Genetic Variants and Dyslipidemia

Dr. Kari North

09 December, 2016

Introduction

Dyslipidemia in children

- Dyslipidemia is an important risk factor for chronic cardiometabolic diseases.
- Dsylipidemia represents any abnormal levels of lipid, lipoprotein, or apolipoprotein factors (Kwiterovich 2008), including:
  - total cholesterol (TC)
  - low density lipoprotein cholesterol (LDL-C)
  - triglycerides (TG)
  - high density lipoprotein choleseterol (HDL-C)

Introduction

Heritability of dyslipidemia

- Lipid traits are heritable (h^2 can exceed 0.50) (Goode et al. 2007) and strongly associated with cardiovascular disease sustaining strong interest in genetic research.
- By 2013, researchers have identified more than 150 established loci influencing lipid levels in adults (C. J. Willer et al. 2013).

Introduction

Lipid variants

Source: Willer, C. J., Schmidt, E. M., Sengupta, S., Peloso, G. M., Gustafsson, S., Kanoni, S., Abecasis, G. R. (2013). Discovery and refinement of loci associated with lipid levels. Nature Genetics, 45(11), 1274–1283. https://doi.org/10.1038/ng.2797

Introduction

Generalizability across ancestral groups

- Results found for adults have been found to generalize to children in a Finnish population (Tikkanen et al. 2011; Buscot et al. 2016).
- Certain variants that associate with a trait such as dyslipdemia in one ancestral group may not associate in other groups (Carlson et al. 2013).
  - Why? Differences across ancestral groups include:
    - Variant frequencies
    - Linkage disequilibrium
- No research exists examining the association between genetic variants and dyslipidemia studies in Hispanic/Latino (HL) children

Introduction

Primary Aim

- Examine the association of known lipid variants with lipid traits identified in large study of adult participants from a Chilean infancy cohort of primarily European-descent.
  - Compare results to those found in a Finnish population.

Methods

Association tests

- We assessed single variant associations using linear regression for high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG), assuming an additive genetic model, adjusted for sex and ancestry (via principal components).
- Sample Model for HDL
  - $HDL_i = \beta_0 + SNP_i\beta_1 + sex_i\beta_2 + ANCESTRY_i\beta + \epsilon_i$
  - SNP_i represents one SNP with "genotypes were coded as 0, 1, or 2 when directly genotyped or as a predicted allele dosage (range, 0–2) when imputed." (Tikkanen et al. 2011)
- Only six variants from the Chilean sample met the *a priori* threshold of power > 0.8 to detect an association based on effect sizes from GWAS (T. M. Teslovich et al. 2010).

Methods

Polygenic risk scores

- Regress phenotypes onto weighted trait-specific polygenic risk scores (PRS).
- Sample model for HDL
  - $HDL_i = \beta_0 + \beta_1 PRS1_i + \epsilon_i$
  - PRS for HDL-C
    - (0.48 * rs4660293 + 0.49 * rs2814944 + 0.59 * rs4731702 + 0.41 * rs2923084 + 0.4 * rs7134375 + 0.44 * rs7134594 + 1.45 * rs1532085 + 3.39 * rs3764261 + 0.45 * rs2925979 + 0.42 * rs4148008 + 0.39 * rs4129767 + 0.64 * rs737337 + 1.88 * rs1800961 + 0.93 * rs6065906 + 0.47 * rs1689800 + 0.61 * rs4846914 + 0.68 * rs12328675 + 0.46 * rs2972146 + 0.49 * rs6450176 + 0.39 * rs605066 + 1.95 * rs1084651 + 1.21 * rs9987289 + 0.44 * rs2293889 + 0.65 * rs581080 + 0.94 * rs1883025 + 0.78 * rs3136441 + 0.86 * rs4759375 + 0.44 * rs4765127 + 0.61 * rs838880 + 0.39 * rs2652834 + 1.27 * rs16942887 + 0.48 * rs11869286 + 1.31 * rs7241918 + 0.42 * rs12967135 + 0.45 * rs7255436 + 0.83 * rs386000 + 0.46 * rs181362 + 0.84 * rs13107325) / 29.79

Methods

Proportion of variance explained by lipid-related SNPs

- Linear models containing all SNPs related to a specific phenotype, such as HDL-C, will be covariates.
- The continuous lipid phenotype is the outcome.
- Differences in R^2 will be calculated between models with and without the SNPs to estimate h^2.
  - Model for HDL:
    - HDL_i = b0 + b1 * rs4660293 + b2 * rs2814944 + b3 * rs4731702 + b4 * rs2923084 + b5 * rs7134375 + b6 * rs7134594 + b7 * rs1532085 + b8 * rs3764261 + b9 * rs2925979 + b10 * rs4148008 + b11 * rs4129767 + b12 * rs737337 + b13 * rs1800961 + b14 * rs6065906 + b15 * rs1689800 + b16 * rs4846914 + b17 * rs12328675 + b18 * rs2972146 + b19 * rs6450176 + b20 * rs605066 + b21 * rs1084651 + b22 * rs9987289 + b23 * rs2293889 + b24 * rs581080 + b25 * rs1883025 + b26 * rs3136441 + b27 * rs4759375 + b28 * rs4765127 + b29 * rs838880 + b30 * rs2652834 + b31 * rs16942887 + b32 * rs11869286 + b33 * rs7241918 + b34 * rs12067135 + b35 * rs7255436 + b36 *

Results

Descriptive statistics

Descriptive statistics by gender, median (interquartile range)

Female

Male
Trait

(n=263)

(n=283)
TG (mmol/l)

4.2 (2.26)

3.99 (2.53)
LDL-C (mmol/l)

Results

Explained variance

Proportion of lipid traits variance explained by lipid-related variants, by gender

Gender

HDL-C

LDL-C

TG

female

0.137

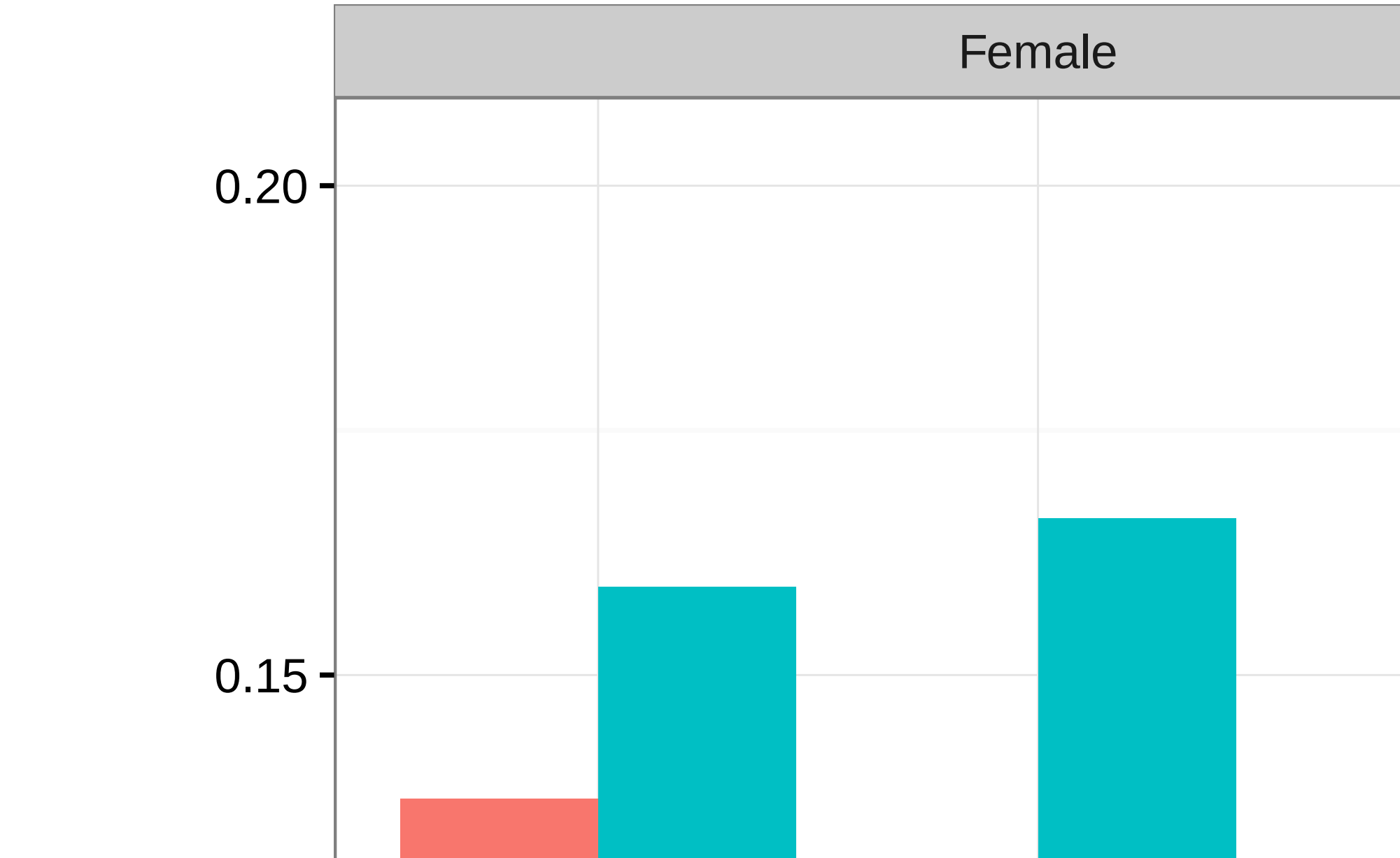
0.049

0.125

male

Results

Explained variance by gender and country



Results

Candidate single variant tests of association

Association between single variants and and serum lipid levels, additive model

Ref. Allele	G	A	C	A	C
Minor allele	A	C	A	C	T
MAF	0.33	0.31	0.31	0.31	0.31
Effect (se)	0.053 (0.038)	0.158 (0.04)	0.158 (0.04)	0.158 (0.04)	0.158 (0.04)
p-value	0.1655	1e-04	1e-04	1e-04	1e-04

Results

Polygenic risk scores (PRS)

Association between the genetic risk score and serum lipid levels, coefficient (SE)

Female

Male
Outcome/trait

Not adjusted
Adjusted for BMI

Not adjusted
Adjusted for BMI
HDL

0.1285 (0.0339)
0.1304 (0.0316)

Conclusion

Evidence for associations

- There is evidence that lipid loci from a HL sample of adolescents contain similar associations as those from European children and adults.
- Despite the small sample size and possibility for bias with different ancestral groups we found meaningful and statistically significant associations relating lipid loci in a HL cohort of Chilean adolescents with those found in European ancestral groups.
- These associations emphasize the importance of adolescence as a time for disease prevention given studies demonstrating both the persistence of associations between PRS and lipids over the life course and the increasing role PRS plays in predicting disease.

Extra slides, estimates from Tikkanen et al. (Tikkanen et al. 2011)

Descriptive statistics

Descriptive statistics
Outcome/Trait

Female

Male
N

661

555
TG (log(mmol/l))

0.90 (0.37)

0.91 (0.30)

Extra slides, estimates from Tikkanen et al. (Tikkanen et al. 2011)

Proportion variance explained by lipid variants

Proportion of lipid traits variance explained by lipid-related variants, by gender

Gender
HDL-C
LDL-C
TG
Female
0.159
0.166
0.128
Male
0.152
0.137
0.118

Extra slides, estimates from Tikkanen et al. (Tikkanen et al. 2011)

Single variant association tests

Association between the genetic risk score and serum lipid levels, coefficient (SE)
rs id
Trait
Effect (se)
Locus
p-value
rs3764261
HDL-C
0.0676 (0.012)
CETP
1.5e-08
rs1532085
HDL-C
0.0435 (0.011)

Extra slides, estimates from Tikkanen et al. (Tikkanen et al. 2011)

Polygenic risk score

Association between the genetic risk score and serum lipid levels, coefficient (SE)
Outcome/Trait

Female

Male
HDL

0.08 (0.01)

0.06 (0.01)
LDL

0.25 (0.03)

Extra slides: effect sizes used in PRS from Teslovich et al. 2010 (T. M. Teslovich et al. 2010).

Locus	Chr	Lead SNP	Lead trait	Other traits	Alleles/M
LDLRAP1	1	rs12027135	TC	LDL	T/A/0.4
PABPC4	1	rs4660293	HDL		A/G/0.2
PCSK9	1	rs2479409	LDL	TC	A/G/0.3
ANGPTL3	1	rs2131925	TG	TC, LDL	T/G/0.3
EVI5	1	rs7515577	TC		A/C/0.2
SORT1	1	rs629301	LDL	TC	T/G/0.2
ZNF648	1	rs1689800	HDL		A/G/0.3
MOSC1	1	rs2642442	TC	LDL	T/C/0.3
GALNT2	1	rs4846914	HDL	TG	A/G/0.4
IRF2BP2	1	rs514230	TC	LDL	T/A/0.4
APOB	2	rs1367117	LDL	TC	G/A/0.3
	NA	rs1042034	TG	HDL	T/C/0.2
GCKR	2	rs1260326	TG	TC	C/T/0.4
ABCG5/8	2	rs4299376	LDL	TC	T/G/0.3
RAB3GAP1	2	rs7570971	TC		G/A/0.3

Extra slides: Other work

1. AHA EPI/Lifestyle 2015 Poster: Childhood body mass index (BMI) z-scores associated with low HDL-C levels in adolescence in a Chilean cohort
2. UNC EPID 726 class presentation in advance of AHA predoctoral (successful) grant application (2016-2018)
3. Questions about analyses? Please visit the github web page!
4. Assistance with slides by Ann Von Holle, doctoral student

References

Buscot, Marie-jeanne, Costan G. Magnussen, Markus Juonala, Niina Pitkänen, Terho Lehtimäki, Jorma S. A. Viikari, Mika Kähönen, et al. 2016. "The Combined Effect of Common Genetic Risk Variants on Circulating Lipoproteins Is Evident in Childhood: A Longitudinal Analysis of the Cardiovascular Risk in Young Finns Study." Edited by David Fardo. *PLOS ONE* 11 (1): e0146081. doi:10.1371/journal.pone.0146081.

Carlson, Christopher S., Tara C. Matise, Kari E. North, Christopher A. Haiman, Megan D. Fesinmeyer, Steven Buyske, Fredrick R. Schumacher, et al. 2013. "Generalization and Dilution of Association Results from European GWAS in Populations of Non-European Ancestry: The PAGE Study." Edited by Greg Gibson. *PLoS Biology* 11 (9): e1001661. doi:10.1371/journal.pbio.1001661.

Goode, Ellen L., Stacey S. Cherny, Joe C. Christian, Gail P. Jarvik, and Mariza de Andrade. 2007. "Heritability of Longitudinal Measures of Body Mass Index and Lipid and Lipoprotein Levels in Aging Twins." *Twin Research and Human Genetics* 10 (5): 703–11. doi:10.1375/twin.10.5.703.