists might possibly be able to "*identify drugs that can mimic nature's successful strategy"* [WEISMAN R., "*Meet Your Gene: An Introduction to the Marfan gene and Current Research*", January 10, 2017].

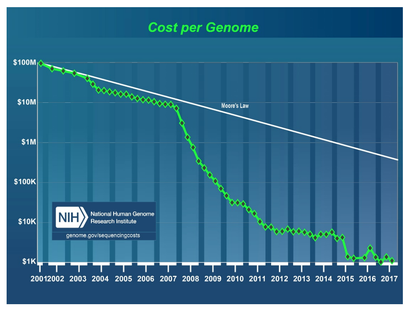
Unfortunately, scientists do not yet have access to the bioinformatics tool that would allow this research to be conducted. Such a tool implies **a paradigm shift** since it is not a question of studying an isolated gene but of **studying the interactions of a gene with the whole human genome (Whole Genome Sequencing - WGS)** without limiting the study to the 3% of coding parts of it (**Whole Exome Sequencing -WES)**. This paradigm shift is the **shift from genetics to genomics**.







This evolution was made possible by the development of bioinformatics tools and the gradual reduction in the cost of using **New Generation Sequencing tools (NGS)**, which **plunged** from $100,000,000 in 2001 **to $1,000 in 2017** (and which could continue to fall if the WGS were to become widespread and/or if competition between the two main operators (Illumina and BGI) were to intensify).



Each genome sequenced in WGS represents a volume of about **300GB of data** (BAM|FASTQ|VCF) that must be kept securely and whose integrity must be absolute. The examination of these data and their cross-referencing with phenotypic data requires the involvement of different domains of expertise.

Method

The 101 Genome Marfan Project (P101GM) is the pilot project of the F101G and is dedicated to **Marfan syndrome (MFS)**. It is built on an **expandable starting cohort of 101 patients** with MFS. The P101GM will initially focus on **cardiovascular manifestations**, but is extendable in a later stage to other MFS related manifestations. Individuals harboring the same recurrent *FBN1* mutations but with variation in their cardiovascular phenotype are chosen for the composition of the initial cohort, after which the patients at the extreme ends of the phenotypical spectrum will be selected for further analysis. **WGS** data will be generated from the selected participants and stored in a secure computer platform.

The scientific committee aims to identify MFS families segregating specific recurrent *FBN1* mutations with phenotypical cardiovascular variability. These *FBN1* mutations have been selected based on their relatively high incidence in the *FBN1-UMD* database. This criterion was used in order to increase the chance of identifying a sufficiently large cohort of patients that could be used for modifier identification strategy. From this cohort in a later stage the extreme ends (young and cardiovascularly affected versus old and no cardiovascular disease) will be selected for genome sequencing with the aim to identify modifiers. The specific selected *FBN1* variants are:

Exon	cDNA annotation	Protein annotation
2-3	c.247+1G>A (c.IVS2+1G>A)	
6	c.640G>A	p.Gly214Ser
21	c.2645C>T	p.Ala882Val
46-47	c.5788+5G>A (c.IVS46+5G>A)	
57	c.7039_7040del AT	p.Met2347ValfsX19
59	c.7454A>T	p.Asp2485Val
62	c.7754T>C	p.Ile2585Thr

Clinical centers/doctors worldwide have been invited to answer to the 3 following questions for each of those selected *FBN1* variants:

1. How many probands (as such families) are known with this specific mutation in your center?
2. For each proband/family, how many mutation carrying individuals have been tested (so mutation positives beyond the proband of that family)?
3. How many of these mutation carrying individuals (proband included) are above age 40 and do not present an aortic dilatation (Z-score < 2 or absolute size < 40 mm) and how many already have aortic dilation above Z>2 below age 25yrs?

Conclusion

The platform will allow researchers to better understand the clinical variability in MFS and identifying possible protective modifier genes that prevent cardiovascular manifestations caused by MFS.

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