

Package ‘mrMLM’

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Type Package

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

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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 HIVmrMLM 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](https://doi.org/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](https://doi.org/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

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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	12
Phe	13
Phenotype	13
pKWmEB	14
pLARmEB	15
ReadData	16
ResultFinal	16
ResultIntermediate	17
Index	18

DoData	<i>process raw data</i>
--------	-------------------------

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.
covmatrixRaw	raw covariate matrix.
trait	which trait to analysis.
type	which type to transform.
PopStrType	The type of population structure.

Author(s)

Zhang Ya-Wen, Wang Jing-Tian, Li Pei, Zhang Yuan-Ming
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Examples

```
G1=data(Gen)
P1=data(Phe)
readraw=ReadData(fileGen=Gen,filePhe=Phe,fileKin=NULL,filePS=NULL,
fileCov=NULL,Genformat=1)
result=DoData(readraw$genRaw,Genformat=1,readraw$pheRaw1q,readraw$kkRaw,
readraw$psmatrixRaw,readraw$covmatrixRaw,trait=1,type=2,PopStrType=NULL)
```

 FASTmrEMMA

To perform GWAS with FASTmrEMMA method

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)

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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="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<soy Zhang@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="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	<i>Genotype data</i>
-----	----------------------

Description

Numeric format of genotype dataset.

Usage

```
data(Gen)
```

Details

Dataset input of Genotype for mrMLM function.

Author(s)

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

Genotype	<i>Genotype of real data</i>
----------	------------------------------

Description

Numeric format of genotype dataset.

Usage

```
data(Genotype)
```

Details

Dataset input of Genotype for mrMLM function.

Author(s)

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

inputData	<i>Input data which have been transformed</i>
-----------	---

Description

Input all the dataset which have been transformed

Usage

```
inputData(readdraw,Genformat,method,trait,PopStrType)
```

Arguments

readdraw	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<soy Zhang@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	<i>To perform GWAS with ISIS EM-BLASSO method</i>
------	---

Description

Iterative Sure Independence Screening EM-Bayesian LASSO

Usage

```
ISIS(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 Ya-Wen, Li Pei, Zhang Yuan-Ming
 Maintainer: Yuan-Ming Zhang<soy Zhang@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="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

Package: mrMLM
Type: Package
Version: 5.0.1
Date: 2022-3-27
Depends: lars
Imports: methods,foreach,ncvreg,coin,sampling,data.table,doParallel,BEDMatrix
License: GPL version 2 or newer
LazyLoad: yes

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)

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References

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Examples

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

```
method=c("FASTmrMLM"), trait=1, CriLOD=3, DrawPlot=FALSE,
dir=tempdir(), PC=FALSE, RAM=4)
```

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<soy Zhang@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 $-\log_{10}(\text{P-value})$; 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.

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<soy Zhang@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<soy Zhang@mail.hzau.edu.cn>

Examples

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

Phe	<i>Phenotype dataset</i>
-----	--------------------------

Description

Phenotype dataset of multiple traits.

Usage

```
data(Phe)
```

Details

Dataset input of phenotype in mrMLM function.

Author(s)

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

Phenotype	<i>Phenotype of real data</i>
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Description

Phenotype dataset of multiple traits.

Usage

```
data(Phenotype)
```

Details

Dataset input of phenotype in mrMLM function.

Author(s)

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

pKWmEB

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 Ya-Wen, Wang Jing-Tian, Li Pei, Zhang Yuan-Ming
 Maintainer: Yuan-Ming Zhang<soy Zhang@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="pKWmEB", trait=1)
result=pKWmEB(InputData$doMR$gen, InputData$doMR$phe, InputData$doMR$outATCG,
InputData$doMR$genRaw, InputData$doMR$kk, InputData$doMR$psmatrix,
0.05, svmlod=3, Genformat=1, CLO=1)
```

pLARMmEB

*To perform GWAS with pLARMmEB method***Description**

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

Usage

```
pLARMmEB(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<soyzzhang@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="pLARMmEB",trait=1)
result=pLARMmEB(InputData$doMR$gen,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	<i>read raw data</i>
----------	----------------------

Description

read raw data which have not been transformed

Usage

```
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<soyzzhang@mail.hzau.edu.cn>

Examples

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

ResultFinal	<i>Final result used to draw manhattan plot.</i>
-------------	--

Description

Final result used to draw manhattan plot.

Usage

```
data(ResultFinal)
```

Details

Final result used to draw manhattan plot.

Author(s)

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

ResultIntermediate *Intermediate result used to draw manhattan plot.*

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<soy Zhang@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](#)