Integrating GWAS with omic data

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CCBR
Outline

- Introduction: problem
- Review: Transcriptome-Wide Association Study (TWAS)/PrediXcan
- Our method: (weighted) aSPU test.
- GWAS + gene expression: application to the Lipid data
- GWAS + EPI + Methylation: application to the SCZ data
- On-going: Mendelian randomization (MR) determining causal direction between two variables: LDL/HDL vs CAD.
Introduction

- Problem: to detect SNP-disease associations in GWAS (or sequencing studies).
  **Big question:** mechanistic interpretation?
- Approach: integrating GWAS data with eQTL data
  1) to boost power;
  2) to enhance interpretation.
- Motivation: DNA $\implies$ mRNA $\implies$ ...$\implies$ Disease.
  Known: many disease-associated SNPs are eQTL.
TWAS/PrediXcan: GWAS + eQTL

- Set-up: 2 independent data sets, one GWAS (main), one eQTL (smaller).
  - GWAS: SNPs, Y (disease);
  - eQTL: SNPs, X (gene expression).
- Conventional GWAS: $Y \sim SNP$.
- PrediXcan (Gamazon et al 2015, Nat Genet), TWAS (Gusev et al 2016, Nat Genet):
  1. eQTL: $E(X) = \text{SNPs'} \ast w \Rightarrow \hat{w}$;
  2. GWAS: 1) $\hat{X} = \text{SNPs'} \ast \hat{w}$; 2) $Y \sim \hat{X}$
- Why? why not $Y \sim X$?
  Biologically: genetically regulated component of gene expression (GReX);
  $X$ not available in the GWAS data, often.
Our views

- Statistically: (two-sample) 2SLS related to Mendelian randomization (MR); causal inference!

- Our **key** obs: PrediXcan/TWAS = weighted SPU(1)! weight each SNP $j$ by $\hat{w}_j$, then ...

- Why not use aSPU (or other more powerful tests)? (Xu et al 2017, *Genetics*; Su et al 2018, *AJHG*)

- Why not use other weights derived from other omic or endophenotypes? brain imaging for AD (Xu et al 2017, *NeuroImage*); enhancer-promoter interactions (EPIs) (Wu and Pan 2018, *Genetics*); EPIs + meQTL (Wu and Pan 2019, *BI*).
Lipid GWAS + eQTL

- Discovery data: a large 2010 Lipid dataset (Teslovich et al 2010, *Nat Genet*).
  - Summary stats of meta-analysis of 46 GWAS with \( n \approx 100,000 \) individuals;
  - Lipid traits: LDL, HDL, TG, TC; use LDL here.
- Validation data: a larger 2013 dataset (GLGC 2013, *Nat Genet*).
  - \( n = 188,577 \).
- Three eQTL datasets: NTR, YFS and METSIM;
  - extracted the (optimal) weights constructed by Gusev et al (2016);
  - containing 1264, 3555 and 2295 (and 1223 for a combined analysis) genes.
- As in Gusev et al (2016), for gene-based analysis, conservatively use
  - genome-wide significance level=0.05/8500=5.88E-6.
- Applied our aSPU and TWAS=SPU(1).
Table: The numbers of the significant genes identified by analyzing the 2010 lipid data. a/b/c indicate the numbers of (a) the significant genes; (b) the significant genes that covered a genome-wide significant SNPs in the 2010 lipid data; (c) the significant genes that covered a genome-wide significant SNPs in the 2013 lipid data.

<table>
<thead>
<tr>
<th>Trait</th>
<th>Test</th>
<th>NTR</th>
<th>YFS</th>
<th>METSIM</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL</td>
<td>aSPU</td>
<td>19/16/17</td>
<td>29/27/29</td>
<td>22/19/22</td>
<td>21/17/17</td>
</tr>
<tr>
<td></td>
<td>TWAS</td>
<td>16/14/15</td>
<td>25/22/24</td>
<td>19/15/19</td>
<td>20/16/17</td>
</tr>
<tr>
<td>LDL</td>
<td>aSPU</td>
<td>15/15/15</td>
<td>19/18/18</td>
<td>17/16/17</td>
<td>14/13/13</td>
</tr>
<tr>
<td></td>
<td>TWAS</td>
<td>8/7/8</td>
<td>10/9/9</td>
<td>7/7/7</td>
<td>7/7/7</td>
</tr>
<tr>
<td>TG</td>
<td>aSPU</td>
<td>17/16/17</td>
<td>33/30/32</td>
<td>15/14/14</td>
<td>20/19/19</td>
</tr>
<tr>
<td></td>
<td>TWAS</td>
<td>9/9/9</td>
<td>17/16/17</td>
<td>8/7/7</td>
<td>12/11/11</td>
</tr>
<tr>
<td>TC</td>
<td>aSPU</td>
<td>26/25/26</td>
<td>28/26/27</td>
<td>28/28/28</td>
<td>20/20/20</td>
</tr>
<tr>
<td></td>
<td>TWAS</td>
<td>15/14/15</td>
<td>18/16/17</td>
<td>15/14/15</td>
<td>14/13/13</td>
</tr>
</tbody>
</table>
**Figure**: Manhattan plots for the pooled results of aSPU and aSPU-O for traits HDL based on the 2013 lipid data.
Figure: Manhattan plots for the pooled results of aSPU and aSPU-O for traits LDL based on the 2013 lipid data.
Figure: Left: significant genes; right: significant and novel ones for "EPI+meQTL".
**Figure:** Left: significant genes; right: significant and novel ones.
Combined SPU(1) and SPU(2).
EPI prediction

- Ours: use DNA seq with two main contributions:
  1) only CNN;
  2) transfer learning: use all cell lines before cell line specific learning.
Our CNN

Figure: Our CNN architecture for EPI prediction.
Figure: AUPR for the six cell lines based on SPEID (red/bottom bars), our CNN (yellow/middle bars) and our CNN+transfer learning (orange/top bars).
Orienting the causal relation

Question: causal direction between X and Y?
X ⇒ Y, or Y ⇒ X?

Previous applications: gene expression ⇒ LDL (or SCZ)?

Example: LDL ⇒ CAD?
Statins; Mendelian randomization (MR) analyses.

Example: HDL ⇒ CAD?
Failed drug trials; MR analyses: inconclusive.

Example: Education level ⇒ AD?
A *Lancet* Commission (Livingston et al 2017): possible to prevent about 35% of dementia by controlling nine risk factors: education to a maximum of age 11-12 years, midlife hypertension, midlife obesity, hearing loss, late-life depression, diabetes, physical inactivity, smoking, and social isolation.
Genetics-based methods

▶ *Using genetic data to strengthen causal inference* ... (Pingault et al 2018, *Nat Rev Genet*).

▶ Use SNPs as anchors/instrumental variables (IVs) (Schadt et al 2005, *Nat Genet*; Chen et al 2007, *Genom Biol*; ...).

SNPs $\rightarrow$ ...; not the reverse!

SNPs: somewhat randomized.

take advantage of many existing large-scale GWAS!

▶ Mediation analysis:

Causal inference test (CIT) (Millstein et al 2009, *BMC Genet*)

Limitations: 1) require data (SNP, X, Y);

often have two samples: (SNP, X), (SNP, Y).

2) less robust to measurement errors.

▶ MR: Steiger’s test (Hemani et al 2017, *PLOS Genet*)

Theory: If SNP $\rightarrow$ X $\rightarrow$ Y, then $|\rho_{gX}| > |\rho_{gY}|$!

Main idea: test their difference!

Limitation: based on a single SNP, thus low statistical efficiency and low robustness! —–our task here!

▶ Others: Pickrell’s (2016, *Nat Genet*); bi-directional MR...
Our method

- Motivation: extending MR Steiger’s method from using a single SNP to multiple SNPs.
  1) multiple correlated SNPs in a locus;
  2) multiple independent loci.

- Theory: If SNP $\rightarrow X \rightarrow Y$, then $\rho_{Yg} = \rho_{Xg} \rho_{YX}$. 
  $\frac{\rho_{Yg}}{\rho_{Xg}} = \rho_{YX} := K, |K| < 1$, independent of $g$. 
  Similarly, if SNP $\rightarrow Y \rightarrow X$, then ...

- Limitation: cannot distinguish $X \leftarrow SNP \rightarrow Y$

- Main idea: combining multiple estimates $r_{Yg}/r_{Xg}$ across $g$’s...
  1) one locus: GLSE;
  2) multi-loci: IVW (meta-analysis).
Example: LDL/HDL vs CAD

  Reference panel: 489 individuals of EA in the 1000 Genomes Project.
- Partition the genome into 1703 (approximately) independent loci (Berisa and Pickrell 2016, *Bioinformatics*).
- Consider 8 (or 4) indep loci significant for both LDL (or HDL) and CAD (at $p < 5E-6$).
- In each locus, pruned out highly correlated SNPs with $|r| > 0.8$. 
LDL vs CAD: Locus 1

**Figure:** LDL vs CAD locus 1.
LDL vs CAD: Locus 6

![LDL/CAD 5e−06 scatter plot](image)

![CAD/LDL 5e−06 scatter plot](image)
LDL vs CAD: all 8 loci
LDL vs CAD: 7 loci
HDL vs CAD: all loci

**HDL/CAD, 5e−6**

**CAD/HDL, 5e−6**

Figure: LDL vs CAD in all 8 loci.
Estimating causal effects

- MR: using SNPs as IVs. IV assumptions:

\[
\begin{align*}
SNP & \rightarrow X \quad \text{---} \rightarrow Y \\
& \quad \rightarrow U
\end{align*}
\]

- With a valid IV: \( \beta_{YX} = \beta_{Yg}/\beta_{Xg} \).
Wald ratios: \( \hat{\beta}_{Yg}/\hat{\beta}_{Xg} \) for \( g = 1, 2, ... \)
IVW (meta-analysis for multiple indep SNPs).

- More generally,
  \[
  \hat{\beta}_{Yg} = \beta_{YX}\hat{\beta}_{Xg} + \epsilon_g; \text{ IVW, PS (Zhao et al 2018)}
  \]
  \[
  \hat{\beta}_{Yg} = \beta_0 + \beta_{YX}\hat{\beta}_{Xg} + \epsilon_g; \text{ Egger reg}
  \]
  \[
  \hat{\beta}_{Yg} = \beta_{0g} + \beta_{YX}\hat{\beta}_{Xg} + \epsilon_g, \beta_{0g} \sim iid \ N(0, \tau^2); \text{ APS/RAPS}
  \]

- Alternatively, use (weighted) median or mode of the Wald ratios (\( \hat{\beta}_{Yg}/\hat{\beta}_{Xg} \)'s).
On-going ...

- More applications:
  LDL/HDL vs CAD: larger datasets;
  brain imaging ROIs $\rightarrow$ AD?
- Co-localization testing
- Fine mapping
- TWAS/2SLS and MR: accounting for SNPs as invalid IVs
- Rare variants (RVs)
- ......
http://www.biostat.umn.edu/~weip
Code: http://www.biostat.umn.edu/~weip/prog.html
R packages aSPU, highmean, GLMaSPU, GEEaSPU, POMaSPU, MiSPU; TLPglm; ...; all on CRAN.
Websites with example code:
www.wuchong.org/IWAS.html
www.wuchong.org/TWAS.html

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Thank you!