GEMS – Une évocation de la recherche en cours…

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The future…

“I like the dreams of the future better than the history of the past.”

Thomas Jefferson

"I would not say that the future is necessarily less predictable than the past. I think the past was not predictable when it started.”

Donald Rumsfeld

“People ask me to predict the future, when all I want to do is prevent it.”

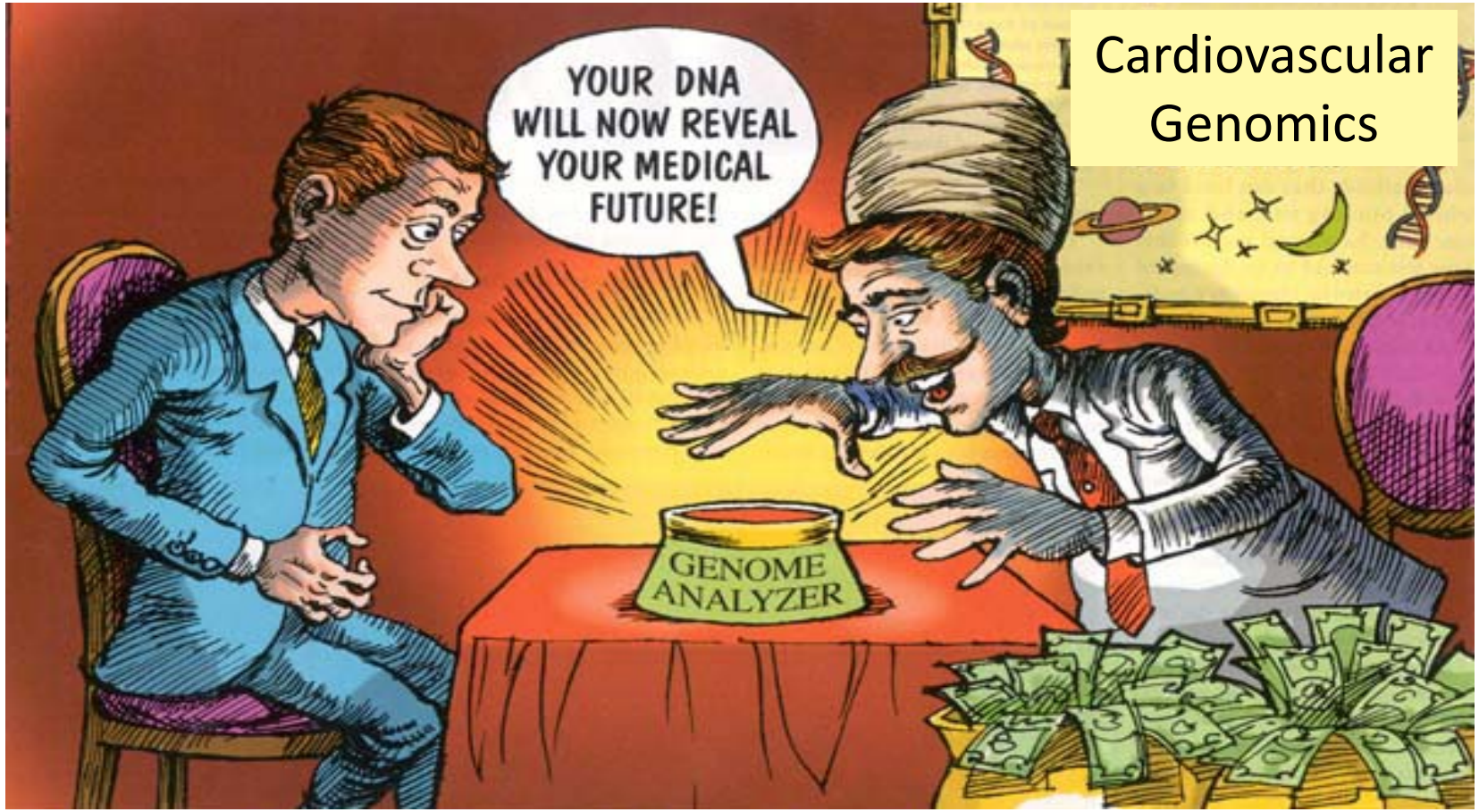
George W. Bush

“I am the future, no need to predict it.”

Donald Trump

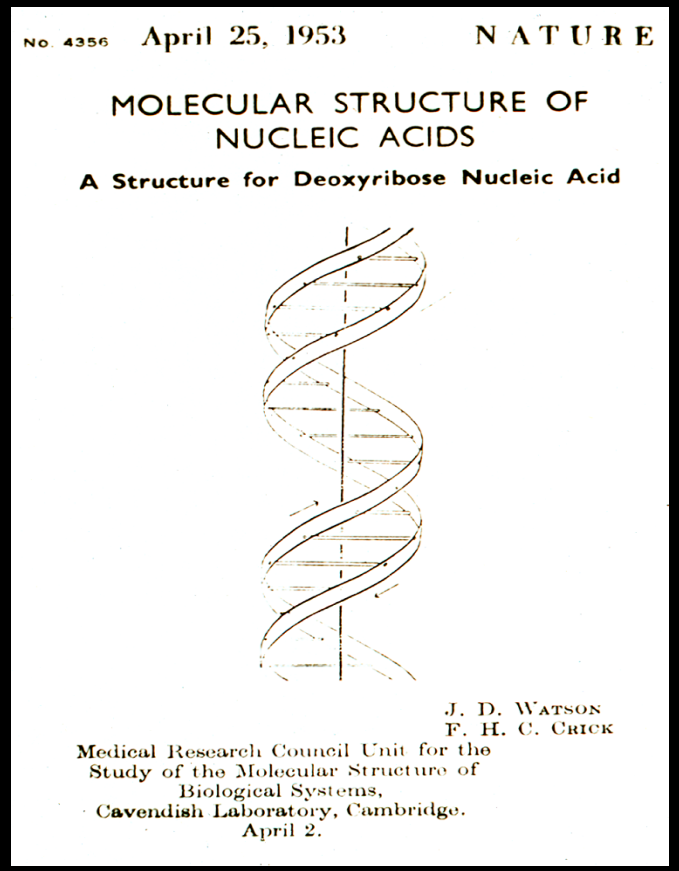
My disclaimer

- No liability for false predictions in this presentation



1853
1866, 1900

April, 1953



No. 4356 April 25, 1953 NATURE

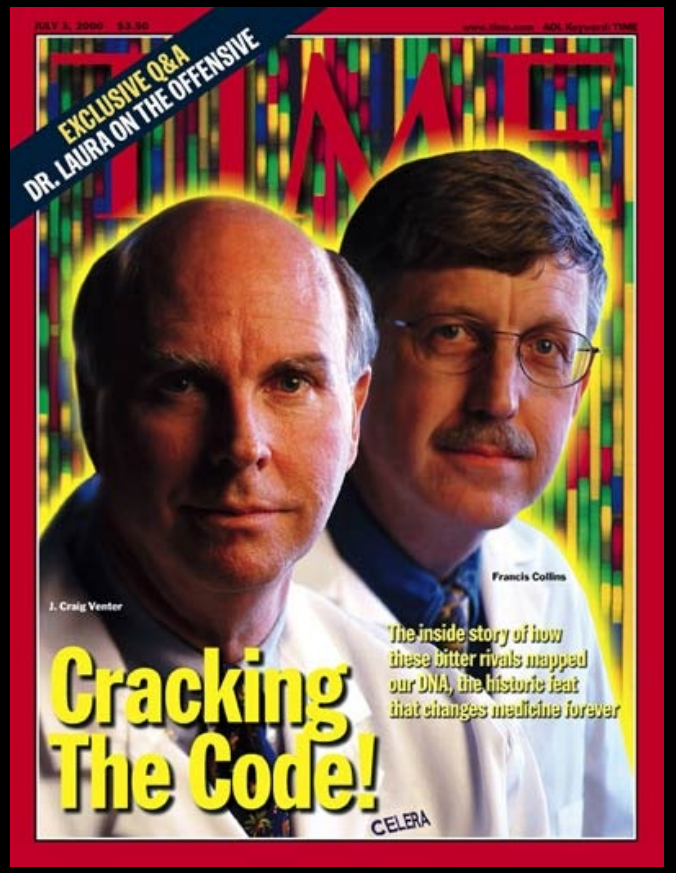
MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

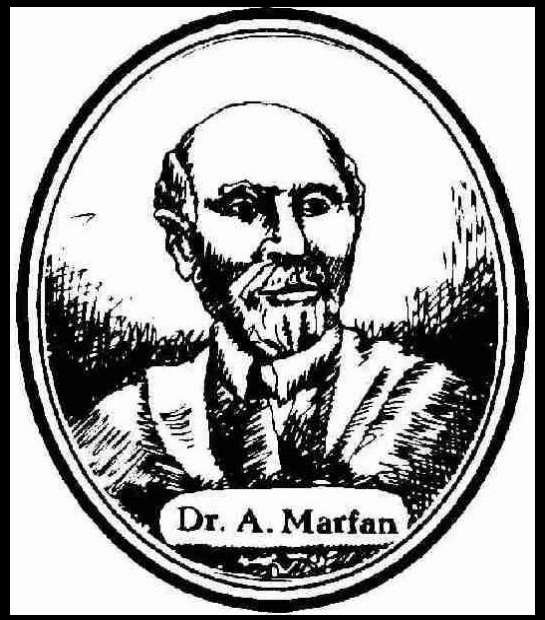
J. D. Watson
F. H. C. Crick

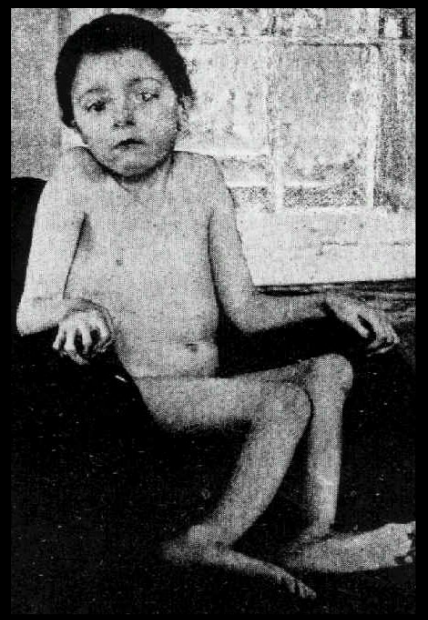
Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems, Cavendish Laboratory, Cambridge. April 2.

April, 2003



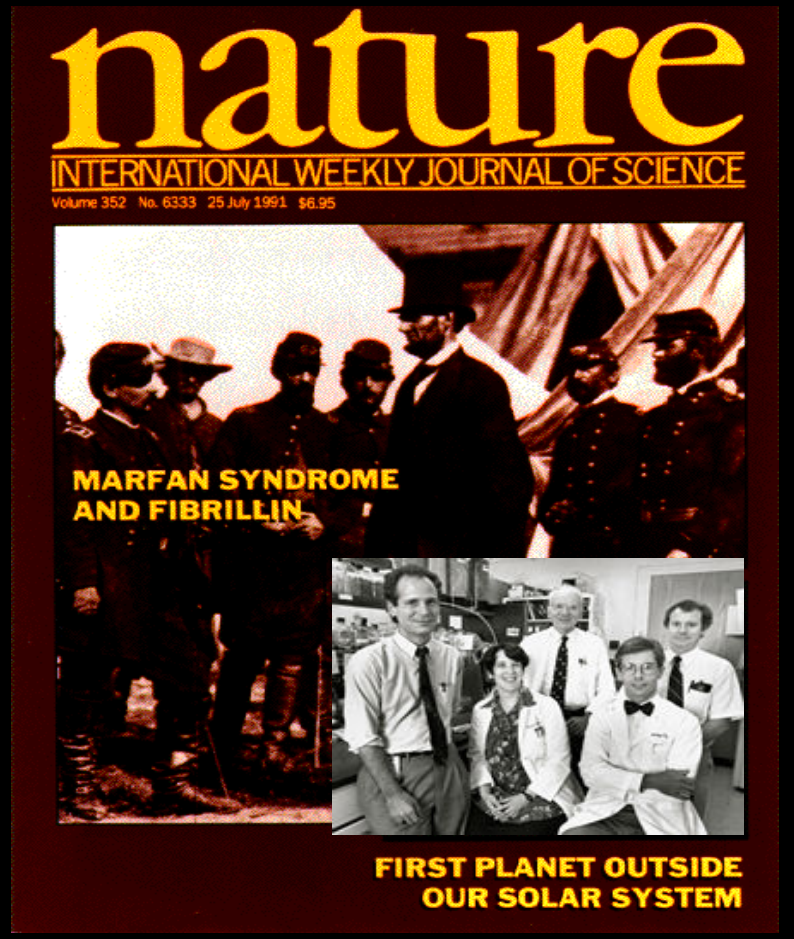
1896





1955

1991



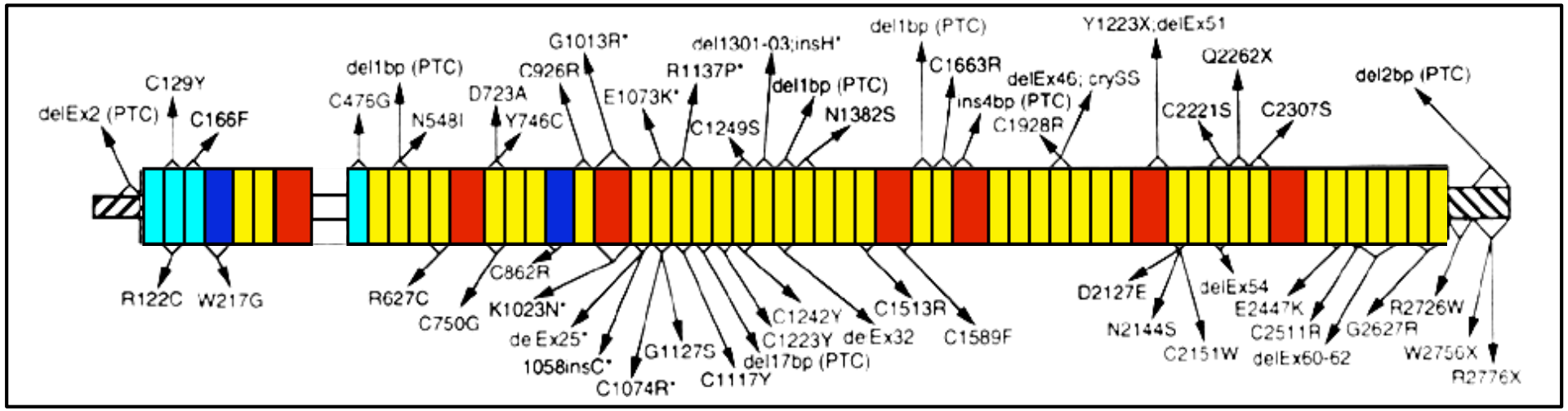
The 2019 challenges for Marfan disease…

1. *FBN1* gene mutations explain > 90% of all Marfan patients.
2. Genotype guided prediction of phenotype evolves slowly.
3. Current aortic risk models are poor at precisely predicting aortic dissection.
4. Contemporary treatment strategies do not stop aortic growth.

Bold future predictions for Marfan disease… in 2030

1. We will be able to identify all *FBN1* mutations predisposing for Marfan syndrome.
2. We will have identified dozens of genetic modifiers explaining variable expressivity of aortopathy.
3. We will have built a integrated aortic risk models allowing accurate prediction of aortic dissection.
4. We will have created gene specific designer drugs available for specific forms of thoracic aortic aneurysm/dissection, including Marfan syndrome.

FBN1 – associated phenotypes



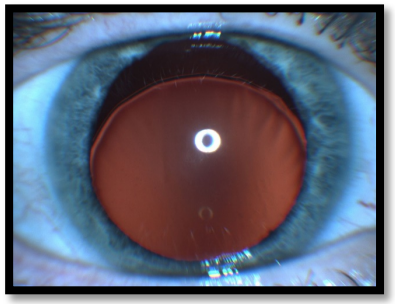
Widespread *FBN1* mutations cause:

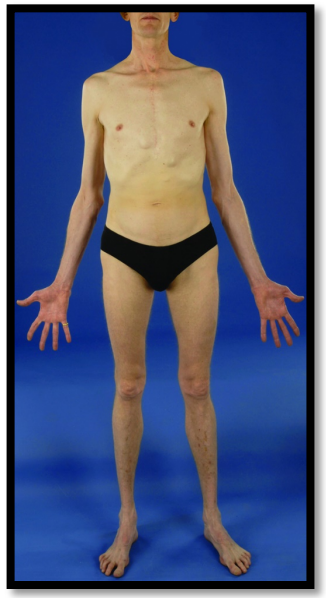
- Marfan syndrome
- Ectopia Lentis Syndrome
- Familial marfanoid body habitus
- Familial aortic aneurysm, MASS phenotype, MVP syndrome
- Weill-Marchesani syndrome (microspherophakia, short stature, brachydactyly)

Domain specific *FBN1* mutations cause:

- Stiff skin syndrome (4th LTBP domain – RGD motif)
- Acromicric/geleophysic dysplasia (5th LTBP domain): short stature, joint stiffness

Marfan syndrome





1 in 5000

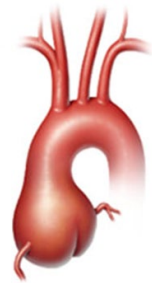
FBN1

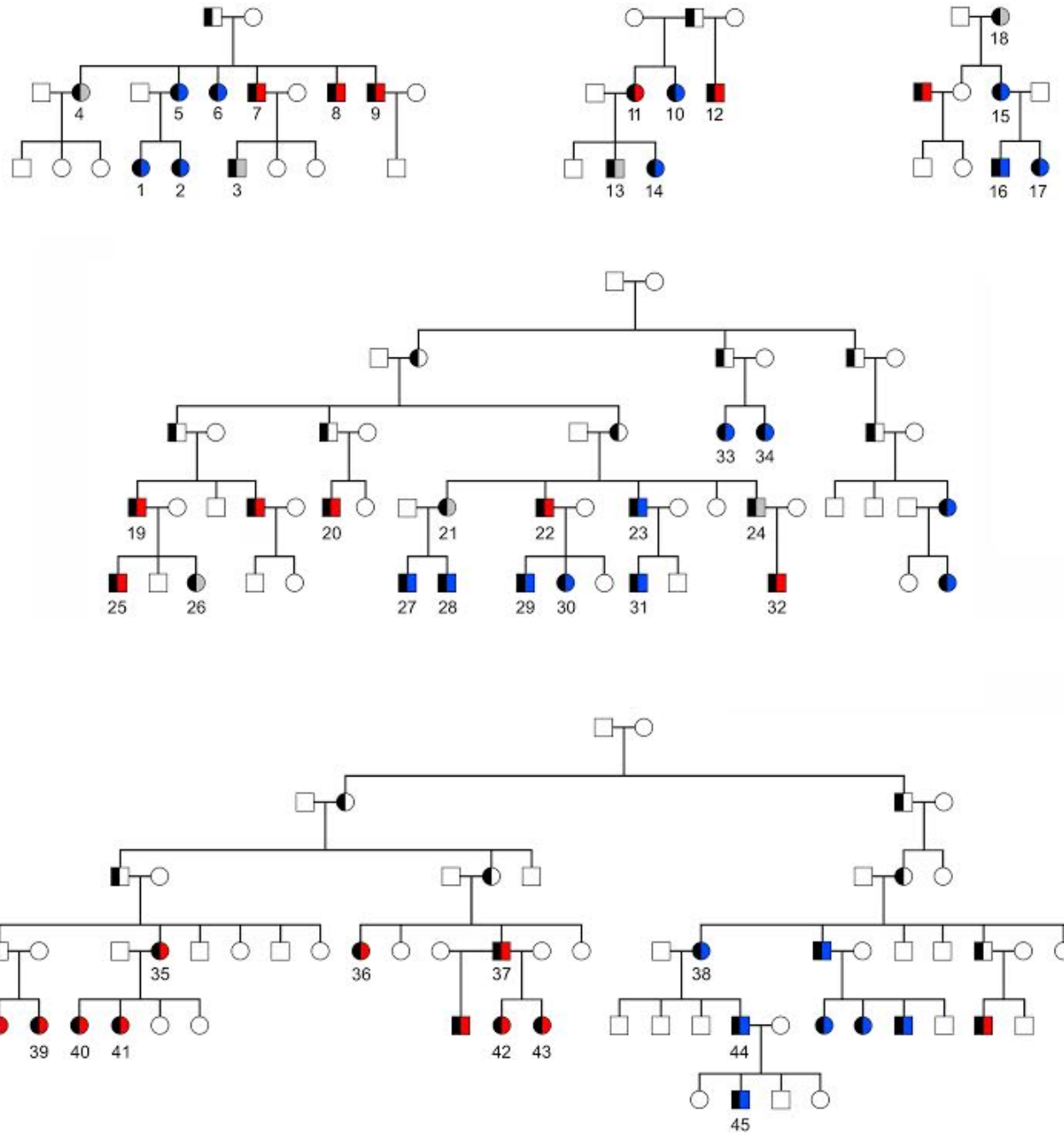
Identical *FBN1* mutation

Variable aortopathy expressivity

Normal

Severe





Marfan syndrome presents with variable clinical presentation

MFS mild or no aortic disease

MFS with severe aortic disease

MFS with indeterminate data

No MFS

Based on aortic Z-score, events and age

What explains the inter- and intrafamilial variability in phenotypical severity ?

Is the type of *FBN1* mutation important ?

Heart, 2017

Aortic and vascular disease

ORIGINAL RESEARCH ARTICLE

Relationship between fibrillin-1 genotype and severity of cardiovascular involvement in Marfan syndrome

Romy Franken,[1,2] Gisela Teixido-Tura,[1] Maria Brion,[3] Alberto Forteza,[4] Jose Rodriguez-Palomares,[1] Laura Gutierrez,[1] David Garcia Dorado,[1] Gerard Pals,[5] Barbara JM Mulder,[2,6] Artur Evangelista[7]

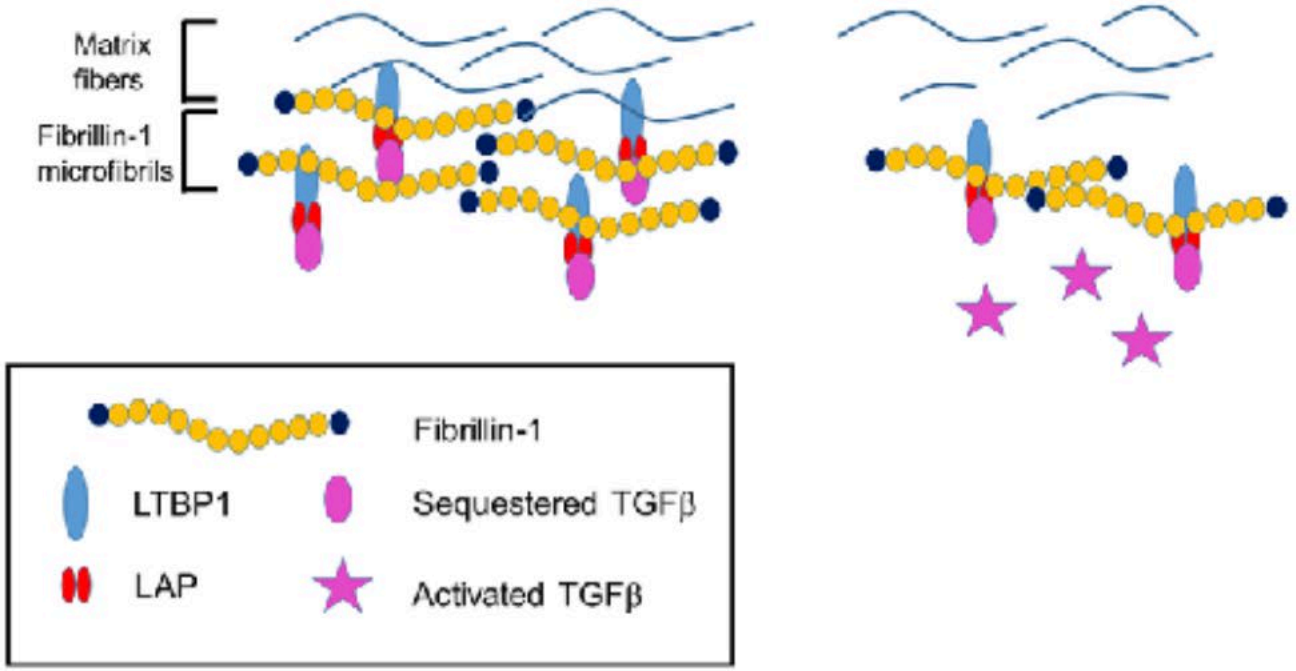
HMG, 2015

The clinical presentation of Marfan syndrome is modulated by expression of wild-type *FBN1* allele

Mélodie Aubart[1], Marie-Sylvie Gross[1], Nadine Hanna[1,2], Marie-Thérèse Zabot[4], Marc Sznajder[5], Delphine Detaint[1,3,†], Laurent Gouya[3], Guillaume Jondeau[1,3], Catherine Boileau[1,3] and Chantal Stheneur[3,*]

FBN1 HI and DN classification

	Normal	Haplo-insufficiency (HI)
DNA	No abnormalities	Most commonly nonsense, frameshift, splice site or deletion
Protein	Normal	Not made or degraded



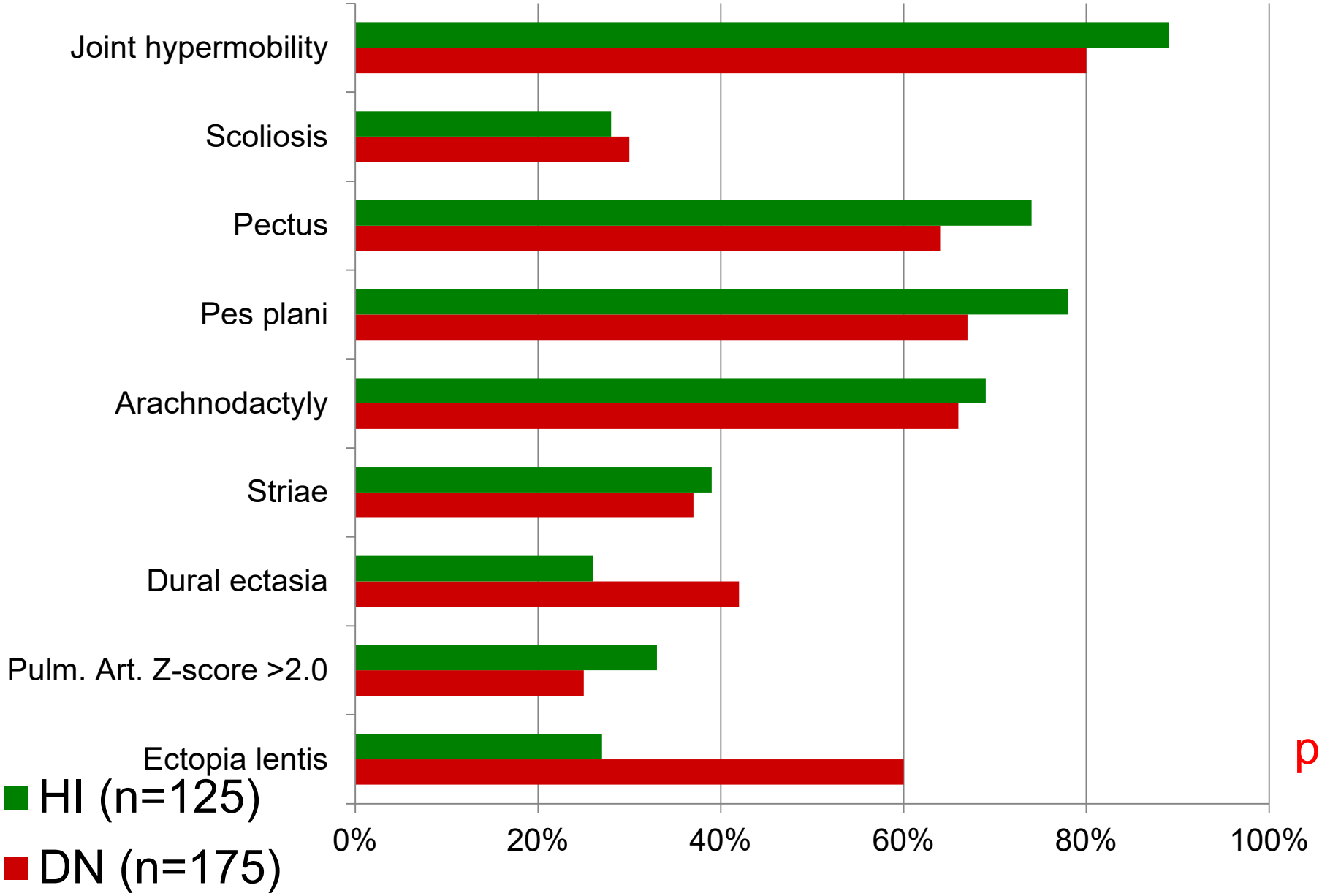
Marfan trial: genetics ancillary study

Pediatric Heart Network Marfan Clinical Trial
Included and randomized Patients: 608 patients from 21 clinical sites

Genetics Ancillary Study to Marfan Clinical Trial
Voluntary participation by donating additional blood sample and signing additional informed consent

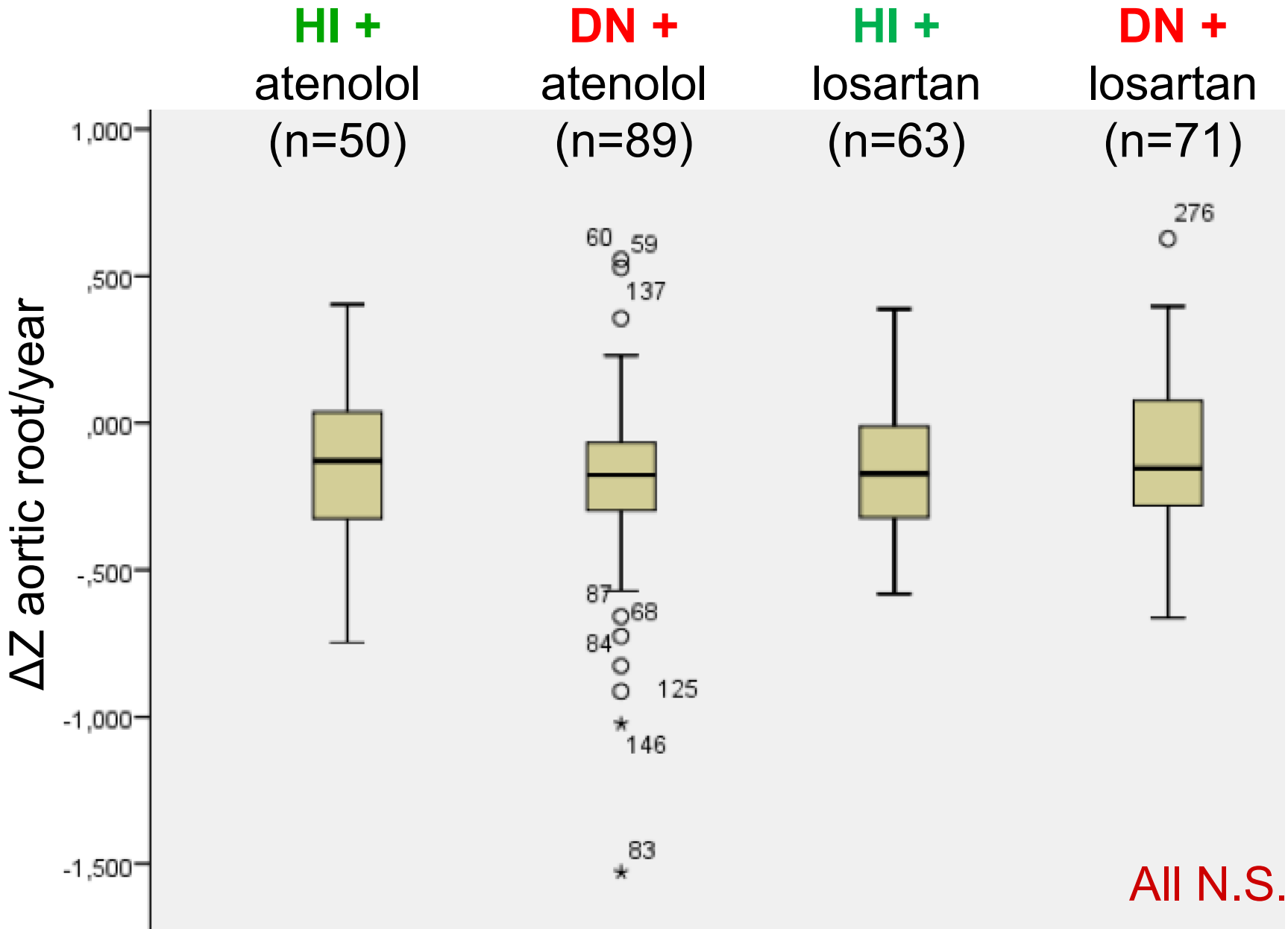
Patients included in the Genetics Ancillary Study:
-> 304 trial patients (50%) donated blood sample

Comparison DN vs HI for clinical feaures



p=<0.0000001

Effect of genotype on treatment outcome



Intra- and interfamilial variable severity of Marfan aortopathy

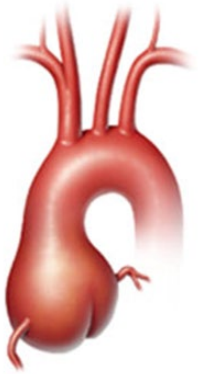
Identical *FBN1*-gene mutation

Variable aortopathy expressivity

Normal

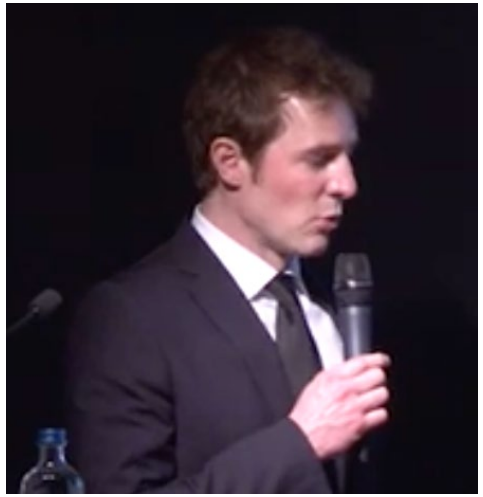
Severe

Genetic modifiers ?



Overall future goal

Apply current genomic technology into precision medicine in order to answer questions on rare diseases that were previously difficult to answer and that require an international collaborative effort



Fondation 101 Génomes

FONDATION PRIVÉE

Development of scientific strategy

1. What is the best approach to identify these genomic modifiers?

2. Is the approach feasible?

3. What is needed to carry out the ideal approach?

1. Selection of the best approach

- Discussion concerning all possible approaches (n=7) among world Marfan experts from Ghent, Paris and Antwerp involved in F101G

- First choice strategy: Identify MFS individuals with specific *FBN1* variants that are common enough to collect sufficient patients AND present a wide range of cardiovascular phenotypical severity

-> **G**enome-wide **E**pistasis for cardiovascular severity in **M**arfan **S**tudy

GEMS

As a proof of concept for 101genomes project

2. Preliminary data supporting feasibility

Selection of the 7 most recurrent (familial) *FBN1* variants

	***FBN1* mutation**	**UMD-*FBN1* (n=3077)**	**Published (n=4343)**
#1	c.IVS2+1G>A (c.247+1G>A) – exon 2-3	21	31
#2	p.Gly214Ser; c.640G>A – exon 6	16	17
#3	p.Ala882Val; c.2645C>T – exon 21	15	18
#4	c.IVS46+5G>A (c.5788+5G>A) – exon 46-47	29	34
#5	p.Met2347ValfsX19; c.7039_7040del AT – exon 57	16	18
#6	p.Asp2485Val; c.7454A>T – exon 59	16	18
#7	p.Ile2585Thr; c.7754T>C – exon 62	30	35

Mutation present in 1% of all MFS patients

UMD-*FBN1* http://www.umd.be/FBN1/
Published as reviewed in Groth et al, Genet in Med, 2017, 2018

2. Preliminary data supporting feasibility

Most common missense variant: *FBN1* p.Ile2585Thr

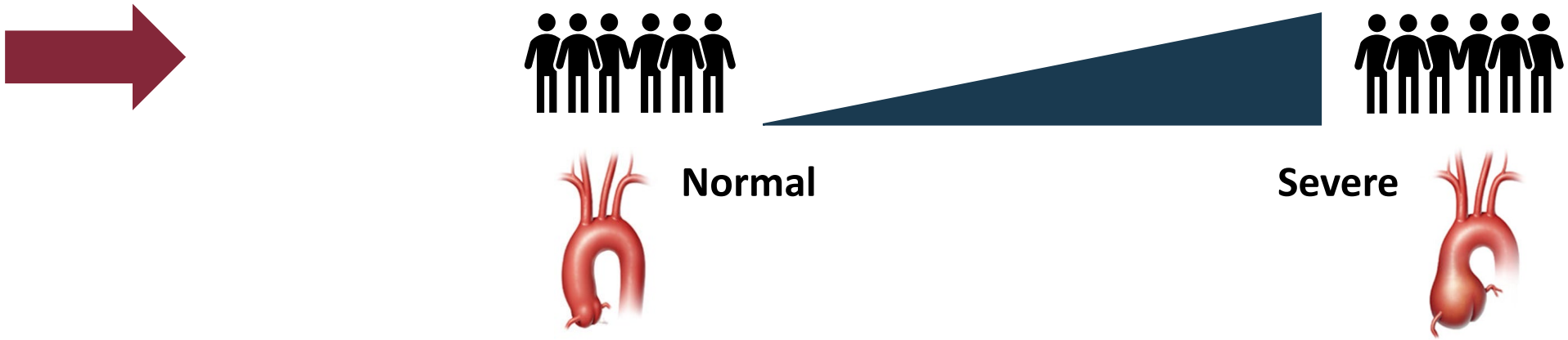
Cohort: > 200 mutation carriers assembled

GnomAD: asymptomatic cases

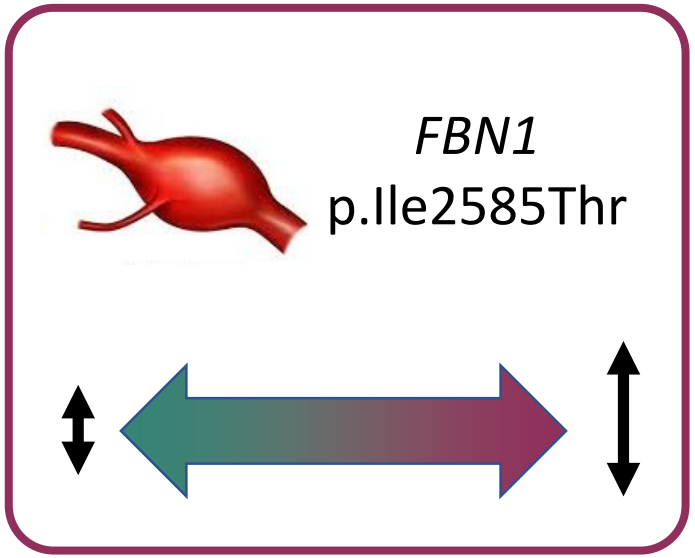
Clinical phenotyping: extreme variability demonstrated

UMC: unaffected mutation carrier

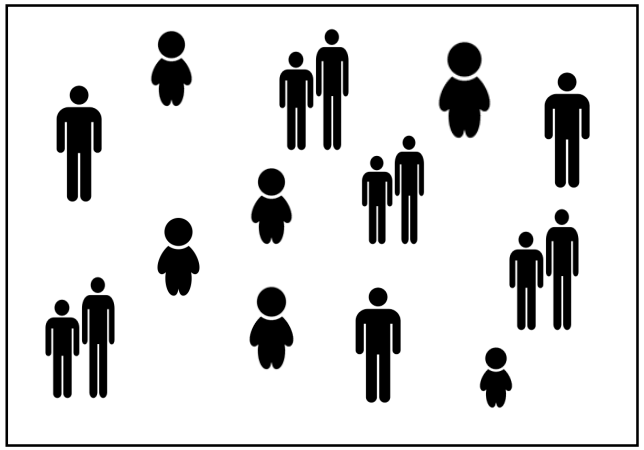
AMC: affected mutation carrier



3. Methodology: identification of modifier genes



Extremes ~ Z-score & age

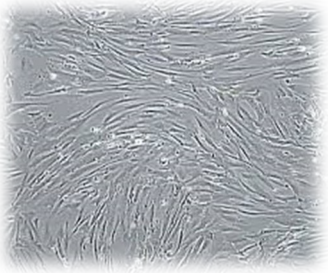


n= at least 200

P0-P25 & P75-P100

WGS (n=100)

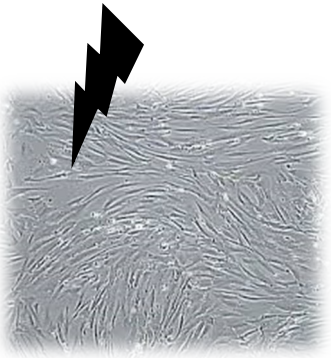
iPSC-VSMC

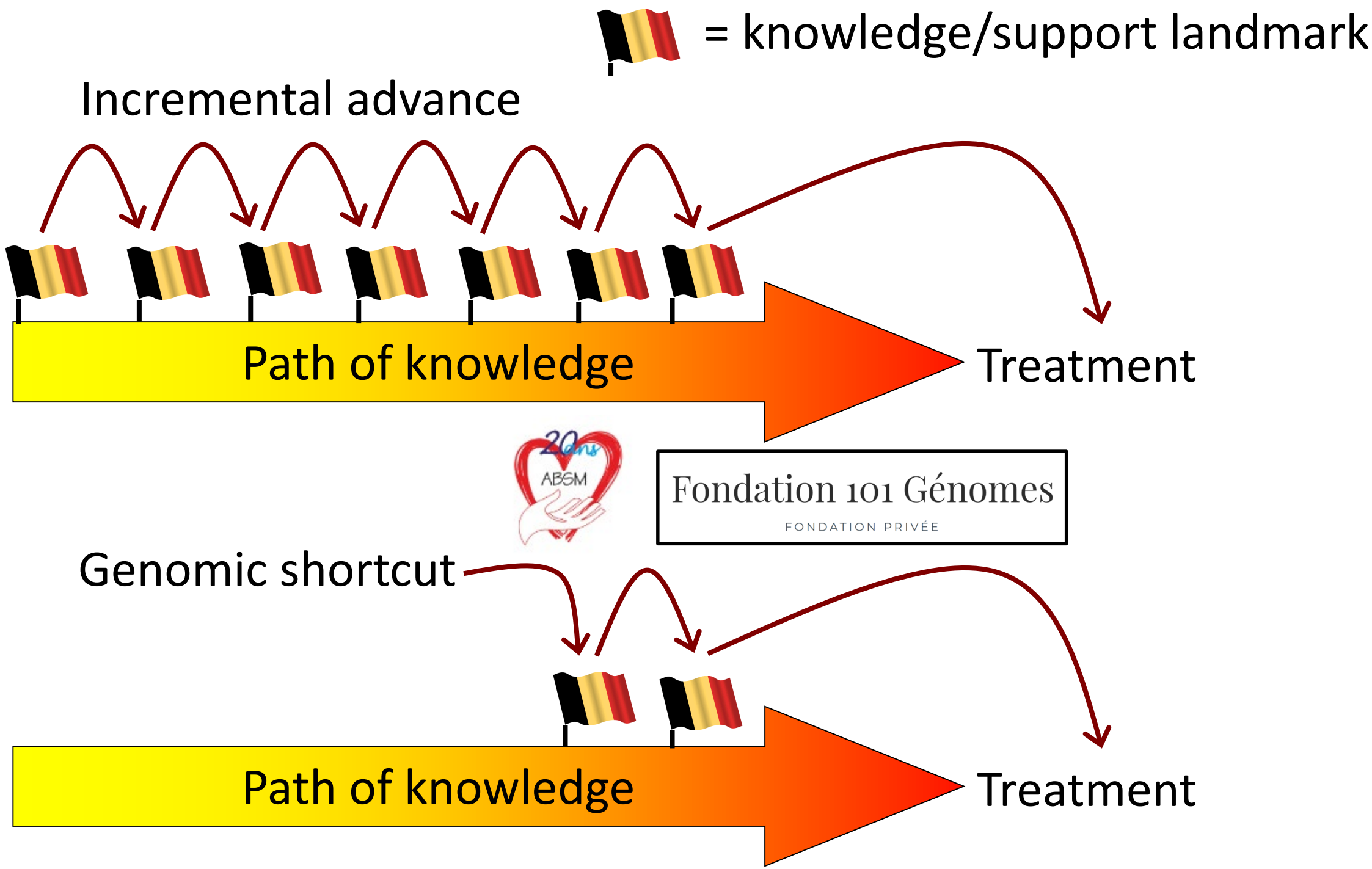


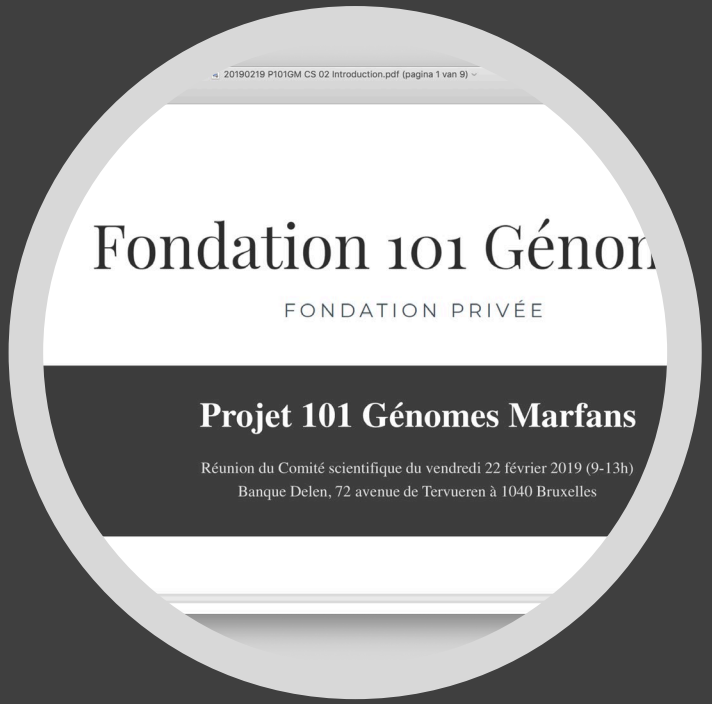
P0-P5 (UMC) & P95-P100 (AMC)

RNA-seq (n=20)

CRISPR-Cas9




= knowledge/support landmark
Incremental advance
Path of knowledge
Treatment
Fondation 101 Génomes
FONDATION PRIVÉE
Genomic shortcut
Path of knowledge
Treatment



Félicitations et merci à Mme Yvonne Jousten et l'ABSM !