**eMERGE Network Proposal for Analysis**

Project/Manuscript Concept Sheet

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| **Submission Date** | April 7th 2015 |
| **Project Title** | Investigation of CETP SNPs with LDL-C, BMI and risk of T2D |
| **Tentative Lead Investigator (first author)** | Brendan J Keating |
| **Tentative Senior Author (last author)** | Marylyn D. Ritchie |
| **All other authors** |  |
| **Sites Involved** | We would like participation from all eMERGE sites. |
| **Background / Significance** | Persons with specific *CETP* variants have lower LDL cholesterol levels and CHD risk, and CETP inhibitors are efficacious at reducing LDL cholesterol. Several compounds are in phase III clinical trials for clinical events.  Statins, the most widely used lipid lowering drugs increase the risk of type 2 diabetes (T2D).  We wish to investigate whether CETP inhibition will be free from effects on T2D risk. This will be conducted through a drug target Mendelian randomization analysis. We wish to use eMERGE data in conjunction with data from other large prospective cohorts in USA and Europe to bolster statistical power. |
| **Outline of Project** | 1. Stratify analyses into different ancestry datasets. . 2. Identify SNPs in *CETP* and +/- 50Kb from the locus 3. Investigate the association of SNPs with lipids, BMI through linear regression 4. Investigate the association of SNPs with risk of T2D through logistic regression 5. Repeat steps 3 and 4 in subgroups according to gender, age (< or >=60 yrs), BMI (<25, 25-30, >30), LDL-C tertiles, T2D status (where applicable) 6. Meta-analyse data with other datasets 7. Write-up results and publish paper |
| **Desired**  **Variables (essential for analysis**  **indicated by \*)** | T2D case-control status\*  Age at diagnosis for cases\*  Age\*  Sex\*  Race/ancestry (self-report compared with genetically derived ancestry from genotypic data to assess concordance [along with gender concordance assessment)  BMI\*  Smoking  Lipids\* |
| **Desired data** | Phenotype data is all that would be needed from the sites. We have the merged genotype imputed dataset. |
| **Planned Statistical Analyses** | Linear regression for continuous traits, on a per-allele model. Logistic regression for case-control outcome. Using per-allele model.  Subgroup analyses as per outline of plan (i.e. based on gender, age, BMI, LDL-C, DM status). |
| **Ethical considerations** | none |
| **Target Journal** | JACC or EHJ |
| **Milestones\*\*** | * Analysis completed by June 15 * 1st draft of manuscript by July 15 * 2nd draft of manuscript by Aug 15 * Submit by Sept 30th, 2015 |

**\*\*** This section should include: Timeline for completion of project, including approval, project duration, first and second draft of the paper and submission.