Weekly logs of Master thesis

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Contents

1 Week 1

Date: 2023/2/8

1.1 Software Download

REGENIE: Stacked block ridge regression method for Mixed Linear Model.

Advantages:

1. Fast and Memory friendly.
2. Can process both quantitative and binary traits.
3. When Case-control unbalanced, h^2_{SNP} will get too high due to the too low MAC(minor allele count). REGENIE can fix this.

Plink

Bolt-LMM

GEMMA

SAIGE problems occur

1.2 QC

Filter out SNPs with genotype missingness > 10%, samples with > 10% missingness, MAF < 5%, minor allele count(MAC) < 100.

Cmd:

```
./software/plink --bfile data --geno 0.1 --mind 0.1 --maf 0.05 --mac 100 \
--make-bed --out data_qc
```

Output: data_qc

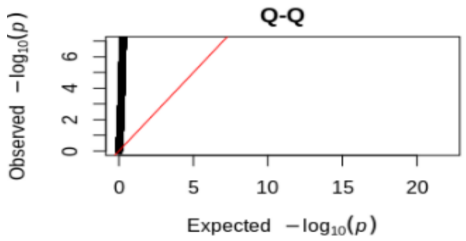
1.3 Plink

Worst result ever.

Cmd:

```
./software/plink --bfile data_qc --linear --pheno height.pheno --allow-no-sex\
--out data_plink_height
```

Q-Q plot: Figure 1



(a) Manhattan plot of REGENIE on height

Figure 1: **QQ plot of plink**

1.4 REGENIE for association study

I took height as the phenotype.

Step 1:

Input files: data_qc(3 files), covar1.covars, height1.pheno. Since REGENIE required labels in each column, I modified covar.covars and height.pheno with labels.

Cmd:

```
    regenie \
--step 1 \
--bed data_qc \
--covarFile covar1.covars \
--phenoFile height1.pheno \
--bsize 100 \
--out data_regenie_out
```

Output: A predicting matrix W for h^2_{SNP}, in file: data_regenie_out_pred.list

Step 2: Association test and LRT

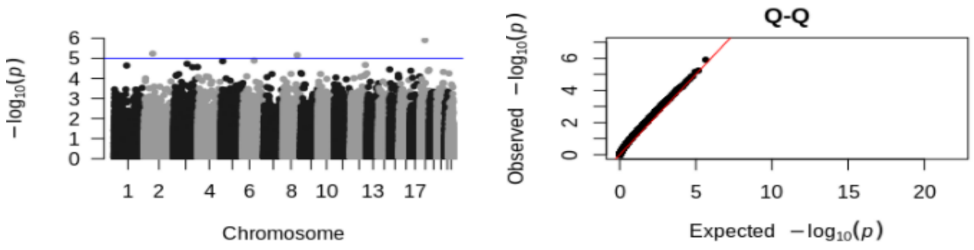
Cmd:

```
    regenie \
--step 2 \
--bgen data_qc.bgen \
```

```
--covarFile covar1.covars \
--phenoFile height1.pheno \
--bsize 200 \
--qt \
--firth --approx \
--pThresh 0.01 \
--pred data_regenie_out_pred.list \
--out data_regenie_out_firth
```

Output: data_regenie_out_firth_Phenotype.regenie

The result can be seen in Figure 2



(a) Manhattan plot of REGENIE on height (b) QQ plot of REGENIE on height

Figure 2: **GWAS results from REGENIE on height (a)**Manhattan plot. **(b)**QQ plot.

Benchmark:

See in Table 1

Method	Step	CPU time	Elapsed time(s)	Memory usage(GB)
REGENIE(null)	1		1492.8	10
REGENIE-Firth	2		4992.47	0.289

Table 1: **Computational performance of REGENIE-Firth**

Refer to: Mbatchou et al. (2021)

1.5 GEMMA

1. Before using GEMMA, the 6th column of .fam should be replaced by real phenotypes.

2. Calculate Kinship Matrix

```
gemma -bfile data_qc -gk 2 -o data_gemma_height
```

While it stuck here for hours, as in Figure 3

(a) Problem with GEMMA

Figure 3: **Problem with GEMMA**

1.6 fastGWA

1. After download, see: **gcta** in ./software folder

2. GCTA-GRM: calculating the genetic relationship matrix (GRM) from all the autosomal SNPs:

```
./software/gcta --bfile data_qc --chr 1 --maf 0.01 --make-grm \
--out data_qc_chr1 --thread-num 10
./software/gcta --bfile data_qc --chr 2 --maf 0.01 --make-grm \
--out data_qc_chr2 --thread-num 10
...
./software/gcta --bfile data_qc --chr 22 --maf 0.01 --make-grm \
--out data_qc_chr22 --thread-num 10
```

Output: .grm.bin, .grm.N.bin, .grm.id

3. To generate a sparse GRM from SNP data:

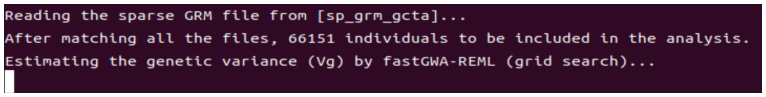
```
./software/gcta --bfile data_qc --autosome --maf 0.01 --make-grm \
--out data_qc_gcta --thread-num 10
./software/gcta --grm data_qc_gcta --make-bK-sparse 0.05 \
--out sp_grm_gcta
```

4. Association study

I didn't use PCs

```
./software/gcta --bfile data_qc --grm-sparse sp_grm_gcta \
--fastGWA-mlm --pheno height.pheno --qcovar covar.covars \
--thread-num 10 --out data_fastgwa_height
```

Problem comes from step 4, Figure 4:



(a) Problem with GEMMA

Figure 4: **Problem with fastGWA**

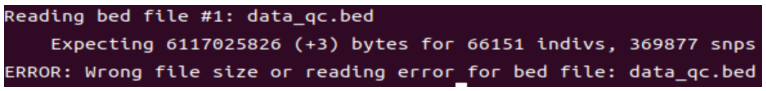
It is stuck here also for hours, is it normal? I'll open the computer for the night and see.

Still stuck there in the morning...

1.7 Bolt-lmm

```
./software/BOLT-LMM_v2.4/bolt --bfile=data_qc --phenoFile=height1.pheno --phenoCol=I
--covarFile=covar1.covars --qCovarCol --lmmForceNonInf --statsFile=data_bolt_height
```

The problem occurs at Figure 5.



(a) Problem

Figure 5: **Problem with Bolt-LMM**

1.8 Question

1. What should I do with CV and LOOCV? What for?

2. How can I detect the Type I errors? By prediction? 3. When I tried SAIGE, I found it need me to use Rscript, how to do?

```
Rscript createSparseGRM.R       \
--plinkFile=${LD pruned PLINK file} \
--nThreads=72   \
--outputPrefix=${OUTNAME}       \
--numRandomMarkerforSparseKin=5000      \
--relatednessCutoff=0.05
```

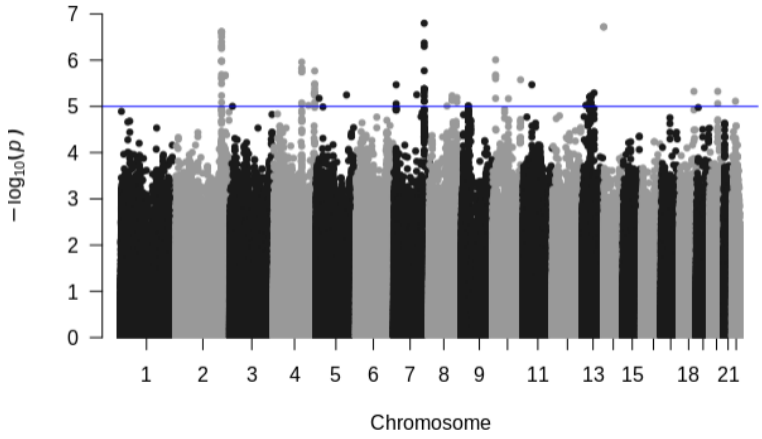
2 Week 2

2.20 - 2.26

Since there are a lot problems occuring with UKBB data, I use 1000g as a demo. If it can work, I'll run on UKBB.

See in commands_Week2.md

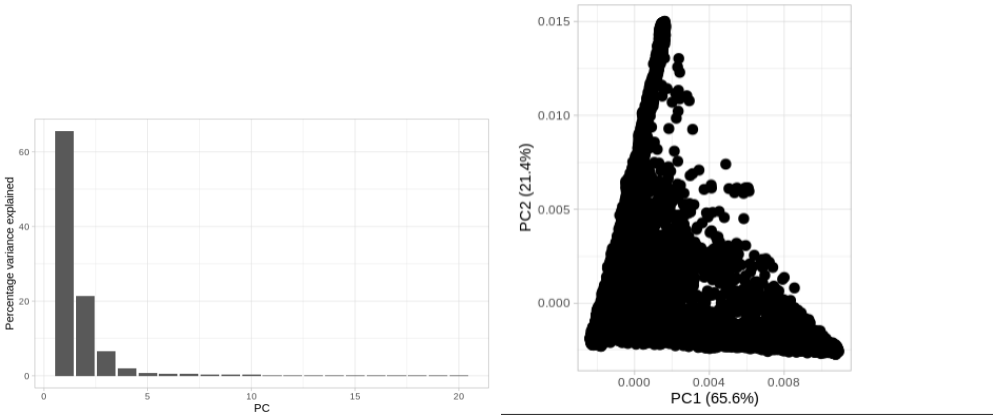
2.1 fastGWA



(a) Manhattan plot of fastGWA on 1000g, qt

Figure 6: **fastGWA on 1000g**

2.2 PCA



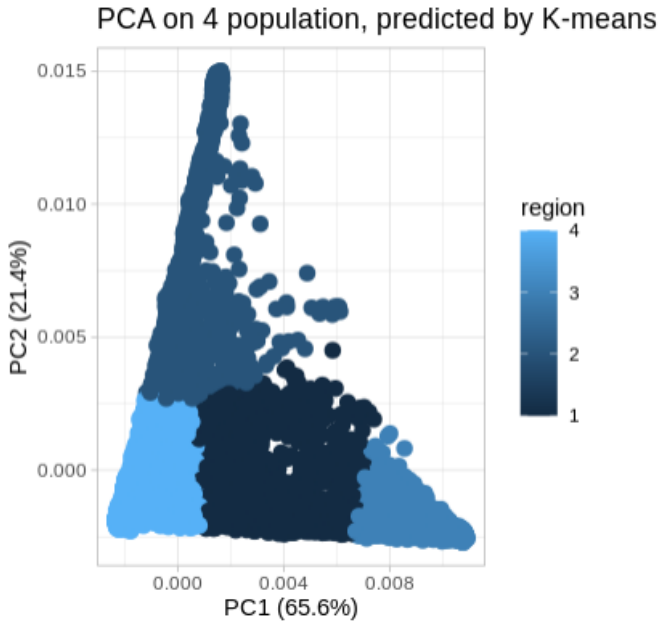
(a) PCs explained

(b) PCA

Figure 7: **GWAS results from REGENIE on height**

2.3 PCA for population prediction, K-means

$y <- > PC1 + PC2$

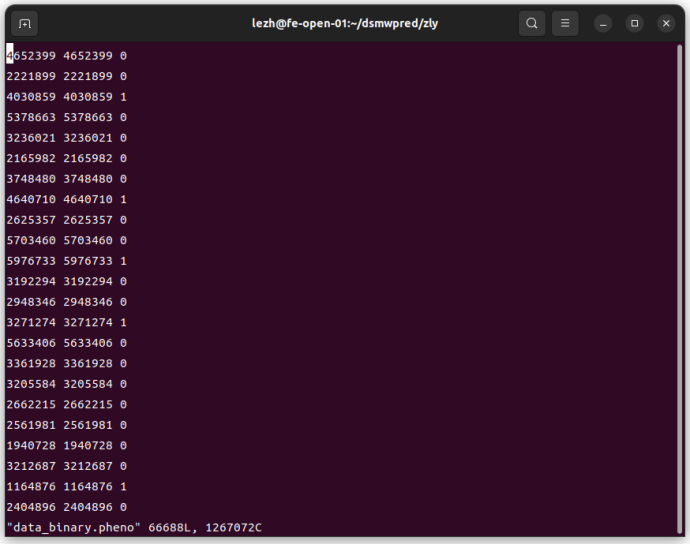


(a) 4 populations

Figure 8: **K-means clustering on PCA**

Problem: I cannot evaluate the result.

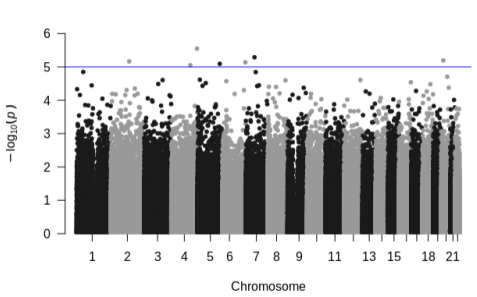
2.4 Simulate Binary Phenotype with LDAK



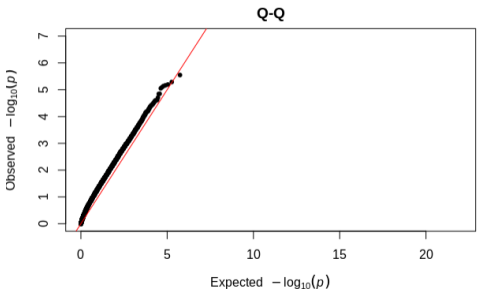
(a) ukbb, simulation

Figure 9: **Binary Phenotypes UKBB simulation**

2.5 Regenie for UKBB, binary



(a) Manhattan plot, UKBB, Binary



(b) QQ plot, UKBB, Binary

Figure 10: **Regenie results of UKBB on binary traits**

References

Mbatchou, J., Barnard, L., Backman, J., Marcketta, A., Kosmicki, J. A., Ziyatdinov, A., ... Marchini, J. (2021, 7). Computationally efficient whole-genome regression for quantitative and binary traits. *Nature Genetics*, *53*, 1097-1103. DOI: 10.1038/s41588-021-00870-7