ARIC Manuscript Proposal #2186

PC Reviewed: 8/13/13 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

GO ESP Manuscript Proposal Form

INSTRUCTIONS: Please send proposal by e-mail to the ESP P&P Chairs James Wilson, Charles Kooperberg and the ESP P&P Coordinator Jenny Schoenberg
Date of Submission: Date of ESP GO P&P Approval:

I. ADMINISTRATIVE INFORMATION

1. On behalf of which approved ESP Project Team/Working Group is this proposal being submitted?
   Lipids Project team

2. Full Title of Proposed Manuscript:
   Working Title: Identification of novel triglyceride genes in a genetically heterogeneous family
   Requested Name of Resulting Writing Team (1-3 words): novel triglyceride genes

3. Investigator Information:

   a. Convener: Elisabeth Rosenthal
   Affiliation: UW
   E-Mail Address: erosen@uw.edu
   Junior Author Y/N: Yes

   b. Co-convener: Gail Jarvik
   Affiliation: UW
   E-Mail Address: gjarvik@medicine.washington.edu
   Junior Author Y/N: No

4. Names of Proposed ESP GO Writing Team members including affiliations and E-mail addresses.
   a. **I Elisabeth Rosenthal** attest that all Writing Team members listed below have reviewed and approved this manuscript proposal**.**

Name/Degree	Affiliation	E-Mail Address	Junior. Investigator	Author/Role Contribution	Author Position
Gail Jarvik	UW	gjarvik@medicine.washington.edu	no	Lab head	last
Elisabeth Rosenthal	Primary author	erosen@uw.edu	yes	Primary analyst	first
David R. Crosslin	UW, Jarvik lab	davidcr@uw.edu	yes	Statistical analyst	middle
Deborah A. Nickerson	UW	debnick@uw.edu	yes	Exomes	middle

(If more space is required, please attach an additional page with this information, Thank you.)

5. Names of proposed NON ESP GO Writing Team members including affiliations and E-mail addresses.
   a. I Elisabeth Rosenthal attest that all NON ESP GO Writing Team members have reviewed and approved this manuscript proposal.

Name/Degree	Affiliation	E-Mail Address	Junior Investigator	Author/Role Contribution	Author Position
Jane Ranchalis	UW, Jarvik Lab	janer@u.washington.edu	no	Wet lab	middle
John D. Brunzell	UW	jbrunzell@medicine.washington.edu	no	Collected patients	middle
Arno G. Motulsky	UW	agmot@u.washington.edu	no	Collected patients	middle
Ellen M. Wijsman	UW	wijsman@uw.edu	no	Statistical and computational support	middle
Amber Burt	UW	aaburt@uw.edu	no	Computational support	middle

(If more space is required, please attach an additional page with this information)

6. I Elisabeth Rosenthal agree to comply with the NIH Public Access Policy

II. SCIENTIFIC INFORMATION

1. Scientific Rationale (please be specific and concise)
We are verifying an association between SLC25A40 variants and triglyceride level. We have found a novel variant that segregates with high triglycerides in a large family. Since our variant is novel, we would like to verify that the gene has a relationship with triglyceride levels.

2. Objectives and Plan (with timeline)

a. Main Question / Hypotheses
We hypothesize that rare (q<0.001) high GERP (>5) SNVs in SLC25A40 associate with high triglycerides.

b. Study Populations
We use all individuals that have measured triglycerides. This includes the following cohorts:
Broad:EOMI contains ESP cohorts PennCATH, TRIUMPH, and Cleveland Clinic
HeartGO contains ESP cohorts ARIC, CARDIA, CHS, FHS, JHS and MESA
WHISP contains ESP cohort WHI

c. Main Statistical analysis plans and methods
We use linear models, and adjust for age, sex, and race.

Added 7/12/13:

Methods using the NHLBI GO ESP data:

We sought confirmation of association with TG for any gene containing a novel SNV that remained associated with the trait after genotyping of the full pedigree. Using TG data from unrelated individuals in the PennCATH, TRIUMPH, Cleveland Clinic, ARIC, CARDIA, CHS, FHS, JHS, MESA and WHI cohorts in the dbGaP posted ESP data {{840 NHLBI GO Exome Sequencing Project (ESP)}} March 2013, (see supplementary material), we combined all rare (MAF < 0.5%) missense, nonsense and splice sites with GERP>4.8 into a single genotype factor (1=presence of a minor allele and 0=absence of all minor alleles) in individuals with measured TG. We used a GERP cutoff of 4.8 since this is the 75th percentile for GERP of all identifiable LDL-raising pathogenic SNPs in *LDLR* {{826 Kent,W.J. 2002; 827 Davydov,E.V. 2010; 828 Cooper,G.M. 2005; 829 Sherry,S.T. 2001}} (data not shown). We assumed that individuals missing genotypes at these rare SNVs were non-carriers. We performed this two-sided whole gene test using a linear model for log(TG) on the 0, 1 genotype factor, using the package R {{786 R Core Team 2012}} with and without adjusting for race (first 3 principal components or ethnic group), age, and sex.

d. Location of Analysis
UW

3. Sources of Data to be used – Provide rational for any data
Broad:EOMI contains ESP cohorts PennCATH, TRIUMPH, and Cleveland Clinic
HeartGO contains ESP cohorts ARIC, CARDIA, CHS, FHS, JHS and MESA
WHISP contains ESP cohort WHI

4. List of Sources
Subset of ESP6800 data release that have measured triglycerides

5. Aggregate summary data to be generated by investigator of studies selected above.
Table including age, sex and race, broken down by quantile in log(triglyceride).

6. Conflict of Interest:
Do you or any member of your WG/PT or PWG intend to patent and process? Y/N: NO

7. I Elisabeth Rosenthal affirm that this proposal has been reviewed and approved by the Lipids Project team Project Team and by all listed investigators, I further affirm that the project team conveners, Leslie Lange and Russ Tracy, concur in this statement.

8. References (Limit 15)

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