Fine-Mapping Genetic Loci showing Novel Associations with Incident Cardiovascular Disease in Type 2 Diabetes

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Abstract

- Individuals with type 2 diabetes (T2D) are at a greater risk of developing cardiovascular disease (CVD)
- A genome-wide association study (GWAS) of individuals of varying ancestries diagnosed with T2D was conducted, which is uncommon in the literature
  - we identified **3 novel regions** of the genome containing variants that reached **genome-wide significance** ($P < 5\times10^{-8}$): **rs147138607, rs77142250, and rs335407.**
- The goal of this project was to use statistical fine-mapping to **identify the most likely causal genetic variants of incident CVD in patients with T2D in each novel region.**
- Ancestry-specific Z-scores and ancestry-specific pairwise linkage-disequilibrium were used to run fine-mapping software MsCAVIAR.
- **For rs147138607 and rs335407** regions, the 95% **credible sets included 21 and 38 variants**, respectively.
  - These results will help prioritize likely causal variants for functional follow-up
- Future fine-mapping work will include incorporating functional annotations, as well as running ancestry-specific analyses

Background

Incident CVD

First CVD event (ex. stroke) that occurs at least a year after diagnosis of T2D

Statistical Fine-Mapping

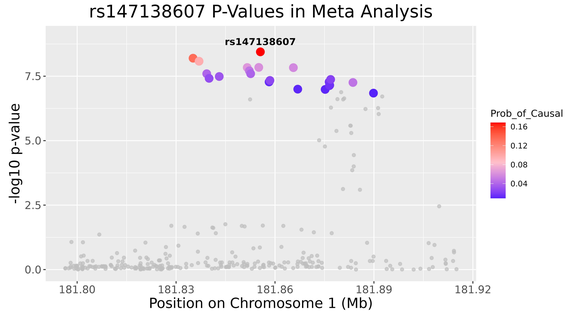
Use of summary statistics to assign probabilities of causality to variants

Pairwise Linkage Disequilibrium (LD)

Correlation between alleles of two variants

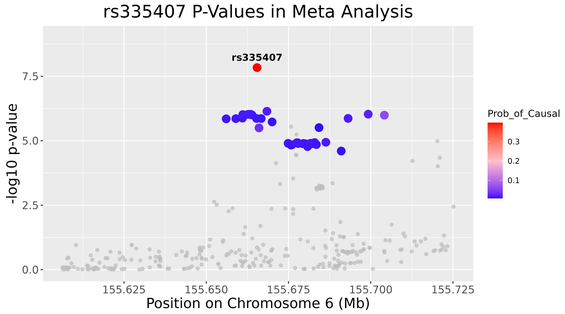
- We conducted a genome-wide association study (GWAS) of 48,138 individuals of varying ancestries (African, East Asian, European, Hispanic)
- This GWAS aimed to determine associations between single base pair genetic variants with incident CVD
- In this study, we identified 3 novel regions containing variants that reached genome-wide significance: rs147138607, rs77142250, and rs335407
  - If genome-wide significant ($P < 5\times10^{-8}$), we can say variant is associated with trait
- Statistical fine-mapping is one option for further analysis of GWAS results
  - MsCAVIAR utilizes pairwise linkage disequilibrium (LD) and z-scores from original GWAS

Results



Variant ID	*P*-value	Z-Score	Causal Probability
1:181855562:C:G (rs147138607)	3.6×10^{-9}	5.9	0.17
1:181835150:T:C	6.3×10^{-9}	5.8	0.13
1:181836968:D:I	8.3×10^{-9}	-5.8	0.10
1:181851578:T:C	1.5×10^{-8}	5.7	0.06
1:181855077:T:C	1.4×10^{-8}	5.7	0.06

Figure 1: Regional Plot of rs147138607 Region after Fine-Mapping. 294 variants were included, and colored points represent variants in the 95% credible set. Coloring based on probability of causality. Table above represents the top 5 variants in terms of causal probability.



Variant ID	*P*-value	Z-Score	Causal Probability
6:155665441:T:C (rs335407)	1.5×10^{-8}	5.7	0.40
6:155704129:A:G	1.0×10^{-6}	-4.9	0.06
6:155666036:A:G	3.2×10^{-6}	-4.7	0.04
6:155699223:A:C	9.3×10^{-7}	-4.9	0.02
6:155668440:A:G	7.2×10^{-7}	-5.0	0.02

Figure 2: Regional Plot of rs335407 Region after Fine-Mapping. 319 variants were included, and colored points represent variants in the 95% credible set. Coloring based on probability of causality. Table above represents the top 5 variants in terms of causal probability.

Conclusion

- **rs147138607** and **rs335407** had **highest probabilities of causality** in their respective regions, so they're the most-likely causal variants

Most-likely causal in Chromosome 1 Region: **rs147138607**

Probability of Causality: **17%**

Most-likely causal in Chromosome 6 Region: **rs335407**

Probability of Causality: **40%**

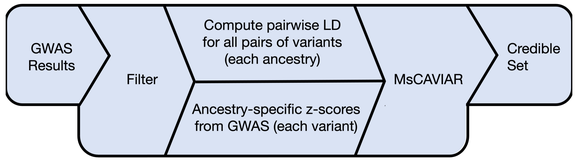
- Region containing **rs147138607** – more *broad* distribution of probabilities
  - Related to *higher* LD between variants
- Region containing **rs335407** – more *focused* distribution of probabilities
  - Related to *lower* LD between variants

- Both regions had **relatively large 95% credible sets**
  - Region containing **rs147138607** had **21 variants**
  - Region containing **rs335407** had **38 variants**
  - Smaller credible sets of 2-3 variants are favorable due to high cost of laboratory follow-up

- Large **credible set size** likely **due to limitations of analysis**, including
  - Exclusion of variants not present in all ancestries (in GWAS results)
  - Exclusion of variants with more than 2 alleles
  - Relatively small sample size

- **Future work** will attempt to address limitations by
  - Conducting **ancestry-specific analyses** – less variants excluded
  - Incorporating **functional annotations** – further reduce credible set

Methods



Filter: variant must be within 60 kilobases from lead (most associated) variant and must have Minor Allele Count (MAC) > 40 in ALL ancestries

References

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