The Association of Candidate Gene Variants with Blood Lipids in NHANES III (1991-1994)

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Background:

- Previous studies have reported a strong relationship between cardiovascular disease and:
  - High levels of serum total cholesterol (STC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG)
  - An inverse relationship with high-density lipoprotein cholesterol (HDL-C)
- Genetic variation, in addition to numerous modifiable and non-modifiable environmental factors, has been shown to have a significant effect on serum lipid levels

Objectives:

- Examine the association between postulated candidate genes and serum lipid levels (HDL-C, LDL-C, STC, and TG) among the three major racial and ethnic groups in the U.S. (non-Hispanic white, non-Hispanic black, and Mexican-American)
- Determine gene-environment interactions, which present opportunities for risk modification in these populations

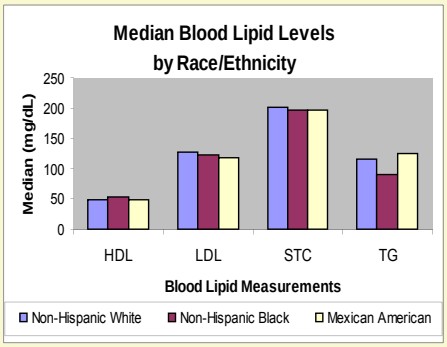
Methods:

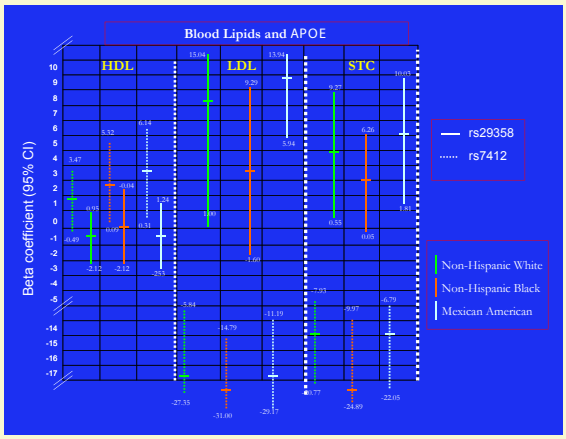
- Study population
  - Used participants aged ≥17 years that self-reported as non-Hispanic white, non-Hispanic black, or Mexican American (n=6,016) with available data in the NHANES III DNA bank, 1991-1994
- Genotyping methods
  - TaqMan and MGB Eclipse assays
- Study was conducted as part of the CDC/NCI NHANES III Collaborative Genomics Project
- Null hypothesis
  - HDL-C, LDL-C, STC, and TG levels do not differ by increasing minor allele copy number assumed in an additive model of inheritance
- Health outcomes and phenotypic covariates
  - Blood lipid measurements: HDL-C and STC (all participants), LDL-C and TG (those fasting ≥ 9 hours)
  - Covariates: age, sex, education, physical activity, alcohol intake, smoking status, BMI, total dietary fat intake
- Statistical analysis
  - Used SAS-Callable SUDAAN 9.01 and SAS 9.1
  - Performed multivariable regression models
  - Used NHANES III genetic sample weights due to complex survey design

27 variants in 17 genes

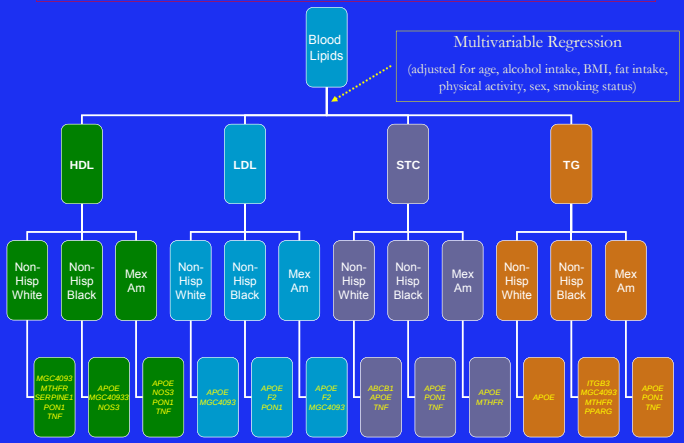
ABCB1 (rs1045642)	MTHFR (rs1801131, rs1801133, rs2066470)
ADH1C (rs698, rs1693482)	MTRR (rs1801394)
ADRB2 (rs1042713, rs1042714)	NOS3 (rs1799983, rs2070744)
ADRB3 (rs4994)	PON1 (rs662, rs854560)
APOE (rs7412, rs429358)	PPARG (rs1801282)
F2 (rs1799963)	SERPINE (rs1799762)
F5 (rs6025)	TGFB1 (rs1982073)
ITGB3 (rs5918)	TNF (rs1800750, rs1800629, rs361525)
MGC4093 (rs1800468, rs1800469)	

Results:





Genetic Variants with Significant Associations



Genes with Significant Haplotypes in Association with Blood Lipids

HDL		
Non-Hispanic White	Non-Hispanic Black	Mexican American
APOE MTHFR PON1	NONE	NOS3 PON1 TNF

LDL		
Non-Hispanic White	Non-Hispanic Black	Mexican American
APOE	ADH1C APOE	APOE NOS3

STC		
Non-Hispanic White	Non-Hispanic Black	Mexican American
APOE TNF	ADH1C APOE PON1	APOE

TG		
Non-Hispanic White	Non-Hispanic Black	Mexican American
NONE	NONE	APOE PON1 TNF

Conclusions:

- These findings suggest that genetic variants, particularly those in *APOE, PON1, TNF, NOS3,* and *MTHFR*, are associated with blood lipid levels among the three major race/ethnic groups in the U.S.
- Haplotype analyses indicate a collective effect of multiple genetic variants on these blood lipid indicators
- Further examination of gene-gene and gene-environment interactions may present opportunities in the identification of disease susceptibility
- Given the body of evidence demonstrating strong relationships between blood lipid levels and risk of CVD, the role of these genetic variants and CVD deserves further exploration