ARIC Manuscript Proposal #2373

PC Reviewed: 5/13/14                        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?

   Early-Onset Myocardial Infarction (EOMI)

   (This is the name of the already existing PT/WG that has approved this proposal, not the writing team that will form upon approval)

2. Full Title of Proposed Manuscript:

   Inactivating mutations in NPC1L1 and protection from coronary heart disease

   Requested Name of Resulting Writing Team (1-3 words):

   ESP-EOMI NPC1L1 LOF

3. Investigator Information:
   a. Convener: Sekar Kathiresan
      Affiliation: Broad GO
      E-Mail Address: sekar@broadinstitute.org
      Junior Author Y/N: No
   b. Co-convener:
      Affiliation:
      E-Mail Address:
      Junior Author Y/N:

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

<table>
<thead>
<tr>
<th>Name/degree</th>
<th>Affiliation</th>
<th>E-Mail Address</th>
<th>Junior Investigator</th>
<th>Author/Role Contribution</th>
<th>Author Position</th>
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<td>No</td>
<td>Supervisory</td>
<td>Last</td>
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   Additional ESP Members and co-authors are:
   Muredach Reilly
   Shamil Sunyaev
   Goncalo Abecasis
   Russell Tracy
   Rebecca Jackson
   Sharon Cresci
   John Spertus
   Daniel Rader
5. Names of proposed NON ESP GO Writing Team members including affiliations and E-mail addresses.
   a. I ___________ attest that all NON ESP GO Writing Team members have reviewed and approved this manuscript proposal.

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

6. I __Sekar Kathiresan________ agree to comply with the NIH Public Access Policy

II. SCIENTIFIC INFORMATION
1. Scientific Rationale (please be specific and concise)

Ezetimibe lowers plasma low-density lipoprotein (LDL) cholesterol by inactivating its target gene, Niemann-Pick C1-Like 1 (NPC1L1); however, it is unknown if ezetimibe therapy reduces risk for coronary heart disease (CHD). Human mutations that inactivate a gene encoding a drug target can mimic pharmacological action of a drug and can be used to infer the probable clinical efficacy of that drug.

2. Objectives and Plan (with timeline)
   a. Main Question / Hypotheses
      1. Are loss of function mutations in NPC1L1 associated with lower risk for CHD?
      2. Are loss of function mutations in NPC1L1 associated with lower LDL?
   b. Study Populations
      The study consists of two phases: discovery and replication.
      For the discovery study we will analyze NPC1L1 sequence from existing exome sequences generated through ESP EOMI and the Myocardial Infarction Genetics Exome Sequencing Consortium (MIGen ExS). These exomes formed the main dataset of the ESP EOMI working group manuscript (Do et al., Nature, 2014 In Press).
      For the replication study, we will analyze NPC1L1 sequence from 1) additional exome sequences generated through MIGen ExS and 2) exome sequences of JHS participants sequenced through ESP, T2D Genes, and MH-GRID. We will also use exome chip genotypes generated as part of the Myocardial Infarction Genetics Exome Array Consortium (MIGen ExA).
   c. Main Statistical analysis plans and methods
      We will test for association with CHD and NPC1L1 loss of function mutations using a Mantel-Haenszel meta-analysis. We will also test for association with carrier status for cholesterol levels using linear regression.
   d. Location of Analysis
      Broad Institute

3. Sources of Data to be used – Provide rational for any data

   Cases and Controls from ESP EOMI. As detailed above we will also use additional exomes sequenced as part of the Myocardial Infarction Genetics Exome Sequencing Consortium (MIGen ExS) and from JHS along with exome chip genotypes generated as part of the Myocardial Infarction Genetics Exome Array Consortium (MIGen ExA).

4. List of Sources
   N/A

5. Aggregate summary data to be generated by investigator of studies selected above.
   N/A

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 __Sekar Kathiresan____ affirm that this proposal has been reviewed and approved by the __EOMI____ Project Team and by all listed investigators, I further affirm that the project team convener, __Christopher O’Donnell____, concurs in this statement.

8. References (Limit 15)