

The coMET User Guide

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Edited: July 2015; Compiled: April 24, 2017

1 Citation

```
citation(package='coMET')  
  
##  
## To cite 'coMET' in publications use:  
##  
## Martin, T., Erte, I, Tsai, P-C, Bell, J.T. coMET: an R plotting package to  
## visualize regional plots of epigenome-wide association scan results QG14, 2014  
##  
## Martin, T., Yet, I, Tsai, P-C, Bell, J.T. coMET: visualisation of regional  
## epigenome-wide association scan results and DNA co-methylation patterns BMC  
## Bioinformatics, 2015 (accepted)  
##  
## To see these entries in BibTeX format, use 'print(<citation>, bibtex=TRUE)',  
## 'toBibtex(.)', or set 'options(citation.bibtex.max=999)'.
```

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Contents

1	Citation	1
2	Introduction	4
3	Usage	5
3.1	Install the development version of coMET from Bioconductor	7
3.2	Install the version of coMET from gitHub	7
4	Functions in coMET	8
5	File formats	9
5.1	Format of the info file (for option: mydata.file , mandatory)	9
5.2	Format of correlation matrix (for option: cormatrix.file , mandatory)	10
5.3	Format of extra info file (for option: mydata.large.file)	11
5.4	Format of annotation file (for option biofeat.user.file)	11
5.5	Option of config.file	11
6	Creating a plot like the webservice: comet.web	14
6.1	coMET plot: usage and plot like in the webservice	14
6.2	Hidden values of comet.web function	14
7	Creating a plot with the generic function: comet	17
7.1	coMET plot: pvalue plot, annotation tracks, and correlation matrix	17
7.1.1	Input from data files	17
7.1.2	coMET plot using input from a data frame	19
7.2	coMET plot: annotation tracks and correlation matrix	21
7.3	coMET plot: Manhattan plot and anonation track	23
8	Extract the significant correlations between omic features	25
9	Annotation tracks	26
9.1	Ensembl	26
9.1.1	Genes and transcripts from Ensembl	27
9.1.2	Regulatory elements from Ensembl	27
9.1.3	structureBiomart from Ensembl	27
9.1.4	miRNA Target Regions from Ensembl	27
9.1.5	Binding Motif Biomart from Ensembl	27
9.1.6	Other Regulatory Regions Biomart from Ensembl	28
9.1.7	Regulatory Features Biomart from Ensembl	29
9.1.8	Other Regulatory Segments Biomart from Ensembl	29
9.1.9	Binding Motif Biomart from Ensembl	29
9.2	UCSC	30
9.2.1	ChromHMM from UCSC	31
9.2.2	ISCA track (obsolete database)	31
9.2.3	Other potential data from UCSC	31
9.3	ROADMAP epigenomics project	32
9.3.1	Chromatin state	32

9.3.2	DNA Motif Positional Bias in Digital Genomic Footprinting Sites	33
9.3.3	DNaseI-accessible regulatory regions	33
9.3.4	Processed data and Imputed data	34
9.4	ENCODE and GENCODE data	36
9.4.1	Predicting motifs and active regulators	36
9.5	GTEX Portal	39
9.6	Hi-C data	45
9.6.1	Hi-C data at 1kb resolution at Lieberman Aiden lab	45
9.6.2	Hi-C Data Browser	45
9.6.3	Hi-C project at Ren Lab	45
9.7	FANTOM5 database	48
9.8	BLUEprint project	50
9.9	Our data	50
9.9.1	eQTL data	50
9.9.2	metQTL data	50
10	coMET: Shiny web-service	51
10.1	How to use the coMET web-service	51
10.2	How to install the coMET web-service	51
11	FAQs	54
12	SessionInfo	56

2 Introduction

The CoMET package is a web-based plotting tool and R-based package to visualize omic-WAS results in a genomic region of interest, such as EWAS (epigenome-wide association scan). 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 in any species, e.g. gene expression array data.

coMET generates a multi-panel plot to visualize EWAS results, co-methylation patterns, and annotation tracks in a genomic region of interest. A coMET figure (cf. Fig. 1) includes three components:

1. the upper plot shows the strength and extent of EWAS association signal;
2. the middle panel provides customized annotation tracks;
3. the lower panel shows the correlation between selected CpG sites in the genomic region.

The structure of the plots builds on `snp.plotter` (Luna et al., 2007) [1], with extensions to incorporate genomic annotation tracks and customized functions. coMET produces plots in PDF and Encapsulated Postscript (EPS) format.

The current version of coMET can visualise EWAS results and annotations from a genomic region up to an entire chromosome in the upper and middle panels of the coMET plot. However, the lower panel (co-methylation) is restricted to visualising a maximum of 120 single-CpG or region-based datapoints. This limitation is due to limitations in the size of a standard A4 plot, and may be updated in the near future. However, the user can use the function `comet.list` to extract all significant correlations beyond a given threshold in the dataset from either a genomic region or from an entire chromosome if required.

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** to visualise omci-WAS results.

- The function **comet.web** generates output plot with the same settings of genomic annotation tracks as that of the webservice (<http://epigen.kcl.ac.uk/comet> or directly <http://comet.epigen.kcl.ac.uk:3838/coMET/>).
- The function **comet** generates output plots with the customized annotation tracks defined by user.

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

CoMET uses the packages called "psych", "corrplot" and "colortools", which are not available from bioconductor. This must be installed before the installation of coMET.

```
install.packages("psych")
install.packages("corrplot")
install.packages("colortools")
```

coMET has a development version on gitHub, go to the section "Install the development version of coMET from Bioconductor".

You can install also on the version R 3.2.2 via the master version of package on gitHub. The same steps must be followed as described in the section "Install the development version of coMET from Bioconductor".

After downloading from Bioconductor or gitHUB, and installing on your computer, CoMET can be loaded into a R session using this command:

```
library("coMET")

## Loading required package: grid
## Loading required package: biomaRt
## Loading required package: Guiz
## Loading required package: S4Vectors
## Loading required package: stats4
## 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 objects are masked from 'package:stats':
##
##   IQR, mad, sd, var, xtabs
## The following objects are masked from 'package:base':
##
##   Filter, Find, Map, Position, Reduce, anyDuplicated, append, as.data.frame,
##   cbind, colMeans, colSums, colnames, do.call, duplicated, eval, evalq, get,
##   grep, grepl, intersect, is.unsorted, lapply, lengths, mapply, match, mget,
##   order, paste, pmax, pmax.int, pmin, pmin.int, rank, rbind, rowMeans,
##   rowSums, rownames, sapply, setdiff, sort, table, tapply, union, unique,
##   unsplit, which, which.max, which.min
##
## Attaching package: 'S4Vectors'
## The following object is masked from 'package:base':
##
##   expand.grid
## Loading required package: IRanges
## Loading required package: GenomicRanges
## Loading required package: GenomeInfoDb
## Loading required package: psych
##
## Attaching package: 'psych'
## The following object is masked from 'package:IRanges':
##
##   reflect
## Loading required package: ggbio
## Loading required package: ggplot2
##
## Attaching package: 'ggplot2'
## The following objects are masked from 'package:psych':
##
##   %+%, alpha
## 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
```

```
## The following object is masked from 'package:psych':  
##  
##   rescale  
## Loading required package: trackViewer
```

The configuration file specifies the options for the coMET plot. Example configuration and input files are also provided on <http://epigen.kcl.ac.uk/comet>. Information about the package can be viewed from within R using this command:

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

3.1 Install the development version of coMET from Bioconductor

To install coMET from the development version of Bioconductor, the user must install R-devel from <http://www.bioconductor.org/developers/how-to/useDevel/>. Following this installation, use standard Bioconductor command line, e.g.

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

3.2 Install the version of coMET from gitHub

Another way to install coMET is to download the master package from gitHub <https://github.com/TiphaineCMartin/coMET> or the devel package <https://github.com/TiphaineCMartin/coMet/tree/devel>. Once downloaded use command line:

```
install.packages("YourPath/coMET_YourVersion.tar.gz", repos=NULL, type="source")  
##This is an example  
install.packages("YourPath/coMET_0.99.9.tar.gz", repos=NULL, type="source")
```

4 Functions in coMET

Currently, there are 3 main functions:

1. **comet.web** is the pre-customized function that allows us to visualise quickly EWAS (or other omic-WAS) results, annotation tracks, and correlations between features. This version is installed in the Shiny web-service. Currently, it is formatted only to visualise human data.
2. **comet** is the generic function that allows us to visualise quickly EWAS results, annotation tracks, and correlations between features. Users can visualise more personalised annotation tracks and give multiple extra EWAS/omic-WAS results to plot.
3. **comet.list** is an additional function that allows us to extract the values of correlations, the pvalues, and estimates and confidence intervals for all datapoints that surpass a particular threshold.

The functions can read the data input files, but it is also possible to use data frames within R for all data input except for the configuration file. The latter can be achieved with the two functions **comet** and **comet.list**. The structure of the data frames (number of columns, type, format) follows the same rules as for the data input files (cf. section "File formats").

5 File formats

There are five types of files that can be given by the user to produce the plot:

1. Info file is defined in the option **mydata.file**. This is mandatory and has to be in tabular format with a header.
2. Correlation file is defined in the option **cormatrix.file**. This is mandatory and has to be in tabular format with a header.
3. Extra info files are defined in the option **mydata.file.large**. This is optional, and if provided has to be in tabular format with a header.
4. Annotation info file is defined in the option **biofeat.user.file**. This option exists only in the function **comet.web** and the user should inform also the format to visualise this data with the options **biofeat.user.type** and **biofeat.user.type.plot**.
5. Configuration file contains the values of these options instead of defining these by command line. Each line in the file is one option. The name of the option is in capital letters and is separated by its value by "=". If there are multiple values such as for the option **list.tracks** or the options for additional data, you need to separated them by a "comma".

5.1 Format of the info file (for option: mydata.file, mandatory)

This file is mandatory and has to be in tabular format with a header. The name of features has to start by a letter. Info files can be a list of CpG sites with/without Beta value (for example DNA methylation level) 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 can be either a numeric value (positive or negative values) or only direction sign ("+", "-"). The number of columns and their types are defined by the option **mydata.format**.

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
infofile <- file.path(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	2.749858e-01
## 2	cg11656478	2	38297759	7.794549e-01
## 3	cg14407177	2	38298023	2.863869e-01
## 4	cg02162897	2	38300537	3.148201e-07
## 5	cg20408276	2	38300586	1.467739e-06
## 6	cg00565882	2	38300707	7.563132e-03

Alternatively, the info file can be region-based and if so, the region-based info file must have the 5 columns (see below) with headers in this order. The beta or direction can be included in the 6th column (optional).

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
infoexp <- file.path(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	3.064357e-17	+
## 2	ENSG00000138061.7_38301489_38302532	2	38301489	38302532	1.145430e-07	+
## 3	ENSG00000138061.7_38302919_38303323	2	38302919	38303323	1.014050e-08	-

In summary, there are 4 possible formats for the info file:

1. **site**: 4 columns with a header:
 - (a) Name of omic feature
 - (b) Name of chromosome
 - (c) Position of omic feature
 - (d) P-value of omic feature
2. **region**: 5 columns with a header:
 - (a) Name of omic feature
 - (b) Name of chromosome
 - (c) Start position of omic feature
 - (d) End position of omic feature
 - (e) P-value of omic feature
3. **site_asso**: 5 columns with a header:
 - (a) Name of omic feature
 - (b) Name of chromosome
 - (c) Position of omic feature
 - (d) P-value of omic feature
 - (e) Direction of association related to this omic feature. This can be the sign or an actual value of association effect size.
4. **region_asso**: 6 columns with a header:
 - (a) Name of omic feature
 - (b) Name of chromosome
 - (c) Start position of omic feature
 - (d) End position of omic feature
 - (e) P-value of omic feature
 - (f) Direction of association related to this omic feature. This can be the sign or an actual value of association effect size.

5.2 Format of correlation matrix (for option: **cormatrix.file**, mandatory)

This file is mandatory and has to be in tabular format with an header. The data file used for the correlation matrix is described in the option **cormatrix.file**. This tab-delimited file can take 3 formats described in the option **cormatrix.format**:

1. **cormatrix**: pre-computed correlation matrix provided by the user; Dimension of matrix : CpG_number X CpG_number. Need to put the CpG sites/regions in the ascending order of positions and to have a header with the name of CpG sites/regions;
2. **raw**: Raw data format. Correlations of these can be computed by one of 3 methods Spearman, Pearson,

Kendall (option **cormatrix.method**). Dimension of matrix : sample_size X CpG_number. Need to have a header with the name of CpG sites/regions ;

3. **raw_rev**: Raw data format. Correlations of these can be computed by one of 3 methods Spearman, Pearson, Kendall (option **cormatrix.method**). Dimension of matrix : CpG_number X sample_size. Need to have the row names of CpG sites/regions and a header with the name of samples ;

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
corfile <- file.path(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 -0.08636815 -0.4896557  1.6718967  0.52423342  0.1659252  0.224221521
## 2 -0.00107899 -0.6330666  0.3150612 -0.29820805 -0.4339332 -0.007794883
## 3  0.31656883 -0.2610083 -0.4942691  0.04657351  0.1840397  0.313967471
## 4 -0.40914999  0.6816058 -0.3251337 -0.58656175 -0.2069954  0.150719803
## 5  1.29953262  0.3985525  0.1119045  0.81181511  0.1833470  0.194928273
## 6 -1.11948826  0.3035820 -1.2794597 -0.49785237  0.1076348 -0.876011670
```

5.3 Format of extra info file (for option: mydata.large.file)

This file is optional file and if provided has to be in tabular format with an header. The name of features has to start by a letter. The extra info files can be described in the option **mydata.large.file** and their format in **mydata.large.format**. More than one extra info file can be used, each should be separated by a comma.

This can be another type of info file (e.g expression or replication data) and should follow the same rules as the standard info file.

5.4 Format of annotation file (for option biofeat.user.file)

The file is defined in the option **biofeat.user.file** and the format of file is the format accepted by GViz (BED, GTF, and GFF3).

5.5 Option of config.file

Each line in the file is one option. The name of the option is in lowercase letters and is separated by its value by "=" without space. If there are multiple values such as for the option **list.tracks** or options for additional data, these need to be separated them by a "comma" without space. If you would like to make your own changes to the plot you can download the configuration file, make changes to it, and upload it into R as shown in the example below.

The important options of a coMET figure include three components:

1. The **upper plot** shows the strength and extent of EWAS association signal on a regional Manhattan plot.
 - **pval.threshold**: Significance threshold to be displayed as a red dashed line

- **pval.threshold2**: Another Significance threshold (optional)
 - **disp.pvalueplot**: Value can be TRUE or FALSE. Used to either display or hide Manhattan plot.
 - **disp.beta.association**: Value can be TRUE or FALSE. Used to show the effect size.
 - **disp.association**: This logical option works only if **mydata.file** contains the effect direction (**mydata.format=site_asso** or **region_asso**). The value can be TRUE or FALSE: if FALSE (default), for each point of data in the p-value plot, the colour of symbol is the colour of co-methylation pattern between the point and the reference site; if TRUE, the effect direction is shown. If the association is positive, the colour is the one defined with the option **color.list**. On the other hand, if the association is negative, the colour is the inverse to that selected.
 - **disp.region**: This logical option works only if **mydata.file** contains regions (**mydata.format=region** or **region_asso**). The value can be TRUE or FALSE (default). If TRUE, the genomic element will be shown as a continuous line with the colour of the element, in addition to the symbol at the center of the region. If FALSE, only the symbol is shown.
2. The **middle panel** provides customized annotation tracks;
- **list.tracks** (for *comet.web* function): List of annotation tracks to be visualised. Tracks currently available: geneENSEMBL, CGI, ChromHMM, DNase, RegENSEMBL, SNP, transcriptENSEMBL, SNPstoma, SNPstru, SNPstrustoma, ISCA, COSMIC, GAD, ClinVar, GeneReviews, GWAS, ClinVarCNV, GCcontent, genesUCSC, xenogenesUCSC, metQTL, eQTL, BindingMotifsBiomart, chromHMM_Roadmap, miRNATargetRegionsBiomart, OtherRegulatoryRegionsBiomart, RegulatoryEvidenceBiomart, RegulatorySegmentsBiomart and segmentalDupsUCSC. The elements are separated by a comma.
 - **tracks.gviz**, **tracks.ggbio**, **tracks.trackviewer** (for *comet* function): For each option, it is possible to give a list of annotation tracks that is created by the Gviz, GGBio, and TrackViewer bioconductor packages. The integration of plots from ggbio and trackviewer can be sometimes not really perfect. It is better to create plots from Gviz and use tracks.gviz
3. The **lower panel** shows the correlation between selected CpG sites in the genomic region (heatmap).
- **cormatrix.format**: Format of the input file **cormatrix.file**: either raw data (option RAW if CpG sites are by column and samples by row or option RAW_REV if CpG sites are by row and samples by column) or correlation matrix (option CORMATRIX)
 - **cormatrix.method**: If raw data are provided it will be necessary to produce the correlation matrix using one of 3 methods (spearman, pearson and kendall).
 - **cormatrix.color.scheme**: There are 5 colour schemes (heat, bluewhitered, cm, topo, gray, blue-tored)
 - **disp.cormatrixmap**: logical option TRUE or FALSE. TRUE (default), if FALSE correlation matrix is not shown)
 - **cormatrix.conf.level**: Alpha level for the confidence interval. Default value= 0.05. CI will be the alpha/2 lower and upper values.)
 - **cormatrix.sig.level**: Significant level to visualise the correlation. If the correlation has a pvalue under the significant level, the correlation will be colored in "goshwhite", else the color is related to the correlation level and the color scheme chosen. Default value =1.)
 - **cormatrix.adjust**: Indicates which adjustment for multiple tests should be used. "holm", "hochberg", "hommel", "bonferroni", "BH", "BY", "fdr", "none". Default value="none".)

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
configfile <- file.path(extdata, "config_cyp1b1_zoom_4webserver_Grch38.txt")

data_config <- read.csv(configfile, quote = "", sep="\t", header=FALSE)
data_config
```

##

V1

```
## 1             disp.mydata=TRUE
## 2             mydata.format=site
## 3             sample.labels=CpG
## 4             symbols=circle-fill
## 5             lab.Y=log
## 6             disp.color.ref=TRUE
## 7             mydata.ref=cg02162897
## 8             pval.threshold=4.720623e-06
## 9             disp.association=FALSE
## 10            disp.region=FALSE
## 11            start=38066017
## 12            end=38108036
## 13            mydata.large.format=region_asso
## 14            disp.association.large=TRUE
## 15            disp.region.large=TRUE
## 16            sample.labels.large=Gene expression
## 17            color.list.large=green
## 18            symbols.large=diamond-fill
## 19            cormatrix.format=raw
## 20            disp.cormatrixmap=TRUE
## 21            cormatrix.method=spearman
## 22            cormatrix.color.scheme=bluewhitered
## 23            cormatrix.conf.level=0.05
## 24            cormatrix.sig.level=1
## 25            cormatrix.adjust=none
## 26            disp.phys.dist=TRUE
## 27            disp.color.bar=TRUE
## 28            disp.legend=TRUE
## 29 list.tracks=geneENSEMBL,CGI,ChromHMM,DNAse,RegENSEMBL,SNP
## 30            disp.mult.lab.X=FALSE
## 31            image.type=pdf
## 32 image.title="Example a-DMR in CYP1B1 in Adipose tissue"
## 33            image.name=cyp1b1_zoom_plus_name_expr
## 34            image.size=3.5
## 35            genome=hg38
## 36            dataset.geneE=hsapiens_gene_ensembl
```

6 Creating a plot like the webservice: comet.web

6.1 coMET plot: usage and plot like in the webservice

The user can create a coMET plot via the coMET website (<http://epigen.kcl.ac.uk/comet>). It is possible to reproduce the web service plotting defaults by using the function `comet.web`, for example see Figure 1.

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
myinfofile <- file.path(extdata, "cyp1b1_infofile_Grch38.txt")
myexpressfile <- file.path(extdata, "cyp1b1_infofile_exprGene_region_Grch38.txt")
mycorrelation <- file.path(extdata, "cyp1b1_res37_rawMatrix.txt")
configfile <- file.path(extdata, "config_cyp1b1_zoom_4webserver_Grch38.txt")
comet.web(config.file=configfile, mydata.file=myinfofile,
          cormatrix.file=mycorrelation, mydata.large.file=myexpressfile,
          print.image=FALSE, verbose=FALSE)
```

6.2 Hidden values of comet.web function

Hidden values of **comet.web** function are shown in the section. If these values do not correspond to what you want to visualise, you need to use the function **comet**, as a more generic option.

Option	Value
mydata.type	FILE
mydata.large.type	LISTFILE
cormatrix.type	LISTFILE
disp.cormatrixmap	TRUE
disp.pvalueplot	TRUE
disp.mydata.names	TRUE
disp.connecting.lines	TRUE
disp.mydata	TRUE
disp.type	symbol
biofeat.user.type.plot	histogram
tracks.gviz	NULL
tracks.ggbio	NULL
tracks.trackviewer	NULL
biofeat.user.file	NULL
palette.file	NULL
disp.color.bar	TRUE
disp.phys.dist	TRUE
disp.legend	TRUE
disp.marker.lines	TRUE
disp.mult.lab.X	FALSE
connecting.lines.factor	1.5
connecting.lines.adj	0.01
connecting.lines.vert.adj	-1
connecting.lines.flex	0

Continued on next page

Table 1 – continued from previous page

Option	Value
color.list	red
font.factor	NULL
dataset.gene	hsapiens_gene_ensembl
DATASET.SNP	hsapiens_snp
VERSION.DBSP	snp142Common
DATASET.SNP.STOMA	hsapiens_snp_som
DATASET.REGULATION	hsapiens_feature_set
DATASET.STRU	hsapiens_structvar
DATASET.STRU.STOMA	hsapiens_structvar_som
BROWSER.SESSION	UCSC

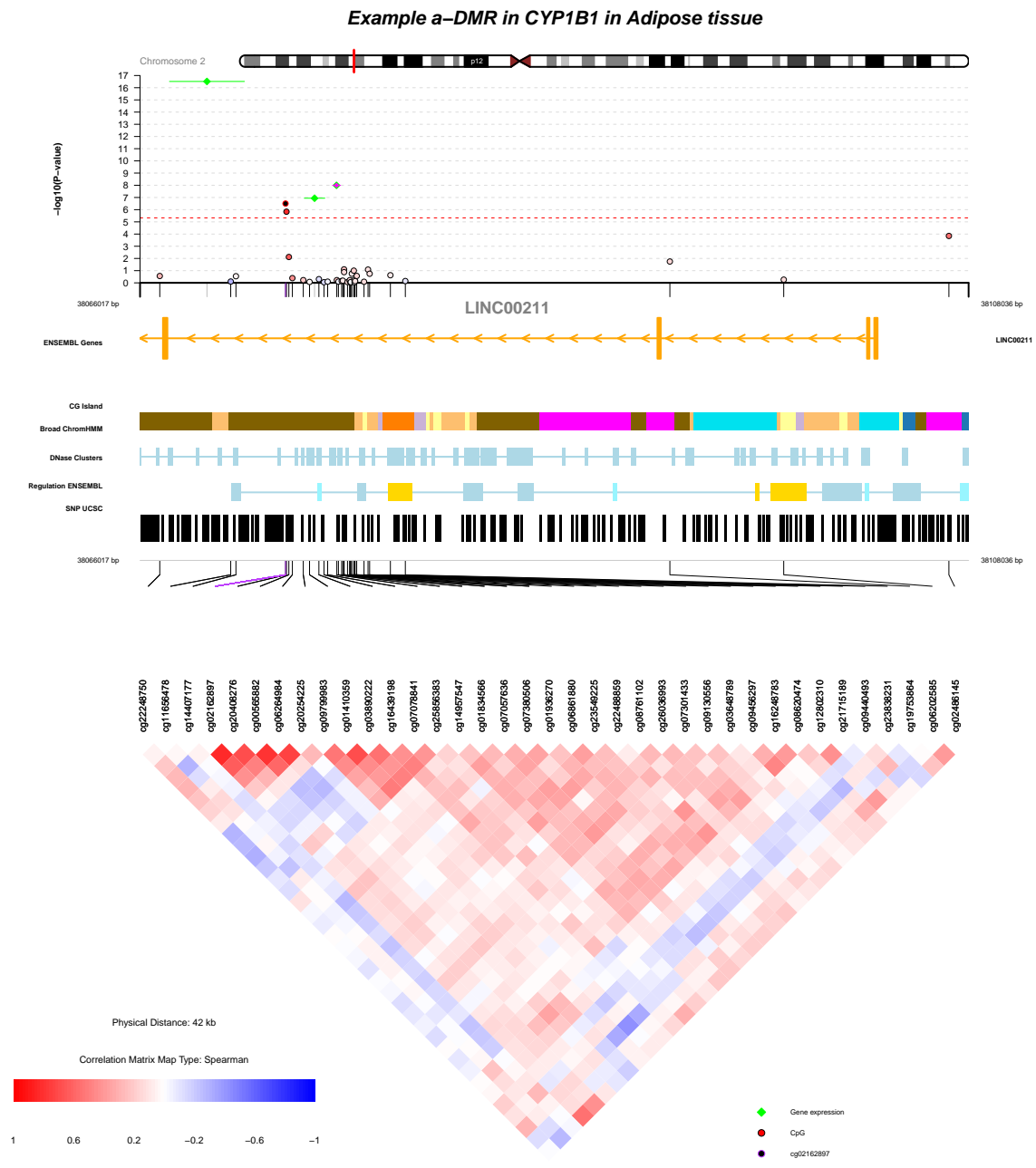


Figure 1: Plot with comet.web function.

7 Creating a plot with the generic function: comet

It is possible to create the annotation tracks by Gviz, trackviewer or ggbio, for example see Figure 2. Currently, the Gviz option for annotation tracks, in combination with the heatmap of correlation values between genomic elements, provides the most informative and easy approach to visualize graphics.

7.1 coMET plot: pvalue plot, annotation tracks, and correlation matrix

7.1.1 Input from data files

In this figure 2, we create different tracks outside to coMET with Gviz. The list of annotation tracks and different files are given to the function coMET.

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
configfile <- file.path(extdata, "config_cyp1b1_zoom_4comet.txt")
myinfofile <- file.path(extdata, "cyp1b1_infofile.txt")
myexpressfile <- file.path(extdata, "cyp1b1_infofile_exprGene_region.txt")
mycorrelation <- file.path(extdata, "cyp1b1_res37_rawMatrix.txt")

chrom <- "chr2"
start <- 38290160
end <- 38303219
gen <- "hg19"
strand <- "*"

BROWSER.SESSION="UCSC"
mySession <- browserSession(BROWSER.SESSION)
genome(mySession) <- gen

genetrack <- genes_ENSEMBL(gen, chrom, start, end, showId=TRUE)
snptrack <- snpBiomart_ENSEMBL(gen, chrom, start, end, dataset="hsapiens_snp_som", showId=FALSE)
cpgIstrack <- cpgIslands_UCSC(gen, chrom, start, end)

prombedFilePath <- file.path(extdata, "/RoadMap/regions_prom_E063.bed")
promRMtrackE063 <- DNaseI_RoadMap(gen, chrom, start, end, prombedFilePath,
                                featureDisplay='promotor', stacking_type="squish")

bedFilePath <- file.path(extdata, "RoadMap/E063_15_coreMarks_mnemonics.bed")
chromHMM_RoadMapAllE063 <- chromHMM_RoadMap(gen, chrom, start, end, bedFilePath, featureDisplay = "

listgviz <- list(genetrack, snptrack, cpgIstrack, promRMtrackE063, chromHMM_RoadMapAllE063)

comet(config.file=configfile, mydata.file=myinfofile, mydata.type="file",
      cormatrix.file=mycorrelation, cormatrix.type="listfile",
      mydata.large.file=myexpressfile, mydata.large.type="listfile",
      tracks.gviz=listgviz, verbose=FALSE, print.image=FALSE)
```

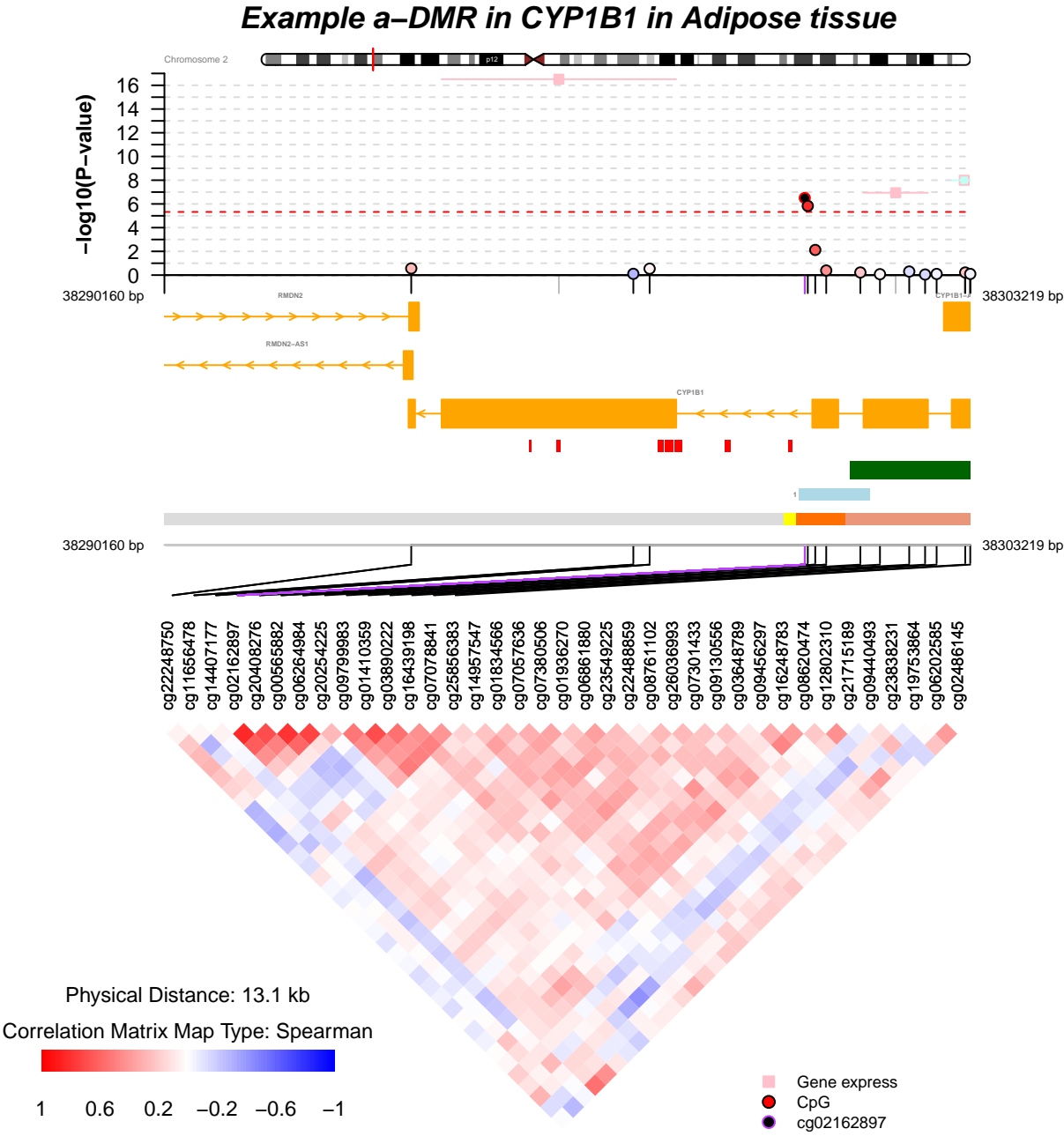


Figure 2: Plot with comet function from files.

7.1.2 coMET plot using input from a data frame

In this figure 3, we visualize the same data as in figure 2, but the data is in data frame format and not read in from an input file.

In addition, if the user would like to visualise only the correlations between CpG sites with P-value less than or equal to 0.05 in the upper plot, this option can be included. The correlations with a P-value greater than 0.05 can have the colour "goshwhite" whereas the other correlations will be displayed using a colour related to the correlation level. Conversely, in the P-value plot (upper plot), the points of each omic feature have their colours related to their correlations with the reference omic feature without taking into account the P-value associated with the correlation matrix.

Eventually, we increase the size of font using the option **fontsize.gviz**

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
configfile <- file.path(extdata, "config_cyp1b1_zoom_4comet.txt")
myinfofile <- file.path(extdata, "cyp1b1_infofile.txt")
myexpressfile <- file.path(extdata, "cyp1b1_infofile_exprGene_region.txt")
mycorrelation <- file.path(extdata, "cyp1b1_res37_rawMatrix.txt")

chrom <- "chr2"
start <- 38290160
end <- 38303219
gen <- "hg19"
strand <- "*"

BROWSER.SESSION="UCSC"
mySession <- browserSession(BROWSER.SESSION)
genome(mySession) <- gen

genetrack <- genes_ENSEMBL(gen, chrom, start, end, showId=TRUE)
snptrack <- snpBiomart_ENSEMBL(chrom, start, end, dataset="hsapiens_snp_som", showId=FALSE)
iscatrack <- ISCA_UCSC(gen, chrom, start, end, mySession, table="iscaPathogenic")

listgviz <- list(genetrack, snptrack, iscatrack)

matrix.dnamethylation <- read.delim(myinfofile, header=TRUE, sep="\t", as.is=TRUE,
                                   blank.lines.skip = TRUE, fill=TRUE)
matrix.expression <- read.delim(myexpressfile, header=TRUE, sep="\t", as.is=TRUE,
                                blank.lines.skip = TRUE, fill=TRUE)
cormatrix.data.raw <- read.delim(mycorrelation, sep="\t", header=TRUE, as.is=TRUE,
                                blank.lines.skip = TRUE, fill=TRUE)

listmatrix.expression <- list(matrix.expression)
listcormatrix.data.raw <- list(cormatrix.data.raw)
comet(config.file=configfile, mydata.file=matrix.dnamethylation,
      mydata.type="dataframe", cormatrix.file=listcormatrix.data.raw,
      cormatrix.type="listdataframe", cormatrix.sig.level=0.05,
      cormatrix.conf.level=0.05, cormatrix.adjust="BH",
```

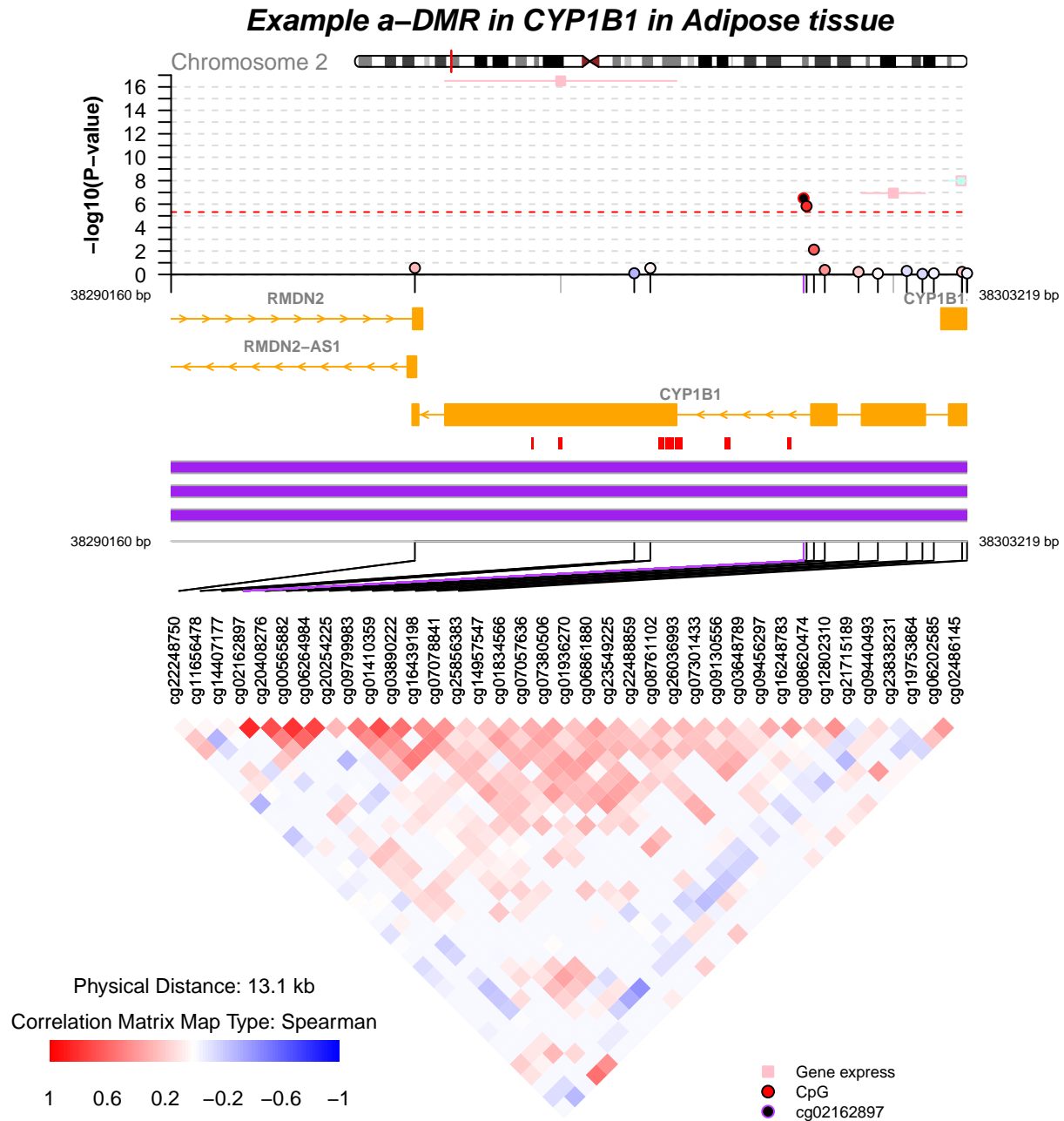


Figure 3: Plot with comet function from matrix data and with a pvalue threshold for the correlation between omics features (here CpG sites).

```
mydata.large.file=listmatrix.expression, mydata.large.type="listdataframe",
fontsize.gviz =12,
tracks.gviz=listgviz,verbose=FALSE, print.image=FALSE)
```

7.2 coMET plot: annotation tracks and correlation matrix

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`, for example see Figure 4.

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
configfile <- file.path(extdata, "config_cyp1b1_zoom_4cometnopval.txt")
myinfofile <- file.path(extdata, "cyp1b1_infofile.txt")
mycorrelation <- file.path(extdata, "cyp1b1_res37_rawMatrix.txt")

chrom <- "chr2"
start <- 38290160
end <- 38303219
gen <- "hg19"
strand <- "*"

genetrack <- genes_ENSEMBL(gen, chrom, start, end, showId=FALSE)
snptrack <- snpBiomart_ENSEMBL(chrom, start, end,
                              dataset="hsapiens_snp_som", showId=FALSE)
strutrack <- structureBiomart_ENSEMBL(chrom, start, end,
                                      strand, dataset="hsapiens_structvar_som")
clinVariant <- ClinVarMain_UCSC(gen, chrom, start, end)
clinCNV <- ClinVarCnv_UCSC(gen, chrom, start, end)
gwastrack <- GWAScatalog_UCSC(gen, chrom, start, end)
geneRtrack <- GeneReviews_UCSC(gen, chrom, start, end)

listgviz <- list(genetrack, snptrack, strutrack, clinVariant,
                 clinCNV, gwastrack, geneRtrack)
comet(config.file=configfile, mydata.file=myinfofile, mydata.type="file",
       cormatrix.file=mycorrelation, cormatrix.type="listfile",
       fontsize.gviz=12,
       tracks.gviz=listgviz, verbose=FALSE, print.image=FALSE, disp.pvalueplot=FALSE)
```

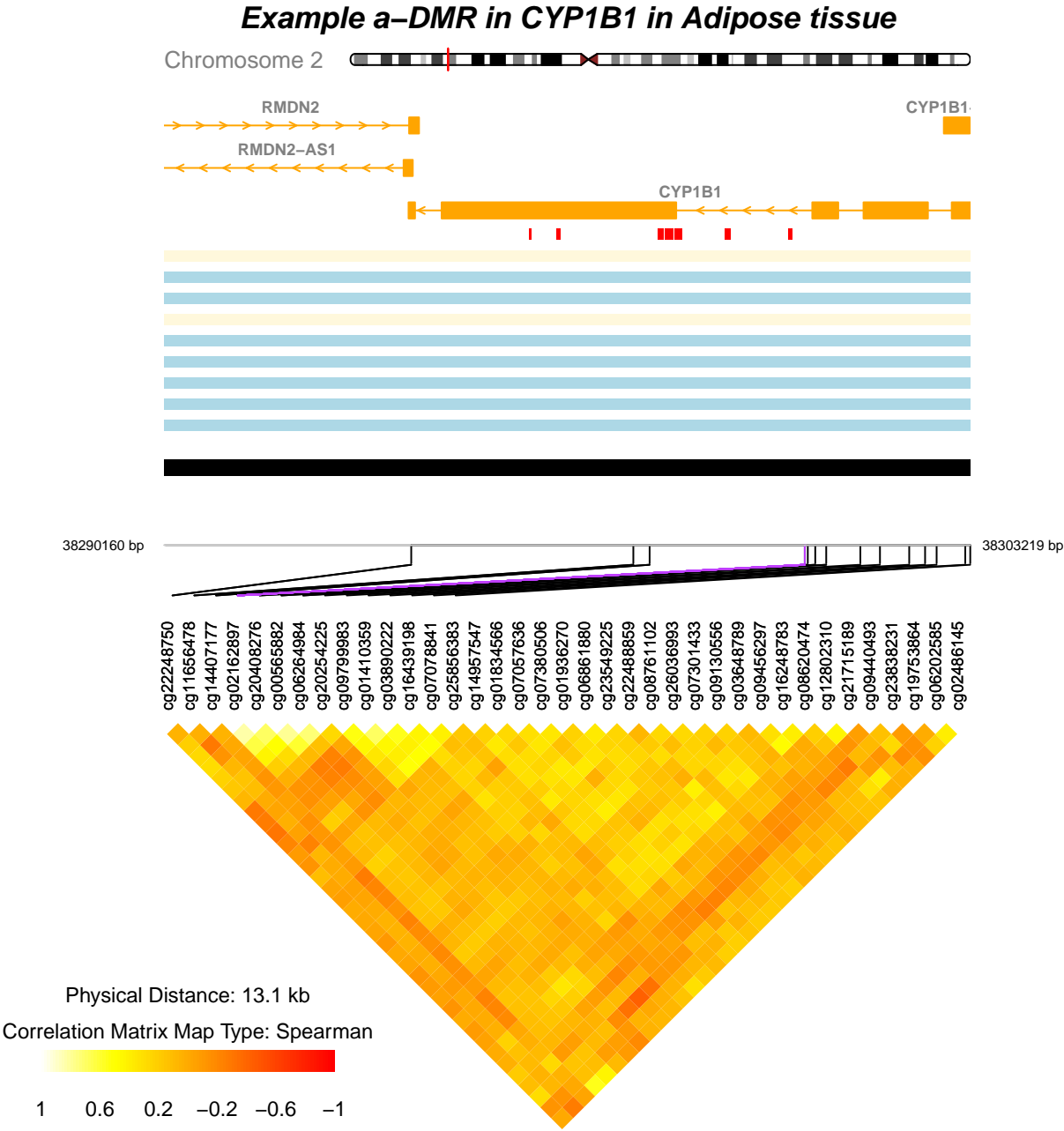


Figure 4: Plot with comet function without pvalue plot.

7.3 coMET plot: Manhattan plot and annotation track

It is possible to visualise only The Manhattan plot and the annotation tracks. In this case, we need to use the option `disp.cormatrixmap = FALSE`, for example see Figure 5.

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
configfile <- file.path(extdata, "config_cyp1b1_zoom_4nomatrix.txt")
myinfofile <- file.path(extdata, "cyp1b1_infofile.txt")
mycorrelation <- file.path(extdata, "cyp1b1_res37_rawMatrix.txt")

chrom <- "chr2"
start <- 38290160
end <- 38303219
gen <- "hg19"
strand <- "*"

genetrack <- genes_ENSEMBL(gen, chrom, start, end, showId=FALSE)
snptrack <- snpBiomart_ENSEMBL(chrom, start, end,
                              dataset="hsapiens_snp_som", showId=FALSE)
strutrack <- structureBiomart_ENSEMBL(chrom, start, end,
                                      strand, dataset="hsapiens_structvar_som")
clinVariant <- ClinVarMain_UCSC(gen, chrom, start, end)
clinCNV <- ClinVarCnv_UCSC(gen, chrom, start, end)
gwastrack <- GWAScatalog_UCSC(gen, chrom, start, end)
geneRtrack <- GeneReviews_UCSC(gen, chrom, start, end)

listgviz <- list(genetrack, snptrack, strutrack, clinVariant,
                 clinCNV, gwastrack, geneRtrack)
comet(config.file=configfile, mydata.file=myinfofile, mydata.type="file",
       cormatrix.file=mycorrelation, cormatrix.type="listfile",
       fontsize.gviz =12, font.factor=3,
       tracks.gviz=listgviz, verbose=FALSE, print.image=FALSE)
```

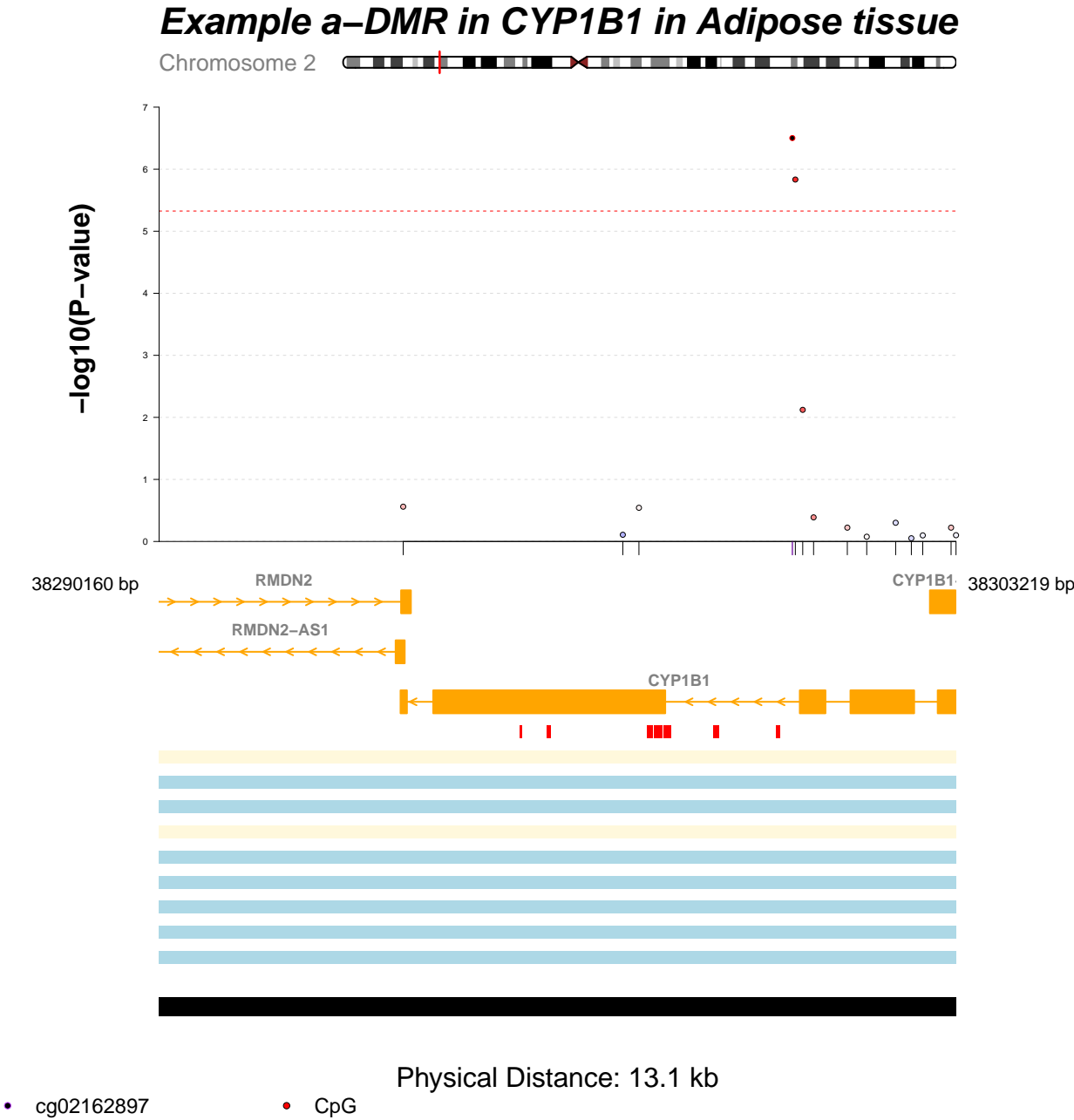


Figure 5: Plot with comet function without the correlation matrix.

8 Extract the significant correlations between omic features

CoMET can help to visualise the correlations between omic features with EWAS results and other omic data. In addition, a function **comet.list** can extract the significant correlations according the method (**cormatrix.method**) and significance level (**cormatrix.sig.level**).

The output file has 7 columns:

1. the name of the first omic feature
2. the name of the second omic feature
3. the correlation between the omic features
4. the alpha/2 lower value (e.g. 0.05 (**cormatrix.conf.level**))
5. the alpha/2 upper value (e.g. 0.05 (**cormatrix.conf.level**))
6. the pvalue
7. the pvalue adjusted with the method selected (e.g. Benjamin and Hochberg) (**cormatrix.adjust**)

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
mycorrelation <- file.path(extdata, "cyp1b1_res37_rawMatrix.txt")
myoutput <- file.path(extdata, "cyp1b1_res37_cormatrix_list_BH05.txt")

comet.list(cormatrix.file=mycorrelation, cormatrix.method = "spearman",
           cormatrix.format= "raw", cormatrix.conf.level=0.05,
           cormatrix.sig.level= 0.05, cormatrix.adjust="BH",
           cormatrix.type = "listfile", cormatrix.output=myoutput,
           verbose=FALSE)

listcorr <- read.csv(myoutput, header = TRUE,
                    sep = "\t", quote = "")
dim(listcorr)
## [1] 336 7
head(listcorr)
##  omicFeature1 omicFeature2 correlation  lowerCI  upperCI  pvalue
## 1  cg22248750  cg14407177  0.2153743  0.11294792  0.3132713  4.975020e-05
## 2  cg22248750  cg02162897  0.2761912  0.17632357  0.3704308  1.575519e-07
## 3  cg22248750  cg20408276  0.2807258  0.18108231  0.3746643  9.649818e-08
## 4  cg22248750  cg00565882  0.2345897  0.13288218  0.3314082  9.478992e-06
## 5  cg22248750  cg06264984  0.1793832  0.07583111  0.2791072  7.613440e-04
## 6  cg22248750  cg09799983 -0.2979454 -0.39070492 -0.1991959  1.382644e-08
##  pvalue.adjusted
## 1  2.029592e-04
## 2  1.178984e-06
## 3  7.472999e-07
## 4  4.477311e-05
## 5  2.414548e-03
## 6  1.261426e-07
```

9 Annotation tracks

Annotation tracks can be created with Gviz using four different functions:

1. **UcscTrack**. Different UCSC tracks can be selected for visualisation from the table Browser of UCSC http://genome-euro.ucsc.edu/cgi-bin/hgTables?hgsid=202842745_Dlvit14QO0G6ZPpLoEVABG8aqfrm&clade=mammal&org=Human&db=hg19&hgta_group=varRep&hgta_track=cpgIslandExt&hgta_table=0&hgta_regionType=genome&position=chr6%3A32726553\discretionary{-}{-}{-}32727053&hgta_outputType=primaryTable&hgta_outFileName=
2. **BiomartGeneRegionTrack**. A connection should be established to the Biomart database to visualise the genetic elements.
3. **DataTrack**. This allows the visualisation of numerical data.
4. **AnnotationTrack**. This allows the visualisation of any annotation data.

For more information consult the user guide for Gviz.

9.1 Ensembl

The Ensembl project [2] produces genome databases for vertebrates and other eukaryotic species, and makes this information freely available online <http://www.ensembl.org/index.html>. A set of wrap R functions were created to extract data from Ensembl BioMart for human genome using Ensembl REST [3], but they can be extended to other genomes. You can ask help to *tiphaine.martin@kcl.ac.uk*.

This is the list of R functions created in coMET to visualise ENSEMBL data. Below described the colors of tracks and specific characteristics of some annotation tracks.

- **bindingMotifsBiomart_ENSEMBL** : Visualise the binding motifs in the genomic region of interest
- **genes_ENSEMBL** : Visualise the genes from ENCODE in the genomic region of interest
- **genesName_ENSEMBL** : Visualise the name of genes from ENCODE in the genomic region of interest
- **interestGenes_ENSEMBL** : Visualise the genes from ENCODE in the genomic region of interest with a specific color for genes of interest
- **interestTranscript_ENSEMBL** : Visualise the transcripts from ENCODE in the genomic region of interest with a specific color for exons of interest
- **miRNATargetRegionsBiomart_ENSEMBL** : Visualise the miRNA target regions in the genomic region of interest
- **otherRegulatoryRegions_ENSEMBL** : Visualise the other regulatory regions in the genomic region of interest
- **regulationBiomart_ENSEMBL** (obsolete function): Visualise the other regulatory regions in the genomic region of interest
- **regulatoryEvidenceBiomart_ENSEMBL** : Visualise the regulatory evidence regions in the genomic region of interest
- **regulatoryFeaturesBiomart_ENSEMBL** : Visualise the regulatory features regions in the genomic region of interest
- **regulatorySegmentsBiomart_ENSEMBL** : Visualise the regulatory segment regions in the genomic region of interest
- **snpBiomart_ENSEMBL** : Visualise the SNPs in the genomic region of interest
- **structureBiomart_ENSEMBL** : Visualise the structural variations in the genomic region of interest
- **transcript_ENSEMBL** : Visualise the transcripts in the genomic region of interest

Below described the colors of tracks and specific characteristics of some annotation tracks.

9.1.1 Genes and transcripts from Ensembl

The color of the genetic elements is defined by the R package Gviz.

It is possible to change the colour of some exons by using the function *interestGenesENSEMBL* or *interestTranscriptENSEMBL*. The elements and the colours to be displayed must be given as list. An example is given below:

```
gen <- "hg38"
chr <- "chr15"
start <- 75011669
end <- 75019876
interestfeatures <- rbind(c("75011883", "75013394", "bad"), c("75013932", "75014410", "good"))
interestcolor <- list("bad"="red", "good"="green")

interestgenesENSEMBLtrack<-interestGenes_ENSEMBL(gen,chr,start,end,interestfeatures,
                                                    interestcolor,showId=TRUE)
plotTracks(interestgenesENSEMBLtrack, from=start, to=end)
```

9.1.2 Regulatory elements from Ensembl

This function is now obsolete in coMET as Ensembl have restructured their databases due to the new version of the genome GRCh38. The same data is now available by using the function 'RegulatoryFeaturesBiomart'.

The colors were :



Element Type	Start	End	Color
Enhancer	75011883	75013394	red
Enhancer	75013932	75014410	green
Enhancer	75014410	75014410	yellow
Enhancer	75014410	75014410	blue

9.1.3 structureBiomart from Ensembl

Listed below are the colours for somatic structural variation and structural variation.



9.1.4 miRNA Target Regions from Ensembl

The colour of the miRNA target regions is set to Plum4 (hex code: #8B668B)

9.1.5 Binding Motif Biomart from Ensembl

Listed on the next page are the colours used for the different types of binding motifs. The frequency shown is that found in GRCh38 (hg38). Motifs with red text are found only in GRCh37 (hg19), motifs with blue text are found only in GRCh38 (hg38)

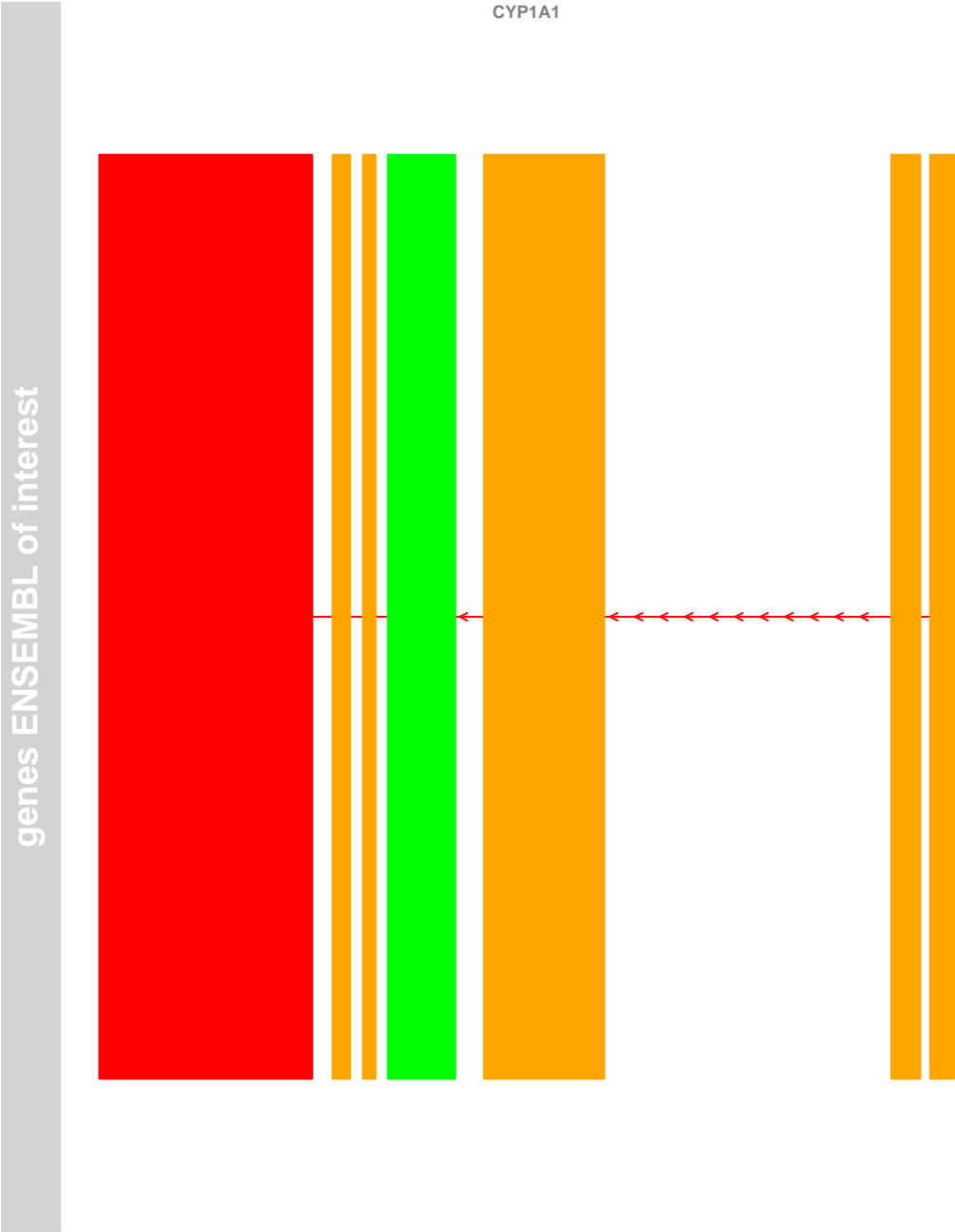


Figure 6: Plot genes with different colors according user's choice.



9.1.6 Other Regulatory Regions Biomart from Ensembl

Listed below are the colours used for the different types of regulatory regions. The frequency shown is that found in GRCh38 (hg38).



9.1.7 Regulatory Features Biomart from Ensembl

Listed below are the colours used for the different types of regulatory features. The frequency shown is that found in GRCh38 (hg38).



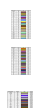
9.1.8 Other Regulatory Segments Biomart from Ensembl

Listed below are the colours used for the different types of regulatory segments. The frequency shown is that found in GRCh38 (hg38). Segments with red text are found only in GRCh37 (hg19).



9.1.9 Binding Motif Biomart from Ensembl

Listed on the next 3 pages are the colours used for the different types of regulatory evidence elements. The frequency shown is that found in GRCh37 (hg19). At the current time this track has not been optimised for GRCh38 (hg38) meaning any elements found exclusively in GRCh38 do not have an assigned colour and will be displayed in the default track colour of Gviz.



9.2 UCSC

the UCSC Genome Browser [4] website <http://genome-euro.ucsc.edu/> contains the reference sequence and working draft assemblies for a large collection of genomes.

This is the list of R wrapping functions of some tracks found in UCSC genome browser. Below described the colors of tracks and specific characteristics of some annotation tracks.

- **chromatinHMMAll_UCSC** : Visualise the chromHMM Broad found in UCSC genome browser of all tissues in the genomic region of interest.
- **chromatinHMMOne_UCSC** : Visualise the chromHMM Broad found in UCSC genome browser of the tissue of interest in the genomic region of interest.
- **ClinVarCnv_UCSC** : Visualise clinical CNVs found in ClinVar tracks of UCSC genome browser in the genomic region of interest.
- **ClinVarMain_UCSC** : Visualise clinical SNPs found in ClinVar tracks of UCSC genome browser in the genomic region of interest.
- **CoreilCNV_UCSC** : Visualise CNV found in Coreil tracks of UCSC genome browser in the genomic region of interest.
- **COSMIC_UCSC** : Visualise SNPs found in COSMIC tracks of UCSC genome browser in the genomic region of interest.
- **cpGIslands_UCSC** : Visualise CpG Island found in CpGIsland tracks of UCSC genome browser in the genomic region of interest.
- **DNase_UCSC** : Visualise clinical CNV found in ClinVar tracks of UCSC genome browser in the genomic region of interest.
- **GAD_UCSC** : Visualise genes found in GAD tracks of UCSC genome browser in the genomic region of interest.
- **gcContent_UCSC** : Visualise GC content found in UCSC genome browser in the genomic region of interest.
- **GeneReviews_UCSC** : Visualise clinical genes found in GeneReviews tracks of UCSC genome browser in the genomic region of interest.
- **GWAScatalog_UCSC** : Visualise SNPs found in GWAS catalog tracks of UCSC genome browser in the genomic region of interest.
- **HistoneAll_UCSC** : Visualise histone patterns found in UCSC genome browser of all tissues in the genomic region of interest.
- **HistoneOne_UCSC** : Visualise histone patterns found in UCSC genome browser of one tissue of interest in the genomic region of interest.
- **ISCA_UCSC** (obsolete) : Visualise clinical CNV found in UCSC genome browser in the genomic region of interest.
- **knownGenes_UCSC** : Visualise known genes found in UCSC genome browser in the genomic region of interest.
- **refGenes_UCSC** : Visualise reference genes found in UCSC genome browser in the genomic region of interest.
- **repeatMasker_UCSC** : Visualise repeat elements found in UCSC genome browser in the genomic region of interest.
- **segmentalDups_UCSC** : Visualise segmental duplications found in UCSC genome browser in the genomic region of interest.
- **snpLocations_UCSC** : Visualise SNPs found in UCSC genome browser in the genomic region of interest.
- **xenorefGenes_UCSC** : Visualise xeno reference genes found in UCSC genome browser in the genomic region of interest.

9.2.1 ChromHMM from UCSC

For this function there are two possible colour schemes to choose from. The selection between schemes is made with the variable 'colour'. The default scheme is 'coMET', the colours chosen have been selected so that different elements can be easily distinguished. The second scheme is 'UCSC', these are the set colours used by UCSC, in certain plots it may be difficult to distinguish elements apart. These UCSC colours are correct at the time this document was writtern however if these change in the future and this is not reflected here please contact us.

the colours used in both schemes are listed below:



9.2.2 ISCA track (obsolete database)

International Standards of Cytogenomic Arrays Consortium defined a set of phenotypes for CNVs. Different colours are defined to represent them. This database is not more accessible from UCSC.



9.2.3 Other potential data from UCSC

You can access to other data via UCSC track hub [5] :

- Other tracks and table accessible to UCSC genome browser https://genome.ucsc.edu/cgi-bin/hgTables?hgsid=444062899_lxuSrw4J9exVt1OafMuY4LDbVs1F&clade=mammal&org=Human&db=hg19&hgta_group=allTracks&hgta_track=knownGene&hgta_table=0&hgta_regionType=genome&position=chr21%3A33031597-33041597&hgta_outputType=primaryTable&hgta_outFileName=
- Track HUB of UCSC genome browser <https://genome-euro.ucsc.edu/cgi-bin/hgHubConnect?hubUrl=http%3A%2F%2Fphantom.gsc.riken.jp%2F5%2Fdatahub%2Fhub.txt&hgHubConnect.remakeTrackHub=on&redirect>manual&source=genome.ucsc.edu>

and use DataTrack or AnnotationTrack or UCSCTrack of Gviz to visualise them.

9.3 ROADMAP epigenomics project

ROADMAP epigenomics projects <http://www.roadmapepigenomics.org/> [6] aims to produce a public resource of human epigenomic data to catalyze basic biology and disease-oriented research. The project has generated high-quality, genome-wide maps of several key histone modifications, chromatin accessibility, DNA methylation and mRNA expression across 100s of human cell types and tissues (111 consolidated epigenomes from the Roadmap Epigenomics Project and 16 epigenomes from The Encyclopedia of DNA Elements (ENCODE) project).

Release 9 of the compendium contains uniformly pre-processed and mapped data from multiple profiling experiments (technical and biological replicates from multiple individuals and/or datasets from multiple centers) spanning 183 biological samples and 127 consolidated epigenomes.

More information on each type data are on the site of ROADMAP http://egg2.wustl.edu/roadmap/web_portal/index.html and the meta-data on different tissues (more for correspondance between Epigenome ID (EID) and the standartized epigenome name), you need to look at this spreadsheet <https://docs.google.com/spreadsheets/d/1yikGx4MsO9Ei36b64yOy9Vb6oPC5IBGIFbYEt-N6gOM/edit#gid=15>

The current data are done on Release 9. The data are mapped on the reference genome **hg19**. Below described the colors of tracks and specific characteristics of some annotation tracks.

- **chromHMM_RoadMap** : Visualisation of chromatin states defined in RoadMap project
- **dgfootprints_RoadMap**: Visualisation of DNA motif positional bias in digital genomic Footprinting Sites
- **DNaseI_RoadMap** : Visualisation of promoter/enhancer regions

9.3.1 Chromatin state

There are 3 chromatin states defined in RoadMap project (15 states, 18 states and 25 states). For 18 and 25 states, there are the choice beteen 2 set of colors. First, the colors defined by RoadMap and second, the colors defined by us for a better differentiation between states.

you can use *chromHMM_RoadMap* to visualise chromatin state in :

- 15-states, go to <http://egg2.wustl.edu/roadmap/data/byFileType/chromhmmSegmentations/ChmmModels/coreMarks/jointModel/final/> and select the MNEMONICS BED FILES, where bins with the same state label are merged and a label is assigned to the entire merged regions, related to your tissue of interest.
- 18-states, go to http://egg2.wustl.edu/roadmap/data/byFileType/chromhmmSegmentations/ChmmModels/core_K27ac/jointModel/final/ and select the MNEMONICS BED FILES, where bins with the same state label are merged and a label is assigned to the entire merged regions, related to your tissue of interest .
- 25-states, go to <http://egg2.wustl.edu/roadmap/data/byFileType/chromhmmSegmentations/ChmmModels/imputed12marks/jointModel/final/> and select your tissue of interest.

You can have more information about these data from ROADMAP website http://egg2.wustl.edu/roadmap/web_portal/chr_state_learning.html#core_15state.

You can visualise this bed using the function *chromHMM_RoadMap* and you can choice the color between *roadmap15*, *roadmap18*, *comet18*, *roadmap25* and *comet25*.

Below you can find the color code for each state depending if 15-,18- or 25-state

Listed below are the colours used for the different elements contained in ROADmap data with 15 states.



Listed below are the colours used for the different elements contained in ROADmap data with 18 states with RoadMap colors.



Listed below are the colours used for the different elements contained in ROADmap data with 18 states with coMET colors.



Listed below are the colours used for the different elements contained in ROADmap data with 25 states with RoadMap colors.



Listed below are the colours used for the different elements contained in ROADmap data with 25 states with coMET colors.



9.3.2 DNA Motif Positional Bias in Digital Genomic Footprinting Sites

The Digital Genomic Footprinting (DGF) sites in each cell type can be visualised using the function *dgfootprints.RoadMap* using the file of DNase/DGF Footprint calls <http://egg2.wustl.edu/roadmap/data/byDataType/dgfootprints/>

9.3.3 DNaseI-accessible regulatory regions

Using the core 15-state chromatin state model across any of the 111 Roadmap reference epigenomes, and focusing on states TssA, TssAFlnk, and TssBiv for promoters, and EnhG, Enh, and EnhBiv for enhancers, and state BivFlnk (flanking bivalent Enh/Tss) for ambiguous regions, 3 set of data were constructed. The data can be visualised using the function *DNaseI.RoadMap* with the good name of data (variable *featureDisplay*) like in Fig. 2:

- for **promoter** regions the file of tissue of interest http://egg2.wustl.edu/roadmap/data/byDataType/dnase/BED_files_prom/ or RData files containing matrice of chromatin state call for promoter. Thus, user can select for different tissues.
- for **enhancer** regions the file of tissue of interest http://egg2.wustl.edu/roadmap/data/byDataType/dnase/BED_files_enh/
- for **dyadic** promoter/enhancer region the file of tissue of interest http://egg2.wustl.edu/roadmap/data/byDataType/dnase/BED_files_dyadic/

```
chr<-"chr2"
start <- 38290160
end <- 38303219
```

```
gen<-"hg19"

extdata <- system.file("extdata", package="coMET",mustWork=TRUE)
prombedFilePath <- file.path(extdata, "/RoadMap/regions_prom_E001.bed")

promRMtrack<- DNaseI_RoadMap(gen,chr,start, end, prombedFilePath,
                             featureDisplay='promotor', type_stacking="squish")

enhbedFilePath <- file.path(extdata, "/RoadMap/regions_enh_E001.bed")

enhRMtrack<- DNaseI_RoadMap(gen,chr,start, end, enhbedFilePath,
                             featureDisplay='enhancer', type_stacking="squish")

dyabedFilePath <- file.path(extdata, "/RoadMap/regions_dyadic_E001.bed")

dyaRMtrack<- DNaseI_RoadMap(gen,chr,start, end, dyabedFilePath,
                             featureDisplay='dyadic', type_stacking="squish")

genetrack <-genes_ENSEMBL(gen,chr,start,end,showId=TRUE)

listRoadMap <- list(genetrack,promRMtrack,enhRMtrack,dyaRMtrack)
plotTracks(listRoadMap, chromosome=chr,from=start,to=end)
```

9.3.4 Processed data and Imputed data

BED and BigWIG file can be visualised with DataTrack objects from files of Gviz package. The data are in <http://www.genboree.org/EdaccData/Release-9/sample-experiment/> and <http://www.genboree.org/EdaccData/Release-9/experiment-sample/> or go to http://egg2.wustl.edu/roadmap/web_portal/processed_data.html for processed data or to http://egg2.wustl.edu/roadmap/web_portal/imputed.html#imp_sig for imputed data.

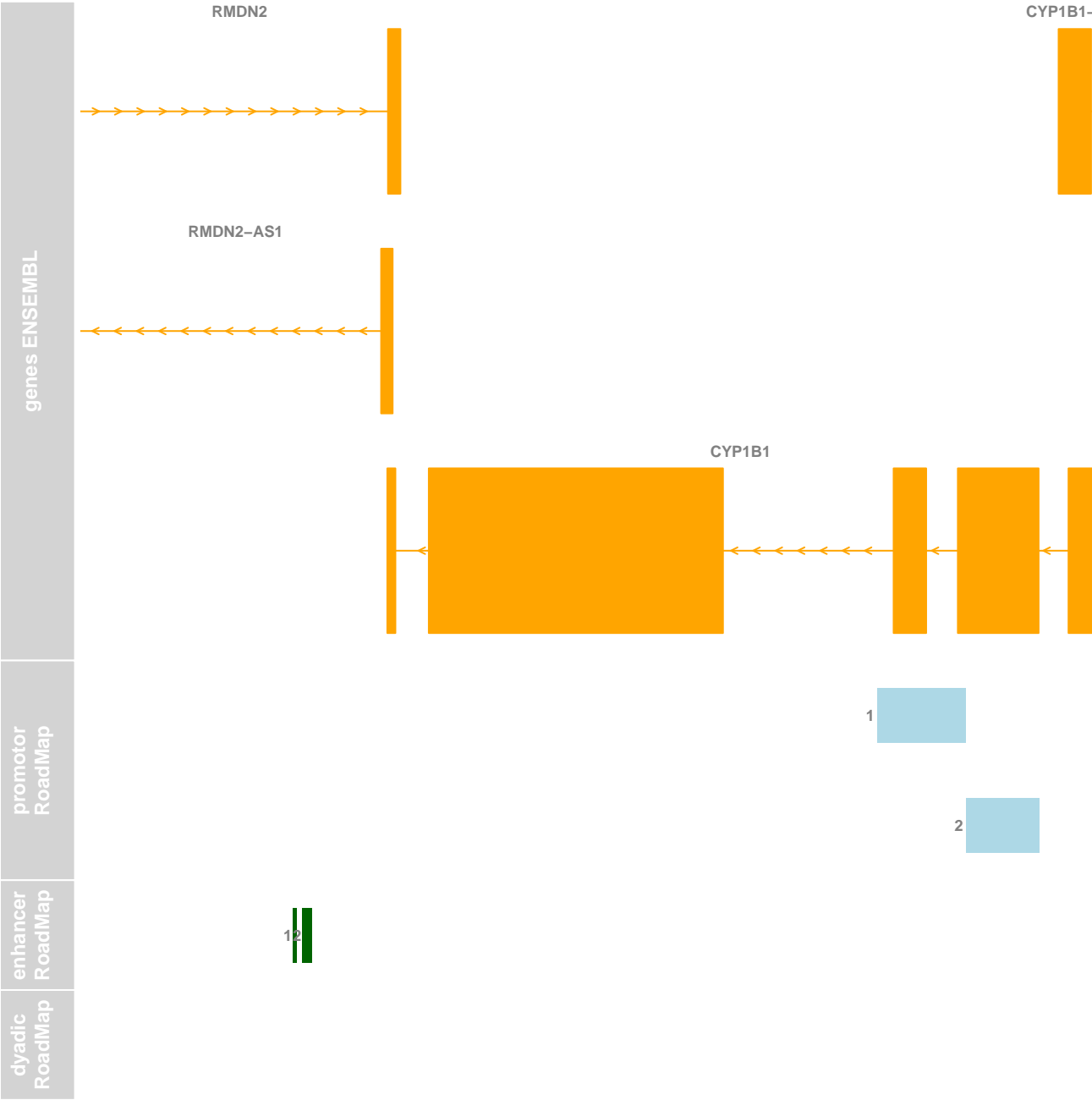


Figure 7: Plot of ROADMAP data.

9.4 ENCODE and GENCODE data

The ENCODE (Encyclopedia of DNA Elements) Consortium is an international collaboration of research groups funded by the National Human Genome Research Institute (NHGRI) <https://www.encodeproject.org/>. The goal of ENCODE is to build a comprehensive parts list of functional elements in the human genome, including elements that act at the protein and RNA levels, and regulatory elements that control cells and circumstances in which a gene is active.

Genes and transcripts of GENCODE are accessible from ENSEMBL biomart or can be visualised with GeneRegionTrack of Gviz. Other data are in BED or BAM format that can be visualised with Gviz tracks.

```
#Genes from GENCODE
chr<-3
start <- 132239976
end <- 132541303
gen<-"hg19"

extdata <- system.file("extdata", package="coMET",mustWork=TRUE)
gtfFilePath <- file.path(extdata, "/GTEX/gencode.v19.genes.patched_contigs.gtf")
options(ucscChromosomeNames=FALSE)
grtrack <- GeneRegionTrack(range=gtfFilePath ,chromosome = chr, start= start,
                           end= end, name = "Gencode V19",
                           collapseTranscripts=TRUE, showId=TRUE,shape="arrow")
plotTracks(grtrack, chromosome=chr,from=start,to=end)
```

9.4.1 Predicting motifs and active regulators

You can browse known and discovered motifs for the ENCODE TF ChIP-seq datasets. The position of motifs can be visualised using the function **motif.ENCODE** using one of files from <http://compbio.mit.edu/encode-motifs/> [7] such as <http://compbio.mit.edu/encode-motifs/matches.txt.gz>

```
#TF Chip-seq data
gen <- "hg19"
chr<-"chr1"
start <- 1000
end <- 329000
extdata <- system.file("extdata", package="coMET",mustWork=TRUE)
bedFilePath <- file.path(extdata, "ENCODE/motifs1000_matches_ENCODE.txt")
motif_color <- file.path(extdata, "ENCODE/TFmotifs_colors.csv")

chipTFtrack <- ChIPTF_ENCODE(gen,chr,start, end, bedFilePath,
                             featureDisplay=c("AHR::ARNT::HIF1A_1",
                                                "AIRE_1","AIRE_2","AHR::ARNT_1"),
                             motif_color,type_stacking="squish",showId=TRUE)

plotTracks(chipTFtrack, chromosome=chr,from=start,to=end)
```



Gencode V19

Figure 8: Plot of genes defined by GeneCode.

TF motifs ENCODE

Figure 9: Plot ENCODE TF ChIP-seq datasets of ENCODE.

9.5 GTEx Portal

The Genotype-Tissue Expression (GTEx) [8] project aims to provide to the scientific community a resource with which to study human gene expression and regulation and its relationship to genetic variation. By analyzing global RNA expression within individual tissues and treating the expression levels of genes as quantitative traits, variations in gene expression that are highly correlated with genetic variation can be identified as expression quantitative trait loci, or eQTLs. The data are accessible via <http://www.gtexportal.org/>. A set of data are downloadable from <http://www.gtexportal.org/home/datasets2> (need to have login).

The data were mapped on the reference genome **hg19**. Below described the colors of tracks and specific characteristics of some annotation tracks.

2 functions were created to visualise data from GTEx version 6:

1. **eQTL_GTEx** visualise eGene and significant snp-gene associations based on permutations in a tissue specific. The name of folder in GTEx version 6 is *GTEx_Analysis_V6_eQTLs.tar.gz*.
2. **geneExpression_GTEx** (need to update) visualise fully processed, normalized and filtered gene expression data, which was used as input into Matrix eQTL for eQTL discovery in a tissue specific. The name of folder in GTEx version 6 is *GTEx_Analysis_V6_eQTLInputFiles_geneLevelNormalizedExpression.tar.gz*
3. **GeneRegionTrack** from Gviz can visualise gene level model based on the GENCODE transcript model (cf. example below. Isoforms have been collapsed to single genes. The name of file in GTEx version 6 is *gencode.v19.genes.patched_contigs.gtf*.

```
## eQTL data
chr<-"chr3"
start <- 132239976
end <- 132541303
gen<-"hg19"

extdata <- system.file("extdata", package="coMET",mustWork=TRUE)
bedFilePath <- file.path(extdata, "/GTEx/eQTL_Uterus_Analysis_extract100.snpgenes")

eGTEx<- eQTL_GTEx(gen,chr, start, end, bedFilePath, featureDisplay = 'all',
                  showId=TRUE, type_stacking="squish", just_group="left" )

eGTEx_SNP<- eQTL_GTEx(gen,chr, start, end, bedFilePath,
                      featureDisplay = 'SNP', showId=FALSE,
                      type_stacking="dense", just_group="left")

#Genes from
gtfFilePath <- file.path(extdata, "/GTEx/gencode.v19.genes.patched_contigs.gtf")
options(ucscChromosomeNames=FALSE)
grtrack <- GeneRegionTrack(genome="hg19",range=gtfFilePath ,chromosome = chr,
                           start= start, end= end, name = "Gencode V19",
                           collapseTranscripts=TRUE, showId=TRUE,shape="arrow")
eGTExTracklist <- list(grtrack,eGTExTrackSNP)
plotTracks(eGTExTracklist, chromosome=chr,from=start,to=end)
```

2 other functions were created to visualise supplement data from GTEx version 3

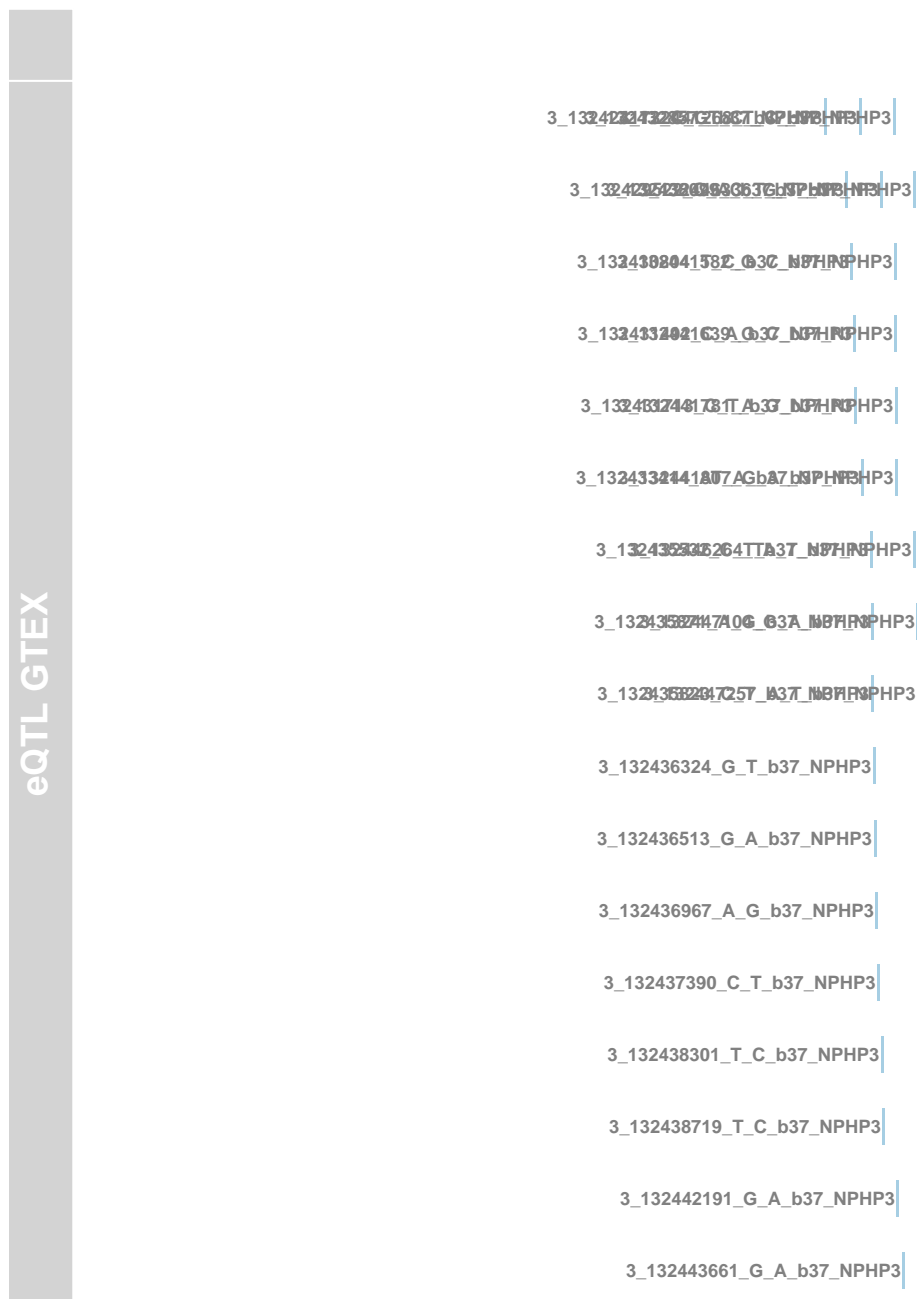


Figure 10: Plot eQTL from GTex.

1. **psiQTL_GTEx** visualise results from the protein truncating variants QTL (psiQTL) analysis for mine main tissues, plus brain, plus multi-tissue that averages the exons where data for three or more tissues is available. The name of file in GTEx version 3 is *gtex.psiqtls.zip*.
2. **imprintedGenes_GTEx** visualise gene imprinting genes in different tissues [9] via url <http://www.gtexportal.org/home/imprintingPage>. There are 33 tissues and 5 classification

```
### psiQTL
chr<-"chr13"
```



```

start <- 52713837
end <- 52715894
gen<-"hg19"

extdata <- system.file("extdata", package="coMET",mustWork=TRUE)
psiQTLFilePath <- file.path(extdata, "/GTEX/psiQTL_Assoc-total.AdiposeTissue.txt")

psiGTex<- psiQTL_GTex(gen,chr,start, end, psiQTLFilePath, featureDisplay = 'all',
                      showId=TRUE, type_stacking="squish",just_group="above" )

genetrack <-genes_ENSEMBL(gen,chr,start,end,showId=TRUE)

psiTrack <- list(genetrack,psiGTex)
plotTracks(psiTrack, chromosome=chr,from=start,to=end)

```

```

data(imprintedGenesGTex)
as.character(unique(imprintedGenesGTex$Tissue.Name))

## [1] "Pancreas" "Whole_Blood"
## [3] "Pituitary" "Lung"
## [5] "Cells_EBV-transformed_lymphocytes" "Thyroid"
## [7] "Adipose_Subcutaneous" "Artery_Tibial"
## [9] "Skin_Sun_Exposed_Lower_leg" "Skin_Not_Sun_Exposed_Suprapubic"
## [11] "Brain" "Muscle_Skeletal"
## [13] "Breast_Mammary_Tissue" "Nerve_Tibial"
## [15] "Adrenal_Gland" "Colon_Transverse"
## [17] "Prostate" "Artery_Coronary"
## [19] "Heart_Left_Ventricle" "Heart_Atrial_Appendage"
## [21] "Uterus" "Liver"
## [23] "Vagina" "Testis"
## [25] "Adipose_Visceral_Omentum" "Fallopian_Tube"
## [27] "Esophagus_Muscularis" "Ovary"
## [29] "Cells_Transformed_fibroblasts" "Esophagus_Mucosa"
## [31] "Kidney_Cortex" "Stomach"
## [33] "Artery_Aorta"

as.character(unique(imprintedGenesGTex$Classification))

## [1] "consistent with biallelic" "imprinted" "NC"
## [4] "consistent with imprinting" "biallelic"

```

```

### inprinted genes
chr<- "chr1"
start <- 7895752
end <- 7914572
gen<-"hg19"

genesTrack <- genes_ENSEMBL(gen,chr,start,end,showId=TRUE)

```

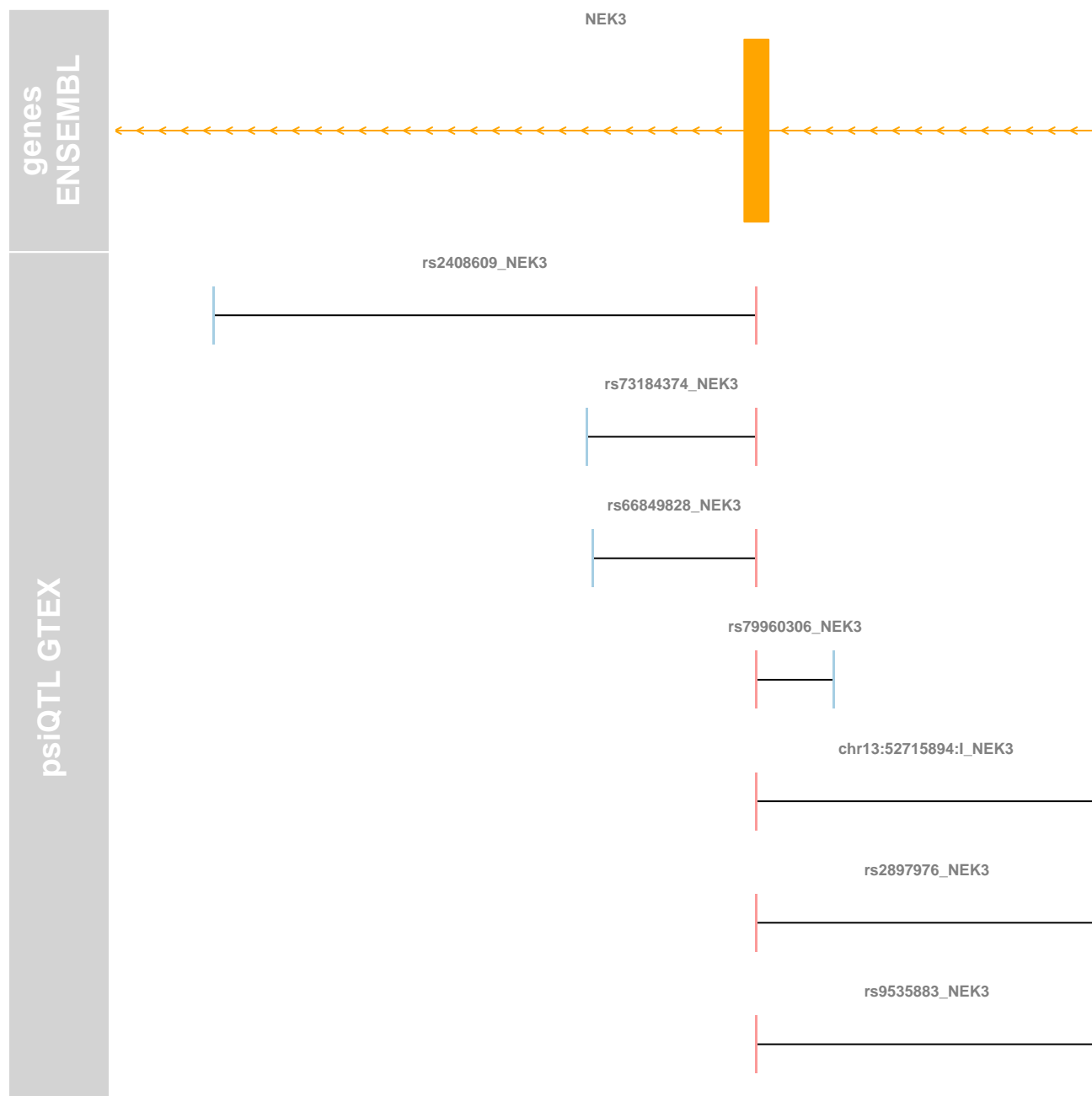


Figure 11: Plot psiQTL from GTEx.

```
allIG <- imprintedGenes_GTEEx(gen,chr,start, end, tissues="all",
                             classification="imprinted",showId=TRUE)

allimprintedIG <- imprintedGenes_GTEEx(chr,start, end, tissues="all",
                                       classification="imprinted",showId=TRUE)

StomachIG <-imprintedGenes_GTEEx(gen,chr,start, end, tissues="Stomach",
```

```
                                classification="all",showId=TRUE)

PancreasIG <- imprintedGenes_GTEx(gen,chr,start, end,
                                tissues="Pancreas",
                                classification="all",showId=TRUE)
PancreasimprintedIG <- imprintedGenes_GTEx(gen,chr,start, end, tissues="Pancreas",
                                classification="imprinted",showId=TRUE)

plotTracks(list(genesTrack, allIG, allimprintedIG,
               StomachIG,PancreasIG,PancreasimprintedIG),
           chromosome=chr, from=start, to=end)
```

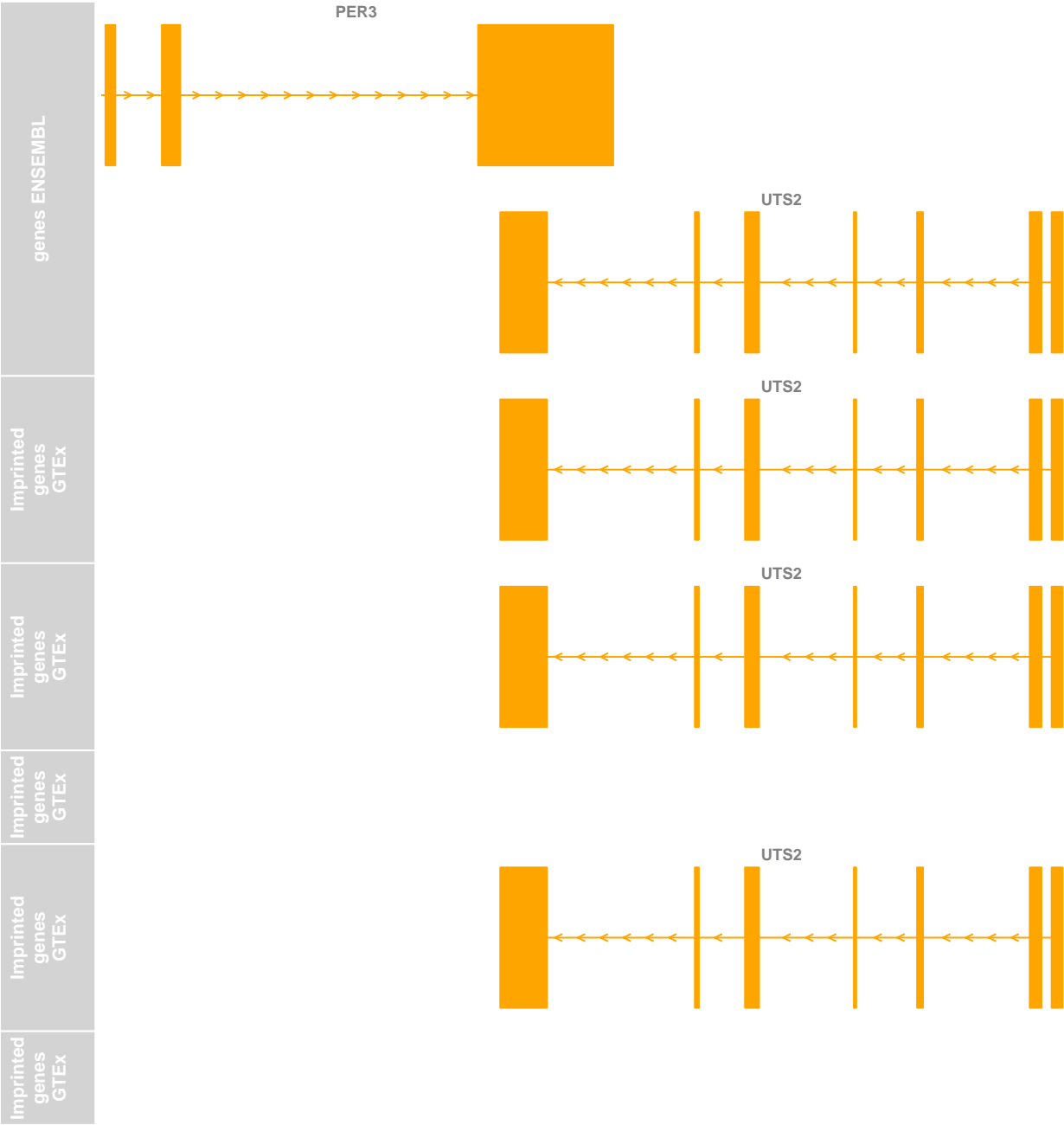


Figure 12: Plot imprinted genes from GTEx.

9.6 Hi-C data

Below are examples of Hi-C data available for different tissues.

9.6.1 Hi-C data at 1kb resolution at Lieberman Aiden lab

They [10] used in situ Hi-C to probe the three-dimensional architecture of genomes, constructing haploid and diploid maps of nine cell types. The densest, in human lymphoblastoid cells, contains 4.9 billion contacts, achieving 1-kilobase resolution. The data were mapped on **hg19** reference genome.

You can download intrachromosomal matrix from <http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE63525> for the cell-type of interest.

```
library('corrplot')
#Hi-C data
gen <- "hg19"
chr<-"chr1"
start <- 5000000
end <- 9000000
extdata <- system.file("extdata", package="coMET",mustWork=TRUE)
bedFilePath <- file.path(extdata, "HiC/chr1_1mb.RAWobserved")

matrix_HiC <- HiCdata2matrix(chr,start, end, bedFilePath)
cor_matrix_HiC <- cor(matrix_HiC)
diag(cor_matrix_HiC)<-1
corrplot(cor_matrix_HiC, method = "circle")
```

You can quick visualise this data using this HiC-interaction tool http://promoter.bx.psu.edu/hi-c/view.php?species=human&assembly=hg19&source=inside&tissue=GM12878&resolution=1&c_url=&gene=CTXN1&sessionID=

9.6.2 Hi-C Data Browser

You can download heatmap of your region of interest from two cell-line GM06690 (immortalized lymphoblast) or K562 (leukemia) using their website <http://hic.umassmed.edu/heatmap/heatmap.php>. This data was produced by [11]. The region that you want to visualise with this data need to large more than either 100Kb or 1Mb as Heatmaps were generated by dividing the chromosome up into 100 Kb or 1 Mb windows. The data were mapped on **hg19** reference genome.

You need to create info file to define the position of each bin composing your interaction matrix in using the row name of matrix as the name of bin contain the start and end of bin.

9.6.3 Hi-C project at Ren Lab

Interaction matrices for each of the four cell types analysis (mouse ES cell, mouse cortex, human ES cell (H1), and IMR90 fibroblasts) by Ren Lab (to cite them, you need to select the publication for this url <http://promoter.bx.psu.edu/hi-c/publications.html>) are accessible via url <http://chromosome.sdsc.edu/mouse/hi-c/download.html>. The interaction matrices are created using either a 40kb bin size throughout the genome. So

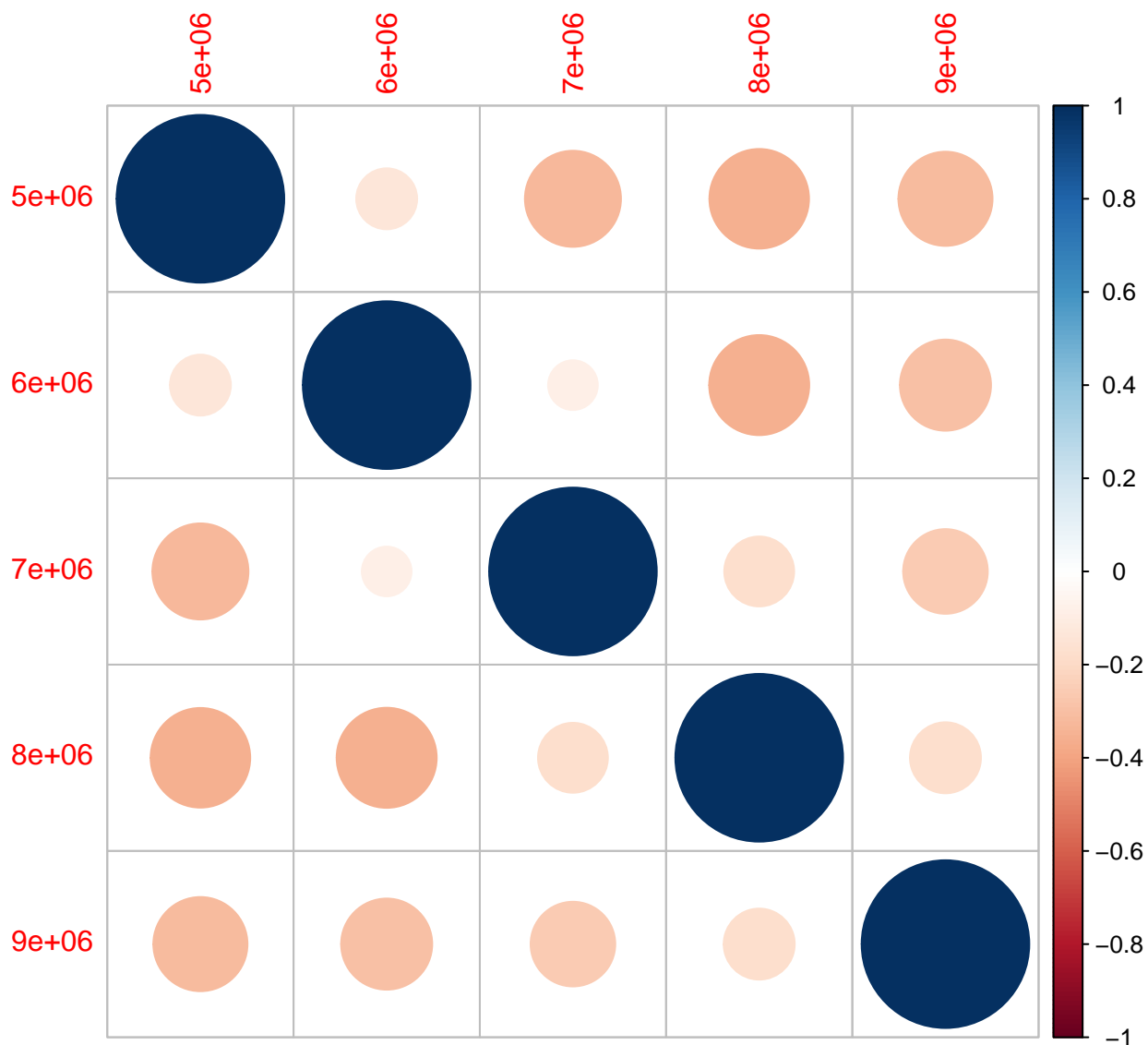


Figure 13: plot HiC data.

the region that you want to visualise with this data need to large more than 40Kb. The data were mapped on **hg19** reference genome.

You need to :

1. Extract from the BED file that contains the locations of each of the topological domains the region of interest
2. Extract in either raw or normalised matrice only the sub-matrice of interest

```
extdata <- system.file("extdata", package="coMET", mustWork=TRUE)
info_HiC <- file.path(extdata, "Human_IMR90_Fibroblast_topological_domains.txt")
data_info_HiC <- read.csv(info_HiC, header = FALSE, sep = "\t", quote = "")

intrachr_HiC <- file.path(extdata, "Human_IMR90_Fibroblast_Normalized_Matrices.txt")
data_intrachr_HiC <- read.csv(intrachr_HiC, header = TRUE, sep = "\t", quote = "")

chr_interest <- "chr2"
start_interest <- "1"
end_interest <- "160000"
list_bins <- which(data_info_HiC[,1] == chr_interest &
                  data_info_HiC[,2] >= start_interest &
                  data_info_HiC[,2] <= end_interest )

subdata_info_HiC <- data_info_HiC[list_bins,]
subdata_intrachr_HiC <- data_intrachr_HiC[list_bins, list_bins]
```

9.7 FANTOM5 database

FANTOM <http://fantom.gsc.riken.jp/> established the FANTOM database (transcripts, transcription factors, promoters and enhancers active,TSS) and the FANTOM full-length cDNA clone bank, which are available worldwide for about 400 distinct cell types. Currently, FANTOM is in version FANTOM5 phase 2 where data were mapped on reference genome **hg19** for human or **mm9** for mouse [12].

To extract data

- from <http://fantom.gsc.riken.jp/5/>
- from <http://fantom.gsc.riken.jp/data/> or <http://fantom.gsc.riken.jp/views/>
- from BED file used by UCSC HUB <http://fantom.gsc.riken.jp/5/datahub/>, more information here <http://fantom.gsc.riken.jp/5/datahub/description.html>

As the data are in classical format such as BED file, you can use easily Gviz's DataTrack function to visualise them. However, there are some comment lines that you need to remove in the top of files.

2 functions were created :

- **DNaseI_FANTOM** helps to visualise enhancer regions defined by FANTOM5
- **TFBS_FANTOM** helps to visualise TFBS regions defined by FANTOM5

```
gen <- "hg19"
chr<- "chr1"
start <- 6000000
end <- 6500000

extdata <- system.file("extdata", package="coMET",mustWork=TRUE)

##Enhancer
enhFantomFile <- file.path(extdata, "/FANTOM/human_permissive_enhancers_phase_1_and_2.bed")
enhFANTOMtrack <-DNaseI_FANTOM(gen,chr,start, end, enhFantomFile, featureDisplay='enhancer')

### TFBS motif
AP1FantomFile <- file.path(extdata, "/FANTOM/Fantom_hg19.AP1_MA0099.2.sites.txt")
tfbsFANTOMtrack <- TFBS_FANTOM(gen,chr,start, end, AP1FantomFile)
```

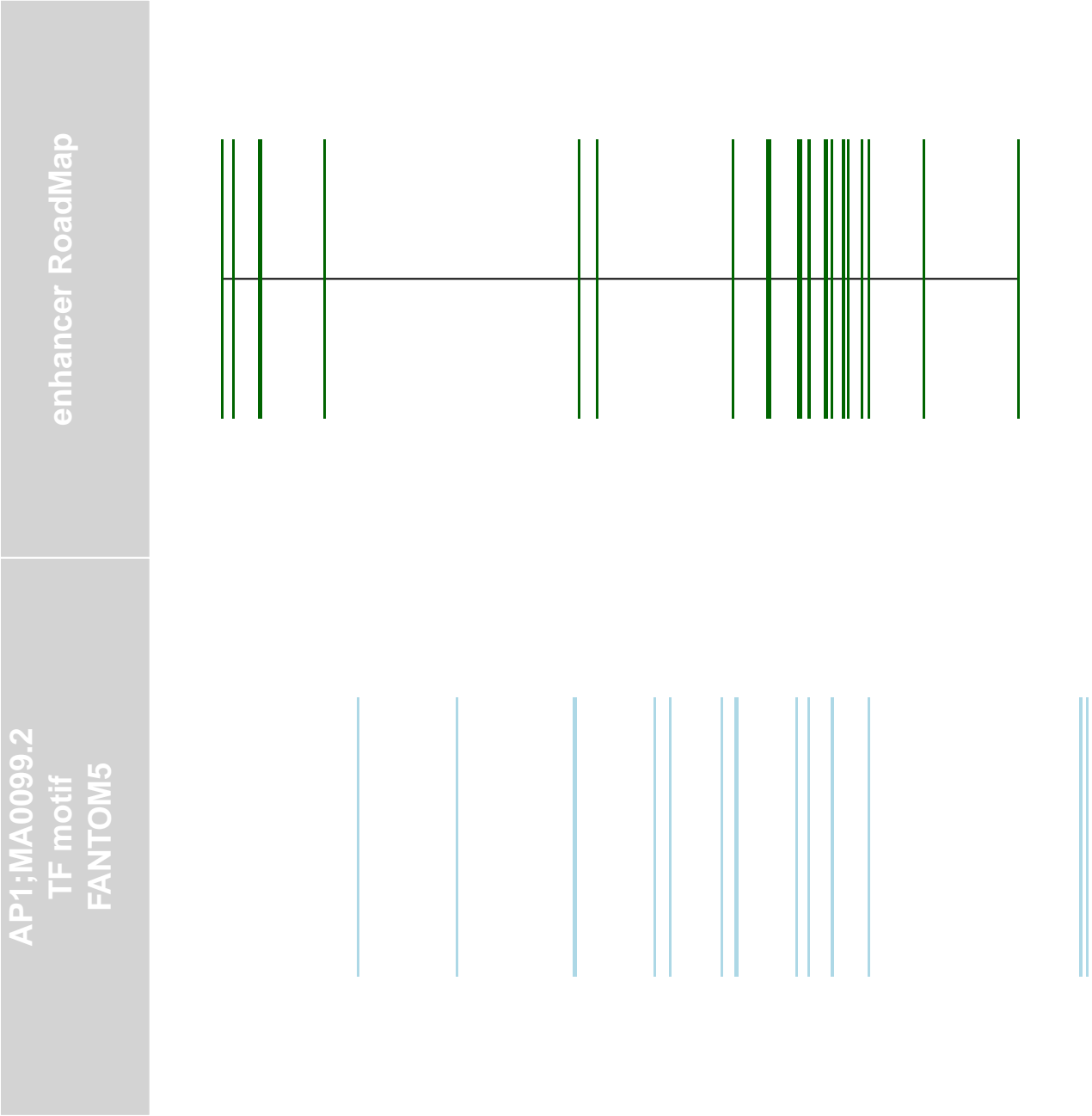



Figure 14: plot FANTOM5 data.

9.8 BLUEprint project

BLUEprint <http://www.blueprint-epigenome.eu/> aims to further the understanding of how genes are activated or repressed in both healthy and diseased human cells. BLUEPRINT will focus on distinct types of haematopoietic cells from healthy individuals and on their malignant leukaemic counterparts.

the data were mapped on reference genome partially on **GRCh37** and all on **GRCh38**.

As the data are in classical format such as BED file, BigWig or GTF, you can use easily DataTrack or AnnotationTrack of Gviz to visualise them.

9.9 Our data

9.9.1 eQTL data

You can visualise our eQTL using **eQTL** function. Listed below are the colours used for the different elements contained in eQTL data.



9.9.2 metQTL data

You can visualise our eQTL using **metQTL** function.

Listed below are the colours used for the different elements contained in metQTL data.



10 coMET: Shiny web-service

10.1 How to use the coMET web-service

If you want to use coMET via its webservice, please go to <http://epigen.kcl.ac.uk/comet> and select one of different instances or directly access one of the instances, for example <http://comet.epigen.kcl.ac.uk:3838/coMET/>. We have created different instances of coMET because we did not have access to the pro version of Shiny. All instances use the same version of coMET.

If you use coMET from a Shiny webservice, you do not need to install the coMET package on your computer. The web service is user friendly and requires input files and configuration of the plot. The creation of the coMET plot can take some time because it makes a live connection to UCSC or/and ENSEMBL for the annotation tracks. First, the plot is created on the webpage, and then it can be saved as an output file. For better quality plots please use the download option and the plot will be recreated in a file in pdf or eps format.

10.2 How to install the coMET web-service

These are different steps to install coMET on your Shiny web-service and you need to be root to install it.

1. You need to install R, Bioconductor and the coMET package under root.
2. You need first to install the *shiny* and *rmarkdown* R package before Shiny Server.

```
sudo su - -c "R -e \"install.packages('shiny', repos='http://cran.rstudio.com/')\""
```

```
sudo su - -c "R -e \"install.packages('rmarkdown', repos='http://cran.rstudio.com/')\""
```
3. You can install Shiny Server <http://shiny.rstudio.com/>, go to <https://www.rstudio.com/products/shiny/download-server/>.

```
sudo apt-get install gdebi-core
```

```
wget https://download3.rstudio.org/ubuntu-12.04/x86_64/shiny-server-1.4.2.786-amd64.deb
```

```
sudo gdebi shiny-server-1.4.2.786-amd64.deb
```
4. Shiny Server should now be installed and running on port 3838. You should be able to see a default welcome screen at http://your_server_ip:3838/. You can make sure your Shiny Server is working properly by going to http://your_server_ip:3838/sample-apps/hello/.
5. You now have a functioning Shiny Server that can host Shiny applications or interactive documents. The configuration file for Shiny Server is at `/etc/shiny-server/shiny-server.conf`. By default it is configured to serve applications in the `/srv/shiny-server/` directory. This means that any Shiny application that is placed at `/srv/shiny-server/app_name` will be available to the public at http://your_server_ip:3838/app_name/.
6. In a Shiny's folder (e.g. `/var/shiny-server/www`), you can create a folder called "COMET".
7. Following this, you can install the two coMET scripts in `www` of the coMET package, within this new folder.
8. You need to change owner and permissions to access this folder. Only the user called Shiny can access it.

```
mkdir -p /var/shiny-server/www/COMET
```

```
chmod -R 755 /var/shiny-server/www/COMET
```

```
chown -R shiny:shiny /var/shiny-server/www/COMET
```

```
mkdir -p /var/shiny-server/log
```

- ```
chmod -R 755 /var/shiny-server/log
chown -R shiny:shiny /var/shiny-server/log
```
9. You need now to update the configuration file of Shiny (e.g. /etc/shiny-server/shiny-server.conf).
  10. You need to change owner and the permission to access this file

```
chmod 744 /etc/shiny-server/shiny-server.conf
chown shiny:shiny /etc/shiny-server/shiny-server.conf
```
  11. At the end, you should restart the service Shiny via the command line:

```
###2.13.0.1 systemd (RedHat 7, Ubuntu 15.04+, SLES 12+)
#File to change:
/etc/systemd/system/shiny-server.service

#How to define the environment variable:
[Service]
Environment="SHINY_LOG_LEVEL=TRACE"

#Commands to run for the changes to take effect:
sudo systemctl stop shiny-server
sudo systemctl daemon-reload
sudo systemctl start shiny-server

###2.13.0.2 Upstart (Ubuntu 12.04 through 14.10 and RedHat 6)
#File to change:
/etc/init/shiny-server.conf

#How to define the environment variable:
env SHINY_LOG_LEVEL=TRACE

#Commands to run for the changes to take effect:
sudo restart shiny-server
```

Your Shiny's configuration file:

```
run_as shiny;
Define a top-level server which will listen on a port
server {
Instruct this server to listen on port 3838
listen 3838;
Define the location available at the base URL
location / {
Run this location in 'site_dir' mode, which hosts the entire directory
tree at '/srv/shiny-server'
site_dir /var/shiny-server/www;

Define where we should put the log files for this location
log_dir /var/shiny-server/log;

Should we list the contents of a (non-Shiny-App) directory when the user
visits the corresponding URL?
directory_index off;

app_init_timeout 3600;
app_idle_timeout 3600;
}

}
```

## 11 FAQs

---

- **I cannot see my plot after running comet or comet.web. What should I do?**

If the previous time comet or comet.web ran and error was produced it prevents the plot from being closed. to fix this use the command '*dev.off()*' as many times as necessary.

- **How do we know if my track has data? and what the data is?**

Type the name of your track, visualise the track with `plotTrack` or read different parameters with `str` function.

```
genetrack <-genesENSEMBL(gen,chrom,start,end,showId=TRUE)

plotTracks(genetrack)

str(genetrack)
```

- **How do you increase the size of the font of the name of an object?**

To enlarge the name of gene, as the object is Gviz object, you can use the option from Gviz  
You can see the value of different parameters via this command line:

```
genetrack <-genesENSEMBL(gen,chrom,start,end,showId=TRUE)

displayPars(genetrack)
```

So if you want to enlarge the name of gene, you need to do use the option `fontsize.gviz` in the coMET function, an example is given below:

```
comet(config.file = configfile, mydata.file = myinfofile, mydata.format = "file",
 cormatrix.file = mycorrelation, cormatrix.type = "listfile",
 mydata.large.file = mylargedata,mydata.large.type = "listfile",
 tracks.gviz = listGviz, verbose = TRUE,
 print.image=TRUE,fontsize.gviz=10)
```

- **Can I make a selection of which genes or transcripts to display?**

To make a selection of genes to display first create the track like you would if you were displaying all genes. From this track create another with only the genes you want to display like in the example below. Please note it is not possible to select genes based on their names unless the option to display gene names instead of gene reference is used, in other cases it is possible to make a selection based on the genes reference number.

```
geneTrack <- refGenesUCSC(gen, chr, start, end, IdType = "name", showId = TRUE)

geneTrackShow <- geneTrack[gene(geneTrack) %in% c("AHRR")]
```

- **How can I better understand where the comet function stopped?**

Use option *VERBOSE=TRUE* in the function `coMET` or `coMET.web`

If this does not help resolve the issue, please to send your command line with *VERBOSE=TRUE* and its error message to [tiphaine.martin@kcl.ac.uk](mailto:tiphaine.martin@kcl.ac.uk). Do not forget to give also information about the session by using `sessionInfo()`.

## 12 SessionInfo

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The following is the session info that generated this vignette:

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

- R version 3.4.0 (2017-04-21), x86\_64-pc-linux-gnu
- Locale: LC\_CTYPE=en\_US.UTF-8, LC\_NUMERIC=C, LC\_TIME=en\_US.UTF-8, LC\_COLLATE=C, LC\_MONETARY=en\_US.UTF-8, LC\_MESSAGES=en\_US.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
- Running under: Ubuntu 16.04.2 LTS
- Matrix products: default
- BLAS: /home/biocbuild/bbs-3.6-bioc/R/lib/libRblas.so
- LAPACK: /home/biocbuild/bbs-3.6-bioc/R/lib/libRlapack.so
- Base packages: base, datasets, grDevices, graphics, grid, methods, parallel, stats, stats4, utils
- Other packages: BiocGenerics 0.23.0, GenomInfoDb 1.13.0, GenomicRanges 1.29.0, Gviz 1.21.0, IRanges 2.11.0, S4Vectors 0.15.0, biomaRt 2.33.0, coMET 1.9.0, corrplot 0.77, ggbio 1.25.0, ggplot2 2.2.1, knitr 1.15.1, psych 1.7.3.21, trackViewer 1.13.0
- Loaded via a namespace (and not attached): AnnotationDbi 1.39.0, AnnotationFilter 1.1.0, AnnotationHub 2.9.0, BSgenome 1.45.0, Biobase 2.37.0, BiocInstaller 1.25.3, BiocParallel 1.11.0, BiocStyle 2.5.0, Biostrings 2.45.0, DBI 0.6-1, DelayedArray 0.3.0, Formula 1.2-1, GGally 1.3.0, GenomInfoDbData 0.99.0, GenomicAlignments 1.13.0, GenomicFeatures 1.29.0, Hmisc 4.0-2, Matrix 1.2-9, OrganismDbi 1.19.0, ProtGenerics 1.9.0, R6 2.2.0, RBGL 1.53.0, RColorBrewer 1.1-2, RCurl 1.95-4.8, RSQLite 1.1-2, Rcpp 0.12.10, Rsamtools 1.29.0, SummarizedExperiment 1.7.0, VariantAnnotation 1.23.0, XML 3.98-1.6, XVector 0.17.0, acepack 1.4.1, backports 1.0.5, base64enc 0.1-3, biovizBase 1.25.0, bitops 1.0-6, checkmate 1.8.2, cluster 2.0.6, colorspace 1.3-2, colortools 0.1.5, compiler 3.4.0, data.table 1.10.4, dichromat 2.0-0, digest 0.6.12, ensemblDb 2.1.0, evaluate 0.10, foreign 0.8-67, grImport 0.9-0, graph 1.55.0, gridExtra 2.2.1, gtable 0.2.0, hash 2.2.6, highr 0.6, htmlTable 1.9, htmltools 0.3.5, htmlwidgets 0.8, httpuv 1.3.3, httr 1.2.1, interactiveDisplayBase 1.15.0, lattice 0.20-35, latticeExtra 0.6-28, lazyeval 0.2.0, magrittr 1.5, matrixStats 0.52.2, memoise 1.1.0, mime 0.5, mnormt 1.5-5, munsell 0.4.3, nlme 3.1-131, nnet 7.3-12, pbapply 1.3-2, plyr 1.8.4, reshape 0.8.6, reshape2 1.4.2, rmarkdown 1.4, rpart 4.1-11, rprojroot 1.2, rtracklayer 1.37.0, scales 0.4.1, shiny 1.0.2, splines 3.4.0, stringi 1.1.5, stringr 1.2.0, survival 2.41-3, tibble 1.3.0, tools 3.4.0, xtable 1.8-2, yaml 2.1.14, zlibbioc 1.23.0



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