Fondation 101 Génomes

FONDATION PRIVÉE

The 101 Genomes Marfan Project

EURORDIS

Brussels, October 22nd 2018

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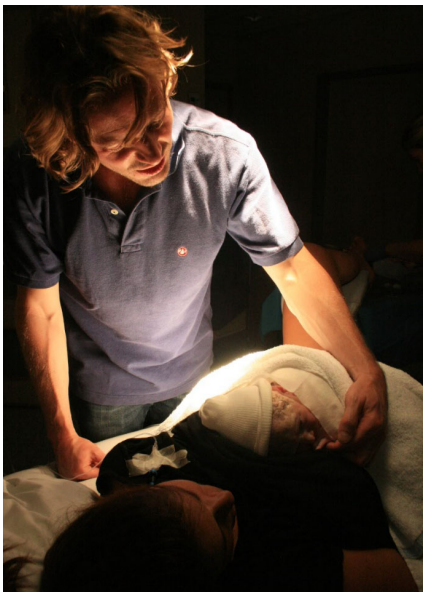
Aurélien

- Aurélien was born on **3rd September 2015**.
- Seven days after his birth, the pediatrician suspected a **connective tissue anomaly**.
- **A diagnostic odyssey** ended 11 months later with the the discovery of a ***de novo*** **mutation on exon 26 of our child's FBN1 gene**.
- This discovery confirmed that, as a result of a spontaneous mutation, Aurélien has **Marfan syndrome**.



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I.
Marfan syndrome

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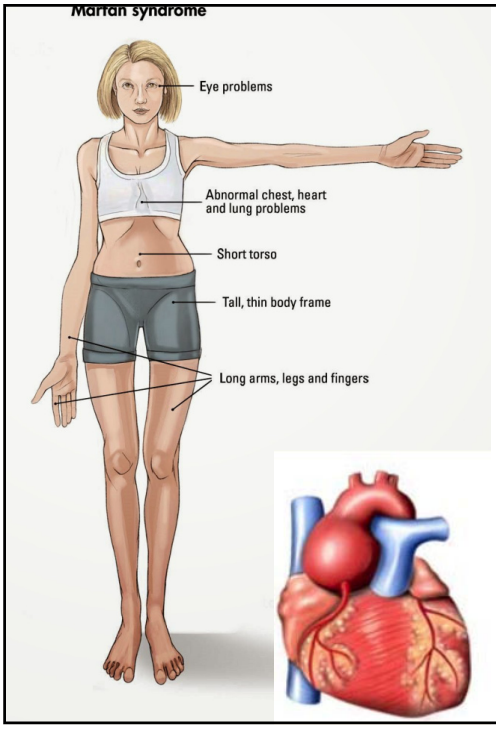

Marfan syndrome (1/5)

FBN1 & fibrillin

- Marfan syndrome results from an **anomaly in the connective tissues** that hold the cells that make up the human body together.
- This abnormality is caused by a **defect in the fibrillin protein** encoded by the **FBN1 gene** following a pathogenic mutation.
- **The disease is multisystemic** and affects, among other things, the **musculoskeletal, pulmonary, ocular and cardiovascular systems**.
- The main danger for patients with the syndrome is that of **aortic dissection**, the consequences of which are generally fatal.

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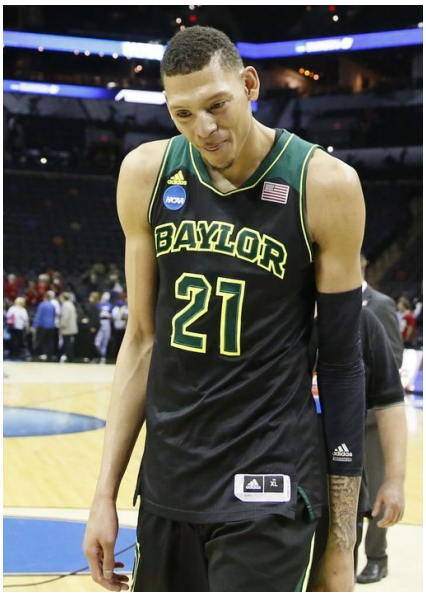
Marfan syndrome (2/5)

Prevalence

- **The prevalence** of the disease is about **1/5000**, so there are an estimated **2,200 people affected in Belgium and 148,200 across Europe**.
- However, the disease is **not well known and under-diagnosed**. Many people do not know they are sick.
- In **70% of cases the disease is transmitted** by one of the parents (autosomal dominant disease) and
- **In 30% of cases the disease appears spontaneously** while neither parent is a carrier following a ***de novo*** mutation.



Isaiah Austin

Marfan syndrome (3/5)

The intensity of the afflictions is very variable (even within families)

Javier Botet

- Some people affected by the syndrome have few disorders.
- At the other end of the spectrum, **the statistical life expectancy** of some **neonatal Marfans** reported in the scientific literature is barely **16 months**. In neonatal Marfans, mutations are found in most cases on **exons 24 to 32** of the FBN1 gene.
- Between these two extremities, we find the majority of Marfan patients who are sometimes severely handicapped by the disease and who must regularly control the dilation of their aorta.

In the current state of scientific knowledge, the cause of this great variability in the extent and intensity of the damage is not yet well understood.

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Marfan syndrome (4/5)

Association Belge du Syndrome de Marfan | ABSM asbl

- The Belgian Marfan Syndrome Association welcomed us.
- ABSM was created by **Mrs Yvonne Jousten** in 1999.
- **ABSM supports Belgian patients and their families and has been funding research for almost 20 years.**
- https://www.marfan.be/
- https://www.facebook.com/marfanbe/
- https://twitter.com/marfanbe

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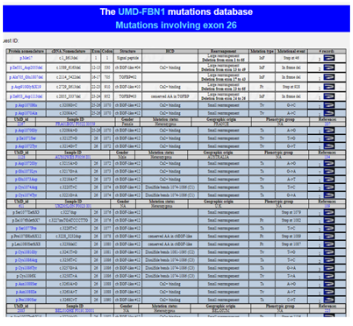
Marfan syndrome (5/5)

Association Marfans & UMD-FBN1

- The French Marfan Syndrome Association (Association Marfans) also played an important role.
- This association has largely funded the **UMD-FBN1 database** set up by **Dr. Gwenaëlle Collod-Beroud**.
- This **database is available for free access** (at www.umd.be/FBN1/)
- It provides access to an inventory of **3044 mutations of the FBN1** gene encoding the Fibrillin 1 protein on chromosome 15, which have been identified in the scientific literature and in laboratories **as pathogenic** and at the origin of Marfan syndrome.
- **UMD-FBN1 feeds the work of many researchers around the world and is an important tool for the diagnosis of the disease.**
- UMD-FBN1 was the starting point for our Project.



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II.
Genomics

Genomic revolution

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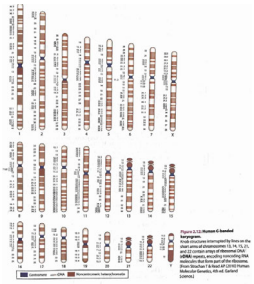
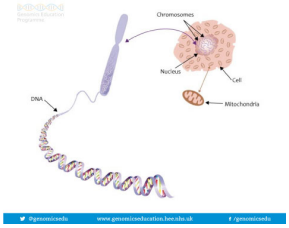
Genomics (1/9)

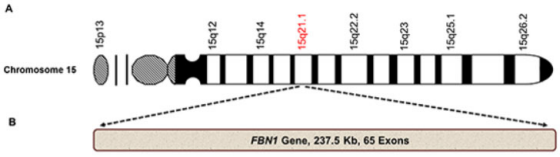
23 pairs of chromosomes

- Our cells store **23 pairs of chromosomes** in their nucleus.
- Each chromosome contains **genes (DNA)** that retain the necessary information for the production of proteins that condition our **phenotype** (observable traits).
- **Chromosome 15** contains the **FBN1 gene** that produces **fibrillin**.

Note: besides the DNA contained in the chromosomes, mitochondrial DNA is also found (stored outside the cell nucleus).



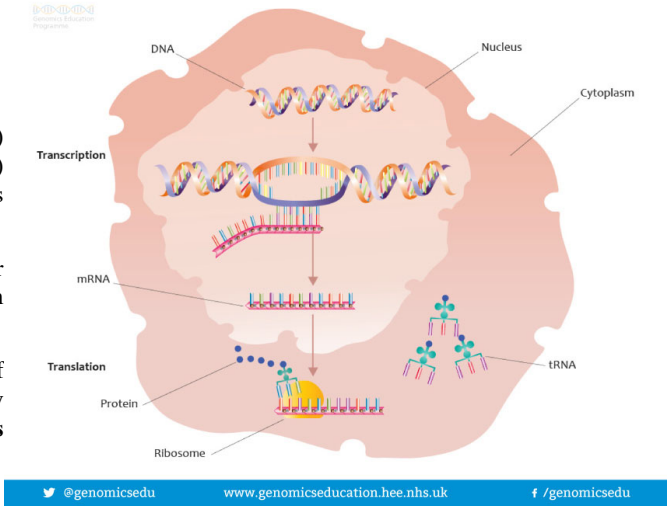




Genomics (2/9)

DNA & RNA | Genome & Exome

- There is an intermediate step in which genes (**DNA**) generate copies of their coding sequences (**RNA**) that will synthesize proteins outside the cell's nucleus.
- The **genome** is the genetic information (coding or not, chromosomal or mitochondrial) of a human being.
- The **coding exome** is the whole of the regions of the genome of a human being which directly participates in the production of proteins (**that is 3% of the genome**).



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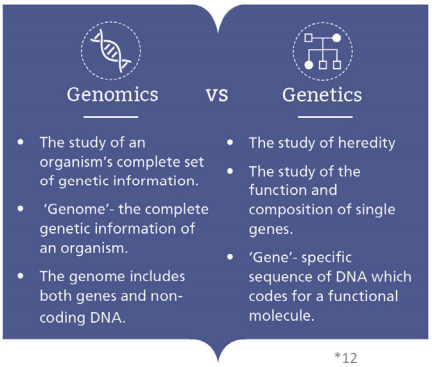
Genomics (3/9)

Sequencing

Today the emergence of new generation sequencers has paved the way to three different approaches to the study of genes:

1. The **"traditional" sequencing** of individual genes (or by panels of a few genes);
2. New generation sequencing (NGS) of the whole exome called **Whole Exome Sequencing (WES)** 3% of the genome and;
3. New Generation Sequencing (NGS) of the entire genome called **Whole Genome Sequencing (WGS)**.

With the new sequencers, scientists have gradually entered the era of genomics



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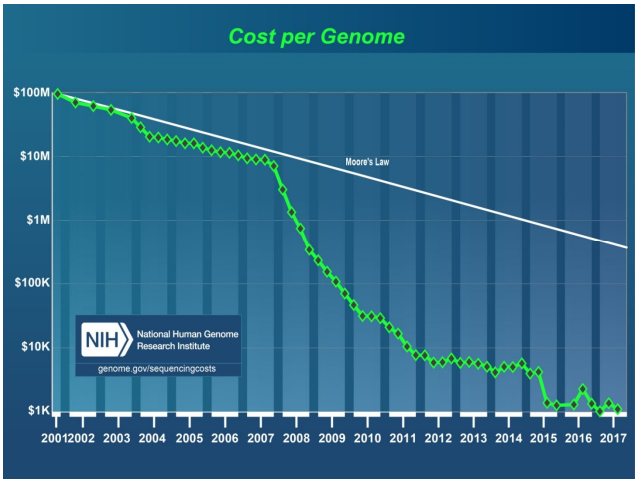
Genomics (4/9)

$1000 for a WGS

And the progressive reduction of sequencing costs facilitates this transition:

- The cost of sequencing has thus decreased from **$100,000,000** per genome in **2001** to
- **$1000** per genome in **2017**!



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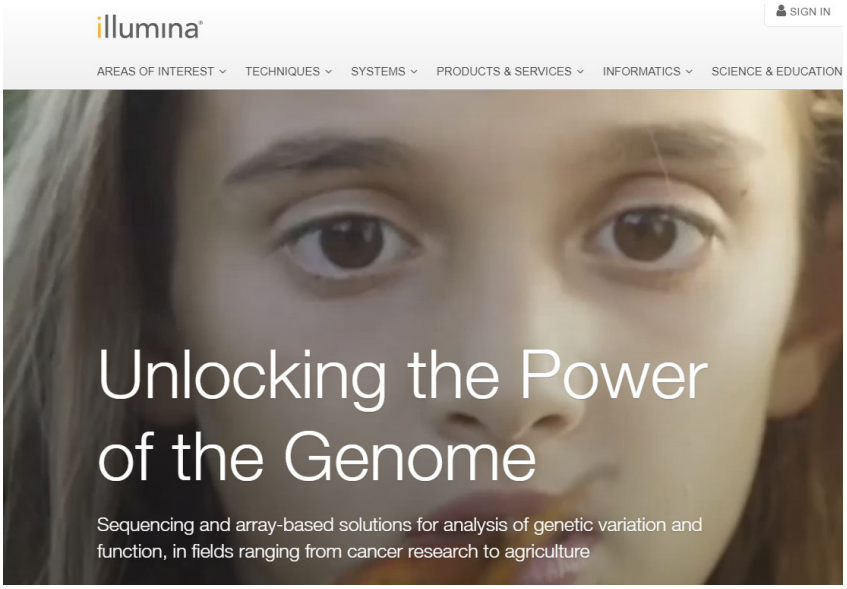
Genomics (5/9)



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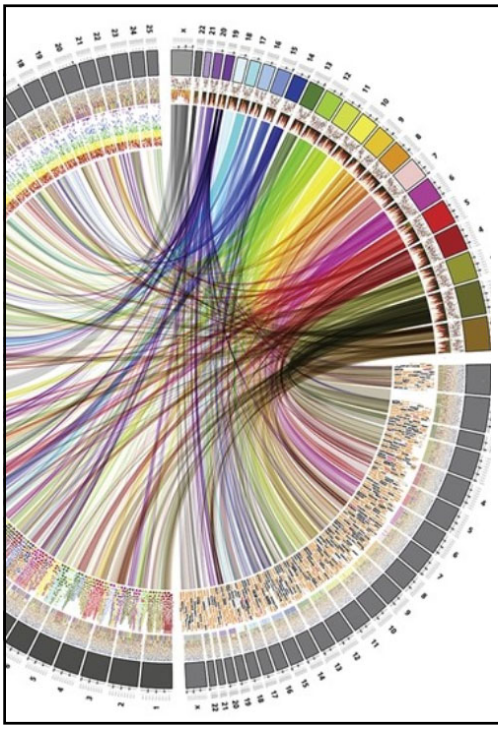

Genomics (6/9)

Genome mapping

- The addition of each new sequenced genome progressively **improves** the understanding of the **"human genome"**.
- Each new sequenced genome - shared and coupled with phenotypic data - contributes to "**mapping the genome"** and to **understanding the interactions between different genes.**
- Genome mapping technology has opened the way to **personalized medicine.**

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Genomics (7/9)

The Resilience Project

- In this project **589,306 "genomes"** (actually a combination of WES and WGS) collected **at random** in other contexts **have been re-examined.**
- This study identified **13 apparently healthy adults** who carry pathogenic mutations that should have caused severe rare diseases in them that normally develop in childhood.

nature biotechnology

ARTICLES

Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases

Rong Chen[1,2,12], Lisong Shi[1,2,12], Jörg Hakenberg[1,2], Brian Naughton[3,11], Pamela Sklar[1,2,4], Jianguo Zhang[5], Hanlin Zhou[5], Lifeng Tian[6], Om Prakash[7], Mathieu Lemire[8], Patrick Sleiman[6], Wei-yi Cheng[1,2], Wanting Chen[5], Hardik Shah[1,2], Yulan Shen[5], Menachem Fromer[1,2,4], Larsson Omberg[9], Matthew A Deardorff[6], Elaine Zackai[6], Jason R Bobe[1,2], Elissa Levin[1,2], Thomas J Hudson[8], Leif Groop[7], Jun Wang[10], Hakon Hakonarson[6], Anne Wojcicki[3], George A Diaz[1,2], Lisa Edelmann[1,2], Eric E Schadt[1,2] & Stephen H Friend[1,2,9]

CHEN R. et al., « *Analysis of 589,306 genomes identifies individuals resilient to severe Mendelian childhood diseases* », Nature Biotechnology, 34, 531–538 (2016) doi:10.1038/nbt.3514, Received 29 July 2015 Accepted 12 February 2016 Published online 11 April 2016, Disponible à l'adresse: https://www.nature.com/nbt/journal/v34/n5/pdf/nbt.3514.pdf

- The people discovered by the **Resilience Project should have been sick but are not.**
- These people may be protected by the **action of protective modifier genes**.

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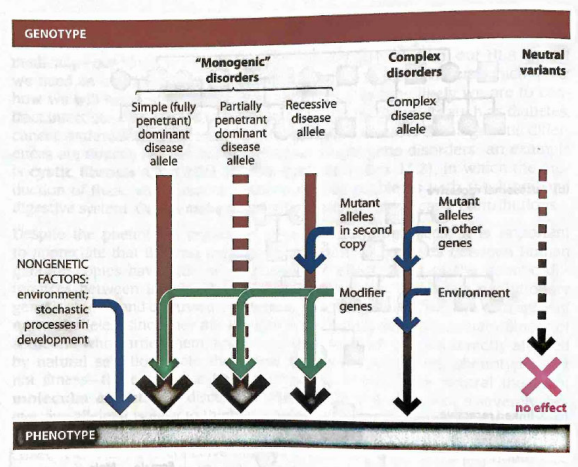
Genomics (8/9)

Modifier genes? Epistatic genes?

- A **modifier gene** is a gene that affects the expression of one or more genes (=**epistasis**).
- A **protective gene** is a modifier gene (= **epistatic gene**) whose action protects an individual from the harmful influence of a gene carrying a pathogenic mutation (= **hypostatic gene**).



TYLER-SMITH et al., Human evolutionary genetics (second edition), Garland Science, 2014, ISBN 978-0-8153-4148-2, page 46

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Genomics (9/9)

Professor Hal Dietz

- The Marfan Foundation, in the US, published an interview with Professor Hal Dietz.
- Professor Hal Dietz mentions that **the crossing of genomic and phenotypic data** could make it possible to understand "***how natural genetic variants can protect some people from the consequences of a fibrillin-1 mutation***" and on this basis 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*», 10 January 2017. Available at : http://blog.marfan.org/meet-your-gene-an-introduction-to-the-marfan-gene-and-current-research

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III.
101 Genomes

101 Genomes Foundation and 101 Genomes Marfan Project

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101 Genomes (1/7)

101 Genomes Foundation : creation & objective

- The **101 Genomes Foundation (F101G)** aims **to advance research** by 10 years through the creation of **an innovative database** that will allow researchers **to tame the genome** in order to better understand and treat rare diseases.
- **The disruptive innovation** of the **genomics and bioinformatics revolution** makes this objective possible today.

According to Professor Anne De Paepe, ProRector of Ghent University, this is "*a unique and unprecedented example of* ***patient participation in scientific research***".

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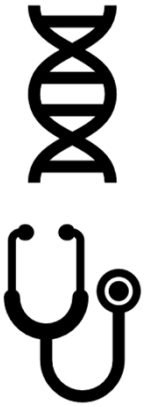
101 Genomes (2/7)

Bioinformatics tool: genomic and phenotypic data



In practice, F101G will create a **bioinformatics tool** containing **complete genomic** (Whole Genome Sequencing) **and phenotypic cross data** of patients with **rare diseases**.

- This tool will be **freely accessible to the scientific community** through a **secure computer platform** to help them **better understand the causes of rare diseases** and the **variability of the disorders** they cause.
- The tool thus aims to **identify possible modifier genes which protect against** the major damages caused by rare diseases.
- Such a discovery could lead to the **development of new treatments that replicate these protective effects**.

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101 Genomes (3/7)

101 Genomes Marfan Project

- **The 101 Genomes Marfan Project (P101GM) is the pilot project of the F101G.** This Project is dedicated to **Marfan syndrome.**
- It is built on an extensible starting cohort of **101 patients**.
- It is not excluded to **enlarge the cohort (+1… +x)**.
- **The bioinformatics tool** set up as part of the pilot project can then **be extended to host other projects dedicated to other rare diseases** that will benefit from the experience gained.

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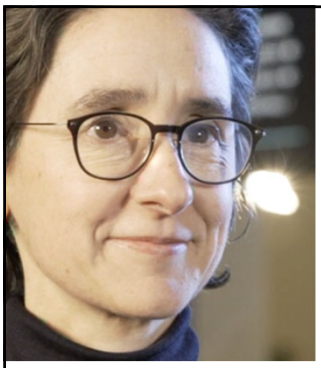




101 Genomes (4/7)

Scientific Committee

- **The P101GM Scientific Committee** is composed of **leading scientists** who are world leaders in the fields of Marfan syndrome, genomics and algorithms.
- Among the members of the committee are the professors **Julie De Backer, Bart Loeys, Guillaume Smits, Guillaume Jondeau, Catherine Boileau and Anne De Paepe.**

101 Genomes (5/7)

& European Associations

ABSM

- The P101GM is supported by the European network by several **European Marfan Patient Associations:**
  - **Associations Belge du Syndrome de Marfan**;
  - **Associations Française du Syndrome de Marfan**;
  - **Marfan Europe Network**.

marfans

- The P101GM has received the **Edelweiss 2018 Prize** awarded by the Belgian Alliance for Rare Diseases: **RaDiOrg**.

RaDiOrg.be
Rare Diseases Organisation

Marfan Europe Network

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101 Genomes (6/7)

VASCERN "incubator"

European Reference Network

VASCERN

Gathering the best expertise in Europe to provide accessible cross-border healthcare to patients with rare vascular diseases

- The P101GM is part of the **European dynamic created by the launch of the European reference networks: ERNs.**
- It is actively supported by the **VASCERN network dedicated to cardiovascular diseases** and by the main members of the HTAD group within it.
- This support was evident in the development of the composition strategy for the **analysis cohort**:

p.Asp1070Ala	c.3209A>C	25-26	1070	cb EGF-like #12	Ca2+ binding	Small rearrangement	Tv	A->C
p.Asp1070Gly	c.3209A>G	25-26	1070	cb EGF-like #12	Ca2+ binding	Small rearrangement	Ts	A->G
p.Ile1071Ser	c.3212T>G	26	1071	cb EGF-like #12	Ca2+ binding	Small rearrangement	Tv	T->G
p.Asp1072Tyr	c.3214G>T	26	1072	cb EGF-like #12	Ca2+ binding	Small rearrangement	Tv	G->T
p.Asp1072Gly	c.3215A>G	26	1072	cb EGF-like #12	Ca2+ binding	Small rearrangement	Ts	A->G
p.Glu1073Lys	c.3217G>A	26	1073	cb EGF-like #12	Ca2+ binding	Small rearrangement	Ts	G->A
p.Glu1073Asp	c.3219A>T	26	1073	cb EGF-like #12	Ca2+ binding	Small rearrangement	Tv	A->T
p.Cys1074Arg	c.3220T>C	26	1074	cb EGF-like #12	Disulfide bonds 1074-1086 (C1)	Small rearrangement	Ts	T->C
p.Cys1074Tyr	c.3221G>A	26	1074	cb EGF-like #12	Disulfide bonds 1074-1086 (C1)	Small rearrangement	Ts	G->A

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101 Genomes (7/7)

100.000 Genomes Project UK

- VASCERN also provided a link to the **100,000 Genomes Project in the United Kingdom**.
- The British Secretary of State for Health announced on 2 October the extension of this Project from 100,000 to **1 million genomes** with
- The ambition to reach **5 million genomes within 5 years.**

Secretary of State for Health and Social Care announces ambition to sequence 5 million genomes within five years

Posted on October 2, 2018 at 5:00 pm

Secretary of State for Health and Social Care, the Rt Hon Matt Hancock MP, today set out an ambitious vision for genomic medicine in the NHS – with plans to sequence 5 million genomes over the next five years.

Health and Social Care Secretary Matt Hancock

The announcement, made as part of the Secretary of State's speech to the Conservative Party Conference in Birmingham, recognises the critical importance of genomic medicine to the future of the NHS. Mr Hancock announced:

- Expansion of the 100,000 Genomes Project to see 1 million whole genomes sequenced by the NHS and UK Biobank in five years.
- That from 2019, the NHS will offer whole genome analysis for all seriously ill children with a suspected genetic disorder, including those with cancer. The NHS will also offer the same for all adults suffering from certain rare diseases or hard to treat cancers.
- Revealed the aspiration to sequence 5 million genomes in the UK, within an unprecedented five-year period.

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IV.
Odyssey
Genomics et Diagnostics

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Odyssey (1/2)
The anguish of not knowing

"Le plus dur, c'est de ne pas savoir. Une fois qu'on a identifié la maladie, on peut établir un plan d'action"
Ludivine Verboogen, maman d'Aurélien, 2 ans et demi

Partager sur Facebook

Vivre avec une maladie rare

À l'âge de dix mois, le diagnostic génétique est tombé : Aurélien es Marfan, une maladie rare qui touche les tissus conjonctifs. Une foi se sont plongés dans l'étude de cette maladie et même de la géné Fonds 101 Génomes, co-géré par la Fondation Roi Baudouin et la veut mettre à la disposition des scientifiques un outil bioinformati recherches sur la maladie.

Déjà mère de deux enfants, Ludivine Verboogen s'est rendu com Aurélien, n'évoluait pas comme les autres. " Je le trouvais trop ca avis des médecins diffèrent. Ludivine n'est pas rassurée : au fond et son instinct de mère lui disent qu'il y a 'quelque chose'...

Finalement, c'est lorsqu'un souffle au cœur est détecté chez Aur des tests génétiques approfondis sont menés. "Nous avons alor atteint du syndrome de Marfan : cette maladie rare est causée p perturbe la production de fibrilline, une protéine essentielle au bo conjonctif. Or ce tissu est un peu la glue qui tient ensemble tout affecté, il en résulte diverses conséquences qui touchent l'ensem principalement chez les Marfans d'atteintes cardiovasculaires, o squelettiques", explique Ludivine Verboogen.

Plan d'action
Le diagnostic a été un choc, mais aussi un soulagement, poursuit-elle : "Le plus dur, c'est de ne pas savoir. Une fois qu'on a identifié la maladie, on peut établir un plan d'action. Cela a quelque chose de rassurant."

Fondation 101 Genomes a retweeté

David Cameron @David_Cameron · 28 févr.
On world @rarediseaseday, what I learnt from our son's rare disease & how genetic testing, like that carried out by @illumina, is making a transformational change in healthcare, ending the anguish & uncertainty #ShowYourRare

À l'origine en anglais

What I learnt from our son's rare disease
Originally published in The Times on 28 February 2018. (Photo credit: Roger Taylor/ Rex Features) Picture this. The most precious thing in the world
linkedin.com

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Odyssey (2/2)

Reliable and fast diagnosis

- **Our history:**
  - multiplication of genetic tests before reaching diagnosis (false hopes and cruel lessons);
- **Testimonials:**
  - 11 years of waiting;
  - 6 years without care;
  - Adults still waiting....

- According to the **Foundation for People with Rare Diseases** in Zurich, Switzerland, it is faster and more economical to use WGS sequencing to make a reliable diagnosis as quickly as possible.
- P101GM may also contribute to thinking about **the use of the genome in the context of diagnosis.**

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V.
Conclusion

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Conclusion (1/2)

Sparkle

- Limited to 101 genomes, our Project is only a **sparkle** in comparison, for example, with the English 100,000 Genomes project from which we drew inspiration.
- This sparkle is concentrated on **Marfan's syndrome** and we hope that in the dynamics created **by VASCERN**, it will **ignite continental Europe** and that it will eventually **spread to the study of other rare diseases**.
- Above all, we hope that this sparkle will lead to **a better understanding of Marfan syndrome** and we dream that, perhaps, it could **contribute to the development of new drugs able to replicate the effects of possible protective genes**.

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Conclusion (2/2)

The time is now

« ***Genetics has undergone a veritable technological revolution in recent years and the time is now right to use that technology to discover genetic explanations for clinical variation between Marfan patients*** »

Prof. Bart Loeys

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Aknowledgements

- **To Scientists:** Guillaume Smits, Anne De Paepe, Julie De Backer, Bart Loeys, Guillaume Jondeau, Catherine Boileau, Paul Coucke, Aline Verstraeten, et Marjolijn Renard.
- **To ABSM:** Yvonne Jousten, Véronique Vrinds, Lauriane Janssen, Rémi Rondia, Léon Brandt, Muriel Vandenbossche, Cathy Kaye.
- **To French Association Marfans:** Jean-Michel Adda, Stéphanie Delaunay, Guillemette Pardoux.
- **To VASCERN:** Natasha Barr et Marine Hurard.
- **To:** René Havaux, Annemie T'Seyen et Gerrit Rauws.
- **To:** Michael Lognoul, Joëlle Froidmont, Filip Ragolle, Sébastien Snoeck, Frederique Pirenne, Janik De Goÿ, François Deprez, Eleonore Pauwels et Bruno Fonteyn.
- **To:** Sébastien Van Neylen, Cécile Chabot, Dessie Lividikou, Florence Roth, Peter O'Donnell, Julien Wolf et Alisa Herrero.
- **To:** Carole Wininger, Patrice Touboulie et sa famille.

www.f101g.org

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Communication structurée :
017/1730/00036

France | Fondation de France
FR76 3005 6005 0205 0200 0363 678
BIC : CCFRFRPP
Communication :
00459/ TGE-Fonds 101 Genomes

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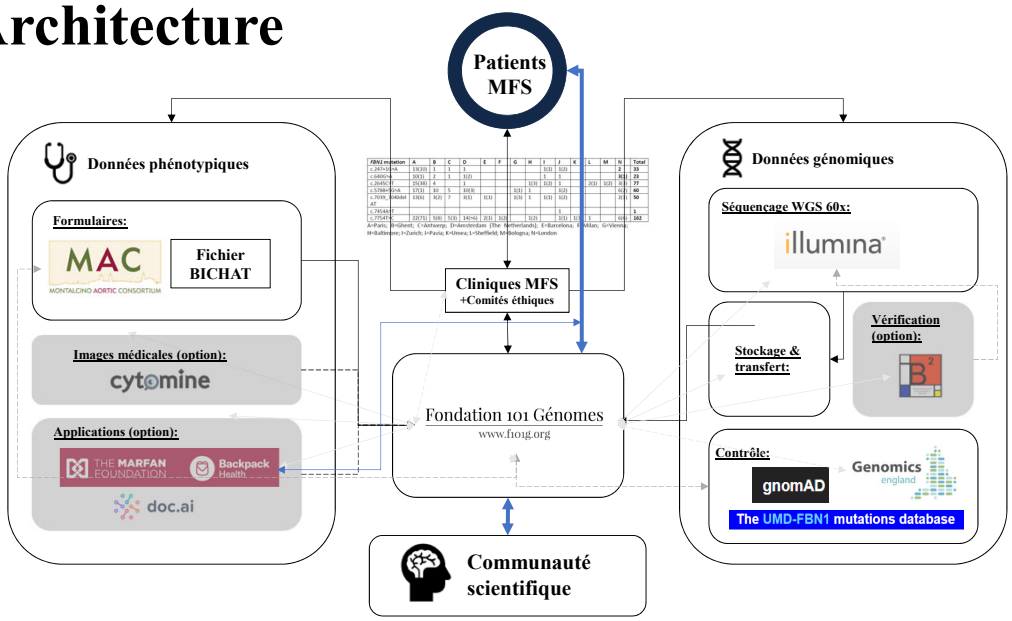
Architecture



Organigram

President: Michel Verboogen
Vice-President: Cécile Jacquet
Secretary: Ludivine Verboogen
Treasurer: Romain Alderweireldt
CEO in the daily Management: Ludivine Verboogen

Fondation Roi Baudouin
Agir ensemble pour une société meilleure

Fondation de France
La Fondation de toutes les causes

Fonds 101 Génomes

Fondation 101 Génomes
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Prof. Anne De Paepe (UZGENT)
Members
Gerrit Rauws
Ludivine Verboogen
Romain Alderweireldt
Secrétaire:
Annemie T'Seyen

European Reference Network
for rare or low prevalence complex diseases
Network Vascular Diseases (VASCERN)

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Co-Presidents
Prof. Julie De Backer (UZGENT)
Prof. Bart Loeys (UZA)
Members
Prof. Anne De Paepe (UZGENT)
Prof. Catherine Boileau (BICHAT Hospital)
Dr. Guillaume Smits (HUDERF)
Dr. Aline Verstraeten (UZA)
Dr. Marjolijn Renard (UZGENT)
Prof. Paul Coucke (UZGENT)

101 GENOMES MARFANS PROJECT

Marfan Europe Network

marfans

ABSM

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