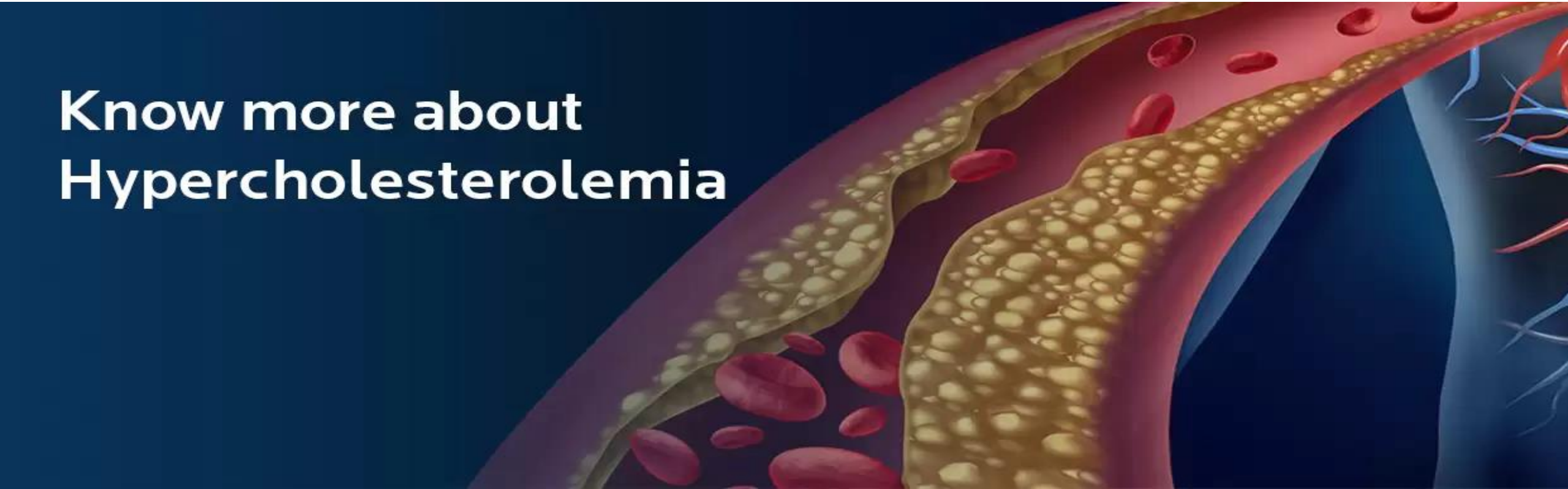
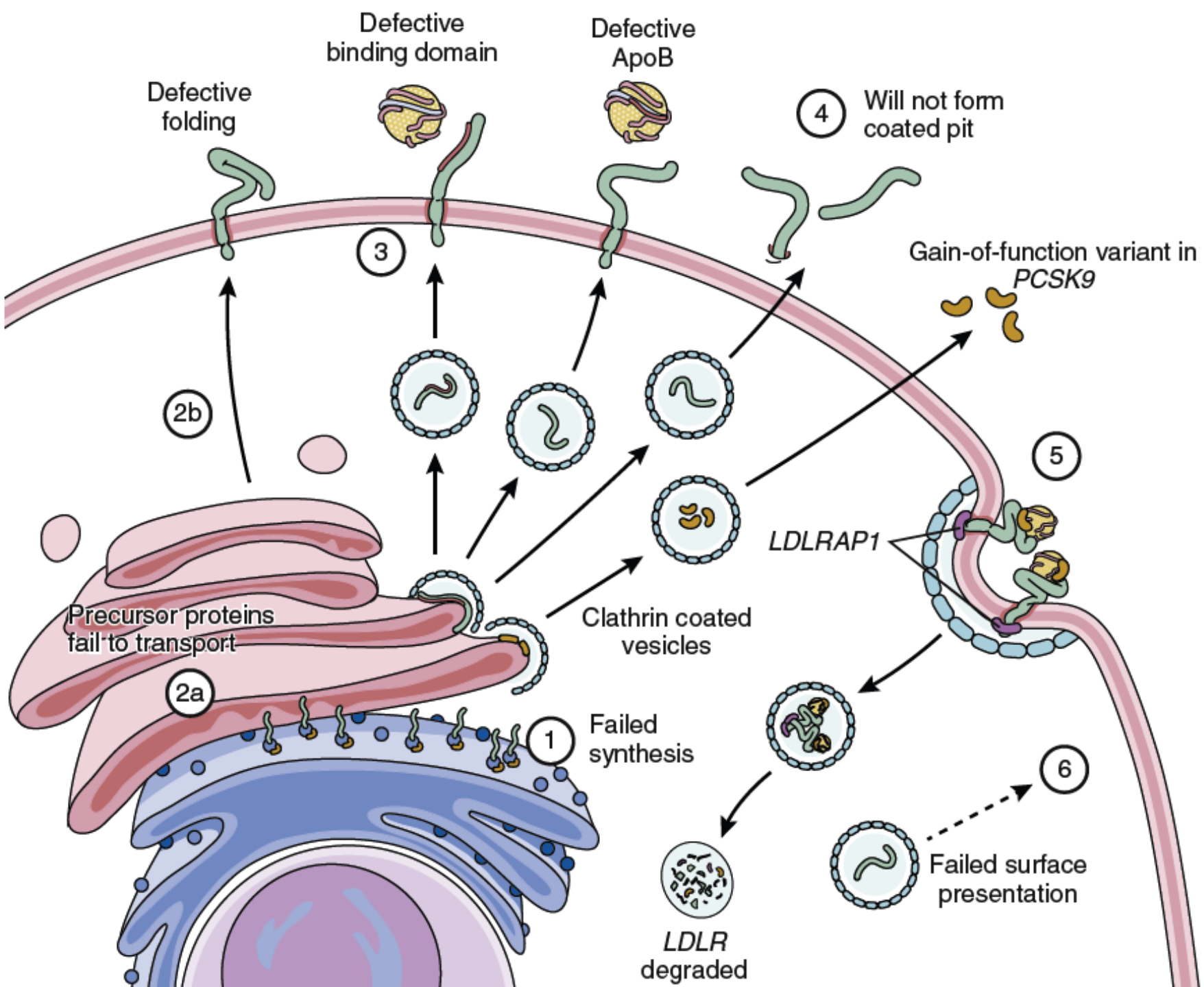
Applications of Genetics to Cardiovascular Medicine

Pradeep Natarajan and Kiran Musunuru

Hypercholesterolemia and Coronary Artery Disease

- FH afflicts approximately 1 in 300 individuals, manifesting as severely elevated blood cholesterol levels and increased risk for early-onset myocardial infarction.




Defective binding domain
Defective ApoB
Defective folding
4
Will not form coated pit
3
Gain-of-function variant in PCSK9
2b
5
LDLRAP1
Precursor proteins fail to transport
Clathrin coated vesicles
2a
1
Failed synthesis
6
Failed surface presentation
LDLR degraded

However, a single pathogenic variant in the canonical FH-genes (*LDLR, APOB or PCSK9*) is identified in only **15–50%** of phenotypical FH patients (classified by clinical scoring systems)

in the early 2000s, linkage and cloning analyses of families with autosomal recessive FH prioritized a large region on chromosome 1.

Ultimately, homozygous mutations in LDLRAP1 (previously known as ARH, autosomal recessive hypercholesterolemia).

LDLRAP1 encodes LDL receptor adaptor protein 1, which is required for endocytosis of the LDL receptor.

At present, over **3100** common genetic variants have been shown to be associated with LDL-C levels

PRS is constructed by summing the number of alleles from trait-affecting variants an individual has, weighted by their effect size as reported in the GWAS.

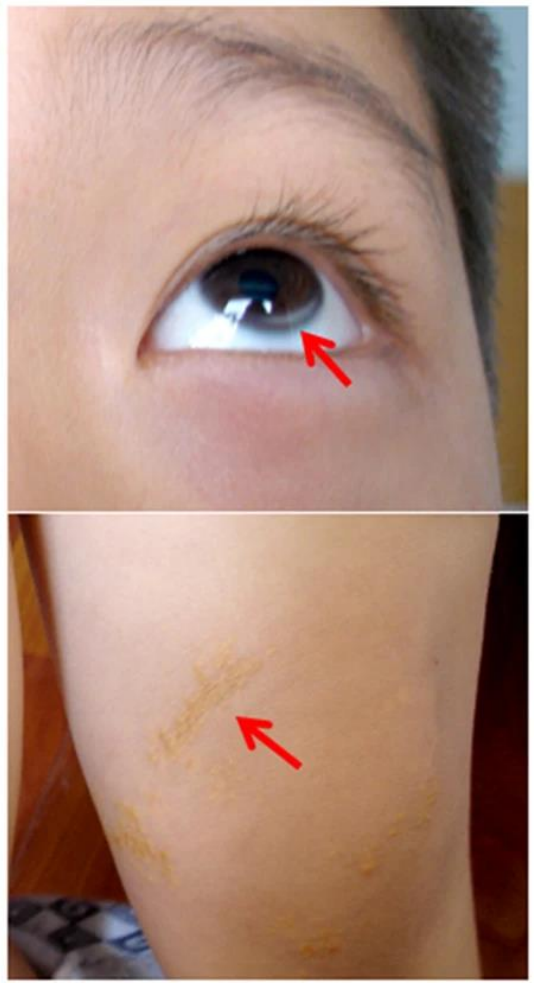
LDLR Mutations:
Patients with mutations in the LDLR gene have a more severe form of FH and may respond less effectively to statins compared to those with mutations in other genes like APOB or PCSK9.

APOB Mutations:
Statins are generally more effective in patients with APOB mutations compared to those with LDLR mutations.

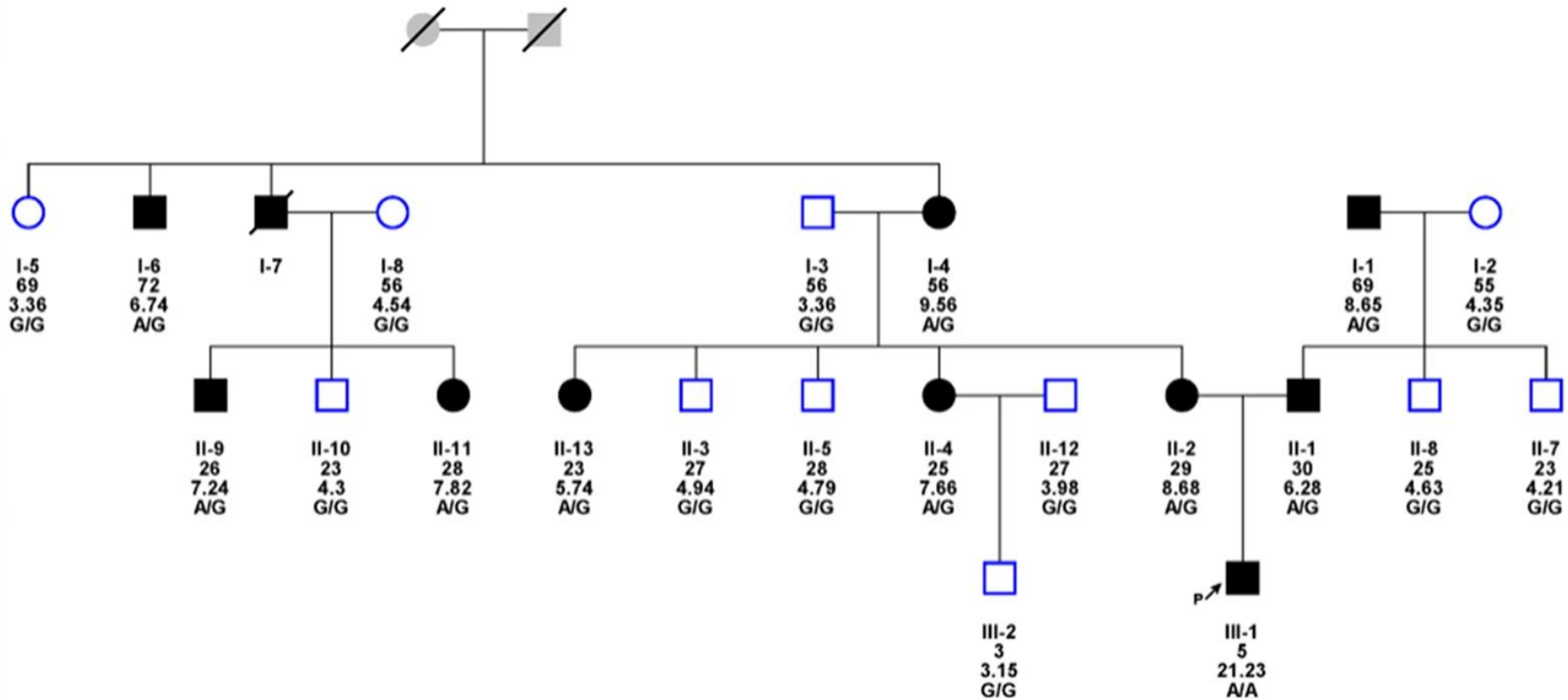
PCSK9 Mutations:
Patients with gain-of-function mutations in PCSK9 may also have a different response to statins. While statins can still lower LDL cholesterol levels, these patients may require additional therapies, such as PCSK9 inhibitors, for optimal management due to their unique genetic profile.

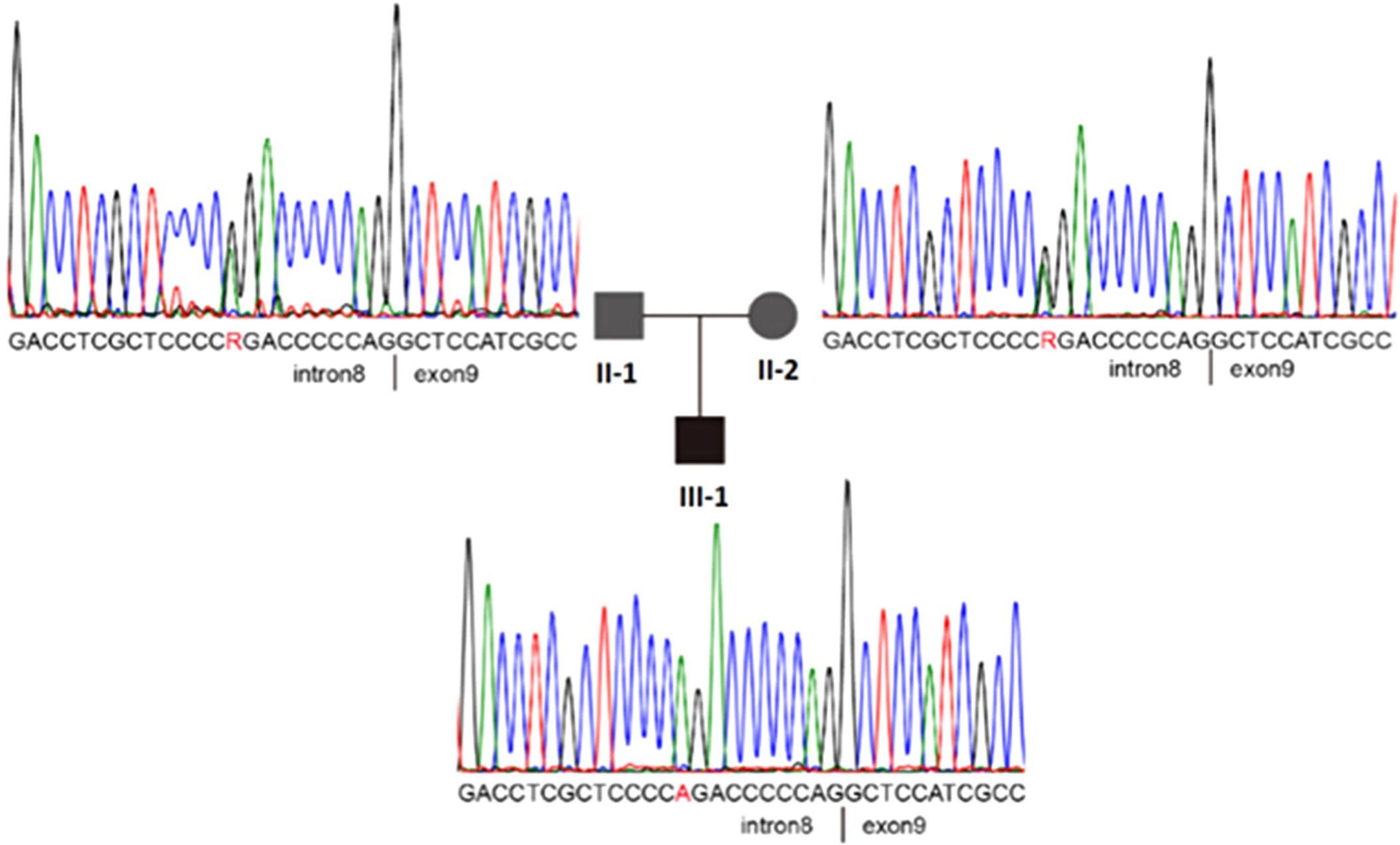
For patients who do not respond adequately to statins due to their genetic makeup, other medications such as **ezetimibe or PCSK9 inhibitors** may be recommended.

(A)



(B)


I-5
69
3.36
G/G
I-6
72
6.74
A/G
I-7
I-8
56
4.54
G/G
I-3
56
3.36
G/G
I-4
56
9.56
A/G
I-1
69
8.65
A/G
I-2
55
4.35
G/G
II-9
26
7.24
A/G
II-10
23
4.3
G/G
II-11
28
7.82
A/G
II-13
23
5.74
A/G
II-3
27
4.94
G/G
II-5
28
4.79
G/G
II-4
25
7.66
A/G
II-12
27
3.98
G/G
II-2
29
8.68
A/G
II-1
30
6.28
A/G
II-8
25
4.63
G/G
II-7
23
4.21
G/G
III-2
3
3.15
G/G
P
III-1
5
21.23
A/A


GACCTCGCTCCCCRGACCCCCAGGCTCCATCGCC
intron8 | exon9
II-1
II-2
GACCTCGCTCCCCRGACCCCCAGGCTCCATCGCC
intron8 | exon9
III-1
GACCTCGCTCCCCAGACCCCCAGGCTCCATCGCC
intron8 | exon9

- This mutation was first identified in Chinese patients and this homozygous mutation is a new genetic type of FH.

- This is the first time that WES was used in Chinese FH patients.

- They detected a novel genetic type *of LDLR* homozygous mutation.

- WES is powerful tools to identify specific FH families with potentially pathogenic gene mutations.

Metabolic Syndrome and Coronary Artery Disease

In 2007, linkage analysis of an extended family of Iranian ancestry with premature CAD and features of the metabolic syndrome resulted in the identification of a causal missense variant in LRP6.

Whole exome sequencing and focused analysis within the prioritized region identified a perfectly co-segregating missense variant in DYRK1B in all three families.

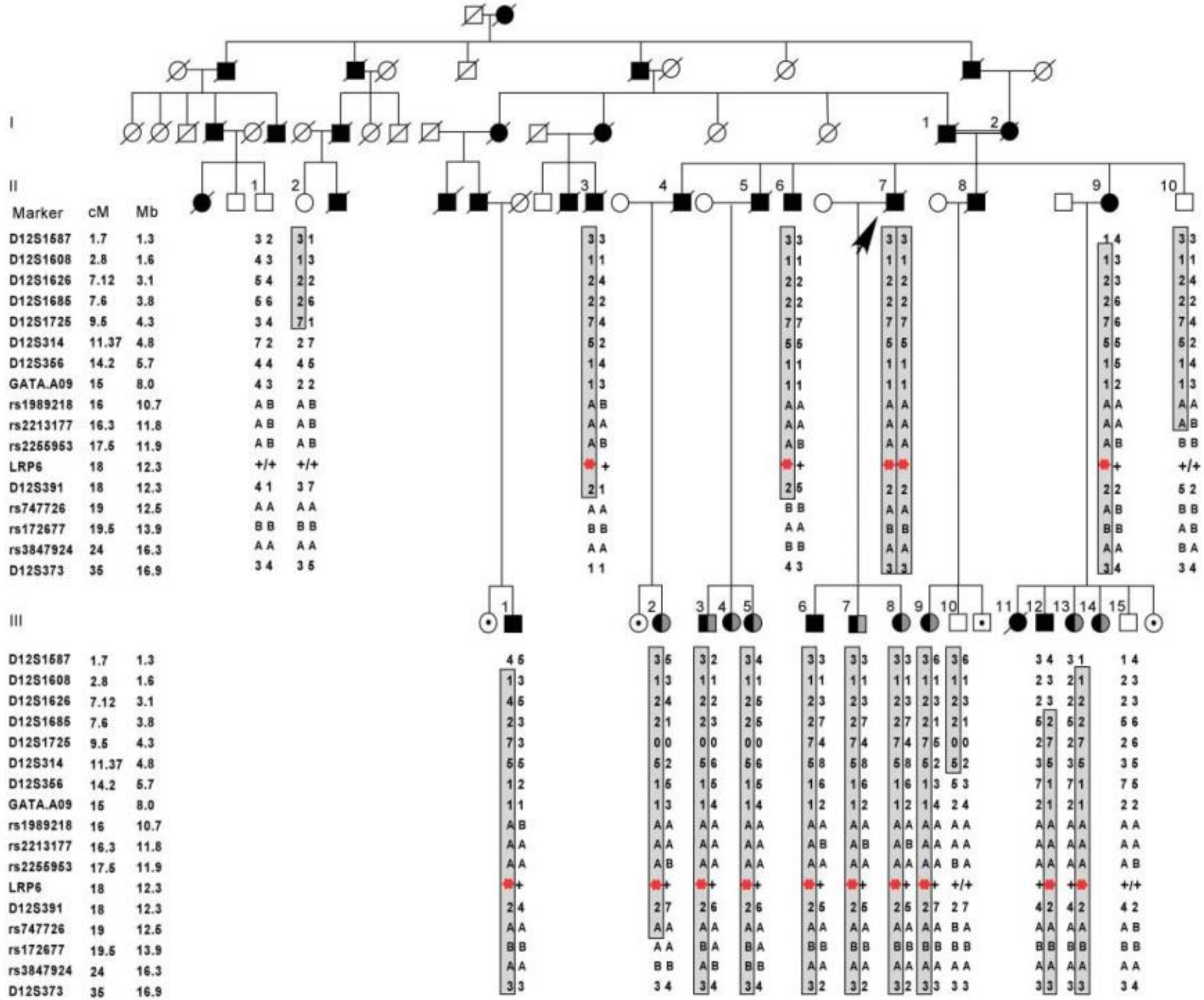
Screening of morbidly obese individuals of European descent with CAD and multiple metabolic phenotypes identified a family with co-segregation of a different missense variant in DYRK1B

- In 2007, researchers studied a **large Iranian family** with early coronary artery disease (CAD) and metabolic syndrome.
- They found a specific genetic change (missense variant) in the **LRP6 gene** that disrupted a key signaling pathway called **Wnt signaling**.

LRP6 Mutation in a Family with Early Coronary Disease and Metabolic Risk Factors

Arya Mani,[1*] Jayaram Radhakrishnan,[1] He Wang,[2] Alaleh Mani,[3] Mohammad-Ali Mani,[4] Carol Nelson-Williams,[1] Khary S. Carew,[1] Shrikant Mane,[1] Hossein Najmabadi,[5] Dan Wu,[2] Richard P. Lifton[1*]

Coronary artery disease (CAD) is the leading cause of death worldwide and is commonly caused by a constellation of risk factors called the metabolic syndrome. We characterized a family with autosomal dominant early CAD, features of the metabolic syndrome (hyperlipidemia, hypertension, and diabetes), and osteoporosis. These traits showed genetic linkage to a short segment of chromosome 12p, in which we identified a missense mutation in *LRP6*, which encodes a co-receptor in the Wnt signaling pathway. The mutation, which substitutes cysteine for arginine at a highly conserved residue of an epidermal growth factor–like domain, impairs Wnt signaling in vitro. These results link a single gene defect in Wnt signaling to CAD and multiple cardiovascular risk factors.



Marker	cM	Mb
D12S1587	1.7	1.3
D12S1608	2.8	1.6
D12S1626	7.12	3.1
D12S1685	7.6	3.8
D12S1725	9.5	4.3
D12S314	11.37	4.8
D12S356	14.2	5.7
GATA.A09	15	8.0
rs1989218	16	10.7
rs2213177	16.3	11.8
rs2256953	17.5	11.9
LRP6	18	12.3
D12S391	18	12.3
rs747726	19	12.5
rs172677	19.5	13.9
rs3847924	24	16.3
D12S373	35	16.9

Marker	cM	Mb
D12S1587	1.7	1.3
D12S1608	2.8	1.6
D12S1626	7.12	3.1
D12S1685	7.6	3.8
D12S1725	9.5	4.3
D12S314	11.37	4.8
D12S356	14.2	5.7
GATA.A09	15	8.0
rs1989218	16	10.7
rs2213177	16.3	11.8
rs2256953	17.5	11.9
LRP6	18	12.3
D12S391	18	12.3
rs747726	19	12.5
rs172677	19.5	13.9
rs3847924	24	16.3
D12S373	35	16.9

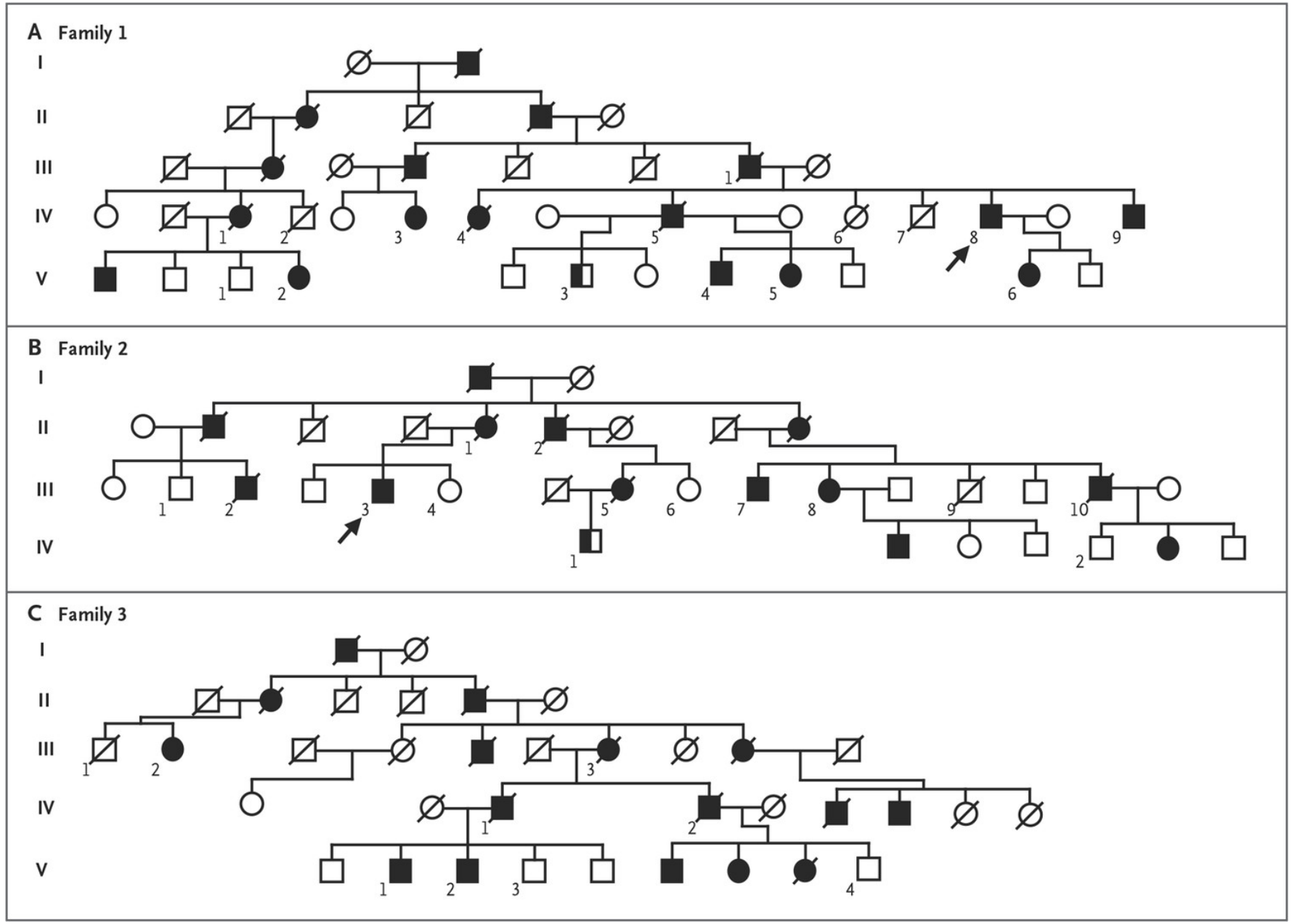
the same team examined three additional large Iranian families with similar health issues.

ORIGINAL ARTICLE

A Form of the Metabolic Syndrome Associated with Mutations in *DYRK1B*

Authors: Ali R. Keramati, M.D., Mohsen Fathzadeh, Ph.D., Gwang-Woong Go, Ph.D., Rajvir Singh, Ph.D., Murim Choi, Ph.D., Saeed Faramarzi, M.D., Shrikant Mane, Ph.D., +9, and Arya Mani, M.D. Author Info & Affiliations

Published May 15, 2014 | N Engl J Med 2014;370:1909-1919 | DOI: 10.1056/NEJMoa1301824 | VOL. 370 NO. 20


A Family 1
I
II
III
IV
V
B Family 2
I
II
III
IV
C Family 3
I
II
III
IV
V

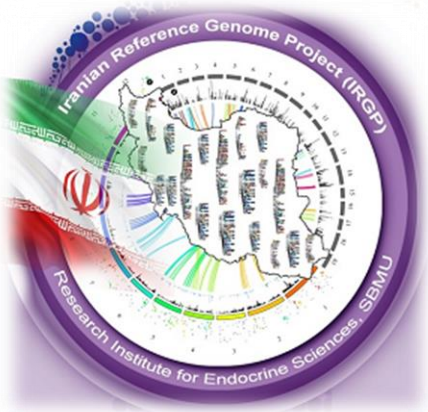
- They used linkage analysis to narrow down a specific area on **chromosome 19** that was linked to these conditions.
- By performing whole exome sequencing in this region, they discovered another missense variant in the **DYRK1B gene** that was consistently found in all three families.

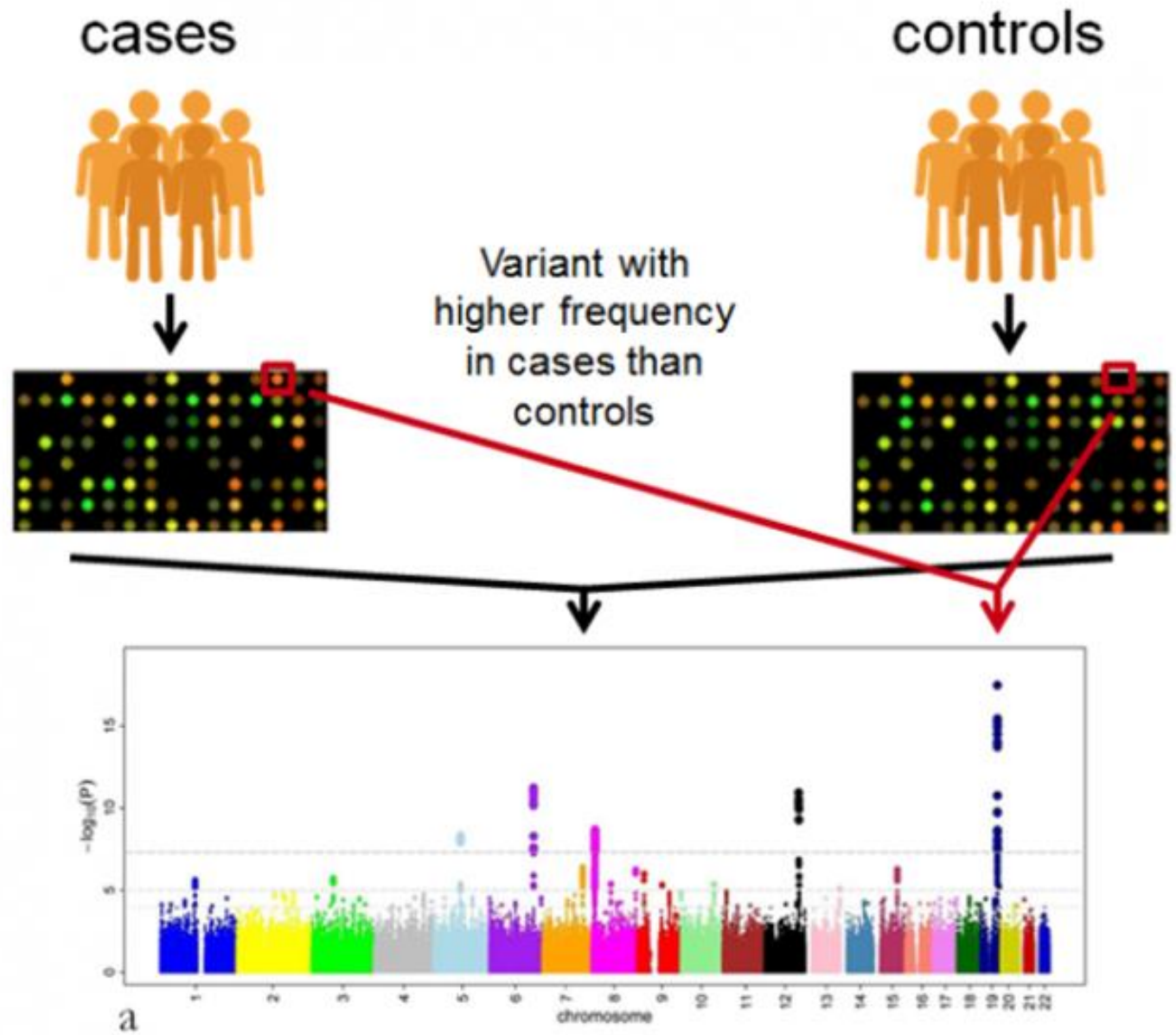
These findings indicate a role for *DYRK1B* in adipogenesis and glucose homeostasis and associate its altered function with an inherited form of the metabolic syndrome.

Case-Control and Population-Based Studies

- A GWAS (Genome-Wide Association Study) is a research approach used to identify genetic variations across the entire genome that may be associated with a particular disease or trait.

- Scanning the genome of large groups
- High-throughput technologies (like SNP arrays or sequencing) to
- For cardiovascular diseases: lipid metabolism, blood pressure regulation, inflammation, or the structure and function of the vascular system.



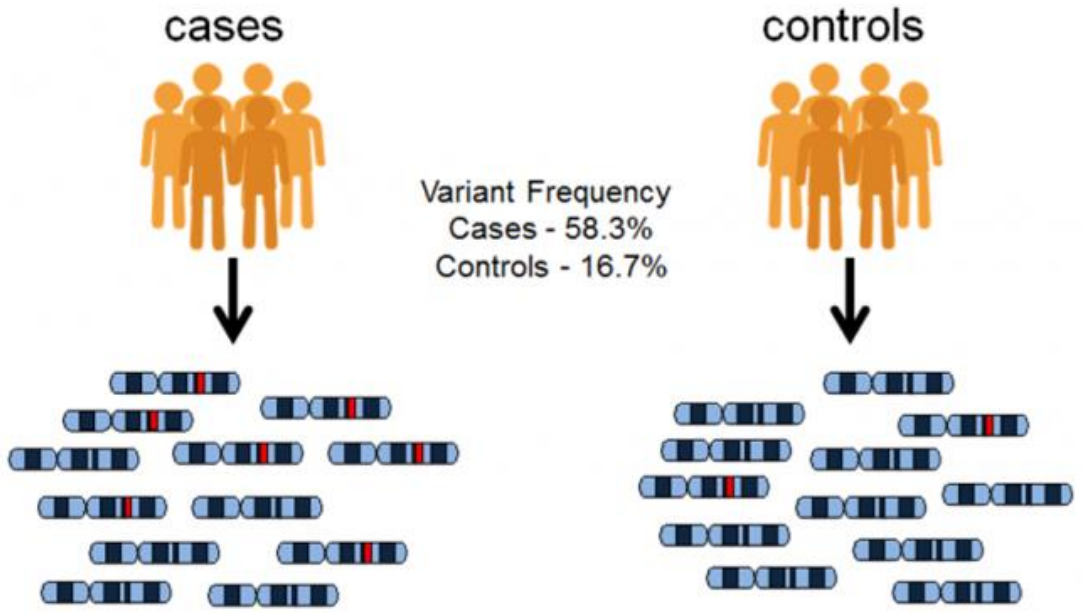

cases
controls
Variant with higher frequency in cases than controls
chromosome
a

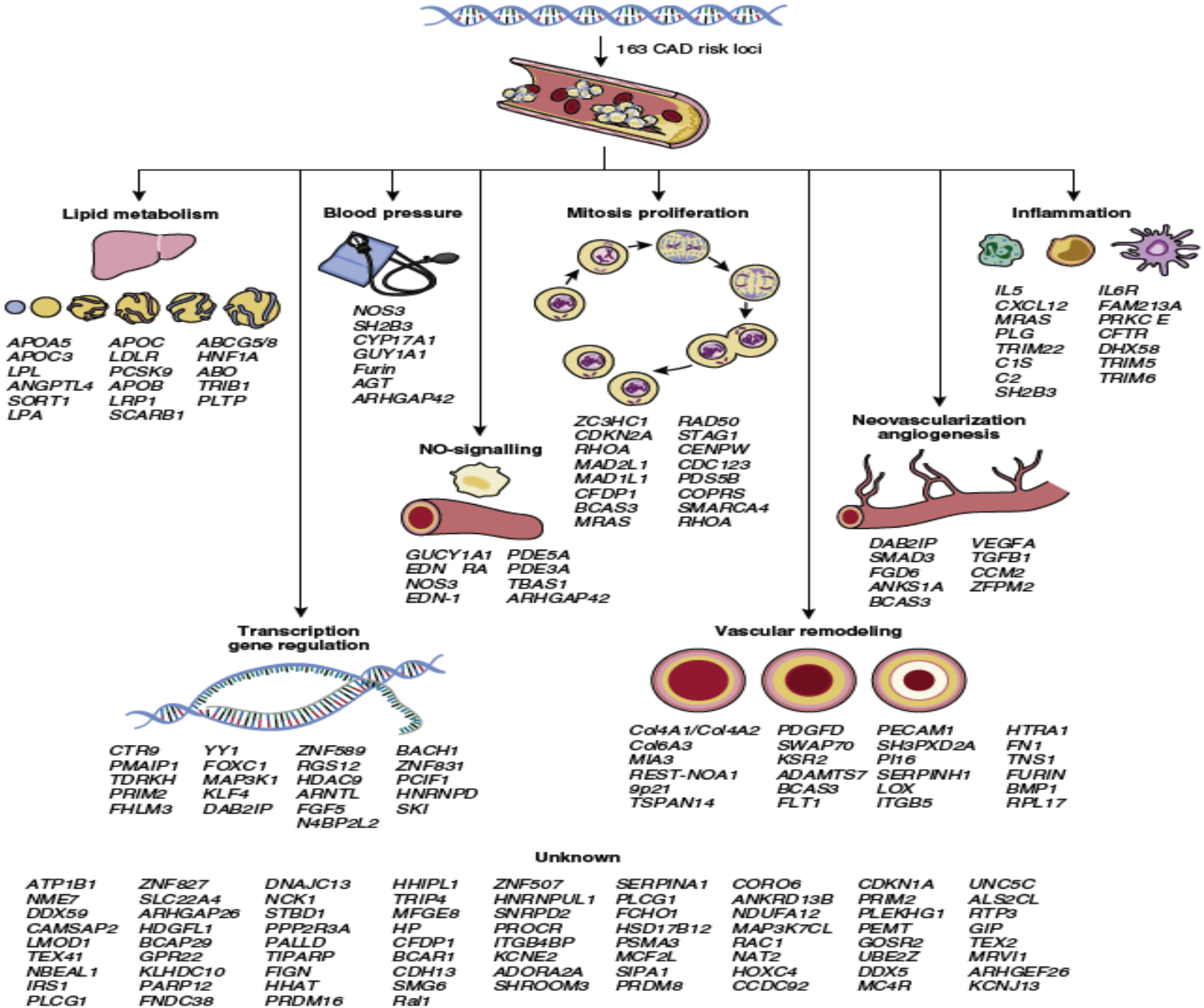
Genome-Wide Association Studies for Lipids

Genome-Wide Association Studies for Coronary Artery Disease

Advances driving GWAS success:

1. Larger sample sizes.
2. Improved genotyping arrays.
3. Inclusion of diverse ethnicities.
4. Genotype imputation improvements.




163 CAD risk loci
Lipid metabolism
APOA5 APOC ABCG5/8
APOC3 LDLR HNF1A
LPL PCSK9 ABO
ANGPTL4 APOB TRIB1
SORT1 LRP1 PLTP
LPA SCARB1
Blood pressure
NOS3
SH2B3
CYP17A1
GUY1A1
Furin
AGT
ARHGAP42
NO-signalling
GUCY1A1 PDE5A
EDN RA PDE3A
NOS3 TBAS1
EDN-1 ARHGAP42
Mitosis proliferation
ZC3HC1 RAD50
CDKN2A STAG1
RHOA CENPW
MAD2L1 CDC123
MAD1L1 PDS5B
CFDP1 COPRS
BCAS3 SMARCA4
MRAS RHOA
Inflammation
IL5 IL6R
CXCL12 FAM213A
MRAS PRKC E
PLG CFTR
TRIM22 DHX58
C1S TRIM5
C2 TRIM6
SH2B3
Neovascularization angiogenesis
DAB2IP VEGFA
SMAD3 TGFB1
FGD6 CCM2
ANKS1A ZFPM2
BCAS3
Transcription gene regulation
CTR9 YY1 ZNF589 BACH1
PMAIP1 FOXC1 RGS12 ZNF831
TDRKH MAP3K1 HDAC9 PCIF1
PRIM2 KLF4 ARNTL HNRNPD
FHLM3 DAB2IP FGF5 SKI
N4BP2L2
Vascular remodeling
Col4A1/Col4A2 PDGFD PECAM1 HTRA1
Col6A3 SWAP70 SH3PXD2A FN1
MIA3 KSR2 PI16 TNS1
REST-NOA1 ADAMTS7 SERPINH1 FURIN
9p21 BCAS3 LOX BMP1
TSPAN14 FLT1 ITGB5 RPL17
Unknown
ATP1B1 ZNF827 DNAJC13 HHIPL1 ZNF507 SERPINA1 CORO6 CDKN1A UNC5C
NME7 SLC22A4 NCK1 TRIP4 HNRNPUL1 PLCG1 ANKRD13B PRIM2 ALS2CL
DDX59 ARHGAP26 STBD1 MFGE8 SNRPD2 FCHO1 NDUFA12 PLEKHG1 RTP3
CAMSAP2 HDGFL1 PPP2R3A HP PROCR HSD17B12 MAP3K7CL PEMT GIP
LMOD1 BCAP29 PALLD CFDP1 ITGB4BP PSMA3 PEMT GOSR2 TEX2
TEX41 GPR22 TIPARP BCAR1 KCNE2 MCF2L RAC1 UBE2Z MRVI1
NBEAL1 KLHDC10 FIGN CDH13 ADORA2A SIPA1 NAT2 DDX5 ARHGEF26
IRS1 PARP12 HHAT SMG6 SHROOM3 PRDM8 HOXC4 MC4R KCNJ13
PLCG1 FNDC38 PRDM16 Ral1 CCDC92

Show 5 entries

Column visibility | Export | Clear search

Variant and risk allele	P-value	P-value annotation	RAF	OR	Beta	CI	Mapped gene	Reported trait	Trait(s)	Background trait(s)	Study accession	Location
rs629301-T	2×10^{-17}	-	0.937	-	0.22 unit increase	[0.17-0.27]	CELSR2	LDL cholesterol levels	LDL cholesterol change measurement	-	GCST009917	1:109275684
rs7185272-C	5×10^{-8}	-	0.74	-	0.08 unit increase	[0.06-0.1]	PKD1L3	LDL cholesterol levels	LDL cholesterol change measurement	-	GCST009917	16:71979898
rs151193009-T	8×10^{-32}	-	0.013	-	0.64 unit decrease	[0.54-0.74]	PCSK9	LDL cholesterol levels	LDL cholesterol change measurement	-	GCST009917	1:55043912
rs200990725-T	3×10^{-8}	-	0.001	-	0.91 unit increase	[0.58-1.24]	LDLR	LDL cholesterol levels	LDL cholesterol change measurement	-	GCST009917	19:11106639
rs13306194-A	1×10^{-12}	-	0.128	-	0.13 unit decrease	[0.091-0.169]	APOB	LDL cholesterol levels	LDL cholesterol change measurement	-	GCST009917	2:21029662

Showing 1 to 5 of 11,366 entries

« 1 2 3 4 5 … 2274 »

feedback

Search results for "low density lipoprotein cholesterol measurement"

All results 40 | Traits 20 | Publications 20

low density lipoprotein cholesterol measurement

EFO_0004611 | Cardiovascular measurement | Lipid or lipoprotein measurement

The measurement of LDL cholesterol in blood used as a risk indicator for heart disease.

Associated PGS 104 » Show Reported Traits

An Examination of the Relationship between Lipid Levels and Associated Genetic Markers across Racial/Ethnic Populations in the Multi-Ethnic Study of Atherosclerosis.

Johnson L et al. (2015) - PLoS One | **PMID**:25951326 | **doi**:10.1371/journal.pone.0126361 | **PGP**000045

PGS developed 4 - PGS evaluated 4

The power of genetic diversity in genome-wide association studies of lipids.

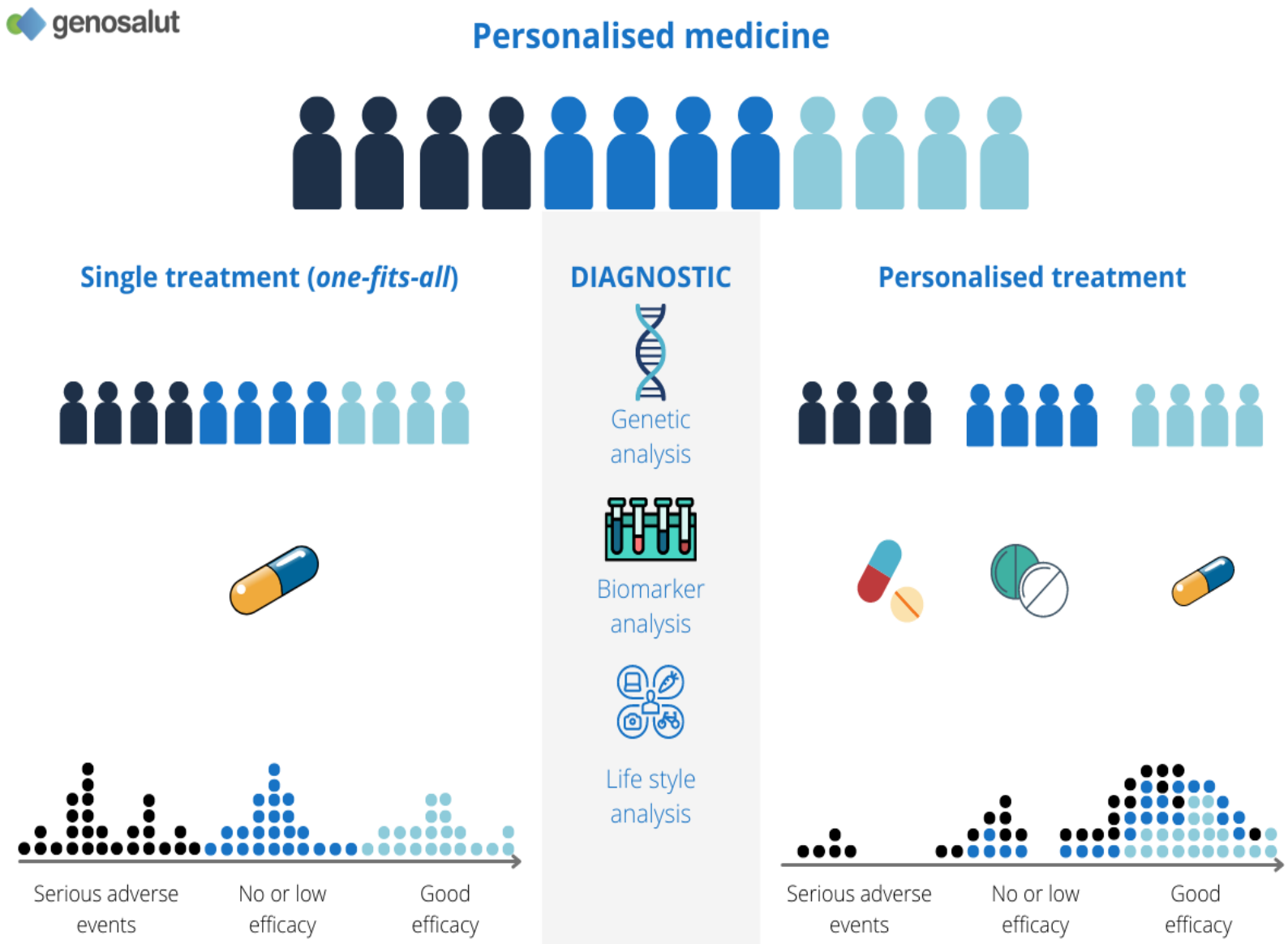
Graham SE et al. (2021) - Nature | **PMID**:34887591 | **doi**:https://doi.org/10.1038/s41586-021-04064-3 | **PGP**000230

PGS developed 12 - PGS evaluated 12

Trans-ancestry polygenic models for the prediction of LDL blood levels: An analysis of the UK Biobank and Taiwan Biobank

Hassanin E et al. (2023) - medRxiv | **doi**:10.1101/2023.08.03.23293320 | **PGP**000514

As a result, precision medicine, by incorporating established biomarkers, functional tests, imaging, and new genomics and omics developments for each population, aims to provide the "**right treatment to the right patient at the right time**"



THERAPEUTIC RESPONSE PREDICTION

- Genetic variants that change protein activity can help predict how effective drugs will be before they are developed.

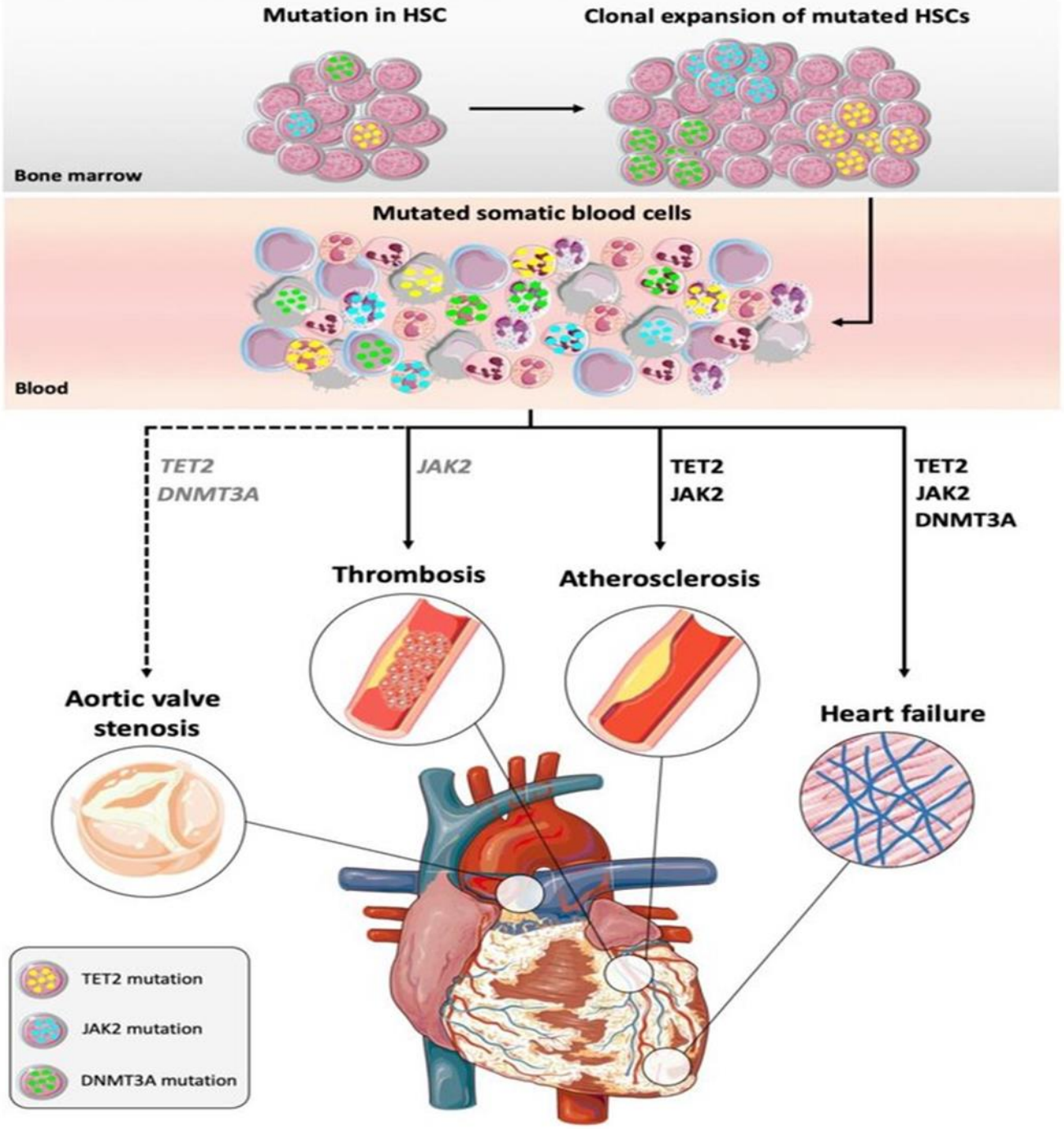
PCSK9

APOC3

CYP2C19

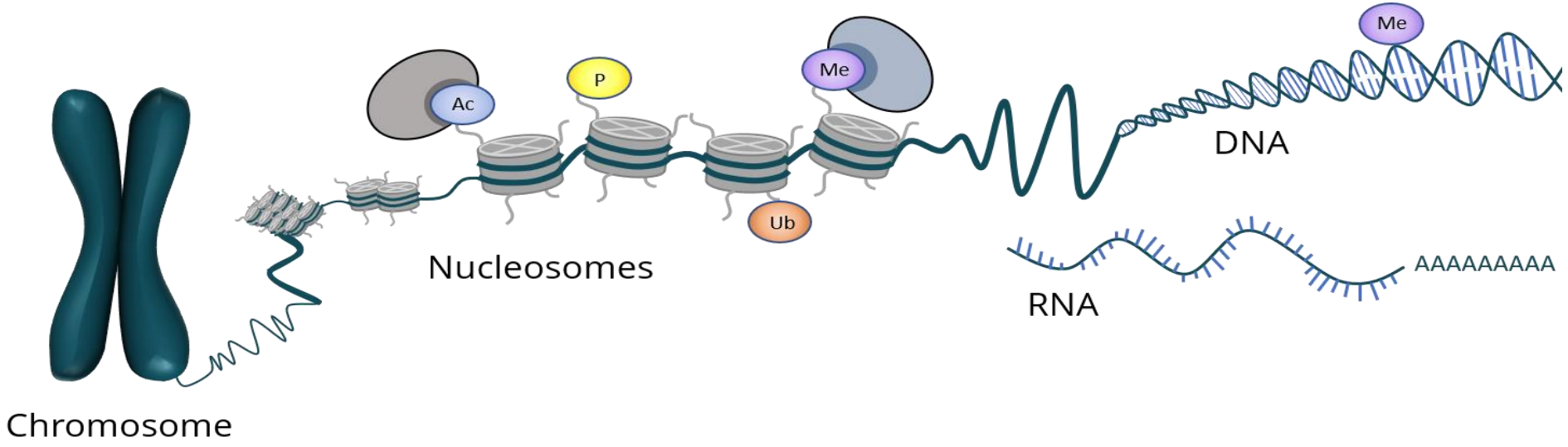
Somatic Genomics

- Age is a major risk factor for coronary artery disease (CAD), but its specific contributors are not fully understood.
- Many adults over 70 have clonal hematopoiesis of indeterminate potential (CHIP), which is linked to both cancer and CAD.
- Studies suggest that inhibiting the NLRP3 **inflammasome** may better reduce atherosclerosis in those with CHIP, indicating that targeting inflammation could be particularly beneficial for these individuals.



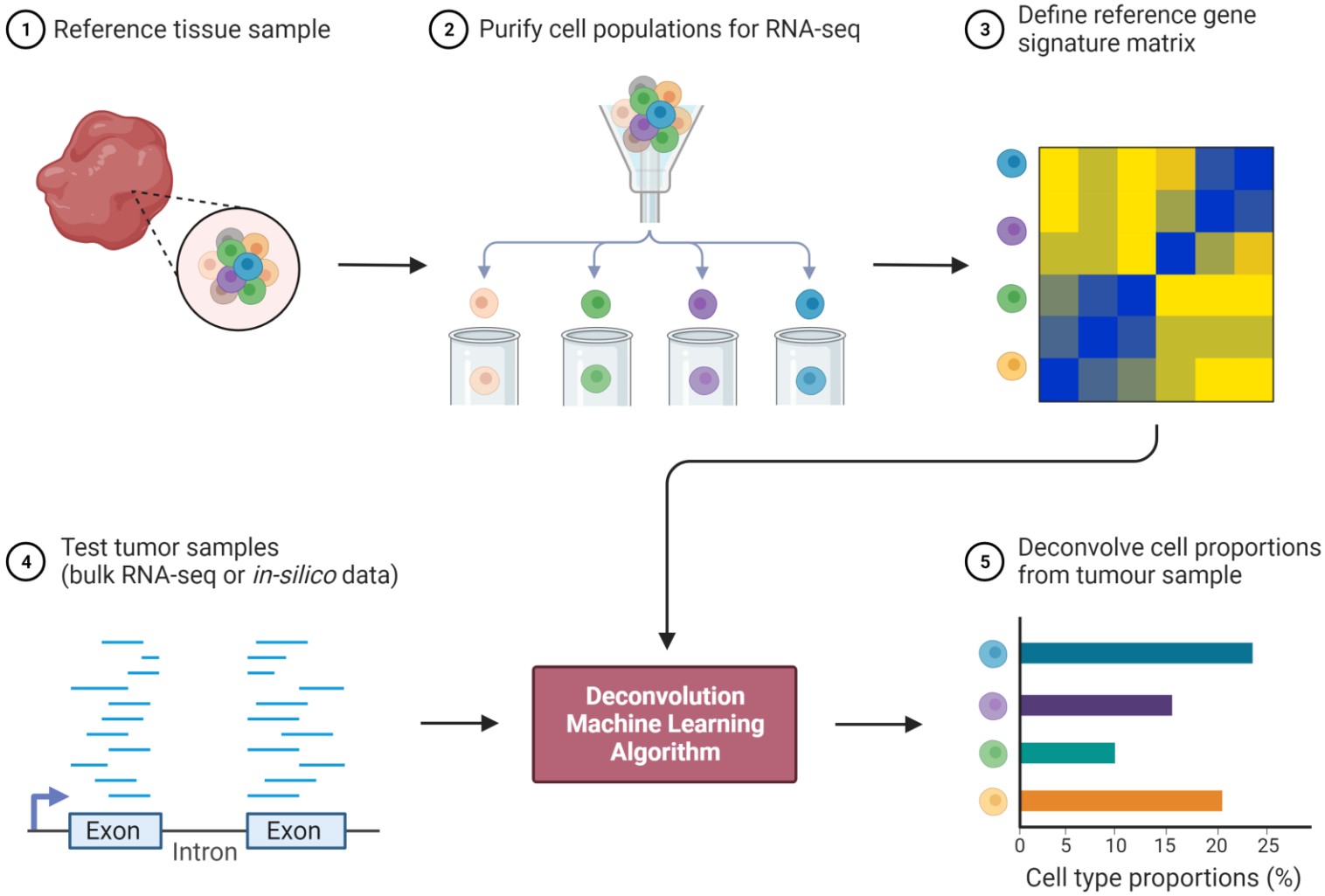
Epigenetics

- Epigenetics may play a role in CAD because environmental factors that cause changes in DNA methylation and histone acetylation are linked to CAD risk and advanced atherosclerosis.
- For instance, higher levels of **histone deacetylase 3 and 9** have been found in areas prone to plaque buildup, and inflammation in atherosclerotic plaques.
- Recent studies identified 52 specific **DNA methylation** sites related to CAD risk, with two showing a causal link.
- Additionally, certain genetic variants affect genes involved in CAD, such as ITGA6 and **long noncoding RNA**s (lncRNAs). These lncRNAs, like ANRIL, may influence atherosclerosis development and progression.



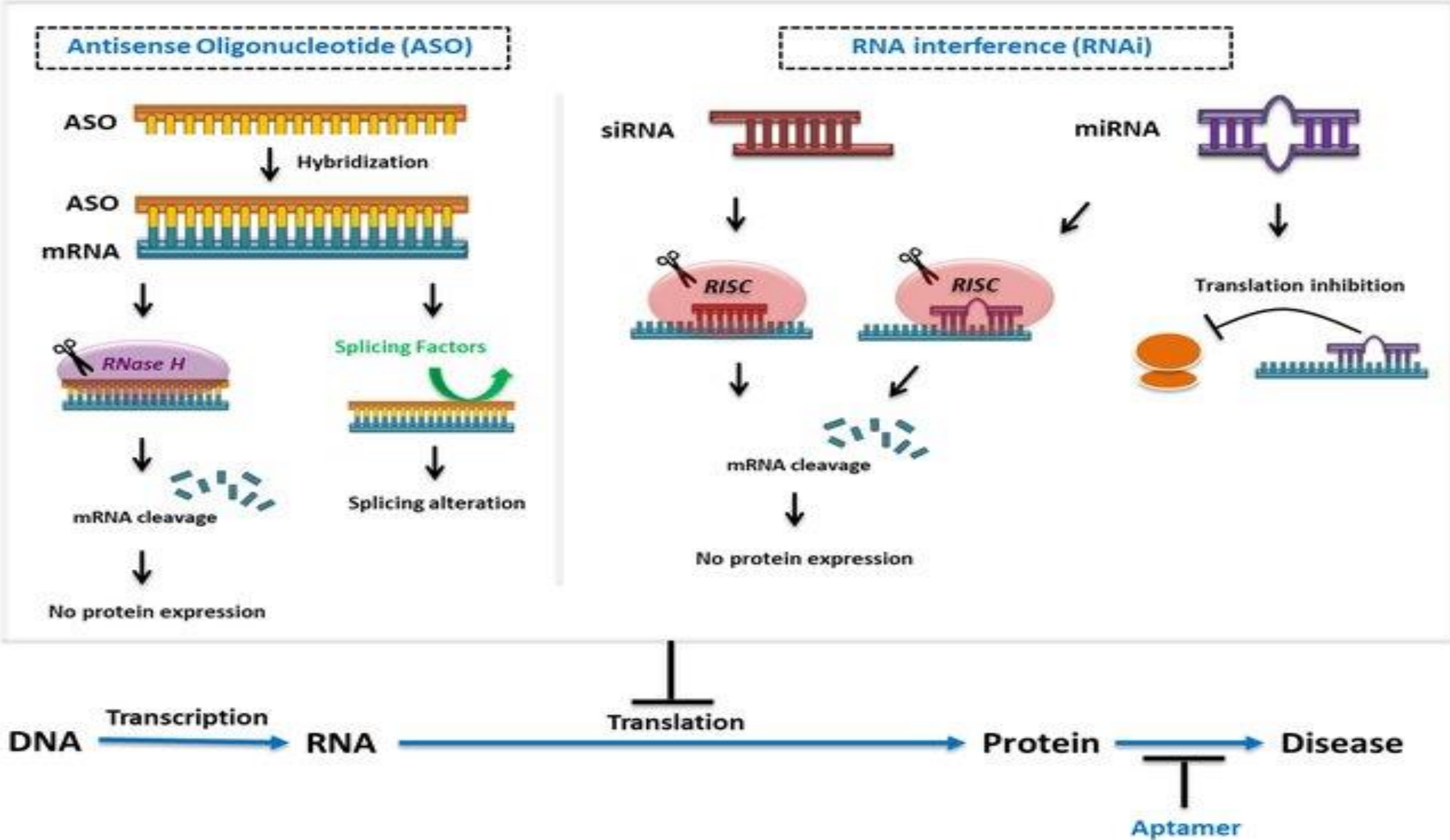
Single-cell RNA sequencing

- Single-cell RNA sequencing (scRNA-seq) is a valuable technique for studying atherosclerosis by analyzing individual cells in plaques.
- It provides detailed insights into the unique gene expression profiles of various cell types, revealing new populations like activated macrophages and "fibromyocytes."
- This technology helps researchers understand the roles of these cells in disease progression and how specific genes influence atherosclerosis.
- Overall, scRNA-seq enhances our understanding of cellular interactions and potential therapeutic targets in atherosclerosis.


1 Reference tissue sample
2 Purify cell populations for RNA-seq
3 Define reference gene signature matrix
4 Test tumor samples (bulk RNA-seq or *in-silico* data)
5 Deconvolve cell proportions from tumour sample
Exon
Intron
Exon
Deconvolution Machine Learning Algorithm
0 5 10 15 20 25
Cell type proportions (%)

Therapeutically Targeting the Genome

- Human genetics has inspired new therapeutic strategies that target mRNAs instead of just proteins.
- Key approaches include antisense oligonucleotides (ASOs) and RNA interference (RNAi), both of which inhibit mRNA translation.
- Gene therapy can replace deficient gene products or enhance protective genes, while emerging gene editing techniques aim to directly correct harmful genetic variants.


Antisense Oligonucleotide (ASO)
ASO
Hybridization
ASO
mRNA
RNase H
mRNA cleavage
No protein expression
Splicing Factors
Splicing alteration
RNA interference (RNAi)
siRNA
miRNA
RISC
RISC
Translation inhibition
mRNA cleavage
No protein expression
DNA
Transcription
RNA
Translation
Protein
Disease
Aptamer

- **Mipomersen** (INN; trade name Kynamro) is a drug used to treat homozygous familial hypercholesterolemia and is administered by subcutaneous injection.
-
- There is a serious risk of liver damage from this drug, and it can only be prescribed in the context of a risk management plan.


Thank You