Investigating the Utility of Pharmaceutically Informed, Partitioned Type-2 Diabetes Mellitus Polygenic Scores in the UK Biobank

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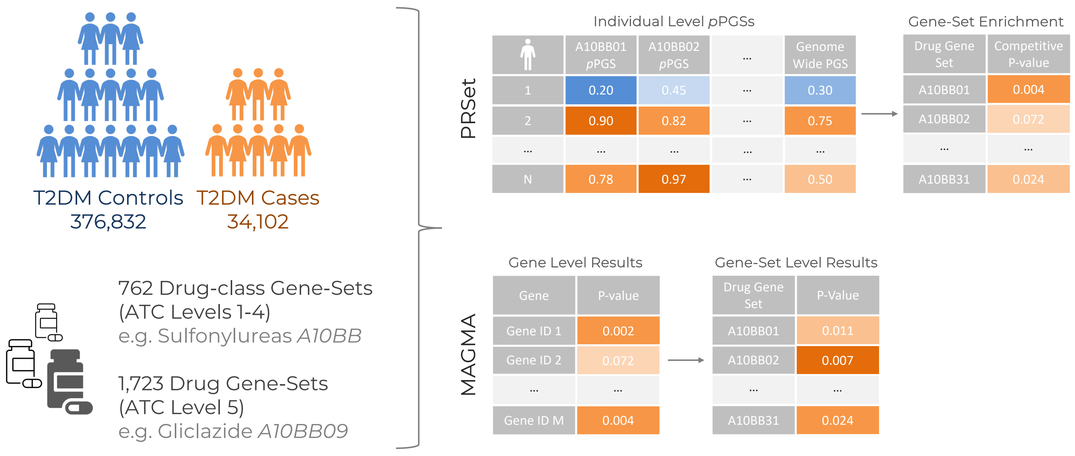
Introduction

Inspiration
- Cost of developing novel pharmaceutics is high, driven by high failure rates.
- MAGMA gene-set analysis: opportunities for drug repurposing in schizophrenia.[1, 2]
- MAGMA provides group level results, but no individual level information.

Goals
- Assess the utility of partitioned polygenic scores (*p*PGSs), generated using PRSet[3], for identifying enriched target-indication pairs, for Type-2 Diabetes Mellitus (T2DM).
- Compare results to existing pathway analysis methods.
- Suggest future directions for pharmaceutically informed *p*PGSs.



Methodology

UK Biobank (UKBB)
- Over 500,000 individuals, aged 40-69 at recruitment (2006 – 2010).
- Standard sample and SNP QC, removed relatives, filtered for European descent.
- Identified cases (n=34,102) and controls (n=376,832) for T2DM, removing diagnoses at ages under 35 to avoid Type-1 diabetes contamination.

Partitioned Polygenic Scores (*p*PGS)
- Generated *p*PGSs for T2DM using PRSet, and extension of PRSice-2.
- *p*PGSs based on 762 and 1,723,previously developed, drug-class and drug gene-sets.[2]
- Drug gene-sets mapped to WHO Anatomical Therapeutic Chemical (ATC) codes.
- Competitive *p*-value of association between *p*PGSs and T2DM status obtained via PRSet's competitive enrichment testing.
- Competitive *p*-values bounded by the permutations (M = 10,000) performed comparing *p*PGSs against randomized scores from background set.

$$P_{Competitive} = \frac{\sum_{m=1}^{M} I(P_{Null} < P_{Observed}) + 1}{M+1}$$

MAGMA Pathway Analysis
- MAGMA's competitive pathway analysis used as comparator to PRSet's enrichment.[1]
- Summary statistics for T2DM in UKBB, used by MAGMA, computed using Regenie.[4]
- Drug-class analysis differs from PRSet – tests compare drug-gene sets within one ATC class to those not present in that class.
- Provides additional gene-level results showing GWAS signal captured by each gene.

Results

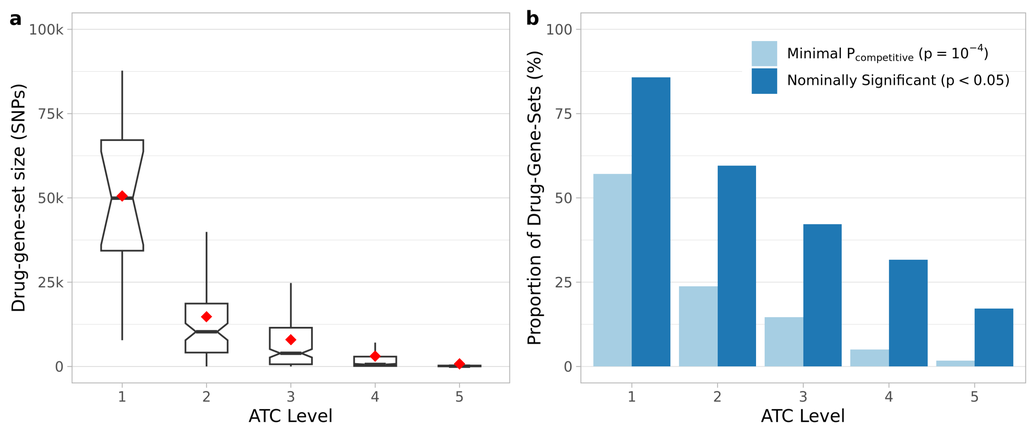


Figure 1. (a) Distributions of gene-set size across ATC levels. (b) Proportion of gene sets showing nominal or minimal competitive p-values from PRSet's competitive analysis.

- PRSet: No gene-sets reached statistical significance for enrichment due to bounded competitive *p*-value.
- 108 gene-sets reached minimal competitive *p*-value achievable ($p = 10^{-4}$).
- Inflation of competitive *p*-values for broader sets observed, despite PRSet's control for set size differences in its competitive testing methodology.
- Inflation could be due to increased residual LD in larger sets compared to the *null* set, as genes in pathways likely to have non-random gene proximities.

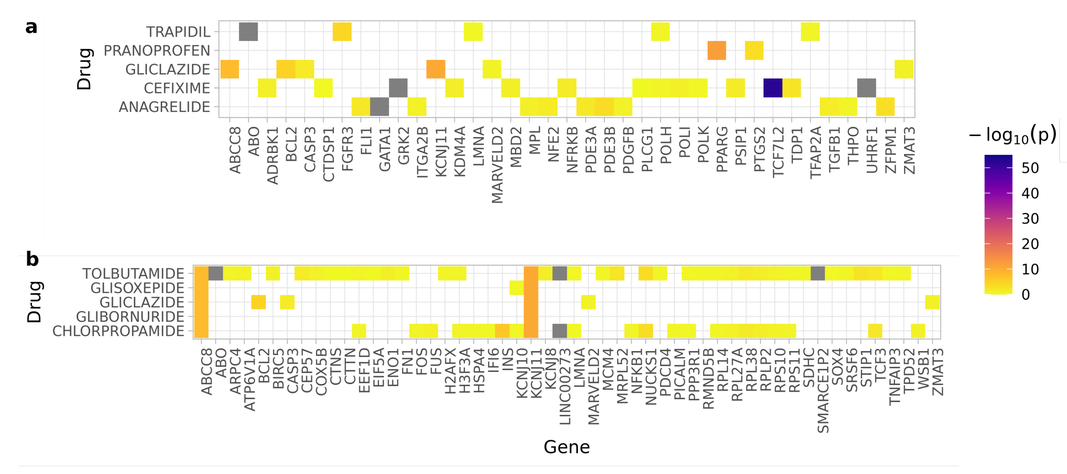


Figure 3. MAGMA gene-level association results for (a) enriched drug gene-sets and (b) drug gene-sets belonging to the sulfonylurea drug-class. Grey genes were missing from MAGMA analyses.

- MAGMA gene-level results highlight key genes driving pathway enrichment.
  - Gliclazide's enrichment is mainly due to two genes: ABBC8 and KCNJ11, which encode subunits of the sulfonylurea 1 receptor.
  - Variants in these genes are linked to increased sensitivity to sulfonylureas.[6]
- Sulfonylurea drug sets also derive enrichment from ABBC8 and KCNJ11 primarily.
- Pranoprofen primarily driven by PPARG: encodes the PPARγ transcription factor.
  - Increased expression is associated with increased risk of T2DM development.[7]
  - Main target of T2DM treatment drug-class thiazolidinediones.

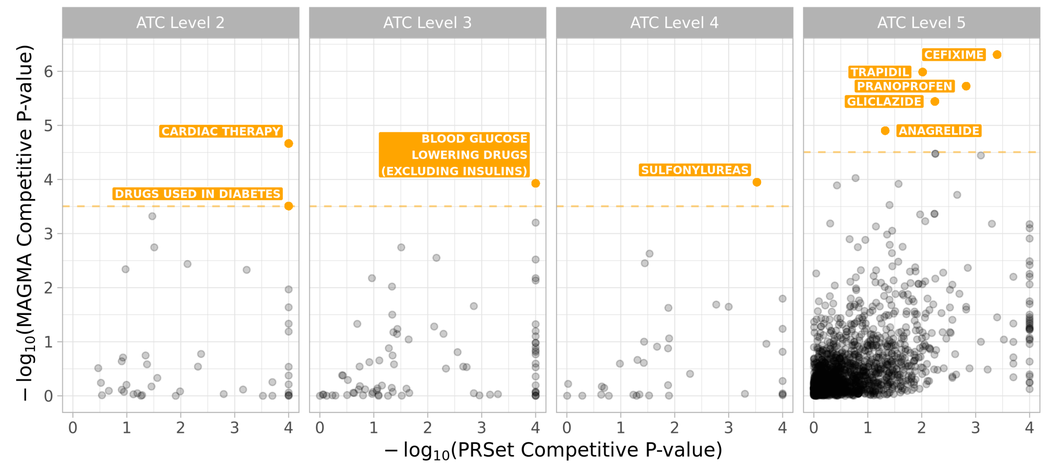


Figure 2. Comparison of PRSet and MAGMA competitive pathway analysis for drug/drug-class gene-sets. Bonferroni corrected significance thresholds are marked by red dashed lines.

- MAGMA's pathway analysis demonstrated greater specificity.
- 5 drug and 3 drug-class gene-sets with statistically significant enrichment for T2DM, including Sulfonylureas at ATC Level 4.
- One approved T2DM treatment gene-set enriched: Gliclazide, a sulfonylurea.
- Sulfonylurea drug class result is supported by existing literature, identifying insulin secretagogues as enriched for T2DM signal through similar methods.[5]
- Enriched sets from MAGMA do not achieve minimal p-value from PRSet, suggesting PRSet not supported by existing methods, in this context.

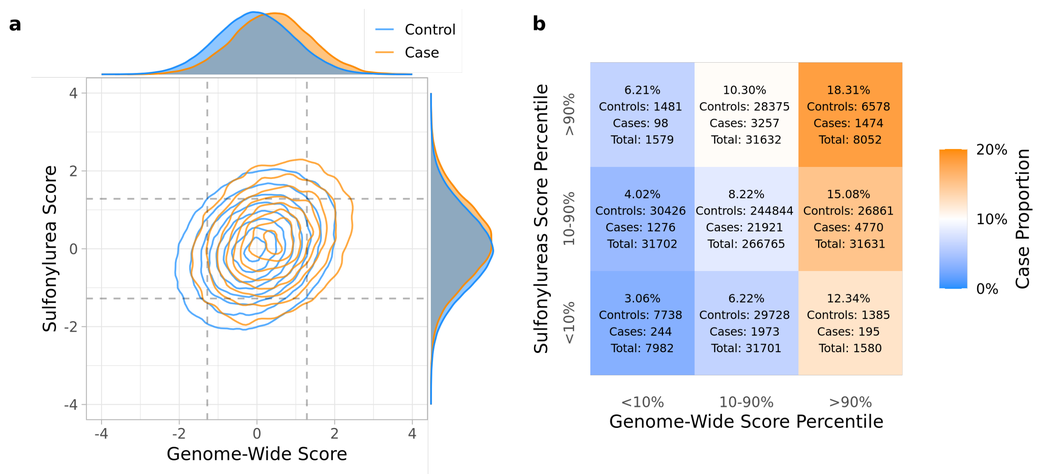


Figure 4. (a) Sulfonylurea and genome-wide T2DM PGS's distributions and (b) T2DM prevalence across sulfonylurea partitioned and genome-wide PGS (Z-scores) deciles.

- Some individuals exhibit uneven distribution of risk alleles across the sets, and when compared to the T2DM genome-wide PGS.
- Individuals in the top decile for both the sulfonylurea *p*PGS and genome-wide PGS were of higher risk for T2DM than those only in the top decile of the genome-wide score.
- Such *p*PGSs could be used to further stratify individuals with regards to T2DM clinically relevant outcomes, such as treatment response.

Conclusion

- PRSet competitive testing for enriched drug/drug-class gene-sets not supported by existing methods.
- Due to methodology of PRSet's competitive testing, PRSet may not be suitable for high-throughput enrichment analyses for discovery purposes.
- MAGMA gene level results point toward the clinical relevance for these gene-sets, and pharmaceutical *p*PGSs demonstrate an ability to capture genetic heterogeneity.
- No gene effect annotation in drug sets limits ability to infer directionality from *p*PGSs.
- Use of pharmaceutically informed *p*PGSs in further stratifying clinically relevant outcomes, or for improving on the predictive performance of the T2DM genome-wide PGS's for treatment response[8] remains for further investigation.

References

Acknowledgements & Conflicts of Interests

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