A Genetic Analysis Package with R

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Contents

1 Introduction

This package was initiated to integrate some C/Fortran/SAS programs I have written or used over the years. As such, it would rather be a long-term project, but an immediate benefit would be something complementary to other packages currently available from CRAN, e.g. **genetics**, **hwde**, etc. I hope eventually this will be part of a bigger effort to fulfill most of the requirements foreseen by many, e.g. Guo and Lange (2000), within the portable environment of R for data management, analysis, graphics and object-oriented programming. My view has been outlined more formally in Zhao and Tan (2006b) and Zhao and Tan (2006a) in relation to other package systems. Also reported are Zhao (2005) and Zhao (2006) on package **kinship**.

The number of functions are quite limited and experimental, but I already feel the enormous advantage by shifting to R and would like sooner rather than later to share my work with others. I will not claim this workas exclusively done by me, but would like to invite others to join me and enlarge the collections and improve them.

2 Implementation

The following list shows the data and functions currently available.

BFDP	Bayesian false-discovery probability
FPRP	False-positive report probability
SNP	Functions for single nucleotide polymorphisms (SNPs)
ab	Test/Power calculation for mediating effect
aldh2	ALDH2 markers and alcoholism
apoeapoc	APOE/APOC1 markers and schizophrenia
asplot	Regional association plot
bt	Bradley-Terry model for contingency table
b2r	Obtain correlation coefficients and their variance-covariances
ccsize	Power and sample size for case-cohort design
chow.test	Chow's test for heterogeneity in two regressions
cf	Cystic Fibrosis data
comp.score	score statistics for testing genetic linkage of quantitative trait
crohn	Crohn's disease data
ESplot	Effect-size plot
fa	Friedreich ataxia data
fbsize	Sample size for family-based linkage and association design
fsnps	A case-control data involving four SNPs with missing genotype
gc.em	Gene counting for haplotype analysis
gcontrol	genomic control
gcontrol2	genomic control based on p values
gcp	Permutation tests using GENECOUNTING
genecounting	Gene counting for haplotype analysis
gif	Kinship coefficient and genetic index of familiality
hap	Haplotype reconstruction
hap.em	Gene counting for haplotype analysis
hap.score	Score statistics for association of traits with haplotypes
hla	HLA markers and schizophrenia
htr	Haplotype trend regression
h2	Heritability estimation according to twin correlations
hwe	Hardy-Weinberg equilibrium test for a multiallelic marker
hwe.cc	A likelihood ratio test of population Hardy-Weinberg equilibrium for case-control studies
hwe.hardy	Hardy-Weinberg equilibrium test using MCMC
kin.morgan	kinship matrix for simple pedigree
klem	Haplotype frequency estimation based on a genotype table of two multiallelic markers
LD22	LD statistics for two diallelic markers
LDkl	LD statistics for two multiallelic markers
lukas	An example pedigree

makeped	A function to prepare pedigrees in post-MAKEPED format
mao	A study of Parkinson's disease and MAO gene
masize	Sample size calculation for mediation analysis
metap	Meta-analysis of p values
metareg	Fixed and random effects model for meta-analysis
mhtplot	Manhattan plot of p values
mia	multiple imputation analysis for hap
mtdt	Transmission/disequilibrium test of a multiallelic marker
mtdt2	Transmission/disequilibrium test of a multiallelic marker by Bradley-Terry model
muvar	Means and variances under 1- and 2- locus (diallelic) QTL model
mvmeta	Multivariate meta-analysis based on generalized least squares
nep499	A study of Alzheimer's disease with eight SNPs and APOE
pbsize	Power for population-based association design
pbsize2	Power for case-control association design
pedtodot	Converting pedigree(s) to dot file(s)
pfc	Probability of familial clustering of disease
pfc.sim	Probability of familial clustering of disease
pgc	Preparing weight for GENECOUNTING
plot.hap.score	Plot haplotype frequencies versus haplotype score statistics
print.hap.score	Print a hap.score object
qqfun	Quantile-comparison plots
qqunif	Q-Q plot for uniformly distributed random variable
read.ms.output	A utility function to read ms output
s2k	Statistics for 2 by K table
snca	A study of Parkinson's disease and SNCA markers
tscc	Power calculation for two-stage case-control design
twinan90	Classic twin models
whscore	Whittemore-Halpern scores for allele-sharing

Assuming proper installation, you will be able to obtain the list by typing `library(help=gap)` or view the list within a web browser via `help.start()`. A PDF version of this file can be viewed with command `vignette("gap",package="gap")`.

You can cut and paste examples at end of each function's documentation.

Both *genecounting* and *hap* are able to handle SNPs and multiallelic markers, with the former be flexible enough to include features such as X-linked data and the later being able to handle large number of SNPs. But they are unable to recode allele labels automatically, so functions *gc.em* and *hap.em* are in *haplo.em* format and used by a modified function *hap.score* in association testing.

It is notable that multilocus data are handled differently from that in **hwde** and elegant definitions of basic genetic data can be found in **genetics** package.

Incidentally, I found my C mixed-radixed sorting routine as in Zhao and Sham (2003) is much faster than R's internal function.

With exceptions such as function *pfc* which is very computer-intensive, most functions in the package can easily be adapted for analysis of large datasets involving either SNPs or multiallelic markers. Some are utility functions, e.g. *muvar* and *whscore*, which will be part of the other analysis routines in the future.

The benefit with R compared to standalone programs is that for users, all functions have unified format. For developers, it is able to incorporate their C/C++ programs more easily and avoid repetitive work such as preparing own routines for matrix algebra and linear models. Further advantage can be taken from packages in **Bioconductor**, which are designed and written to deal with large number of genes.

I have included ms code and .xls files to accompany *read.ms.output* and *FPRP* and *BFDP* functions as with a classic twin example for ACE model in **OpenMx**. The package can be installed with command,

```
source('http://openmx.psyc.virginia.edu/getOpenMx.R')
```

3 Demos

You can also try several simple examples via *demo*:

```
library(gap)
demo(gap)
```

4 Examples

I would like to highlight *pbsize*, *fbsize* and *ccsize* functions used for power/sample calculations in a genome-wide asssociatoin study as reported in Zhao (2007).

4.1 Study design

Family-based design

The example involving family-based design is as follows,

```
> library(gap)

[1] "R/gap is loaded"

> models <- matrix(c(4, 0.01, 4, 0.1, 4, 0.5, 4, 0.8, 2, 0.01,
+     2, 0.1, 2, 0.5, 2, 0.8, 1.5, 0.01, 1.5, 0.1, 1.5, 0.5, 1.5,
+     0.8), ncol = 2, byrow = TRUE)
> outfile <- "fbsize.txt"
> cat("gamma", "p", "Y", "N_asp", "P_A", "H1", "N_tdt", "H2", "N_asp/tdt",
+     "L_o", "L_s\n", file = outfile, sep = "\t")
> for (i in 1:12) {
```

```
+     g <- models[i, 1]
+     p <- models[i, 2]
+     z <- fbsize(g, p)
+     cat(z$gamma, z$p, z$y, z$n1, z$pA, z$h1, z$n2, z$h2, z$n3,
+         z$lambdao, z$lambdas, file = outfile, append = TRUE,
+         sep = "\t")
+     cat("\n", file = outfile, append = TRUE)
+ }
> table1 <- read.table(outfile, header = TRUE, sep = "\t")
> nc <- c(4, 7, 9)
> table1[, nc] <- ceiling(table1[, nc])
> dc <- c(3, 5, 6, 8, 10, 11)
> table1[, dc] <- round(table1[, dc], 2)
> unlink(outfile)
> g <- 4.5
> p <- 0.15
> cat("\nAlzheimer's:\n\n")

Alzheimer's:

> fbsize(g, p)

$gamma
[1] 4.5

$p
[1] 0.15

$y
[1] 0.6256916

$n1
[1] 162.6246

$pA
[1] 0.8181818

$h1
[1] 0.4598361

$n2
[1] 108.994

$h2
[1] 0.6207625

$n3
```

```
[1] 39.97688

$lambdao
[1] 1.671594

$lambdas
[1] 1.784353
```

```
> table1
```

```
   gamma    p    Y   N_asp  P_A   H1 N_tdt   H2 N_asp.tdt  L_o  L_s
1    4.0 0.01 0.52    6402 0.80 0.05  1201 0.11       257 1.08 1.09
2    4.0 0.10 0.60     277 0.80 0.35   165 0.54        53 1.48 1.54
3    4.0 0.50 0.58     446 0.80 0.50   113 0.42        67 1.36 1.39
4    4.0 0.80 0.53    3024 0.80 0.24   244 0.16       177 1.12 1.13
5    2.0 0.01 0.50  445964 0.67 0.03  6371 0.04      2155 1.01 1.01
6    2.0 0.10 0.52    8087 0.67 0.25   761 0.32       290 1.07 1.08
7    2.0 0.50 0.53    3753 0.67 0.50   373 0.47       197 1.11 1.11
8    2.0 0.80 0.51   17909 0.67 0.27   701 0.22       431 1.05 1.05
9    1.5 0.01 0.50 6944779 0.60 0.02 21138 0.03      8508 1.00 1.00
10   1.5 0.10 0.51  101926 0.60 0.21  2427 0.25      1030 1.02 1.02
11   1.5 0.50 0.51   27048 0.60 0.50  1039 0.49       530 1.04 1.04
12   1.5 0.80 0.51  101926 0.60 0.29  1820 0.25      1030 1.02 1.02
```

Population-based design

The example involving population-based design is as follows,

```
> library(gap)
> kp <- c(0.01, 0.05, 0.1, 0.2)
> models <- matrix(c(4, 0.01, 4, 0.1, 4, 0.5, 4, 0.8, 2, 0.01,
+     2, 0.1, 2, 0.5, 2, 0.8, 1.5, 0.01, 1.5, 0.1, 1.5, 0.5, 1.5,
+     0.8), ncol = 2, byrow = TRUE)
> outfile <- "pbsize.txt"
> cat("gamma", "p", "p1", "p5", "p10", "p20\n", sep = "\t", file = outfile)
> for (i in 1:dim(models)[1]) {
+     g <- models[i, 1]
+     p <- models[i, 2]
+     n <- vector()
+     for (k in kp) n <- c(n, ceiling(pbsize(k, g, p)))
+     cat(models[i, 1:2], n, sep = "\t", file = outfile, append = TRUE)
+     cat("\n", file = outfile, append = TRUE)
+ }
> table5 <- read.table(outfile, header = TRUE, sep = "\t")
> table5
```

```
   gamma    p      p1     p5    p10   p20
1    4.0 0.01   46681   8959   4244  1887
```

```
2    4.0 0.10    8180   1570    744   331
3    4.0 0.50   10891   2091    991   441
4    4.0 0.80   31473   6041   2862  1272
5    2.0 0.01  403970  77530  36725 16323
6    2.0 0.10   52709  10116   4792  2130
7    2.0 0.50   35285   6772   3208  1426
8    2.0 0.80   79391  15237   7218  3208
9    1.5 0.01 1599920 307056 145448 64644
10   1.5 0.10  192105  36869  17465  7762
11   1.5 0.50   98013  18811   8911  3961
12   1.5 0.80  192105  36869  17465  7762
```

Case-cohort design

For case-cohort design, we obtain results for ARIC and EPIC studies.

```
> library(gap)
> outfile <- "aric.txt"
> n <- 15792
> pD <- 0.03
> p1 <- 0.25
> alpha <- 0.05
> theta <- c(1.35, 1.4, 1.45)
> beta1 <- 0.8
> s_nb <- c(1463, 722, 468)
> cat("n", "pD", "p1", "hr", "q", "power", "ssize\n", file = outfile,
+     sep = "\t")
> for (i in 1:3) {
+     q <- s_nb[i]/n
+     power <- ccsize(n, q, pD, p1, alpha, log(theta[i]))
+     ssize <- ccsize(n, q, pD, p1, alpha, log(theta[i]), beta1)
+     cat(n, "\t", pD, "\t", p1, "\t", theta[i], "\t", q, "\t",
+         signif(power, 3), "\t", ssize, "\n", file = outfile,
+         append = TRUE)
+ }
> read.table(outfile, header = TRUE, sep = "\t")

      n   pD   p1   hr          q power ssize
1 15792 0.03 0.25 1.35 0.09264184   0.8  1463
2 15792 0.03 0.25 1.40 0.04571935   0.8   722
3 15792 0.03 0.25 1.45 0.02963526   0.8   468

> unlink(outfile)
> outfile <- "epic.txt"
> n <- 25000
> alpha <- 5e-08
> power <- 0.8
> s_pD <- c(0.3, 0.2, 0.1, 0.05)
```

```
> s_p1 <- seq(0.1, 0.5, by = 0.1)
> s_hr <- seq(1.1, 1.4, by = 0.1)
> cat("n", "pD", "p1", "hr", "alpha", "ssize\n", file = outfile,
+     sep = "\t")
> for (pD in s_pD) {
+     for (p1 in s_p1) {
+         for (hr in s_hr) {
+             ssize <- ccsize(n, q, pD, p1, alpha, log(hr), power)
+             if (ssize > 0)
+                 cat(n, "\t", pD, "\t", p1, "\t", hr, "\t", alpha,
+                   "\t", ssize, "\n", file = outfile, append = TRUE)
+         }
+     }
+ }
> read.table(outfile, header = TRUE, sep = "\t")

       n  pD  p1  hr alpha ssize
1  25000 0.3 0.1 1.3 5e-08 14391
2  25000 0.3 0.1 1.4 5e-08  5732
3  25000 0.3 0.2 1.2 5e-08 21529
4  25000 0.3 0.2 1.3 5e-08  5099
5  25000 0.3 0.2 1.4 5e-08  2613
6  25000 0.3 0.3 1.2 5e-08 11095
7  25000 0.3 0.3 1.3 5e-08  3490
8  25000 0.3 0.3 1.4 5e-08  1882
9  25000 0.3 0.4 1.2 5e-08  8596
10 25000 0.3 0.4 1.3 5e-08  2934
11 25000 0.3 0.4 1.4 5e-08  1611
12 25000 0.3 0.5 1.2 5e-08  7995
13 25000 0.3 0.5 1.3 5e-08  2786
14 25000 0.3 0.5 1.4 5e-08  1538
15 25000 0.2 0.1 1.4 5e-08  9277
16 25000 0.2 0.2 1.3 5e-08  7725
17 25000 0.2 0.2 1.4 5e-08  3164
18 25000 0.2 0.3 1.3 5e-08  4548
19 25000 0.2 0.3 1.4 5e-08  2152
20 25000 0.2 0.4 1.2 5e-08 20131
21 25000 0.2 0.4 1.3 5e-08  3648
22 25000 0.2 0.4 1.4 5e-08  1805
23 25000 0.2 0.5 1.2 5e-08 17120
24 25000 0.2 0.5 1.3 5e-08  3422
25 25000 0.2 0.5 1.4 5e-08  1713
26 25000 0.1 0.2 1.4 5e-08  8615
27 25000 0.1 0.3 1.4 5e-08  3776
28 25000 0.1 0.4 1.3 5e-08 13479
29 25000 0.1 0.4 1.4 5e-08  2824
30 25000 0.1 0.5 1.3 5e-08 10837
```

```
31 25000 0.1 0.5 1.4 5e-08  2606
```

```
> unlink(outfile)
```

4.2 Kinship calculation

Next, I will provide an example for kinship calculation using *kin.morgan*. It is recommended that individuals in a pedigree are ordered so that parents always precede their children. In this regard, package **pedigree** can be used, and package **kinship** can be used to produce pedigree diagram as with kinship matrix.

Pedigree diagram

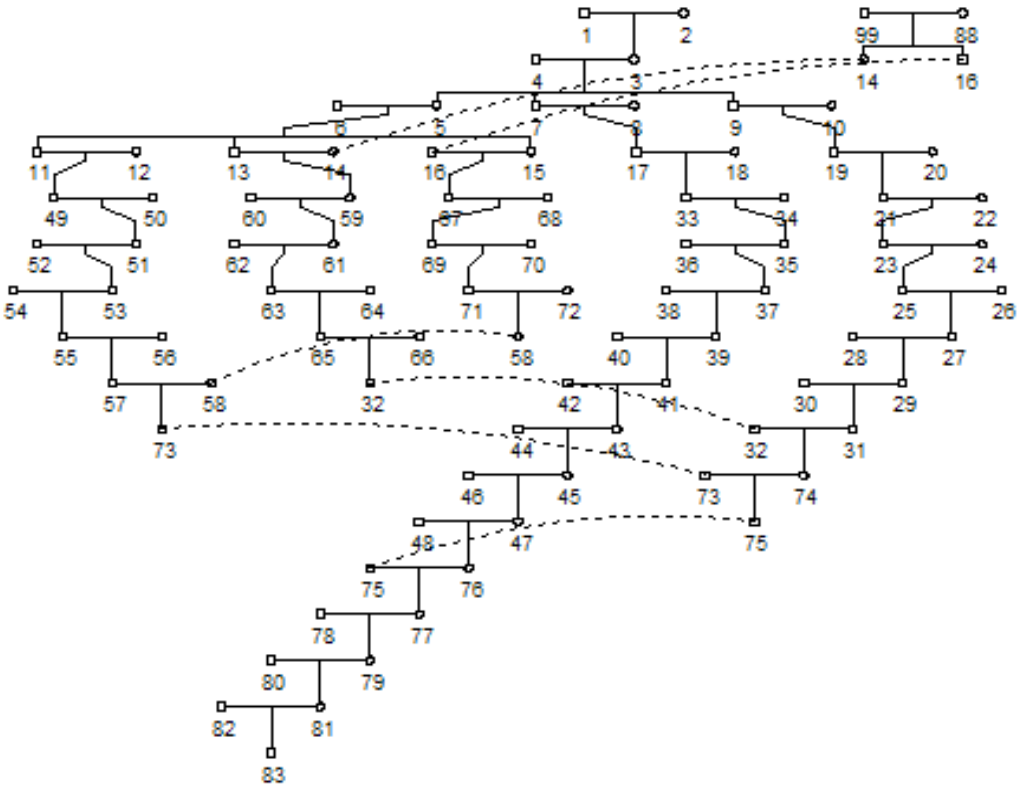
```
> data(lukas, package = "gap")
> library(kinship)
```

```
[1] "kinship is loaded"
```

```
> kmat <- with(lukas, kinship(id, father, mother))
> ped <- with(lukas, pedigree(id, father, mother, sex))
> png("figures/lukas.png")
> par(xpd = TRUE)
> with(ped, plot(ped, id = paste("\n", id)))
> dev.off()
```

```
null device
          1
```

The pedigree diagram is as follows,



Kinship calculation

We then turn to the kinship calculation.

```
> library(gap)
> gk1 <- kin.morgan(lukas)
> write.table(gk1$kin.matrix, "results/gap_1.txt", quote = FALSE)
> library(kinship)
> kk1 <- kinship(lukas[, 1], lukas[, 2], lukas[, 3])
> write.table(kk1, "results/kinship_1.txt", quote = FALSE)
> d <- gk1$kin.matrix - kk1
> sum(abs(d))

[1] 2.443634

> library(pedigree)
> op <- orderPed(lukas)
```

```
> olukas <- lukas[order(op), ]
> gk2 <- kin.morgan(olukas)
> write.table(olukas, "olukas.csv", quote = FALSE)
> write.table(gk2$kin.matrix, "results/gap_2.txt", quote = FALSE)
> kk2 <- kinship(olukas[, 1], olukas[, 2], olukas[, 3])
> write.table(kk2, "results/kinship_2.txt", quote = FALSE)
> z <- gk2$kin.matrix - kk2
> sum(abs(z))

[1] 0
```

We see that in the second case, the result agrees with **kinship**.

4.3 Graphics examples

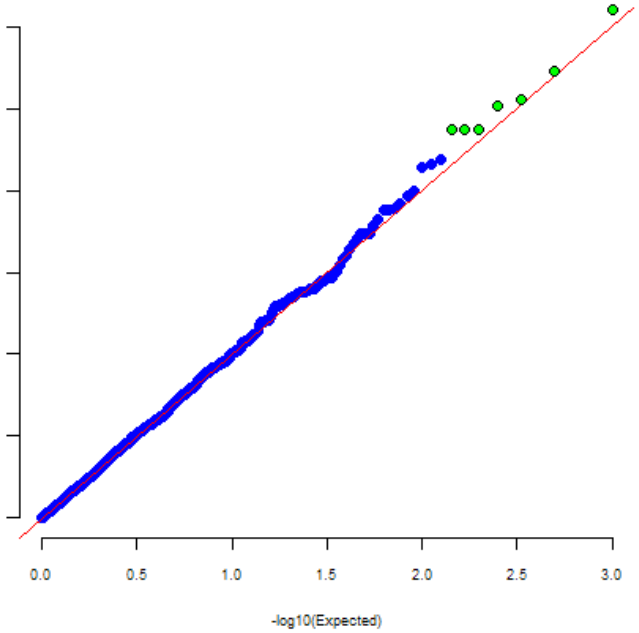
I now include some figures from the documentation that may be of interest.

Genome-wide association

The following code is used to obtain a Q-Q plot via *qqunif* function,

```
> library(gap)
> png("figures/qqunif.png")
> u_obs <- runif(1000)
> r <- qqunif(u_obs, pch = 21, bg = "blue", bty = "n")
> u_exp <- r$y
> hits <- u_exp >= 2.30103
> points(r$x[hits], u_exp[hits], pch = 21, bg = "green")
> dev.off()

null device
          1
```



The code below obtains a Manhattan plot via the *mhtplot* function,

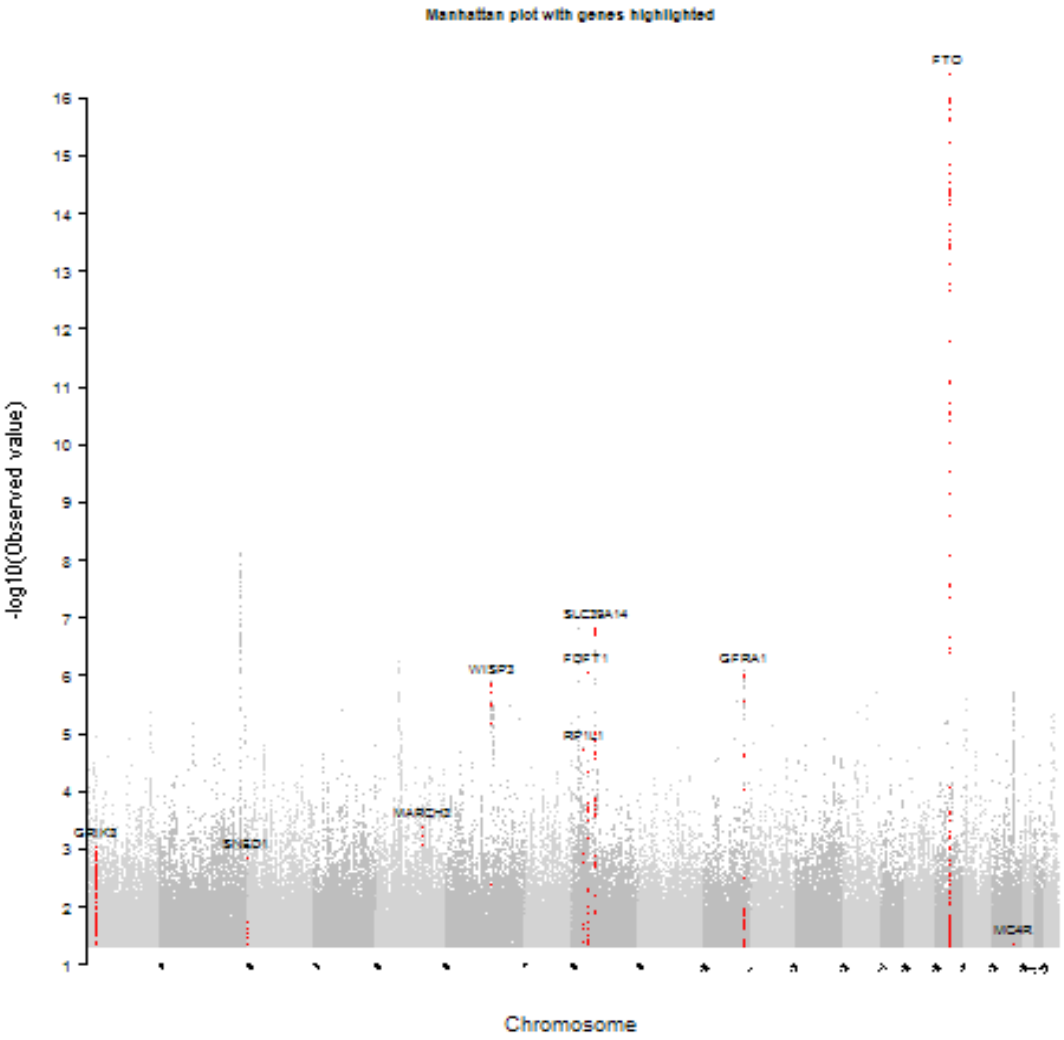
```
> library(gap)
> png("figures/mhtplot.png")
> data <- with(mhtdata, cbind(chr, pos, p))
> glist <- c("IRS1", "SPRY2", "FTO", "GRIK3", "SNED1", "HTR1A",
+     "MARCH3", "WISP3", "PPP1R3B", "RP1L1", "FDFT1", "SLC39A14",
+     "GFRA1", "MC4R")
> hdata <- subset(mhtdata, gene %in% glist)[c("chr", "pos", "p",
+     "gene")]
> color <- rep(c("lightgray", "gray"), 11)
> glen <- length(glist)
> hcolor <- rep("red", glen)
> par(las = 2, xpd = TRUE, cex.axis = 1.8, cex = 0.4)
> ops <- mht.control(colors = color, yline = 1.5, xline = 3)
> hops <- hmht.control(data = hdata, colors = hcolor)
> mhtplot(data, ops, hops, pch = 19)

Plotting points  1 - 12123
Plotting points  12124 - 26444
Plotting points  26445 - 37326
Plotting points  37327 - 47549
Plotting points  47550 - 58877
Plotting points  58878 - 71908
Plotting points  71909 - 79690
Plotting points  79691 - 90464
```

```
Plotting points  90465 - 101267
Plotting points  101268 - 109000
Plotting points  109001 - 116159
Plotting points  116160 - 124094
Plotting points  124095 - 130329
Plotting points  130330 - 134176
Plotting points  134177 - 139300
Plotting points  139301 - 143751
Plotting points  143752 - 148345
Plotting points  148346 - 153379
Plotting points  153380 - 155466
Plotting points  155467 - 157052
Plotting points  157053 - 159312
  ... highlighting 1559 - 1657 GRIK3
  ... highlighting 26343 - 26349 SNED1
  ... highlighting 55142 - 55144 MARCH3
  ... highlighting 66533 - 66539 WISP3
  ... highlighting 81546 - 81551 RP1L1
  ... highlighting 82146 - 82168 FDFT1
  ... highlighting 83425 - 83458 SLC39A14
  ... highlighting 107866 - 107894 GFRA1
  ... highlighting 141457 - 141576 FTO
  ... highlighting 152037 - 152037 MC4R

> axis(2, pos = 2, at = 1:16)
> title("Manhattan plot with genes highlighted", cex.main = 1.8)
> dev.off()

null device
          1
```



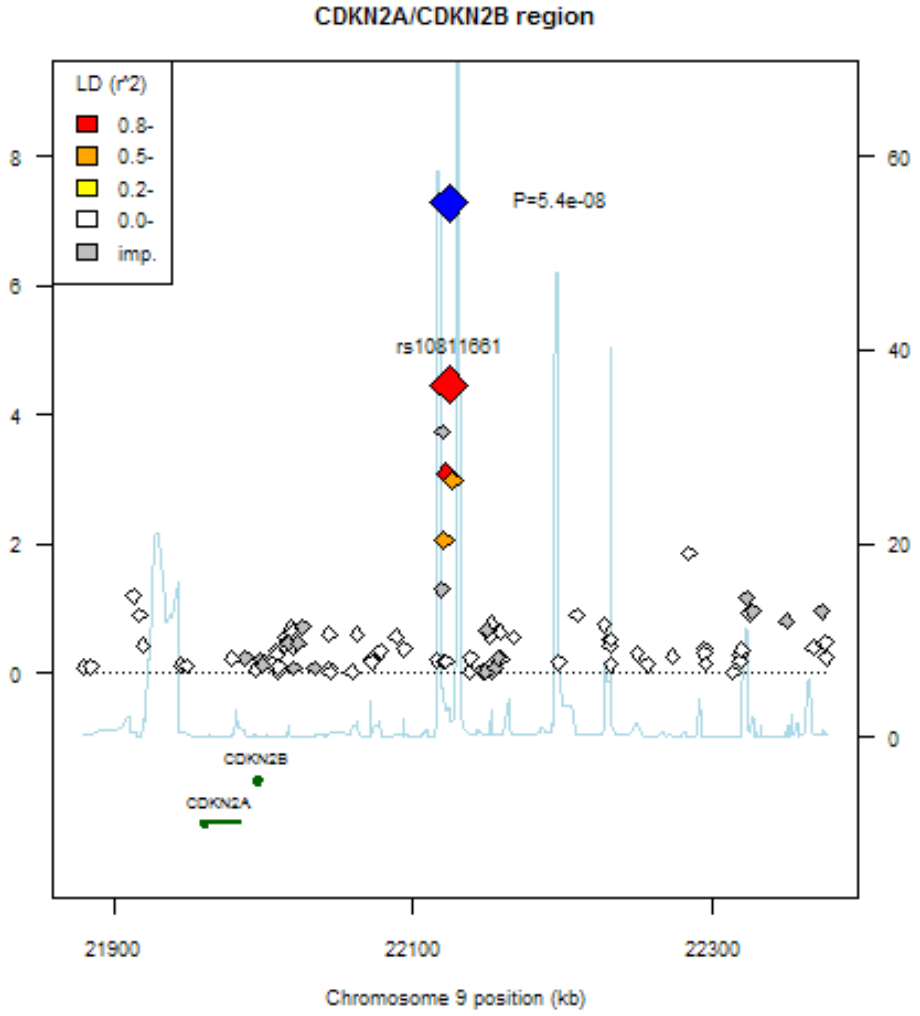
The code below obtains a regional association plot with the *asplot* function,

```
> library(gap)
> png("figures/asplot.png")
> asplot("rs10811661", "CDKN2A/CDKN2B region", "9", CDKNlocus,
+     CDKNmap, CDKNgenes, 5.4e-08, c(3, 6))

       START     STOP  SIZE STRAND   GENE
295 21957751 21984490 26739      - CDKN2A
483 21992902 21999312  6410      - CDKN2B

> dev.off()

null device
          1
```

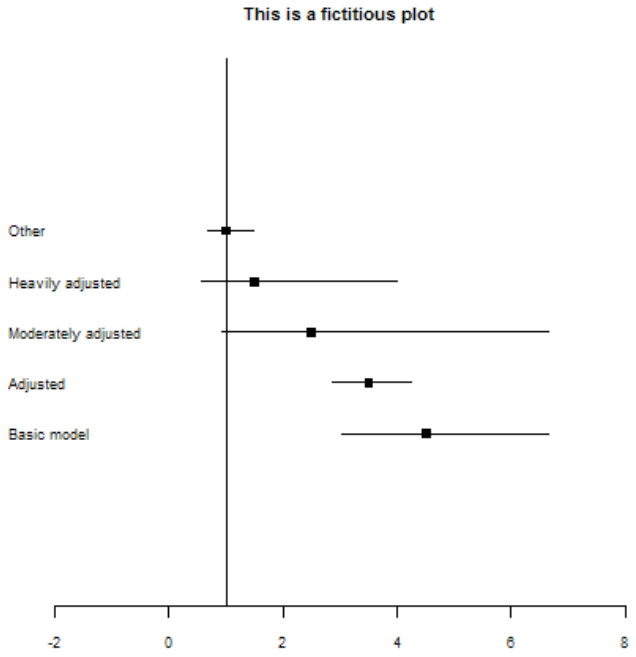


Effect size plot

The purpose of this function is simply for illustration.
The code below obtains an effect size plot via the ESplot function,

```
> library(gap)
> png("figures/ESplot.png")
> options(stringsAsFactors = FALSE)
> testdata <- data.frame(models = c("Basic model", "Adjusted",
+     "Moderately adjusted", "Heavily adjusted", "Other"), OR = c(4.5,
+     3.5, 2.5, 1.5, 1), SElogOR = c(0.2, 0.1, 0.5, 0.5, 0.2))
> ESplot(testdata, v = 1)
> title("This is a fictitious plot")
> dev.off()

null device
          1
```



Note that all these can serve as templates to customize features of your own.

5 Known bugs

Unaware of any bug. However, better memory management is expected.

6 Bibliographic note

The main references are Chow (1960), Guo and Thompson (1992), Williams et al. (1992), Gholamic and Thomas (1994), Hartung et al. (2008), Risch and Merikangas (1996), Spielman and Ewens (1996), Risch and Merikangas (1997), Miller (1997), Sham (1997), Elston (1975), Sham (1998), Devlin and Roeder (1999), Zhao et al. (1999), Guo and Lange (2000), Hirotsu et al. (2001), Zhao et al. (2002), Zaykin et al. (2002), Zhao (2004), Wacholder et al. (2004), Wang (2005), Skol et al. (2006), Wakefield (2007).

References

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