Genomic Privacy Challenges when Sharing Quantitative Trait GWAS Results

Hae Kyung Im

THE UNIVERSITY OF CHICAGO

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Genomic Data Surge Since First Draft of Human Genome

- Biomedical research revolutionized by massive amounts of genomic data
- Huge potential for new discoveries
- "Few blockbuster new cures" (NYTimes)
- For full advantage, broad sharing of data and results is needed
- However, privacy of study participants has to be protected

Challenges in Sharing Genomic Results

- Summary statistics in large studies considered safe to publish
  proportion of females vs. males,
  average LDL cholesterol levels, etc.
- Genome wide association studies GWAS
  - for millions of SNPs
    differential mutations frequencies in cases vs. controls are generated
- Frequency of mutations in cases and controls used to be publicly available

Forensic Study Revealed Vulnerability

- Forensic application - Homer et al (2008) Plos Genetics
- Efficiency of new genotyping chips in forensic application
  - DNA sample from crime scene
  - DNA from suspect
  - Determine whether suspect's DNA is part of the sample

	Id 1	Id 2	Id 3	Id 4	Sample	Popul	Suspect
SNP 1	1	2	0	0	0.75	1.10	0
SNP 2	1	0	0	1	0.50	1.25	1
	...	...	...	...	...	...	...
SNP M	1	0	1	2	1.00	1.50	2

- Implication for GWAS results
- NIH withdrew public access to aggregate results

Quantitative Trait GWAS - What Are the Risks of Sharing?

- Quantitative Trait GWAS
  - $Y_i = \alpha_j + \beta_j X_{i,j} + e_i$
  - $\hat{\beta}_j = \left(\tilde{\mathbf{X}}_j' \tilde{\mathbf{X}}_j\right)^{-1} \tilde{\mathbf{X}}_j' \tilde{\mathbf{Y}}$
- My colleagues wanted to publish regression coefficients for studies in dbGaP
  but wanted a mathematical proof that re-identification was not possible

Betas and Genotype Are Known

$\hat{\beta}_1$	$X_{I,1}$
$\hat{\beta}_2$	$X_{I,2}$
$\vdots$	$\vdots$
$\hat{\beta}_M$	$X_{I,M}$

Average the product

$$\frac{1}{M}\sum_{j=1}^{M}\hat{\beta}_j X_{I,j}$$

Testing the Average Statistic

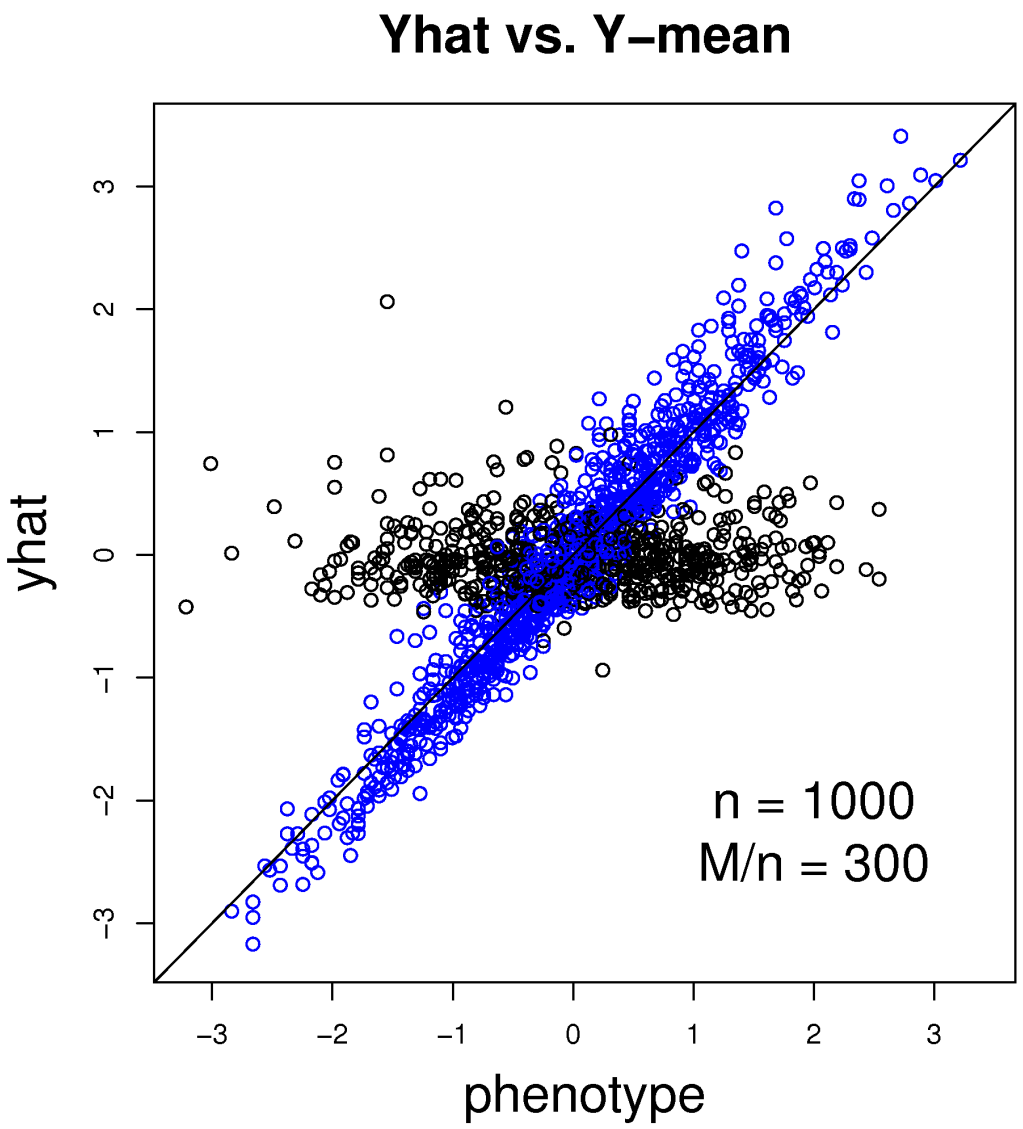
- Dataset from The Genetics of Kidneys in Diabetes Study long-term Type 1 diabetes adults
- phenotype: rank normalized cholesterol level
- Random sample of 1000 individuals
- Remaining 600 used as reference
- using only the 1000 sample ran GWAS

$$\hat{\beta}_1, \hat{\beta}_2, ..., \hat{\beta_M}$$

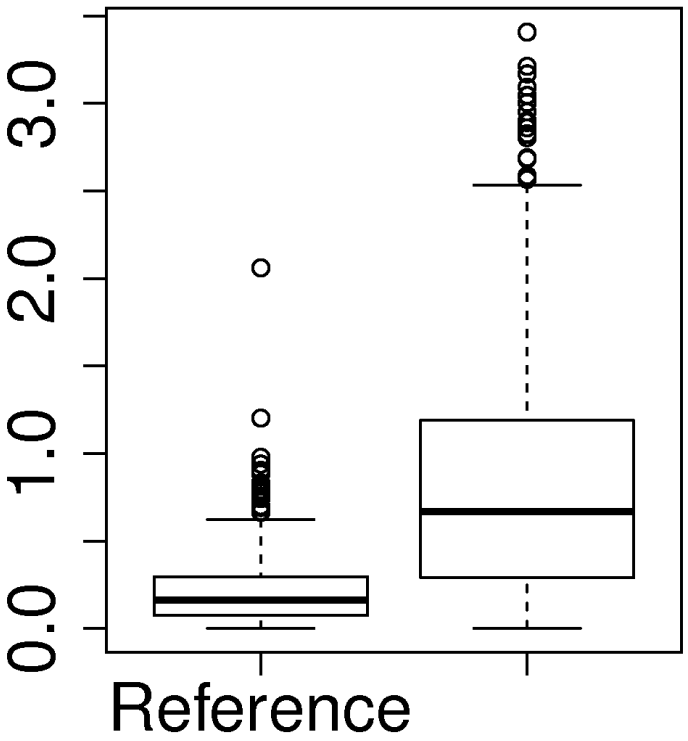
- computed the statistic for all 1600

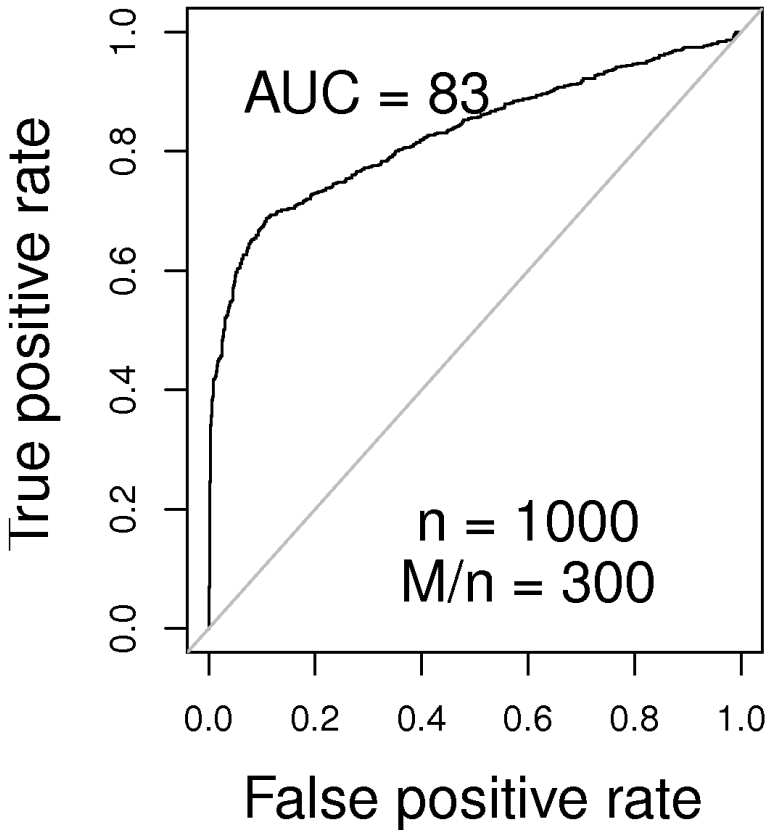
$$\text{Yhat}_I = \frac{1}{M} \sum_{j=1}^{M} \hat{\beta}_j X_{I,j}$$

$\hat{Y}$ as predictor of Y - GoKinD data



$\hat{Y}$ distribution and performance - GoKinD data





$\hat{Y}$ Statistics

$$\hat{Y}_I = \frac{n}{M} \sum_{j=1}^{M} \hat{\beta}_j (X_{I,j} - \hat{X}_j)$$

M	# of SNPs
n	# of individuals in the test sample
$X_{I,j}$	allelic dosage of individual I at SNP j
$\hat{X}_j$	estimated mean using the reference group
$\hat{\beta}_j$	estimated β for $Y_i = \alpha_j + \beta_j X_{i,j} + e_i$

Conditional Distribution of $\hat{Y}$

$$
\begin{aligned}
\mathbb{E}\ \hat{Y} \mid X_I, Y_I, \text{in} &\approx (Y_I - \mu) \\
\mathbb{E}\ \hat{Y} \mid X_I, Y_I, \text{out} &\approx O_p\left(\frac{n}{M}\right) \\
\text{Var}(\hat{Y}) \mid X_I, Y_I, \text{in} &\approx \sigma^2 \frac{n}{M} \\
\text{Var}(\hat{Y}) \mid X_I, Y_I, \text{out} &\approx \sigma^2 \frac{n}{M}
\end{aligned}
$$

Power of the Method

$$\text{power} \approx \Phi\left(\frac{|Y_I - \mu|}{\sigma}\sqrt{\frac{M}{n}} - z_{\alpha/2}\right)$$

α: type 1 error

For comparison, when frequencies were known

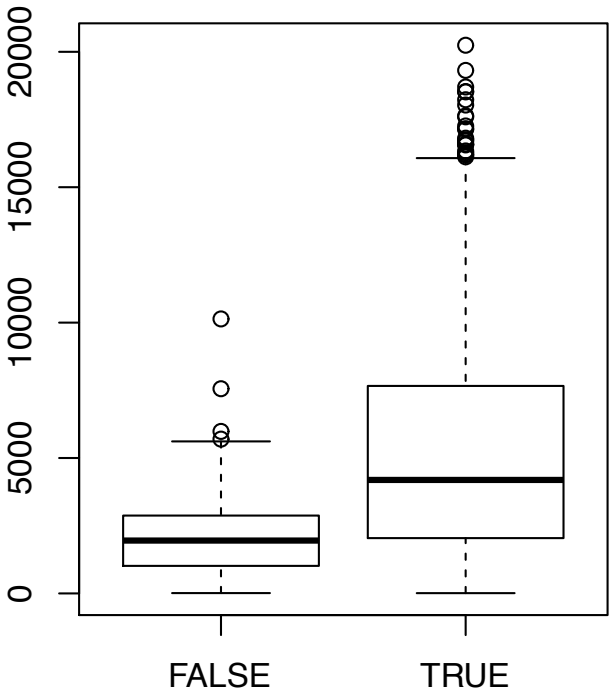
$$\text{power} \approx \Phi\left(\sqrt{\frac{M}{n}} - z_{\alpha}\right)$$

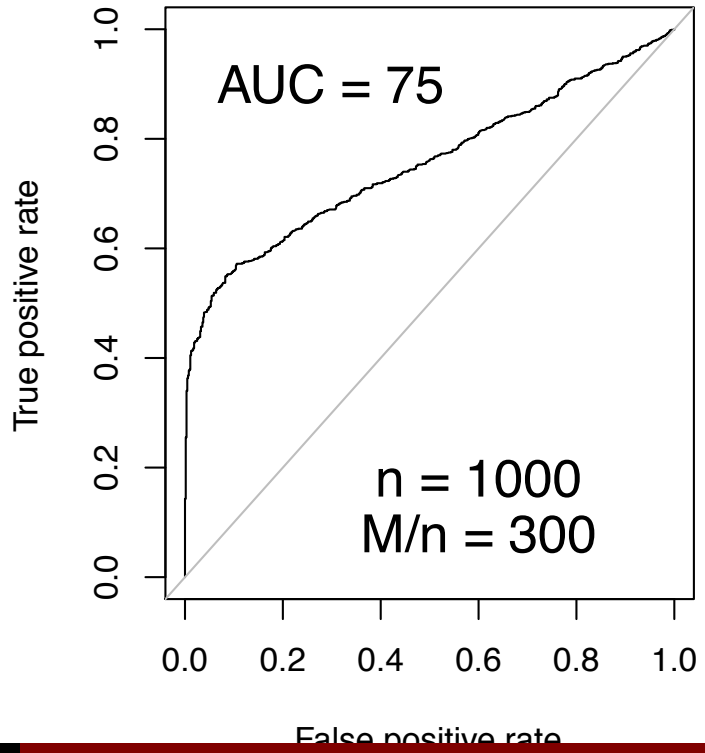
for 5%, 90% power, for $Y_I = \mu + \sigma$

$$13 = \frac{M}{n}$$

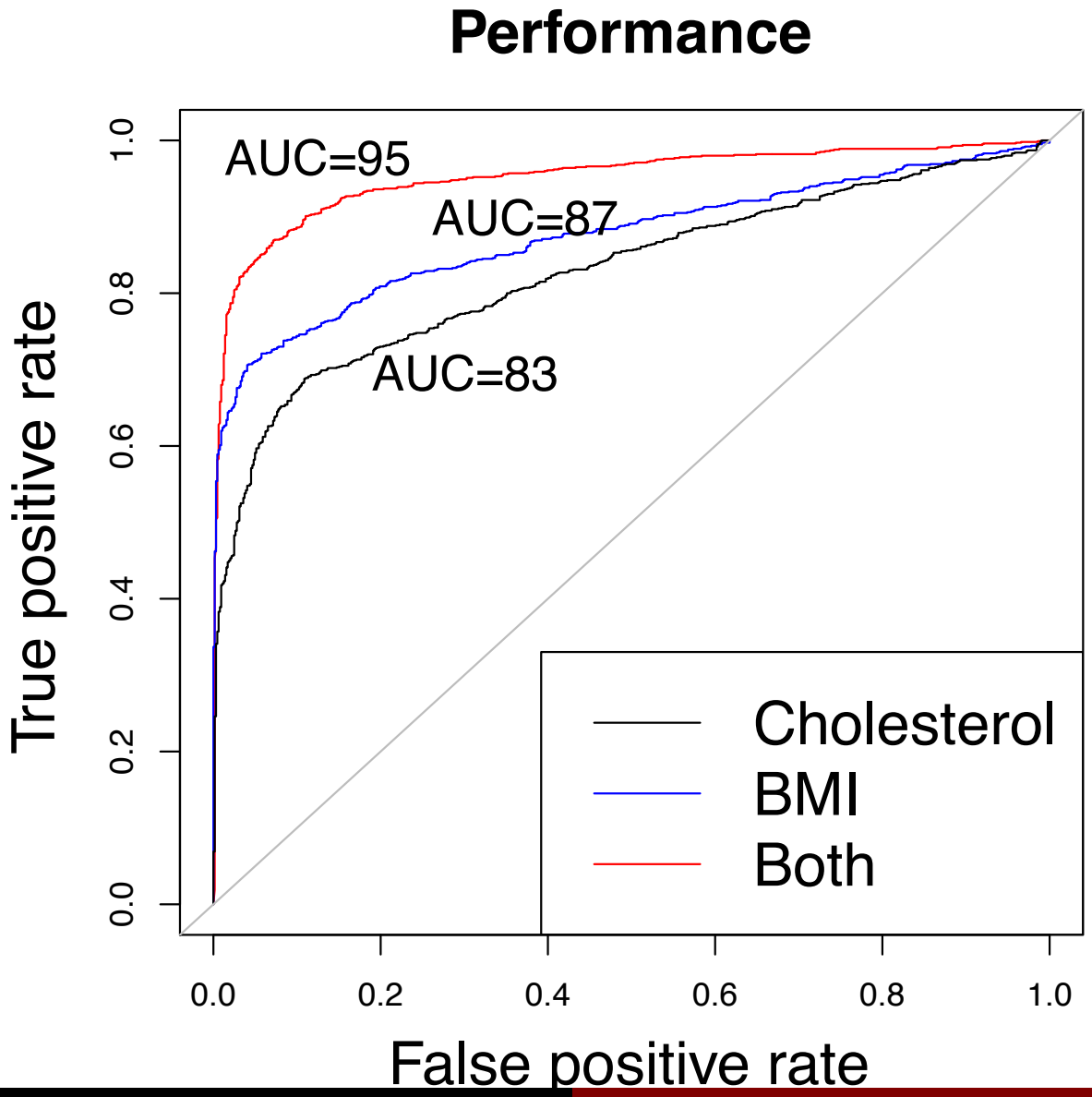
What if Only Direction of Effects Are Known

$$\hat{S} = \sum_{j=1}^{M} \text{sign}(\hat{\beta})\text{sign}(X_{ij} - \hat{X}_j)$$





Performance Improves with Multiple Phenotypes



Summary

- Showed that aggregate results from quantitative GWAS can reveal individual's participation and phenotype
- Computed power of the identification method
- Determined that the direction of effects contains most of the individual's information
- Established that identification becomes more accurate when results from multiple phenotypes are combined
- Thus, there is need to develop data sharing strategies that protect participant's privacy but also facilitate access to data

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Data Sources

GoKinD NIDDK dbGaP Study

Accession: phs000088.v1.p1

IBD NIDDK dbGaP Study

Accession: phs000130.v1.p1

Im, Hae Kyung, Eric R Gamazon, Dan L Nicolae, and Nancy J Cox. 2012. On Sharing Quantitative Trait GWAS Results in an Era of Multiple-Omics Data and the Limits of Genomic Privacy. American Journal of Human Genetics 90 (4): 59198. doi:10.1016/j.ajhg.2012.02.008.