
Sociedad Española de Medicina Interna
Grupo de Riesgo Vascular
Valencia 6 de Mayo DE 2011
Marcadores genéticos de riesgo vascular
¿Pueden incorporarse a la clínica?
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Servicio de Medicina Interna
Hospital Universitario de Bellvitge

ANÁLISIS GENÉTICOS

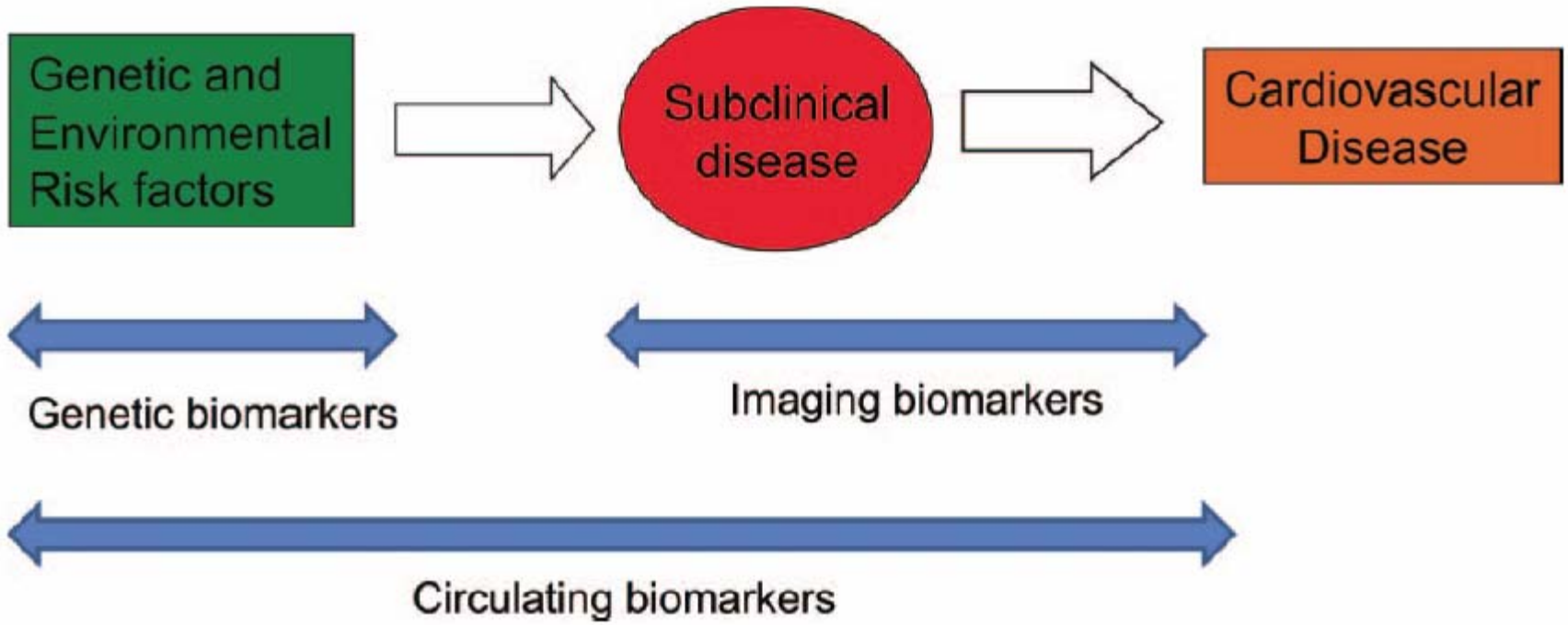
ANÁLISIS DE LOS CROMOSOMAS, DEL ADN O DEL ARN PARA IDENTIFICAR VARIANTES GENÉTICAS QUE PUEDAN TENER SIGNIFICACIÓN CLÍNICA

Indicaciones

- Diagnóstico: En paciente con manifestaciones clínicas
- Predisposición: En enfermedades multifactoriales
- Farmacogenética: Para aumentar la eficacia y disminuir el riesgo de efectos secundarios

Robin NH et al. JACC2007

THE STAGES AT WHICH CIRCULATING, GENETIC, AND IMAGING BIOMARKERS ARE MOST INFORMATIVE



Never make forecasts. Especially about the future.
—Samuel Goldwyn

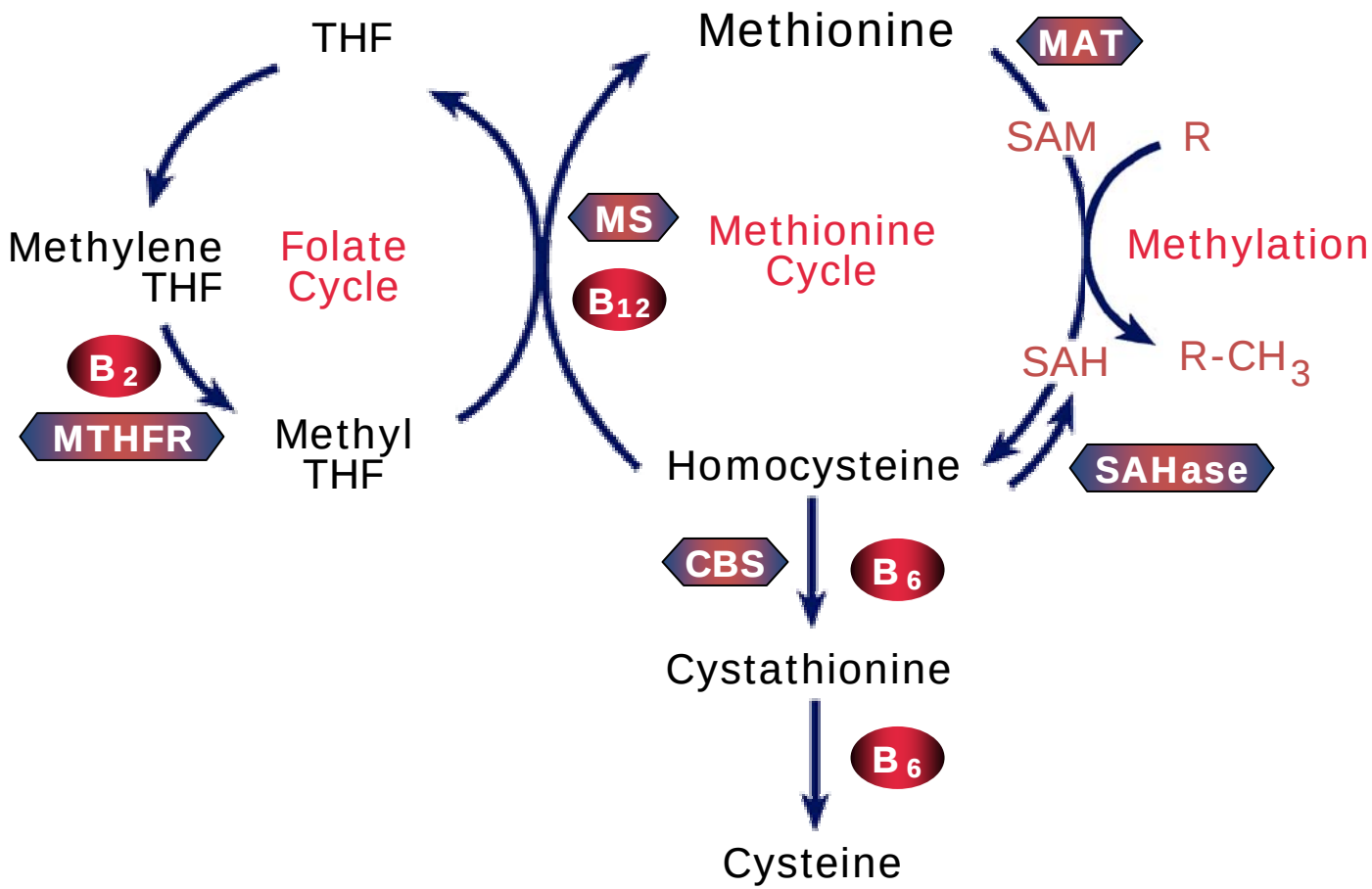
Wang TJ. *Circulation* 2011;123:551-565

CANDIDATE GENE VARIANTS FOR CARDIOVASCULAR DISEASE

Gene	Risk Allele	Reported Risk Ratio†
MTHFR	C677T	1.14–1.21
Cholesterol ester transfer protein (*CETP*)	TaqIB	0.78
Paraoxonase (*PON1*)	Q192R	1.14–1.21
Endothelial nitric oxide synthase (*eNOS*)	T-786C	1.31
Prothrombin	G20210A	1.21
APOB	Ins/Del (DD)	1.30
Glycoprotein IIIa	PI(A2)	1.10
APOE	$\epsilon 4/\epsilon 4$	1.42
ACE insertion/deletion	DD	1.16–1.21
APOB	SpIns/Del (DD), EcorI (AA)	1.19–1.73
PAI1	4G/5G	1.20
Fibrinogen β-chain	G-455A	0.68
Endothelial nitric oxide	Glu298Asp, Intron-4	1.31–1.34

Arnett DK et al. Circulation 2007

Homocysteine Metabolism - Key Enzymes & Vitamins



Ueland PM et al., Ed. Robinson K, Homocysteine and Vascular Disease, 2000, 59-84

MTHFR = 5,10-Methylenetetrahydrofolate reductase

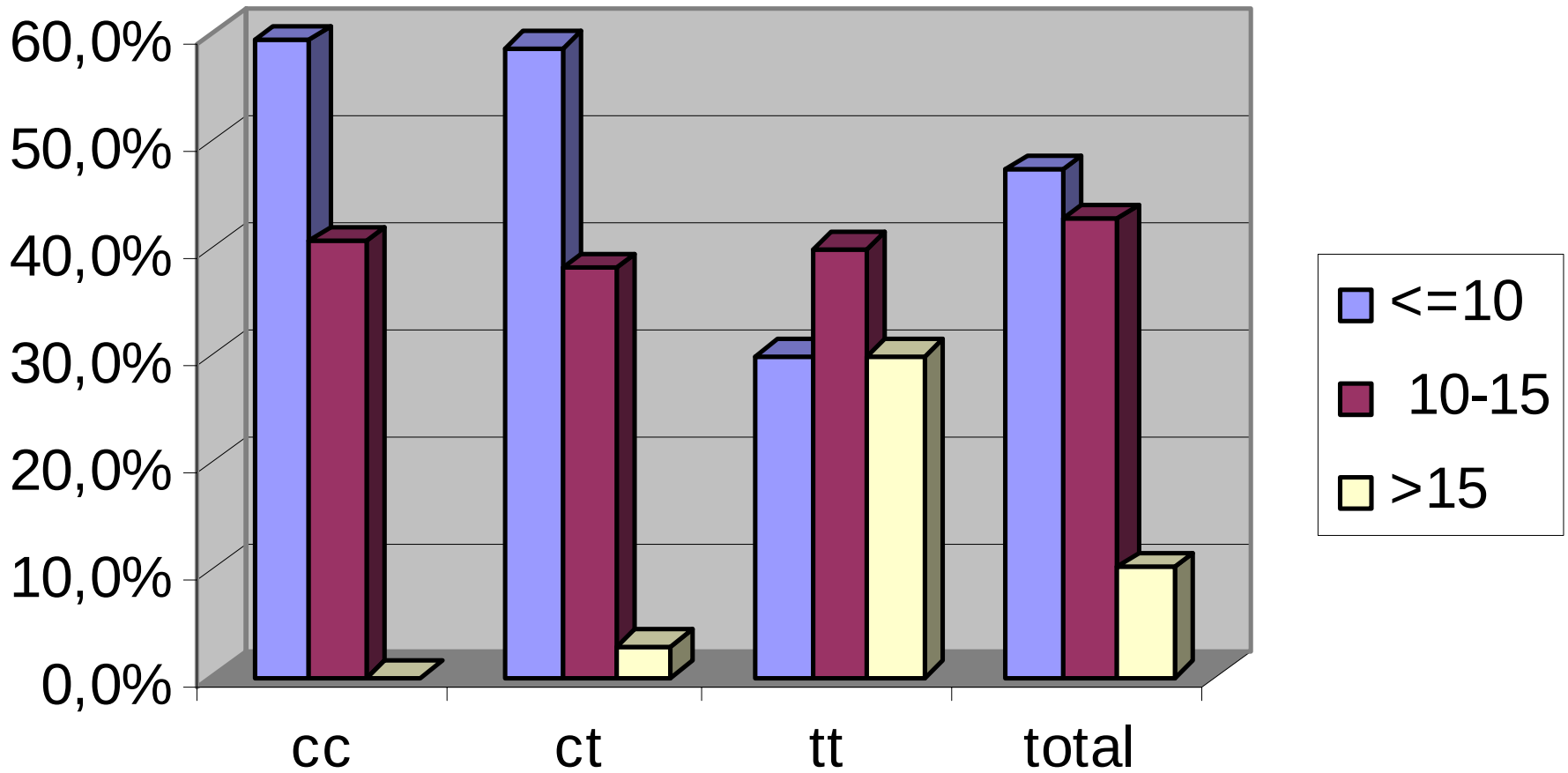
MS = Methionine synthase

CBS = Cystathionine, β-synthase

MAT = Methionine adenosyltransferase

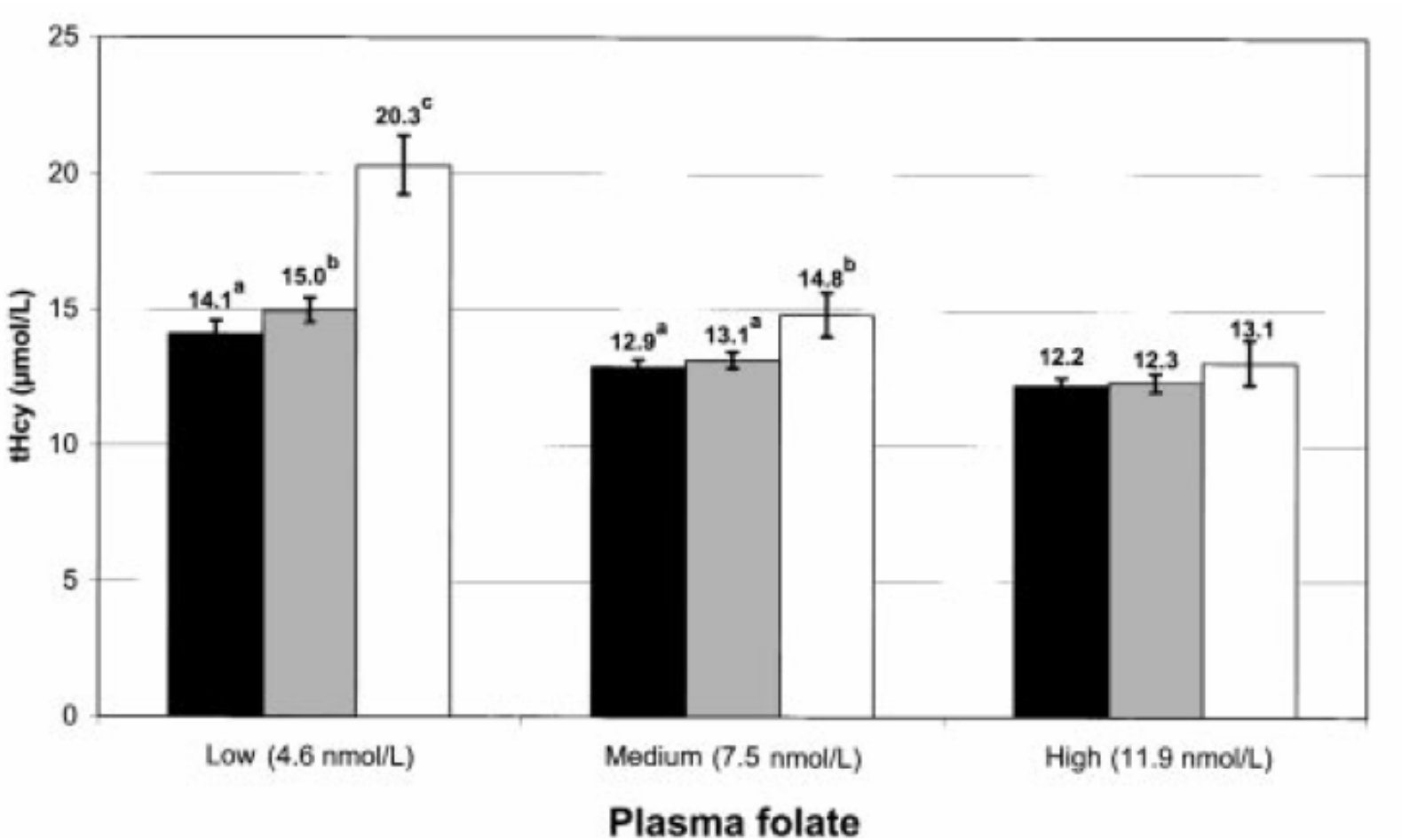
SAHase = S-adenosyl-homocysteine hydrolase

Homocisteína



N= 188 pacientes isquémicos

Geometric mean adjusted plasma total homocysteine (tHcy) concentrations according to the MTHFR genotypes stratified by tertiles of plasma folate concentrations



de Bree A et al. Am J Clin Nutr 2003;77:687–93.

LIPOPROTEÍNA (a)

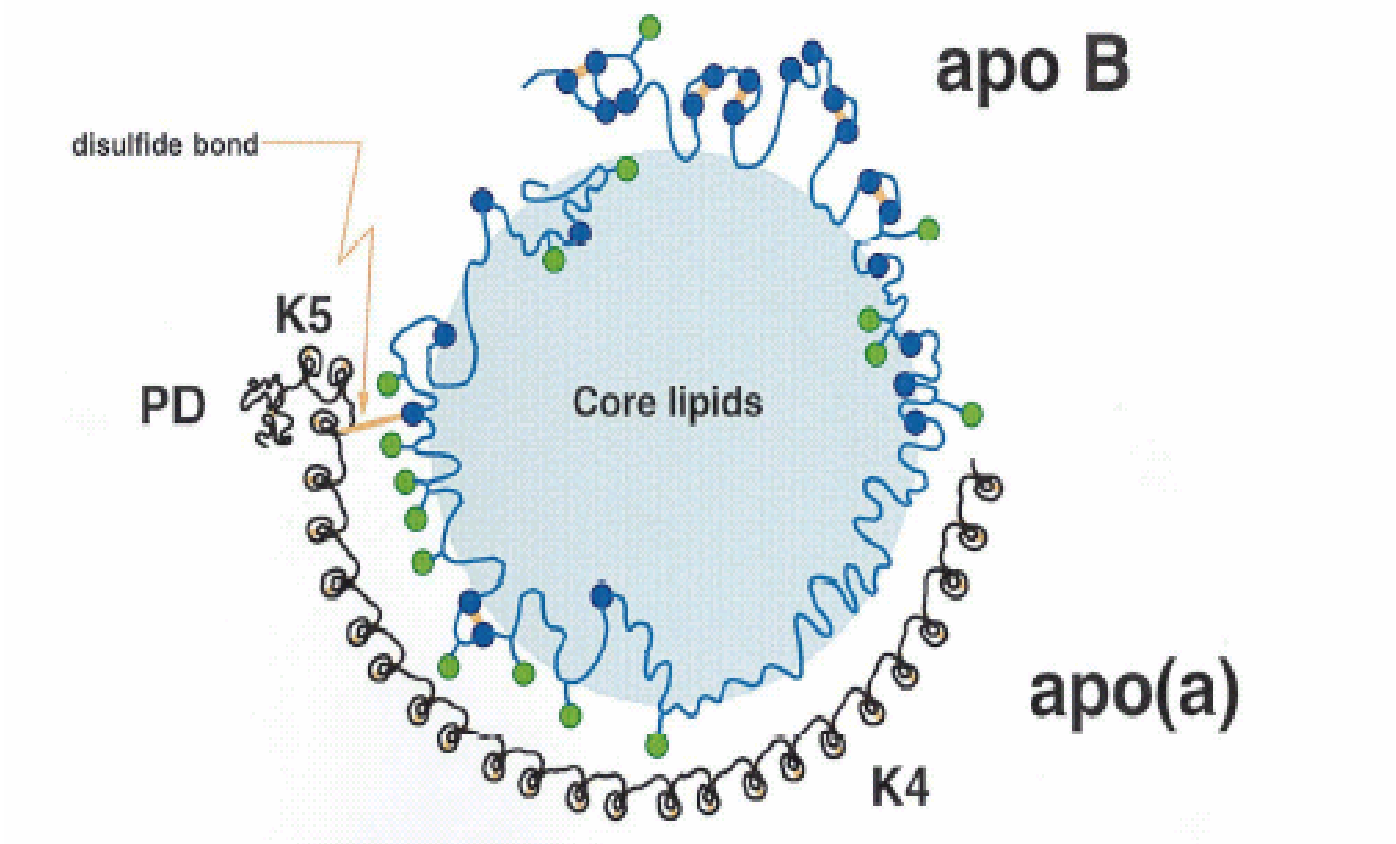
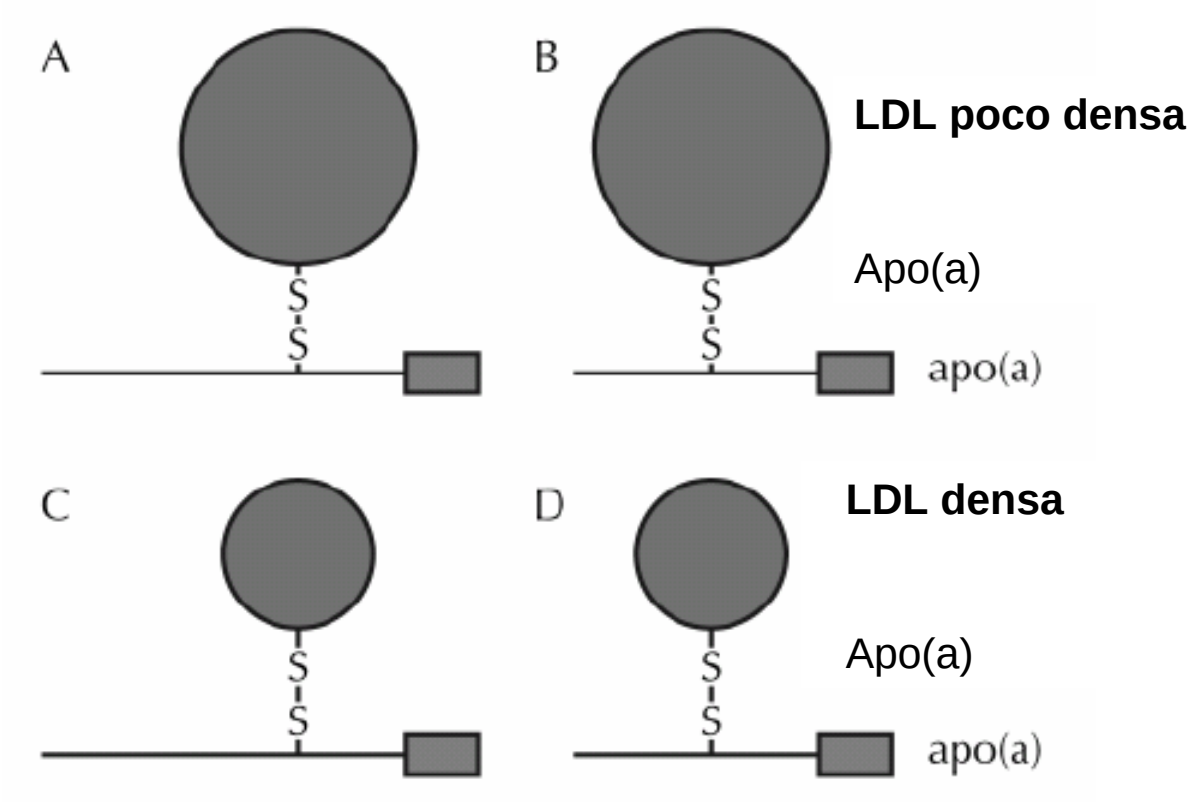


FIGURE 1. Schematic representation of the lipoprotein(a) [Lp(a)] particle. Lp(a) is distinguishable from low-density lipoprotein (LDL) by the presence of apolipoprotein(a) [apo(a)], which is covalently linked to the apoprotein B (apo B) component of the LDL moiety by a single disulfide bond. The structure of apo(a) is characterized by repeated copies of kringle motifs that resemble plasminogen kringle 4 (K4), followed by a single copy of the plasminogen kringle 5-like (K5) and protease-like domains (PD).



Heterogeneidad de la partícula de lipoproteína(a)

La aterogenicidad de la Lp(a) depende de la densidad de la LDL que contiene y del tamaño de la apo(a). A: LDL poco densa y apo(a) grande, la menos aterogénica. B: LDL poco densa y apo(a) pequeña. C: LDL densa y apo(a) grande. D: LDL densa y Lp(a) pequeña, la más aterogénica.

Según Scanu AM

FORMAS MENDELIANAS DE HIPERCOLESTEROLEMIA

Mutaciones del receptor LDL

Apo B-100 defectuosa

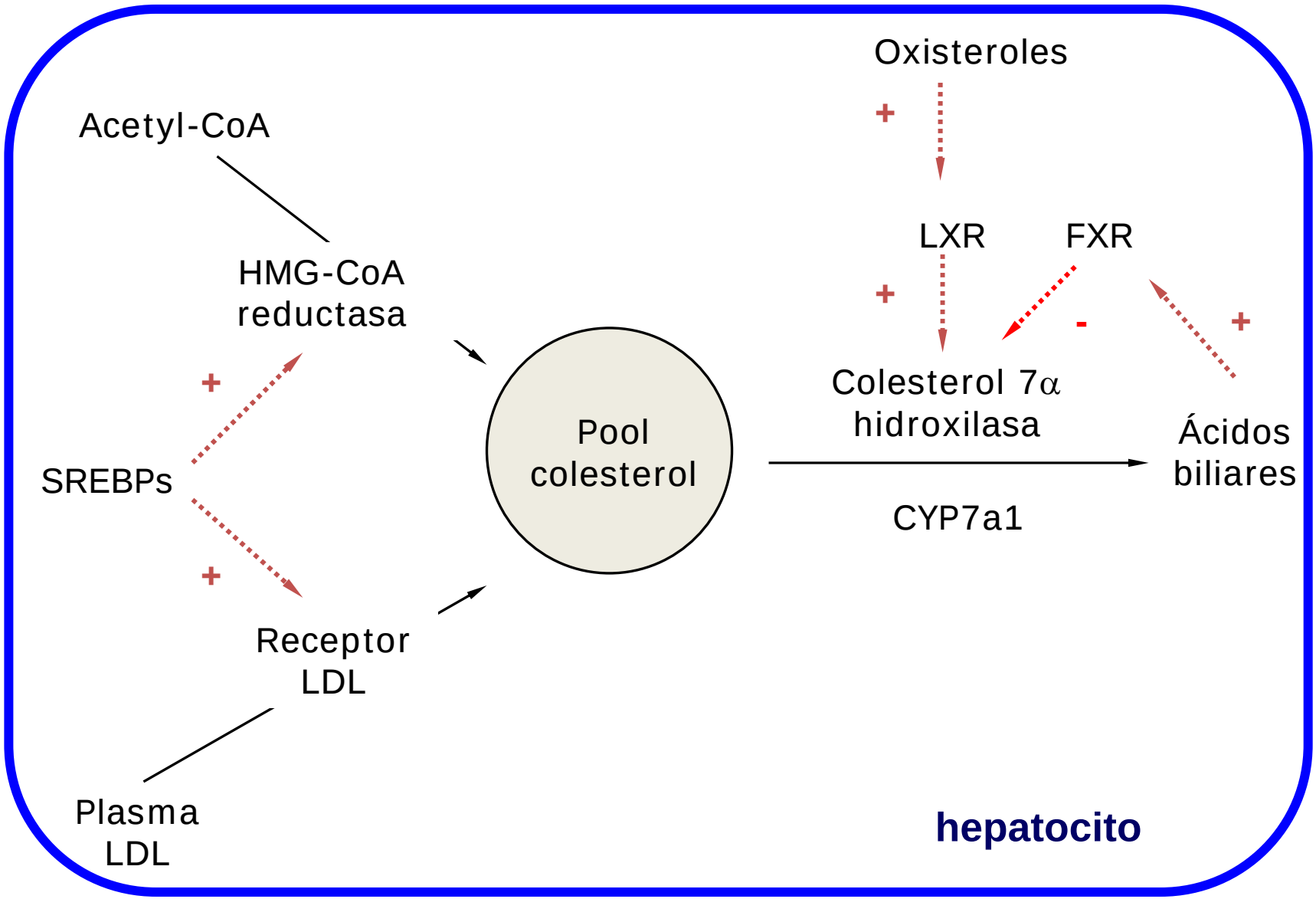
Proproteina convertasa, subtilisina/kexina-type, 9 gene (PCSK9)

Hipercolesterolemia autosómica recesiva

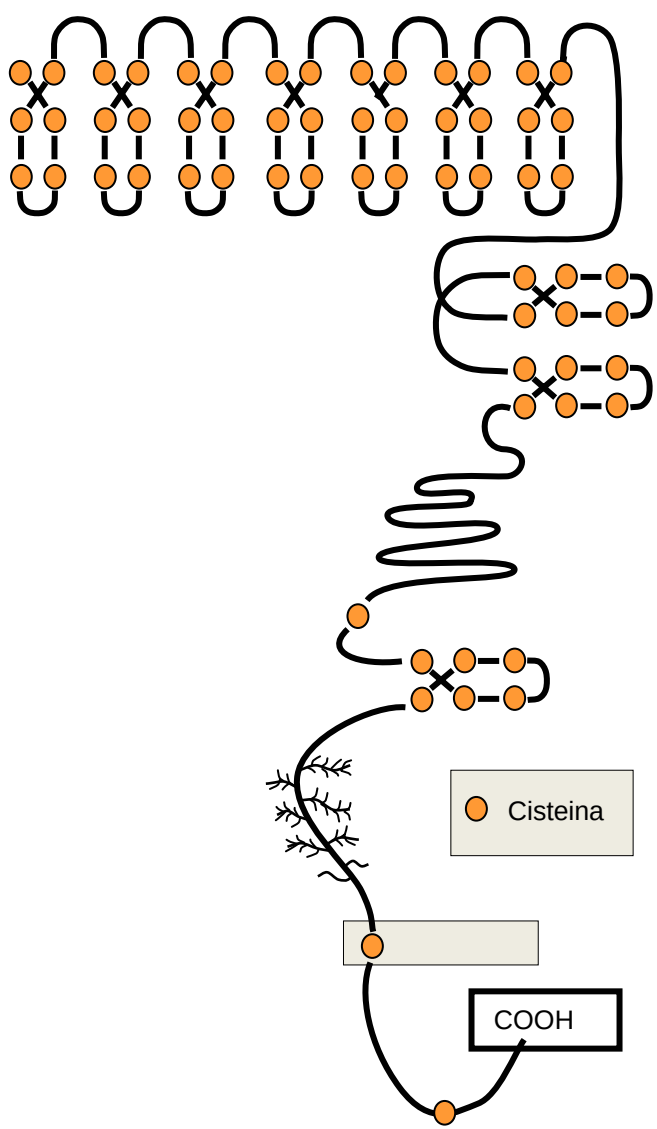
Hipercolesterolemia con déficit de 7-hidroxilasa

Arnett DK et al. *Circulation* 2007;115:2878-2901

Regulación de la homeostasis del colesterol



Zonas del Receptor LDL



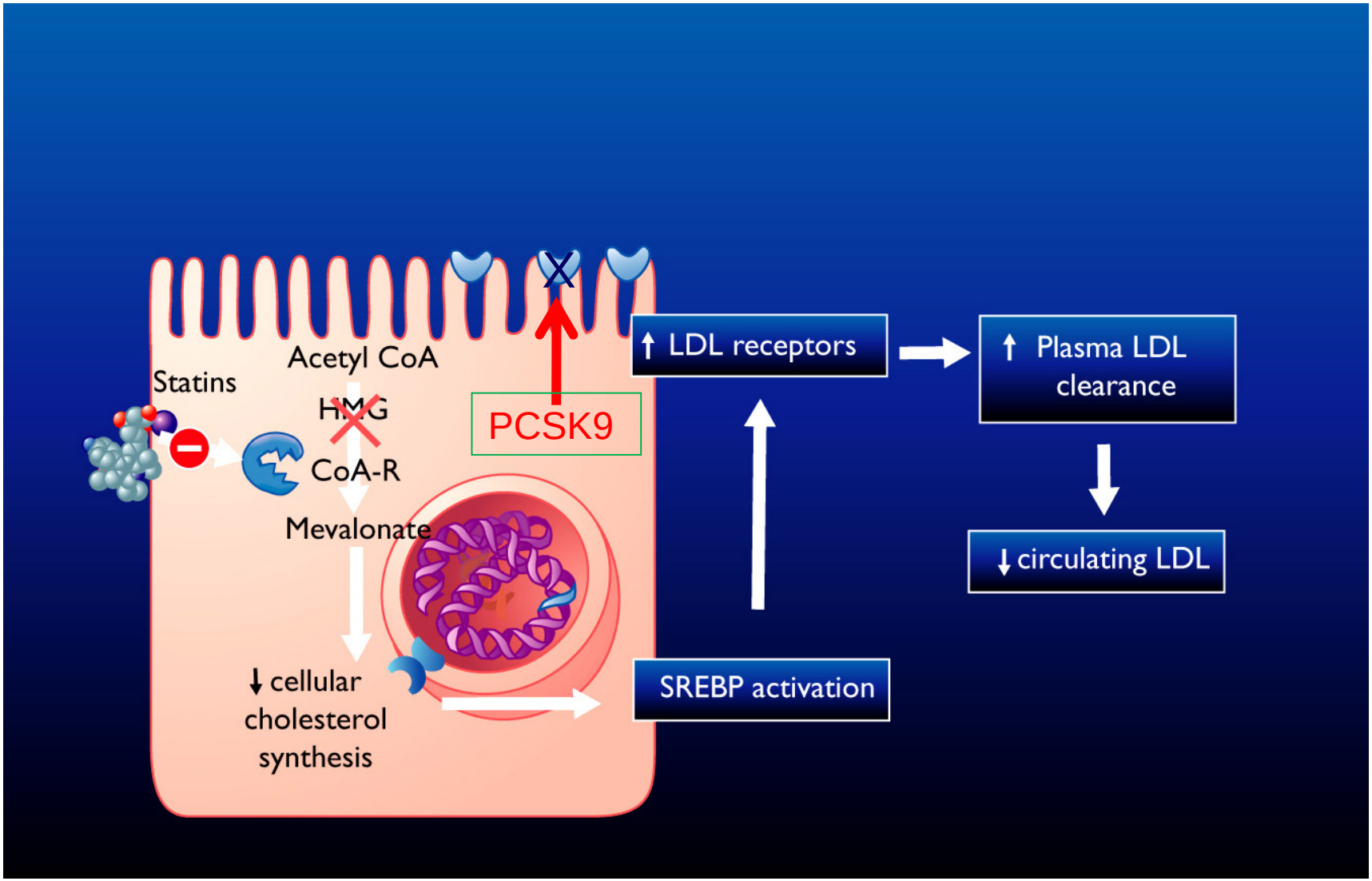
1. Unión al ligando 292 aa

2. Homología Precursor EGF. 400 aa

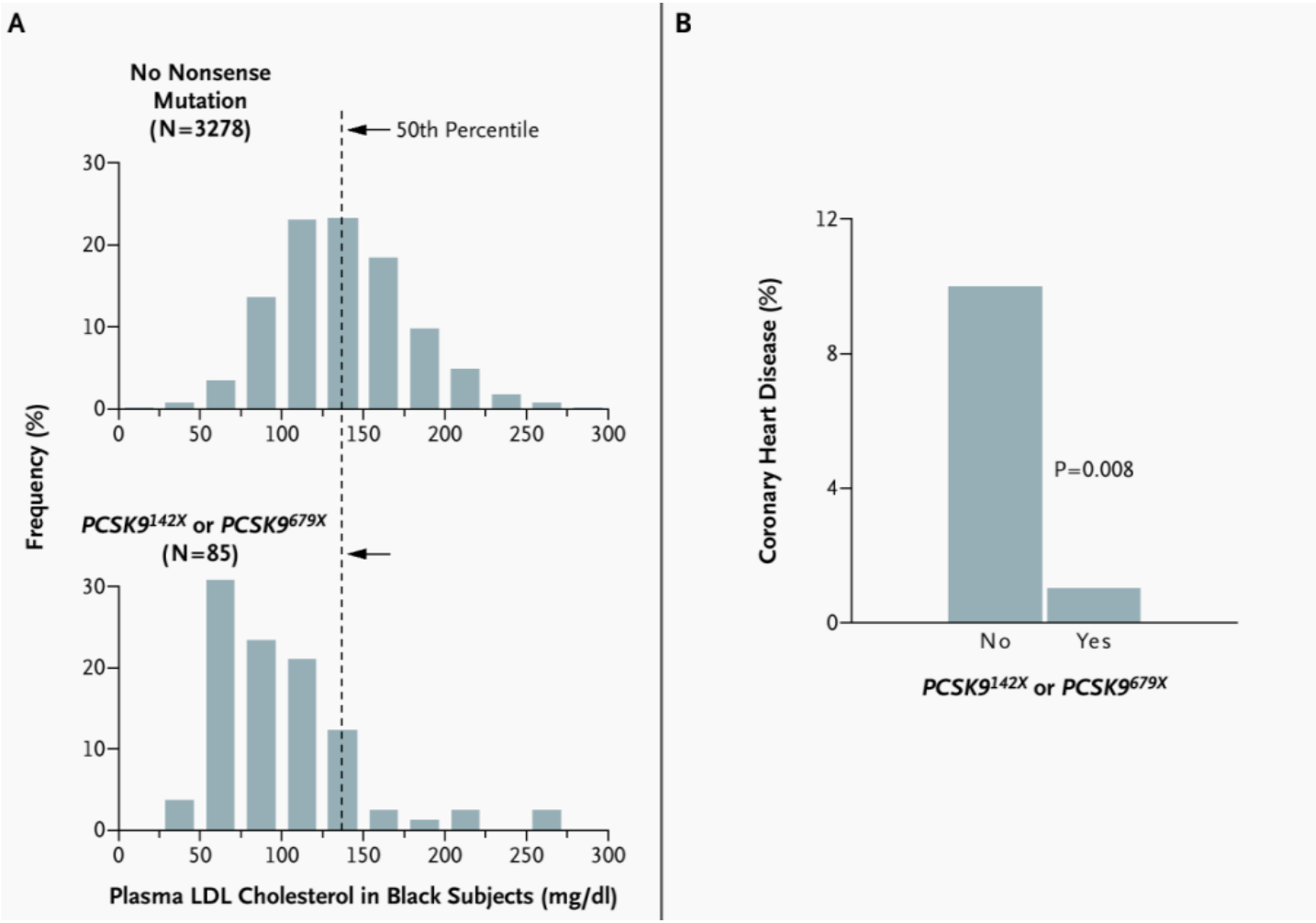
3. O-Polisacáridos 58 aa

4. Transmembrana 22 aa

5. Citoplasmática 50 aa


Acetyl CoA
Statins
HMG
CoA-R
Mevalonate
PCSK9
↓ cellular cholesterol synthesis
SREBP activation
↑ LDL receptors
↑ Plasma LDL clearance
↓ circulating LDL

Distribución de colesterol-LDL e incidencia de enfermedad coronaria en función de la presencia o ausencia de mutaciones en el gen *PCSK9 142X* o *PCSK9 679X*



Jonathan C.Cohen, et al, N Engl J Med 2006;354:1264-72

MICROARRAY CHIPS

A large-scale genetic screening tool onto which thousands of DNA segments covering a specific chromosomal region (or the entire genome) are fixed.

The hybridization patterns (to the chip's DNA) of a normal DNA sample and that of an affected patient are compared.

When a fluorescent signal suggests that a mutation is present, more detailed analytical methods follow.

This technology would be reliable, quick, and cost effective genetic testing for diseases that display dramatic locus and allelic heterogeneity.

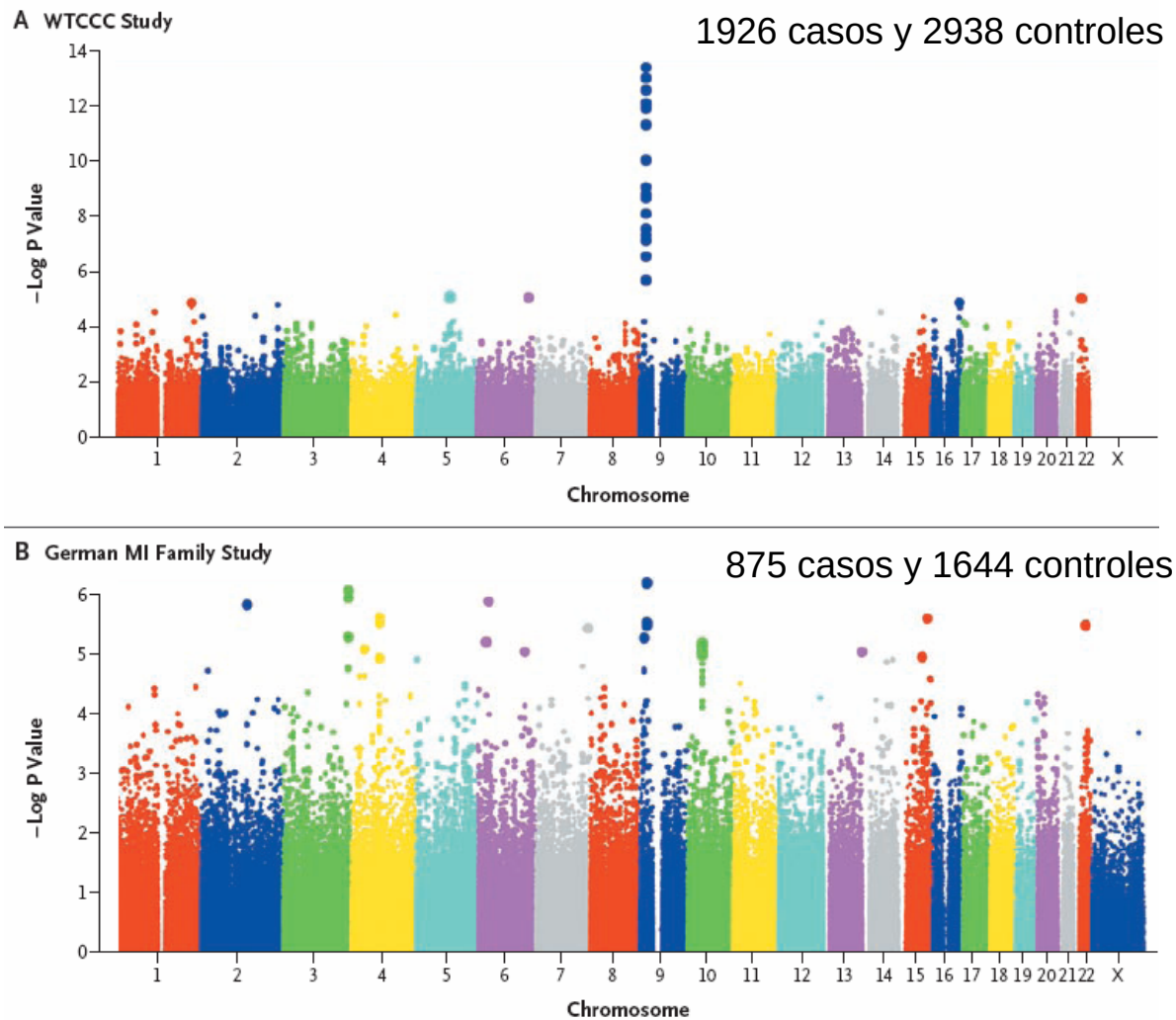
Wang TJ. *Circulation* 2011;123:551-565

LOCI ASSOCIATED WITH MIOCARDIAL INFARCTION FROM GWAS

Locus	Nearest Gene	Risk Allele Frequency	*P*	Relative Risk for MI
3q22.3	*MRAS*	0.15	7×10^{-13}	1.15 (1.11–1.19)
12q24.31	*HNF1A*	0.36	5×10^{-7}	1.08 (1.05–1.11)
9p21.3	*CDKN2A, CDKN2B*	0.56	3×10^{-44}	1.29 (1.25–1.34)
1p13.3	*CELSR2, PSRC1, SORT1*	0.81	8×10^{-12}	1.19 (1.13–1.26)
21q22.11	*SLC5A3, MRPS6, KCNE2*	0.13	6×10^{-11}	1.20 (1.14–1.27)
1q41	*MIA3*	0.72	1×10^{-9}	1.14 (1.10–1.19)
6p24.1	*PHACTR1*	0.65	1×10^{-9}	1.12 (1.08–1.17)
19p13.2	*LDLR*	0.75	2×10^{-9}	1.15 (1.10–1.20)
10q11.21	*CXCL12*	0.84	7×10^{-9}	1.17 (1.11–1.24)
1p32.3	*PCSK9*	0.81	1×10^{-8}	1.15 (1.10–1.21)
2q33.1	*WDR12*	0.14	1×10^{-8}	1.17 (1.11–1.23)
6q25.3	*SLC22A3,LPAL2,LPA*	0.02	4×10^{-15}	1.82 (1.57–2.12)
6q25.3	*SLC22A3,LPAL2,LPA*	0.16	1×10^{-9}	1.20 (1.13–1.28)
12q24.12	*SH2B3*	0.38	9×10^{-8}	1.13 (1.08–1.18)

Thanassoulis t T et al. Circulation 2010;122:2323-2334

Asociacción de los SNPs (polimorfismos de nucleotido simple) con la enfermedad coronaria en el análisis GWAS (genome wide association analysis)



Genechip Human Mapping 500K Array Set

Samani NJ et al. NEJM 2007;357443-53

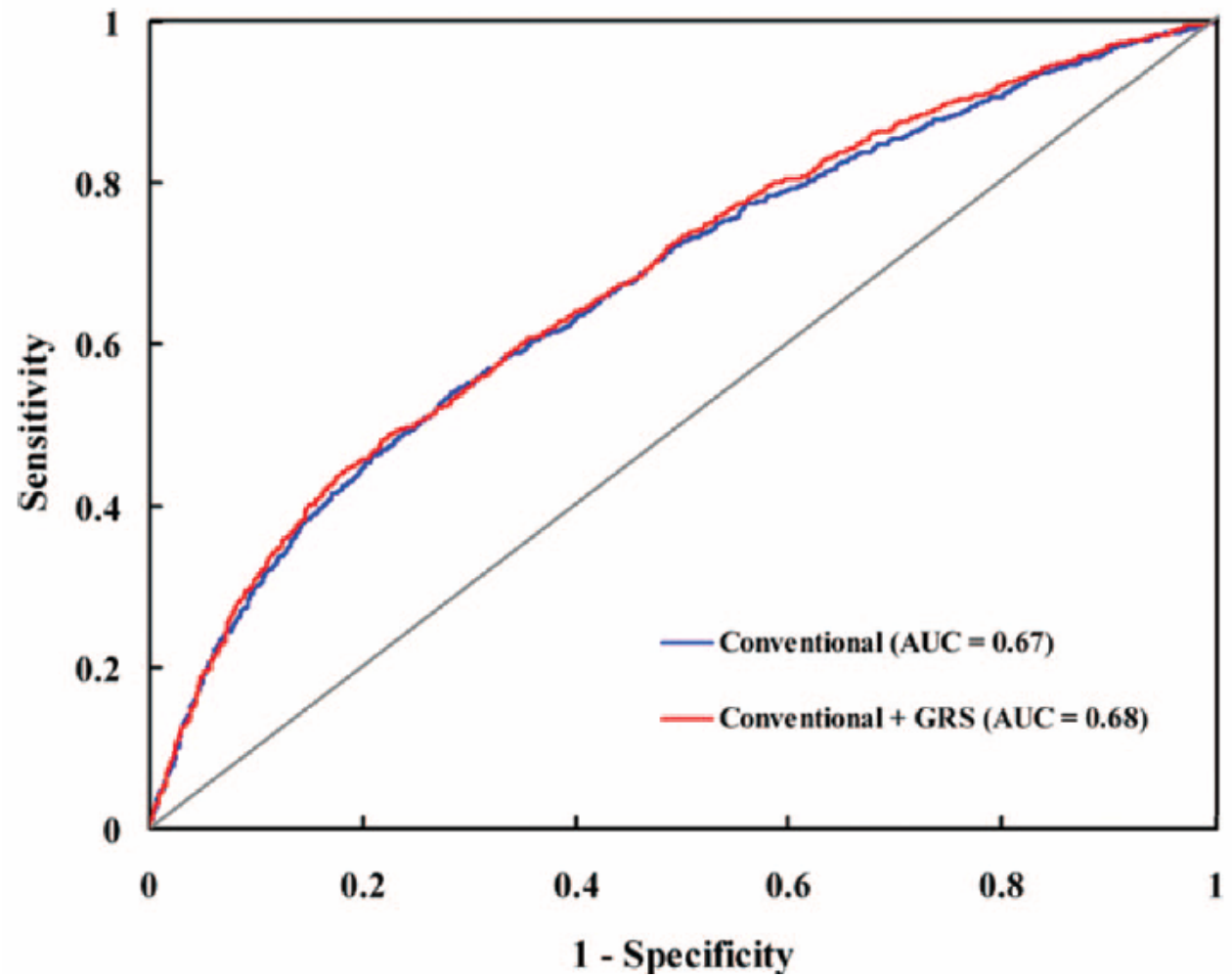
Table 2. Loci from the WTCCC Study with Significant Associations with Coronary Artery Disease That Were Replicated in the German MI Family Study.*

Chromosome	Lead SNP	Minor Allele in Controls	Risk Allele	Data	Frequency of Minor Allele		Odds Ratio for Risk Allele (95% CI)	Population Attributable Fraction	P Value
					Case Subjects	Controls			
2	rs2943634	A	C	WTCCC	0.30	0.34	1.22 (1.11–1.33)		1.19×10^{-5}
				German	0.32	0.37	1.20 (1.06–1.35)		0.004
				Adjusted German			1.08 (0.90–1.31)	0.10	0.03
6	rs6922269	A	A	WTCCC	0.29	0.25	1.23 (1.13–1.35)		6.33×10^{-6}
				German	0.30	0.26	1.24 (1.09–1.41)		0.001
				Adjusted German			1.23 (1.01–1.50)	0.11	0.009
9	rs1333049	C	C	WTCCC	0.55	0.47	1.37 (1.26–1.48)		1.80×10^{-14}
				German	0.54	0.48	1.33 (1.18–1.51)		6.80×10^{-6}
				Adjusted German			1.28 (1.07–1.53)	0.22	6.12×10^{-5}

SNP Rs6922269, cromosoma 6q25.1. genes para *MTHFD1L* que codifica para C1-THF
SNP rs1333049 cromosoma 9p21.3: genes para *CDKN2A y CDKN2B* (ciclo celular-TGF-β)
SNP Rs2943634, cromosoma 2q36.3

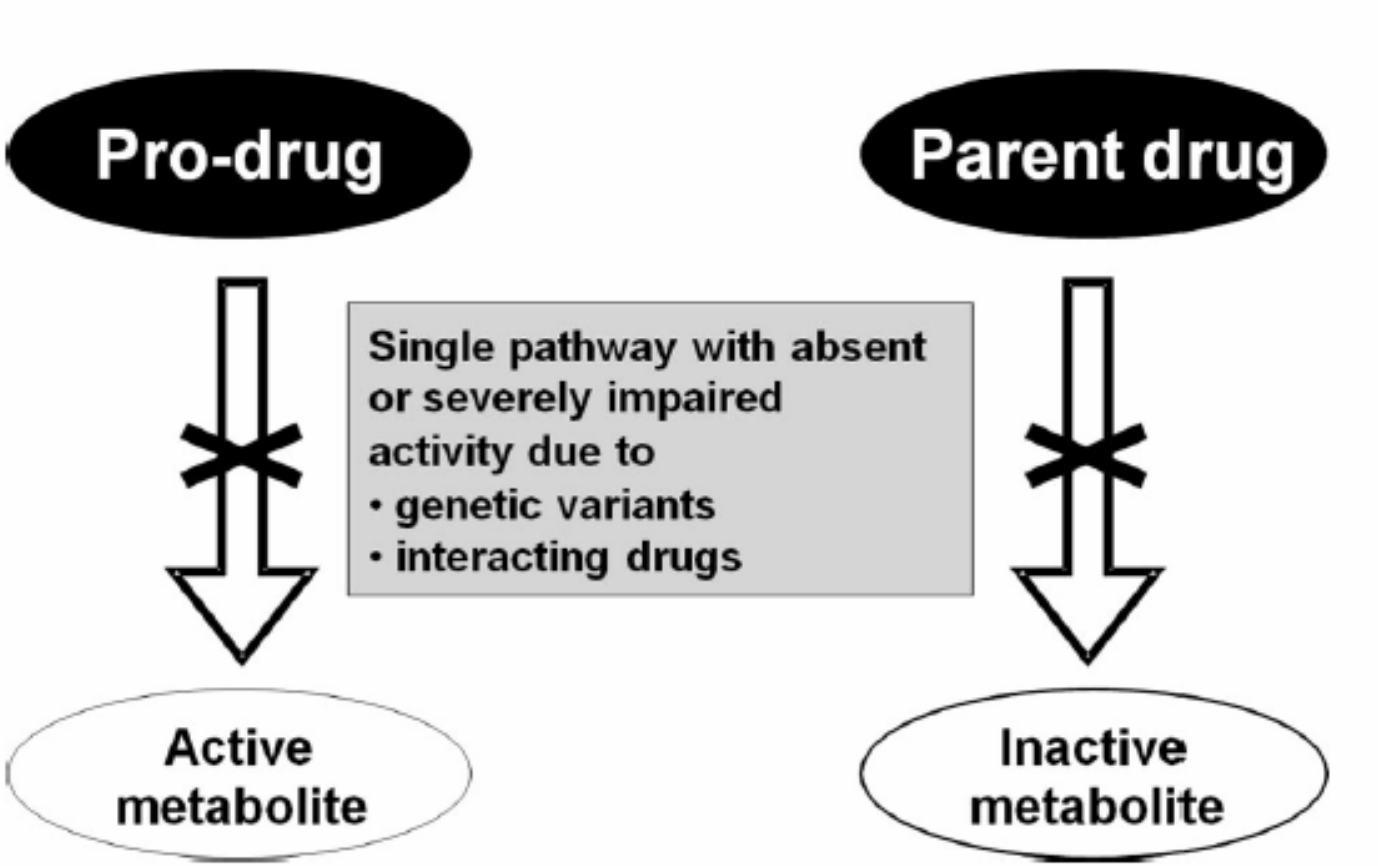
Samani NJ et al. NEJM 2007;357443-53

Receiver-operating characteristic curves for MI based on logistic regression models incorporating conventional risk factors with and without the Genetic Risc Score



Qi L et al. Circulation 2011;123:374-80

FARMACOCINÉTICA DE ALTO RIESGO



Roden DM et al. Circulation 2011;123:1661-70

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 21, 2008 VOL. 359 NO. 8

SLCO1B1 Variants and Statin-Induced Myopathy A Genomewide Study

The SEARCH Collaborative Group*

N Engl J Med 2008;359:789-99

SEARCH: Assaig clínic, aleatoritzat

12.064 pacients amb IAM previ

Intervenció: Simvastatina 80 vs 20 mg/dia x 6 anys

Pacients

Entre els 6031 pacients que prenien simvastatina 80 mg/dia:

- Miopatia establerta (mialgia o debilitat + CK > 10 VMN) en 49 casos

- Miopatia incipient (CK x 3 VMN + ALT x 1,7 valor basal +/- símptomes) en 49 casos

- 96 controls ajustats per sexe, edat, FG estimat, tract. amb amiodarona

Mètodes

Sentrix HumanHap300-Duo BeadChip (Illumina) amb 318.237 SNP

RR DE MIOPATÍA SEGÚN LAS CARACTERÍSTICAS BASALES

Baseline Characteristic	No. of Participants	Definite or Incipient Myopathy in First Year (N=56)		Definite or Incipient Myopathy at Any Time (N=98)	
		No.	Relative Risk (95% CI)	No.	Relative Risk (95% CI)
Age					
<65 yr	3019	17	1.0	31	1.0
≥65 yr	3012	39	2.3 (1.3–4.1)	67	2.2 (1.4–3.4)
Sex					
Male	5005	42	1.0	72	1.0
Female	1026	14	1.6 (0.9–3.0)	26	1.8 (1.1–2.8)
Estimated glomerular filtration rate					
≥60 ml/min/1.73 m^2	5209	41	1.0	71	1.0
<60 ml/min/1.73 m^2	822	15	2.4 (1.3–4.3)	27	2.5 (1.6–3.9)
Creatinine					
<85 μmol/liter (1.0 mg/dl)	2731	14	1.0	29	1.0
≥85 μmol/liter (1.0 mg/dl)	3300	42	2.5 (1.4–4.6)	69	2.0 (1.3–3.1)
Use of amiodarone					
No	5893	47	1.0	86	1.0
Yes	138	9	8.8 (4.2–18.4)	12	6.4 (3.4–12.1)
Use of calcium antagonists					
No	4459	29	1.0	61	1.0
Yes	1572	27	2.7 (1.6–4.5)	37	1.7 (1.2–2.6)
Diabetes mellitus					
No	5398	49	1.0	82	1.0
Yes	633	7	1.2 (0.6–2.7)	16	1.7 (1.0–2.9)

6031 participantes del estudio SEARCH tratados con simvastatina 80 mg/d

FACTORES DE RIESGO DE MIOPATÍA

Edad > 65 a

Sexo femenIno

Filtrado glomerular < 60 ml/min/1,73m2

Creatinina > 85 umol/L (1 mg/dl)

Tratamiento con amiodarona

Tratamiento con antagonistes de los canales del calcio

Diabetes mellitus

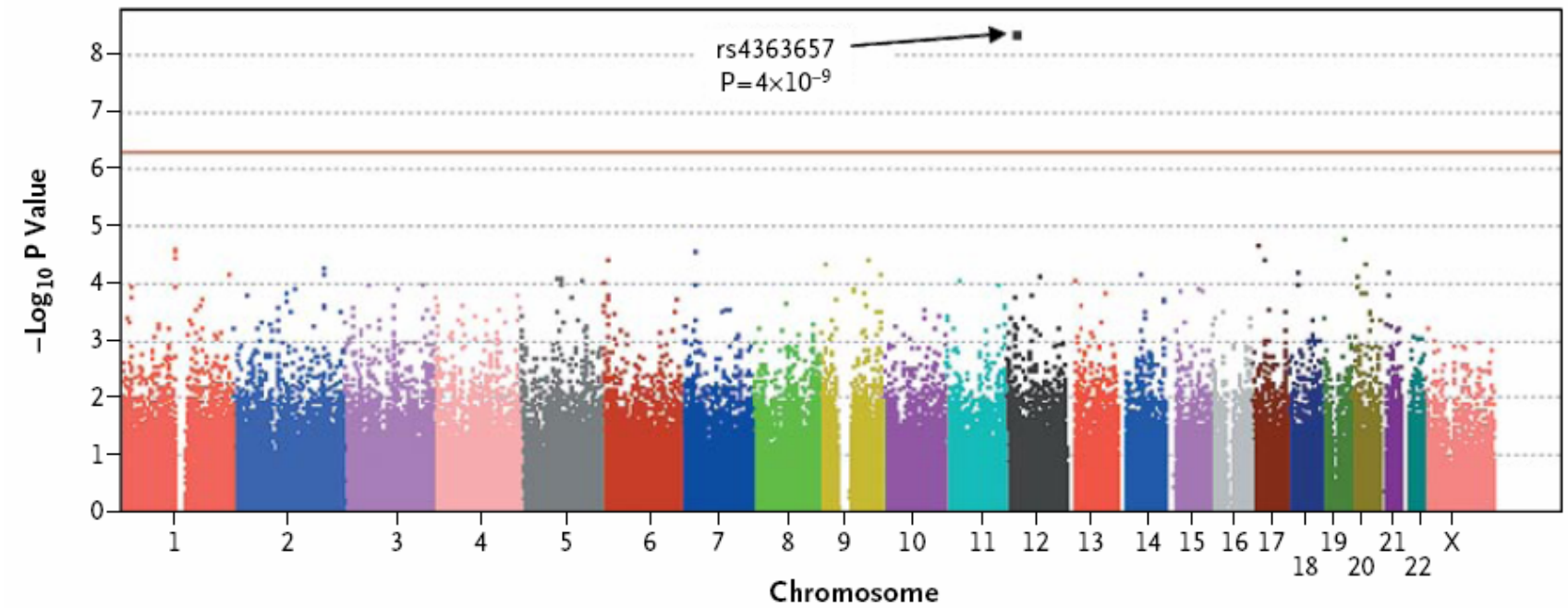


Figure 1. Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genome-wide Association Study.

P values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap300-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association ($P<5\times10^{-7}$).

El SNP rs4363657 localizado en el intrón 11 del gen *SLCO1B1* del cromosoma 12

OR de miopatía 4,3 (IC95%, 2,5-7,2) en CT, 17,4 (IC95% 4,8-62,9) en CC vs TT

CONCLUSIONES

- **Se estan desarrollando nuevas herramientas de diagnóstico genético que incluyen a un amplio número de polimorfismos para la predicción del riesgo cardiovascular y también para el uso apropiado de los fármacos**

- **Actualmente una de las áreas més bien establecidas de los análisis genéticos en el campo de la prevención de las enfermedades cardiovasculares está en el diagnóstico de las dislipemias genéticas**