

A Tutorial for the R Package SNPRelate

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Contents

1	Overview	1
2	Preparing Data	3
2.1	Data formats used in SNPRelate	3
2.2	Create a GDS File of Your Own	5
2.3	Format conversion from PLINK binary files	6
2.4	Format conversion from VCF files	7
3	Data Analysis	7
3.1	LD-based SNP pruning	8
3.2	Principal Component Analysis	9
3.3	Relatedness Analysis	12
3.3.1	PLINK method of moments (MoM)	13
3.3.2	IBD Using Maximum Likelihood Estimation (MLE)	14
3.4	Identity-By-State Analysis	15
4	Resources	19
5	References	20
6	Acknowledgements	20

1 Overview

Genome-wide association studies (GWAS) are widely used to help determine the genetic basis of diseases and traits, but they pose many computational challenges. We developed

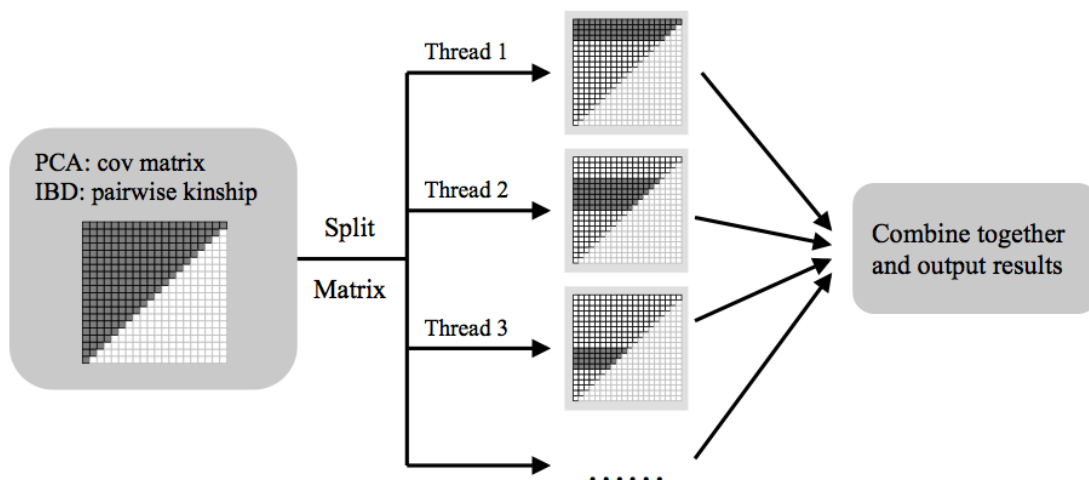


Figure 1: Flowchart of parallel computing for principal component analysis and identity-by-descent analysis.

`gdsfmt` and `SNPRelate` (high-performance computing R packages for multi-core symmetric multiprocessing computer architectures) to accelerate two key computations in GWAS: principal component analysis (PCA) and relatedness analysis using identity-by-descent (IBD) measures ¹. The kernels of our algorithms are written in C/C++ and have been highly optimized. The calculations of the genetic covariance matrix in PCA and pairwise IBD coefficients are split into non-overlapping parts and assigned to multiple cores for performance acceleration, as shown in Figure 1. Benchmarks show the uniprocessor implementations of PCA and IBD are ~ 8 to 50 times faster than the implementations provided in the popular `EIGENSTRAT` (v3.0) and `PLINK` (v1.07) programs respectively, and can be sped up to 30~300 folds by utilizing multiple cores.

GDS is also used by an R/Bioconductor package `GWASTools` as one of its data storage formats ^{2,3}. `GWASTools` provides many functions for quality control and analysis of GWAS, including statistics by SNP or scan, batch quality, chromosome anomalies, association tests, etc.

R is the most popular statistical programming environment, but one not typically optimized for high performance or parallel computing which would ease the burden of large-scale GWAS calculations. To overcome these limitations we have developed a project named `CoreArray` (<http://corearray.sourceforge.net/>) that includes two R packages: `gdsfmt` to provide efficient, platform independent memory and file management for genome-wide numerical data, and `SNPRelate` to solve large-scale, numerically intensive GWAS calculations (i.e., PCA and IBD) on multi-core symmetric multiprocessing (SMP) computer architectures.

This vignette takes the user through the relatedness and principal component analysis

¹**A High-performance Computing Toolset for Relatedness and Principal Component Analysis of SNP Data.** Xiuwen Zheng; David Levine; Jess Shen; Stephanie M. Gogarten; Cathy Laurie; Bruce S. Weir. Bioinformatics 2012; doi: 10.1093/bioinformatics/bts606

used for genome wide association data. The methods in these vignettes have been introduced in the paper of Zheng *et al.* (2012)¹. For replication purposes the data used here are taken from the HapMap Phase II project. These data were kindly provided by the Center for Inherited Disease Research (CIDR) at Johns Hopkins University and the Broad Institute of MIT and Harvard University (Broad). The data supplied here should not be used for any purpose other than this tutorial.

2 Preparing Data

2.1 Data formats used in SNPRelate

To support efficient memory management for genome-wide numerical data, the `gdsfmt` package provides the genomic data structure (GDS) file format for array-oriented bioinformatic data, which is a container for storing annotation data and SNP genotypes. In this format each byte encodes up to four SNP genotypes thereby reducing file size and access time. The GDS format supports data blocking so that only the subset of data that is being processed needs to reside in memory. GDS formatted data is also designed for efficient random access to large data sets.

```
> # load the R packages: gdsfmt and SNPRelate
> library(gdsfmt)
> library(SNPRelate)
```

Here is a typical GDS file:

```
> snpgdsSummary(snpgdsExampleFileName())
```

The file name: /private/var/folders/m3/hrfnm36n27x3ppdl3hk4czfr0000gn/T/RtmpBPCYcJ/Rinst

The total number of samples: 279

The total number of SNPs: 9088

SNP genotypes are stored in individual-major mode.

`snpgdsExampleFileName()` returns the file name of a GDS file used as an example in `SNPRelate`, and it is a subset of data from the HapMap project and the samples were genotyped by the Center for Inherited Disease Research (CIDR) at Johns Hopkins University and the Broad Institute of MIT and Harvard University (Broad). `snpgdsSummary()` summarizes the genotypes stored in the GDS file. “Individual-major mode” indicates listing all SNPs for an individual before listing the SNPs for the next individual, etc. Conversely, “SNP-major mode” indicates listing all individuals for the first SNP before listing all individuals for the second SNP, etc. Sometimes “SNP-major mode” is more computationally efficient than “individual-major model”. For example, the calculation of genetic covariance matrix deals with genotypic data SNP by SNP, and then “SNP-major mode” should be more efficient.

```
> # open a GDS file
> (genofile <- openfn.gds(snpGdsExampleFileName()))
```

```
file name: /private/var/folders/m3/hrfnm36n27x3ppdl3hk4czfr0000gn/T/RtmpBPCYcJ/Rinst2e86
```

```
+      [    ]
|--+ sample.id      [ FStr8 279 ZIP(23.10%) ]
|--+ snp.id         [ Int32 9088 ZIP(34.76%) ]
|--+ snp.rs.id      [ FStr8 9088 ZIP(42.66%) ]
|--+ snp.position   [ Float64 9088 ZIP(51.77%) ]
|--+ snp.chromosome [ Int32 9088 ZIP(0.33%) ]
|--+ snp.allele     [ FStr8 9088 ZIP(14.45%) ]
|--+ genotype       [ Bit2 9088x279 ] *
|--+ sample.annot   [    ] *
| |--+ sample.id    [ FStr8 279 ZIP(23.10%) ]
| |--+ family.id    [ FStr8 279 ZIP(28.37%) ]
| |--+ geneva.id     [ Int32 279 ZIP(80.29%) ]
| |--+ father.id    [ FStr8 279 ZIP(12.98%) ]
| |--+ mother.id    [ FStr8 279 ZIP(12.86%) ]
| |--+ plate.id     [ FStr8 279 ZIP(1.29%) ]
| |--+ sex          [ FStr8 279 ZIP(28.32%) ]
| |--+ pop.group    [ FStr8 279 ZIP(7.89%) ]
```

The output lists all variables stored in the GDS file. At the first level, it saves variables **sample.id**, **snp.id**, etc. The second-level variables **sex** and **pop.group** are both stored in the directory of **sample.annot**. All of the functions in **SNPRelate** require a minimum set of variables in the SNP annotation data. The minimum required variables are

- **snp.id**, a unique identifier for each SNP.
- **snp.chromosome**, an integer mapping for each chromosome, with values 1-26, mapped in order from 1-22, 23=X, 24=XY (the pseudoautosomal region), 25=Y, 26=M (the mitochondrial probes), and 0 for probes with unknown positions; it does not allow NA.
- **snp.position**, the base position of each SNP on the chromosome, and 0 for unknown position; it does not allow NA.

```
> # Take out snp.id
> head(read.gdsn(index.gdsn(genofile, "snp.id")))
```

```
[1] 1 2 3 4 5 6
```

```
> # Take out snp.rs.id
> head(read.gdsn(index.gdsn(genofile, "snp.rs.id")))
```

```
[1] "rs1695824" "rs13328662" "rs4654497" "rs10915489" "rs12132314"
[6] "rs12042555"
```

There are two additional variables:

- **snp.rs.id**, a character string for reference SNP ID that may not be unique.
- **snp.allele**, it is not necessary for the analysis, but it is necessary when merging genotypes from different platforms. The format of **snp.allele** is “A allele/B allele”, like “T/G” where T is A allele and G is B allele.

There are four possible values stored in the variable **genotype**: 0, 1, 2 and 3. For bi-allelic SNP sites, “0” indicates two B alleles, “1” indicates one A allele and one B allele, “2” indicates two A alleles, and “3” is a missing genotype. For multi-allelic sites, it is a count of the reference allele (3 meaning no call). “Bit2” indicates that each byte encodes up to four SNP genotypes since one byte consists of eight bits.

```
> # Take out genotype data for the first 3 samples and the first 5 SNPs
> (g <- read.gdsn(index.gdsn(genofile, "genotype"), start=c(1,1), count=c(5,3)))
```

```
      [,1] [,2] [,3]
[1,]    2    1    2
[2,]    1    1    1
[3,]    0    0    1
[4,]    1    1    2
[5,]    2    2    2
```

```
> # read population information
> pop <- read.gdsn(index.gdsn(genofile, c("sample.annot", "pop.group")))
> table(pop)
```

```
pop
CEU HCB JPT YRI
 92 47 47 93
```

```
> # close the GDS file
> closefn.gds(genofile)
```

2.2 Create a GDS File of Your Own

The function **snpgdsCreateGeno** helps to create a GDS file of your own. There are possible values stored in the input genotype matrix: 0, 1, 2 and other values. “0” indicates two B alleles, “1” indicates one A allele and one B allele, “2” indicates two A alleles, and other values indicate a missing genotype. For example,

```

> # load data
> data(hapmap.geno)
> # create a gds file
> with(hapmap.geno, snpgdsCreateGeno("test.gds", genmat=genotype,
+   sample.id=sample.id, snp.id=snp.id, snp.chromosome=snp.chromosome,
+   snp.position=snp.position, snp.allele=snp.allele, snpfirstorder=TRUE))
> # open the gds file
> (genofile <- openfn.gds("test.gds"))

```

file name: test.gds

```

+      [   ]
|---+ sample.id      [ FStr8 279 ZIP(23.10%) ]
|---+ snp.id         [ FStr8 1000 ZIP(45.02%) ]
|---+ snp.position    [ Float64 1000 ZIP(55.97%) ]
|---+ snp.chromosome  [ Int32 1000 ZIP(2.00%) ]
|---+ snp.allele      [ FStr8 1000 ZIP(17.37%) ]
|---+ genotype       [ Bit2 1000x279 ] *

```

```

> # close the genotype file
> closefn.gds(genofile)

```

2.3 Format conversion from PLINK binary files

The SNPRelate package provides a function `snpgdsBED2GDS` for converting a PLINK binary file to a GDS file:

```

> # the PLINK BED file
> bed.fn <- system.file("extdata", "plinkhapmap.bed", package="SNPRelate")
> bim.fn <- system.file("extdata", "plinkhapmap.bim", package="SNPRelate")
> fam.fn <- system.file("extdata", "plinkhapmap.fam", package="SNPRelate")
> # convert
> snpgdsBED2GDS(bed.fn, fam.fn, bim.fn, "test.gds")

```

Start snpgdsBED2GDS ...

```

    open /private/var/folders/m3/hrfnm36n27x3ppdl3hk4czfr0000gn/T/RtmpBPCYcJ/Rinst2e
    open /private/var/folders/m3/hrfnm36n27x3ppdl3hk4czfr0000gn/T/RtmpBPCYcJ/Rinst2e
    open /private/var/folders/m3/hrfnm36n27x3ppdl3hk4czfr0000gn/T/RtmpBPCYcJ/Rinst2e
Sat Jan  5 02:49:38 2013      store sample id, snp id, position, and chromosome.
    start writing: 279 samples, 5000 SNPs ...
    Sat Jan  5 02:49:38 2013      0%
    Sat Jan  5 02:49:38 2013      100%
Sat Jan  5 02:49:38 2013      Done.

```

```
> # summary
> snpgdsSummary("test.gds")

The file name: test.gds
The total number of samples: 279
The total number of SNPs: 5000
SNP genotypes are stored in individual-major mode.
```

2.4 Format conversion from VCF files

The SNPRelate package provides a function **snpgdsVCF2GDS** to reformat a VCF file. There are two options for extracting markers from a VCF file for downstream analyses: (1) to extract and store dosage of the reference allele only for biallelic SNPs and (2) to extract and store dosage of the reference allele for all variant sites, including bi-allelic SNPs, multi-allelic SNPs, indels and structural variants.

```
> # the VCF file
> vcf.fn <- system.file("extdata", "sequence.vcf", package="SNPRelate")
> # reformat
> snpgdsVCF2GDS(vcf.fn, "test.gds", method="biallelic.only")

Start snpgdsVCF2GDS ...
  Extracting bi-allelic and polymorphic SNPs.
  Scanning ...
  file: /private/var/folders/m3/hrfnm36n27x3ppdl3hk4czfr0000gn/T/RtmpBPCYcJ/Rinst2
  content: 5 rows x 12 columns
Sat Jan  5 02:49:39 2013      store sample id, snp id, position, and chromosome.
  start writing: 3 samples, 2 SNPs ...
  file: /private/var/folders/m3/hrfnm36n27x3ppdl3hk4czfr0000gn/T/RtmpBPCYcJ/Rinst2
Sat Jan  5 02:49:39 2013      Done.

> # summary
> snpgdsSummary("test.gds")

The file name: test.gds
The total number of samples: 3
The total number of SNPs: 2
SNP genotypes are stored in SNP-major mode.
```

3 Data Analysis

We developed **gdsfmt** and **SNPRelate** (high-performance computing R packages for multi-core symmetric multiprocessing computer architectures) to accelerate two key computations in GWAS: principal component analysis (PCA) and relatedness analysis using identity-by-descent (IBD) measures.

```
> # open the GDS file
> genofile <- openfn.gds(snpGdsExampleFileName())
```

3.1 LD-based SNP pruning

It is important to use a pruned set of SNPs which are in approximate linkage equilibrium with each other to avoid the strong influence of SNP clusters in principal component analysis and relatedness analysis.

```
> set.seed(1000)
> # try different LD thresholds for sensitivity analysis
> snpset <- snpGdsLDpruning(genofile, ld.threshold=0.2)
```

SNP pruning based on LD:

Sliding window: 500000 basepairs, Inf SNPs

|LD| threshold: 0.2

Removing 365 non-autosomal SNPs

Removing 1 SNPs (monomorphic, < MAF, or > missing rate)

Working space: 279 samples, 8722 SNPs

Chromosome 1: 75.70%, 542/716

Chromosome 2: 72.24%, 536/742

Chromosome 3: 74.55%, 454/609

Chromosome 4: 73.49%, 413/562

Chromosome 5: 77.03%, 436/566

Chromosome 6: 75.04%, 424/565

Chromosome 7: 75.21%, 355/472

Chromosome 8: 71.52%, 349/488

Chromosome 9: 77.64%, 323/416

Chromosome 10: 73.71%, 356/483

Chromosome 11: 77.40%, 346/447

Chromosome 12: 76.35%, 326/427

Chromosome 13: 75.87%, 261/344

Chromosome 14: 76.60%, 216/282

Chromosome 15: 76.72%, 201/262

Chromosome 16: 73.02%, 203/278

Chromosome 17: 74.88%, 155/207

Chromosome 18: 74.06%, 197/266

Chromosome 19: 85.00%, 102/120

Chromosome 20: 71.62%, 164/229

Chromosome 21: 76.19%, 96/126

Chromosome 22: 75.86%, 88/116

6543 SNPs are selected in total.

```
> names(snpset)
```



```

[1] "chr1" "chr2" "chr3" "chr4" "chr5" "chr6" "chr7" "chr8" "chr9"
[10] "chr10" "chr11" "chr12" "chr13" "chr14" "chr15" "chr16" "chr17" "chr18"
[19] "chr19" "chr20" "chr21" "chr22"

> head(snpset$chr1) # snp.id

[1] 1 2 4 5 7 10

> # get all selected snp id
> snpset.id <- unlist(snpset)

```

3.2 Principal Component Analysis

The functions in `SNPRelate` for PCA include calculating the genetic covariance matrix from genotypes, computing the correlation coefficients between sample loadings and genotypes for each SNP, calculating SNP eigenvectors (loadings), and estimating the sample loadings of a new dataset from specified SNP eigenvectors.

```

> pca <- snpgdsPCA(genofile, maf=0.05, missing.rate=0.05,
+                 snp.id=snpset.id, num.thread=2)

```

Principal Component Analysis (PCA) on SNP genotypes:

Removing 1109 SNPs (monomorphic, < MAF, or > missing rate)

Working space: 279 samples, 5434 SNPs

Using 2 CPU cores.

```

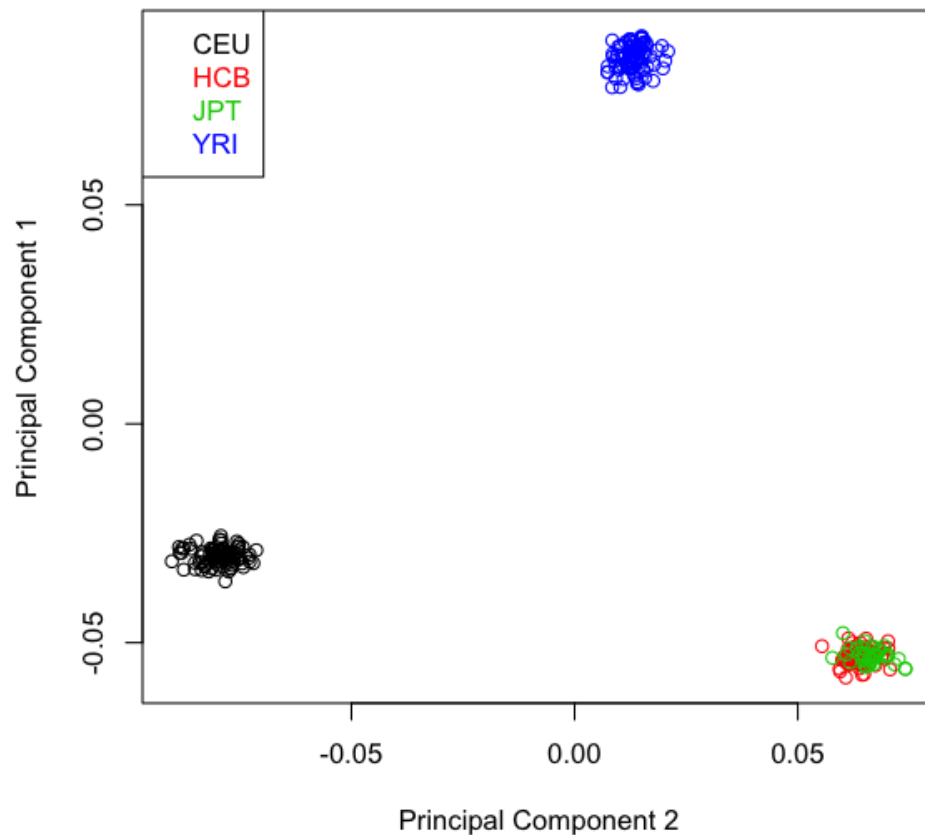
PCA:      the sum of all working genotypes (0, 1 and 2) = 1520268
PCA:      Sat Jan 5 02:49:39 2013      0%
PCA:      Sat Jan 5 02:49:39 2013      100%
PCA:      Sat Jan 5 02:49:39 2013      Begin (eigenvalues and eigenvectors)
PCA:      Sat Jan 5 02:49:39 2013      End (eigenvalues and eigenvectors)

```

```

> plot(pca$eigenvect[,2], pca$eigenvect[,1], xlab="Principal Component 2",
+      ylab="Principal Component 1", type="n")
> # uses different colors with respect to ethnicities
> race <- as.factor(read.gdsn(index.gdsn(genofile,
+      c("sample.annot", "pop.group"))))
> points(pca$eigenvect[,2], pca$eigenvect[,1], col=race)
> legend("topleft", legend=levels(race), text.col=1:nlevels(race))

```



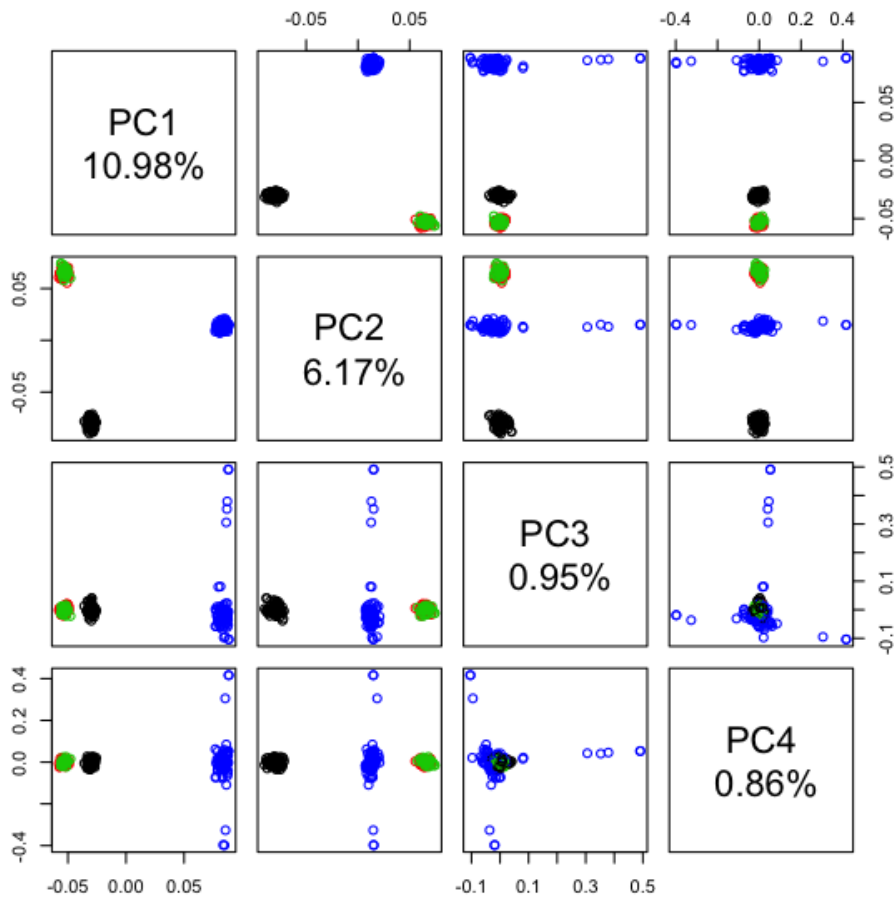
The code below shows how to calculate the percent of variation is accounted for by the principal component for the first 16 PCs. It is clear to see the first two eigenvectors hold the largest percentage of variance among the population, although the total variance accounted for is still less the one-quarter of the total.

```
> pc.percent <- 100 * pca$eigenval[1:16]/sum(pca$eigenval)
> pc.percent

[1] 10.9751270  6.1747791  0.9482941  0.8578218  0.7980118  0.7767799
[7]  0.7558140  0.7147553  0.6763739  0.6640410  0.6623270  0.6568874
[13]  0.6511425  0.6505608  0.6371916  0.6301307
```

Plot the principal component pairs for the first four PCs:

```
> lbls <- paste("PC", 1:4, "\n", format(pc.percent[1:4], digits=2), "%", sep="")
> pairs(pca$eigenvect[,1:4], col=race, labels=lbls)
```



To calculate the SNP correlations between eigenvectors and SNP genotypes:

```
> # get chromosome index
> chr <- read.gdsn(index.gdsn(genofile, "snp.chromosome"))
> CORR <- snpgdsPCACorr(pca, genofile, eig.which=1:4)
```

SNP correlations:

Working space: 279 samples, 9088 SNPs

Using 1 CPU core.

Using the top 32 eigenvectors.

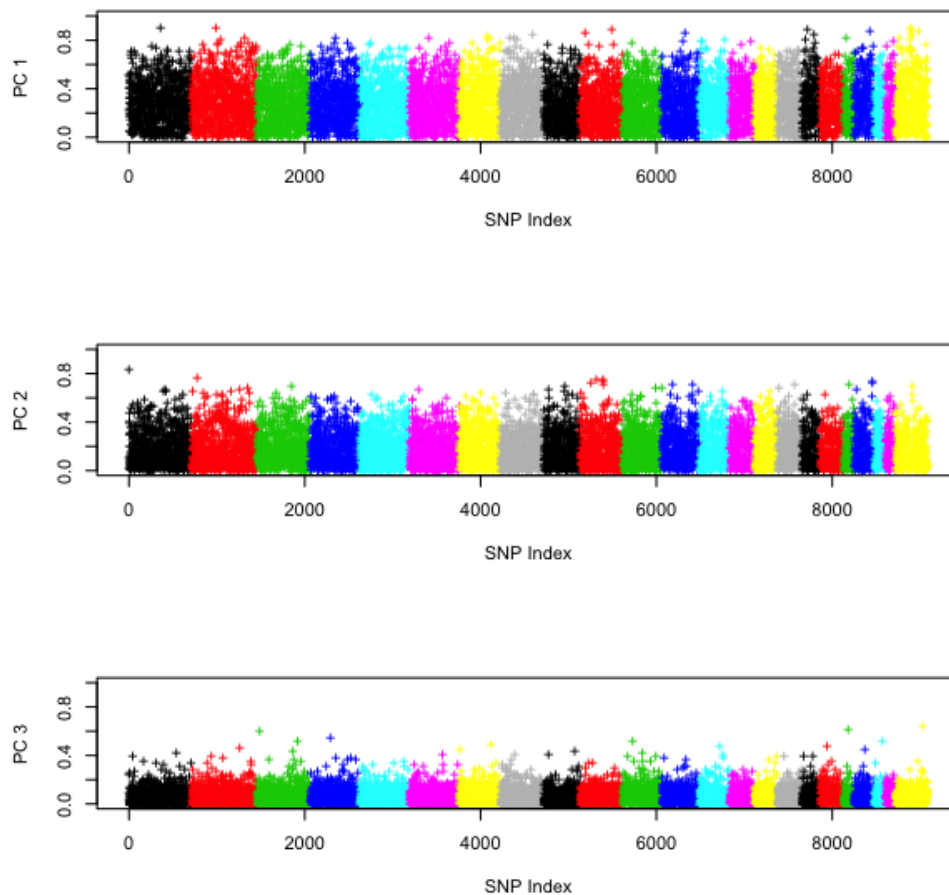
SNP Correlations: the sum of all working genotypes (0, 1 and 2) = 2553065

SNP Correlations: Sat Jan 5 02:49:39 2013 0%

SNP Correlations: Sat Jan 5 02:49:40 2013 100%

```
> par( mfrow=c(3,1))
> for (i in 1:3)
+ {
```

```
+      plot(abs(CORR$snpcorr[i,]), ylim=c(0,1), xlab="SNP Index",
+           ylab=paste("PC", i), col=chr, pch="+")
+ }
```



3.3 Relatedness Analysis

For relatedness analysis, identity-by-descent (IBD) estimation in **SNPRelate** can be done by either the method of moments (MoM) (Purcell et al., 2007) or maximum likelihood estimation (MLE) (Milligan, 2003; Choi et al., 2009). Although MLE estimates are more reliable than MoM, MLE is significantly more computationally intensive. For both of these methods it is preferred to use a LD pruned SNP set.

```
> # YRI samples
> sample.id <- read.gdsn(index.gdsn(genofile, "sample.id"))
> YRI.id <- sample.id[read.gdsn(index.gdsn(genofile,
+      c("sample.annot", "pop.group"))) == "YRI"]
```

3.3.1 PLINK method of moments (MoM)

```
> # estimate IBD coefficients
> ibd <- snpgdsIBDMoM(genofile, sample.id=YRI.id, snp.id=snpset.id,
+ maf=0.05, missing.rate=0.05)
```

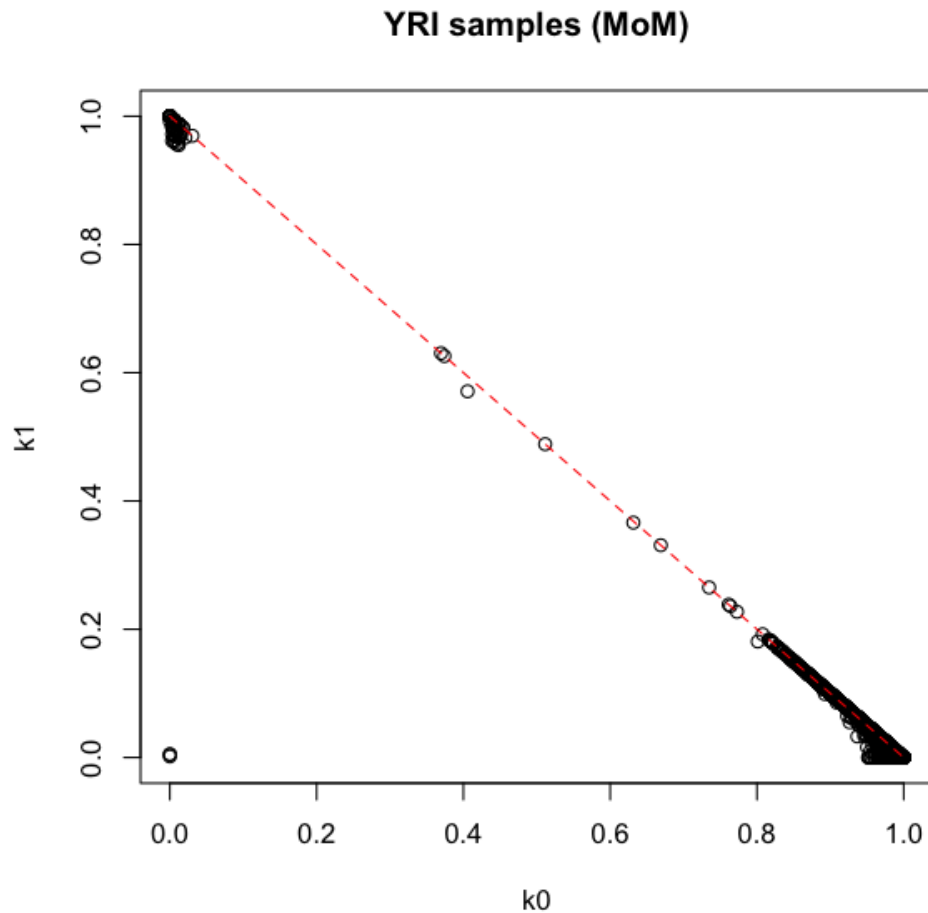
Identity-By-Descent analysis (PLINK method of moment) on SNP genotypes:
Removing 1294 SNPs (monomorphic, < MAF, or > missing rate)
Working space: 93 samples, 5249 SNPs
Using 1 CPU core.

```
PLINK IBD:      the sum of all working genotypes (0, 1 and 2) = 484063
PLINK IBD:      Sat Jan  5 02:50:08 2013      0%
PLINK IBD:      Sat Jan  5 02:50:08 2013      100%
```

```
> ibd.coeff <- snpgdsIBDSelection(ibd)
> head(ibd.coeff)
```

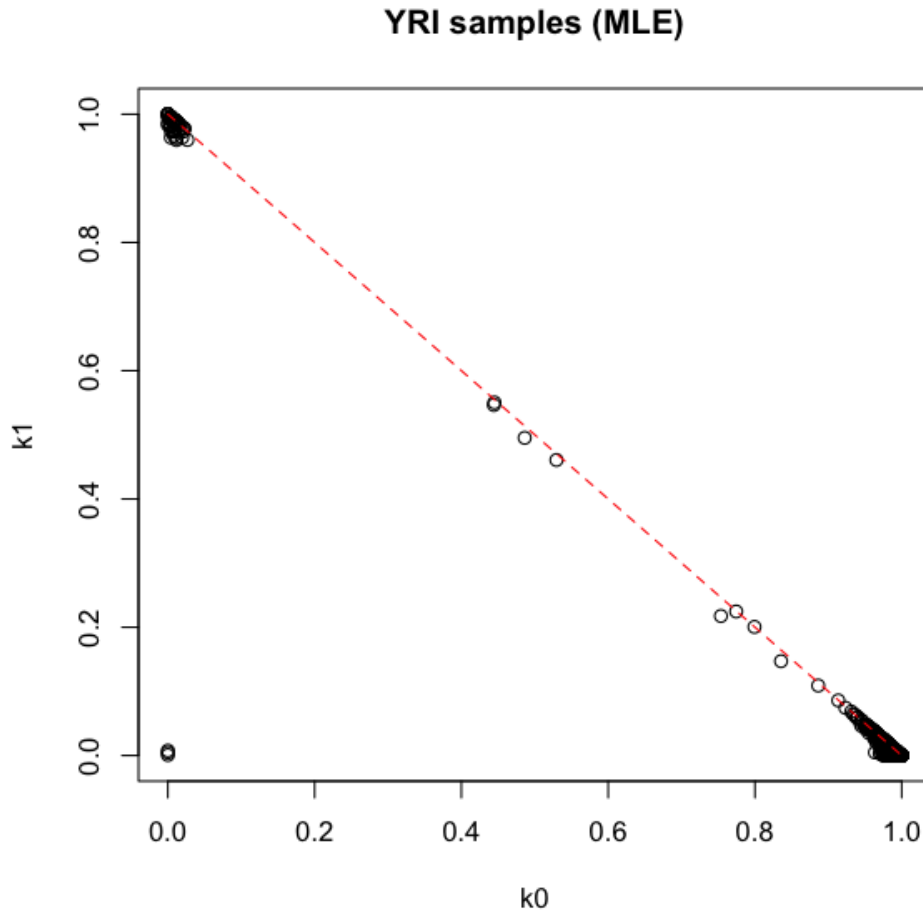
	sample1	sample2	k0	k1	kinshipcoeff
1	NA19152	NA19139	0.9237838	0.07621619	0.01905405
2	NA19152	NA18912	1.0000000	0.00000000	0.00000000
3	NA19152	NA19160	1.0000000	0.00000000	0.00000000
4	NA19152	NA18515	0.9252310	0.07476900	0.01869225
5	NA19152	NA19222	1.0000000	0.00000000	0.00000000
6	NA19152	NA18508	0.9342476	0.06575239	0.01643810

```
> plot(ibd.coeff$k0, ibd.coeff$k1, xlim=c(0,1), ylim=c(0,1),
+ xlab="k0", ylab="k1", main="YRI samples (MoM)")
> lines(c(0,1), c(1,0), col="red", lty=2)
```



3.3.2 IBD Using Maximum Likelihood Estimation (MLE)

```
> # estimate IBD coefficients
> set.seed(1000)
> snp.id <- sample(snpset.id, 5000) # random 5000 SNPs
> ibd <- snpgdsIBDMLE(genofile, sample.id=YRI.id, snp.id=snp.id,
+   maf=0.05, missing.rate=0.05)
> ibd.coeff <- snpgdsIBDSelection(ibd)
> plot(ibd.coeff$k0, ibd.coeff$k1, xlim=c(0,1), ylim=c(0,1),
+   xlab="k0", ylab="k1", main="YRI samples (MLE)")
> lines(c(0,1), c(1,0), col="red", lty=2)
```



3.4 Identity-By-State Analysis

For the n individuals in a sample, **snpgdsIBS** can be used to create a $n \times n$ matrix of genome-wide average IBS pairwise identities:

```
> ibs <- snpgdsIBS(genofile, num.thread=2)
```

Identity-By-State (IBS) analysis on SNP genotypes:

Removing 365 non-autosomal SNPs

Removing 1 SNPs (monomorphic, < MAF, or > missing rate)

Working space: 279 samples, 8722 SNPs

Using 2 CPU cores.

IBS: the sum of all working genotypes (0, 1 and 2) = 2446510

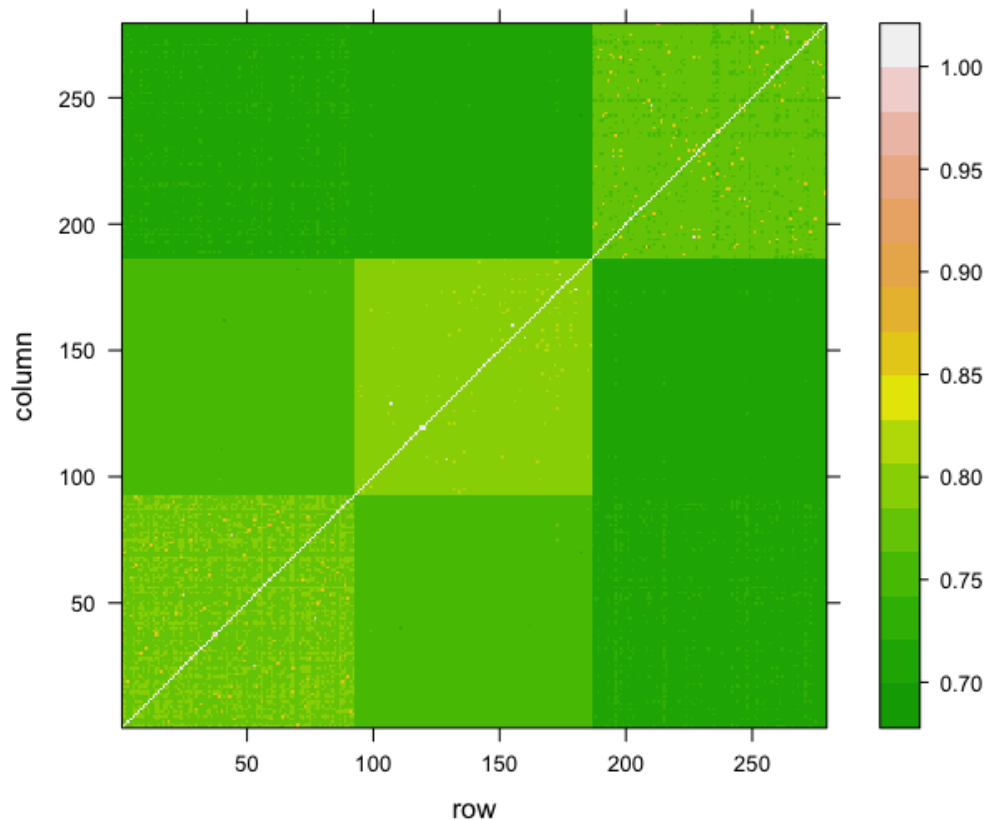
IBS: Sat Jan 5 02:50:08 2013 0%

IBS: Sat Jan 5 02:50:08 2013 100%

```
> pop <- read.gdsn(index.gdsn(genofile, c("sample.annot", "pop.group")))
```

The heat map is shown:

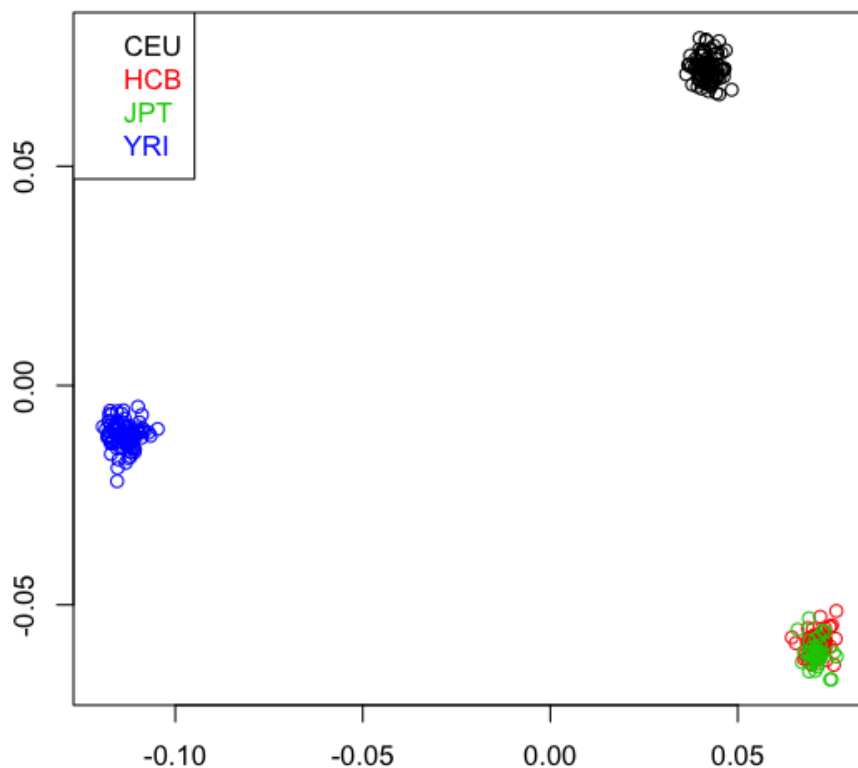
```
> library(lattice)
> L <- order(pop)
> levelplot(ibs$ibs[L, L], col.regions = terrain.colors)
```



To perform multidimensional scaling analysis on the $n \times n$ matrix of genome-wide IBS pairwise distances:

```
> loc <- cmdscale(1 - ibs$ibs, k = 2)
> x <- loc[, 1]; y <- loc[, 2]
> race <- as.factor(pop)
> plot(x, y, col=race, xlab = "", ylab = "",
+      main = "Multidimensional Scaling Analysis (IBS Distance)")
> legend("topleft", legend=levels(race), text.col=1:nlevels(race))
```


Multidimensional Scaling Analysis (IBS Distance)



To perform cluster analysis on the $n \times n$ matrix of genome-wide IBS pairwise distances, and determine the groups by a permutation score:

```
> set.seed(100)
> ibs.hc <- snpgdsHCluster(snpgdsIBS(genofile, num.thread=2))
```

Identity-By-State (IBS) analysis on SNP genotypes:

Removing 365 non-autosomal SNPs

Removing 1 SNPs (monomorphic, < MAF, or > missing rate)

Working space: 279 samples, 8722 SNPs

Using 2 CPU cores.

IBS: the sum of all working genotypes (0, 1 and 2) = 2446510

IBS: Sat Jan 5 02:50:11 2013 0%

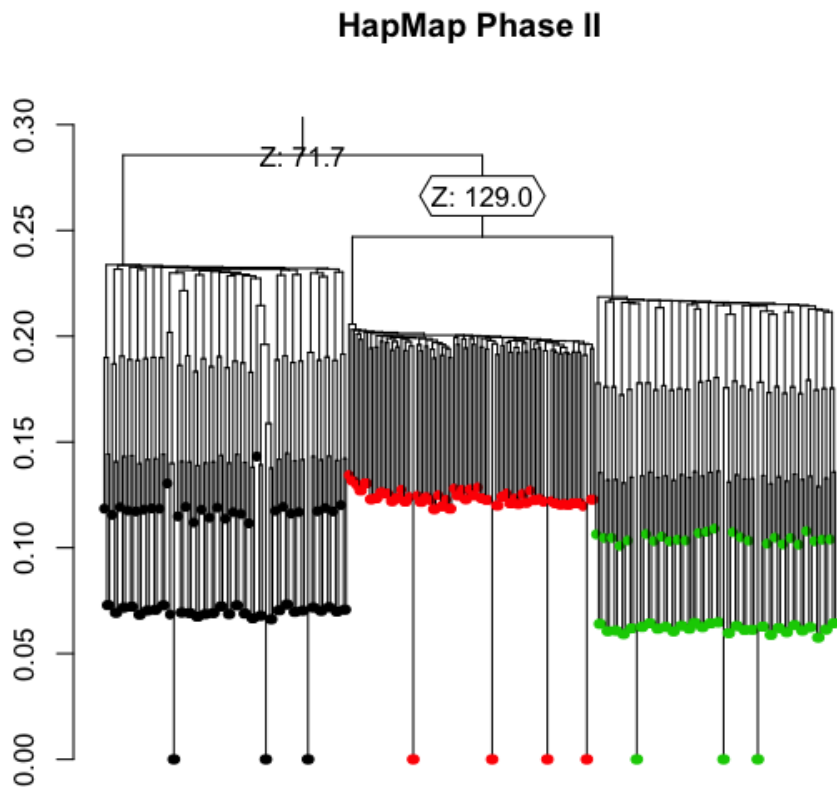
IBS: Sat Jan 5 02:50:11 2013 100%

```
> rv <- snpgdsCutTree(ibs.hc)
```

Determine groups by permutation (Z threshold: 15, outlier threshold: 5):
Create 3 groups.

```
> plot(rv$dendrogram, leaflab="none", main="HapMap Phase II")
> table(rv$samp.group)
```

```
G001 G002 G003
  93   94   92
```

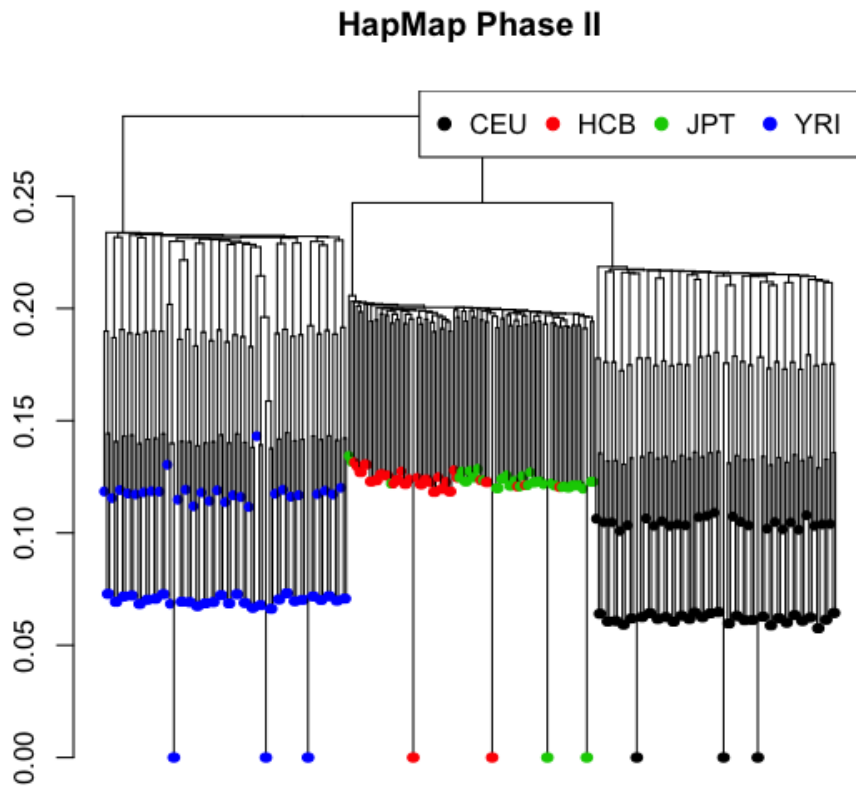


Here is the population information we have known:

```
> rv2 <- snpgdsCutTree(ibs.hc, samp.group=as.factor(pop))
```

Create 4 groups.

```
> plot(rv2$dendrogram, leaflab="none", main="HapMap Phase II")
> legend("topright", legend=levels(race), col=1:nlevels(race), pch=19, ncol=4)
```



```
> # close the GDS file
> closefn.gds(genofile)
```

4 Resources

1. CoreArray project: <http://corearray.sourceforge.net/>
2. gdsfmt R package: <http://cran.r-project.org/web/packages/gdsfmt/index.html>
3. SNPRelate R package: <http://cran.r-project.org/web/packages/SNPRelate/index.html>
4. GENEVA R package: <https://www.genevastudy.org/Accomplishments/software>
5. GWASTools: an R/Bioconductor package for quality control and analysis of Genome-Wide Association Studies <http://www.bioconductor.org/packages/2.11/bioc/html/GWASTools.html>

5 References

1. **A High-performance Computing Toolset for Relatedness and Principal Component Analysis of SNP Data.** Xiuwen Zheng; David Levine; Jess Shen; Stephanie M. Gogarten; Cathy Laurie; Bruce S. Weir. Bioinformatics 2012; doi: 10.1093/bioinformatics/bts606.
2. **GWASTools: an R/Bioconductor package for quality control and analysis of Genome-Wide Association Studies.** Stephanie M. Gogarten, Tushar Bhangale, Matthew P. Conomos, Cecelia A. Laurie, Caitlin P. McHugh, Ian Painter, Xiuwen Zheng, David R. Crosslin, David Levine, Thomas Lumley, Sarah C. Nelson, Kenneth Rice, Jess Shen, Rohit Swarnkar, Bruce S. Weir, and Cathy C. Laurie. Bioinformatics 2012; doi:10.1093/bioinformatics/bts610.
3. **Quality control and quality assurance in genotypic data for genome-wide association studies.** Laurie CC, Doheny KF, Mirel DB, Pugh EW, Bierut LJ, Bhangale T, Boehm F, Caporaso NE, Cornelis MC, Edenberg HJ, Gabriel SB, Harris EL, Hu FB, Jacobs KB, Kraft P, Landi MT, Lumley T, Manolio TA, McHugh C, Painter I, Paschall J, Rice JP, Rice KM, Zheng X, Weir BS; GENEVA Investigators. Genet Epidemiol. 2010 Sep;34(6):591-602.

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