Package ‘mrMLM’

March 27, 2022

Type Package

Title Multi-Locus Random-SNP-Effect Mixed Linear Model Tools for GWAS

Version 5.0.1

Date 2022-3-27

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Description Conduct multi-locus genome-wide association study under the framework of multi-locus random-SNP-effect mixed linear model (mrMLM). First, each marker on the genome is scanned. Bonferroni correction is replaced by a less stringent selection criterion for significant test. Then, all the markers that are potentially associated with the trait are included in a multi-locus genetic model, their effects are estimated by empirical Bayes, and all the nonzero effects were further identified by likelihood ratio test for significant QTL. The program may run on a desktop or laptop computers. If marker genotypes in association mapping population are almost homozygous, these methods in this software are very effective. If there are many heterozygous marker genotypes, the IIIMrMLM software is recommended. Wen YJ, Zhang H, Ni YL, Huang B, Zhang J, Feng JY, Wang SB, Dunwell JM, Zhang YM, Wu R (2018, <doi:10.1093/bib/bbw145>), and Li M, Zhang YW, Zhang ZC, Xiang Y, Liu MH, Zhou YH, Zuojf, Zhang HQ, Chen Y, Zhang YM (2022, <doi:10.1016/j.molp.2022.02.012>).

Depends R (>= 3.5.0),lars

Imports Rcpp (>= 0.12.14),methods,foreach,ncvreg.coin(>= 1.1-0),sampling,data.table,doParallel,sbl,BEDMatrix

License GPL (>= 2)

LinkingTo Rcpp, RcppEigen

NeedsCompilation yes

Repository CRAN

Date/Publication 2022-03-27 08:50:02 UTC

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R topics documented:

- DoData [2]
- FASTmrEMMA [3]
- FASTmrMLM [4]
- Gen [5]
- Genotype [5]
- inputData [6]
- ISIS [6]
- mrMLM [7]
- mrMLMFun [10]
- MultiManhattan [11]
- multiplication_speed [11]
- Phe [13]
- Phenotype [13]
- pKWmEB [14]
- pLARmEB [15]
- ReadData [16]
- ResultFinal [16]
- ResultIntermediate [17]

Index 18

DoData process raw data

Description

process raw data for later use

Usage

DoData(genRaw, Genformat, pheRaw1q, kkRaw, psmatrixRaw, covmatrixRaw, trait, type, PopStrType)

Arguments

- genRaw: raw genotype matrix.
- Genformat: genotype format.
- pheRaw1q: raw phenotype matrix.
- kkRaw: raw kinship matrix.
- psmatrixRaw: raw population structure matrix.
- trait: which trait to analysis.
- type: which type to transform.
- PopStrType: The type of population structure.
**FASTmrEMMA**

**Description**

FAST multi-locus random-SNP-effect EMMA

**Usage**

```
FASTmrEMMA(gen,phe,outATCG,genRaw,kk,psmatrix,svpal,svmlod,Genformat,Likelihood,CLO)
```

**Arguments**

- `gen`: genotype matrix.
- `phe`: phenotype matrix.
- `outATCG`: genotype for code 1.
- `genRaw`: raw genotype.
- `kk`: kinship matrix.
- `psmatrix`: population structure matrix.
- `svpal`: Critical P-value for selecting variable.
- `svmlod`: Critical LOD score for significant QTN.
- `Genformat`: Format for genotypic codes.
- `Likelihood`: restricted maximum likelihood (REML) and maximum likelihood (ML).
- `CLO`: number of CPU.

**Author(s)**

Zhang Ya-Wen, Wang Jing-Tian, Li Pei, Zhang Yuan-Ming
Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>
Examples

```r
G1=data(Gen)
P1=data(Phe)
Readraw=ReadData(fileGen=Gen,filePhe=Phe,fileKin=NULL,filePS =NULL,
   Genformat=1)
InputData=inputData(readraw=Readraw,Genformat=1,method="FASTmrEMMA",trait=1)
result=FASTmrEMMA(InputData$doFME$gen,InputData$doFME$phe,
   InputData$doFME$outATCG,InputData$doFME$genRaw,
   InputData$doFME$kk,InputData$doFME$psmatrix,0.005,
   svmlod=3,Genformat=1,Likelihood="REML",CLO=1)
```

---

**FASTmrMLM**

To perform GWAS with FASTmrMLM method

**Description**

FAST multi-locus random-SNP-effect Mixed Linear Model

**Usage**

```
FASTmrMLM(gen,phe,outATCG,genRaw,kk,psmatrix,svpal,svrad,svmlod,Genformat,CLO)
```

**Arguments**

- `gen`: genotype matrix.
- `phe`: phenotype matrix.
- `outATCG`: genotype for code 1.
- `genRaw`: raw genotype.
- `kk`: kinship matrix.
- `psmatrix`: population structure matrix.
- `svpal`: Critical P-value for selecting variable.
- `svrad`: Search Radius in search of potentially associated QTN.
- `svmlod`: Critical LOD score for significant QTN.
- `Genformat`: Format for genotypic codes.
- `CLO`: number of CPU.

**Author(s)**

Zhang Ya-Wen, Wang Jing-Tian, Li Pei, Zhang Yuan-Ming
Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>
Examples

```r
G1=data(Gen)
P1=data(Phe)
Readraw=ReadData(fileGen=Gen,filePhe=Phe,fileKin=NULL,filePS=NULL,
Genformat=1)
InputData=inputData(readraw=Readraw,Genformat=1,method="FASTmrMLM",trait=1)
result=FASTmrMLM(InputData$doMR$gen,InputData$doMR$phe,
InputData$doMR$outATCG,InputData$doMR$genRaw,
InputData$doMR$kk,InputData$doMR$psmatrix,0.01,svrad=20,
svmlod=3,Genformat=1,CLO=1)
```

---

**Gen**

**Genotype data**

**Description**

Numeric format of genotype dataset.

**Usage**

```r
data(Gen)
```

**Details**

Dataset input of Genotype for mrMLM function.

**Author(s)**

Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>

---

**Genotype**

**Genotype of real data**

**Description**

Numeric format of genotype dataset.

**Usage**

```r
data(Genotype)
```

**Details**

Dataset input of Genotype for mrMLM function.

**Author(s)**

Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>
inputData

Description
Input data which have been transformed

Usage
inputData(readraw, Genformat, method, trait, PopStrType)

Arguments
readraw genotype matrix.
Genformat genotype format.
method which method to analysis.
trait which trait to analysis.
PopStrType The type of population structure.

Author(s)
Zhang Ya-Wen, Wang Jing-Tian, Li Pei, Zhang Yuan-Ming
Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>

Examples
G1=data(Gen)
P1=data(Phe)
Readraw=ReadData(fileGen=Gen, filePhe=Phe, fileKin=NULL, filePS=NULL, fileCov=NULL, Genformat=1)
result=inputData(readraw=Readraw, Genformat=1, method="mrMLM", trait=1, PopStrType=NULL)

ISIS

Description
To perform GWAS with ISIS EM-BLASSO method

Usage
ISIS(gen, phe, outATCG, genRaw, kk, psmatrix, svpal, svmlod, Genformat, CLO)
mrMLM

Arguments

- `gen`: genotype matrix.
- `phe`: phenotype matrix.
- `outATCG`: genotype for code 1.
- `genRaw`: raw genotype.
- `kk`: kinship matrix.
- `psmatrix`: population structure matrix.
- `svpal`: Critical P-value for selecting variable.
- `svmlod`: Critical LOD score for significant QTN.
- `Genformat`: Format for genotypic codes.
- `CLO`: number of CPU.

Author(s)

Zhang Ya-Wen, Li Pei, Zhang Yuan-Ming
Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>

Examples

```r
G1=data(Gen)
P1=data(Phe)
Readraw=ReadData(fileGen=Gen,filePhe=Phe,fileKin=NULL,filePS =NULL, Genformat=1)
InputData=inputData(readraw=Readraw,Genformat=1,method="ISIS EM-BLASSO", trait=1)
result=ISIS(InputData$doMR$gen,InputData$doMR$phe,InputData$doMR$outATCG, InputData$doMR$genRaw,InputData$doMR$kk,InputData$doMR$psmatrix, 0.01,svmlod=3,Genformat=1,CLO=1)
```

mrMLM

*Multi-Locus Random-SNP-Effect Mixed Linear Model Tools for GWAS*

Description

Conduct multi-locus genome-wide association study under the framework of multi-locus random-SNP-effect mixed linear model (mrMLM). First, each marker on the genome is scanned. Bonferroni correction is replaced by a less stringent selection criterion for significant test. Then, all the markers that are potentially associated with the trait are included in a multi-locus genetic model, their effects are estimated by empirical Bayes, and all the nonzero effects were further identified by likelihood ratio test for true QTL. The program may run on a desktop or laptop computers. If marker genotypes in association mapping population are almost homozygous, these methods in this software are very effective. If there are many heterozygous marker genotypes, the IIIVmrMLM software is recommended. Wen YJ, Zhang H, Ni YL, Huang B, Zhang J, Feng JY, Wang SB, Dunwell JM, Zhang YM, Wu R (2018, <doi:10.1093/bib/bbw145>), and Li M, Zhang YW, Zhang ZC, Xiang Y, Liu MH, Zhou YH, Zuo JF, Zhang HQ, Chen Y, Zhang YM (2022, <doi:10.1016/j.molp.2022.02.012>).
Usage

mrMLM(fileGen, filePhe, fileKin, filePS, PopStrType, fileCov, Genformat, method, Likelihood, trait, SearchRadius, CriLOD, SelectVariable, Bootstrap, DrawPlot, Plotformat, dir, PC, RAM)

Arguments

fileGen  File path and name in your computer of Genotype, i.e., "D:/Users/Genotype_num.csv".
filePhe  File path and name in your computer of Phenotype, i.e., "D:/Users/Phenotype.csv".
fileKin  File path and name in your computer of Kinship, i.e., "D:/Users/Kinship.csv".
filePS   File path and name in your computer of Population Structure, i.e., "D:/Users/PopStr.csv".
PopStrType  The type of population structure, i.e., Q (Q matrix), PCA (principal components), EvolPopStr (evolutionary population structure).
fileCov  File path and name in your computer of covariate, i.e., "D:/Users/Covariate.csv".
Genformat Format for genotypic codes, Num (number), Cha (character) and Hmp (Hapmap).
method  Six multi-locus GWAS methods. Users may select one to six methods, including mrMLM, FASTmrMLM, FASTmrEMMA, pLARmEB, pKWmEB and ISIS EM-BLASSO.
Likelihood  This parameter is only for FASTmrEMMA, including REML (restricted maximum likelihood) and ML (maximum likelihood).
trait  Traits analyzed from number 1 to number 2, i.e., 1:2.
SearchRadius  This parameter is only for mrMLM and FASTmrMLM, indicating Search Radius in search of potentially associated QTN, the default is 20.
CriLOD  Critical LOD score for significant QTN.
SelectVariable  This parameter is only for pLARmEB. SelectVariable=50 indicates that 50 potentially associated variables are selected from each chromosome. Users may change this number in real data analysis in order to obtain the best results as final results, the default is 50.
Bootstrap  This parameter is only for pLARmEB, including FASLE and TRUE. Bootstrap=FALSE indicates the analysis of only real dataset, Bootstrap=TRUE indicates the analysis of both real dataset and four resampling datasets, the default is FALSE.
DrawPlot  This parameter is for all the six methods, including FALSE and TRUE. DrawPlot=FALSE indicates no figure output, DrawPlot=TRUE indicates the output of the Manhattan, QQ figures, the default is TRUE.
Plotformat  This parameter is for all the figure files, including *.jpeg, *.png, *.tiff and *.pdf, the default is "tiff".
dir  This parameter is for the save path, i.e., "D:/Users"
PC  This parameter is used to specify whether only small RAM device is available to run the mrMLM program, such as desktop or laptop. The default value is PC=FALSE. PC=TRUE indicates running the program on low RAM desktop or laptop.
RAM  This parameter is the RAM of your desktop or laptop. The default value is RAM=4. RAM=4 indicates the RAM of your device is 4G.
### Details

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<thead>
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<th>mrMLM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type:</td>
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</tr>
<tr>
<td>Version:</td>
<td>5.0.1</td>
</tr>
<tr>
<td>Date:</td>
<td>2022-3-27</td>
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<tr>
<td>Depends:</td>
<td>lars</td>
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<tr>
<td>Imports:</td>
<td>methods,foreach,ncvreg,coin,sampling,data.table,doParallel,BEDMatrix</td>
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<td>License:</td>
<td>GPL version 2 or newer</td>
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### Note

Once the running of the software mrMLM v5.0.1 is ended, the "results" files should appear on the Directory, which was set up by users before running the software. The results for each trait include "*_intermediate result.csv", "*_Final result.csv", Manhattan plot, and QQ plot. If only pLARmEB and ISIS EM-BLASSO methods are selected, there will be no intermediate results and figures output. Users can decompress the mrMLM package and find the User Manual file (name: Instruction.pdf) in the folder of "/mrMLM/inst".

### Author(s)

Zhang Ya-Wen, Wang Jing-Tian, Li Pei, Zhang Yuan-Ming
Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>

### References


### Examples

```
Ge1=data(Genotype)  
Ph1=data(Phenotype)  
mrMLM(fileGen=Genotype,filePhe=Phenotype,Genformat="Num",)
```
mrMLMFun

To perform GWAS with mrMLM method

Description
multi-locus random-SNP-effect Mixed Linear Model

Usage
mrMLMFun(gen, phe, outATCG, genRaw, kk, psmatrix, svpal, svrad, svmlod, Genformat, CLO)

Arguments
- **gen**: genotype matrix.
- **phe**: phenotype matrix.
- **outATCG**: genotype for code 1.
- **genRaw**: raw genotype.
- **kk**: kinship matrix.
- **psmatrix**: population structure matrix.
- **svpal**: Critical P-value for selecting variable.
- **svrad**: Search Radius in search of potentially associated QTN.
- **svmlod**: Critical LOD score for significant QTN.
- **Genformat**: Format for genotypic codes.
- **CLO**: number of CPU.

Author(s)
Zhang Ya-Wen, Wang Jing-Tian, Li Pei, Zhang Yuan-Ming
Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>

Examples
G1=data(Gen)
P1=data(Phe)
Readraw=ReadData(fileGen=Gen, filePhe=Phe, fileKin=NULL, filePS =NULL, Genformat=1)
InputData=inputData(readraw=Readraw, Genformat=1, method="mrMLM", trait=1)
result=mrMLMFun(InputData$doMR$gen, InputData$doMR$phe, InputData$doMR$outATCG, InputData$doMR$genRaw, InputData$doMR$kk, InputData$doMR$psmatrix,
0.01, svrad=20, svmlod=3, Genformat=1, CLO=1)
MultiManhattan

Drawing multi-locus Manhattan plot

Description
Using the results of the mrMLM software to draw a multi-locus Manhattan plot

Usage
MultiManhattan(ResultIntermediate, ResultFinal, mar=c(2.9, 2.8, 0.7, 2.8),
LabDistance=1.5, ScaleDistance=0.4, LabelSize=0.8, ScaleSize=0.7,
AxisLwd=5, TckLength=-0.03, LogTimes=2, LODTimes=1.2, lodline=3,
dirplot=getwd(), PlotFormat="tiff",
width=28000, height=7000, pointsize = 60, res=600,
MarkGene=FALSE, Pos.x=NULL, Pos.y=NULL, GeneName=NULL,
GeneNameColour=NULL,...)

Arguments

ResultIntermediate
Intermediate results obtained by the mrMLM software, "D:/Users/ResultIntermediate.csv".

ResultFinal
Final results obtained by the mrMLM software, "D:/Users/ResultFinal.csv".

mar
A numerical vector of the form c(bottom, left, top, right) which gives the number of lines of margin to be specified on the four sides of the plot, and the default is c(2.9, 2.8, 0.7, 2.8).

LabDistance
Distance between label and axis; the default is 1.5.

ScaleDistance
Distance between scale values and axis; the default is 0.4.

LabelSize
Size of all the three labels; the default is 0.8.

ScaleSize
Size of scale values; the default is 0.7.

AxisLwd
The width of axis, a positive number; the default is 5.

TckLength
The length of tick marks; the default is -0.03.

LogTimes
Magnification of -log10(P-value); the default is 2.

LODTimes
Magnification of LOD score; the default is 1.2.

lodline
The significant LOD score; the default is 3.

dirplot
Path to save plot; the default is current working directory

PlotFormat
Format of the plot, i.e., *.tiff, *.png, *.jpeg, *.pdf

width
Figure width; the default is 28000.

height
Figure height; the default is 7000.

pointsize
Word resolution, with the unit of 1/72 inch, being pixels per inch (ppi); the default is 60.

res
Figure resolution, with the unit of pixels per inch (ppi); the default is 600.
multiplication_speed

MarkGene To mark genes in plot or not; if "TRUE" is selected, a file, namely "Reference information to mark gene.csv", that contains the x and y axis information of all the significant QTNs will generate. The default is "FALSE", indicating that no candidate or known gene names are marked in Manhattan plot.

Pos_x Numeric vectors of x axis where the text labels should be written.

Pos_y Numeric vectors of y axis where the text labels should be written.

GeneName A character vector or expression specifying the text to be written.

GeneNameColour The colour of gene names.

... Arguments passed to points, axis, text.

Author(s)

Zhang Ya-Wen, Wang Jing-Tian, Li Pei, and Zhang Yuan-Ming
Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>

Examples

inter<-data(ResultIntermediate)
fin<-data(ResultFinal)
MultiManhattan(ResultIntermediate=ResultIntermediate,ResultFinal=ResultFinal,dirplot=tempdir())

multiplication_speed Matrix multiplication acceleration algorithm.

Description

Matrix multiplication acceleration algorithm.

Usage

multiplication_speed(A,B)

Arguments

A matrix A.

B matrix B.

Author(s)

Zhang Ya-Wen, Wen Yang-Jun, Wang Shi-Bo, and Zhang Yuan-Ming
Maintainer: Yuanming Zhang<soyzhang@mail.hzau.edu.cn>
## Examples

```r
## Not run:
A<-matrix(1:10,2,5)
B<-matrix(1:10,5:2)
result<-multiplication_speed(A,B)

## End(Not run)
```

---

### Phe

**Phenotype dataset**

**Description**

Phenotype dataset of multiple traits.

**Usage**

```r
data(Phe)
```

**Details**

Dataset input of phenotype in mrMLM function.

**Author(s)**

Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>

---

### Phenotype

**Phenotype of real data**

**Description**

Phenotype dataset of multiple traits.

**Usage**

```r
data(Phenotype)
```

**Details**

Dataset input of phenotype in mrMLM function.

**Author(s)**

Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>
To perform GWAS with pKWmEB method

**Description**
Kruskal-Wallis test with empirical Bayes under polygenic background control

**Usage**

```
pKWmEB(gen, phe, outATCG, genRaw, kk, psmatrix, svpal, svmlod, Genformat, CLO)
```

**Arguments**
- **gen**: genotype matrix.
- **phe**: phenotype matrix.
- **outATCG**: genotype for code 1.
- **genRaw**: raw genotype.
- **kk**: kinship matrix.
- **psmatrix**: population structure matrix.
- **svpal**: Critical P-value for selecting variable.
- **svmlod**: Critical LOD score for significant QTN.
- **Genformat**: Format for genotypic codes.
- **CLO**: number of CPU.

**Author(s)**
Zhang Yu-Wen, Wang Jing-Tian, Li Pei, Zhang Yuan-Ming
Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>

**Examples**

```R
G1=data(Gen)
P1=data(Phe)
Readraw=ReadData(fileGen=Gen, filePhe=Phe, fileKin=NULL, filePS =NULL, Genformat=1)
InputData=inputData(readraw=Readraw, Genformat=1, method="pKWmEB", trait=1)
result=pKWmEB(InputData$doMR$gen, InputData$doMR$phe, InputData$doMR$psmatrix, InputData$doMR$genRaw, InputData$doMR$kk, InputData$doMR$outATCG, 0.05, svmlod=3, Genformat=1, CLO=1)
```
pLARmEB

To perform GWAS with pLARmEB method

Description
polygene-background-control-based least angle regression plus Empirical Bayes

Usage
pLARmEB(gen, phe, outATCG, genRaw, kk, psmatrix, CriLOD, lars1, Genformat, Bootstrap, CLO)

Arguments
- gen: genotype matrix.
- phe: phenotype matrix.
- outATCG: genotype for code 1.
- genRaw: raw genotype.
- kk: kinship matrix.
- psmatrix: population structure matrix.
- CriLOD: Critical LOD score for significant QTN.
- lars1: No. of potentially associated variables selected by LARS.
- Genformat: Format for genotypic codes.
- Bootstrap: Bootstrap=FALSE indicates the analysis of only real dataset, Bootstrap=TRUE indicates the analysis of both real dataset and four resampling datasets.
- CLO: number of CPU.

Author(s)
Zhang Ya-Wen, Wang Jing-Tian, Li Pei, Zhang Yuan-Ming
Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>

Examples
G1=data(Gen)
P1=data(Phe)
Readraw=ReadData(fileGen=Gen, filePhe=Phe, fileKin=NULL, filePS =NULL, Genformat=1)
InputData=inputData(readraw=Readraw, Genformat=1, method="pLARmEB", trait=1)
result=pLARmEB(InputData$doMR$gen, InputData$doMR$phe, InputData$doMR$phe, InputData$doMR$outATCG,
InputData$doMR$genRaw, InputData$doMR$kk, InputData$doMR$psmatrix,
CriLOD=3, lars1=20, Genformat=1, Bootstrap=FALSE, CLO=1)
ReadData

*read raw data*

**Description**

read raw data which have not been transformed

**Usage**

```r
ReadData(fileGen, filePhe, fileKin, filePS, fileCov, Genformat)
```

**Arguments**

- `fileGen`: genotype matrix.
- `filePhe`: phenotype matrix.
- `fileKin`: kinship matrix.
- `filePS`: population structure matrix.
- `fileCov`: Covariate matrix.
- `Genformat`: genotype format.

**Author(s)**

Zhang Ya-Wen, Wang Jing-Tian, Li Pei, Zhang Yuan-Ming
Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>

**Examples**

```r
G1 = data(Gen)
P1 = data(Phe)
result = ReadData(fileGen=G1, filePhe=P1, fileKin=NULL, filePS=NULL, fileCov=NULL, Genformat=1)
```

---

ResultFinal

*Final result used to draw manhattan plot.*

**Description**

Final result used to draw manhattan plot.

**Usage**

```r
data(ResultFinal)
```

**Details**

Final result used to draw manhattan plot.
ResultIntermediate

Author(s)
Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>

Description
Intermediate result used to draw manhattan plot.

Usage
data(ResultIntermediate)

Details
Intermediate result used to draw manhattan plot.

Author(s)
Maintainer: Yuan-Ming Zhang<soyzhang@mail.hzau.edu.cn>
Index

<phenotype> (Phe), 13
33-16 (Genotype), 5
A4226 (Genotype), 5
chrom (Gen), 5
Chromosome (ResultFinal), 16
DoData, 2
FASTmrEMMA, 3
FASTmrMLM, 4
Gen, 5
Genotype, 5
inputData, 6
ISIS, 6
LOD.score (ResultFinal), 16
mrMLM, 7
mrMLMFun, 10
MultiManhattan, 11
multiplication_speed, 12
Nov-38 (Genotype), 5
Phe, 13
Phenotype, 13
pKWmEB, 14
pLARmEB, 15
pos (Gen), 5
QTN.effect (ResultFinal), 16
ReadData, 16
rep-1 (Phe), 13
rep-2 (Phe), 13
rep-3 (Phe), 13
ResultFinal, 16
ResultIntermediate, 17
RS. (ResultIntermediate), 17
rs# (Gen), 5
Trait.ID (ResultIntermediate), 17
Trait.name (ResultIntermediate), 17
trait1 (Phenotype), 13
trait2 (Phenotype), 13
trait3 (Phenotype), 13