

# Data-adaptive SNP-set-based Association Tests of Longitudinal Traits

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- Longitudinal data analysis strategy in GWAS

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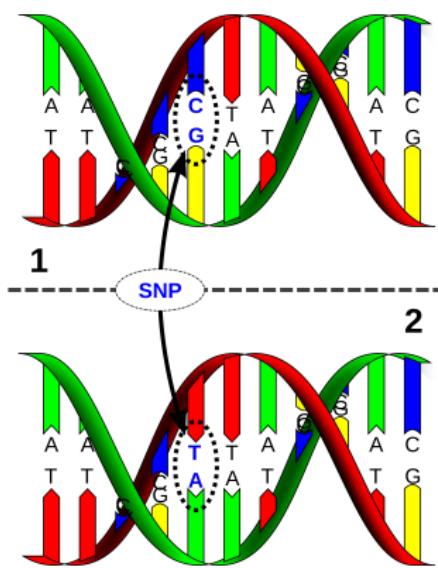
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# Introduction to Genome-wide association study (GWAS)

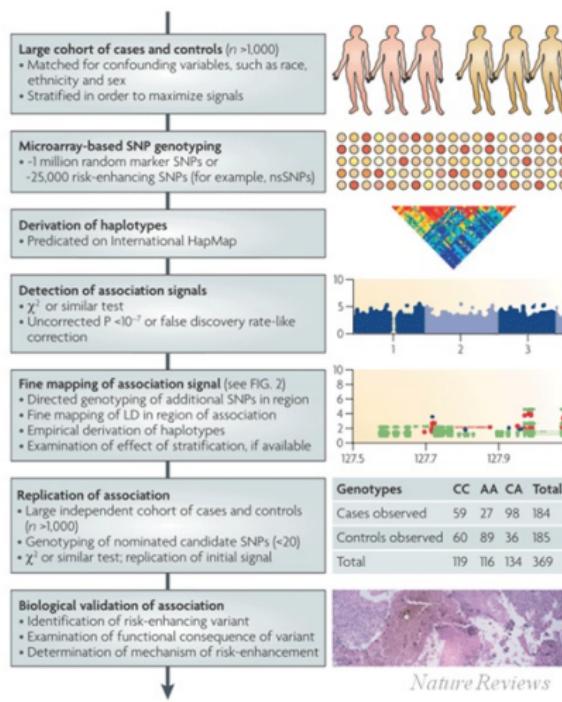
## What is SNP?



A Single Nucleotide Polymorphism (SNP) is a DNA sequence variation occurring commonly within a population (e.g. 1%) in which a single nucleotide A, T, C or G in the genome (or other shared sequence) differs between members of a biological species or paired chromosomes.

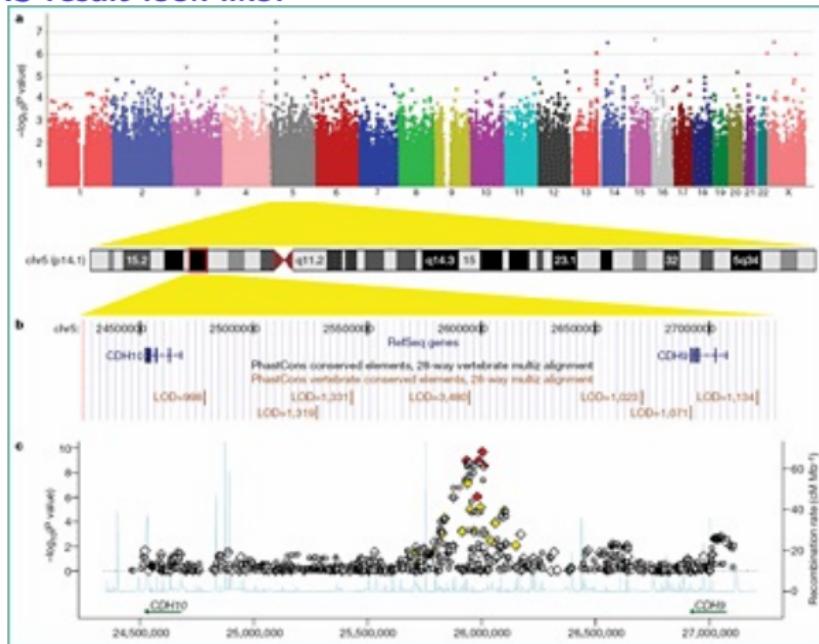
# Introduction to GWAS

## A flowchart of GWAS



# Introduction to GWAS

How does GWAS result look like?

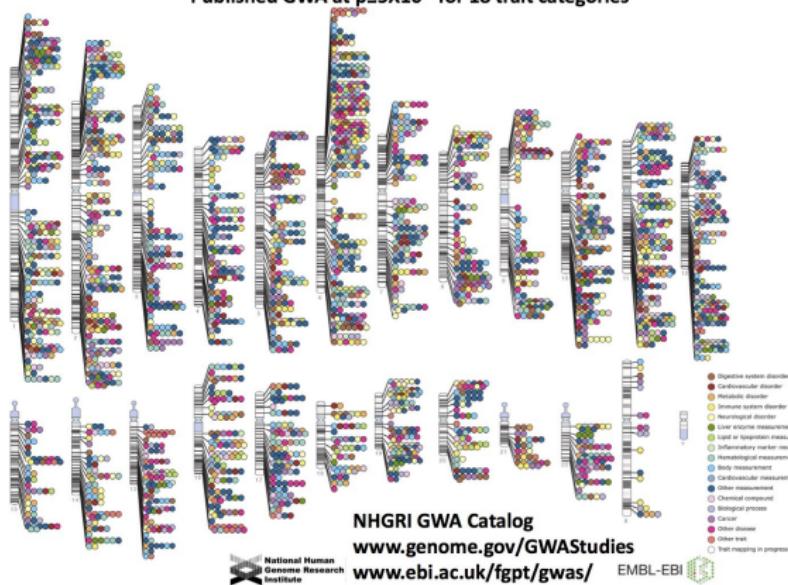


**Figure:** Common genetic variants on 5p14.1 associate with autism spectrum disorders [WZM<sup>+</sup>09]

# Introduction to GWAS

## GWAS Catalog

Published Genome-Wide Associations through 07/2012  
Published GWA at  $p \leq 5 \times 10^{-8}$  for 18 trait categories



**Figure:** Published GWAS results for 18 trait categories

# Introduction to GWAS

GWAS contribute to personalized medicine

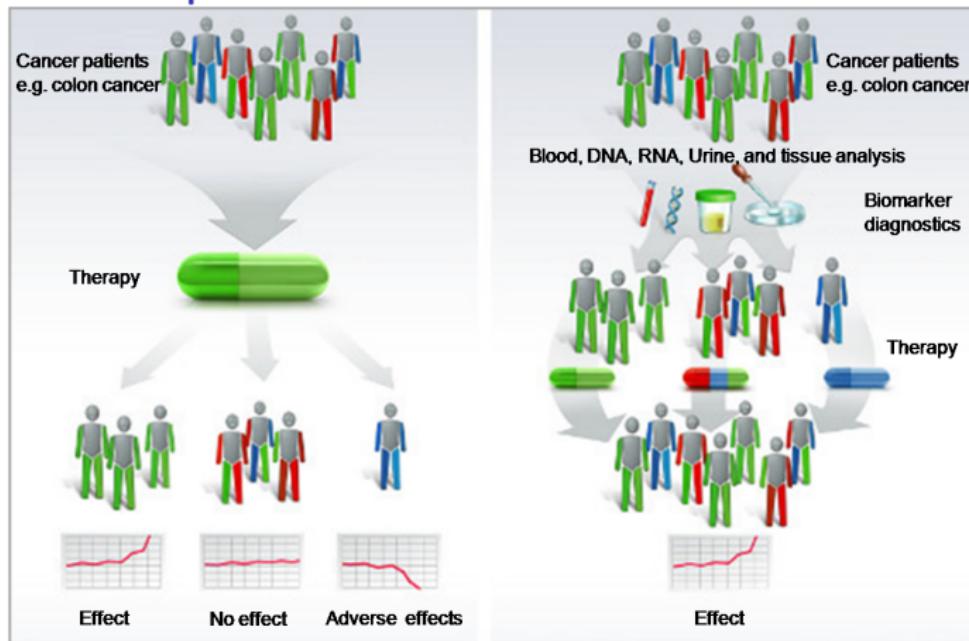
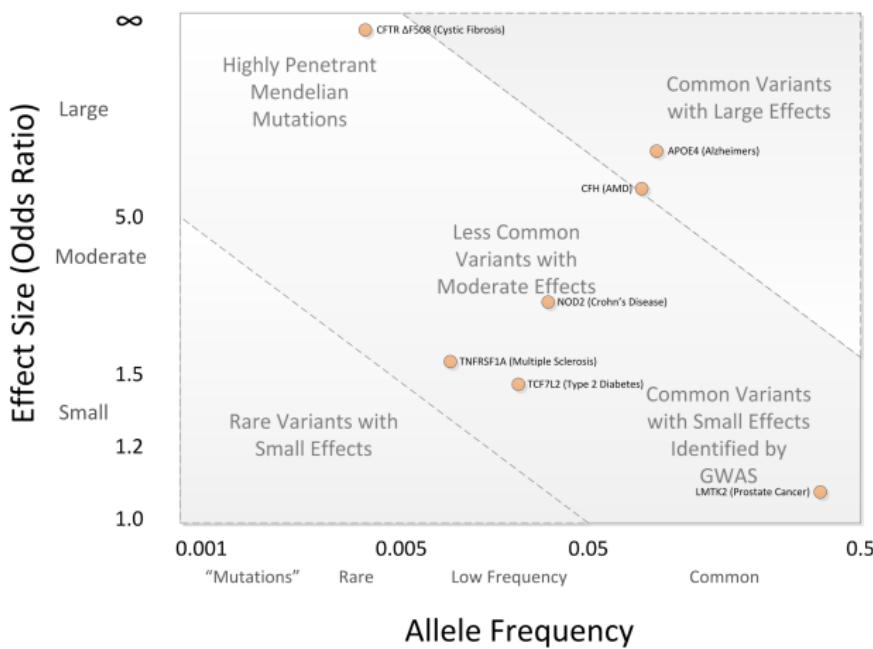


Figure: GWAS contribute to personalized medicine

# Introduction to GWAS

## Common variants and rare variants



**Figure:** effect size of Single Nucleotide Variant [BM12]

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# single-SNP based association tests

## the classical method

For individual  $i$  with SNP  $j$  coded as  $x_{ij}$  ( $x_{ij} = 0, 1, 2$  representing copies of minor alleles) and a vector of covariates  $\varphi_i$ ,

$$g(\mu_i) = \beta_0 + x_{ij}\beta_j + z_i\varphi_i,$$

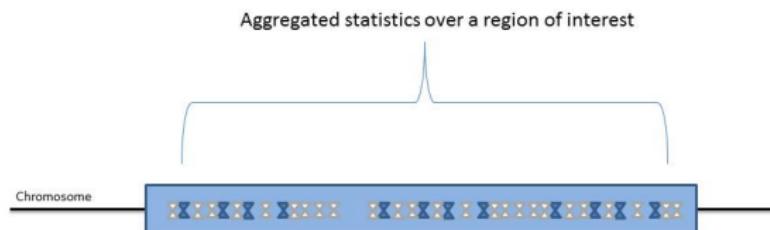
However, this method suffers from at least two disadvantages:

- 1), it will generate millions of tests thus increase the multiple test error correction burden;
- 2), the coefficient estimate of SNP  $j$  will become unstable or even the estimation algorithm cannot converge when SNP minor allele frequency (MAF) becomes smaller, e.g. MAF < 0.01.

# SNP-set based association tests I

## A brief review

By pooling multiple low MAF SNVs together, the SNP-set based association test can detect the signal(s) from a region (such as a gene) instead of from a single SNV.



# SNP-set based association tests II

## A brief review

Major categories of SNP-set based association tests:

- the so-called "burden test", which used MAF based weighting scheme to combine the sum statistics from multiple SNVs in a region [LL08, MB09];
- the variance-component test, which includes SKAT, C-alpha, SSU, etc [Pan09, NRV<sup>+</sup>11, WLC<sup>+</sup>11].
- the Lasso and group-penalized regression based methods [ZSSL10, KPS14].
- the functional linear model and functional principal component analysis based methods [LZX12b, LZX12a, LBX11, FWM<sup>+</sup>13].
- the adaptive test combines statistics of burden test and variance-component test, such as SKAT-O, aSum, aSSU, aScore, an exponential combination (EC) framework for set-based association tests, a robust and powerful test using Fisher's method to combine linear and quadratic statistics, a unified mixed-effect model, etc [HP10, PS11, LEB<sup>+</sup>12, LWL12, CHG<sup>+</sup>12, DLS13, SZH13].

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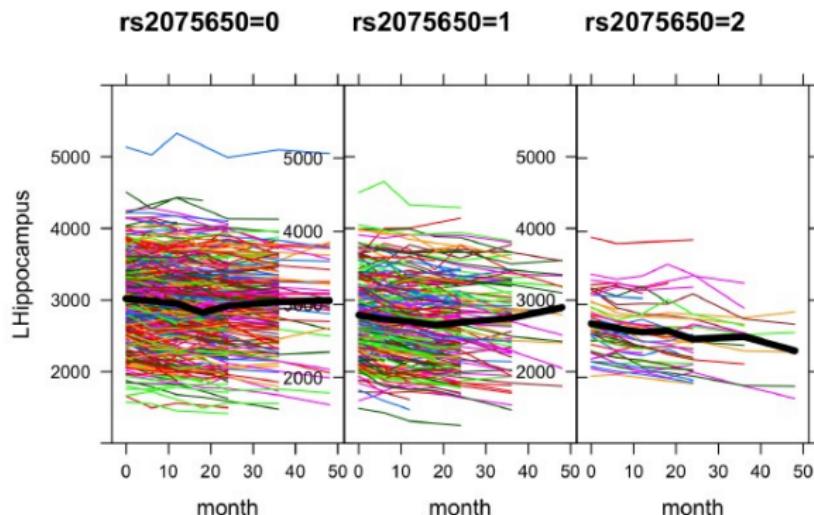
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# How do longitudinal data look like?



**Figure:** Trajectories of phenotype left hippocampus volume over time (in months) in three allele groups of SNP rs2075650 [XSP<sup>+</sup>14]

# Why longitudinal? I

In a cross-sectional study ( $n_i = 1$ ) we are restricted to the model

$$Y_{i1} = \beta_C x_{i1} + \epsilon_{i1}, \quad i = 1, \dots, m,$$

where  $\beta_C$  represents the difference in average  $Y$  across two sub-populations (samples) which differ by one unit in  $x$ . With repeated measurements, the above linear model can be extended to

$$Y_{ij} = \beta_C x_{i1} + \beta_L(x_{ij} - x_{i1}) + \epsilon_{ij}, \quad i = 1, \dots, m; j = 1, \dots, n_i$$

[WDL<sup>+</sup>90].

Based on above formula, we can more obviously explain the merits of longitudinal studies over cross-sectional studies.

- ① Longitudinal studies allow us to estimate both the cross-sectional difference ( $\beta_C$ ) and the rate change over time ( $\beta_L$ ).
- ② Even when  $\beta_C = \beta_L$ , longitudinal studies tend to be more powerful than cross-sectional studies. This is due to the fact that in longitudinal studies, each person can be thought of serving as his/her own control.

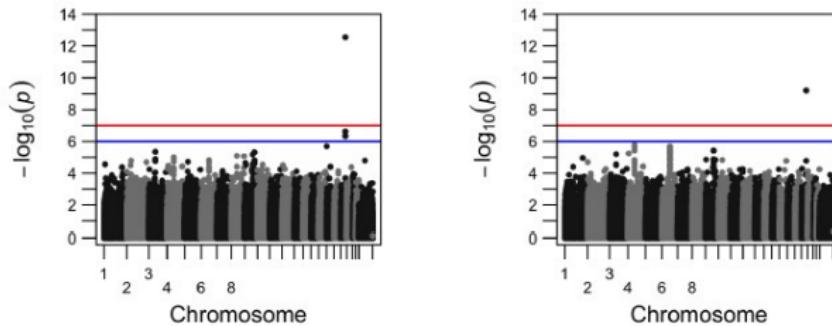
## Why longitudinal? II

- ③ Another merit of the longitudinal study is its ability to distinguish the between-subject variation and within-subject variation.
- ④ With longitudinal studies, we can estimate a person's current and future outcome (behavior trend).

# Why longitudinal? III

## Longitudinal study in GWAS

A recent study by Xu et al [XSP<sup>+</sup>14] demonstrates the power gain from longitudinal data analysis over traditional cross-sectional data analysis used in GWAS.



**Figure:** Comparison of the Manhattan plots for genome-wide p-values for phenotype left hippocampus volume from longitudinal analysis (left) and from cross-sectional analysis (right) [XSP<sup>+</sup>14]

# A brief review of major longitudinal data analysis methods I

Major categories of longitudinal data analysis methods:

- random effect models

Random effect model is a two-stage models, which treat probability distributions for the response vectors of different individuals as a single family and the random-effects parameters which hold the same for the same individual as another distribution [LW82].

- marginal effect models

Marginal effect model is an extension to quasi-likelihood method. Rather than giving subject-specific(SS) estimates as in random effect models, marginal effect models by Generalized Estimating Equation (GEE) give population-averaged (PA) estimates.

- transitional (Markov) models

The transitional (Markov) model, describes the conditional distribution of each response  $y_{ij}$  as an explicit function of first  $q$  prior observations  $y_{ij-1}, \dots, y_{ij-q}$  from history response vector:  $H_{ij} = \{y_{ik}, k = 1, \dots, j-1\}$  and covariates  $x_{ij}$ . The integer  $q$  is referred as the order of the Markov models.

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# Research Aims

- Aim 1: Data-adaptive SNP-set-based association tests (aSPU) for longitudinal data analysis within GEE framework for **Common Variants**;
- Aim 2: Longitudinal aSPU family tests on **Rare Variants**
- Aim 3: **Pathway-based** longitudinal aSPU family tests

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# Aim 1

To develop a data-adaptive longitudinal association test within GEE framework for **common variants**, which will be done in either sliding-window based or gene-based manner for real GWAS data.

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# Aim 1 |

## Methods: introduction to notation and formula

Suppose for each subject  $i = 1, \dots, n$ , we have  $k$  total longitudinal measurements

$$\mathbf{y}_i = (y_{i1}, y_{i2}, \dots, y_{ik})'$$

with  $y_{im}$  as a element,  $p$  SNPs of interest as a row vector

$$\mathbf{x}_i = (x_{i1}, x_{i2}, \dots, x_{ip})$$

with  $x_{ij}$  coded as 0,1 or 2 for the count of the minor allele, and

$$\mathbf{z}_i = (z_{i1}, z_{i2}, \dots, z_{iq})$$

as a row vector for  $q$  variates.

Thus, we have:

$$\mathbf{X}_i = \begin{pmatrix} \mathbf{x}_i \\ \mathbf{x}_i \\ \vdots \\ \mathbf{x}_i \end{pmatrix}, \mathbf{Z}_i = \begin{pmatrix} 1 & z_i \\ 1 & z_i \\ \vdots & \vdots \\ 1 & z_i \end{pmatrix}$$

$\mathbf{X}_i$  is a  $k \times p$  matrix, and  $\mathbf{Z}_i$  is a  $k \times (q + 1)$  matrix.

# Aim 1 II

## Methods: introduction to notation and formula

We then have the GLM equation as,

$$g(\mu_i) = \eta_i = Z_i\varphi + X_i\beta = H_i\theta$$

The consistent and asymptotically normal estimates of  $\beta$  and  $\varphi$  can be obtained by solving the GEE [LZ86]:

$$U(\varphi, \beta) = \sum_{i=1}^n U_i(\varphi, \beta) = \sum_{i=1}^n \left( \frac{\partial \mu_i}{\partial \theta'} \right)' V_i^{-1} (Y_i - \mu_i) = 0,$$

with

$$\frac{\partial \mu_i}{\partial \theta'} = \frac{\partial g^{-1}(H_i\theta)}{\partial \theta'}, V_i = \phi A_i^{\frac{1}{2}} R_w A_i^{\frac{1}{2}},$$

and

$$A_i = \begin{bmatrix} v(\mu_{i1}) & 0 & \cdots & 0 \\ 0 & v(\mu_{i2}) & 0 & 0 \\ \vdots & 0 & \ddots & \vdots \\ 0 & 0 & \cdots & v(\mu_{ik}) \end{bmatrix}$$

# Aim 1 III

## Methods: introduction to notation and formula

With a canonical link function and a working independence model, we have a closed form of the U vector with **two parts** corresponding to SNPs and covariates, and its covariance estimator:

$$U = \left( U'_{.1}, U'_{.2} \right)' = \sum_i (Z_i, X_i)' (Y_i - \mu_i)$$

$$\tilde{\Sigma} = \widehat{\text{Cov}}(U) = \sum_i (Z_i, X_i)' \widehat{\text{var}(Y_i)} (Z_i, X_i) = \sum_i (Z_i, X_i)' (Y_i - \hat{\mu}_i)(Y_i - \hat{\mu}_i)' (Z_i, X_i) = \begin{pmatrix} V_{11} & V_{12} \\ V_{21} & V_{22} \end{pmatrix} \quad (1)$$

# Aim 1 IV

## Methods: introduction to notation and formula

### *Quantitative traits*

We use the identity link, i.e.  $g(\mu_{im}) = \mu_{im}$  and  $v(\mu_{im}) = \phi \times 1 = \phi$ . Then we have:

$$\begin{aligned} U &= \sum_i (Z_i, X_i)' R_w^{-1} (Y_i - \mu_i) \\ \tilde{\Sigma} &= \sum_i (Z_i, X_i)' R_w^{-1} (Y_i - \hat{\mu}_i) (Y_i - \hat{\mu}_i)' R_w^{-1} (Z_i, X_i) \end{aligned} \quad (2)$$

if the assumption of a common covariance matrices across  $Y_i$  for  $i$  is valid, e.g. for quantitative continuous traits study [Pan01], we can adopt a more efficient covariance estimator:

$$\tilde{\Sigma} = \sum_{i=1}^n (Z_i, X_i)' \widehat{\text{var}(Y_i)} (Z_i, X_i) = \sum_{i=1}^n (Z_i, X_i)' \left( \sum_{i=1}^n \frac{(Y_i - \hat{\mu}_i)(Y_i - \hat{\mu}_i)'}{n} \right) (Z_i, X_i) = \begin{pmatrix} V_{11} & V_{12} \\ V_{21} & V_{22} \end{pmatrix}$$

which is used by default for its better finite-sample performance [Pan01].

# Aim 1 V

## Methods: introduction to notation and formula

### Binary traits

For binary traits (trait value coded as 0 and 1), we use the logit link function so that

$g(\mu_{im}) = \log \frac{\mu_{im}}{1-\mu_{im}}$  and  $v(\mu_{im}) = \mu_{im}(1-\mu_{im})$ . Additionally the  $(m, l)$ th element of  $\frac{\partial \mu_i}{\partial \theta'}$  is  $H_{i,ml}\mu_{im}(1-\mu_{im})$  with  $H_{i,ml}$  as the  $(m, l)$ th element of  $H_i$ , which is the short notation for  $(Z_i, X_i)$ .

Then we have:

$$\begin{aligned} U &= \sum_{i=1} (\frac{\partial \mu_i}{\partial \theta'})' V_i^{-1} (Y_i - \mu_i) \\ &= \sum_{i=1} (\frac{\partial \mu_i}{\partial \theta'})' \phi A_i^{-\frac{1}{2}} R_w^{-1} A_i^{-\frac{1}{2}} (Y_i - \mu_i) \end{aligned}$$

and

$$\begin{aligned} \tilde{\Sigma} &= \sum_i \left( \frac{\partial \mu_i}{\partial \theta'} \right)' \phi A_i^{-\frac{1}{2}} R_w^{-1} A_i^{-\frac{1}{2}} (Y_i - \hat{\mu}_i)(Y_i - \hat{\mu}_i)' \phi A_i^{-\frac{1}{2}} R_w^{-1} A_i^{-\frac{1}{2}} \left( \frac{\partial \mu_i}{\partial \theta'} \right) \\ &= \begin{pmatrix} V_{11} & V_{12} \\ V_{21} & V_{22} \end{pmatrix} \end{aligned}$$

# Aim 1 VI

## Methods: introduction to notation and formula

Our goal is to detect whether there is any association between the longitudinal trait and the SNPs via testing on hypothesis

$$H_0 : \beta = (\beta_1, \beta_2, \dots, \beta_p)' = 0$$

We have under the null hypothesis with  $g(Y_i) = Z_i\varphi$  to obtain  $\varphi$  and predict  $\hat{\mu} = g^{-1}(Z\hat{\varphi})$ . We hereby have score vector under the null hypothesis, with a working independence model, is:

$$U(\hat{\varphi}, 0) = (U'_{.1}, U'_{.2})' = \sum_{i=1}^n (U'_{i1}, U'_{i2})'$$

where

$$U_{.1} = \sum_i Z'_i (Y_i - \hat{\mu}_i), U_{.2} = \sum_i X'_i (Y_i - \hat{\mu}_i)$$

As  $U$  asymptotically follows a multivariate normal distribution under  $H_0$ , then the score vector for  $\beta$  also has an asymptotic normal distribution:

$$U_{.2} \sim N(0, \Sigma_{.2}), \Sigma_{.2} = \widehat{\text{Cov}}(U_{.2}) = V_{22} - V_{21}V_{11}^{-1}V_{12}$$

, where  $V_{xx}$  are defined in Equation 1.

# Aim 1 VII

## Methods: introduction to notation and formula

Several classical tests:

- **The Wald Test:** The Wald Test known as  $T = \hat{\beta}'\text{cov}(\hat{\beta})\hat{\beta}$  is most commonly used, where  $\hat{\beta}$  is the estimate of  $\beta$  after fitting the full GEE model with  $g(\mu_i) = Z_i\varphi + X_i\beta$ . Under  $H_0$ , we have  $T \sim \chi_p^2$ . The Wald test is more time consuming by fitting full model, may fail to converge with many SNPs put on RHS of the regression-like equation to test, and more importantly, the type I error tends to inflate in such case [PKZ<sup>+</sup>14, ZXSP14].
- **The Score Test:**  $T = U_{.2}'\Sigma_{.2}^{-1}U_{.2}$ , where  $U_{.2}$  and  $\Sigma_{.2}$  are discussed above; the statistic is asymptotically equivalent to the Wald test with the same null distribution  $T \sim \chi_p^2$ . Since we only need to fit the null model with covariates, it is computationally easier and less likely to have numerical convergence problems. More importantly, the score test controls the type I error well [PKZ<sup>+</sup>14, ZXSP14].
- **The UminP Test:**  $T = \max_j \frac{U_{2,j}^2}{\Sigma_{2,jj}}$  for  $j \in 1, 2, \dots, p$ , of  $j$ th SNP effect. The  $\Sigma_{2,jj}$  is the  $j$ th entry on the diagonal of  $\Sigma_{.2}$ . With  $\max_j T$ , we can get minimal p-value accordingly. A simulation method based on the asymptotic normal distribution of the score vector can be used to calculate its p-value [PKZ<sup>+</sup>14, ZXSP14]. An asymptotic multivariate normal distribution numerical integration based method provided an alternative to calculate its p-value [PHS09, Pan09].

# Aim 1

## Methods: A new class of tests and a data-adaptive test in longitudinal data settings

A general form of score-vector-based statistic can be generalized as:

$$T_w = W' U = \sum_{j=1}^p W_j U_j$$

where  $W = (W_1, \dots, W_p)'$  is a vector of weights for the  $p$  SNVs [LT11].  
with special cases:

$$T_{Sum} = 1' U = \sum_{j=1}^p U_j, \quad T_{SSU} = U' U = \sum_{j=1}^p U_j^2,$$

These two tests are called Sum test and SSU test [Pan09].

# Aim 1 II

## Methods: A new class of tests and a data-adaptive test in longitudinal data settings

If we choose weight to be

$$W_j = U_{.2,j}^{\gamma-1}$$

for a series of integer value  $\gamma = 1, 2, \dots, \infty$ , leading to the sum of powered score ( $U$ ) tests called **SPU** tests:

$$T_{SPU(\gamma)} = \sum_{j=1}^P U_{.2,j}^{\gamma-1} U_{.2,j}$$

When  $\gamma \rightarrow \infty$  as an extreme situation, where  $\infty$  is assumed to be an even number, we have

$$T_{SPU(\gamma)} \propto \|U\|_\gamma = \left( \sum_{j=1}^P |U_{.2,j}|^\gamma \right)^{\frac{1}{\gamma}} \rightarrow \|U\|_\infty = \max_{j=1}^P |U_{.2,j}| \equiv T_{SPU(\infty)}.$$

In our experience, SPU( $\gamma$ ) test with a large  $\gamma > 8$  usually gave similar results as that of SPU( $\infty$ ) test [PKZ<sup>+</sup>14], thus we will only use  $\gamma \in \Gamma = \{1, 2, \dots, 8, \infty\}$  for the whole dissertation work.

# Aim 1 III

Methods: A new class of tests and a data-adaptive test in longitudinal data settings

## Simulation-based P-value estimation of $T_{SPU(\gamma)}$

Suppose  $T$  is short notation of  $T_{SPU(\gamma)}$  for a specific  $\gamma$  and  $\hat{\Sigma}_{.2}$  is the covariance matrix of the score vector  $U_{.2}$  based on original data (see Equation 1). We draw  $B$  samples of the score vector from its null distribution:

$$U_{.2}^{(b)} \sim MVN\left(0, \hat{\Sigma}_{.2}\right),$$

with  $b = 1, 2, \dots, B$ , and thus obtain a statistics under null hypothesis:  $T^{(b)} = \sum_{j=1}^p U_{.2,j}^{(b)} \gamma$ . We then can calculate the p-value of  $T_{SPU(\gamma)}$  as

$$P_{SPU(\gamma)} = \sum_{b=1}^B \frac{I(T^{(b)} \geq T^{obs}) + 1}{B + 1}.$$

# Aim 1 IV

## Methods: A new class of tests and a data-adaptive test in longitudinal data settings

### The aSPU test

Although we have a list of  $SPU(\gamma)$  statistics and p-values, we are not sure which one is **the most powerful** in a specific data situation. Thus, it will be convenient to have a test which data-adaptively and automatically **select/combine the best**  $SPU(\gamma)$  test(s).

We hereby propose an adaptive SPU (aSPU) test to achieve such purpose. Accordingly, we will have the aSPU test statistic:

$$T_{aSPU} = \min_{\gamma \in \Gamma} P_{SPU(\gamma)},$$

# Aim 1 V

Methods: A new class of tests and a data-adaptive test in longitudinal data settings

## Simulation-based P-value estimation of $T_{aSPU}$

Similarly,

$$P_{SPU(\gamma)}^{(b)} = \sum_{b_1 \neq b}^B \frac{I(T_{SPU(\gamma)}^{(b_1)} \geq T_{SPU(\gamma)}^{(b)}) + 1}{(B - 1) + 1}$$

for every  $\gamma$  and every  $b$ . Then, we will have  $T_{aSPU}^{(b)} = \min_{\gamma \in \Gamma} P_{SPU(\gamma)}^{(b)}$ , and the final p-value of aSPU test is:

$$P_{aSPU} = \sum_{b=1}^B \frac{I(T_{aSPU}^{(b)} \leq T_{aSPU}^{obs}) + 1}{B + 1}.$$

It is worth noting again that the same  $B$  simulated score (U) vectors have been used in calculating the  $P_{aSPU}$ .

# Aim 1 VI

Methods: A new class of tests and a data-adaptive test in longitudinal data settings

## The "data-adaptive" genome wide scan strategy

In practice for genome wide scan purpose, we can use a "data-adaptive" aSPU test strategy that is:

- ① we first start with a smaller  $B$ , say  $B = 1000$
- ② we increase  $B$  to say  $10^6$  for just a few groups of SNVs, which passed an pre-determined significance cutoff (e.g. p-value  $\leq 5/B$ ) in 1
- ③ repeat 2 until a pre-determined  $B$  number reached

In this "data-adaptive" way of implementing the simulation based p-value calculating method for aSPU test, we will be able to apply the aSPU test to GWA data.

# Aim 1 VII

## Methods: A new class of tests and a data-adaptive test in longitudinal data settings

### Other versions of aSPU test

- **aSPUw test**

The SPUw test is a *diagonal-variance-weighted* version of the SPU test, defined as:

$$T_{SPUw(\gamma)} = \sum_{j=1}^p \left( \frac{U_{.2,j}}{\sqrt{\hat{\Sigma}_{.2,jj}}} \right)^\gamma$$

- **aSPU(w).Score test**

$$T_{aSPU.Score} = \min \left\{ \min_{\gamma \in \Gamma} P_{SPU(\gamma)}, P_{Score} \right\},$$

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# Aim 1

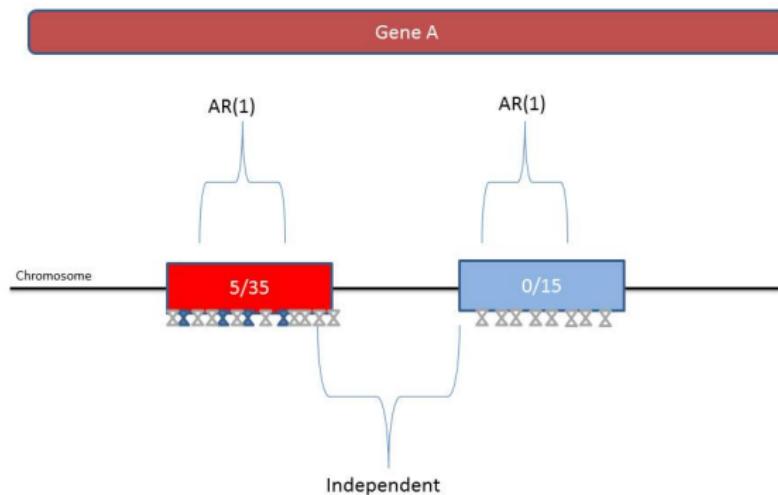
## Methods in data simulation

### Simulation of genotype data

- ① a latent vector  $G_i = (G_{i1}, \dots, G_{ip})'$  was first drawn from a **multivariate Normal distribution**  $N(0, R)$ , where  $R$  had a AR(1) correlation structure with its  $(i, j)$ th element in terms of purely correlation  $r_{ij} = \text{Corr}(G_{if}, G_{ig}) = \rho^{|f-g|}$  between any two latent components,  $G_{if}$  and  $G_{ig}$  for  $f \neq g$ . In our simulations we set  $\rho = 0.8$ ;
- ② the latent vector  $G_i$  was dichotomized to yield a haplotype with each latent element  $G_{ij}$  dichotomized to 0 or 1 with probability  $\text{Prob}(G_{ij} = 1) = \text{MAF}$  of  $j$ th SNP; the MAFs were randomly drawn from a uniform distribution: for causal SNPs the MAFs were set between 0.3 and 0.4; for null SNPs the MAFs were set between 0.1 and 0.5;
- ③ we combined two independent haplotypes to form the genotype  $X_i = (X_{i1}, \dots, X_{ip})'$  for subject  $i$ . The haplotypes for different subject were generated independently.

# Aim 1 II

## Methods in data simulation



**Figure:** Demo graph of genotype simulation

# Aim 1 III

## Methods in data simulation

### Simulation of phenotype data

We setup the mixed effect model to achieve the AR(1) correlation structure as:

$$y_{im} = \mu_i + b_i + \underbrace{\rho e_{i,m-1} + s_{i,m}}_{e_{i,m}}, \quad (3)$$

with  $m = 1, \dots, k$  indexes the longitudinal measurements within subject  $i$ ;

$$\mu_i = Z_i \varphi + X_i \beta = H_i \theta$$

as in quantitative trait case;  $b_i$  is the random intercept representing the subject-level random effect, and

$$\rho e_{i,m-1} + s_{i,m} = e_{i,m},$$

where  $\rho$  is lag-one autocorrelation coefficient, so we can plugin our estimate from real data here by setting up  $\rho = 0.7$ . We assume the following distribution:

# Aim 1 IV

## Methods in data simulation

$$b_i \sim N(0, \sigma_b^2)$$

$$e_{i,m} \sim N(0, \sigma_e^2)$$

$$s_{i,m} \sim N(0, (1 - \rho^2)\sigma_e^2)$$

Under this assumption, the variance-covariance matrix across longitudinal measurements becomes (assuming  $k = 4$  for the number of longitudinal measurements):

$$\Sigma_{4 \times 4} = \text{Var} \begin{pmatrix} b_i + e_{i1} \\ b_i + \rho e_{i1} + s_{i2} \\ b_i + \rho e_{i2} + s_{i3} \\ b_i + \rho e_{i3} + s_{i4} \end{pmatrix} = \sigma_b^2 \begin{pmatrix} 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \end{pmatrix} + \sigma_e^2 \begin{pmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{pmatrix} \quad (4)$$

# Aim 1 V

## Methods in data simulation

### Connect phenotype data with genotype data

Let we first introduce the below splitting of the phenotype variance:

$$\text{Var}(y_{im}) = \text{Var}(X_{ij})\beta_j^2 + \sigma_{oth}^2 = 2f(1-f)\beta_j^2 + \sigma_{oth}^2 \quad (5)$$

Now let we look at the relationship between genetic heritability (narrow-sense heritability) and equation (5):

$$h^2 = \frac{\text{Var}(A)}{\text{Var}(P)} \quad (6)$$

In our situation for  $j$ th SNP, this can be extended to:

$$h_j^2 = \frac{\text{Var}_j(A)}{\text{Var}(P)} = \frac{\text{Var}(X_{ij})\beta_j^2}{\text{Var}(y_{im})} = \frac{\text{Var}(y_{im}) - \sigma_{oth}^2}{\text{Var}(y_{im})} \approx \frac{\text{Var}(y_{im}) - \sigma_b^2 - \sigma_e^2}{\text{Var}(y_{im})} \quad (7)$$

# Aim 1 VI

## Methods in data simulation

### Summary of parameter setup in simulation studies

After this point, by systematically solving the equations (5) and (7), we can easily calculate the  $\beta_j$  for  $j$ th SNP once we have determined the value of  $h_j^2$ ,  $\sigma_b^2$ ,  $\sigma_e^2$  and  $f$ . Usually a  $h_j^2$  for a single SNP  $j$  will not be high for complex disease and we used  $h_j^2 = 0.001$  in our simulation study to control  $\beta_j$ . We summarize the parameters used in simulation studies here:

- $h_j^2 = 0.001$
- $\sigma_b^2 = 1$
- $\sigma_e^2 = 1$
- $n$  varies between 500 and 3000
- $k = 4$
- 1000 replicates of simulated dataset
- $\alpha = 0.05$
- $\rho_y = 0.7$
- $\rho_x = 0.8$
- $R = AR(1)$
- $Rw = I$

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# Aim 1

## Simulation results

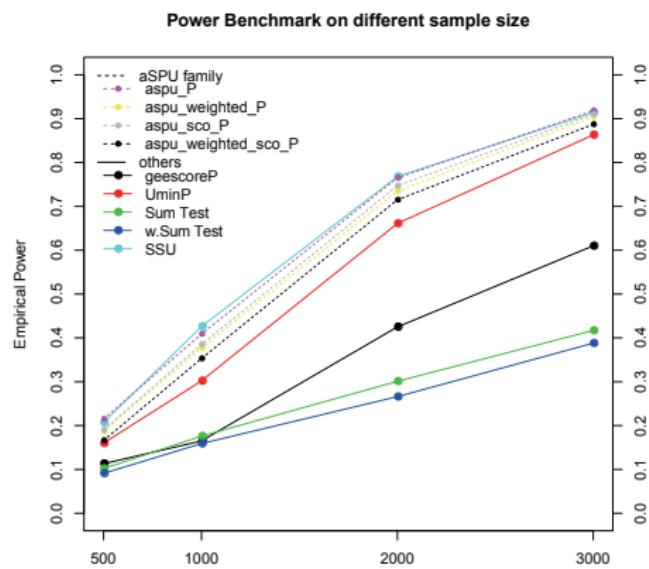
- Tests under default simulation settings with varying sample size

n	Score	UminP	SumP	SumP.w	SSU	aSPU	aSPUw	aSPU.sco	aSPUw.sco
500	0.038	0.056	0.058	0.053	0.044	0.052	0.051	0.050	0.048
1000	0.047	0.054	0.048	0.049	0.065	0.065	0.064	0.059	0.057
2000	0.055	0.041	0.053	0.053	0.059	0.052	0.055	0.058	0.058
3000	0.055	0.054	0.057	0.060	0.065	0.063	0.054	0.056	0.059

**Table:** Type I error under using working independence  $R_w$

# Aim 1 II

## Simulation results



**Figure:** Empirical power benchmark under different  $n$  using working independence  $R_w$

# Aim 1 III

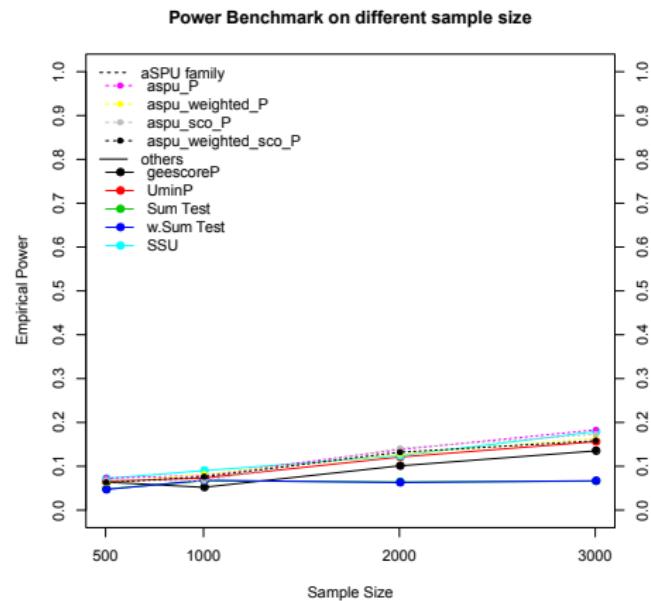
## Simulation results

- **Tests with half number of SNPs in opposite effect direction**

In 5 causal SNPs, we set 2 of them to have opposite effect direction to the left 3 SNPs. The other settings kept the same as the above. We have the empirical power benchmark result as below:

# Aim 1 IV

## Simulation results



**Figure:** Empirical power benchmark under a mixed SNP effects

# Aim 1 V

## Simulation results

- Tests with growing number of Null SNPs

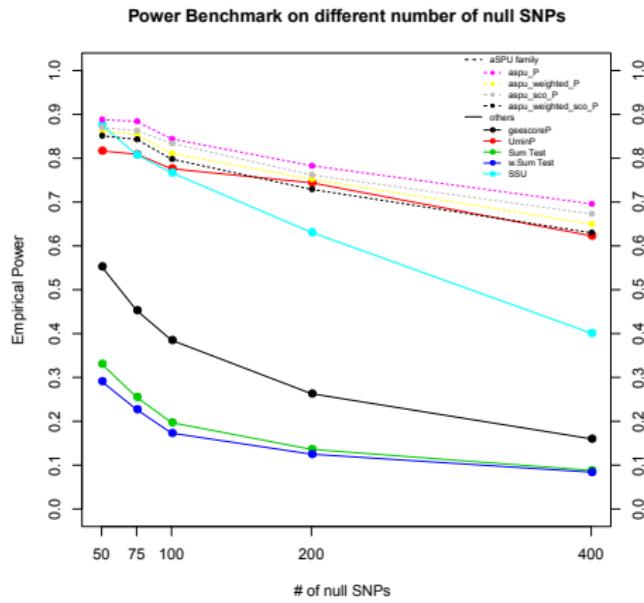


Figure: Empirical power benchmark under an increasing number of Null SNPs

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## Aim 2

Extend the data-adaptive longitudinal association test within GEE framework to work for **rare variants** in a gene-based manner.

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# Aim 2 I

## Methods

For CVs we have:

$$U_{.2}^{(b)} \sim MVN \left( 0, \hat{\Sigma}_{.2} \right)$$

with  $b = 1, 2, \dots, B$ , and thus obtain a statistics under null hypothesis:  $T^{(b)} = \sum_{j=1}^p U_{.2,j}^{(b)\gamma}$ . We then calculate the p-value of  $T_{SPU(\gamma)}$  as  $P_{SPU(\gamma)} = \sum_{b=1}^B \frac{I(T^{(b)} \geq T^{obs}) + 1}{B+1}$ .

The above algorithms will hold in RV case by large, except that the  $U_{.2}^{(b)}$  may **not** follow the multivariate Normal distribution any longer. As a remedy, we propose a permutation algorithm that generates the empirical null distribution of  $U_{.2}^{(b)}$  and in the same time **Maintain the relationship** between longitudinal traits and possible covariates such as age, gender, etc, for subject  $i$ . The algorithm will also be robust to **missing data** as this is a usual case in longitudinal data settings.

# Aim 2 II

## Methods

The permutation algorithm can be implemented as follows:

- ① identify the max  $k$  across all  $n$  subjects, which is the number of longitudinal measurements, e.g.  $k = 4$ .
- ② detect if the data has missing values, if yes, fill the missing value with NA to complement the data dimension (for example, subject  $i$  with  $Y_i = (y_{i,1}, \dots, y_{i,4})'$  has two missing measurements at time 2 and time 3. After missing value complementing, it becomes  $Y_i = (y_{i,1}, NA, NA, y_{i,4})'$ ). Now we should have all the subjects with each  $Y_i$  of dimension equal to  $k \times 1$ .
- ③ complement  $H_i$  to be of full dimension, i.e.  $k \times (p + q + 1)$ , for covariates and SNVs. Now we should have  $(Y_i \quad H_i)$  as an augmented matrix of dimension  $k \times (p + q + 2)$  for each subject  $i$ , where  $H_i = (Z_i, X_i)$ . For total  $n$  subjects, we have row-wise binded matrix

$$M = \begin{pmatrix} Y_1 & H_1 \\ Y_2 & H_2 \\ \vdots & \vdots \\ Y_n & H_n \end{pmatrix}$$

of dimension  $nk \times (p + q + 2)$ .

# Aim 2 III

## Methods

- ④ permute the SNV chunk among different individuals, i.e. the  $X_i$  in  $(Y_i \quad Z_i, X_i)$  with the  $X_j$  in  $(Y_j \quad Z_j, X_j)$ , where  $i \neq j$ .
- ⑤ with permuted

$$M^{*(b)} = \begin{pmatrix} Y_1 & Z_1, X_1^{*(b)} \\ Y_2 & Z_1, X_2^{*(b)} \\ \vdots & \vdots \\ Y_n & Z_1, X_n^{*(b)} \end{pmatrix}$$

we refit the GEE model and get the  $U_{.2}^{*(b)}$

- ⑥ repeat step 4 - 5 B times to produce  $U_{.2}^{*(b)}$  with  $b = 1, 2, \dots, B$ .

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# Aim 2 I

## Methods in data simulation

The simulation strategy of RV data is almost the same with previous strategy for generating CV data , except that:

- ① the MAF of RVs, regardless of casual one or null one, are set between **0.001** and **0.01**.
- ② the casual RVs are **not** excluded from later test as we expect the whole-genome sequencing or exome sequencing/Chip platform will identify high density SNVs including the real casual ones.

We will use the same simulated longitudinal phenotype data as for CVs.

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# Aim 2 I

## Simulation results

If we still use the CVs' strategy on RVs, we will have

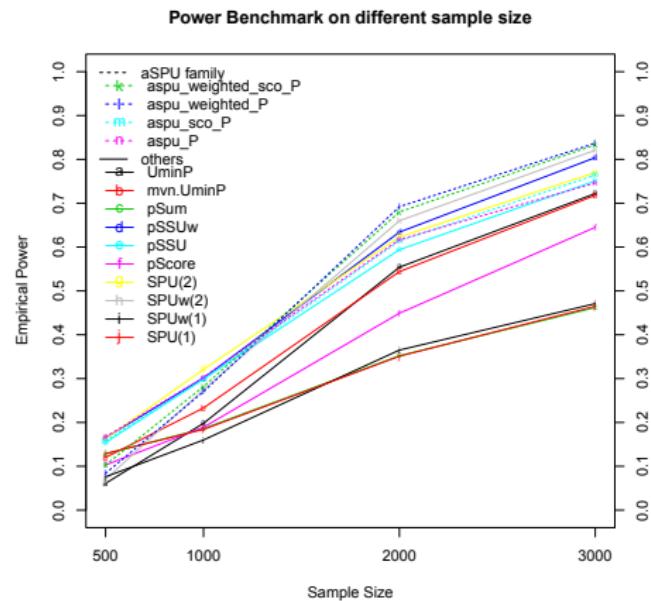
- **Simulation-based Test under default settings with varying sample size**

n	pSSU	pSSUw	pScore	pSum	mvn.UminP	UminP	SPU(1)	SPUw(1)	SPU(2)	SPUw(2)	aSPU	aSPUw	aSPU.sco	aSPUw.sco
500	0.053	0.054	0.052	0.049	0.047	0.022	0.052	0.026	0.063	0.025	0.056	<b>0.021</b>	0.059	<b>0.035</b>
1000	0.055	0.040	0.042	0.048	0.054	0.049	0.048	0.046	0.061	0.044	0.045	0.045	0.053	0.047
2000	0.054	0.050	0.048	0.049	0.046	0.045	0.053	0.044	0.063	0.061	<b>0.066</b>	<b>0.062</b>	<b>0.062</b>	0.062
3000	0.045	0.044	0.039	0.060	0.053	0.055	0.057	0.058	0.058	0.052	0.049	0.055	0.055	0.057

**Table:** Empirical type I error using simulation-based method in RV analysis. mvn.UminP: UminP method based MVN distribution; UminP: UminP method based on simulation.

# Aim 2 II

## Simulation results



**Figure:** Empirical power benchmark using simulation-based method in RV analysis

# Aim 2 III

## Simulation results

- Permutation-based Test under default settings with varying sample size

As noted before, there are some minor issues in using simulated-based aSPU method to test RVs, we thus tested the aSPU performance based on permutation algorithm. The type I error is shown below.

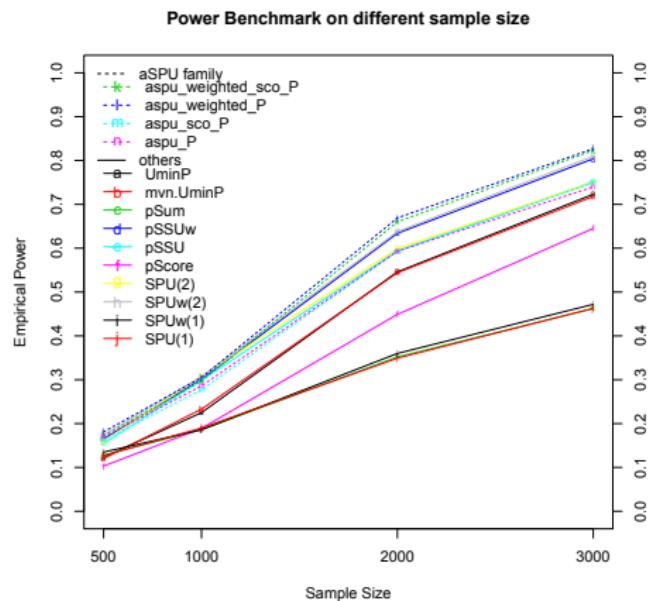
n	pSSU	pSSUw	pScore	pSum	mvn.UminP	UminP	SPU(1)	SPUw(1)	SPU(2)	SPUw(2)	aSPU	aSPUw	aSPU.sco	aSPUw.sco
500	0.053	0.054	0.052	0.049	0.047	0.046	0.050	0.049	0.056	0.061	0.054	0.053	0.060	0.056
1000	0.055	0.040	0.042	0.048	0.054	0.056	0.048	0.049	0.056	0.043	0.047	0.045	0.052	0.051
2000	0.054	0.050	0.048	0.049	0.046	0.046	0.049	0.043	0.053	0.052	0.063	0.057	0.058	0.056
3000	0.045	0.044	0.039	0.060	0.053	0.050	0.058	0.058	0.047	0.048	0.049	0.053	0.049	0.053

**Table:** Empirical type I error using permutation-based method in RV analysis.

mvn.UminP: UminP method based MVN distribution; UminP: UminP method based on permutation.

# Aim 2 IV

## Simulation results



**Figure:** Empirical power benchmark using simulation-based method in RV analysis

# Aim 2 V

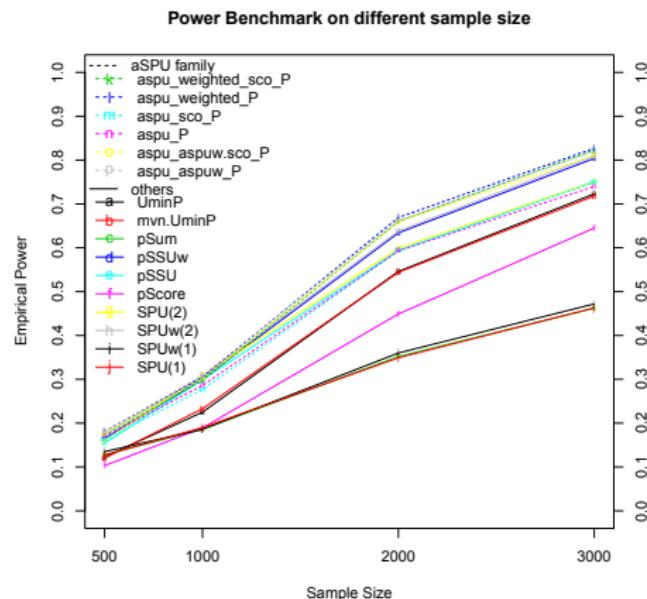
## Simulation results

- An effort to combine the advantages from aSPU, aSPUw and score test. The aSPU.aSPUw.Score test can save user's effort in deploying a best version of aSPU family test on a specific dataset with only a small amount of power loss in the process of compromising among different versions.

$$T_{aSPU.aSPUw.Score} = \min \left\{ \min_{\gamma \in \Gamma} P_{SPU(\gamma)}, \min_{\gamma \in \Gamma} P_{SPUw(\gamma)}, P_{Score} \right\},$$

# Aim 2 VI

## Simulation results



**Figure:** Empirical power benchmark with aSPU.aSPUw.Score test in RV analysis

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## Aim 3

To extend the data-adaptive longitudinal association test within the GEE framework to work for common variants or rare variants in a gene-set/pathway-based manner, i.e. **pathway-based association test**.

# Aim 3 I

## Method

A pathway analysis involves multiple genes (e.g. 20 as a typical number). As the genes within a pathway may contain different numbers of RVs, we need to modify the aSPU test to **adjust for various gene length** to avoid dominant influence from a large (or small) gene.

Suppose we let the short notation  $U_g.$  to represent  $U_{g,2}$  for the RVs  $X_i$ ' part in the whole score vector, and  $U_g. = (U_{g,1}, U_{g,2}, \dots, U_{g,p_g})'$  is the score vector for gene  $g$  with  $p_g$  RVs of itself. Given a pathway (or gene set)  $S$ , the gene-specific SPU statistic is as follows:

$$T_{SPU(\gamma;g)} \propto \|Ug.\|_\gamma = \left( \frac{\sum_{j=1}^{p_g} |U_{g,j}|^\gamma}{p_g} \right)^{\frac{1}{\gamma}} \quad (8)$$

Then accordingly, the pathway-based SPU statistic is

$$T_{Path-SPU(\gamma,\gamma_2;S)} = \sum_{g \in S} (T_{SPU(\gamma;g)})^{\gamma_2} \quad (9)$$

# Aim 3 II

## Method

The pathway-based aSPU statistic is thus

$$T_{Path-aSPU(S)} = \min_{\gamma, \gamma_2} P_{Path-SPU(\gamma, \gamma_2; S)} \quad (10)$$

We propose to use  $\gamma_2 \in \Gamma_2 = \{1, 2, 4, 8\}$ . The 1, 2, 4, 8 will cover Sum-like test, SSU-like test, and two more tests preferring the sparse-casual-gene situation (e.g. only 2 or 3 genes are associated with traits in a pathway, say with 20 genes).

# Aim 3 I

## Methods in data simulation

- We will simulate a pathway with 20 genes; each gene  $g$  will contain  $p_g$  RVs with  $p_g$  randomly drawn from a uniform distribution  $U(5, 30)$ ; 10 of the 20 genes will be randomly selected to be causal, with each causal gene containing 1 causal RV.
- We will test Path-aSPU family on the simulated data to evaluate the type I error and power, with comparison to other existing tests like UminP, SSU, Score and Sum test.

# Aim 3 I

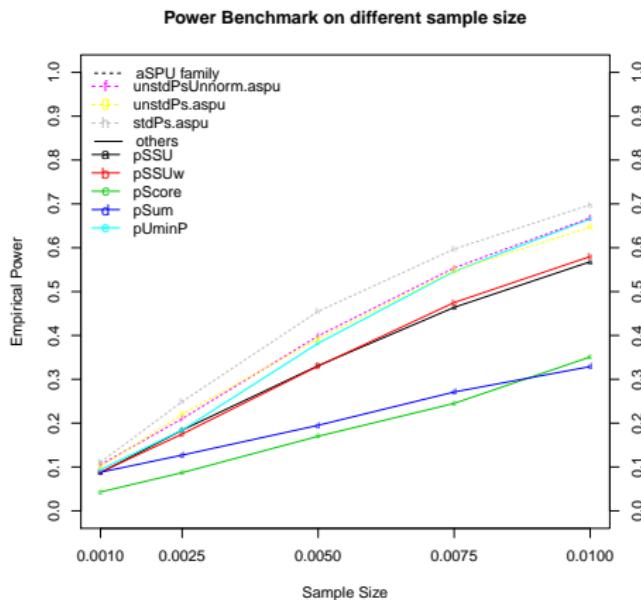
## Simulation results

pSSU	pSSUw	pScore	pSum	pUminP	geescoreP	unstdPsUnnorm	unstdPs	stdPs
0.037	0.042	0.025	0.049	0.050	0.025	0.059	0.063	0.053

**Table:** Empirical type I error using simulation-based method in RV analysis.

# Aim 3 II

## Simulation results



**Figure:** Empirical power benchmark using simulation-based method in pathway analysis

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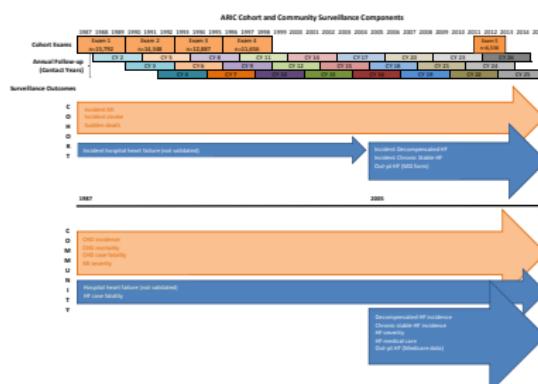
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# Real Data Introduction

The real data used in my dissertation will be obtained from the Atherosclerosis Risk in Communities (ARIC) Study (<https://www2.cscc.unc.edu/aric/>).

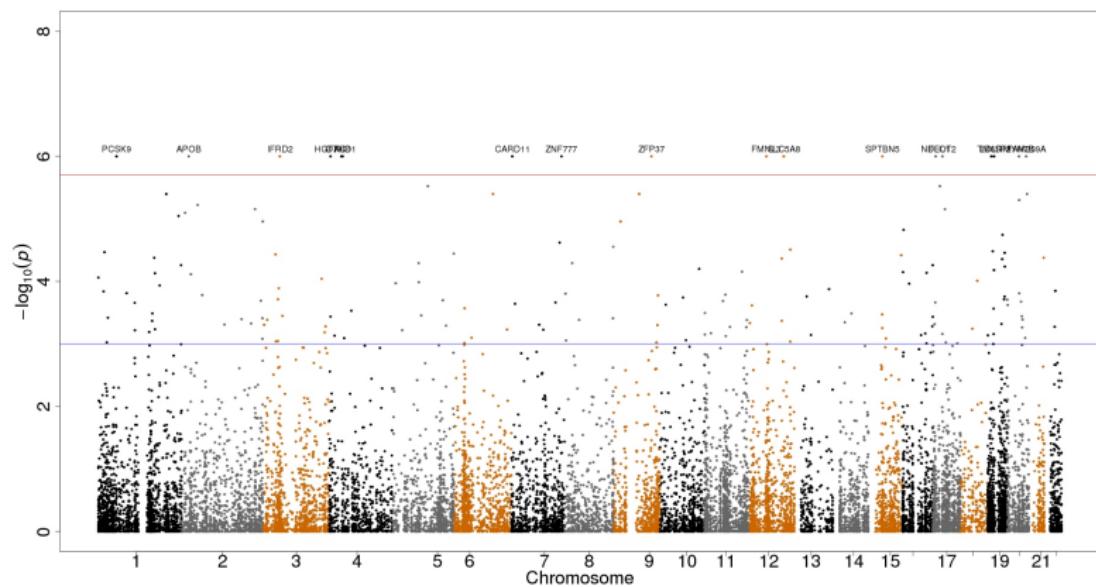
The Cohort Component of the ARIC study began in 1987. A total of 15,792 participants received an extensive examination, including medical, social, and demographic data. These participants were re-examined every three years with the first screen (baseline) occurring in 1987-89, the second in 1990-92, the third in 1993-95, and the fourth exam was in 1996-98. In 2009, the NHLBI funded a fifth exam, which is currently being conducted.



**Figure:** ARIC Cohort and Community Surveillance Components. Figure adopted from the ARIC website

We applied our novel method on ARIC data. Specifically, we will use the four closely cardiovascular-disease-related traits measured in ARIC cohort data, which are **total cholesterol (tch)**, **High-density lipoprotein (HDL)**, **Low-density lipoprotein (LDL)** and **triglycerides (trgs)**. We will exclusively use Caucasian samples ( $n = 11478$ ). For the covariates, we will include but not limited to subject's demographic information such as age, gender, BMI, etc.

# Real Data Result Demo



**Figure:** Manhattan Plot of aSPUw.score test on ARIC data Total Cholesterol trait

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# Acknowledgement

## Advisers:

- Peng Wei, Ph.D, Associate Professor, Division of Biostatistics, School of Public Health, University of Texas
- Wei Pan, Ph.D, Professor, Division of Biostatistics, School of Public Health, University of Minnesota

## Supporting Grant:

Title: Association Analysis of Rare Variants with Sequencing Data

Funding Source: NIH/NHLBI (1R01HL116720)

Total cost: \$1,043,901

# Thanks to Audience



Thank you for your participation!

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