

# Package ‘GMRP’

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**Type** Package

**Title** GWAS-based Mendelian Randomization and Path Analyses

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**Description** Perform Mendelian randomization analysis of multiple SNPs to determine risk factors causing disease of study and to exclude confounding variabels and perform path analysis to construct path of risk factors to the disease.

**License** GPL ( $\geq 2$ )

**Depends** R( $\geq 3.3.0$ ),stats,utils,graphics, grDevices, diagram, plotrix, base,GenomicRanges

**Suggests** BiocStyle, BiocGenerics

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GMRP-package

*GWAS-based Mendelian Randomization Path Analysis*


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## Description

**GMRP** is used to perform Mendelian randomization analysis of causal variables on disease of study using SNP beta data from **GWAS** or **GWAS** meta analysis and furthermore execute path analysis of causal variables onto the disease.

## Details

**GMRP** can perform analyses of Mendelian randomization (MR), correlation, path of causal variables onto disease of interest and SNP annotation summarization analysis. MR includes SNP selection with given criteria and regression analysis of causal variables on the disease to generate beta values of causal variables on the disease. Using the beta values, **GMRP** performs correlation and path analyses to construct path diagrams of causal variables to the disease. **GMRP** consists of 8 functions: *chrp*, *fmerge*, *mktable*, *pathdiagram2*, *pathdiagram*, *path*, *snpPositAnnot*, *ucscannot* and 5 datasets: *beta.data*, *cad.data*, *lpd.data*, *SNP358.data* and *SNP368\_annot.data*. Function *chrp* is used to separate string vector hg19 into two numeric vectors: chromosome number and SNP position on chromosomes. Function *fmerge* is used to merge two datasets into one dataset. Function *mktable* performs SNP selection and creates a standard beta table for function *path* to do path analyses. Function *pathdiagram* is used to create a path diagram of causal variables onto the disease or onto outcome. Function *pathdiagram2* can merge two-level pathdiagrams into one nested pathdiagram where inner path diagram is a path diagram of causal variables contributing onto outcome and the outside path diagram is a diagram of path of causal variables including outcome onto the disease. The five datasets provide examples for running these functions. *lpd.data* and *cad.data* provide an example to create a standard beta dataset for *path* function to do path analysis and SNP data for SNP annotation analysis by performing *mktable* and *fmerge*. *beta.data* are a standard beta dataset for path analysis. *SNP358.data* provide an example for function *snpPositAnnot* to do SNP position annotation analysis and *SNP368\_annot.data* are for function *ucscannot* to do SNP function annotation analysis. It is specially emphasized that except for that making standard beta table using *mktable* must be done in Unix/Linux system, **GMRP** can be performed in Windows or Mac OS. This is because GWAS datasets usually are very huge but standard beta table is small. If users' Unix/Linux system has X11 or the other graphics system, then user should perform **GMRP** in Unix/Linux system, otherwise, user should transfer a standard beta table to a local computer and run **GMRP** in it.

## Author(s)

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## References

- Do, R. et al. 2013. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet* 45: 1345-1352.
- Sheehan, N.A. et al. 2008. Mendelian randomisation and causal inference in observational epidemiology. *PLoS Med* 5: e177.
- Sheehan, N.A., et al. 2010. Mendelian randomisation: a tool for assessing causality in observational epidemiology. *Methods Mol Biol* 713: 153-166.
- Wright, S. 1921. Correlation and causation. *J. Agricultural Research* 20: 557-585.
- Wright, S. 1934. The method of path coefficients *Annals of Mathematical Statistics* 5 (3): 161-215

## See Also

[path](#), [mktable](#), [pathdiagram](#), [pathdiagram2](#), [plotmat](#), [plotweb](#)

## Examples

```
data(beta.data)
mybeta<-DataFrame(beta.data)
CAD<-beta.data$cad
LDL<-beta.data$ldl
HDL<-beta.data$hdl
TG<-beta.data$tg
TC<-beta.data$tc
#par(mfrow=c(2,2))
plot(LDL,CAD,pch=19,col="blue",xlab="beta of SNPs on LDL",ylab="beta of SNP on CAD",
     main="A",cex.lab=1.5,cex.axis=1.5,cex.main=2)
abline(lm(CAD~LDL),col="red",lwd=2)
plot(HDL,CAD,pch=19,col="darkgreen",xlab="beta of SNPs on HDL",ylab="beta of SNP on
     CAD", main="B",cex.lab=1.5,cex.axis=1.5,cex.main=2)
abline(lm(CAD~HDL),col="red",lwd=2)
plot(TG,CAD,pch=19,col=colors()[96],xlab="beta of SNPs on TG",ylab="beta of SNP on
     CAD",main="C",cex.lab=1.5,cex.axis=1.5,cex.main=2)
abline(lm(CAD~TG),col="red",lwd=2)
plot(TC,CAD,pch=19,col=colors()[123],xlab="beta of SNPs on TC",ylab="beta of SNP on
     CAD",main="D",cex.lab=1.5,cex.axis=1.5,cex.main=2)
abline(lm(CAD~TC),col="red",lwd=2)

mod<-cad~ldl+hdl+tg+tc
pathvalue<-path(betav=mybeta,model=mod,outcome="cad")

mypath<-matrix(NA,3,4)
mypath[1,]<-c(1.000000,-0.066678, 0.420036,0.764638)
mypath[2,]<-c(-0.066678,1.000000,-0.559718,0.496831)
mypath[3,]<-c(0.420036,-0.559718,1.000000,0.414346)
colnames(mypath)<-c("ldl","hdl","tg","path")
mypath<-DataFrame(mypath)
#mypath
#DataFrame with 3 rows and 4 columns
#   ldl      hdl      tg      path
# <numeric> <numeric> <numeric> <numeric>
#1  1.000000 -0.066678  0.420036  0.764638
#2 -0.066678  1.000000 -0.559718  0.496831
#3  0.420036 -0.559718  1.000000  0.414346

#> pathdiagram(pathdata=mypath,disease="cad",R2=0.988243,range=c(1:3))
```

```
#Loading required package: shape
#Error in pathcad$path : $ operator is invalid for atomic vectors
mypath<-as.data.frame(mypath)
pathdiagram(pathdata=mypath,disease="cad",R2=0.988243,range=c(1:3))
```

---

beta.data

*Beta Data Of SNP Regressed on Causal Variables and Disease*

---

## Description

Beta data are a matrix dataset consisting of 5 columns: cad, ldl, hdl, tg, and tc with 368 rows.

## Usage

```
data("beta.data")
```

## Format

A data frame with 368 observations on the following 5 variables.

cad a numeric vector

ldl a numeric vector

hdl a numeric vector

tg a numeric vector

tc a numeric vector

## Details

Beta data are a matrix consisting of regression coefficients of 368 SNPs on cad, ldl, hdl, tg, tc where cad is coronary artery disease, ldl is low-density lipoprotein cholesterol, hdl, high-density lipoprotein cholesterol, tg, triglycerides and tc, total cholesterol in plasma. These 368 SNPs were obtained by using `mktable` from **GWAS** meta-analyzed data.

## Value

A set of real regression coefficients of 368 SNPs on disease and causal variables.

## Source

<http://csg.sph.umich.edu//abecasis/public/lipids2013/>

<http://www.cardiogramplusc4d.org/downloads/>

## References

Willer CJ et al. Discovery and refinement of loci associated with lipid levels. *Nat. Genet.* 2013. doi:10.1038/ng.2797.

\Schunkert, H. et al. 2011. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet* 43: 333-338.[online]

\Schunkert H, Konig IR, Kathiresan S, Reilly MP, Assimes TL, Holm H et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet.* 2011 43: 333-338.

## Examples

```
data(beta.data)
## maybe str(beta.data) ; plot(beta.data) ...
```

---

cad.data

*boldGWAS Meta-analyzed Data of Coronary Artery Disease*

---

## Description

cad.data are a matrix dataset consisting of 12 variables such as SNPID, SNP position on chromosomes, allele and alternative allele, allelic frequencies and 1069 SNPs.

## Usage

```
data("cad.data")
```

## Format

A data frame with 1609 observations on the following 12 variables.

SNP a character vector  
chr\_pos\_b36 a character vector  
reference\_allele a character vector  
other\_allele a character vector  
ref\_allele\_frequency a numeric vector  
pvalue a numeric vector  
het\_pvalue a numeric vector  
log\_odds a numeric vector  
log\_odds\_se a numeric vector  
N\_case a numeric vector  
N\_control a numeric vector  
model a character vector

## Details

cad.data, also called CARDIoGRAM **GWAS**, are a meta-analyzed GWAS data from **GWAS** studies of European descent imputed to **HapMap2** involving 22,233 cases and 64,762 controls. The data were downloaded from the following website.

## Value

A data sheet consisting of 1609 rows(SNPs) and 12 columns(character vectors such as SNPID and allele, numeric vector such as allele frequency and beta coefficient. See data format above).

## Source

<http://www.cardiogramplusc4d.org/downloads/>

## References

Schunkert H, König IR, Kathiresan S, Reilly MP, Assimes TL, Holm H et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet.* 2011 **43**: 333-338.

## Examples

```
data(cad.data)
## maybe str(cad.data) ; plot(cad.data) ...
```

---

chrp	<i>Split hg19</i>
------	-------------------

---

## Description

Split string hg19 into two numeric columns: chr and posit.

## Usage

```
chrp(hg)
```

## Arguments

hg                      character vector represented with code chr##.##### where chr## is chromosome number and .##### is SNP site (bp).

## Details

chrp can convert chr##.##### into two numeric columns: chr(chromosome number) and posit(SNP position)

## Value

Return two numeric vectors: chromosome number and SNP position

## Note

If there is chrX.##### in the data sheet, then user should change chrX.##### to chr23.#####.

## Note

hg may also be hg18. User can also use packages GenomicRanges to retrieve chromosome # and SNP position.

## Author(s)

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## See Also

[mktable](#), [link{GenomicRanges}\[Granges\]](#), [link{GenomicRanges}\[IRanges\]](#), [link{GenomicRanges}\[DataFrame\]](#)

**Examples**

```
data(lpd.data)
lpd<-lpd.data
hg19<-lpd$SNP_hg19.HDL
chr<-chrp(hg=hg19)
```

fmerge

*Merge Two GWAS Result Data Sheets***Description**

*fmerge* can be used to merge two **GWAS** result data sheets with the same key ID(SNP ID) into one data sheet.

**Usage**

```
fmerge(f11, f12, ID1, ID2, A, B, method)
```

**Arguments**

f11	R object: data file 1
f12	R object: data file 2
ID1	key id (SNP ID such as rsid) in file 1
ID2	key id (SNP ID such as rsid) in file 2
A	postfix for file 1: A=".W1". W1 may be any identifier in file 1. Default is A="".
B	postfix for file 2: B=".W2". W2 may be any identifier in file2. Default is B="".
method	method for merging. See details.

**Details**

f11 and f12 are two **GWAS** result data files from different studies or with different risk variables. They contain SNPID, hg18, hg19(positions), beta values, allele, frequency, and so on. The method has four options: method="No", "NO" or "no" means that all data with unmatched SNPs are not saved in the merged file; method="All", "ALL" or "all" lets *fmerge* save all the data with unmatched SNPs from two files but they are not paired one-by-one. This is different from R *merge* function. method="file1" will save the data with unmatched SNPs only from file 1 in the merged file and method="file2" allows function *fmerge* to save the data with unmatched SNPs from file2 in the merged file.

**Value**

Return a joined data sheet.

**Note**

Function *fmerge* can also be applied to the other types of data.

**Author(s)**

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**See Also**[merge](#)**Examples**

```

data1<-matrix(NA,20,4)
data2<-matrix(NA,30,7)
SNPID1<-paste("rs",seq(1:20),sep="")
SNPID2<-paste("rs",seq(1:30),sep="")
data1[,1:4]<-c(round(runif(20),4),round(runif(20),4),round(runif(20),4),round(runif(20),4))
data2[,1:4]<-c(round(runif(30),4),round(runif(30),4),round(runif(30),4),round(runif(30),4))
data2[,5:7]<-c(round(seq(30)*runif(30),4),round(seq(30)*runif(30),4),seq(30))
data1<-cbind(SNPID1,as.data.frame(data1))
data2<-cbind(SNPID2,as.data.frame(data2))
dim(data1)
dim(data2)
colnames(data1)<-c("SNP","var1","var2","var3","var4")
colnames(data2)<-c("SNP","var1","var2","var3","var4","V1","V2","V3")
data12<-fmerge(f1=data1,f2=data2,ID1="SNP",ID2="SNP",A=".dat1",B=".dat2",method="No")
#data12[1:3,]
# SNP.dat1 var1.dat1 var2.dat1 var3.dat1 var4.dat1 SNP.dat2 var1.dat2 var2.dat2
#1      rs1      0.9152      0.9853      0.9879      0.9677      rs1      0.5041      0.5734
#2      rs10     0.3357      0.116      0.3408      0.1867      rs10     0.9147      0.9294
#3      rs11     0.8004      0.8856      0.2236      0.4642      rs11     0.9262      0.5831
# var3.dat2 var4.dat2      V1      V2 V3
#1      0.4933      0.6766 0.1864 0.6836 1
#2      0.4104      0.1327 3.2192 1.4166 10
#3      0.8541      0.6228 1.1803 1.9044 11

```

lpd.data

*GWAS Meta-analyzed Data of Lipoprotein Cholesterols***Description**

lpd.data are standard **GWAS** Meta-analyzed dataset of lipoprotein cholesterols. It was constructed by merging four datasets: Mc\_HDL.txt, Mc\_LDL.txt, Mc\_TC.txt and Mc\_TG.txt.

**Usage**

```
data("lpd.data")
```

**Format**

A data frame with 1609 observations on the following 40 variables.

SNP\_hg18.HDL a character vector

SNP\_hg19.HDL a character vector

rsid.HDL a character vector

A1.HDL a character vector

A2.HDL a character vector

beta.HDL a numeric vector

se.HDL a numeric vector  
 N.HDL a numeric vector  
 P.value.HDL a numeric vector  
 Freq.A1.1000G.EUR.HDL a numeric vector  
 SNP\_hg18.LDL a character vector  
 SNP\_hg19.LDL a character vector  
 rsid.LDL a character vector  
 A1.LDL a character vector  
 A2.LDL a character vector  
 beta.LDL a numeric vector  
 se.LDL a numeric vector  
 N.LDL a numeric vector  
 P.value.LDL a numeric vector  
 Freq.A1.1000G.EUR.LDL a numeric vector  
 SNP\_hg18.TG a character vector  
 SNP\_hg19.TG a character vector  
 rsid.TG a character vector  
 A1.TG a character vector  
 A2.TG a character vector  
 beta.TG a numeric vector  
 se.TG a numeric vector  
 N.TG a numeric vector  
 P.value.TG a numeric vector  
 Freq.A1.1000G.EUR.TG a numeric vector  
 SNP\_hg18.TC a character vector  
 SNP\_hg19.TC a character vector  
 rsid.TC a character vector  
 A1.TC a character vector  
 A2.TC a character vector  
 beta.TC a numeric vector  
 se.TC a numeric vector  
 N.TC a numeric vector  
 P.value.TC a numeric vector  
 Freq.A1.1000G.EUR.TC a numeric vector

### Details

These four **GWAS** Meta-analyzed data of lipoprotein cholesterols were downloaded from the following website.

### Value

A data sheet consisting of 1609 rows (SNPs) and 40 columns(character vectors such as SNPID and allele, numeric vector such as allele frequency, beta coefficient. See data format above).

**Source**

<http://csg.sph.umich.edu/abecasis/public/lipids2013/>

**References**

Willer CJ et al. Discovery and refinement of loci associated with lipid levels. *Nat. Genet.* 2013. doi:10.1038/ng.2797.

**Examples**

```
data(lpd.data)
## maybe str(lpd.data) ; plot(lpd.data) ...
```

---

mktable	<i>Selection of SNPs and Creation of A Standard Table for Mendelian Randomization and Path Analyses</i>
---------	---

---

**Description**

mktable is used to choose SNPs with LG, Pv, Pc and Pd and create a standard SNP beta table for Mendelian randomization and path analysis, see details.

**Usage**

```
mktable(cdata, ddata,rt, varname, LG, Pv, Pc, Pd)
```

**Arguments**

cdata	causal variable <b>GWAS</b> data or <b>GWAS</b> meta-analysed data containing SNP ID, SNP position, chromosome, allele, allelic frequency, beta value, sd, sample size, etc.
ddata	disease <b>GWAS</b> data or <b>GWAS</b> meta-analysed data containing SNP ID, SNP position, chromosome, allele, allelic frequency, beta value, sd, sample size, etc.
rt	a string that specifies type of returning table. It has two options: <code>rt="beta"</code> returns beta table or <code>rt="path"</code> returns SNP direct path coefficient table. Default is "beta".
varname	a required string set that lists names of undefined causal variables for Mendelian randomization and path analyses. The first name is disease name. Here an example given is <code>varname &lt;-c("CAD", "LDL", "HD", "TG", "TC")</code> .
LG	a numeric parameter. LG is a given minimum interval distance between SNPs and used to choose SNPs with. Default LG=1
Pv	a numeric parameter. Pv is a given maximum p-value that is used to choose SNPs. Default Pv=5e-8
Pc	a numeric parameter. Pc is a given proportion of sample size to maximum sample size in causal variable data and used to choose SNPs. Default Pc=0.979
Pd	a numeric parameter. Pd is a given proportion of sample size to the maximum sample size in disease data and used to choose SNPs. Default Pd =0.979.

## Details

The standard **GWAS** cdata set should have the format with following columns: chrn, posit, rsid, a1.x1, a1.x2, ..., a1.xn, freq.x1, freq.x2, ..., freq.xn, beta.x1, beta.x2, ..., beta.xn, sd.x1, sd.x2, ..., sd.xn, pvj, N.x1, N.x2, ..., N.xn, pcj. The standard **GWAS** ddata set should have hg.d, SNP.d, a1.d, freq.d, beta.d, N.case, N.ctr, freq.case where x1, x2, ..., xn are causal variables. See example.

**beta** is a numeric vector that is a column of beta values for regression of SNPs on variable vector  $X=\{x_1, x_2, \dots, x_n\}$ .

**freq** is a numeric vector that is a column of frequencies of allele 1 with respect to variable vector  $X=\{x_1, x_2, \dots, x_n\}$ .

**sd** is a numeric vector that is a column of standard deviations of variable  $x_1, x_2, \dots, x_n$  specific to SNP. Note that here sd is not beta standard deviation. If sd is not specific to SNPs, then sd.xi has the same value for all SNPs in variable i.

**d** denotes disease.

**N** is sample size.

**freq.case** is frequency of disease.

**chrn** is a numeric vector for chromosome #.

**posit** is a numeric vector for SNP positions on chromosome #. Some time, chrn and posit are combined into string vector: hg19/hg18.

**pvj** is defined as p-value, pcj and pdj as proportions of sample size for SNP j to the maximum sample size in the causal variable data and in disease data, respectively.

## Value

Return a standard SNP beta or SNP path table containing m SNPs chosen with LG, Pv, Pc and Pd and n variables and disease for Mendelian randomization and path analysis.

## Note

The order of column variables must be chrn posit rsid a1.x1 ...a1.xn freq.x1 ...freq.xn beta.x1 ...beta.x1 ...beta.xn sd.x1 ...sd.xn ...otherwise, mktable would have error. see example.

## Author(s)

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## References

- Do, R. et al. 2013. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet* **45**: 1345-1352.
- Sheehan, N.A. et al. 2008. Mendelian randomisation and causal inference in observational epidemiology. *PLoS Med* **5**: e177.
- Sheehan, N.A., et al. 2010. Mendelian randomisation: a tool for assessing causality in observational epidemiology. *Methods Mol Biol* **713**: 153-166.
- Willer, C.J. Schmidt, E.M. Sengupta, S. Peloso, G.M. Gustafsson, S. Kanoni, S. Ganna, A. Chen, J., Buchkovich, M.L. Mora, S. et al (2013) Discovery and refinement of loci associated with lipid levels. *Nat Genet* **45**: 1274-1283.

**See Also**[path](#)**Examples**

```

data(lpd.data)
#lpd<-DataFrame(lpd.data)
lpd<-lpd.data
data(cad.data)
#cad<-DataFrame(cad.data)
cad<-cad.data
# step 1: calculate pvj
pvalue.LDL<-lpd$P.value.LDL
pvalue.HDL<-lpd$P.value.HDL
pvalue.TG<-lpd$P.value.TG
pvalue.TC<-lpd$P.value.TC
pv<-cbind(pvalue.LDL,pvalue.HDL,pvalue.TG,pvalue.TC)
pvj<-apply(pv,1,min)

#step 2: construct beta table of undefined causal variables:
beta.LDL<-lpd$beta.LDL
beta.HDL<-lpd$beta.HDL
beta.TG<-lpd$beta.TG
beta.TC<-lpd$beta.TC
beta<-cbind(beta.LDL,beta.HDL,beta.TG,beta.TC)

#step 3: construct a matrix for allele 1 in each undefined causal variable:
a1.LDL<-lpd$A1.LDL
a1.HDL<-lpd$A1.HDL
a1.TG<-lpd$A1.TG
a1.TC<-lpd$A1.TC
alle1<-cbind(a1.LDL,a1.HDL,a1.TG,a1.TC)

#step 4: calculate sample sizes of causal variables and calculate pcj
N.LDL<-lpd$N.LDL
N.HDL<-lpd$N.HDL
N.TG<-lpd$N.TG
N.TC<-lpd$N.TC
ss<-cbind(N.LDL,N.HDL,N.TG,N.TC)
sm<-apply(ss,1,sum)
pcj<-sm/max(sm)

#step 5: construct a matrix for frequency of allele1 in each undefined causal variable in 1000G.EUR
freq.LDL<-lpd$Freq.A1.1000G.EUR.LDL
freq.HDL<-lpd$Freq.A1.1000G.EUR.HDL
freq.TG<-lpd$Freq.A1.1000G.EUR.TG
freq.TC<-lpd$Freq.A1.1000G.EUR.TC
freq<-cbind(freq.LDL,freq.HDL,freq.TG,freq.TC)

#step 6: construct matrix for sd of each causal variable (here sd is not specific to SNPj)
# the sd values were averaged over 63 studies see reference Willer et al(2013)
sd.LDL<-rep(37.42,length(pvj))
sd.HDL<-rep(14.87,length(pvj))
sd.TG<-rep(92.73,length(pvj))
sd.TC<-rep(42.74,length(pvj))
sd<-cbind(sd.LDL,sd.HDL,sd.TG,sd.TC)

```

```

#step 7: retriev SNP ID and position:
hg19<-lpd$SNP_hg19.HDL
rsid<-lpd$rsid.HDL

#step 8: invoke chrp to separate chromosome number and SNP position:
chr<-chrp(hg=hg19)

#step 9: get new data of causal variables:
newdata<-cbind(freq,beta,sd,pvj,ss,pcj)
newdata<-cbind(chr,rsid,alle1,as.data.frame(newdata))
dim(newdata)
#[1] 120165      25

#step 10: retrieve cad data from cad and calculate pdj and frequency of cad in population
hg18.d<-cad$chr_pos_b36
SNP.d<-cad$SNP #SNPID
a1.d<-tolower(cad$reference_allele)
freq.d<-cad$ref_allele_frequency
pvalue.d<-cad$pvalue
beta.d<-cad$log_odds
N.case<-cad$N_case
N.ctr<-cad$N_control
N.d<-N.case+N.ctr
freq.case<-N.case/N.d

#step 11: get new cad data:
newcad<-cbind(freq.d,beta.d,N.case,N.ctr,freq.case)
newcad<-cbind(hg18.d,SNP.d,a1.d,as.data.frame(newcad))
dim(newcad)

#step 12: give variable list
varname<-c("CAD","LDL","HDL","TG","TC")
#step 3: create beta table with function mktable
mybeta<-mktable(cdata=newdata,ddata=newcad,rt="beta",varname=varname,LG=1, Pv=0.00000005,
Pc=0.979,Pd=0.979)

beta<-mybeta[,4:8] # save beta for path analysis
snp<-mybeta[,1:3] # save snp for annotation analysis
beta<-DataFrame(beta)

```

---

path

*Path Analysis*


---

### Description

*path* is used to perform path analysis of multiple causal or risk variables on an outcome or disease of study.

### Usage

```
path(betav,model,outcome)
```

**Arguments**

betav	a matrix numeric data with p rows and q columns in which the first column must be outcome and other columns are risk variables.
model	a linear model for multivariate linear regression analysis. The model must be given in R Console. For example, <code>mymodel&lt;-CAD~LDL+HDL+TG+TC</code> .
outcome	a string that is required to give outcome name or disease name. For example, <code>outcome="CAD"</code> .

**Details**

*path* is originally planned to perform causal analysis of risk variables on disease of study based on the results of the Mendelian randomization analysis of SNPs on these risk variables and disease. In the **GMRP** package, the *betav* is a matrix of beta coefficients of linear regression analyses of chosen SNPs on the risk (or causal) variables and disease or outcome. The beta values are equivalently quantitative values, so this *path* function can also be used to analyze direct and indirect contributions of quantitative traits to economic traits.

**Value**

Return three matrices: beta coefficients of regressions of risk variables on outcome or disease, correlation matrix and path matrix and also return director path coefficients and R-square.

**Note**

*betav* may also be a matrix of SNP path coefficients onto risk variables and disease.

**Author(s)**

Yuan-De Tan <tanyuande@gmail.com>

**References**

- Do, R. et al. 2013 Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet* **45**: 1345-1352.
- Sheehan, N.A. et al. 2008 Mendelian randomisation and causal inference in observational epidemiology. *PLoS Med* **5**: e177.
- Sheehan, N.A., et al. 2010 Mendelian randomisation: a tool for assessing causality in observational epidemiology. *Methods Mol Biol* **713**: 153-166.
- Wright, S. 1921 Correlation and causation. *J.Agricultural Research* **20**: 557-585.
- Wright, S. 1934 The method of path coefficients. *Annals of Mathematical Statistics* **5** (3): 161-215.

**See Also**

`link[base]{lm}, link[stats]{cor}`

**Examples**

```
data(beta.data)
mybeta<-DataFrame(beta.data)
#mybeta<-as.data.frame(beta.data)
mod<-cad~ldl+hdl+tg+tc
pathvalue<-path(betav=mybeta, model=mod, outcome="cad")
```

---

pathdiagram	<i>Path Diagram</i>
-------------	---------------------

---

### Description

Create a directed acyclic diagram to represent causal effects of risk factors on the disease of study.

### Usage

```
pathdiagram(pathdata, disease, R2, range)
```

### Arguments

pathdata	R object that is dataset consisting of correlation matrix of risk factors and a numeric vector of direct path coefficients.
disease	a string that specifies outcome name or disease name. If disease name is long or has multiple words, then we suggest an abbreviated name, for example, coronary artery disease may be shortened as CAD.
R2	a numeric parameter, is R-square obtained from path analysis.
range	range of specified columns for correlation matrix. For example, range = c(2:4) means the correlation coefficient begins with column 2 and end at column 4.

### Details

The *pathdata* contains correlation matrix of risk factors and a numeric vector of direct path coefficients obtained from path analysis of beta data of SNPs on risk factors and disease. Columns must have risk factor names and path.

### Value

NULL. pathdiagram will create one-level path diagram labeled with colors.

### Author(s)

Yuan-De Tan <tanyuande@gmail.com>

### See Also

[pathdiagram2](#), [plotmat](#), [plotweb](#)

### Examples

```
mypath<-matrix(NA,3,4)
mypath[1,]<-c(1.000000,-0.066678, 0.420036,0.764638)
mypath[2,]<-c(-0.066678,1.000000,-0.559718,0.496831)
mypath[3,]<-c(0.420036,-0.559718,1.000000,0.414346)
colnames(mypath)<-c("ldl","hdl","tg","path")

#mypath
#      ldl      hdl      tg      path
#1 1.000000 -0.066678 0.420036 0.764638
#2 -0.066678 1.000000 -0.559718 0.496831
```

```
#3 0.420036 -0.559718 1.000000 0.414346

mypath<-as.data.frame(mypath)
pathdiagram(pathdata=mypath,disease="cad",R2=0.988243,range=c(1:3))
```

---

pathdiagram2

*Two-level Nested Pathdiagram*


---

## Description

This function is used to create two-level nested pathdiagram to represent causal effects of risk factors on outcome and on the disease of study. The nested path is a child path, which is related to outcome and the outside path is parent path with respect to disease.

## Usage

```
pathdiagram2(pathD, pathO, ranged, rangeO, disease, R2D, R2O)
```

## Arguments

pathD	R object that is disease path result data consisting of correlation matrix of causal variables to be identified in Mendelian randomization analysis and path coefficient vector of these variables directly causing the disease of study.
pathO	R object that is outcome path result data consisting of correlation matrix of causal variables and path coefficient vector of these variables directly contributing to outcome. This outcome variable may be or not be one of risk factors or causal variables in disease path data. These variables are the same with those in <i>pathD</i> .
ranged	specifies column range for correlation coefficient matrix in <i>pathD</i> , for example, <code>ranged=c(2:4)</code> means the correlation coefficient begins with column 2 and end at column 4.
rangeO	specifies column range for correlation coefficient matrix in <i>pathO</i> , see example in <code>ranged</code> .
disease	a string that specifies disease name. If disease name is long or has multiple words, then we suggest an abbreviated name, for example, "coronary artery disease" can be shortened as CAD.
R2D	a required numeric parameter and its value is R-square obtained from path analysis of disease data.
R2O	a required numeric parameter and its value is R-square obtained from path analysis of outcome data.

## Details

Two path datasets must contain correlation matrix of variables detected to be risk factor of disease and a vector of direct path coefficients obtained from path analysis of beta data of SNPs on causal variables and disease. Columns must have shortened variable names and path word (see examples). *pathdiagram2* requires two path data have the same causal variable names and the same name order. The outcome in the outcome path data must be the last variable in the correlation matrix in disease path data (see examples). Otherwise, *pathdiagram2* would give an error message.

**Value**

Null. Function *pathdiagram2* creates a nested two-level path diagram labeled with color.

**Author(s)**

Yuan-De Tan <tanyuande@gmail.com>

**See Also**

[pathdiagram](#), [plotmat](#), [plotweb](#)

**Examples**

```

mypath<-matrix(NA,3,4)
mypath[1,]<-c(1.000000,-0.066678, 0.420036,0.764638)
mypath[2,]<-c(-0.066678,1.000000,-0.559718,0.496831)
mypath[3,]<-c(0.420036,-0.559718,1.000000,0.414346)
colnames(mypath)<-c("ldl","hdl","tg","path")
mypath<-DataFrame(mypath)
#mypath
#DataFrame with 3 rows and 4 columns
#      ldl      hdl      tg      path
# <numeric> <numeric> <numeric> <numeric>
#1  1.000000 -0.066678  0.420036  0.764638
#2 -0.066678  1.000000 -0.559718  0.496831
#3  0.420036 -0.559718  1.000000  0.414346

#In this pathdiagram, the outcome is TC
pathD<-matrix(NA,4,5)
pathD[1,]<-c(1, -0.070161,0.399038,0.907127,1.210474)
pathD[2,]<-c(-0.070161, 1,-0.552106,0.212201,0.147933)
pathD[3,]<-c(0.399038,-0.552106,1,0.44100,0.64229)
pathD[4,]<-c(0.907127 ,0.212201,0.441007,1,-1.035677)
colnames(pathD)<-c("ldl","hdl","tg","tc","path")

#pathD
#      LDL      HDL      TG      TC      path
#1  1.000000 -0.070161  0.399038  0.907127  1.210474
#2 -0.070161  1.000000 -0.552106  0.212201  0.147933
#3  0.399038 -0.552106  1.000000  0.441000  0.642290
#4  0.907127  0.212201  0.441007  1.000000 -1.035677

pathD<-as.data.frame(pathD)
## tc is outcome in my path
pathdiagram2(pathD=pathD,path0=mypath,rangeD=c(1:4),range0=c(1:3),disease="CAD",
R2D=0.536535,R20=0.988243)

```

**Description**

SNP358.data were obtained from **GWAS** Meta-analyzed datasets of lipoprotein cholesterols and coronary artery disease. The data contain three numeric vectors (columns): SNPID(rsid), chromosome number (chr) and SNP position on chromosome (posit).

**Usage**

```
data("SNP358.data")
```

**Format**

A data frame with 358 observations on the following 3 variables.

rsid a character vector

chr a numeric vector

posit a numeric vector

**Details**

These 358 SNPs were chosen by using mktable with  $P_v = 5 \times 10^{-08}$ ,  $P_c = P_d = 0.979$  from lpd.data and cad.data. They provide a data example for how to perform annotation analysis of SNP positions.

**Value**

A set of data with 358 rows(SNPs) and 3 columns(SNP ID, chromosome # and SNP position on chromosomes).

**Examples**

```
data(SNP358.data)
## maybe str(SNP358.data) ; plot(SNP358.data) ...
```

---

SNP368annot.data	<i>Annotation data of 368SNPs</i>
------------------	-----------------------------------

---

**Description**

The annotation data of 368SNPs are used to construct SNP distribution in gene elements (coding region, introne,UTR, etc). The data contain 12 vectors or variables but only Symbol and function\_unit are used by ucscannot.R to build SNP distribution in gene elements.

**Usage**

```
data("SNP368annot.data")
```

**Format**

A data frame with 1053 observations on the following 6 variables.

SNP a string vector

Allele a string vector

Strand a numeric vector

Symbol a string vector

Gene a string vector

function\_unit a string vector

**Details**

SNP368annot.data were obtained by performing mktable with  $PV=5 \times 10^{-08}$ ,  $P_c=P_d=0.979$  on lpd.data and cad.data and SNP tools. SNP368annot.data provides an practical example for constructing distribution of SNPs in gene elements. Note that function\_units are gene elements.

**Value**

A dataset with 1053 rows and 6 columns for results of SNP annotation analysis. See format above.

**Source**

<http://csg.sph.umich.edu//abecasis/public/lipids2013/>

**References**

[http://snp-nexus.org/test/snpnexus\\_19427/](http://snp-nexus.org/test/snpnexus_19427/)

**Examples**

```
data(SNP368annot.data)
```

---

snpPositAnnot

*SNP Position Annotation*

---

**Description**

This function is used to perform position annotation analysis of SNPs chosen from GWAS.

**Usage**

```
snpPositAnnot(SNPdata, SNP_hg19="chr", main)
```

**Arguments**

SNPdata	SNPdata may be hg19 that is a string vector(chr##.#####) or two numeric vectors (chromosome number and SNP position).
SNP_hg19	a string parameter. It may be "hg19" or "chr". If SNP_hg19="hg19", then SNPdata contain a string vector of hg19 or if SNP_hg19="chr", then SNPdata consist of at least two columns: chr and posit. chr is chromosome number and posit is SNP physical position on chromosomes. If data sheet has chromosome X, then character "X" should be changed to 23 in chr vector or chr23.##### in hg19 vector.
main	a string which is title of graph. If no title is given, then main="".

**Value**

Return a set of numbers of SNPs between which interval length > **LG** on 23 chromosomes. This function also creates a histogram for averaged distances between SNPs and SNP numbers on chromosomes.

**Note**

This function can also be applied to hg18 data with SNP\_hg19="hg18".

**Author(s)**

Yuan-De Tan <tanyuande@gmail.com>

**See Also**

[barplot](#), [text](#), [chrp](#)

**Examples**

```
data(SNP358.data)
SNP358<-DataFrame(SNP358.data)
snpPositAnnot(SNPdata=SNP358,SNP_hg19="chr",main="A")
```

---

ucscannot

*Functional Annotation of SNPs Chosen*

---

**Description**

This function is used to give proportion of *SNPs* derived from functional elements of genes.

**Usage**

```
ucscannot(UCSCannot,SNPn,A=3,B=1.9,C=1.3,method=1)
```

## Arguments

UCSCannot	annotation data obtained by performing SNP tools.
SNPn	numeric parameter for number of SNPs contained in UCSCannot
A	numeric parameter for title size, default=2.5
B	numeric parameter for label size, default=1.5
C	numeric parameter for labelrad distance, default=0.1
method	numeric parameter for choosing figure output methods. It has two options: method=1 has no legend but color and pie components are labeled with gene elements, method=2 has legend over pie. The default = 1.

## Details

SNPs chosen by performing `mktable` should be copied to **Batch Query Box** in SNP annotation tool. After setting parameters and running by clicking run button, *SNP* annotation data will be obtained after running for a while. Consequence sheet of **UCSC** should be copied to excel sheet, "Predicted function" column name is changed to "function\_unit" name and save it as csv format. These parametric defaults are used as graph image for publication, user can expand image to the maximum size and copy it to powerpoint that will give ideal effect. User also can use R package `link{VariantAnnotation}` to get SNP annotation result but the result must be constructed a table with `function_unit` column listing gene elements and `Symbol` column listing genes, otherwise, `ucscannot` will get an error.

## Value

Create a color *pie3D* diagram and return a set of numeric values: proportions of code region, intron, 3' and 5' UTRs and upstream and downstream etc.

## Note

This function just need data of "Predicted function" and "symbol", so the other column data in UCSCannot do not impact the results of analysis.

## Author(s)

Yuan-De Tan <tanyuande@gmail.com>

## References

<http://snp-nexus.org/index.html>

## See Also

`mktable`, `pie3D`, `link{VariantAnnotation}`

## Examples

```
data(SNP368annot.data)
SNP368<-DataFrame(SNP368annot.data)
ucscannot(UCSCannot=SNP368, SNPn=368, A=1.5, B=1, C=1.3)
ucscannot(UCSCannot=SNP368, SNPn=368, A=1.5, B=1, C=1.3, method=2)
```

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