WILL GENOTYPE OR PHENOTYPE DRIVE CARDIAC INTERVENTIONS: PRECISION MEDICINE

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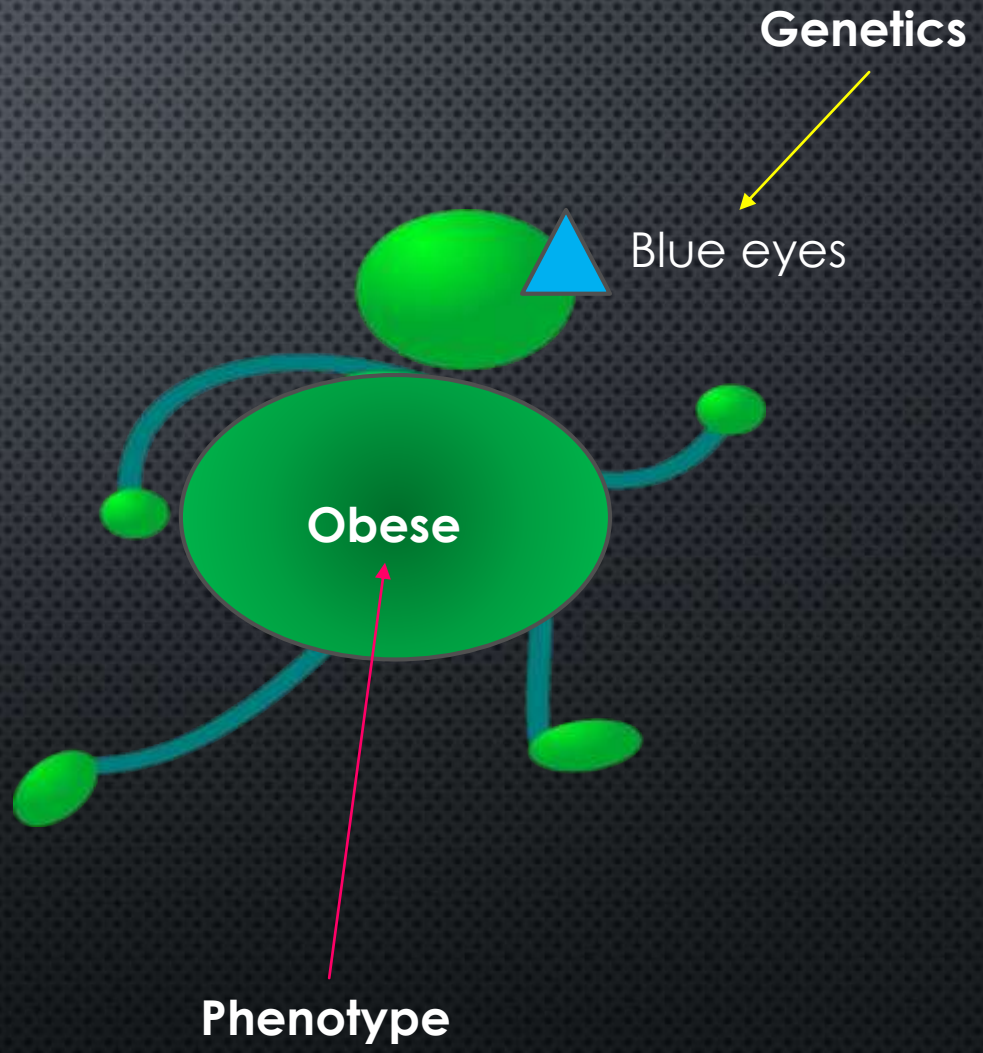
HELPFUL DEFINITIONS

- 'GENOTYPE' IS USUALLY USED WHEN TALKING ABOUT THE GENETICS OF A PARTICULAR TRAIT (LIKE *EYE COLOR*)

- "PHENOTYPE" USED WHEN TALKING ABOUT *PHYSICAL* OR BIOCHEMICAL CHARACTERISTICS OF AN INDIVIDUAL

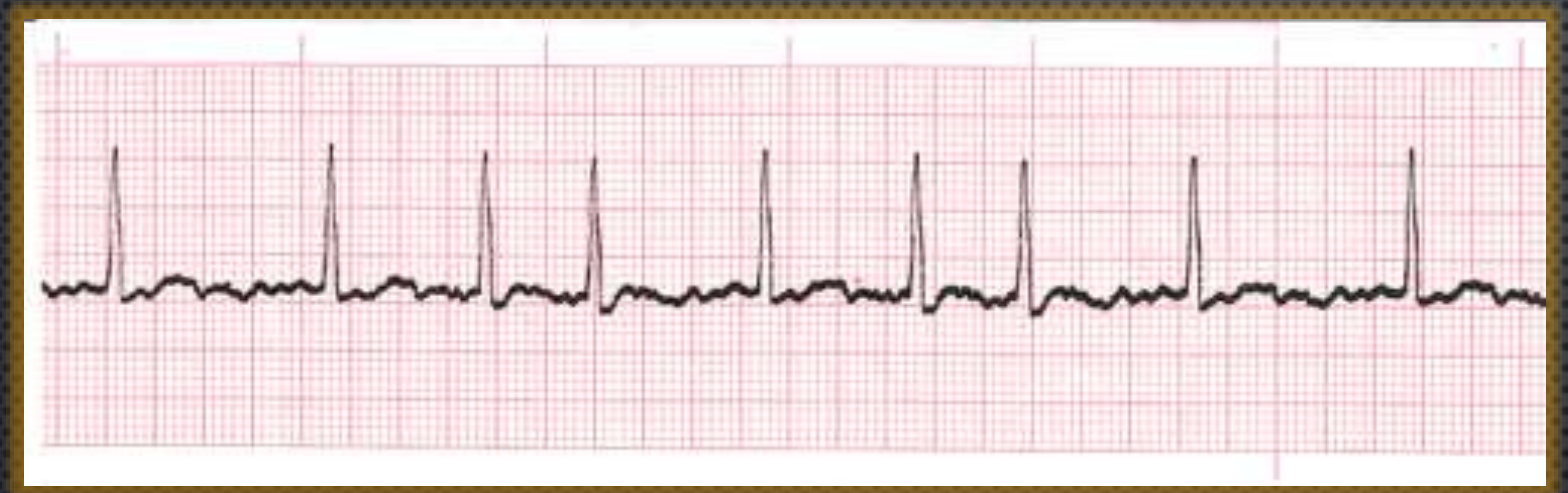


Summary

- Genetic information is good enough to attribute cause to individual ….but
- Phenotype … usually conveys most information clinically

Electrophysiology

PHENOTYPE



Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in humans

1 in 10 patients over age 80

Prevalence in the United States projected to roughly double by the year 2050 to an estimated 6-12 million

GENOTYPE
4q25 locus

INCREASED RISK OF ATRIAL FIBRILLATION ON CHROMOSOME 4Q25: 2 LOCATIONS

Table 2 | Association by age at diagnosis in Iceland and by AF sub-phenotype in the United States

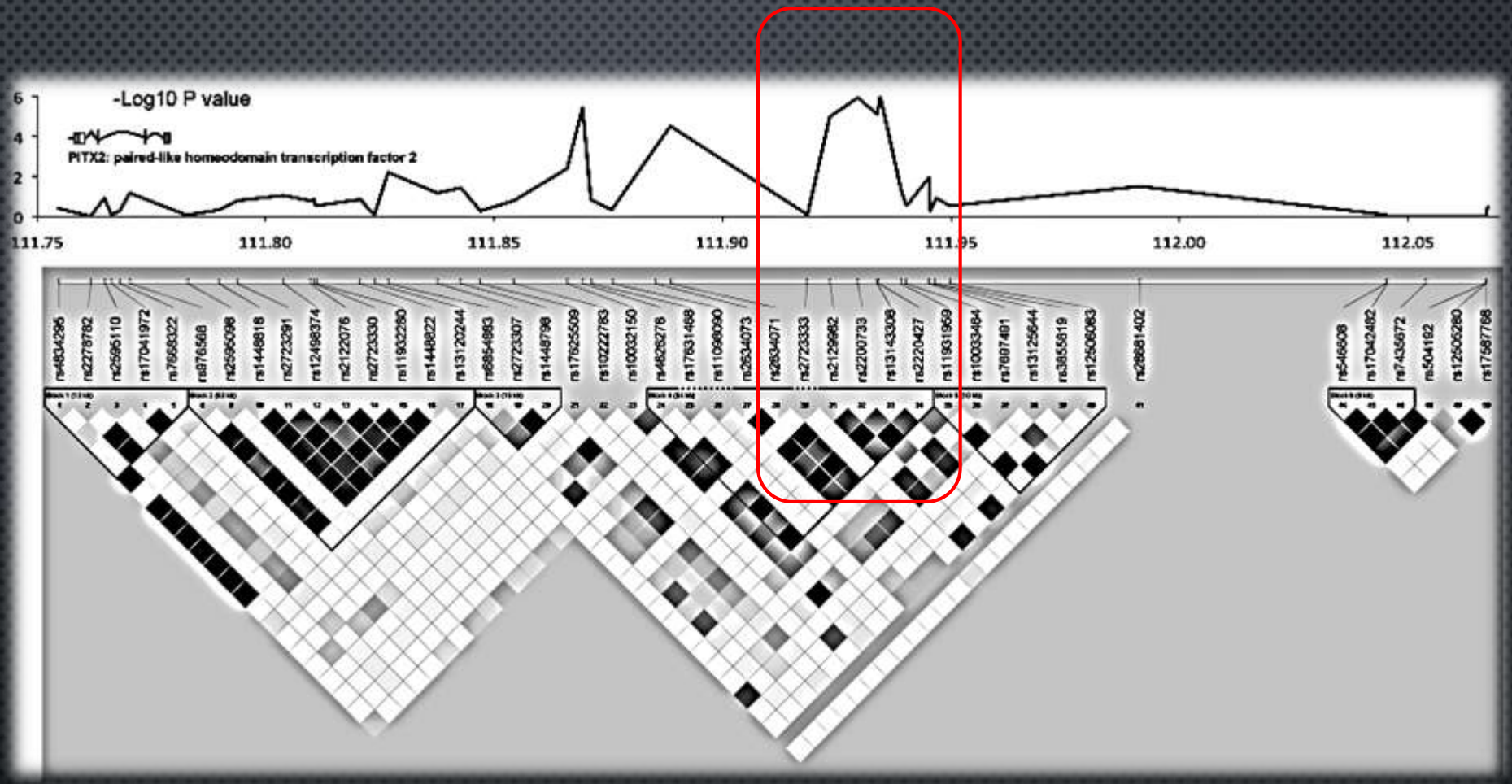
Sample (cases/controls)	Male (%)	Age (yr)	OR (95% CI)		P
			rs2200733*	rs10033464*†	
Iceland‡					
Diagnosis at age ≤60 yr (510/17,714)	77.8	50.7 ± 8.4	2.12 (1.77–2.54)	1.69 (1.34–2.12)	6.3×10^{-18}
Diagnosis at age 60–70 yr (654/17,714)	66.2	65.6 ± 2.9	1.88 (1.60–2.21)	1.44 (1.18–1.77)	6.7×10^{-15}
Diagnosis at age 70–80 yr (958/17,714)	58.9	75.0 ± 2.8	1.60 (1.39–1.84)	1.23 (1.03–1.47)	7.5×10^{-11}
Diagnosis at age >80 yr (679/17,714)	47.4	85.6 ± 4.2	1.20 (1.01–1.43)	1.31 (1.08–1.60)	0.0044
United States					
Lone AF (251/804)	81.7	46.1 ± 11.5	2.32 (1.80–2.99)	1.68 (1.19–2.37)	1.2×10^{-10}
AF + hypertension (67/804)	74.6	54.5 ± 10.2	2.23 (1.43–3.48)	1.66 (0.90–3.04)	0.0010
Other AF (318/804)	52.8	75.2 ± 11.3	1.44 (1.12–1.84)	0.97 (0.69–1.37)	0.015

PHENOTYPE

NATURE 2007 | Vol 448 | 353

MORE POST OP ATRIAL FIBRILLATION ASSOCIATED WITH RS2200733 POLYMORPHISM AT THE 4Q25 LOCUS

CABG Genomics discovery cohort (N=959) postoperative AF (n=289)



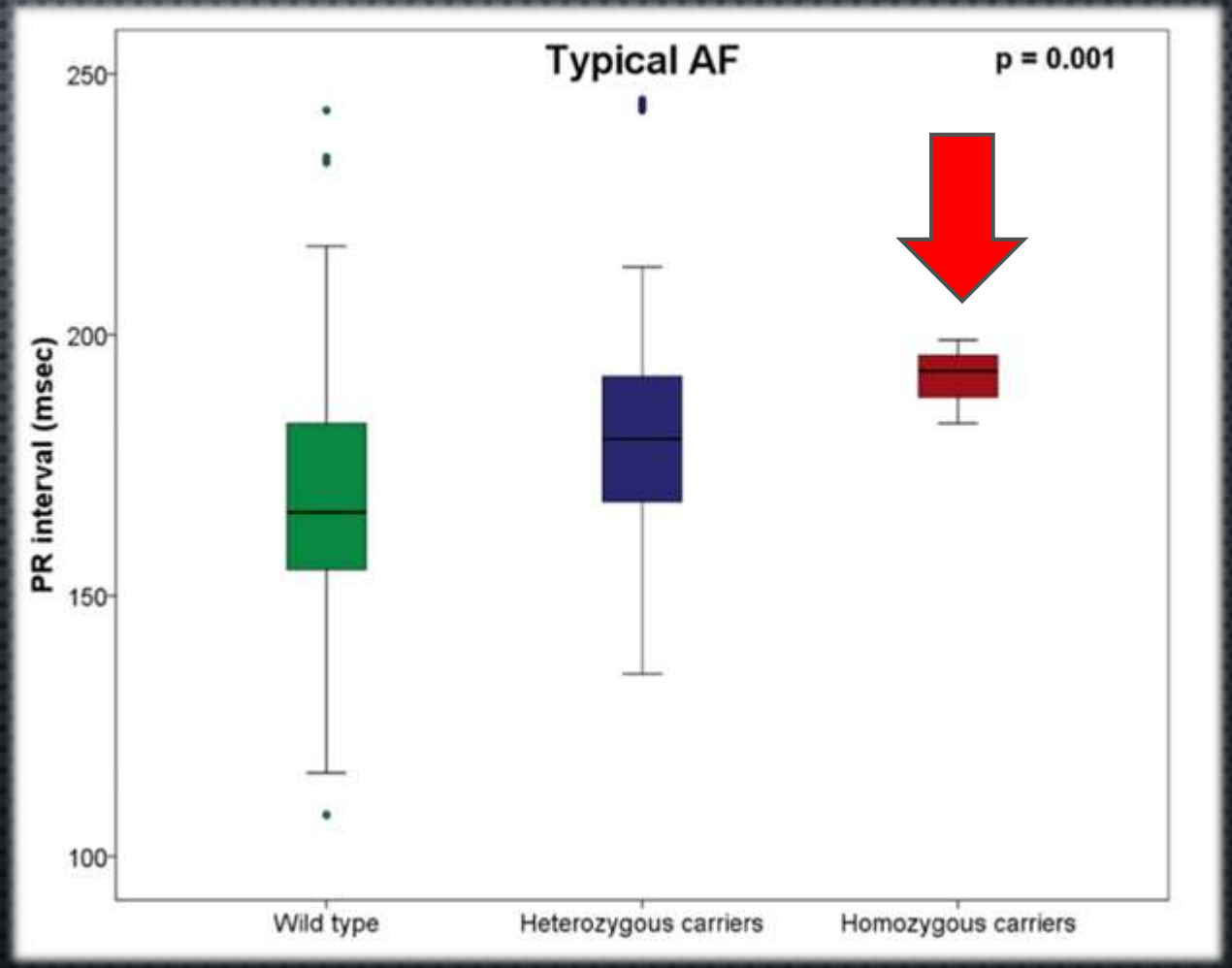
Circ Cardiovasc Genet. 2009;2:499-506

Single Nucleotide Polymorphism Database record ID number ("**rs**#"; e.g. **rs**206437)

HOMOZYGOUS CARRIERS HAVE INCREASED RISK FOR AFIB WITH INCREASED PR INTERVAL

rs2200733 polymorphism at the 4q25 locus was associated with **PR interval** duration in patients typical AF with no history of AF

N=1403 controls
N=269 typical Afib



GENOTYPE

Am J Cardiol. 2014 January 15; 113(2): 309–313

ELECTROCARDIOGRAPHIC PR INTERVAL DURATION (MILLISECONDS) BASED ON RS2200733 GENOTYPE

	Total	CC	CT	TT	P–value
Lone atrial fibrillation	168 [152–188]	162 [148–184]	178 [157–196]	176 [156–181]	0.038
Typical atrial fibrillation	171 [156–187]	166 [155–183]	180 [168–192]	196 [188–206]	0.001
No atrial fibrillation	156 [144–170]	156 [144–169]	156 [144–170]	170 [149–176]	0.4

Am J Cardiol. 2014 January 15; 113(2): 309–313

Are Genetic Tests for Atherosclerosis Ready for Routine Clinical Use?

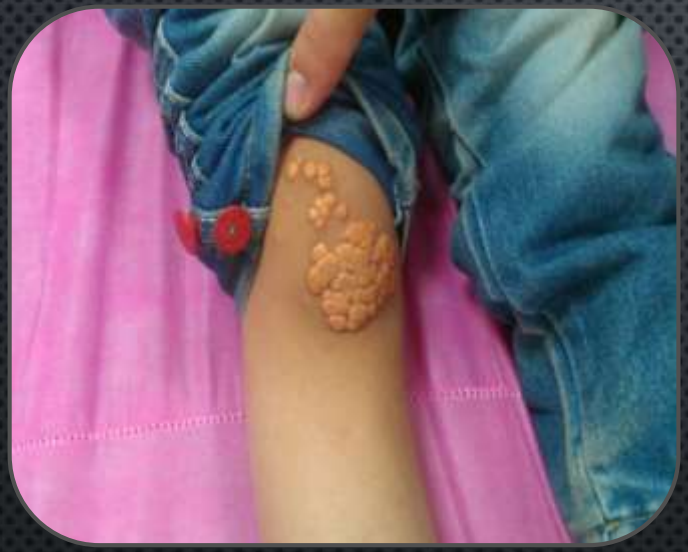
Nina P. Paynter, Paul M Ridker and Daniel I. Chasman

http://dx.doi.org/10.1161/CIRCRESAHA.115.306360Circulation Research. 2016;118:607-619
Originally published February 18, 2016

Lipids

Familial hypercholesterolemia (FH) -inherited disorder high concentration of LDL

Xanthomas, deposits of cholesterol in peripheral tissues, and ↑↑ atherosclerosis from cholesterol deposition in the arterial wall



Mutations in the LDL-receptor gene (LDLR)
Asp461Asn mutation in LDLR gene

4 times higher

HOMO

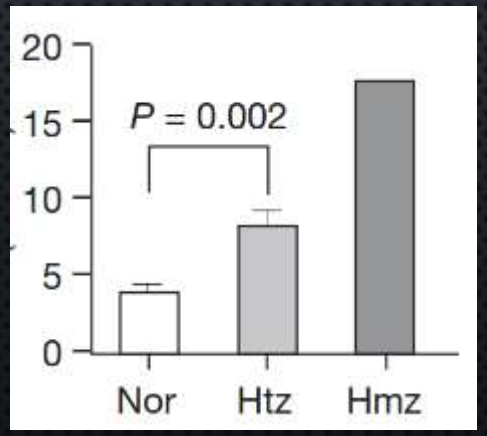
LDL

HETERO

2 times higher

Khachadurian in 1964 in Lebanese FH pedigrees…PHENOTYPE

Plasma Cholesterol mmol/L



Normal

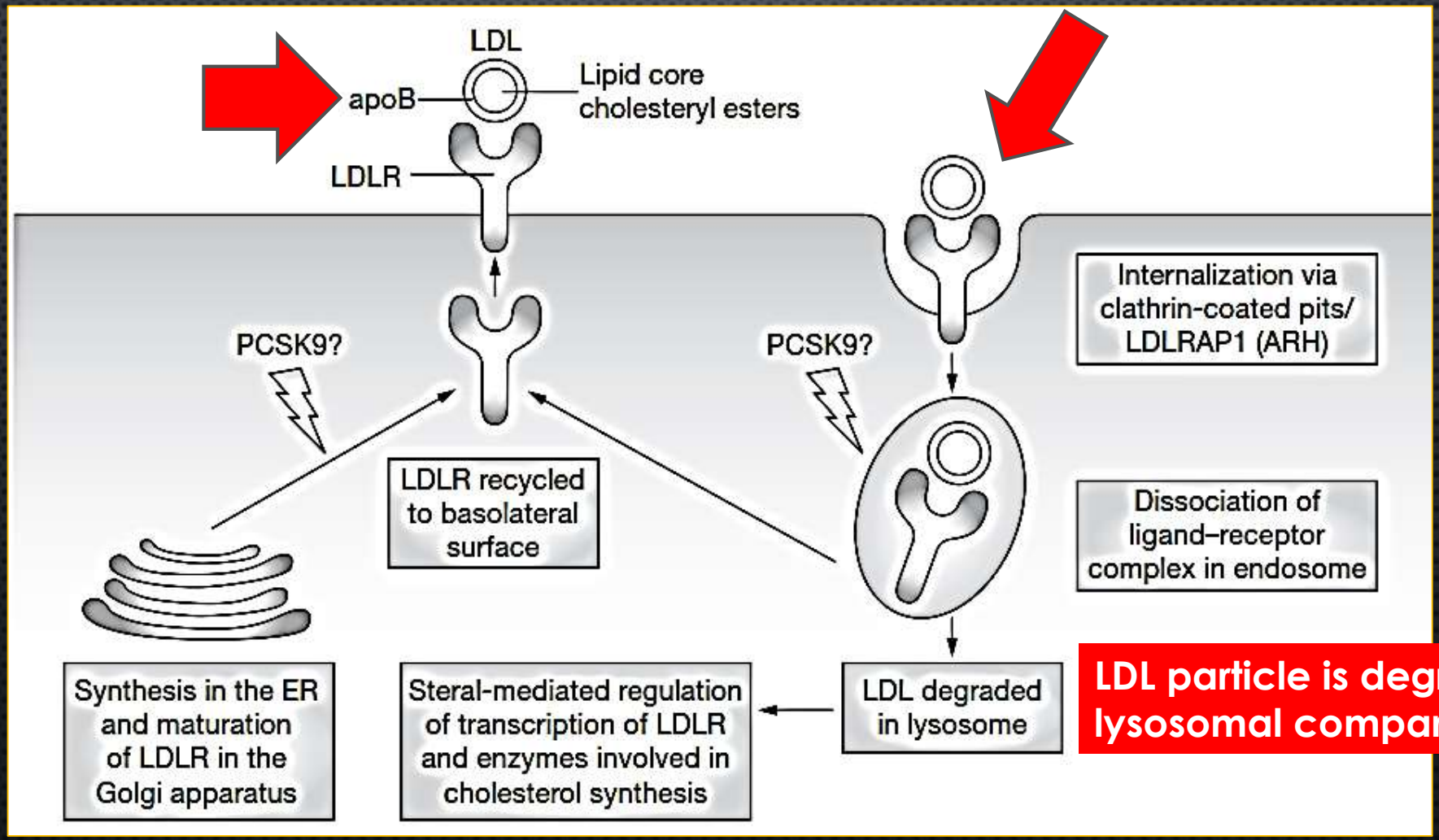
LIPIDSand genome+++.ppt

LIPIDS

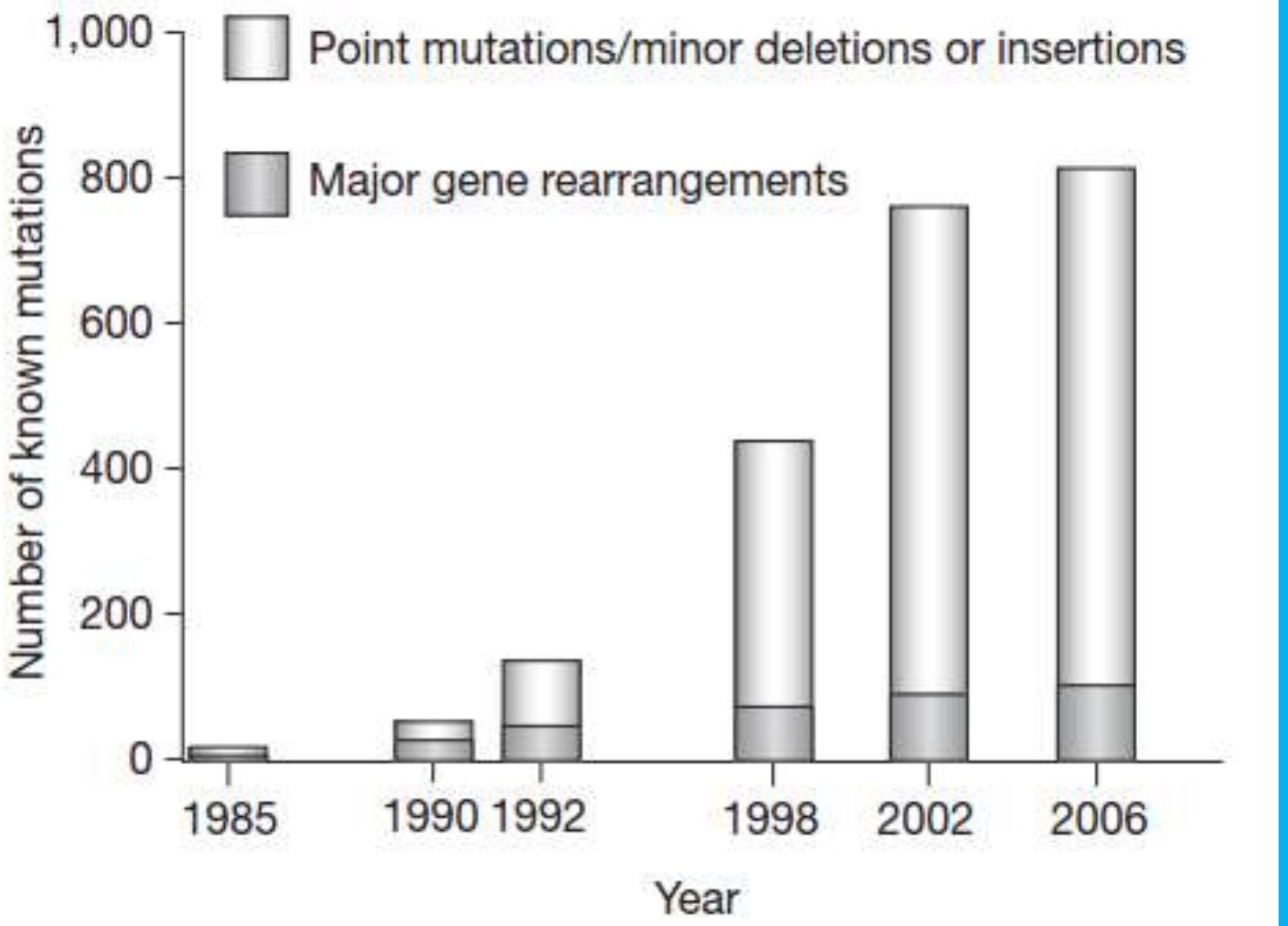
NATURE CLINICAL PRACTICE CARDIOVASCULAR MEDICINE APRIL 2007 VOL 4:21
Journal of Lipid Research Volume1996;37:368

Specific for apolipoprotein B in LDL

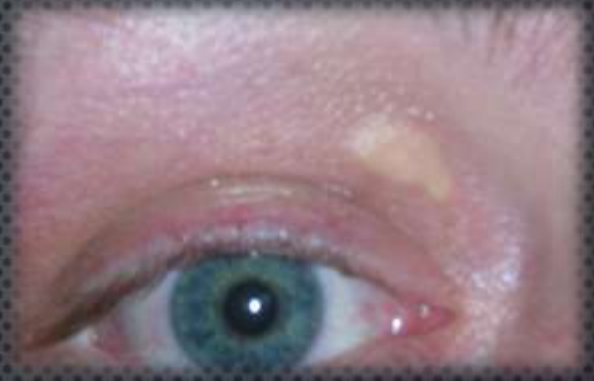
LDL receptor--cell-surface glycoprotein - synthesized as an immature protein and processed in the Golgi apparatus--mature form that is transported to the cell surface



LDL particle is degraded in the lysosomal compartment

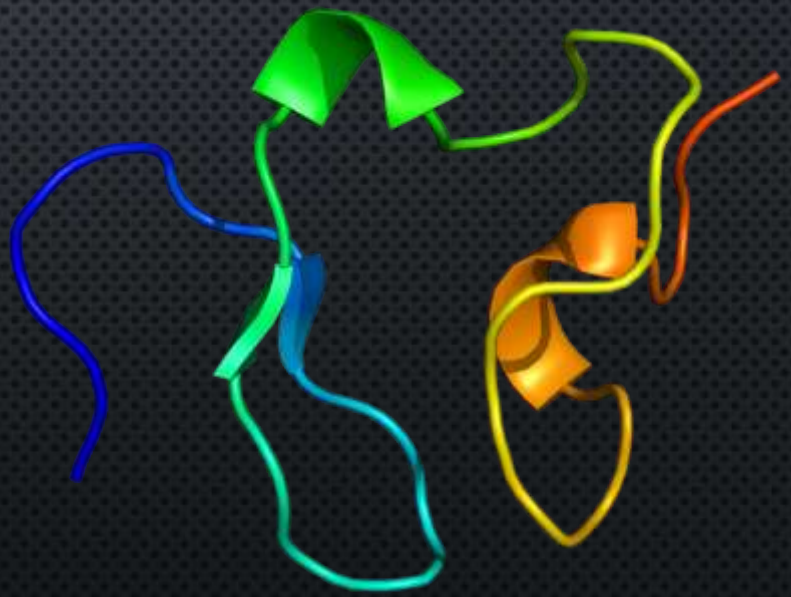


PHENOTYPE



Xanthelasma above right eye

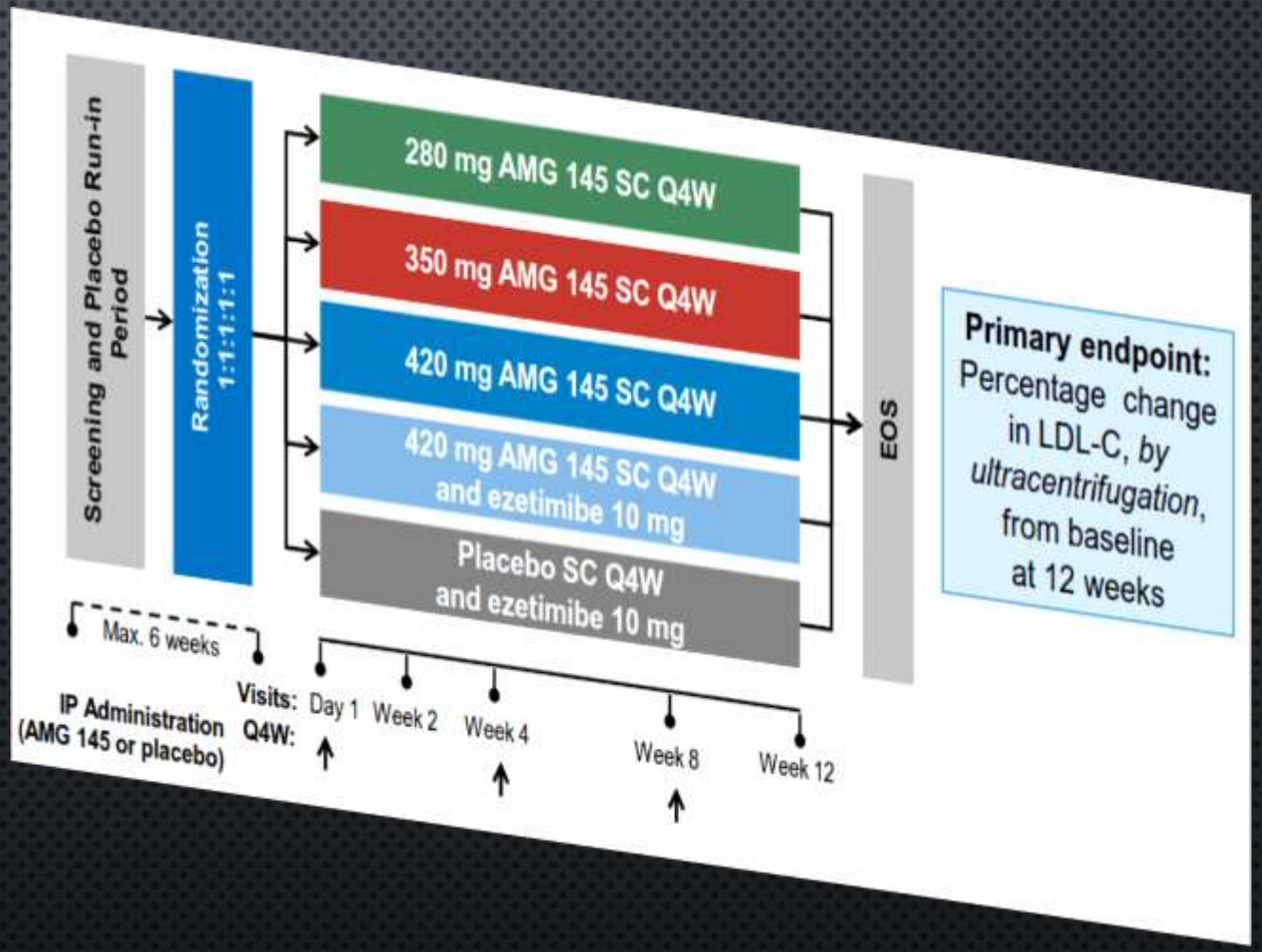
LDL receptor protein



Asp461Asn mutation in LDLR gene-GENOTYPE

GOAL ACHIEVEMENT AFTER UTILIZING AN ANTI-PCSK9 ANTIBODY IN STATIN INTOLERANT SUBJECTS (GAUSS)

- 10% TO 20% OF PATIENTS CANNOT TOLERATE STATINS
- PLASMA PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 (PCSK9) PLAYS A PIVOTAL ROLE IN CELLULAR CHOLESTEROL HOMEOSTASIS, BY BINDING TO, AND MEDIATING THE RECYCLING OF LDL RECEPTORS
- AMG 145 -HUMAN MONOCLONAL ANTIBODY BINDS TO PCSK9 BLOCKS ITS INTERACTION WITH LDL-RS, INCREASING THEIR RECYCLING AND REMOVAL OF LDL-C
- GLOBAL, RANDOMIZED, DOUBLE-BLIND, CONTROLLED STUDY



Clilnical trials.gov 2016

GAUSS TRIAL-BASELINE

Characteristic	AMG 145 Q4W			AMG 145 420 mg + Ezetimibe N = 30	Placebo Q4W + Ezetimibe N = 32
	280 mg N = 32	350 mg N = 31	420 mg N = 32		
Sex, female, n (%)	18 (56)	21 (68)	20 (63)	23 (77)	18 (56)
Age, years, mean (SD)	62 (10)	62 (9)	60 (9)	62 (7)	62 (7)
LDL-C, mg/dL , mean (SD)*	**195 (48)**	**190 (48)**	**204 (60)**	**194 (60)**	**183 (36)**
Free PCSK9, ng/mL, mean (SD)	383 (98)	396 (129)	372 (87)	379 (111)	390 (91)

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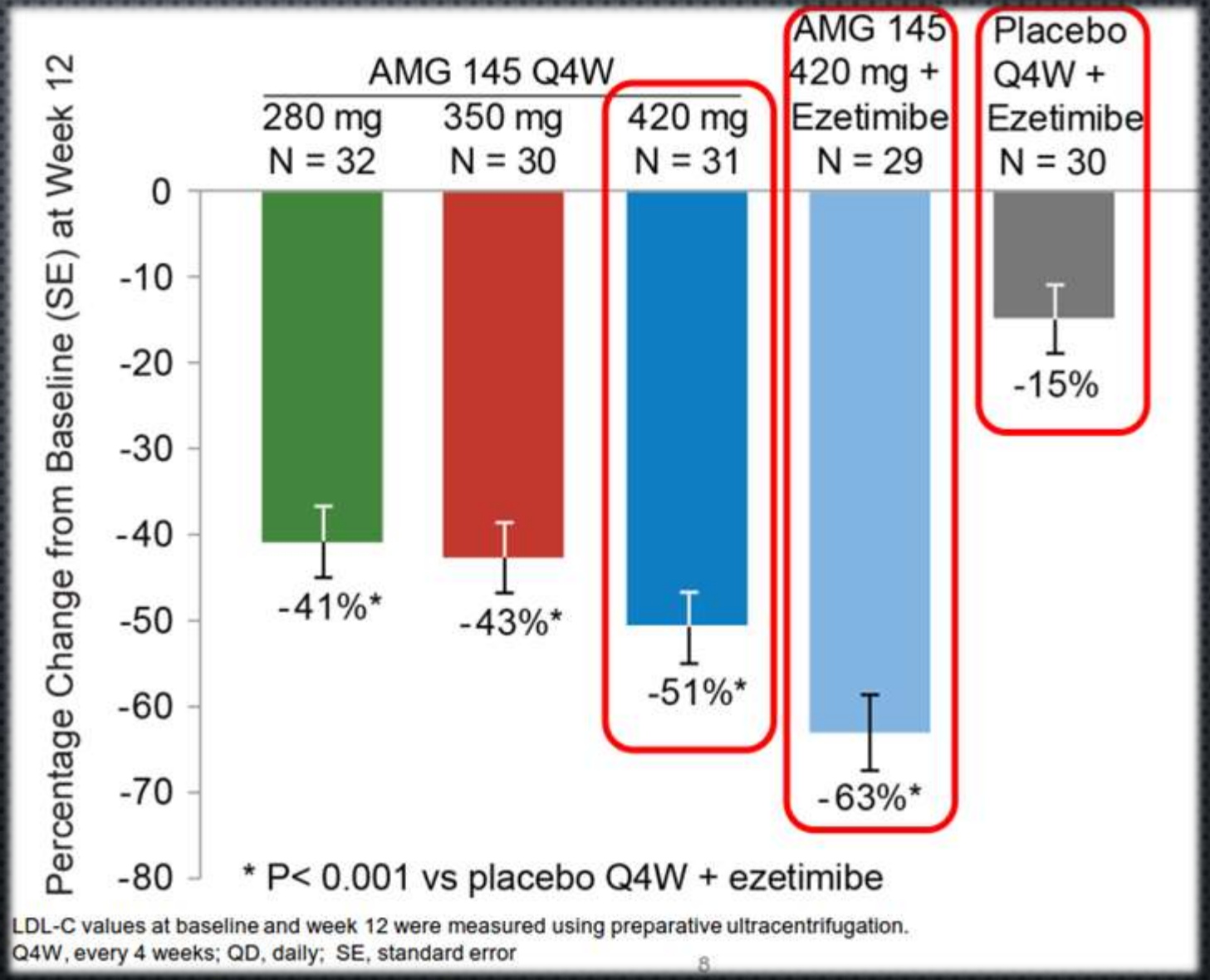
STATIN INTOLLERANCE

Characteristic	AMG 145 Q4W			AMG 145 420 mg + Ezetimibe N = 30	Placebo Q4W + Ezetimibe N = 32
	280 mg N = 32	350 mg N = 31	420 mg N = 32		
Statins failed (muscle-related events)					
≥ 1, n (%)	**32 (100)**	**31 (100)**	**32 (100)**	**30 (100)**	**32 (100)**
≥ 2, n (%)	**28 (53)**	**24 (77)**	**23 (72)**	**21 (70)**	**25 (78)**
≥ 3, n (%)	11 (34)	11 (35)	12 (38)	6 (20)	11 (34)
Worst statin-related events, any statin					
Myalgia, n (%)	31 (97)	30 (97)	29 (91)	29 (97)	29 (91)
Myositis, n (%)	3 (9)	3 (10)	2 (6)	2 (7)	4 (13)
Rhabdomyolysis, n (%)	0 (0.0)	0 (0.0)	1 (3)	0 (0)	0 (0)

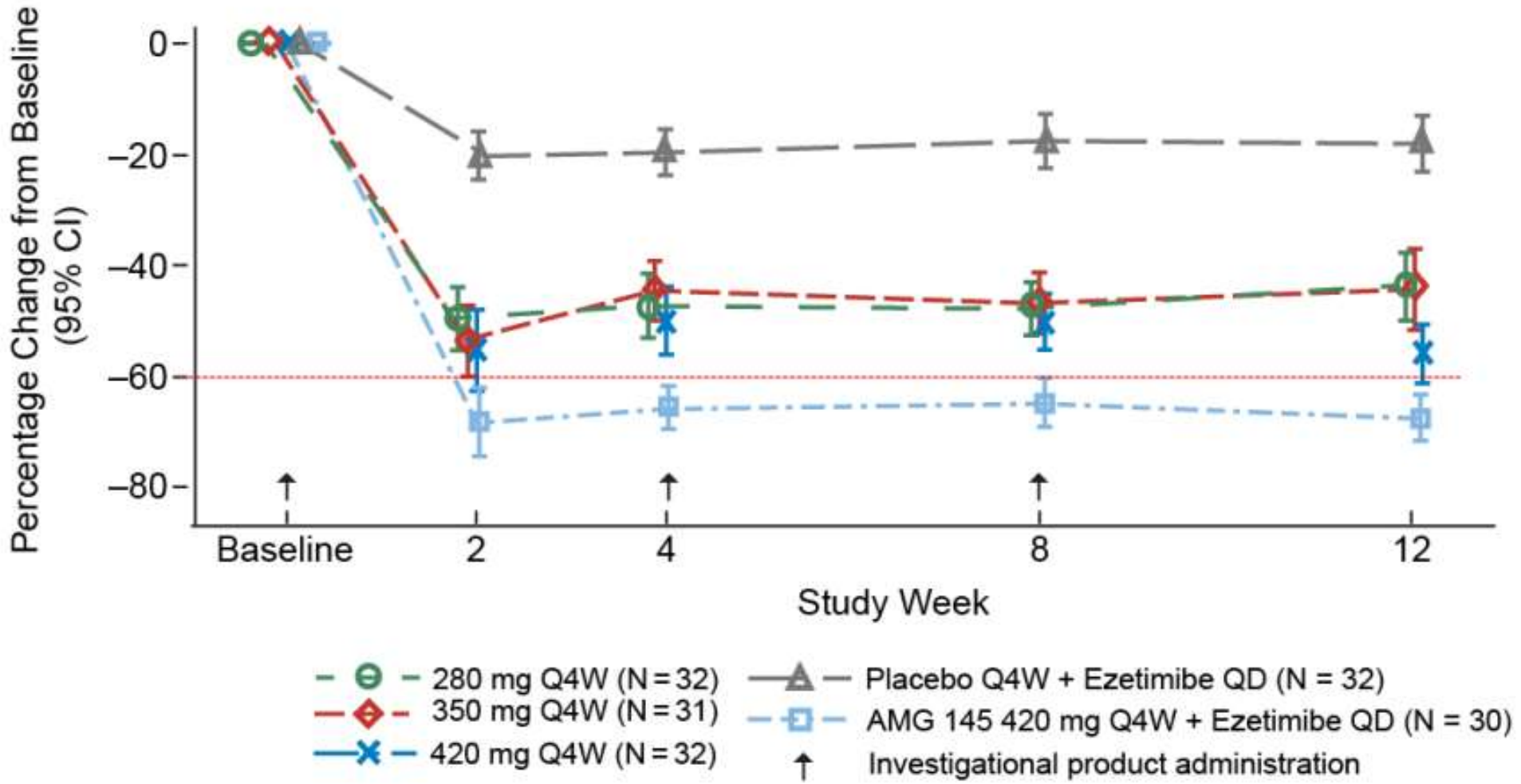
GAUSS trial-Baseline

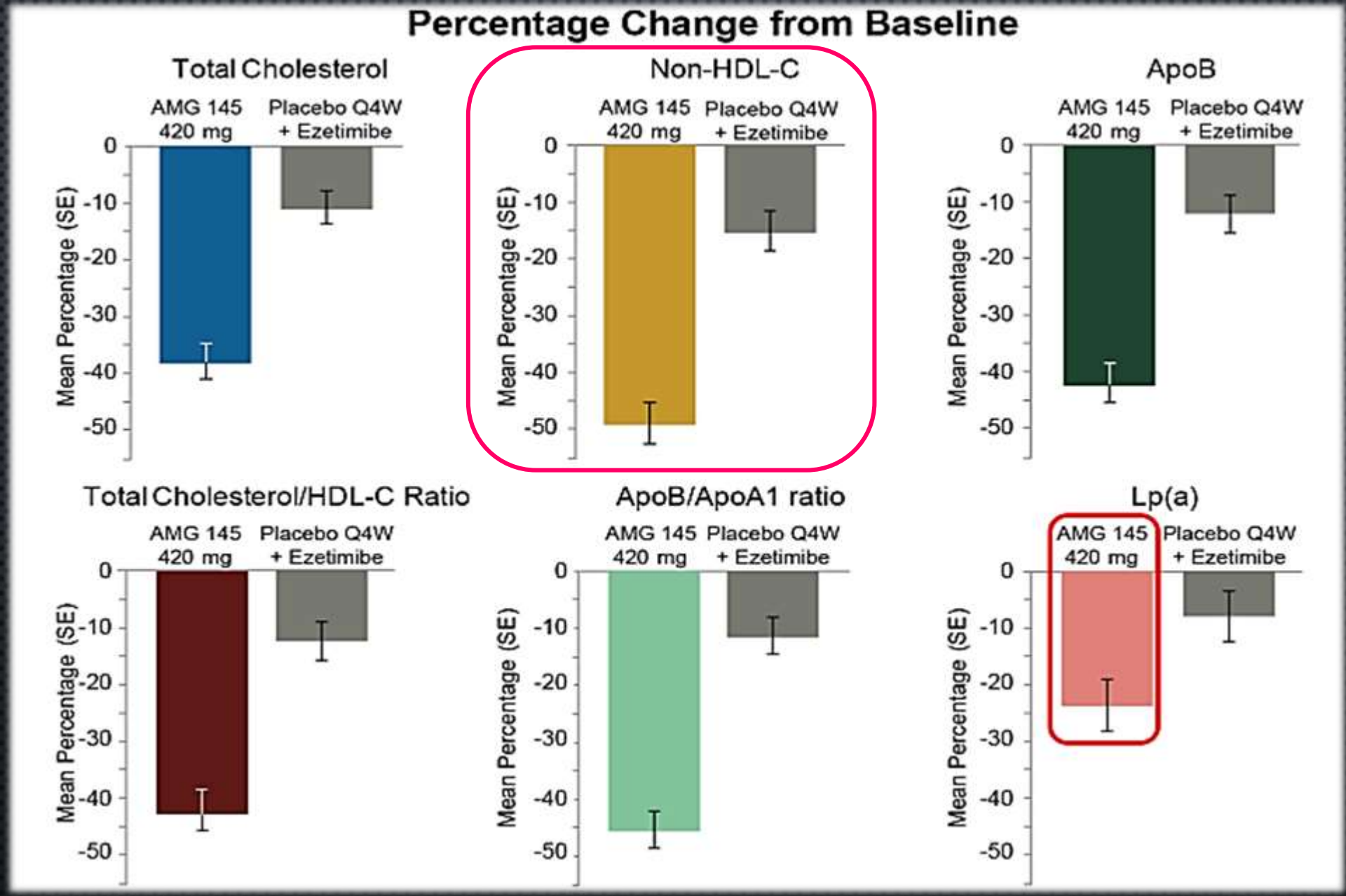
Clilnical trials.gov 2016

PRIMARY ENDPOINT



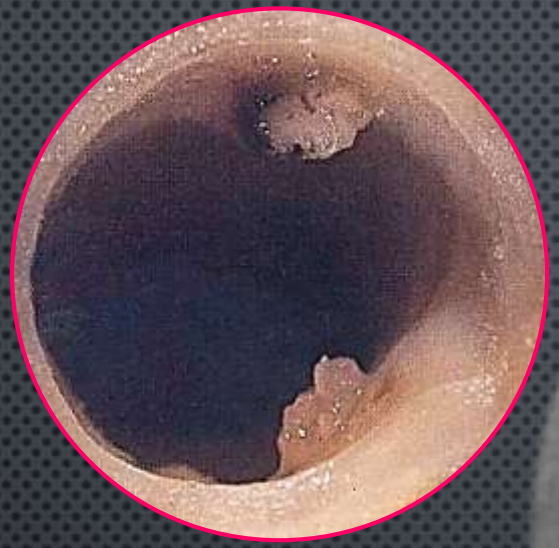
LDL-C values at baseline and week 12 were measured using preparative ultracentrifugation.
Q4W, every 4 weeks; QD, daily; SE, standard error


Percentage Change from Baseline (95% CI)
0
−20
−40
−60
−80
Baseline
2
4
8
12
Study Week
280 mg Q4W (N = 32)
350 mg Q4W (N = 31)
420 mg Q4W (N = 32)
Placebo Q4W + Ezetimibe QD (N = 32)
AMG 145 420 mg Q4W + Ezetimibe QD (N = 30)
Investigational product administration

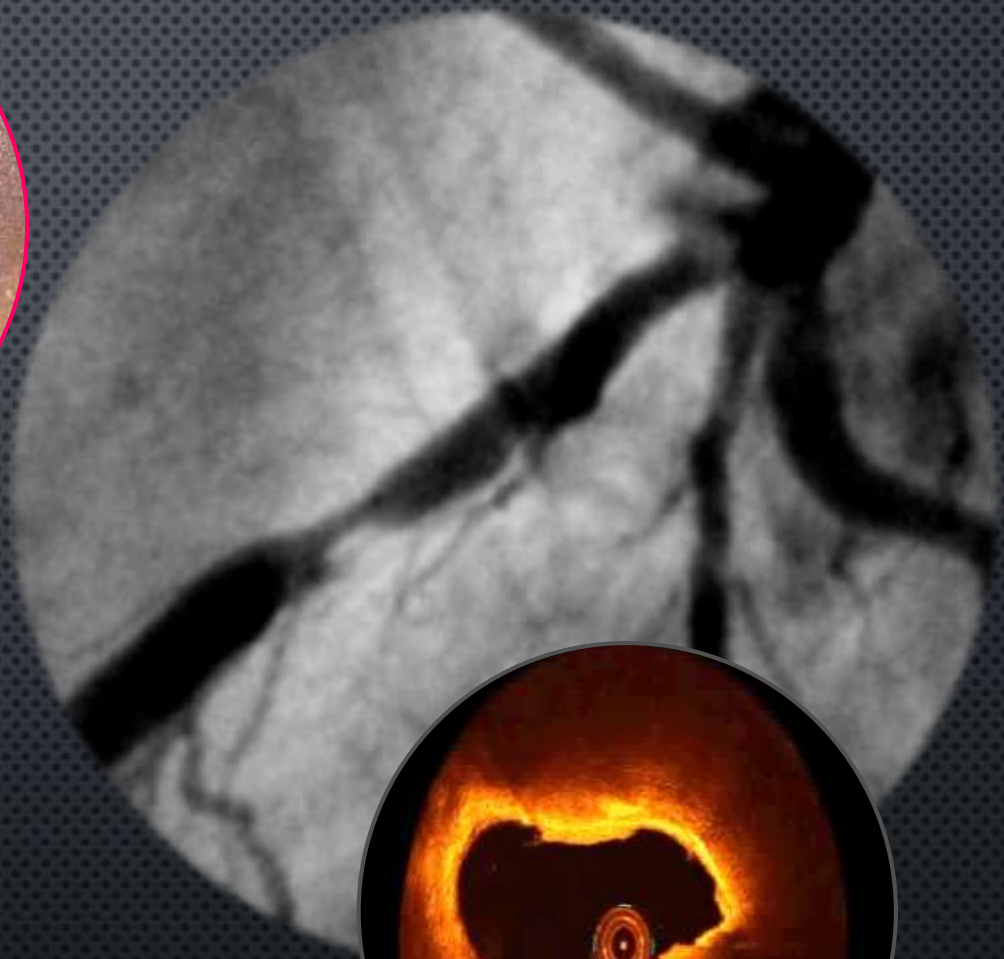

Percentage Change from Baseline
Total Cholesterol
Non-HDL-C
ApoB
Total Cholesterol/HDL-C Ratio
ApoB/ApoA1 ratio
Lp(a)
AMG 145 420 mg
Placebo Q4W + Ezetimibe
Mean Percentage (SE)
0
-10
-20
-30
-40
-50

Adverse Events, Patient Incidence, n (%)	AMG 145			AMG 145 420 mg + Ezetimibe 10 mg	Placebo Q4W + Ezetimibe
	280 mg N = 32	350 mg N = 31	420 mg N = 32	N = 30	N = 32
Treatment-emergent AEs	22 (68.8)	15 (48.4)	18 (56.3)	20 (66.7)	19 (59.4)
Serious AEs*	2 (6.3)	1 (3.2)	1 (3.1)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related AEs	8 (25.0)	3 (9.7)	6 (18.8)	5 (16.7)	7 (21.9)
Muscle-related AEs					
Myalgia	5 (15.6)	1 (3.2)	1 (3.1)	6 (20.0)	1 (3.1)
Muscle fatigue	2 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)
Muscle spasms	1 (3.1)	2 (6.5)	0 (0.0)	0 (0.0)	3 (9.4)
AEs leading to discontinuation	0 (0.0)	1 (3.2)	1 (3.1)	1 (3.3)	2 (6.3)
Other most commonly reported AEs					
Nasopharyngitis	2 (6.3)	2 (6.5)	1 (3.1)	3 (10.0)	5 (15.6)
Nausea	2 (6.3)	1 (3.2)	1 (3.1)	0 (0.0)	1 (3.1)
Fatigue	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.3)

PHENOTYPE

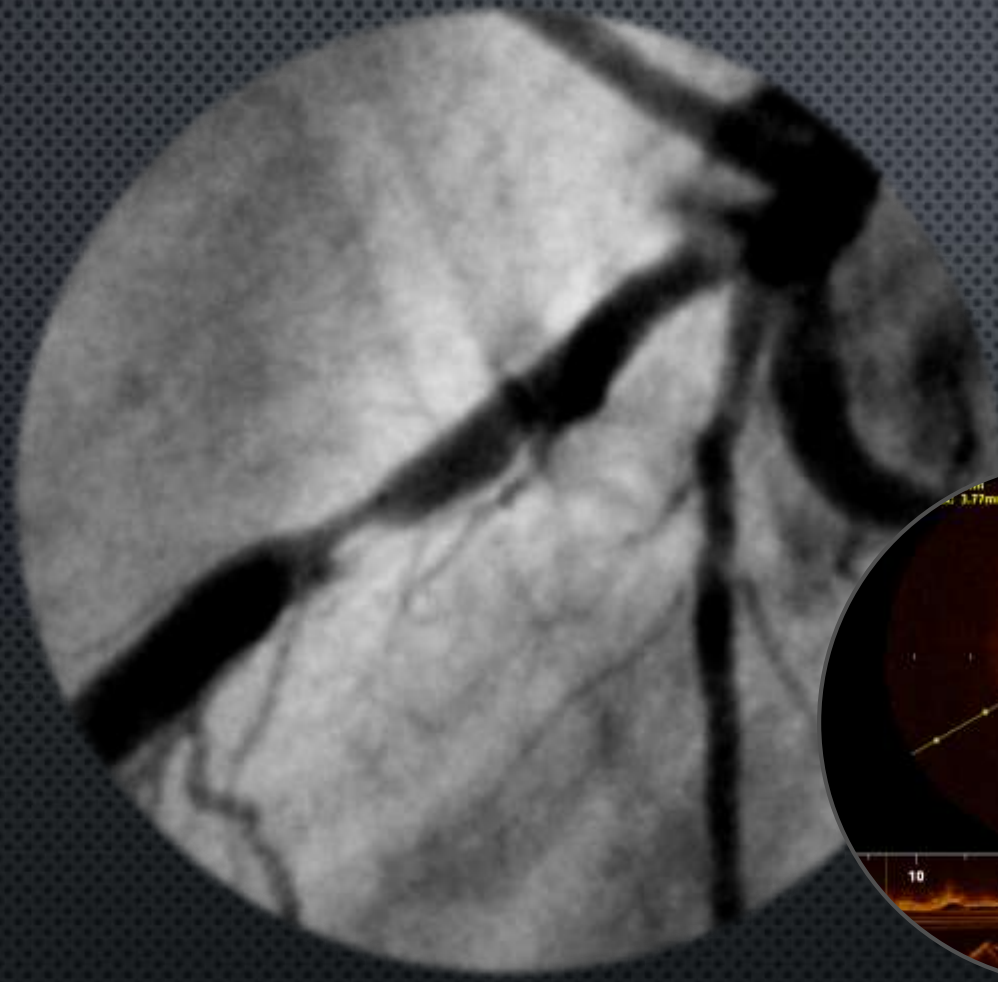


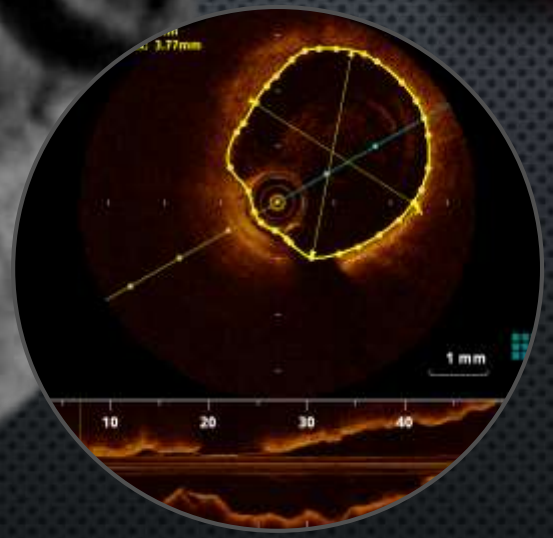
Mural thrombi

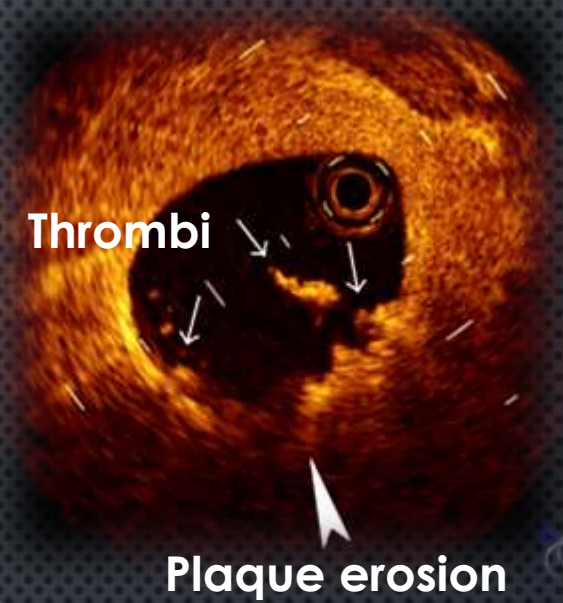


Acute coronary syndrome

Vascular plaque rupture



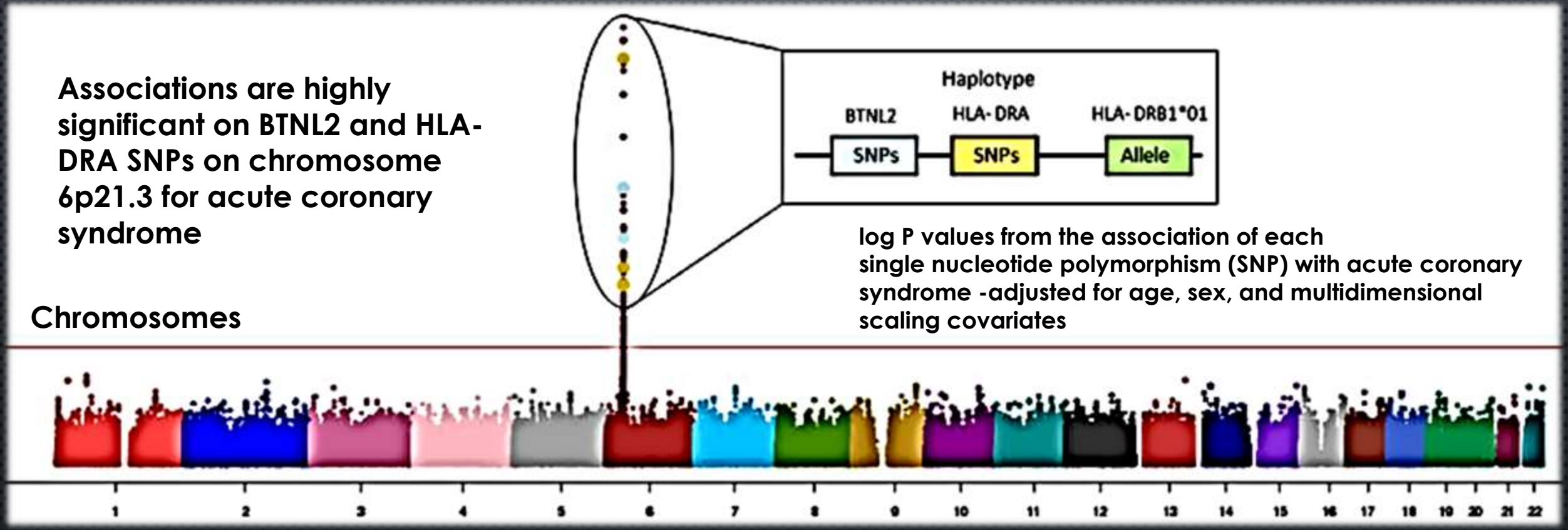




Cardiology Research and Practice: doi:10.4061/2011/312978

GENOTYPE MARKERS FOR INCREASED RISK FOR ACUTE CORONARY SYNDROME

Associations are highly significant on BTNL2 and HLA-DRA SNPs on chromosome 6p21.3 for acute coronary syndrome

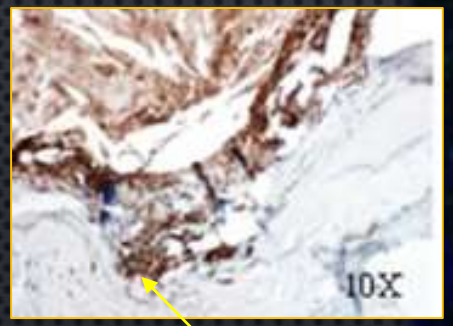


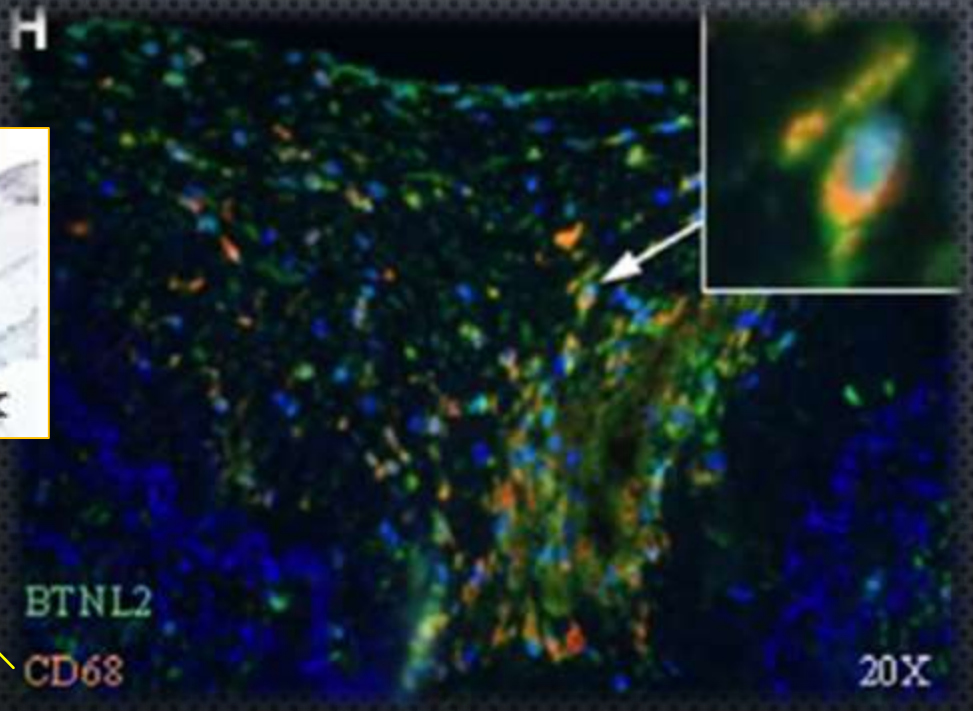
log P values from the association of each single nucleotide polymorphism (SNP) with acute coronary syndrome -adjusted for age, sex, and multidimensional scaling covariates

Manhattan plots of the discovery population with acute coronary syndrome

Circ Cardiovasc Genet. 2016;9:55-63

ACS PLAQUES HAVE INCREASED MACROPHAGES AND BTNL2 TOGETHER





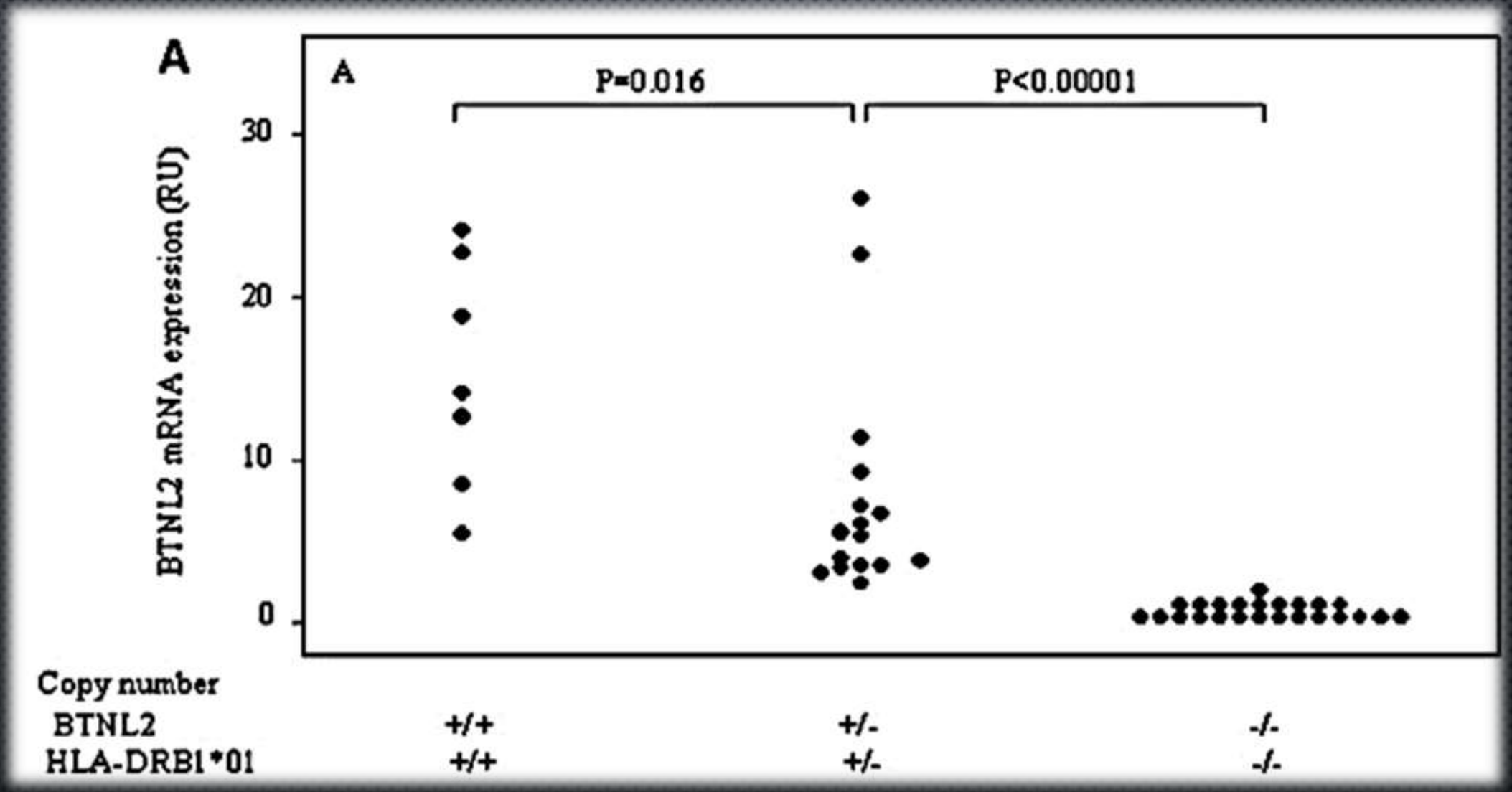
BTNL2 is in green and CD68 in red, and they merge in yellow

Immunofluorescence staining for colocalization of BTNL2 and CD68 in coronary artery macrophages

Increased immune reaction
BTNL2 inhibits FOXP3+T cell proliferation

Circ Cardiovasc Genet. 2016;9:55-63

It is not perfect…but if have both alleles you at higher risk



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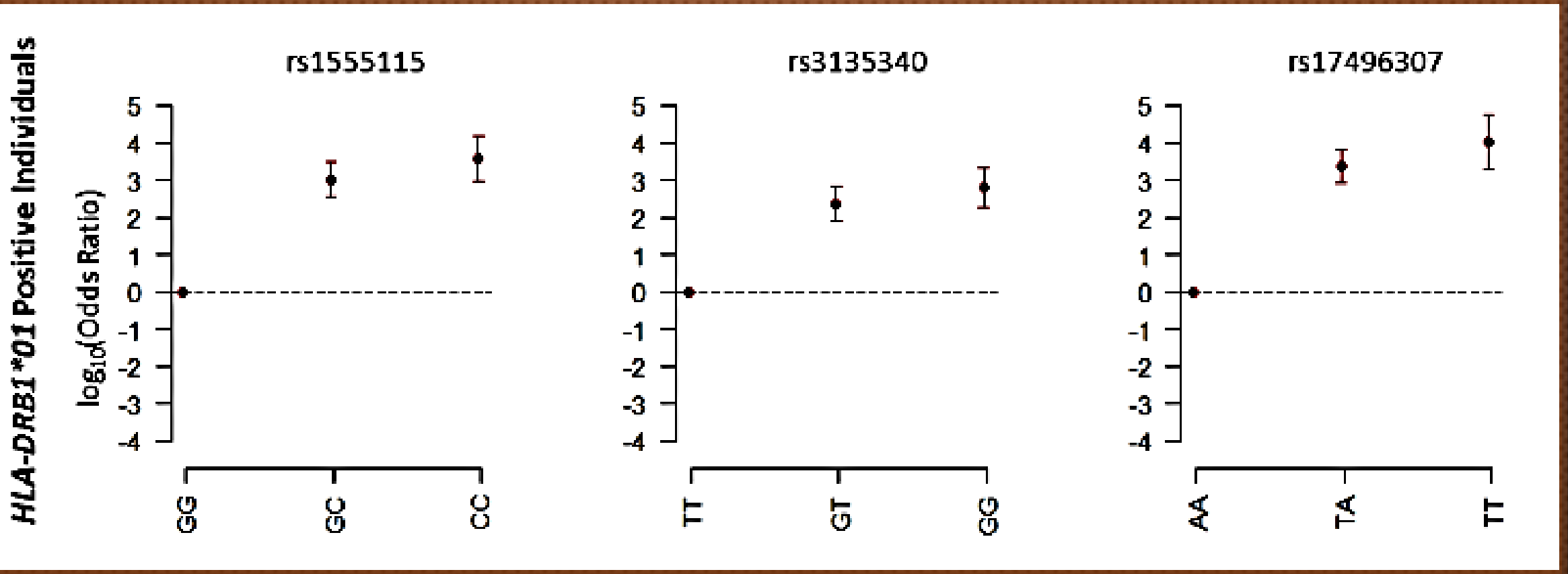

Circ Cardiovasc Genet. 2016;9:55-63

SUMMARY: EXERCISE AND STAY SKINNY

Thank you