Supplementary Manual. Exemplary GWA Analysis plan.

Analysis plan - New GIANT members 2011

(February 11th, 2011)

Background

This analysis plan aims to coordinate collection of data that will further improve our understanding of the biology and genetics of height, weight, BMI, waist, hip, and body fat% phenotypes. We have tried to keep the analyses to a minimum and also tried to provide code, detailed instructions and we will provide assistance to help groups carry out the requested analyses.

Aims

This analysis plan aims to coordinate and standardise the data collection of results (summary statistics) of data from new GIANT members (who joined in 2011) for a new set of meta-analyses that comprises the GWA-meta-analyses published in 2010, these new GWAS-datasets and the metabochip data.

Timeline

Please, provide the summary statistics by **March 31th 2011.**

Helpline

Please let us know if we can help with anything by e-mailing the following people and we will coordinate a response to you: N.N.

Instructions

General instructions

** Always test additive models using linear regression, (accounting for genotype imputation uncertainty (as for example is done with MACHQTL, SNPTEST or PLINK), and familial relatedness).

** If you use SNPTEST, please make sure to use the --expected analysis option

** Always analyse men and women separately and report results in separate files.

** If your population includes related individuals, please also analyse men and women combined, adjusting for sex (in addition to sex-specific analyses).

** If your study is a case-control study, please analyse cases and controls separately (in addition to analysing separately by sex).

** If needed, based on your judgement, please use principal components to correct for population stratification and include principal components as indicated in the analysis models below. If in doubt, we'd be happy to advise.

Chromosomes

All chromosomes, excluding the sex-chromosomes.

Genotypes

Genotyped SNPs (Affymetrix, Illumina, Perlegen) + imputed HapMap CEU SNPs (release r22) (e.g. MACH, IMPUTE, BEAGLE).
No exclusions based on MAF or imputation score.

Data upload

Upload files to the GIANT ftp-site:
username: NA
password: NA
server name: NA
Upload files in the trait-specific folders under '/path/DATA_UPLOAD/'

Only summary statistics are transferred, not individual level genotype or phenotype data.

Trait-specific instructions

1) Results for height

Trait: height (m)

z-score

Model (all study designs): in men and women SEPARATELY and by case status if appropriate

Height (raw trait) = age + other study specific covariates (such as cohort, study center and/or principal components adjusting for population stratification) -> residuals -> make z-scores -> then
SNP association; i.e. Height gender-specific Z-score from residual = SNP (no covariates)

Model (for family-based samples only): in men and women TOGETHER and by case status if appropriate

Height (raw trait) = age + sex + other study specific covariates -> residuals -> make z-scores -> then
SNP association; i.e. Height Z-score from residual = SNP (no covariates)

Please check that height is approximately normally distributed, and exclude any obvious outliers. Typically this would mean removing individuals +/- 4SD, but this can vary depending on study size and on visual inspection of the data.

2) Results for BMI

Trait: BMI = weight (kg)/height^2 (m^2)

Inverse normal transformation

Model (all study designs): in men and women SEPARATELY and by case status if appropriate

BMI (raw trait) = age + **age2** + other study specific covariates -> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

NOTE - from here onwards, analyses include also age^2 !

The rank-based inverse normal transformation can be performed
in SAS as follows :

```
proc rank data=mydata out=inv normal=blom
 var &trait;
run;
```

or in R as follows :

```
#if you have missing data
y<-qnorm((rank(x,na.last="keep")-0.5)/sum(!is.na(x))
```

Model (for family-based samples only): in men and women TOGETHER and by case status if appropriate

BMI (raw trait) = age + **age2** + sex + other study specific covariates -> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

3) Results for WAIST

Traits: WAIST = waist circumference (cm)

Inverse normal transformation

Model (all study designs): in men and women SEPARATELY and by case status if appropriate

WAIST (raw trait) = age + age2 + other study specific covariates -> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

Model (for family-based samples only): in men and women TOGETHER and by case status if appropriate

WAIST (raw trait) = age + age2 + sex + other study specific covariates -> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

4) Results for WHR

Traits: WHR = waist-hip ratio (cm/cm)

Inverse normal transformation

Model (all study designs): in men and women SEPARATELY and by case status if appropriate

WHR (raw trait) = age + age2 + other study specific covariates -> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

Model (for family-based samples only): in men and women TOGETHER and by case status if appropriate

WHR (raw trait) = age + age2 + sex + other study specific covariates -> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

5) Results for HIP

Traits: HIP = hip circumference (cm)

Inverse normal transformation

Model (all study designs): in men and women SEPARATELY and by case status if appropriate

HIP (raw trait) = age + age2 + other study specific covariates -> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

Model (for family-based samples only): in men and women TOGETHER and by case status if appropriate

HIP (raw trait) = age + age2 + sex + other study specific covariates -> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

6) Results for WAIST adjusted for BMI

Traits: WAIST = waist circumference (cm)

Inverse normal transformation

Model (all study designs): in men and women SEPARATELY and by case status if appropriate

WAIST (raw trait) = age + age2 + BMI + other study specific covariates-> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

Model (for family-based samples only): in men and women TOGETHER and by case status if appropriate

WAIST (raw trait) = age + age2 + BMI + sex + other study specific covariates -> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

7) Results for WHR adjusted for BMI

Traits: WHR = waist-hip ratio (cm/cm)

Inverse normal transformation

Model (all study designs): in men and women SEPARATELY and by case status if appropriate

WHR (raw trait) = age + age2 + BMI + other study specific covariates -> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

Model (for family-based samples only): in men and women TOGETHER and by case status if appropriate

WHR (raw trait) = age + age2 + BMI + sex + other study specific covariates -> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

8) Results for HIP adjusted for BMI

Traits: HIP = hip circumference (cm)

Inverse normal transformation

Model (all study designs): in men and women SEPARATELY and by case status if appropriate

HIP (raw trait) = age + age2 + BMI + other study specific covariates -> residual-> inverse normal transformation then

SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

Model (for family-based samples only): in men and women TOGETHER and by case status if appropriate

HIP (raw trait) = age + age2 + BMI + sex + other study specific covariates -> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

9) Results for Weight

Trait: Weight (kg)

Inverse normal transformation

Model (all study designs): in men and women SEPARATELY and by case status if appropriate

Weight (raw trait) = age + age2 + other study specific covariates -> residual -> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

Model (for family-based samples only): in men and women TOGETHER and by case status if appropriate

Weight (raw trait) = age + age2 + sex + other study specific covariates-> residual-> inverse normal transformation then
SNP association; i.e. Inverse normal transformed residual = SNP (no covariates)

10) Results for Body fat %

Trait: Body fat percentage ([DXA or BIA derived fat mass (kg) / total weight (kg)] x 100)

Inverse normal transformation

Model (all study designs): in men and women SEPARATELY and by case status if appropriate

Inverse normal transformed Body fat percentage (men and women transformed separately - as before) = SNP + age + age^2 + other study specific covariates

NOTE - this is somewhat different from the previous traits !

Model (for family-based samples only): in men and women TOGETHER and by case status if appropriate

Inverse normal transformed Body fat percentage (men and women transformed **separately** - as before) = SNP + age + age^2 + sex + other study specific covariates

NOTE - this is somewhat different from the previous traits !