

The coMET User Guide

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Contents

1	Citation	1
2	Introduction	3
3	Usage	3
4	File Formats	5
4.1	Format of info file(mandatory):	6
4.2	Format of correlation matrix(mandatory):	6
4.3	Format of extra info file:	7
4.4	Format of annotation file	7
4.5	Option of config.file	7
5	Creation plot like webservice:	8
6	Creation plot with the generic function: comet	9
6.1	coMET plot: pvalue plot, annotation tracks, and correlation matrice	10
6.2	coMET plot: annotation tracks and correlation matrice	10

2 Introduction

The CoMET package is a web-based plotting tool and R-based package to visualize EWAS (epigenome-wide association scan) results in a genomic region of interest. CoMET provides a plot of the EWAS association signal and visualisation of the methylation correlation between CpG sites (co-methylation). The CoMET package also provides the option to annotate the region using functional genomic information, including both user-defined features and pre-selected features based on the Encode project. The plot can be customized with different parameters, such as plot labels, colours, symbols, heatmap colour scheme, significance thresholds, and including reference CpG sites. Finally, the tool can also be applied to display the correlation patterns of other genomic data, e.g. gene expression array data.

3 Usage

CoMET requires the installation of R, the statistical computing software, freely available for Linux, Windows, or MacOS. CoMET can be downloaded from bioconductor. Packages can be installed using the `install.packages` command in R. The coMET R package includes two major functions `comet.web` and `comet`. the function 'comet.web' generates output plot with the same settings of genomic annotation tracks as that of the webserver (<http://www.epigen.kcl.ac.uk/comet>). the function 'comet' generates output plots with the customized annotation tracks defined by user.

```
source("http://bioconductor.org/biocLite.R")
biocLite("coMET")
```

CoMET can be loaded into R using this command:

```
library(coMET)

## Loading required package: grid
## Loading required package: biomaRt
## Loading required package: Gviz
## Loading required package: BiocGenerics
## Loading required package: parallel
##
## Attaching package: 'BiocGenerics'
##
## The following objects are masked from 'package:parallel':
##
##   clusterApply, clusterApplyLB, clusterCall, clusterEvalQ, clusterExport,
##   clusterMap, parApply, parCapply, parLapply, parLapplyLB, parRapply,
##   parSapply, parSapplyLB
##
## The following object is masked from 'package:stats':
##
##   xtabs
##
## The following objects are masked from 'package:base':
##
##   anyDuplicated, append, as.data.frame, as.vector, cbind, colnames, do.call,
```

```
## duplicated, eval, evalq, Filter, Find, get, intersect, is.unsorted, lapply,
## Map, mapply, match, mget, order, paste, pmax, pmax.int, pmin, pmin.int,
## Position, rank, rbind, Reduce, rep.int, rownames, sapply, setdiff, sort,
## table, tapply, union, unique, unlist
##
## Loading required package: ggbio
## Loading required package: ggplot2
## Need specific help about ggbio? try mailing
## the maintainer or visit http://tengfei.github.com/ggbio/
##
## Attaching package: 'ggbio'
##
## The following objects are masked from 'package:ggplot2':
##
## geom_bar, geom_rect, geom_segment, ggsave, stat_bin, stat_identity, xlim
##
## Loading required package: trackViewer
## Loading required package: GenomicRanges
## Loading required package: IRanges
## Loading required package: GenomeInfoDb
## Loading required package: gWidgetstcltk
## Loading required package: gWidgets
## Loading required package: tcltk
## Loading required package: digest
## Loading required package: rtracklayer
##
## Attaching package: 'rtracklayer'
##
## The following objects are masked from 'package:gWidgetstcltk':
##
## visible, visible<-
##
## The following objects are masked from 'package:gWidgets':
##
## visible, visible<-
##
## Loading required package: colortools
## Loading required package: hash
## hash-2.2.6 provided by Decision Patterns
##
##
## Attaching package: 'hash'
##
## The following object is masked from 'package:rtracklayer':
##
## values
##
```

```
## The following object is masked from 'package:gWidgetstcltk':
##
##   delete
##
## The following object is masked from 'package:gWidgets':
##
##   delete
##
## The following objects are masked from 'package:GenomicRanges':
##
##   values, values<-
##
## The following objects are masked from 'package:IRanges':
##
##   values, values<-
##
## The following objects are masked from 'package:Gviz':
##
##   values, values<-
##
## The following object is masked from 'package:biomaRt':
##
##   keys

## Warning: replacing previous import by 'hash::keys' when loading 'coMET'
## Warning: replacing previous import by 'hash::values' when loading 'coMET'
## Warning: replacing previous import by 'hash::values<-' when loading 'coMET'
```

The configuration file amends the options for the plot to be produced from comet. Example configuration and input files are also provided in the webservice(<http://www.epigen.kcl.ac.uk/comet> and <http://comet.epigen.kcl.ac.uk:3838/comet>). Information about the package can viewed from within R using this command.

```
?comet
?comet.web
```

4 File Formats

4 formats (option CORMATRIX.FORMAT) describes tab-delimited correlation file (option CORMATRIX.FILE):

1. CORMATRIX: the data has already pre-computed by users;
2. RAW: The data is at raw format and can be computed by one of 3 methods Spearman, Pearson, Kendall (option CORMATRIX.METHOD). ;
3. 2 other formats are when the association data and correlation matrix are in the same file defined in the option DATA.FILE (region to visualize (option DATA.FILE) Others describing the P-value and optionally the direction of association (for example gene expression, validation studies) (option DATA.FILE.LARGE))

4.1 Format of info file(mandatory):

Info file can be a list of CpG sites with/without Beta value (or direction sign). If it is a site file then it is mandatory to have the 4 columns as shown below with headers in the same order. Beta can be the 5th column(optional) and it can be either a numeric value (positive or negative values) or only direction sign ("+", "-")

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
infofile <- file.path(extdata, "cyp1b1_infofile.txt")
#infofile <- "../inst/extdata/cyp1b1_infofile.txt"

data_info <- read.csv(infofile, header = TRUE,
                      sep = "\t", quote = "")

head(data_info)
```

##	TargetID	CHR	MAPINFO	Pval
## 1	cg22248750	2	38294160	2.750e-01
## 2	cg11656478	2	38297759	7.795e-01
## 3	cg14407177	2	38298023	2.864e-01
## 4	cg02162897	2	38300537	3.148e-07
## 5	cg20408276	2	38300586	1.468e-06
## 6	cg00565882	2	38300707	7.563e-03

Also it can be region with/without an end start of the base pair. If it is a region file then it is mandatory to have the 5 columns below with headers in this order. Beta can be the 6th column(optional).

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
infoexp <- file.path(extdata, "cyp1b1_infofile_exprGene_region.txt")
#infoexp <- "../inst/extdata/cyp1b1_infofile_exprGene_region.txt"

data_infoexp <- read.csv(infoexp, header = TRUE,
                        sep = "\t", quote = "")

head(data_infoexp)
```

##	TargetID	CHR	MAPINFO.START	MAPINFO.STOP	Pval	BETA
## 1	ENSG00000138061.7_38294652_38298453	2	38294652	38298453	3.064e-17	+
## 2	ENSG00000138061.7_38301489_38302532	2	38301489	38302532	1.145e-07	+
## 3	ENSG00000138061.7_38302919_38303323	2	38302919	38303323	1.014e-08	-

4.2 Format of correlation matrix(mandatory):

The data can be either pre-calculated correlation matrix or raw data. If it is a raw data then you can select the type of correlation method (spearman ,kendall or pearson).

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
corfile <- file.path(extdata, "cyp1b1_res37_rawMatrix.txt")
#corfile <- "../inst/extdata/cyp1b1_res37_rawMatrix.txt"
```

```
data_cor <-read.csv(corfile, header = TRUE,
                    sep = "\t", quote = "")
data_cor[1:6,1:6]

##      cg22248750 cg11656478 cg14407177 cg02162897 cg20408276 cg00565882
## 1  -0.086368   -0.4897      1.6719      0.52423      0.1659      0.224222
## 2  -0.001079   -0.6331      0.3151     -0.29821     -0.4339     -0.007795
## 3   0.316569   -0.2610     -0.4943      0.04657      0.1840      0.313967
## 4  -0.409150    0.6816     -0.3251     -0.58656     -0.2070      0.150720
## 5   1.299533    0.3986      0.1119      0.81182      0.1833      0.194928
## 6  -1.119488    0.3036     -1.2795     -0.49785      0.1076     -0.876012
```

4.3 Format of extra info file:

This can be another type of info file (e.g Expression data or replication data) and it follows the same rules than the info file.

4.4 Format of annotation file

format accepted by GViz such as BED, GTF, and GFF3 format

4.5 Option of config.file

If you would like to make your own changes to the plot you can download the configuration file from this site. After you make the relative changes you can upload it to the server again and plot.

```
extdata <- system.file("extdata", package="coMET",mustWork=TRUE)
configfile <- file.path(extdata, "config_cyp1b1_zoom_4webserver.txt")
#configfile <- "../inst/extdata/config_cyp1b1_zoom_4webserver.txt"

data_config <-read.csv(configfile, quote = "")
data_config

##              DISP.MYDATA.TRUE
## 1              MYDATA.FORMAT=SITE
## 2              MYDATA.REF=cg02162897
## 3              PVAL.THRESHOLD=4.720623e-06
## 4              DISP.ASSOCIATION=FALSE
## 5              DISP.REGION=FALSE
## 6              MYDATA.LARGE.FORMAT=REGION_ASSO
## 7              DISP.ASSOCIATION.LARGE=TRUE
## 8              DISP.REGION.LARGE=TRUE
## 9              SAMPLE.LABELS.LARGE=Gene expression
## 10             COLOR.LIST.LARGE=green
## 11             SYMBOLS.LARGE=diamond-fill
## 12             START=38290160
```

```

## 13                                END=38303219
## 14                                SAMPLE.LABELS=CpG
## 15                                SYMBOLS=circle-fill
## 16                                LAB.Y=log
## 17                                DISP.COLOR.REF=TRUE
## 18                                CORMATRIX.FORMAT=RAW
## 19                                DISP.CORMATRIXMAP=TRUE
## 20                                CORMATRIX.METHOD=spearman
## 21                                CORMATRIX.COLOR.SCHEME=bluewhitered
## 22                                DISP.PHYS.DIST=TRUE
## 23                                DISP.COLOR.BAR=TRUE
## 24                                DISP.TYPE=symbol
## 25                                DISP.LEGEND=TRUE
## 26                                LIST.TRACKS=transcriptENSEMBL
## 27                                CGI
## 28                                ChromHMM
## 29                                DNase
## 30                                RegENSEMBL
## 31                                SNP
## 32                                DISP.MULT.LAB.X=FALSE
## 33                                IMAGE.TYPE=pdf
## 34 IMAGE.TITLE="Example a-DMR in CYP1B1 in Adipose tissue"
## 35                                IMAGE.NAME=cyp1b1_zoom_plus_name_expr
## 36                                IMAGE.SIZE=3.5
## 37                                GENOME=hg19
## 38                                DATASET.GENE=hsapiens_gene_ensembl
## 39                                DATASET.SNP=hsapiens_snp
## 40                                VERSION.DBSNP=snp138
## 41                                DATASET.SNP.STOMA=hsapiens_snp_som
## 42                                DATASET.REGULATION=hsapiens_feature_set
## 43                                DATASET.STRU=hsapiens_structvar
## 44                                DATASET.STRU.STOMA=hsapiens_structvar_som
## 45                                PATTERN.REGULATION=GM12878
## 46                                BROWSER.SESSION=UCSC

```

5 Creation plot like webservice:

It is possible to use simply the creation of plot with the function `comet.web`

```

extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
configfile <- file.path(extdata, "config_cyp1b1_zoom.txt")
#configfile <- "../inst/extdata/config_cyp1b1_zoom.txt"
comet.web(config.file=configfile, PRINT.IMAGE=FALSE, VERBOSE=FALSE)

```

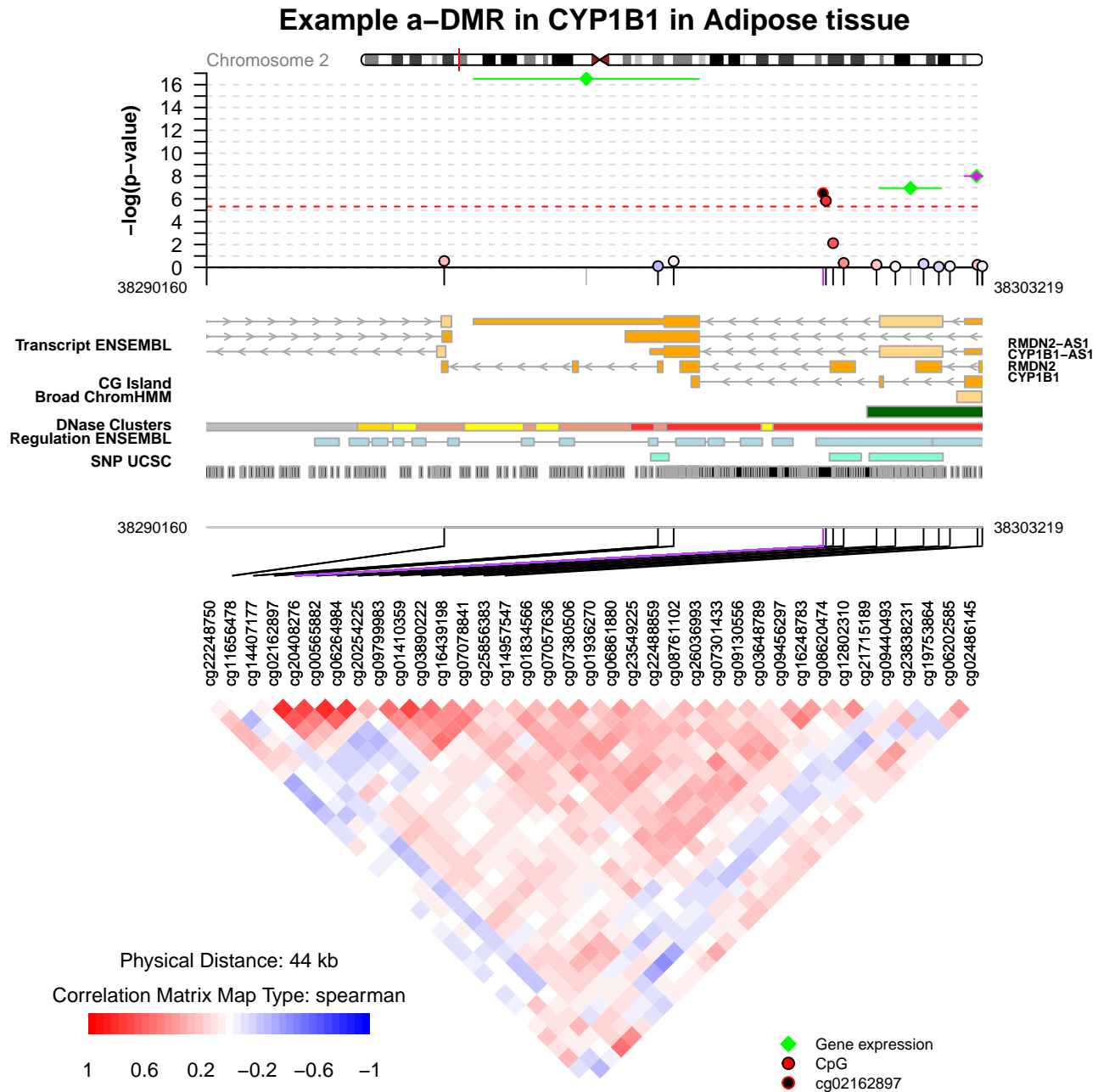



Figure 1: Plot with comet.web function.

6 Creation plot with the generic function: comet

It is possible to create the annotation tracks by Gviz, trackviewer or ggbio. Currently, the combinaison of annotation tracks from Gviz with the heatmap of correlation between genetics elements is better plot in coMET.

6.1 coMET plot: pvalue plot, annotation tracks, and correlation matrice

```
library(Gviz)
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
configfile <- file.path(extdata, "config_cyp1b1_zoom_4comet.txt")
#configfile <- "../inst/extdata/config_cyp1b1_zoom_4comet.txt"
chrom <- "chr2"
start <- 38290160
end <- 38303219
gen <- "hg19"

genetrack <- genesENSEMBL(gen, chrom, start, end, showId=FALSE)
snptrack <- snpBiomart(chrom, start, end, dataset="hsapiens_snp_som", showId=FALSE)
strutrack <- structureBiomart(chrom, start, end, strand,
                             dataset="hsapiens_structvar_som", showId=FALSE)
iscatrack <- ISCATrack(gen, chrom, start, end, table="iscaPathogenic")

listgviz <- list(genetrack, snptrack, iscatrack)
comet(config.file=configfile, TRACKS.GVIZ=listgviz,
      VERBOSE=FALSE, PRINT.IMAGE=FALSE)
```

6.2 coMET plot: annotation tracks and correlation matrice

It is possible to visualise only annotation tracks and the correlation between genetic elements. In this case, we need to use the option `DISP.PVALUEPLOT=FALSE`

```
library(Gviz)
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
configfile <- file.path(extdata, "config_cyp1b1_zoom_4comet.txt")
#configfile <- "../inst/extdata/config_cyp1b1_zoom_4comet.txt"
chrom <- "chr2"
start <- 38290160
end <- 38303219
gen <- "hg19"

genetrack <- genesENSEMBL(gen, chrom, start, end, showId=FALSE)
snptrack <- snpBiomart(chrom, start, end,
                      dataset="hsapiens_snp_som", showId=FALSE)
strutrack <- structureBiomart(chrom, start, end,
                              strand, dataset="hsapiens_structvar_som")
clinVariant <- ClinVarMainTrack(gen, chrom, start, end)
clinCNV <- ClinVarCnvTrack(gen, chrom, start, end)
gwastrack <- GWASTrack(gen, chrom, start, end)
geneRtrack <- GeneReviewsTrack(gen, chrom, start, end)

listgviz <- list(genetrack, snptrack, strutrack, clinVariant,
                 clinCNV, gwastrack, geneRtrack)
```

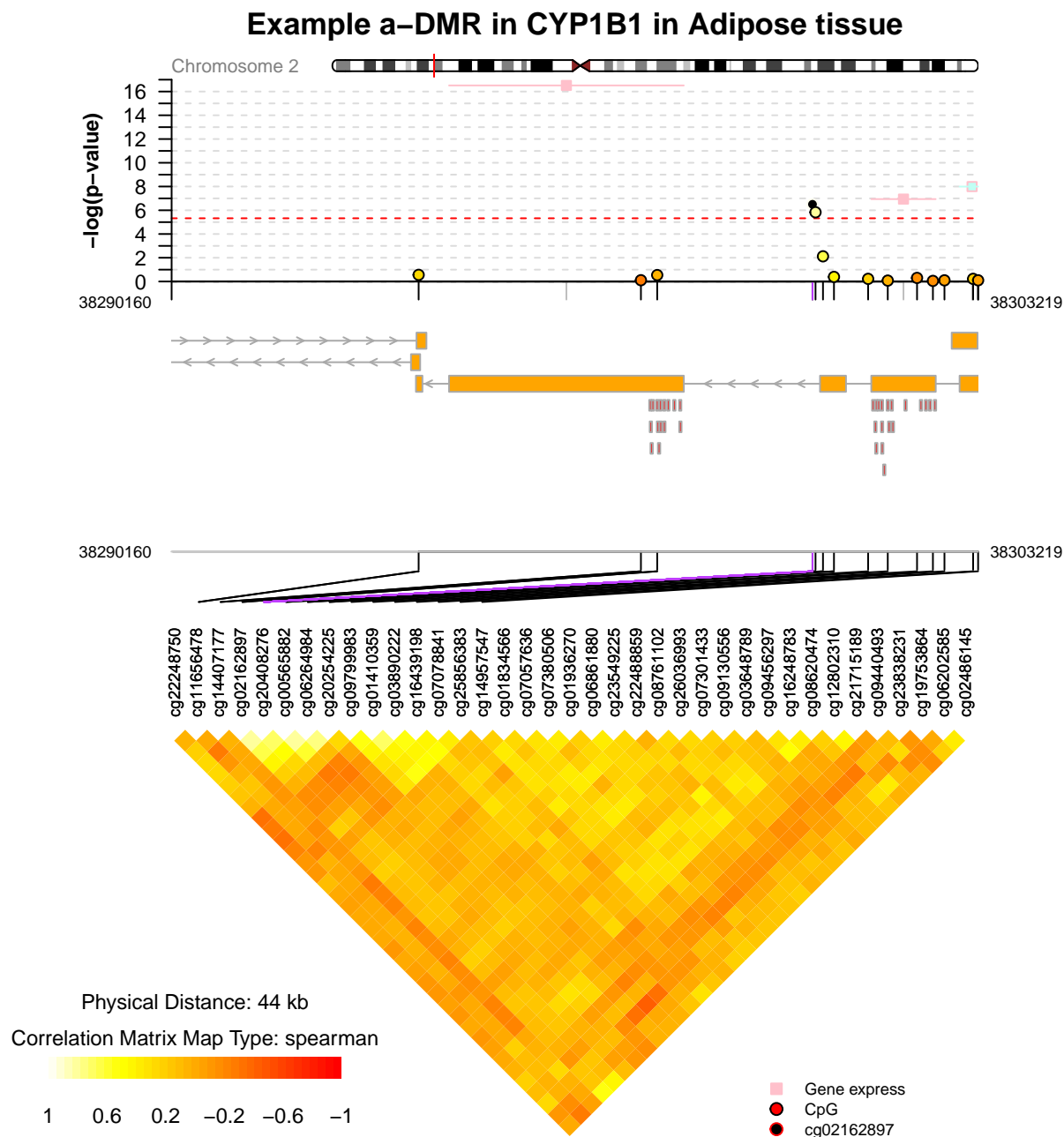


Figure 2: Plot with comet function.

```
comet(config.file=configfile,TRACKS.GVIZ=listgviz,
      VERBOSE=FALSE, PRINT.IMAGE=FALSE,DISP.PVALUEPLOT=FALSE)
```

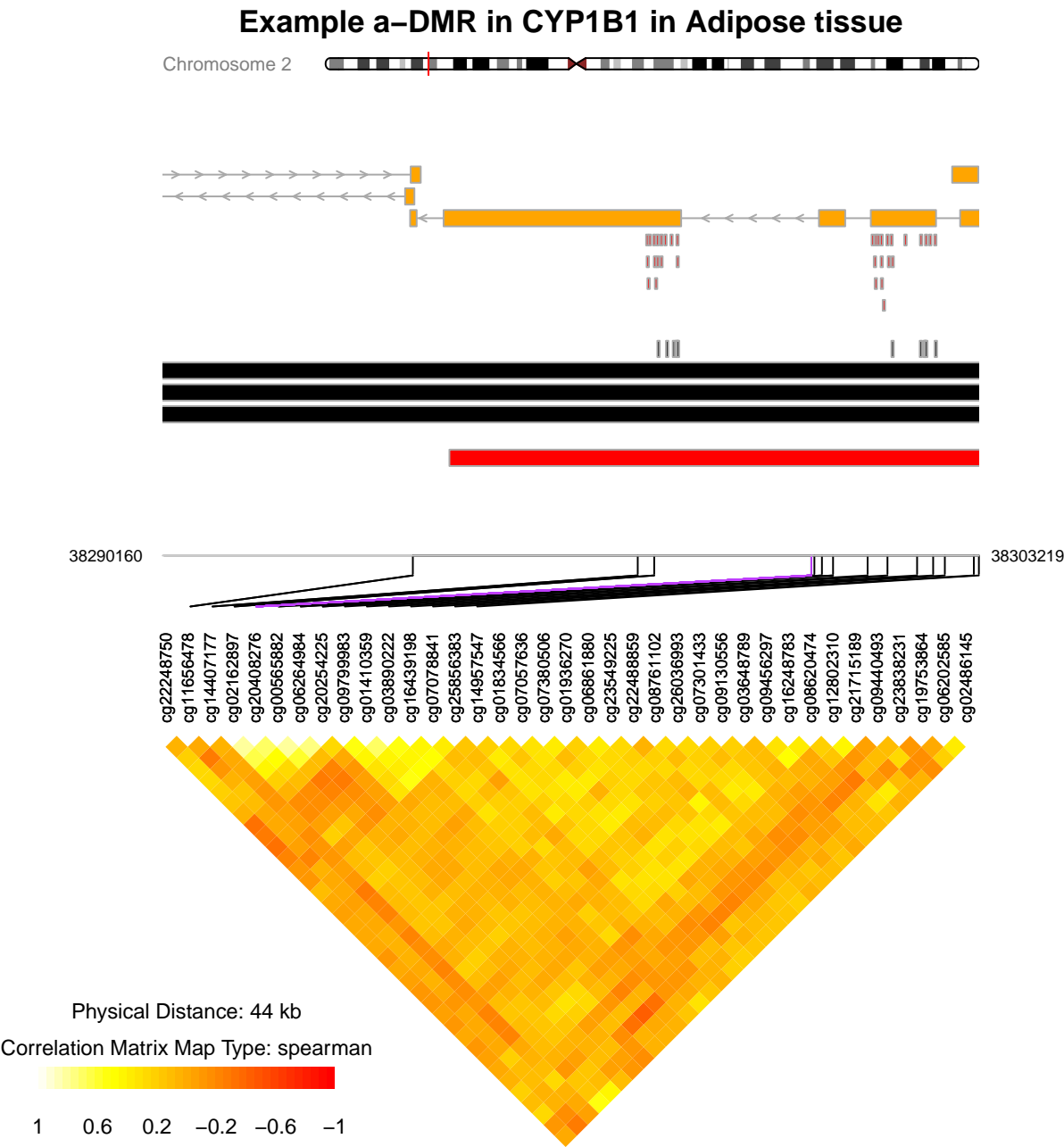


Figure 3: Plot with comet function without pvalue plot.

SessionInfo

The following is the session info that generated this vignette:

```
toLatex(sessionInfo())
```

- R version 3.1.1 (2014-07-10), x86_64-pc-linux-gnu
- Locale: LC_CTYPE=en_GB.UTF-8, LC_NUMERIC=C, LC_TIME=en_US.UTF-8, LC_COLLATE=en_GB.UTF-8, LC_MONETARY=en_US.UTF-8, LC_MESSAGES=en_GB.UTF-8, LC_PAPER=en_US.UTF-8, LC_NAME=C, LC_ADDRESS=C, LC_TELEPHONE=C, LC_MEASUREMENT=en_US.UTF-8, LC_IDENTIFICATION=C
- Base packages: base, datasets, graphics, grDevices, grid, methods, parallel, stats, tcltk, utils
- Other packages: BiocGenerics 0.10.0, biomaRt 2.20.0, colortools 0.1.5, coMET 0.99.0, digest 0.6.4, GenomInfoDb 1.0.2, GenomicRanges 1.16.4, ggbio 1.12.10, ggplot2 1.0.0, Gviz 1.8.4, gWidgets 0.0-54, gWidgetstcltk 0.0-55, hash 2.2.6, IRanges 1.22.10, knitr 1.6, rtracklayer 1.24.2, trackViewer 1.0.2, XVector 0.4.0
- Loaded via a namespace (and not attached): acepack 1.3-3.3, AnnotationDbi 1.26.0, base64enc 0.1-2, BatchJobs 1.3, BBmisc 1.7, Biobase 2.24.0, BiocParallel 0.6.1, BiocStyle 1.2.0, Biostrings 2.32.1, biovizBase 1.12.3, bitops 1.0-6, brew 1.0-6, BSgenome 1.32.0, checkmate 1.4, cluster 1.15.3, codetools 0.2-9, colorspace 1.2-4, DBI 0.3.0, dichromat 2.0-0, evaluate 0.5.5, fail 1.2, foreach 1.4.2, foreign 0.8-61, formatR 1.0, Formula 1.1-2, GenomicAlignments 1.0.6, GenomicFeatures 1.16.2, gridExtra 0.9.1, gtable 0.1.2, highr 0.3, Hmisc 3.14-5, iterators 1.0.7, lattice 0.20-29, latticeExtra 0.6-26, MASS 7.3-34, matrixStats 0.10.0, munsell 0.4.2, nnet 7.3-8, pbapply 1.1-1, plyr 1.8.1, proto 0.3-10, RColorBrewer 1.0-5, Rcpp 0.11.2, RCurl 1.95-4.3, reshape2 1.4, R.methodsS3 1.6.1, rpart 4.1-8, Rsamtools 1.16.1, RSQLite 0.11.4, scales 0.2.4, sendmailR 1.2-1, splines 3.1.1, stats4 3.1.1, stringr 0.6.2, survival 2.37-7, tools 3.1.1, VariantAnnotation 1.10.5, XML 3.98-1.1, zlibbioc 1.10.0