Rare Non-coding Variation Identified by Large Scale Whole Genome Sequencing Reveals Unexplained Heritability of Type 2 Diabetes: Trans-Omics for Precision Medicine (TOPMed) Program

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Current Status:
2020-09-28: Penultimate Draft MS received – undergoing expedited review
2020-10-05: Penultimate Draft approved by Steering Committee How to Proceed

BASICS

Penultimate Draft: Cover Note	
Submission not preceded by an approved paper proposal	○ It is a new meta-analysis that derives from a single "project" or "omnibus" proposal as part of a larger consortium of many cohorts in which CHS has agreed to participate and for which no new data are needed Parent Proposal: Omnibus: The NHLBI Trans-Omics for Precision Medicine (TOPMed) Program
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Location of analysis	local (not at CC)
Analysts	Jennifer Wessel (Indiana University)
CHS Working Group	
Consortium	○ TOPMed
Type of Study	Main |
Data/Analysis type	○ Events ○ Meta-analysis / Pooled analysis
Manuscript Keyword(s)	WGS | diabetes |

1. Assurances

This draft has been reviewed and approved by all coauthors	Yes
Is CHS correctly represented?	Yes
When data are used from ancillary studies, are they included and credited?	No
Do you or any member of your Writing Group intend to patent any process, aspect or outcome of these analyses?	(no response)
Are these analyses to involve a for-profit Corporation?	(no response)
If genetic data are used, does the paper include the required genetic exclusions statement?	No genetic data were used in these analyses
Is CMS data used?	No
If CMS data were used, does the paper include cell sizes greater than 10?	No CMS data were used in these analyses
I included the current (rev. 2018) CHS grant & contract numbers in the funding acknowledgement	Yes
As part of the CHS data use agreement,	Yes

I will update this record when my manuscript has been accepted by a journal	
In accordance with the NIH public access policy, I will submit any resulting publication to PubMed Central & update this record with its PMCID within 6 month	Yes

Abstract

Historically, research on the genetic etiology of type 2 diabetes (T2D) has focused on common
variants in DNA regulatory regions with modest effects on risk1-3. For most of these, regulatory
activity is enriched in pancreatic islets and/or beta cells. Recent exome sequencing studies4-9
have identified rare variant associations with limited contributions to risk. We analyzed 9,639
individuals with T2D and 34,994 controls with whole genome sequence (WGS) data from diverse cohorts in the NHLBI's Trans-Omics for Precision Medicine (TOPMed) program, coupled with pancreatic islet regulatory annotation, to estimate the contribution of rare, noncoding
variants to T2D risk and discover novel associations. Rare, non-coding variants that are poorly captured by genotyping arrays or imputation panels contribute to the genetic component
of risk in the largest ancestry subset; in contrast, pancreatic islet regulatory elements contribute
only a small portion of this genetic risk. Subsequent rare variant association tests identified five
loci containing rare alleles in pancreatic islet regulatory elements, suggesting novel biological
mechanisms linking these variants to function. Our results support the substantial contribution of
rare, non-coding variation to the genetic architecture of T2D extending beyond a common
variant model for T2D and the known regulatory architecture of the pancreatic islets.

2. Review Method

Paper includes NHLBI author	No
Review method	Expedited – this is a meta-analysis (includes pooled) (1-2 weeks)

3. File

Uploaded Supplemental File(s)	T2D.TOPMed.Paper_.17SEP2020.pdf Description: Main Text T2D.TOPMed.Paper_.17SEP2020.SUPPLEMENTARY_NOTE.pdf Description: Supplement SUPPL.TABLES.15SEP2020.xlsx Description: Supp Tables

PUBLICATION STATUS

Publication	

ABSTRACT & PRESENTATIONS

PP manuscript proposal/penultimate manuscript vote

SC manuscript proposal/penultimate manuscript vote

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