Genetic variants and polygenic risk score associated with the HDL-c response to statin treatment: a GoDARTS study

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Introduction

- Statins mainly act on the reduction of low-density lipoprotein-cholesterol (LDL-C) levels.[1]
- Studies have shown that statin therapy also helps in improving high-density lipoprotein-cholesterol (HDL-c) levels up to 10-15%. [2]
- Inter-individual variation in HDL-c response to statins therapy could be partially explained by genetic variation.
- A recent meta analysis suggested only *CETP* locus for with common genetic variants that influence HDL-C response to statins.[3]
- Global Lipids Genetics Consortium (GLGC) 2013, has identified 80 genetic variants associated with HDL-c levels.[4]

Study Objectives

- To investigate genetic variants associated with the HDL-c response to statin treatment in GoDARTS cohorts
- To construct and assess the effect of a polygenic risk score (PRS) for HDL-c response in the study population

Study Methodology

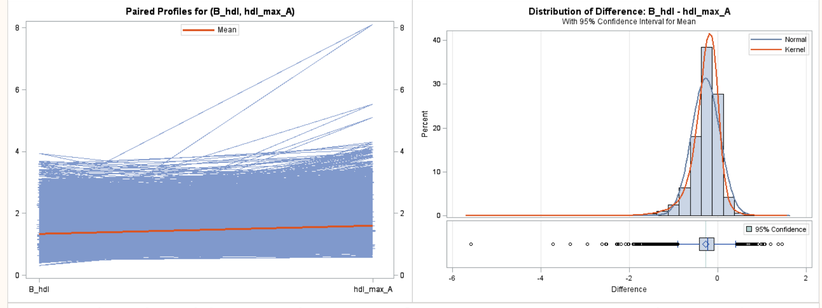
Study population and sample size	• 10,633 statin users in GoDARTS cohorts
Inclusion criteria	• At least, one off treatment HDL-c level and at least one on-treatment level
Exclusion criteria	• Subjects with missing on- or off-treatment measurements
Study outcome	• Change in HDL-c (mmol/L) levels
Study predictor	• Polygenic risk score (Top 22 SNPs for HDL-c from GLGC 2013)

Results

Table 1: Difference between before and after HDL-c value (Paired T test)

N	Mean (SD)	Min	Max	t Value	P value
10,633	-0.27(0.32)	-5.58	1.46	-87.97	<0.0001

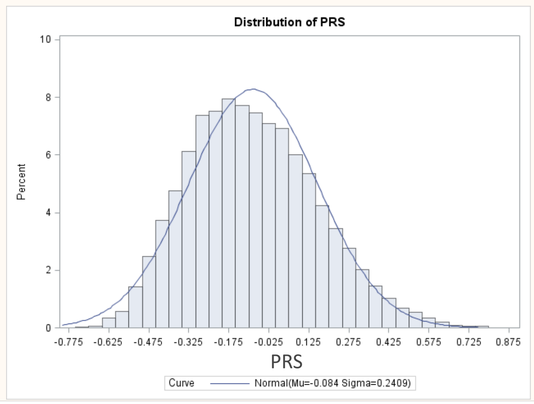
Results



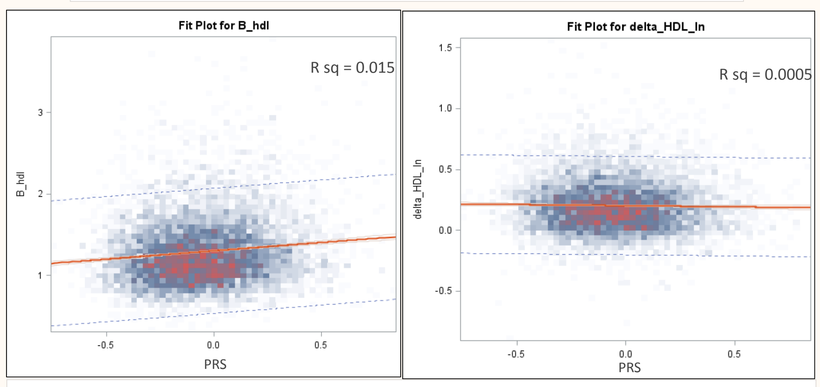
Graph 1 (a &b): Distribution of HDL-c response in the study population

Table 2: Variants associated with HDL-c response (Adjusted for age, sex, dose, Baseline HDL-c, treatment duration)

Parameter	Estimate	Standard Error	t Value	P value
rs247616 (*CETP*)	0.011	0.003	3.71	0.0002
rs1532085 (*LIPC*)	0.011	0.002	-4.08	<.0001



Graph 2: Normal distribution of Polygenic risk score



Graph 3 (a & b): Regression of Baseline HDL-c (a) and response of HDL-c (b) with Polygenic risk score

Table 3: Effect of PRS on baseline HDL-c (adjusted for age, sex) and HDL-c response (Adjusted for age, sex, dose, baseline HDL-c, treatment duration) (n = 8,271)

Outcome	parameter	Estimate	S E	P value	Adjusted R square
Baseline HDL-c	PRS	0.137	0.017	<0.001	0.08
HDL-C response	PRS	0.01	0.008	0.0175	0.28

- Statin induced elevation in HDL-c levels were (0.27±0.32; t-test p-value <0.001) observed (table 1; graph 1).
- Among all reported SNPs, rs3764261 (*CETP*), and rs1532085 (*LIPC*) were among few which significantly associated with raise in HDL-c levels (adjusted) (table 2).
- PRS has a significant effect on Baseline HDL-c levels (R square = 0.015) (table 3; graph 3).

Discussion and conclusion

- This study shows statins also helps to improve high-density lipoprotein-cholesterol (HDL-c) levels up to 20% in the study population.
- Individual genetic variants shows significant positive association with the HDL-c response after adjusting for phenotypic traits.
- Overall effect of PRS with HDL-c response is comparatively less then baseline HDL-c . This suggests that some gene variants differentially contribute to baseline HDL-c levels and HDL-c response.

Way forward

- Preliminary data suggested that HDL profile between the two population [Scottish (1.20±0.33) and India (1.04±0.23)] were significantly different (p value <0.001)[5]. Hence, genetic differences needs to be investigated.
- GWAS using Affymetrix, Illumina, and Broad (genetically adjusted) and meta-analysis will be carried out to find the novel loci in MDRF and GoDARTS data.
- Conditional GWAS will be carried to adjust for variants affecting purely baseline HDL-c levels.
- Discovered novel loci for real pharmacogenetic drug response will be used for polygenic risk score in the study population.

References

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5. INSPIRED WP1 – Unpublished data provided by MK Siddiqui

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