dsQTL: exploring DNA-variants associated with DNaseI hypersensitivity

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1 Introduction

Degner et al. (2012) publish information on associations between DNA variants (SNP, SNV, and indels) and DNaseI hypersensitivity measures acquired via DNase-Seq.

This package includes information from the Chicago group on normalized DNase-seq data for chromosomes 2 and 17, and genotype data from chromosome 2 only.

2 The basic data structure

```
> library(dsQTL)
> data(DSQ_17)
> exptData(DSQ_17)

SimpleList of length 2
names(2): MIAME annotation

> exptData(DSQ_17)[[1]]

Experiment data
  Experimenter name: Degner JF
  Laboratory: Department of Human Genetics, University of Chicago, Chicago, Illinois 60
  Contact information:
  Title: DNaseI sensitivity QTLs are a major determinant of human expression variation.
  URL:
  PMIDs: 22307276

  Abstract: A 252 word abstract is available. Use 'abstract' method.
```

We use summarized experiment structure for the assay data, but the imputed genotype data are kept separate, in the package, in the inst/parts folder.

The data structure on chr2, which will be used to reproduce some findings, is more mature

```
> data(DSQ_2)
> names(assays(DSQ_2))
```

```
[1] "normDHS"
```

```
> assays(DSQ_2)[[1]][1:5,1:5]
```

```
              NA18486     NA18498    NA18499    NA18501    NA18502
dhs_2_1202 -0.2684343 -0.78076674 -0.4840237  2.3894003 -1.0813642
dhs_2_1602 -1.4445813  0.92170439  0.5812017  0.8627376  0.5186581
dhs_2_2002  0.7624075 -0.12340745 -1.1821308  1.4253179  0.3125592
dhs_2_7502  0.1242963  0.60788505  0.6754706 -0.0452303  0.4876332
dhs_2_8802 -0.9554503 -0.06016578 -0.1990696  1.9383937 -1.3758668
```

```
> rowData(DSQ_2)
```

```
GRanges with 96024 ranges and 0 metadata columns:
                  seqnames                 ranges strand
                     <Rle>              <IRanges>  <Rle>
       dhs_2_1202     chr2         [ 1202,  1301]      *
       dhs_2_1602     chr2         [ 1602,  1701]      *
       dhs_2_2002     chr2         [ 2002,  2101]      *
       dhs_2_7502     chr2         [ 7502,  7601]      *
       dhs_2_8802     chr2         [ 8802,  8901]      *
      dhs_2_14202     chr2         [14202, 14301]      *
      dhs_2_14302     chr2         [14302, 14401]      *
      dhs_2_34902     chr2         [34902, 35001]      *
      dhs_2_35102     chr2         [35102, 35201]      *
              ...      ...                    ...    ...
  dhs_2_242689402     chr2 [242689402, 242689501]      *
  dhs_2_242689502     chr2 [242689502, 242689601]      *
  dhs_2_242696902     chr2 [242696902, 242697001]      *
  dhs_2_242697402     chr2 [242697402, 242697501]      *
  dhs_2_242698102     chr2 [242698102, 242698201]      *
  dhs_2_242711702     chr2 [242711702, 242711801]      *
  dhs_2_242737502     chr2 [242737502, 242737601]      *
  dhs_2_242737902     chr2 [242737902, 242738001]      *
  dhs_2_242739902     chr2 [242739902, 242740001]      *
  ---
  seqlengths:
   chr2
     NA
```

To implement the GGBase protocol for on-the-fly generation of smlSet instances from getSS queries, we have an ExpressionSet instance with specific names.

```
> data(eset, package="dsQTL")
> ex
```

```
ExpressionSet (storageMode: lockedEnvironment)
assayData: 96024 features, 70 samples
  element names: exprs
protocolData: none
phenoData
  sampleNames: NA18486 NA18498 ... NA19257 (70 total)
  varLabels: naid one ... isFounder (9 total)
  varMetadata: labelDescription
featureData: none
experimentData: use 'experimentData(object)'
Annotation:
```

The genotype data supplied by Degner et al are imputed to 1000 genomes haplotypes, and are reals in [0,2]. For simplicity the current image of the data uses the rounding of the fractional genotypes x with round(x,0).

The feature data refer to the retained 100bp segments that were summarized for DNaseI hypersensitivity and found to lie in the uppermost 5% of the distribution.

```
> library(Biobase)
> fData(ex)[1:5,,drop=FALSE]
```

```
data frame with 0 columns and 5 rows
```

We can get the integrated container as

```
> library(GGBase)
> ds2 = getSS("dsQTL", "roundGT_2")
```

the name indicates that we simply rounded the imputed fractional genotypes to nearest integer.

A very restricted search is:

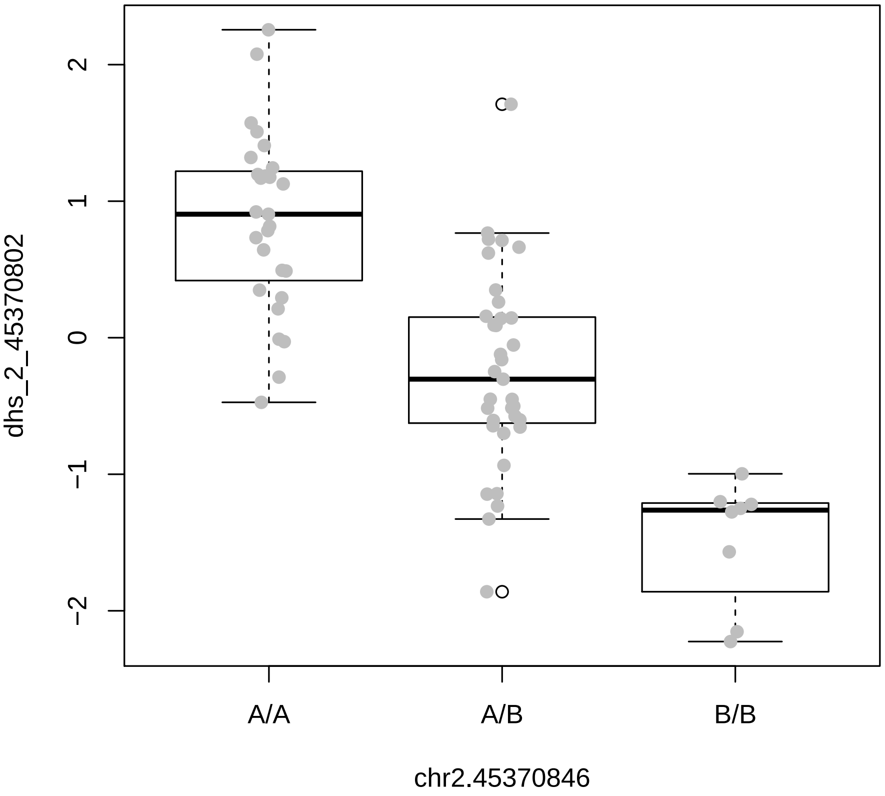
```
> # need to get rid of SNPlocs package getSNPlocs
> getSNPlocs = dsQTL::getSNPlocs  # force
> library(GGtools)
> #library(parallel)
> #options(mc.cores=12)
> n1 = best.cis.eQTLs(smpack="dsQTL", radius=2000, geneannopk="dsQTL",
+   snpannopk="dsQTL", chrnames="2", smchrpref="roundGT_",
+   smFilter = function(x) GTFfilter(x, lower=0.05)[23810:23830,],
+ #  geneApply=mclapply)
+   geneApply=lapply)
```

```
get data...build map...run smFilter...filter probes in map...tests...filter...done.
get data...build map...run smFilter...filter probes in map...tests...filter...done.
get data...build map...run smFilter...filter probes in map...tests...filter...done.
```

```
> n1
```

```
GGtools mcwBestCis instance.  The call was:
best.cis.eQTLs(smpack = "dsQTL", radius = 2000, chrnames = "2",
    smchrpref = "roundGT_", geneApply = lapply, geneannopk = "dsQTL",
    snpannopk = "dsQTL", smFilter = function(x) GTFfilter(x,
        lower = 0.05)[23810:23830, ])
Best loci for 21 probes are recorded.
There were 102 gene:snp tests.
Top  4 probe:SNP combinations:
GRanges with 4 ranges and 5 metadata columns:
                 seqnames               ranges strand |     score         snpid
                    <Rle>            <IRanges>  <Rle> | <numeric>   <character>
  dhs_2_45370802        2 [45368802, 45372901]      * |     38.64 chr2.45370846
  dhs_2_45370702        2 [45368702, 45372801]      * |     29.11 chr2.45370846
  dhs_2_45369802        2 [45367802, 45371901]      * |     19.14 chr2.45370846
  dhs_2_45364602        2 [45362602, 45366701]      * |      5.73 chr2.45366677
                    snploc radiusUsed       fdr
                 <integer>  <numeric> <numeric>
  dhs_2_45370802  45370846       2000 0.0000000
  dhs_2_45370702  45370846       2000 0.0000000
  dhs_2_45369802  45370846       2000 0.0000000
  dhs_2_45364602  45366677       2000 0.2142857
  ---
  seqlengths:
    2
   NA
====
use chromsUsed(), fullreport(), etc. for additional information.
```

```
> plot_EvG(probeId("dhs_2_45370802"), rsid("chr2.45370846"), getSS("dsQTL", "roundGT_
```



3 Provenance

3.1 Normed DNaseI hypersensitivity scores

The dsQTL package data structures `DSQ_2` and `DSQ_17` are generated from GEO GSE31388, from which a collection of 70 compressed BED format files were acquired Aug 9 2011. These are imported using the rtracklayer package to obtain location and score information for all the recorded DNaseI hypersensitivity assay results. For example, after import for NA19257, we have

```
Browse[1]> x
[1] "NA19257"
Browse[1]> tmp
RangedData with 1465907 rows and 3 value columns across 22 spaces
```

```
           space                ranges   |        name       score   strand
        <factor>             <IRanges>   | <character>   <numeric> <factor>
1           chr1       [  402,   501]   |         NOT -0.67088720        +
2           chr1       [  502,   601]   |         NOT -1.69969288        +
3           chr1       [  602,   701]   |         NOT  0.13520754        +
...          ...                   ... ...         ...         ...      ...
1465905    chr22 [49571602, 49571701]   |         NOT  0.62742318        +
1465906    chr22 [49575102, 49575201]   |         NOT -0.09417379        +
1465907    chr22 [49581602, 49581701]   |         NOT -0.29496269        +
```

The scores for locations on chromosome 2 were collected using

```
> proc1 = function(x) {
+  library(rtracklayer)
+  tmp = import(paste(x, ".qnorm.bed.gz", sep=""))
+  stt = split(tmp, space(tmp))
+  obn = paste(x, "_dsq_chr2", sep="")
+  assign(obn, stt[["chr2"]])
+  save(list=obn, file=paste(obn, ".rda", sep=""))
+  NULL
+ }
```

The regions and scores reported are described in the GEO metadata as

> We also provide BED file format data for each individual for the top 5% of the genome in terms of total sensitivity. This data was mapped to hg18 using a custom read-mapping algorithm which we describe in detail in the associated publication. Measures of DNase sensitivity were quantile normalized within each individual to a standard normal distribution. Each individual was corrected for GC bias and the top 4 principle (sic) components were removed from the data (See manuscript).

Score data were structured as a matrix with columns corresponding to Yoruba HapMap subject, and rows corresponding to reported hypersensitivity regions.

The `SummarizedExperiment` container is used to unite range and score data in the assays component, and allied metadata are available in exptData and colData components.

3.2 Genotype data

Textual representation of the allelic doses is provided at `http://eqtl.uchicago.edu/dsQTL_data/GENOTYPES/`. As of Oct 2012, these were rounded to allele counts to allow use of snpMatrix representation for chromosome 2 genotypes; propagation of dosage fractions will be undertaken in late 2012.

4 Session information

```
> sessionInfo()

R version 2.15.1 (2012-06-22)
Platform: x86_64-unknown-linux-gnu (64-bit)

locale:
 [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C
 [3] LC_TIME=en_US.UTF-8        LC_COLLATE=C
 [5] LC_MONETARY=en_US.UTF-8    LC_MESSAGES=en_US.UTF-8
 [7] LC_PAPER=C                 LC_NAME=C
 [9] LC_ADDRESS=C               LC_TELEPHONE=C
[11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C

attached base packages:
[1] stats4    splines   stats     graphics  grDevices utils     datasets
[8] methods   base

other attached packages:
 [1] GGtools_4.6.0        Rsamtools_1.10.1     Biostrings_2.26.1
 [4] dsQTL_0.0.22         GGBase_3.20.0        snpStats_1.8.0
 [7] Matrix_1.0-9         lattice_0.20-10      survival_2.36-14
[10] Biobase_2.18.0       GenomicRanges_1.10.1 IRanges_1.16.2
[13] BiocGenerics_0.4.0

loaded via a namespace (and not attached):
 [1] AnnotationDbi_1.20.0    BSgenome_1.26.1         DBI_0.2-5
 [4] GenomicFeatures_1.10.0  RCurl_1.95-1.1          RSQLite_0.11.2
 [7] VariantAnnotation_1.4.1 XML_3.95-0.1            annotate_1.36.0
[10] biomaRt_2.14.0          bit_1.1-8               bitops_1.0-4.1
[13] ff_2.2-7                genefilter_1.40.0       grid_2.15.1
[16] parallel_2.15.1         rtracklayer_1.18.0      tools_2.15.1
[19] xtable_1.7-0            zlibbioc_1.4.0
```