mTADA

This notebook descibes steps used to jointly analyze two traits by `mTADA` .

I. Introduction

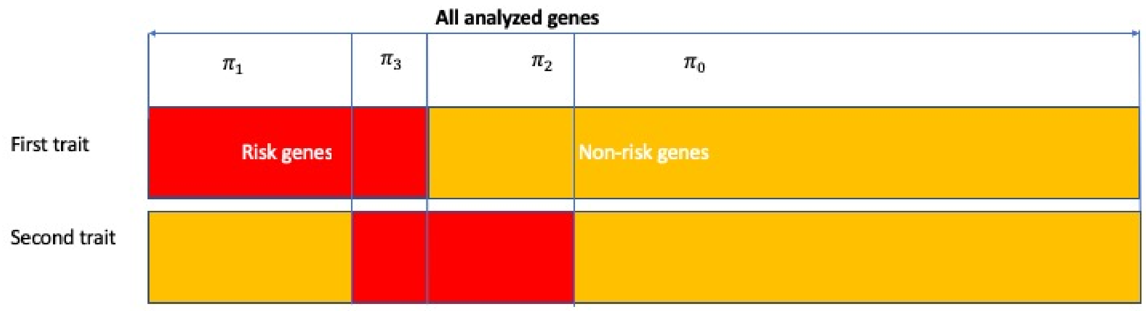
`mTADA` jointly analyze de novo mutations (DNMs) of two traits to 1) estimate the gene-level genetic overlap of the two traits; 2) report shared and specific risk genes; and 3) identify additional risk genes for each analyzed trait.

The method requires genetic parameters from single-trait analyses (the third and fourth columns in Table 1 below). Users can obtain single-trait parameters from `extTADA/TADA` methods.

Table 1. `mTADA` model for one variant category at the *i^{th}* gene.

Hypothesis	Proportion	First trait	Second trait
H_0	π_0	$x_{i1} \sim Poisson(2N_1\mu_i)$	$x_{i2} \sim Poisson(2N_2\mu_i)$
H_1	π_1	$x_{i1} \sim Poisson(2N_1\gamma_1\mu_i)$; $\gamma_1 \sim Gamma(\bar{\gamma}_1\beta_1, \beta_1)$	$x_{i2} \sim Poisson(2N_2\mu_i)$
H_2	π_2	$x_{i1} \sim Poisson(2N_1\mu_i)$	$x_{i2} \sim Poisson(2N_2\gamma_2\mu_i)$; $\gamma_2 \sim Gamma(\bar{\gamma}_2\beta_2, \beta_2)$
H_3	π_3	$x_{i1} \sim Poisson(2N_1\gamma_1\mu_i)$; $\gamma_1 \sim Gamma(\bar{\gamma}_1\beta_1, \beta_1)$	$x_{i2} \sim Poisson(2N_2\gamma_2\mu_i)$; $\gamma_2 \sim Gamma(\bar{\gamma}_2\beta_2, \beta_2)$

Figure 1. `mTADA` framework.



Data for reproducible analyses

Data used in the main manuscript are inside the folder data (data):

1. FullDataSet_DenovoMutations_for_mTADA.txt (data/FullDataSet_DenovoMutations_for_mTADA.txt): all gene-level de novo mutations. These DNMs are used in the main manuscript.

2. SingleTrait_Parameters.txt (data/SingleTrait_Parameters.txt): all single-trait parameters. We used `extTADA` to estimate these parameters from the DNMs above.

   Note: Users can re-run all these single-trait analyses by following an example here: https://github.com/hoangtn/extTADA (https://github.com/hoangtn/extTADA).

II. Requirements

`mTADA` is written in `R` . Other `R` packages are required to run `mTADA` :

- `rstan` : https://mc-stan.org/rstan/ (https://mc-stan.org/rstan/).
- `locfit` : https://cran.r-project.org/web/packages/locfit/index.html (https://cran.r-project.org/web/packages/locfit/index.html).

Software versions were used in our analyses: `R` version 3.5.2, `locfit` version 1.5-9.1, and `rstan` version 2.18.2.

III. An example: joint analysis of DD and EE DNMs

Only one function `mTADA` (in the **Run `mTADA`** section) is used to obtain results. Therefore, users can go directly to the **Run `mTADA`** section to run `mTADA` . However, some additional steps are described here.

Load the source codes

```
dataDir <- "./data/"
source("script/mTADA.R")
```

```
## locfit 1.5-9.1    2013-03-22
```

Read the data and single-trait parameters

```
## De novo data
data <- read.table(paste0(dataDir, "FullDataSet_DenovoMutations_for_mTADA.txt"), header = TRUE, as.is = TRUE)
## Single-trait parameters
sPar <- read.table(paste0(dataDir, "SingleTrait_Parameters.txt"), as.is = TRUE, header = TRUE)

trait1 = "DD"
trait2 = "EE"
##Take a quick look at the single-trait parameters of DD and EE
sPar[grep(trait1, sPar[, 1]), ] ##Trait 1
```

```
##                 Parameter EstimatedValue
## 8                DD_pi[1]     0.02936283
## 9  DD_hyperGammaMeanDN[1]    22.31762802
## 10 DD_hyperGammaMeanDN[2]    86.03966530
## 11      DD_hyperBetaDN[1]     0.82594514
## 12      DD_hyperBetaDN[2]     0.80689775
```

```
sPar[grep(trait2, sPar[, 1]), ] ##Trait 2
```

```
##                 Parameter EstimatedValue
## 18               EE_pi[1]     0.01548789
## 19 EE_hyperGammaMeanDN[1]    51.08181282
## 20 EE_hyperGammaMeanDN[2]    65.15189031
## 21      EE_hyperBetaDN[1]     0.80906448
## 22      EE_hyperBetaDN[2]     0.80774192
```

Set parameters for two traits

As described above, `mTADA` needs single-trait parameters:

- the number of trios: *ntrio*;
- the mean and disperson parameters of relative risks: $\bar{\gamma}_j$ and β_j (j=1, 2);
- the proportion of risk genes: π_1^S and π_2^S.

All these parameters are shown above.

```
### Trait-1 INFORMATION
ntrio1 = 4293 #family numbers
p1 = 0.02936283 #The proportion of risk genes, this is p1S
meanGamma1 = c(22.31762802,  86.03966530) #Mean Gamma of two categories
beta1 = c(0.82594514, 0.80689775) #Beta values inside the distribution RR ~ Gamma(meanRR*beta, beta)
dataT1 <- data[, paste0(c("dn_damaging_", "dn_lof_"), trait1)] #De novo data
muDataT1 <- data[, c("mut_damaging", "mut_lof")] #Mutation data of the first trait
##########################################
### Trait-2 INFORMATION
ntrio2 = 356
p2 = 0.01548789 #This is p2S
meanGamma2 = c(51.08181282, 65.15189031)
beta2 = c(0.80906448, 0.80774192)
dataT2 <- data[, paste0(c("dn_damaging_", "dn_lof_"), trait2)]
muDataT2 <- muDataT1
```

Run `mTADA`

In this example, we only use a small number of iterations and two MCMC chains. However, users can change these parameters to obtain more reliable results.

```
nIteration = 2000 #This should be higher to obtain better results.
nChain = 2 #The number of MCMC chains

##########MAIN ANALYSIS
mTADAresults <- mTADA(geneName = data[, 1],
    #######Trait-1 information
                  ntrio1 = ntrio1, # Trio number of Trait 1
                  p1 = p1, #Risk-gene proportion of Trait 1
                  dataDN1 = data.frame(dataT1), #De novo data of Trait 1
                  mutRate1 = data.frame(muDataT1), # Mutation rates of Trait 1
                  hyperGammaMeanDN1 = c(meanGamma1), # Mean relative risks of Trait 1
                  hyperBetaDN01 = beta1, #NULL, #array(c(1, 1)),
    #######Trait-2 information
                  ntrio2 = ntrio2, # Trio number of Trait 2
                  p2 = p2, #Risk-gene proportion of Trait 2
                  dataDN2 = data.frame(dataT2), # De novo data of Trait 2
                  mutRate2 = data.frame(muDataT2), # Mutation rates of Trait 2
                  hyperGammaMeanDN2 = c(meanGamma2), # Mean relative risks of Trait 2
                  hyperBetaDN02 = beta2, #NULL, #array(c(1, 1)),
    ####Other parameters
                  nIteration = nIteration,
                  useMCMC = TRUE, #If FALSE, it will use the 'Variational Bayes' approach.
                  nChain = nChain
                      )
```

```
## No information for core numbers (nCore); therefore, nCore = nChain: 2 core(s) is/are used

## Loading required package: ggplot2

## Loading required package: StanHeaders

## rstan (Version 2.18.2, GitRev: 2e1f913d3ca3)

## For execution on a local, multicore CPU with excess RAM we recommend calling
## options(mc.cores = parallel::detectCores()).
## To avoid recompilation of unchanged Stan programs, we recommend calling
## rstan_options(auto_write = TRUE)

## ===================
## Building the model
## =================

##
## =======Use MCMC===========

## recompiling to avoid crashing R session

## ====
## Only pi, alpha and hyper parameters are estimated in this step
## The method does not calculate HPDs for hyper betas, just their medians
## ===
```

Obtain analysis results

`mTADA` 's output includes:

1. `data` : main gene-level results (posterior probabilities for the four models as described in the main manuscript: PP0, PP1, PP2 and PP3).
2. `probModel` : a vector of π_j, (j = 0..3) in Table 1.
3. `pars` : the estimated value and credible interval of π_3 (described as p12 in the our code).
4. `mcmcData` : MCMC sampling results for π_3.

The most important information is from `data` . **Users can use this information to obtain top prioritized genes for downstream analyses (e.g., top shared/specific genes, top genes for each trait)**. However, we will also take a quick look at all these information.

Results for downstream analyses (gene-level posterior probabilities (PPs) of four models)

We will demonstrate how to choose top proritized genes from `mTADA` 's results using a PP threshold of 0.8. These genes can be shared genes, specific genes; or genes for single traits.

```
fData <- mTADAresults$data ## Full analysis results of the two-trait analysis.
head(fData)
```

```
##   geneName dn_damaging_DD dn_lof_DD dn_damaging_EE dn_lof_EE        NO
## 1     A1BG              0         0              0         0 0.9785638
## 2 A1BG-AS1              0         0              0         0 0.9648110
## 3     A1CF              0         0              0         0 0.9894511
## 4      A2M              0         0              1         0 0.7728022
## 5  A2M-AS1              0         0              0         0 0.9638173
## 6    A2ML1              0         0              0         0 0.9920417
##           BOTH        FIRST      SECOND
## 1 0.0028849335 0.0102232990 0.008327935
## 2 0.0060903853 0.0204204671 0.008678102
## 3 0.0006499363 0.0026904350 0.007208518
## 4 0.0025131770 0.0002609915 0.224423609
## 5 0.0063273659 0.0211660881 0.008689214
## 6 0.0002100015 0.0009201318 0.006828191
```

Genes with PP3 > 0.8 (Posterior probabilities of Model 3)

Shared risk genes between DD and EE.

```
fData[fData$BOTH > 0.8, ]
```

```
##       geneName dn_damaging_DD dn_lof_DD dn_damaging_EE dn_lof_EE
## 2348   CACNA1A              5         0              2         0
## 3201      CHD2              0         6              0         1
## 6254    GABBR2              2         0              2         0
## 6265    GABRB3              2         0              2         0
## 6610     GNAO1              4         1              2         0
## 7165     HECW2              5         1              1         0
## 7426    HNRNPU              0         7              0         1
## 8283     KCNQ2              9         0              2         0
## 8284     KCNQ3              3         0              1         0
## 10146      MLL              1        26              1         0
## 12480     PHIP              1         2              0         1
## 14673    SCN2A              9         4              2         0
## 14681    SCN8A              6         0              2         0
## 16228   STXBP1              6         5              4         1
##                 NO      BOTH        FIRST       SECOND
## 2348  3.061557e-04 0.9934586 3.857158e-03 2.378089e-03
## 3201  4.538516e-10 0.9373802 6.261984e-02 2.048901e-10
## 6254  2.475216e-03 0.9531470 1.665815e-03 4.271197e-02
## 6265  9.065089e-04 0.9802813 1.552743e-03 1.725944e-02
## 6610  1.573114e-08 0.9984154 1.584264e-03 2.989837e-07
## 7165  1.903578e-06 0.8924003 1.075973e-01 4.761376e-07
## 7426  8.628766e-13 0.9367325 6.326751e-02 3.852893e-13
## 8283  3.189291e-13 0.9982274 1.772551e-03 5.416619e-12
## 8284  4.242399e-03 0.9136293 8.067943e-02 1.448846e-03
## 10146 1.458250e-48 0.8681168 1.318832e-01 2.894838e-49
## 12480 1.444210e-02 0.8916606 8.956108e-02 4.336247e-03
## 14673 3.061183e-18 0.9964569 3.543136e-03 2.596351e-17
## 14681 4.151136e-06 0.9959737 3.990920e-03 3.124247e-05
## 16228 7.521732e-24 1.0000000 9.762103e-09 2.323688e-17
```

Genes with PP1 > 0.8 (Posterior probabilities of Model 1)

Specific risk genes for DD.

```
fData[fData$FIRST > 0.8, ]
```

```
##       geneName dn_damaging_DD dn_lof_DD dn_damaging_EE dn_lof_EE
## 681    ANKRD11              0        32              0         0
## 1001    ARID1B              0        30              0         0
## 1002     ARID2              0         3              0         0
## 1153     ASXL1              0         4              0         0
## 1317     AUTS2              0         4              0         0
## 1450    BCL11A              2         3              0         0
## 1630     BRPF1              0         4              0         0
## 2355   CACNA1E              2         2              0         0
## 2434    CAMTA1              1         2              0         0
## 3202      CHD3              3         1              0         0
## 3203      CHD4              5         1              0         0
## 3206      CHD7              2         2              0         0
## 3457      CLTC              2         3              0         0
## 3516     CNOT3              2         2              0         0
## 3599  COL4A3BP              4         0              0         0
## 3773    CREBBP              7         3              0         0
## 3876   CSNK2A1              4         0              0         0
## 3924      CTCF              5         0              0         0
## 3942    CTNNB1              0        11              0         0
## 4632    DNMT3A              4         1              0         0
## 4832    DYRK1A              4        14              0         0
## 4861      EBF3              2         3              0         0
## 4948    EFTUD2              3         2              0         0
## 4974     EHMT1              2         7              0         0
## 5157     EP300              3        12              0         0
## 6120     FOXP1              4         8              0         0
## 6121     FOXP2              1         2              0         0
## 7330    HIVEP2              2         2              0         0
## 7333       HK1              3         1              0         0
## 8168    KANSL1              0         8              0         0
## 8177     KAT6A              0         8              0         0
## 8178     KAT6B              0         8              0         0
## 8211     KCNB1              2         1              0         0
## 8228     KCNH1              4         0              0         0
## 8336     KDM5B              0         3              0         0
## 9618     LZTR1              2         1              0         0
## 9727    MAP4K4              3         2              0         0
## 9906    MED13L              5        13              0         0
## 9935     MEF2C              4         4              0         0
## 10670    MYT1L              2         2              0         0
## 10978     NFIX              1         4              0         0
## 11282     NSD1              1         7              0         0
## 12004    PACS1              8         0              0         0
## 12831     POGZ              0         6              0         0
## 12994    PPM1D              0         5              0         0
## 13062  PPP2R5D             12         0              0         0
## 13250  PRPF40A              1         2              0         0
## 13538    PUF60              0         3              0         0
## 13540     PUM2              1         2              0         0
## 13541     PURA              3         7              0         0
## 14894    SETD2              1         2              0         0
## 14897    SETD5              2        14              0         0
## 15074    SIN3A              1         3              0         0
## 15133  SLC12A2              2         1              0         0
## 15440   SLC6A1              6         2              0         0
## 15546  SMARCA2              9         0              0         0
## 15752      SON              0         3              0         0
## 15985    SRCAP              1         4              0         0
## 16337  SYNGAP1              0        13              0         0
## 16578    TCF12              1         2              0         0
## 16581    TCF20              0         5              0         0
## 16587     TCF4              4         9              0         0
## 17284    TNPO3              1         2              0         0
## 17548   TRIP12              2         3              0         0
## 18337    WDR26              1         2              0         0
## 18420    WHSC1              0         3              0         0
##                 NO       BOTH     FIRST       SECOND
## 681   2.297741e-60 0.13872908 0.8612709 1.116175e-62
## 1001  1.704450e-56 0.14641883 0.8535812 8.817382e-59
## 1002  2.193691e-03 0.17485453 0.8229377 1.405687e-05
## 1153  1.845391e-05 0.17279546 0.8271860 1.162575e-07
## 1317  1.133833e-05 0.18488529 0.8151033 7.756077e-08
## 1450  7.457047e-07 0.19110833 0.8088909 5.313246e-09
## 1630  7.118090e-05 0.13281732 0.8671112 3.288114e-07
## 2355  4.915877e-02 0.08914968 0.8615381 1.534086e-04
## 2434  1.012129e-02 0.17035744 0.8194578 6.345614e-05
## 3202  5.977087e-02 0.11099360 0.8289942 2.413456e-04
## 3203  5.540230e-04 0.08766979 0.9117746 1.606548e-06
## 3206  4.704508e-02 0.10112344 0.8516630 1.684619e-04
## 3457  6.341962e-05 0.11784625 0.8820901 2.555229e-07
## 3516  1.534432e-04 0.17760910 0.8222365 9.995846e-07
## 3599  1.573369e-03 0.18553072 0.8128851 1.082981e-05
## 3773  1.302498e-10 0.09353761 0.9064624 4.053376e-13
## 3876  8.953515e-04 0.19751095 0.8015870 6.653305e-06
## 3924  3.492562e-05 0.19339259 0.8065722 2.525481e-07
## 3942  1.541043e-19 0.18239881 0.8176012 1.036809e-21
## 4632  3.852259e-05 0.17170928 0.8282520 2.408519e-07
## 4832  5.189173e-31 0.18805603 0.8119440 3.624622e-33
## 4861  8.613568e-07 0.18991149 0.8100876 6.089838e-09
## 4948  2.505835e-05 0.14945560 0.8505192 1.327957e-07
## 4974  2.140993e-13 0.14691102 0.8530890 1.111933e-15
## 5157  4.079682e-23 0.11138649 0.8886135 1.542231e-25
## 6120  1.001012e-18 0.17612505 0.8238750 6.453606e-21
## 6121  5.432492e-03 0.17654382 0.8179883 3.535965e-05
## 7330  1.640057e-03 0.14126349 0.8570883 8.152047e-06
## 7333  2.808436e-03 0.14421099 0.8529663 1.431972e-05
## 8168  1.948521e-13 0.18350266 0.8164973 1.320675e-15
## 8177  2.074813e-12 0.15071096 0.8492890 1.110380e-14
## 8178  1.001571e-12 0.15819723 0.8418028 5.676406e-15
## 8211  8.664847e-03 0.17746796 0.8138102 5.698508e-05
## 8228  2.404097e-03 0.17053318 0.8270478 1.494974e-05
## 8336  3.015563e-02 0.12310789 0.8466042 1.322444e-04
## 9618  2.094615e-02 0.16293339 0.8159943 1.261336e-04
## 9727  2.185163e-04 0.12698830 0.8727922 9.588267e-07
## 9906  1.527178e-28 0.12419530 0.8758047 6.531170e-31
## 9935  2.503506e-11 0.18133828 0.8186617 1.672388e-13
## 10670 5.479651e-04 0.15615945 0.8432895 3.060186e-06
## 10978 2.422783e-07 0.18309500 0.8169048 1.637657e-09
## 11282 2.440202e-11 0.13734200 0.8626580 1.171639e-13
## 12004 5.419168e-09 0.17478338 0.8252166 3.461530e-11
## 12831 1.677565e-09 0.19281239 0.8071876 1.208490e-11
## 12994 5.314446e-08 0.19463984 0.8053601 3.873495e-10
## 13062 5.258058e-15 0.17487375 0.8251263 3.360725e-17
## 13250 8.685049e-03 0.16444484 0.8268180 5.209380e-05
## 13538 2.908053e-04 0.19727664 0.8024304 2.156125e-06
## 13540 8.187980e-03 0.16161836 0.8301456 4.807471e-05
## 13541 2.499371e-16 0.19844222 0.8015578 1.866093e-18
## 14894 4.852918e-02 0.15035019 0.8008459 2.747650e-04
## 14897 1.795241e-27 0.16947547 0.8305245 1.104792e-29
## 15074 2.376476e-04 0.14856417 0.8511969 1.250895e-06
## 15133 5.046412e-02 0.14547211 0.8037883 2.754382e-04
## 15440 2.196975e-10 0.18675291 0.8132471 1.521505e-12
## 15546 1.418853e-08 0.11378454 0.8862154 5.493950e-11
## 15752 3.836161e-03 0.16715345 0.8289871 2.332748e-05
## 15985 3.773627e-05 0.12710945 0.8728526 1.657293e-07
## 16337 1.016582e-22 0.15249346 0.8475065 5.516375e-25
## 16578 3.104402e-03 0.17794702 0.8189282 2.034353e-05
## 16581 1.278363e-07 0.19166762 0.8083323 9.141475e-10
## 16587 1.136552e-20 0.16930787 0.8306921 6.986022e-23
## 17284 6.738068e-03 0.17422658 0.8189921 4.322883e-05
## 17548 4.285968e-05 0.13907921 0.8608777 2.088205e-07
## 18337 1.979577e-03 0.18717380 0.8108328 1.378128e-05
## 18420 3.986182e-03 0.15093289 0.8450595 2.147124e-05
```

Genes with PP2 > 0.8 (Posterior probabilities of Model 2)

Specific risk genes for EE.

```
fData[fData$SECOND > 0.8, ]
```

```
##       geneName dn_damaging_DD dn_lof_DD dn_damaging_EE dn_lof_EE
## 14671    SCN1A              2         0              4         4
##                 NO      BOTH        FIRST    SECOND
## 14671 2.043814e-12 0.1216637 8.537782e-15 0.8783363
```

Use mTADA's results for single-trait analyses.

We can obtain single-trait results by summing PP1 and PP3 (Trait 1) or PP2 and PP3 (Trait 2).

Trait 1

Top prioritized genes of DD.

```
fData[, 'pTrait1'] <- fData[, 'BOTH'] + fData[, 'FIRST']
fData1 <- fData[fData$pTrait1 > 0.8, ]
head(fData1[, c(1:5, 10)])
```

```
##      geneName dn_damaging_DD dn_lof_DD dn_damaging_EE dn_lof_EE   pTrait1
## 347      ADNP              1        19              0         0 1.0000000
## 447     AHDC1              0         8              0         0 1.0000000
## 681   ANKRD11              0        32              0         0 1.0000000
## 1000   ARID1A              1         2              0         0 0.9148468
## 1001   ARID1B              0        30              0         0 1.0000000
## 1002    ARID2              0         3              0         0 0.9977923
```

Trait 2

Top prioritized genes of EE.

```
fData[, 'pTrait2'] <- fData[, 'BOTH'] + fData[, 'SECOND']
fData2 <- fData[fData$pTrait2 > 0.8, ]
head(fData2[, c(1:5, 11)])
```

```
##      geneName dn_damaging_DD dn_lof_DD dn_damaging_EE dn_lof_EE   pTrait2
## 2348  CACNA1A              5         0              2         0 0.9958367
## 3201     CHD2              0         6              0         1 0.9373802
## 6254   GABBR2              2         0              2         0 0.9958590
## 6265   GABRB3              2         0              2         0 0.9975407
## 6610    GNAO1              4         1              2         0 0.9984157
## 7165    HECW2              5         1              1         0 0.8924008
```

Other information

Some additional information can be obtained from mTADA's results.

```
pCI <- mTADAresults$pars ## Genetic parameters
piValue <- mTADAresults$probModel ## Posterior probabilities of genes for four models
mcmcResult <- mTADAresults$mcmcData ##MCMC results
```

The proportions of risk genes

piValue is a vector of π values. In the result below, pNO, pFIRST, pSECOND, and pBOTH are π_0, π_1, π_2 and π_3 respectively in **Table 1**.

```
piValue
```

```
##         pNO      pFIRST     pSECOND       pBOTH
## 0.961928644 0.022583466 0.008708526 0.006779364
```

Estimated information of π_3.

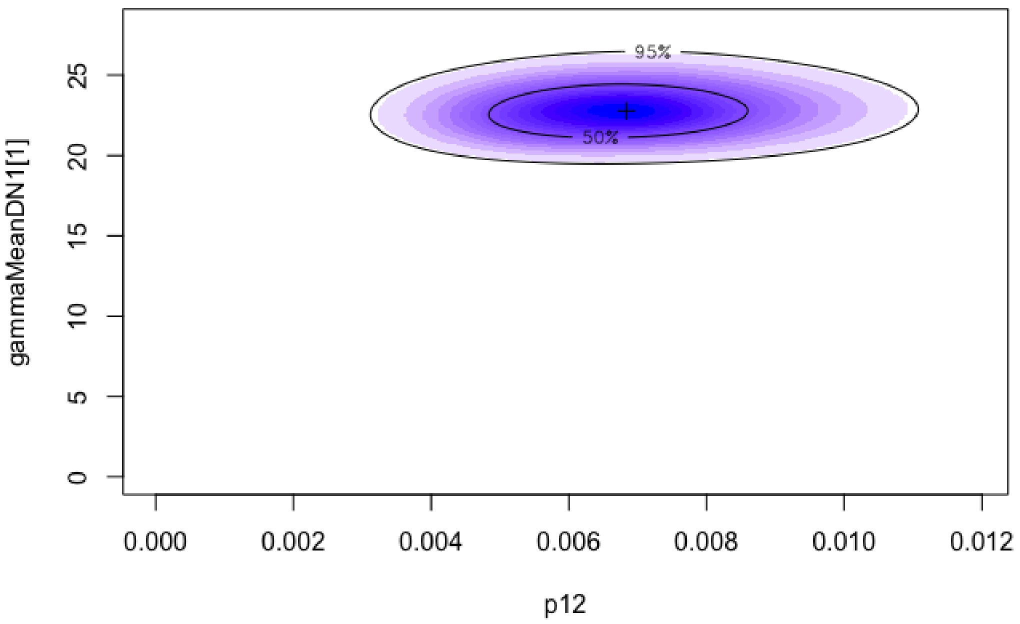
Credible-interval information is from *p**CI***.

```
pCI ## Mode: estimated values; CI: credible interval with low (l) and upper (u) values
```

```
##                           Mode           lCI          uCI
## p12                0.006779364  0.003786445  0.01006793
## gammaMeanDN1[1] 22.848744547 20.082794919 25.60378408
```

To check the convergent information of π_3, we can visualize MCMC results.

```
## p12 is pi3 in the model
plotParHeatmap1(mcmcResult = mcmcResult, pars = c('p12', 'gammaMeanDN1[1]'))
```



Citation

`mTADA` : a framework for identifying risk genes from de novo mutations in multiple traits. Hoang T. Nguyen, Amanda Dobbyn, Ruth C. Brown, Brien P. Riley, Joseph Buxbaum, Dalila Pinto, Shaun M Purcell, Patrick F Sullivan, Xin He, Eli A. Stahl.