Genetic investigation of challenging cardiovascular disease predominant in women

The Two Fridas, 1939
Museo de arte moderno, Mexico

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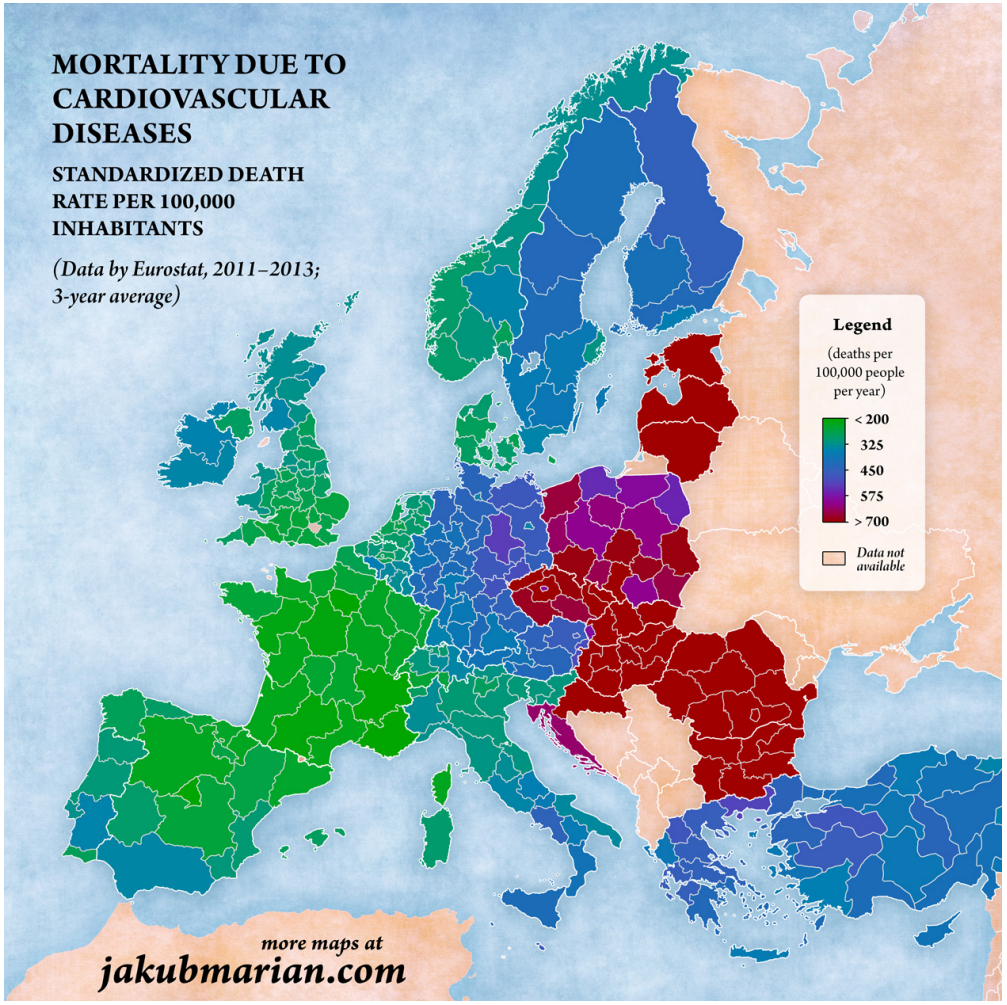
Cardiovascular disease #1 killer

WHO Source

17 million deaths

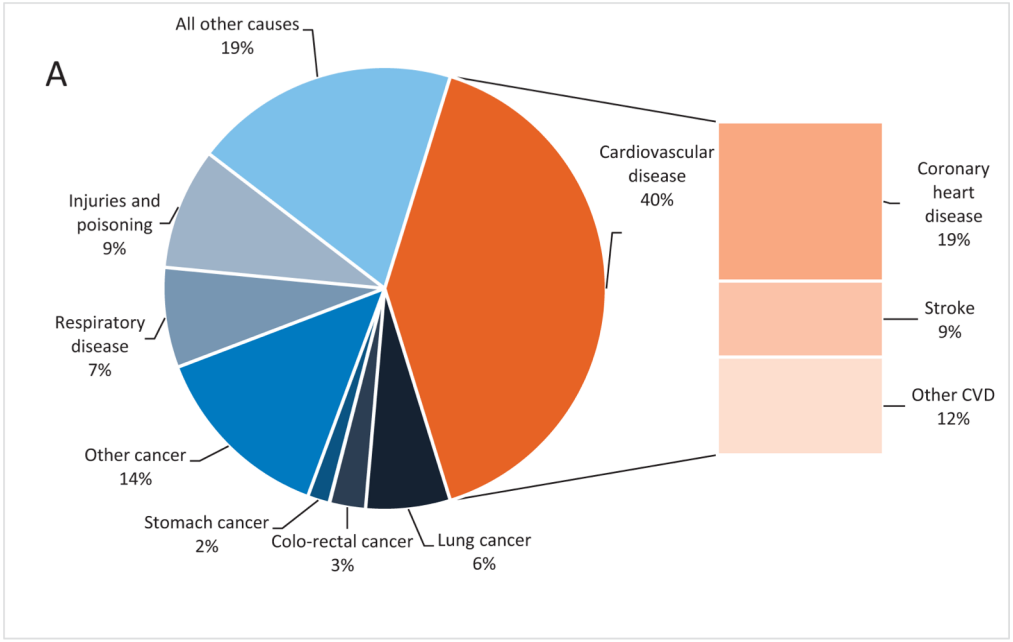


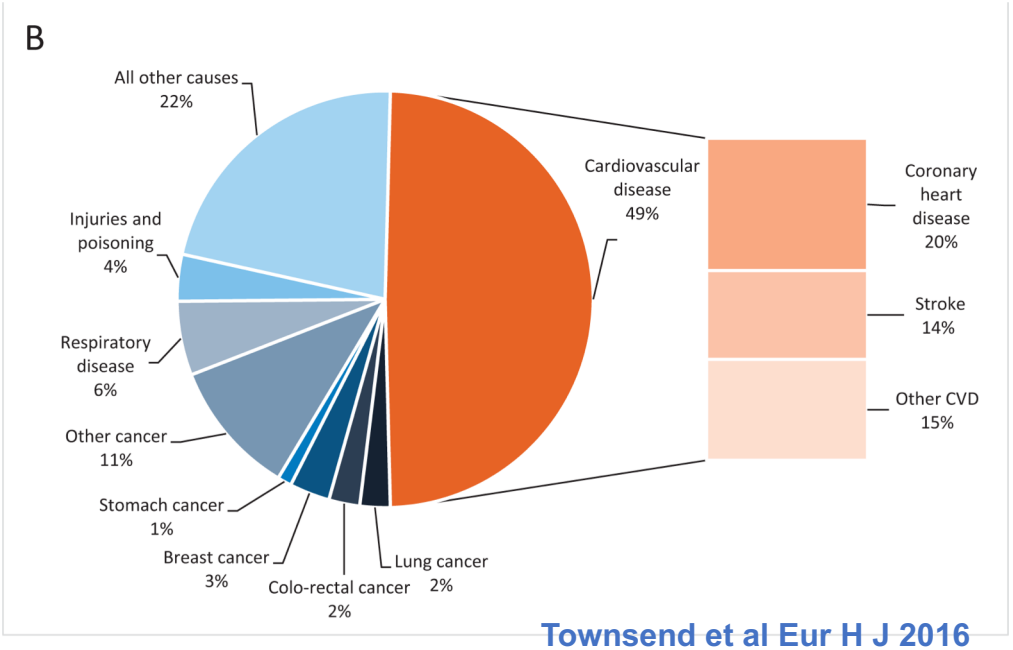
Proportion of deaths due to CVD causes in Europe

Man and woman, Fernando Botero

CVD is 49% of causes in women

Breast Cancer: 3%

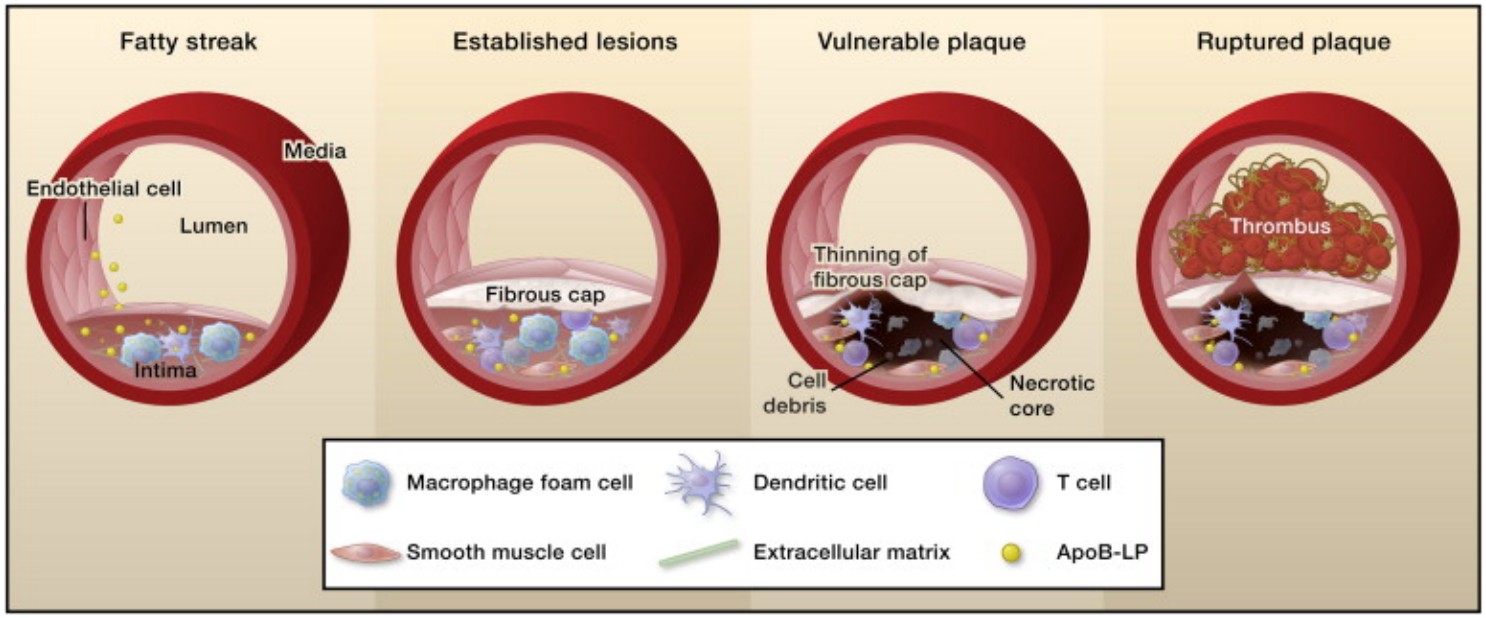




Townsend et al Eur H J 2016

Cardiovascular disease: inflammation is key!

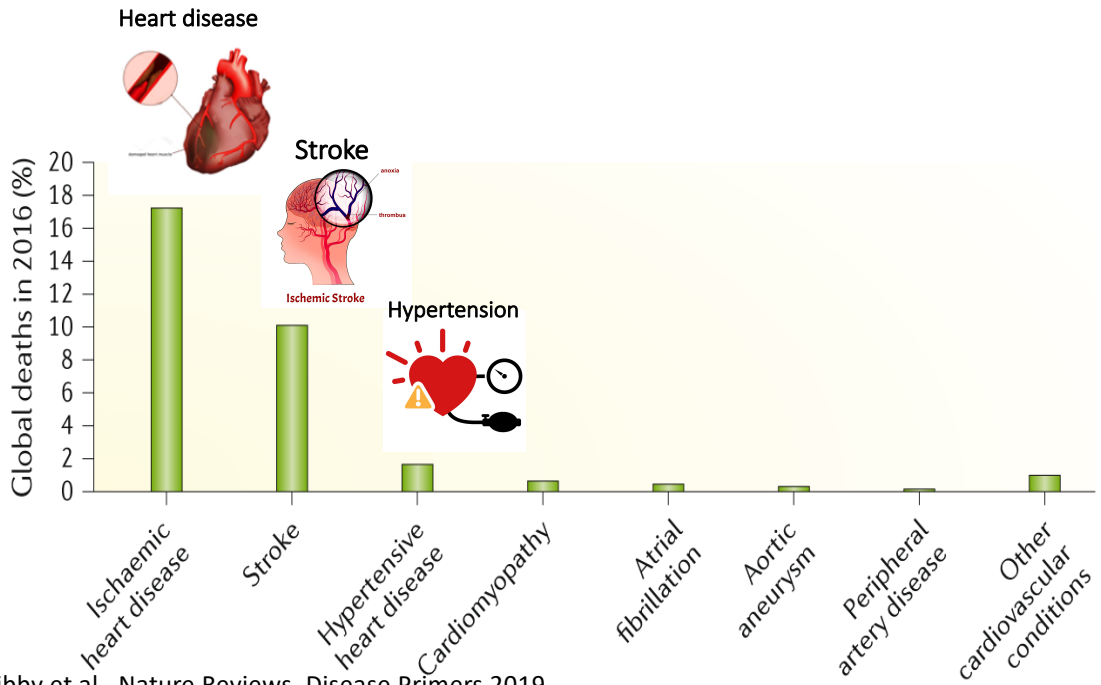
Dialogue between monocytes, macrophages, in response to lipids accumulations



Atherosclerotic plaque evolution

Moore and Tabas, 2011 Cell

CVD is Diverse - lipids accumulation and the progress of inflammation are not always reported



Libby et al., Nature Reviews, Disease Primers 2019

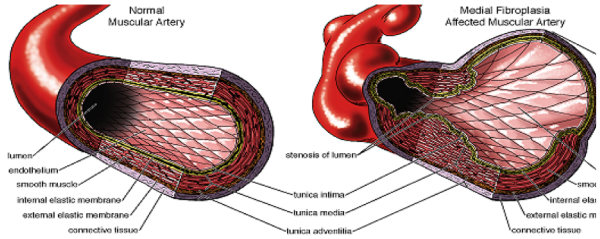
Risk Factors:

- **Smoking**
- Lack of exercise
- Diet
- **Obesity**
- **High blood pressure**
- High LDL or low HDL **cholesterol** levels
- Age

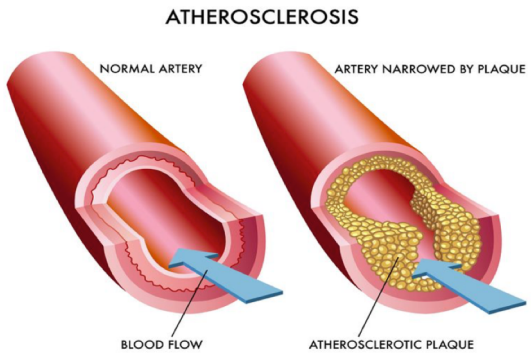
- Underdiagnosed conditions
- Secondary hypertension
- Bad responders to current treatments
- Unexpected events, no typical risk factors

Fibromuscular dysplasia (FMD)

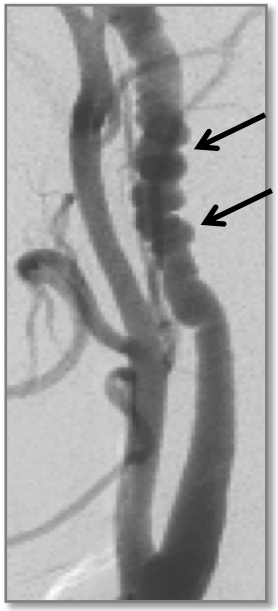
Healthy



FMD



Angiography

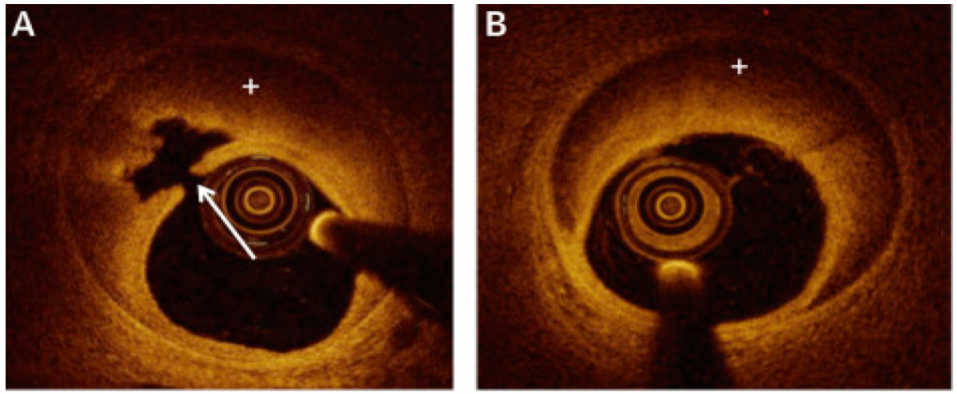


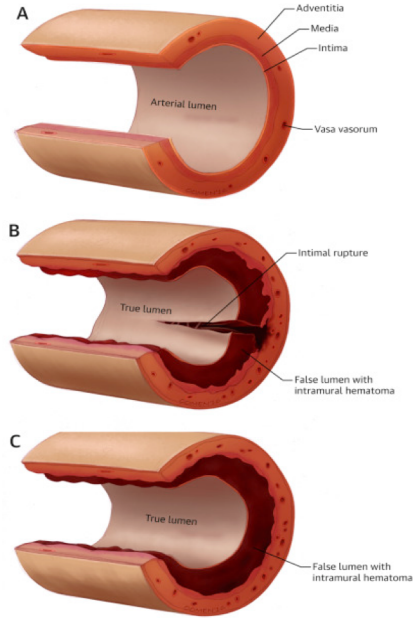
- Succession of stenoses and aneurysms of medium arteries
- Atypical clinical presentation (e.g no dyslipidemia, no obesity)
- Complex imaging-based diagnosis
- Underdiagnosed (stroke or resistant hypertension, often incidentally in 3-4% of kidney donors)
- Diagnosed in 50% of SCAD cases, a rare MI event

Olin et al Circ 2012
Touzé E et al, Int J Stroke 2010
Plouin Hypertension 2017
McKenzie J Vasc Interv Radiol 2013

Spontaneous coronary artery dissection (SCAD)

Optical computed tomography (OCT)





- Nonatherosclerotic acute coronary syndrome: few risk factors (no dyslipidemia, healthy lifestyle)
- Formation of intramural hematoma and/ or intimal disruption
- Age of event ~ 45-50 years ➔ younger than classical heart disease

Motreff EuroIntervention 2017
Tweet Curr Cardiol Rep 2016
Saw JACC 2016
Tweet JACC 2017

FMD and SCAD: female neglected and under-investigated arterial diseases

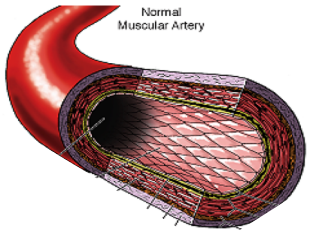
The Two Fridas, 1939
Museo de arte moderno, Mexico

- 80 to 90% of patients are women 44-55 years
- FMD is a cause of renal hypertension in ~ 10% of cases (diagnosis delay ~10 years)
- SCAD represents 25-33% of myocardial infarction in women < 60 yrs
- Awareness among cardiologists is increasing

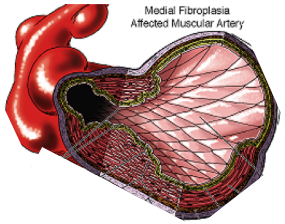
Motreff EuroIntervention 2017
Hayes Circ 2018
Plouin Hypertension 2017
Olin Circ 2012

SCAD and FMD has unknown pathophysiology

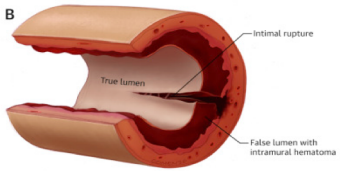
Healthy Artery



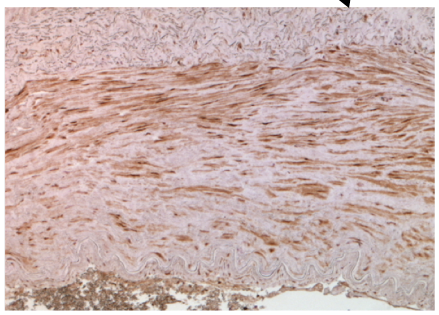
Stenosis/
Aneurysm



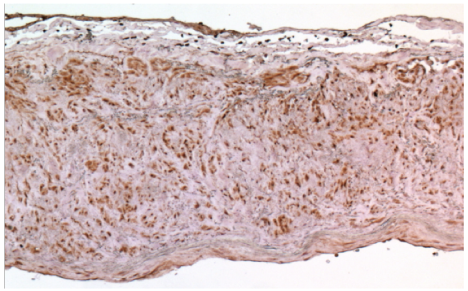
Dissection



?



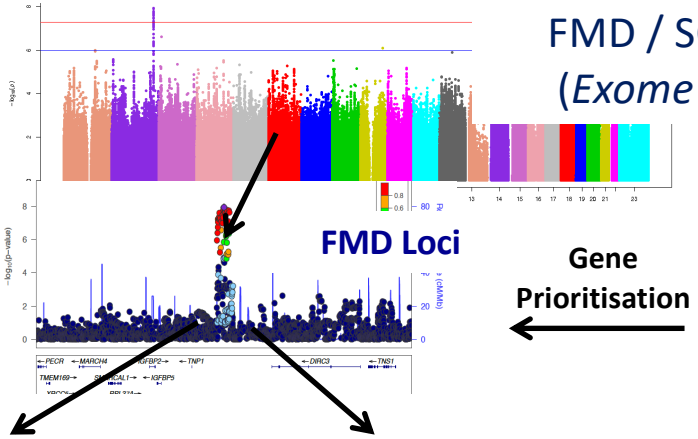
- Mechanical Stress
- Hormones fluctuation
- Smoking
- Genetic factors



ROSALIND Research Program to Investigate SCAD and FMD

European Research Council

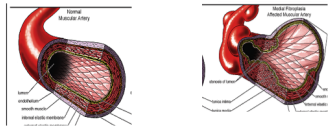
FMD / SCAD Case Control GWAS
(*Exome and Target sequencing*)



FMD Loci

Gene Prioritisation

Global Expression Renal Arteries

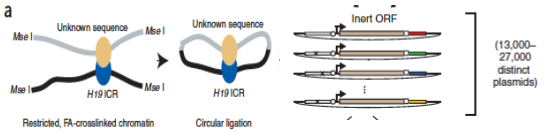


Healthy

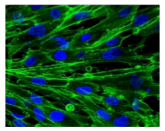
FMD

Aim1: Decipher the genetic basis of FMD and SCAD

Genomic Interactions Open Chrimatin

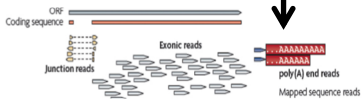


Primary and iPSC induced SMCs



Adhesion/migration

Differential expression profiling



Aim2: Study the Functional Relevance of FMD Risk Loci

High Throughput Functional Genomics

***In Vitro* Functional validation**

Renal Arteries Transcriptomics

Aim3: Explore the Link between FMD Genes and Vascular Function

New actors of vascular physiopathology

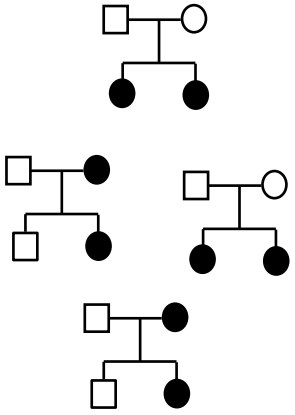
To contribute filling an important existing gap in the investigation of women specific cardiovascular diseases

The challenges of the genetics of FMD and SCAD

Study populations

- Small families (sibs, mother/daughter)
- No large scale case control studies (>10K cases)

  to compensate the clinical heterogeneity



www.genome.gov

Physiopathology

- Most of knowledge: rare syndromes

  (TGF-beta, ECM biology)
- Lack of an animal model

www.cardio-research.com

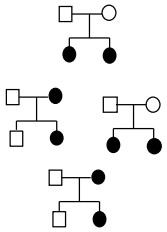
Environmental exposure

- Mechanical stress? Hormones? Others

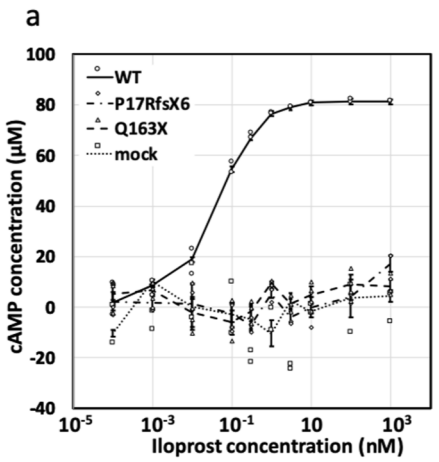
Genetic model ?

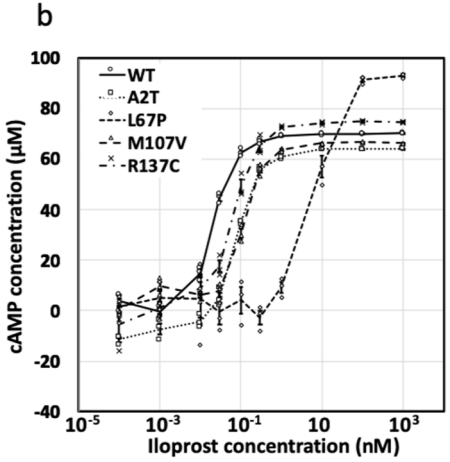
PTGIR rare variants are enriched in FMD and impair receptor activation *in vitro*

Exome and Target sequencing

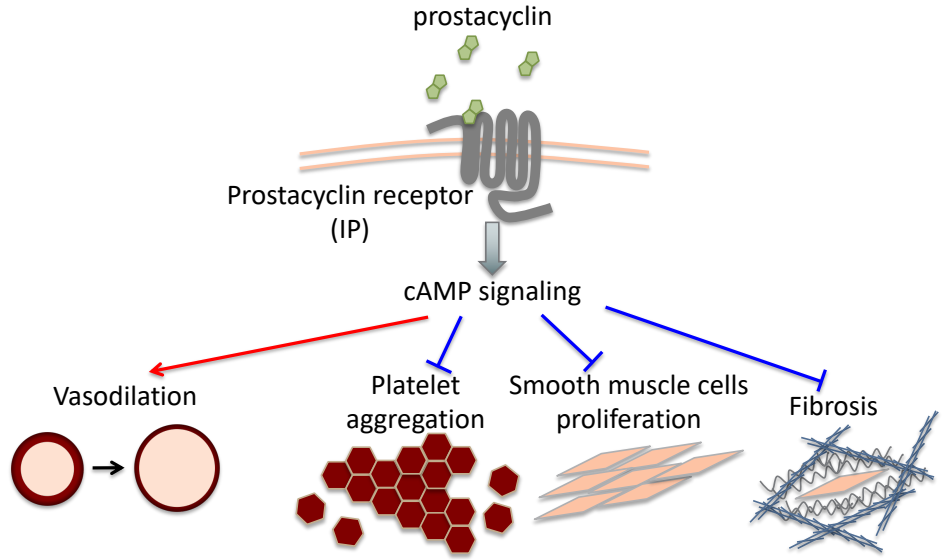


- Exomes Seq 30 FMD patients
- 4 Rare LoF (1,325 FMD, P=0.0008 vs. gnomAD)
- 2 Rare LoF (843 SCAD, P=0.12)





Prostacyclin receptor a well-known player in vascular biology



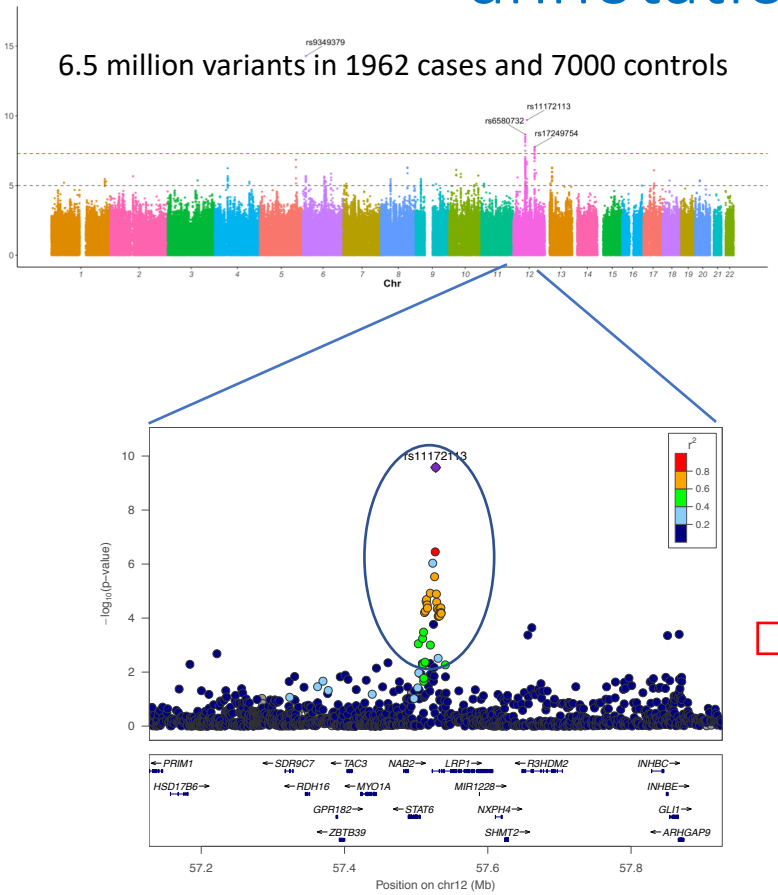
- Strongly expressed in the lungs and vasculature
- Validated therapeutic target in pulmonary arterial hypertension

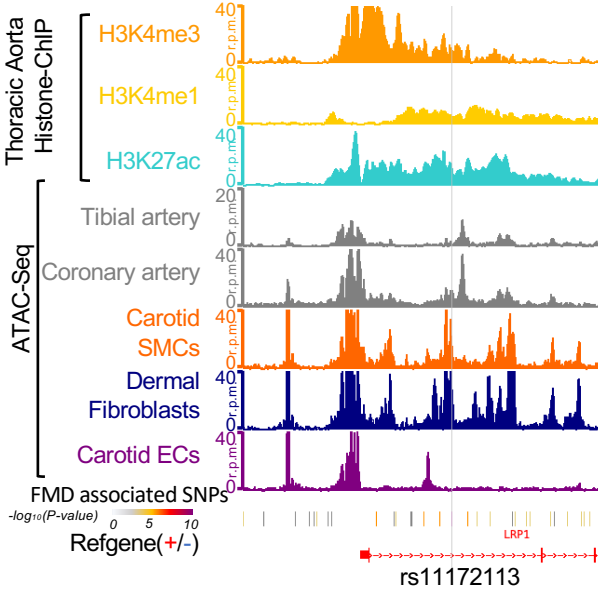
Georges et al, 2020 Cardiovascular Research

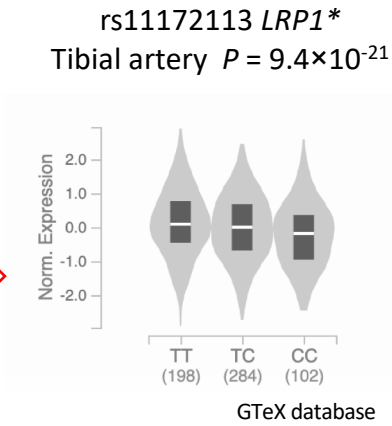
Genetic investigation of FMD leveraging GWAS, genomic annotation and expression in arteries

6.5 million variants in 1962 cases and 7000 controls

SNP-based heritability = 0.29, polygenic







Genomic association context

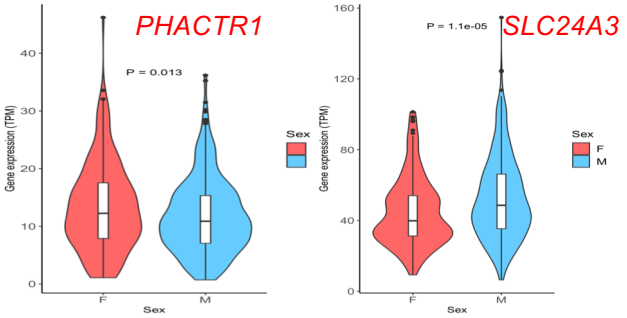
Functional annotation

Genotype / expression correlation

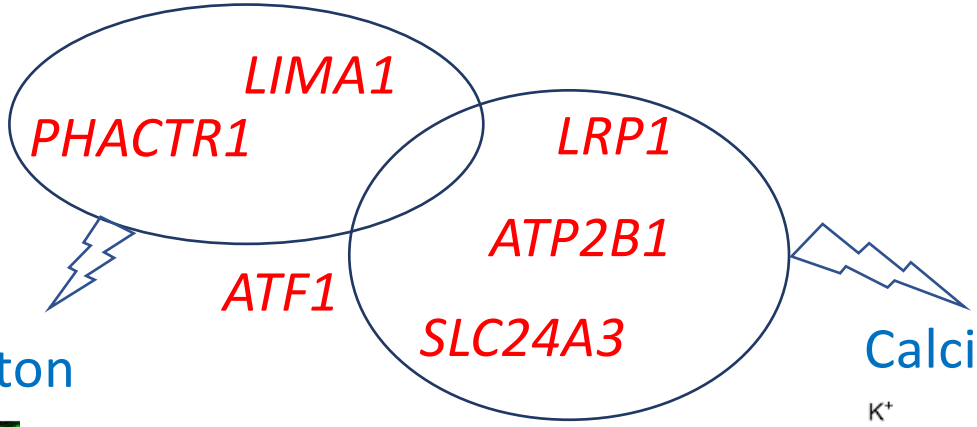
*LRP1: LDL receptor related protein 1

Georges, et al., MedRxiv: https://doi.org/10.1101/2020.09.16.20195701

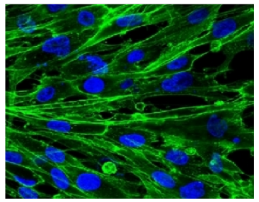
Genes near FMD loci are involved in cell contractility



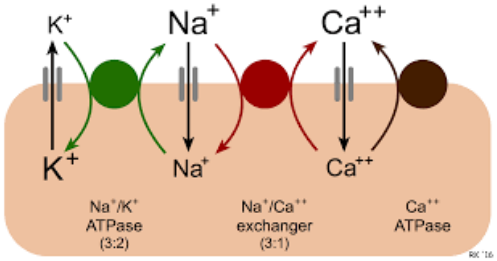
Gene expression by sex in arteries
(GTeX database)

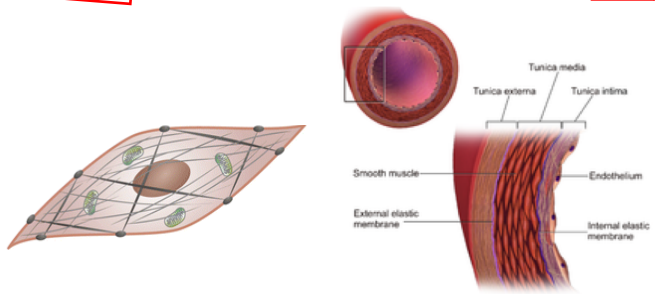


Cytoskeleton



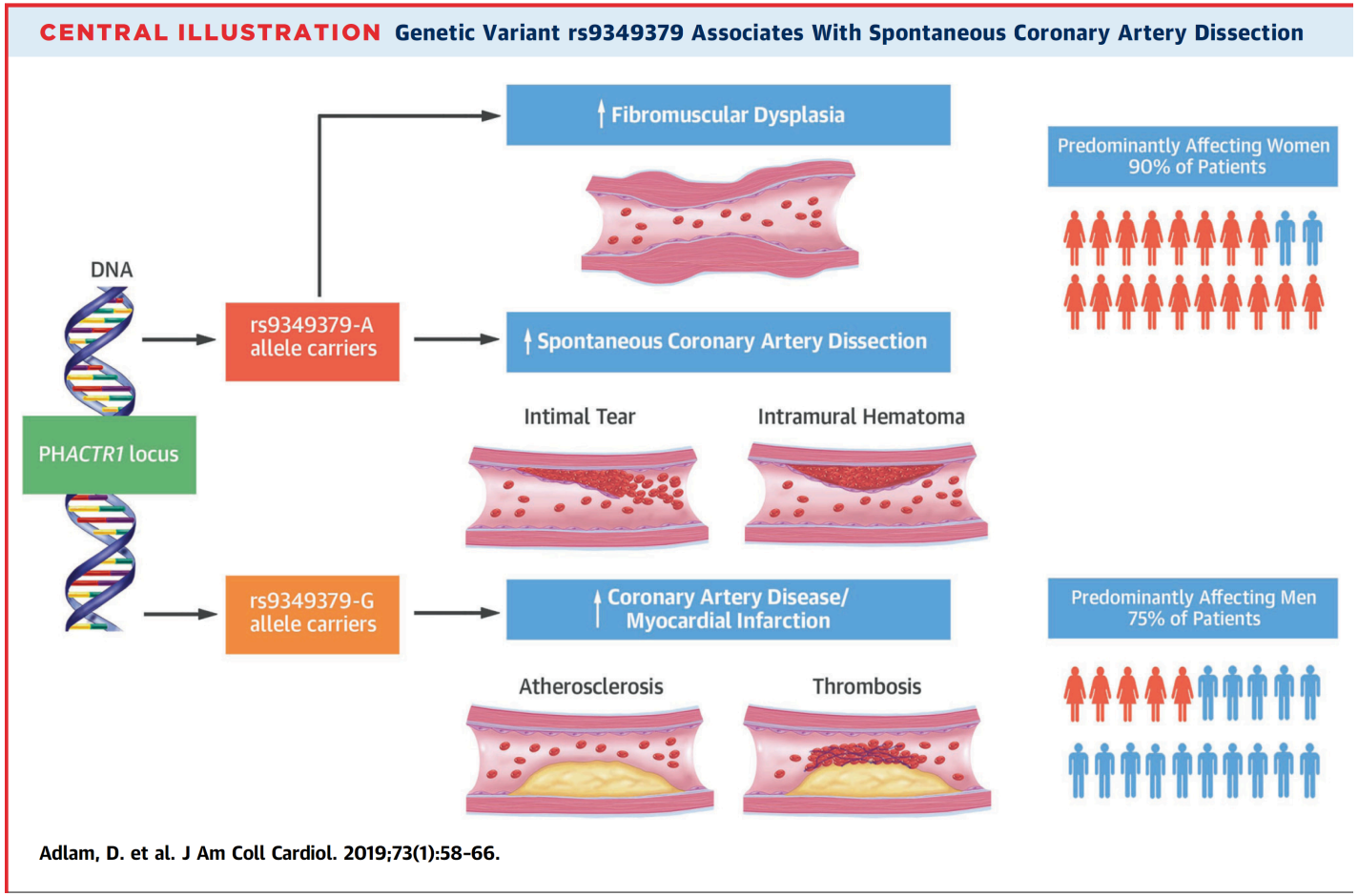
Calcium transport





Contractile function of vascular cells in arteries

Association involving different alleles in FMD and SCAD vs. CVD involving atherosclerosis



Adlam, D. et al. J Am Coll Cardiol. 2019;73(1):58-66.

Summary

- FMD and SCAD atypical neglected CVD predominant in women
- Evidence for complex genetic inheritance involving rare mutations (*PTGIR*) and common risk loci through GWAS (e.g *LRP1*, *PHACTR1)*
- Genes mutated or near FMD GWAS loci involve vasodilation, cytoskeleton biology, and calcium dependant contractile function
- *PHACTR1* is one first example of shared genetic risk allele between FMD and SCAD, opposite to risk allele involving more common atherosclerosis-linked CVD
- Upcoming GWAS for SCAD: not all loci are shared with FMD
- Increasing awareness: CVD in women presents differently, evolves differently, to be managed/treated differently?

Team: Genetics to Understand CVD in Women

French and International Networks

FMD

X Jeunemaitre, Genetics Dept, HEGP
M Azizi,/ L Amar, HTN Dept, HEGP
A Persu/ M Vikkula, UCL, Belgium
A Januszewicz, Warsow, Poland
J Kovacic/J Olin, Mount Sinai, NY, USA
H Gornik, Cleveland Clinic, USA
S Ganesh, U Michigan, USA
I Kullo, Mayo Clinic, USA

SCAD

P Mottreff, CHU C Ferrand, France
D Adlam, Leicester University, UK
S Hayes, Mayo Clinic, USA
T Olsson, Mayo Clinic, USA
B Graham, V Chang Institute, AU

erc European Research Council

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