Integration of methylation QTL and enhancer-target gene maps with schizophrenia GWAS summary results identifies novel genes

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Introduction
Two directions for gene-based analysis in GWAS

- Constructing a powerful test based on the GWAS data itself
  - Sum test; SSU test; adaptive test (aSPU)

- Integrating external information
  - PrediXcan/TWAS: integrating eQTL data sets with GWAS individual data or summary results
  - “E + G”: integrating enhancer-promoter interactions

Goal

Develop a new gene based test by integrating external regulatory information to improve statistical power and enhance interpretability.
How does the enhancer-promoter interaction inform GWAS

- Enhancers: regions that help increase or enhance transcription
- May as far as 2 or 3 Mbp away from the gene
- GWAS risk loci are enriched in enhancers
- Recent biotechnological advances made enhancer-promoter interactions data available
How does the mQTL inform GWAS

- DNA methylation: epigentic; affect gene expression
- mQTL: locus associated with DNA methylation
- Genetic variation influences level of DNA methylation at regulatory regions and can module gene expression
- Some mQTL databases are publicly available

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Method
New method: “E + G + Methyl”

“E + G + Methyl”: integrates enhancer-target gene maps, mQTL databases, and GWAS summary results to identify significant and novel genes

- Use only mQTLs (and exclude other SNPs) located in enhancers, promoters, and coding (including introns) regions
- Apply some well known gene-based tests, such as SPU(1) and SPU(2).
New method “E + G + Methyl”

- Suppose that $Z_j = \hat{\beta}_j / SE_j$ is the Z-statistic for association between the GWAS trait and SNP $j$

- $SPU(1) = \sum_{j=1}^{p} Z_j$

- $SPU(2) = \sum_{j=1}^{p} Z_j^2$

- We use a reference sample (e.g. the 1000 Genome Project samples) to estimate linkage disequilibrium (LD) among the SNPs and thus the correlation matrix for $Z$
Results
Schizophrenia GWAS summary data

- SCZ is a chronic and severe brain disease; affects about 1% of the worldwide population
- Highly heritable (70%–85%)
- Only a few hundred loci have been identified; enriched in non-coding regions
- SCZ1: 8,832 cases and 12,067 controls;
  SCZ2: 36,989 cases and 113,075 controls

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“E + G + Methyl” identifies new significant and novel genes

Figure 1: Venn diagrams of the **significant genes** (left panel), and the **significant and novel** (right panel) genes identified by the different methods applied to the SCZ1 data

- novel gene: one that does not cover any GWAS risk variant within an 500 Kbp extension in the same dataset
Validation analysis of “E + G + Methyl” results

- Highly significant replication rates
  - ‘E + G + Methyl” with SPU(1) identified 10 novel genes in the SCZ1 data, of which 6 (60%) contained genome-wide significant SNPs in the larger SCZ2 data \((p = 9.6 \times 10^{-6})\) by the hypergeometric test

- Reported by other studies
  - Identified 22 significant and novel genes; 14 out of 22 \((p = 1.1 \times 10^{-14})\) have been reported by other studies
Adaptive test results

**Figure 2:** Venn diagrams of the **significant** genes (left panel), and the **significant and novel** (right panel) genes identified by the “E+G+Methyl” with different methods applied to the SCZ1 data.
Conclusion
Conclusion

- Propose a simple but powerful gene-base test by integrating enhancer-promoter interactions and mQTL data with GWAS summary results
- Will be most useful when the enhancers, especially those far away from a gene, contain trait-associated mQTLs.
- It is complementary to the current methods

Thank you!
Reference

