Using RQT, an R/Bioconductor package for gene-level meta-analysis

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1 Overview

Despite the recent advances of modern GWAS methods, it is still remains an important problem of addressing calculation an effect size and corresponding p-value for the whole gene rather than for single variant. We developed an R-package rqt, which offers gene-level GWAS meta-analysis. The package can be easily included into bioinformatics pipeline or used as stand-alone. Contact: ilya.zhbannikov@duke.edu for questions of usage the `rqt` or any other issues.

Below we provide several examples that show GWAS meta-analysis on gene-level layer.

1.1 Methods in brief

The workflow of gene-level meta analysis consists of the following steps: (i) reducing the number of predictors, thereby alleviating correlation problem in variants (accounting for LD); (ii) then the regression mod-el is fitted on the reduced dataset to obtain corresponding regression coefficient ("effect sizes"); (iii) these coefficients are then to be pooled into a total index representing a total gene-level effect size and corresponding statistics is calculated. P- and q- values are then calculated using this statistics from asymptotic approximation or permutation procedure; (iv) the final step is combining gene-level p-values calculated from each study with Fisher's combined probability method.

2 Installation

2.1 Most-recent version from GitHub

```
> require(devtools)
> devtools::install_github("izhbannikov/rqt")
```

3 Data description

3.1 Single dataset

In `rqt` requires two datasets: phenotype (a n by 1) matrix and genotype (a n by m) matrix, where n - is the total number of individuals in the study and m is the total number of genetic variants. Optionally, rqt can accept covariates, in form of n by k matrix, where k is the total number of covariates used in the study. Phenotype can be dichotomous (0/1, where 1 indicates control and 0 case).

3.2 Meta-analysis

In meta-analysis, `rqt` requires a list of M (M - number of datasets used in meta-analysis) and optionally it accepts covariates in form described above.

4 Examples

4.1 Gene-level analysis on a single dataset

4.2 Dichotomous phenotype

```
> library(rqt)
> data <- read.table(system.file("extdata/test.bin1.dat",package="rqt"),
+     header = TRUE)
> pheno <- data$pheno
> geno <- data[, 2:dim(data)[2]]
> obj <- rqtClass(phenotype=pheno, genotype=geno)
> res <- rQTest(obj, method="pca", out.type = "D")
> print(res)
```

```
Phenotype:
[1] 1 1 1 1 1 1
...

Genotype:
  snp1 snp2 snp3 snp4 snp5 snp6 snp7 snp8 snp9 snp10 snp11 snp12 snp13 snp14
1    0    0    0    1    0    2    1    0    0     0     2     1     2     0
2    1    0    1    0    0    1    0    0    0     0     0     0     1     0
3    0    0    0    0    1    0    0    1    0     1     1     1     0     0
4    0    0    1    0    1    0    0    1    1     0     0     0     1     0
5    0    0    1    1    1    1    1    1    0     1     0     1     0     0
6    0    0    1    1    1    0    0    1    0     1     1     0     1     0
  snp15 snp16 snp17 snp18 snp19 snp20 snp21 snp22 snp23 snp24 snp25 snp26 snp27
1     0     2     1     1     0     0     1     0     0     0     0     2     1
2     0     0     2     1     2     1     0     1     0     0     0     2     1
3     0     1     1     0     0     1     1     1     0     0     0     1     0
4     0     0     1     0     0     2     0     1     0     0     0     1     0
5     0     0     0     0     0     0     1     0     0     1     0     1     2
6     0     2     0     0     1     0     1     1     0     0     0     2     0
  snp28 snp29 snp30 snp31 snp32 snp33 snp34 snp35 snp36 snp37 snp38 snp39 snp40
1     0     1     0     0     0     0     0     0     1     1     0     0     1
2     1     2     0     0     0     1     2     1     2     0     1     1     0
3     0     0     0     0     0     0     1     1     1     2     2     0     0
4     2     0     0     0     1     2     2     0     1     1     1     1     0
5     0     0     0     0     0     1     1     0     0     1     1     0     0
6     0     0     0     0     0     1     0     1     1     0     0     2     0
  snp41 snp42 snp43 snp44 snp45 snp46 snp47 snp48 snp49 snp50 snp51 snp52 snp53
1     0     0     1     0     0     0     0     1     1     0     0     0     1
2     1     0     0     1     0     0     0     2     0     1     0     1     0
3     0     1     0     1     0     2     1     1     1     0     0     0     1
4     0     0     1     1     0     0     1     1     2     0     1     0     2
5     2     2     0     0     0     1     2     1     0     0     0     0     1
6     1     1     2     0     0     0     1     1     1     0     0     1     1
  snp54 snp55 snp56 snp57 snp58 snp59 snp60 snp61 snp62 snp63 snp64 snp65 snp66
1     1     1     1     1     0     0     0     0     1     1     0     1     1
2     2     1     0     1     0     0     0     1     0     1     2     2     1
3     2     1     0     0     0     0     0     0     0     1     0     0     1
4     1     1     0     0     0     0     2     1     0     1     0     0     2
```

```
5     1     1     1     0     0     0     2     1     1     0     0     1     1
6     0     1     1     0     0     0     0     0     0     0     1     2     1
  snp67 snp68 snp69 snp70 snp71 snp72 snp73 snp74 snp75 snp76 snp77 snp78 snp79
1     1     0     1     1     2     1     1     1     0     0     2     1     1
2     1     0     1     0     1     0     0     0     0     1     1     2     1
3     1     0     1     2     1     0     1     1     0     0     0     0     1
4     1     0     0     1     1     1     0     0     0     0     0     1     0
5     0     0     1     1     0     0     1     0     1     0     0     1     0
6     1     0     0     0     0     0     1     1     1     1     1     1     2
  snp80 snp81 snp82 snp83 snp84 snp85 snp86 snp87 snp88 snp89 snp90 snp91 snp92
1     1     0     1     1     0     1     1     0     0     0     1     0     1
2     1     2     0     0     0     1     2     0     2     1     0     0     2
3     1     0     0     0     0     2     0     0     2     0     0     0     0
4     1     2     0     1     0     1     2     0     0     0     0     0     0
5     2     0     1     0     0     2     0     0     0     0     1     0     0
6     1     0     0     1     0     0     0     0     2     0     1     0     0
  snp93 snp94 snp95 snp96 snp97 snp98 snp99 snp100
1     1     0     0     0     1     0     1      1
2     1     0     0     0     0     1     1      2
3     1     1     0     0     1     2     0      0
4     1     0     0     0     1     0     0      0
5     1     0     0     1     1     2     1      1
6     0     0     0     1     1     0     1      1
...

Covariates:
data frame with 0 columns and 0 rows


Results:

$Qstatistic
         Q1        Q2        Q3
1 0.9086994 0.9938212 0.9086994

$p.value
       p.Q1      p.Q2      p.Q3
1 0.3404597 0.9285409 0.5654533
```

4.3 Continuous phenotype

```
> library(rqt)
> data <- read.table(system.file("extdata/test.cont1.dat",package="rqt"),
+     header = TRUE)
> pheno <- data$pheno
> geno <- data[, 2:dim(data)[2]]
> obj <- rqtClass(phenotype=pheno, genotype=geno)
> res <- rQTest(obj, method="pca", out.type = "C")
> print(res)

Phenotype:
[1] 3.422452 2.457394 2.708564 4.589394 5.461723 4.438707
```

...

Genotype:

	snp1	snp2	snp3	snp4	snp5	snp6	snp7	snp8	snp9	snp10	snp11	snp12	snp13	snp14
1	0	0	0	1	0	2	1	0	0	0	2	1	2	0
2	1	0	1	0	0	1	0	0	0	0	0	0	1	0
3	0	0	0	0	1	0	0	1	0	1	1	1	0	0
4	0	0	1	0	1	0	0	1	1	0	0	0	1	0
5	0	0	1	1	1	1	1	1	0	1	0	1	0	0
6	0	0	1	1	1	0	0	1	0	1	1	0	1	0

	snp15	snp16	snp17	snp18	snp19	snp20	snp21	snp22	snp23	snp24	snp25	snp26	snp27
1	0	2	1	1	0	0	1	0	0	0	0	2	1
2	0	0	2	1	2	1	0	1	0	0	0	2	1
3	0	1	1	0	0	1	1	1	0	0	0	1	0
4	0	0	1	0	0	2	0	1	0	0	0	1	0
5	0	0	0	0	0	0	1	0	0	1	0	1	2
6	0	2	0	0	1	0	1	1	0	0	0	2	0

	snp28	snp29	snp30	snp31	snp32	snp33	snp34	snp35	snp36	snp37	snp38	snp39	snp40
1	0	1	0	0	0	0	0	0	1	1	0	0	1
2	1	2	0	0	0	1	2	1	2	0	1	1	0
3	0	0	0	0	0	0	1	1	1	2	2	0	0
4	2	0	0	0	1	2	2	0	1	1	1	1	0
5	0	0	0	0	0	1	1	0	0	1	1	0	0
6	0	0	0	0	0	1	0	1	1	0	0	2	0

	snp41	snp42	snp43	snp44	snp45	snp46	snp47	snp48	snp49	snp50	snp51	snp52	snp53
1	0	0	1	0	0	0	0	1	1	0	0	0	1
2	1	0	0	1	0	0	0	2	0	1	0	1	0
3	0	1	0	1	0	2	1	1	1	0	0	0	1
4	0	0	1	1	0	0	1	1	2	0	1	0	2
5	2	2	0	0	0	1	2	1	0	0	0	0	1
6	1	1	2	0	0	0	1	1	1	0	0	1	1

	snp54	snp55	snp56	snp57	snp58	snp59	snp60	snp61	snp62	snp63	snp64	snp65	snp66
1	1	1	1	1	0	0	0	0	1	1	0	1	1
2	2	1	0	1	0	0	0	1	0	1	2	2	1
3	2	1	0	0	0	0	0	0	0	1	0	0	1
4	1	1	0	0	0	0	2	1	0	1	0	0	2
5	1	1	1	0	0	0	2	1	1	0	0	1	1
6	0	1	1	0	0	0	0	0	0	0	1	2	1

	snp67	snp68	snp69	snp70	snp71	snp72	snp73	snp74	snp75	snp76	snp77	snp78	snp79
1	1	0	1	1	2	1	1	1	0	0	2	1	1
2	1	0	1	0	1	0	0	0	0	1	1	2	1
3	1	0	1	2	1	0	1	1	0	0	0	0	1
4	1	0	0	1	1	1	0	0	0	0	0	1	0
5	0	0	1	1	0	0	1	0	1	0	0	1	0
6	1	0	0	0	0	0	1	1	1	1	1	1	2

	snp80	snp81	snp82	snp83	snp84	snp85	snp86	snp87	snp88	snp89	snp90	snp91	snp92
1	1	0	1	1	0	1	1	0	0	0	1	0	1
2	1	2	0	0	0	1	2	0	2	1	0	0	2
3	1	0	0	0	0	2	0	0	2	0	0	0	0
4	1	2	0	1	0	1	2	0	0	0	0	0	0
5	2	0	1	0	0	2	0	0	0	0	1	0	0

```
6     1     0     0     1     0     0     0     0     2     0     1     0     0
  snp93 snp94 snp95 snp96 snp97 snp98 snp99 snp100
1     1     0     0     0     1     0     1      1
2     1     0     0     0     0     1     1      2
3     1     1     0     0     1     2     0      0
4     1     0     0     0     1     0     0      0
5     1     0     0     1     1     2     1      1
6     0     0     0     1     1     0     1      1
...

Covariates:
data frame with 0 columns and 0 rows


Results:

$Qstatistic
         Q1       Q2       Q3
1 0.2846585 2.389537 2.219594

$p.value
      p.Q1      p.Q2      p.Q3
1 0.593664 0.7022459 0.2561996
```

4.4 Preprocessing with Partial Least Square regression (PLS)

This method is used for continous outcome, i.e. out.type = "C".

```
> library(rqt)
> data <- read.table(system.file("extdata/test.cont1.dat",package="rqt"),
+     header = TRUE)
> pheno <- data$pheno
> geno <- data[, 2:dim(data)[2]]
> obj <- rqtClass(phenotype=pheno, genotype=geno)
> res <- rQTest(obj, method="pls", out.type = "C")
> print(res)

Phenotype:
[1] 3.422452 2.457394 2.708564 4.589394 5.461723 4.438707
...

Genotype:
  snp1 snp2 snp3 snp4 snp5 snp6 snp7 snp8 snp9 snp10 snp11 snp12 snp13 snp14
1    0    0    0    1    0    2    1    0    0     0     2     1     2     0
2    1    0    1    0    0    1    0    0    0     0     0     0     1     0
3    0    0    0    0    1    0    0    1    0     1     1     1     0     0
4    0    0    1    0    1    0    0    1    1     0     0     0     1     0
5    0    0    1    1    1    1    1    1    0     1     0     1     0     0
6    0    0    1    1    1    0    0    1    0     1     1     0     1     0
  snp15 snp16 snp17 snp18 snp19 snp20 snp21 snp22 snp23 snp24 snp25 snp26 snp27
1     0     2     1     1     0     0     1     0     0     0     0     2     1
2     0     0     2     1     2     1     0     1     0     0     0     2     1
```

```
3     0     1     1     0     0     1     1     1     0     0     0     1     0
4     0     0     1     0     0     2     0     1     0     0     0     1     0
5     0     0     0     0     0     0     1     0     0     1     0     1     2
6     0     2     0     0     1     0     1     1     0     0     0     2     0
  snp28 snp29 snp30 snp31 snp32 snp33 snp34 snp35 snp36 snp37 snp38 snp39 snp40
1     0     1     0     0     0     0     0     0     1     1     0     0     1
2     1     2     0     0     0     1     2     1     2     0     1     1     0
3     0     0     0     0     0     0     1     1     1     2     2     0     0
4     2     0     0     0     1     2     2     0     1     1     1     1     0
5     0     0     0     0     0     1     1     0     0     1     1     0     0
6     0     0     0     0     0     1     0     1     1     0     0     2     0
  snp41 snp42 snp43 snp44 snp45 snp46 snp47 snp48 snp49 snp50 snp51 snp52 snp53
1     0     0     1     0     0     0     0     1     1     0     0     0     1
2     1     0     0     1     0     0     0     2     0     1     0     1     0
3     0     1     0     1     0     2     1     1     1     0     0     0     1
4     0     0     1     1     0     0     1     1     2     0     1     0     2
5     2     2     0     0     0     1     2     1     0     0     0     0     1
6     1     1     2     0     0     0     1     1     1     0     0     1     1
  snp54 snp55 snp56 snp57 snp58 snp59 snp60 snp61 snp62 snp63 snp64 snp65 snp66
1     1     1     1     1     0     0     0     0     1     1     0     1     1
2     2     1     0     1     0     0     0     1     0     1     2     2     1
3     2     1     0     0     0     0     0     0     0     1     0     0     1
4     1     1     0     0     0     0     2     1     0     1     0     0     2
5     1     1     1     0     0     0     2     1     1     0     0     1     1
6     0     1     1     0     0     0     0     0     0     0     1     2     1
  snp67 snp68 snp69 snp70 snp71 snp72 snp73 snp74 snp75 snp76 snp77 snp78 snp79
1     1     0     1     1     2     1     1     1     0     0     2     1     1
2     1     0     1     0     1     0     0     0     0     1     1     2     1
3     1     0     1     2     1     0     1     1     0     0     0     0     1
4     1     0     0     1     1     1     0     0     0     0     0     1     0
5     0     0     1     1     0     0     1     0     1     0     0     1     0
6     1     0     0     0     0     0     1     1     1     1     1     1     2
  snp80 snp81 snp82 snp83 snp84 snp85 snp86 snp87 snp88 snp89 snp90 snp91 snp92
1     1     0     1     1     0     1     1     0     0     0     1     0     1
2     1     2     0     0     0     1     2     0     2     1     0     0     2
3     1     0     0     0     0     2     0     0     2     0     0     0     0
4     1     2     0     1     0     1     2     0     0     0     0     0     0
5     2     0     1     0     0     2     0     0     0     0     1     0     0
6     1     0     0     1     0     0     0     0     2     0     1     0     0
  snp93 snp94 snp95 snp96 snp97 snp98 snp99 snp100
1     1     0     0     0     1     0     1      1
2     1     0     0     0     0     1     1      2
3     1     1     0     0     1     2     0      0
4     1     0     0     0     1     0     0      0
5     1     0     0     1     1     2     1      1
6     0     0     0     1     1     0     1      1
...

Covariates:
data frame with 0 columns and 0 rows
```

```
Results:

$Qstatistic
         Q1       Q2       Q3
1 0.1910558 71.34471 16.59228

$p.value
       p.Q1         p.Q2       p.Q3
1 0.6620394 1.293491e-05 0.00011429
```

4.5 Preprocessing with Partial Least Square Discriminant Analysis (PLS-DA)

This method of data preprocessing is used for dichotomous outcome.

```
> library(rqt)
> data <- read.table(system.file("extdata/test.bin1.dat",package="rqt"),
+     header=TRUE)
> pheno <- data$pheno
> geno <- data[, 2:dim(data)[2]]
> obj <- rqtClass(phenotype=pheno, genotype=geno)
> res <- rQTest(obj, method="pls", out.type = "D", scale = TRUE)

      R2X(cum) R2Y(cum) Q2(cum) RMSEE pre ort pR2Y pQ2
Total   0.0187    0.301  -0.292   0.2   1   0  0.9 0.9

> print(res)

Phenotype:
[1] 1 1 1 1 1 1
...

Genotype:
  snp1 snp2 snp3 snp4 snp5 snp6 snp7 snp8 snp9 snp10 snp11 snp12 snp13 snp14
1    0    0    0    1    0    2    1    0    0     0     2     1     2     0
2    1    0    1    0    0    1    0    0    0     0     0     0     1     0
3    0    0    0    0    1    0    0    1    0     1     1     1     0     0
4    0    0    1    0    1    0    0    1    1     0     0     0     1     0
5    0    0    1    1    1    1    1    1    0     1     0     1     0     0
6    0    0    1    1    1    0    0    1    0     1     1     0     1     0
  snp15 snp16 snp17 snp18 snp19 snp20 snp21 snp22 snp23 snp24 snp25 snp26 snp27
1     0     2     1     1     0     0     1     0     0     0     0     2     1
2     0     0     2     1     2     1     0     1     0     0     0     2     1
3     0     1     1     0     0     1     1     1     0     0     0     1     0
4     0     0     1     0     0     2     0     1     0     0     0     1     0
5     0     0     0     0     0     0     1     0     0     1     0     1     2
6     0     2     0     0     1     0     1     1     0     0     0     2     0
  snp28 snp29 snp30 snp31 snp32 snp33 snp34 snp35 snp36 snp37 snp38 snp39 snp40
1     0     1     0     0     0     0     0     0     1     1     0     0     1
2     1     2     0     0     0     1     2     1     2     0     1     1     0
3     0     0     0     0     0     0     1     1     1     2     2     0     0
4     2     0     0     0     1     2     2     0     1     1     1     1     0
5     0     0     0     0     0     1     1     0     0     1     1     0     0
```

```
6     0     0     0     0     0     1     0     1     1     0     0     2     0
  snp41 snp42 snp43 snp44 snp45 snp46 snp47 snp48 snp49 snp50 snp51 snp52 snp53
1     0     0     1     0     0     0     0     1     1     0     0     0     1
2     1     0     0     1     0     0     0     2     0     1     0     1     0
3     0     1     0     1     0     2     1     1     1     0     0     0     1
4     0     0     1     1     0     0     1     1     2     0     1     0     2
5     2     2     0     0     0     1     2     1     0     0     0     0     1
6     1     1     2     0     0     0     1     1     1     0     0     1     1
  snp54 snp55 snp56 snp57 snp58 snp59 snp60 snp61 snp62 snp63 snp64 snp65 snp66
1     1     1     1     1     0     0     0     0     1     1     0     1     1
2     2     1     0     1     0     0     0     1     0     1     2     2     1
3     2     1     0     0     0     0     0     0     0     1     0     0     1
4     1     1     0     0     0     0     2     1     0     1     0     0     2
5     1     1     1     0     0     0     2     1     1     0     0     1     1
6     0     1     1     0     0     0     0     0     0     0     1     2     1
  snp67 snp68 snp69 snp70 snp71 snp72 snp73 snp74 snp75 snp76 snp77 snp78 snp79
1     1     0     1     1     2     1     1     1     0     0     2     1     1
2     1     0     1     0     1     0     0     0     0     1     1     2     1
3     1     0     1     2     1     0     1     1     0     0     0     0     1
4     1     0     0     1     1     1     0     0     0     0     0     1     0
5     0     0     1     1     0     0     1     0     1     0     0     1     0
6     1     0     0     0     0     0     1     1     1     1     1     1     2
  snp80 snp81 snp82 snp83 snp84 snp85 snp86 snp87 snp88 snp89 snp90 snp91 snp92
1     1     0     1     1     0     1     1     0     0     0     1     0     1
2     1     2     0     0     0     1     2     0     2     1     0     0     2
3     1     0     0     0     0     2     0     0     2     0     0     0     0
4     1     2     0     1     0     1     2     0     0     0     0     0     0
5     2     0     1     0     0     2     0     0     0     0     1     0     0
6     1     0     0     1     0     0     0     0     2     0     1     0     0
  snp93 snp94 snp95 snp96 snp97 snp98 snp99 snp100
1     1     0     0     0     1     0     1      1
2     1     0     0     0     0     1     1      2
3     1     1     0     0     1     2     0      0
4     1     0     0     0     1     0     0      0
5     1     0     0     1     1     2     1      1
6     0     0     0     1     1     0     1      1
...

Covariates:
data frame with 0 columns and 0 rows


Results:

$Qstatistic
        Q1       Q2       Q3
1 11.12606 2.322913 11.12606

$p.value
          p.Q1         p.Q2         p.Q3
1 0.0008512339 0.0008512339 0.0008512339
```

4.6 Using additional covariates

Quite often, researchers want to supply not only genetic data but also specific covariates, representic some physiological parameters or environment (for example, to evaluate hyphoteses of gene-environment interactions). In such cases, the package `rqt` can accept additional covariates, in form of `N` by `K` matrix, as provided below:

```
> library(rqt)
> data <- read.table(system.file("extdata/test.bin1.dat",package="rqt"),
+     header = TRUE)
> pheno <- data$pheno
> geno <- data[, 2:dim(data)[2]]
> covars <- read.table(system.file("extdata/test.cova1.dat",package="rqt"),
+     header=TRUE)
> obj <- rqtClass(phenotype=pheno, genotype=geno, covariates = covars)
> res <- rQTest(obj, method="pca", out.type = "D")
> print(res)
```

```
Phenotype:
[1] 1 1 1 1 1 1
...

Genotype:
  snp1 snp2 snp3 snp4 snp5 snp6 snp7 snp8 snp9 snp10 snp11 snp12 snp13 snp14
1    0    0    0    1    0    2    1    0    0     0     2     1     2     0
2    1    0    1    0    0    1    0    0    0     0     0     0     1     0
3    0    0    0    0    1    0    0    1    0     1     1     1     0     0
4    0    0    1    0    1    0    0    1    1     0     0     0     1     0
5    0    0    1    1    1    1    1    1    0     1     0     1     0     0
6    0    0    1    1    1    0    0    1    0     1     1     0     1     0
  snp15 snp16 snp17 snp18 snp19 snp20 snp21 snp22 snp23 snp24 snp25 snp26 snp27
1     0     2     1     1     0     0     1     0     0     0     0     2     1
2     0     0     2     1     2     1     0     1     0     0     0     2     1
3     0     1     1     0     0     1     1     1     0     0     0     1     0
4     0     0     1     0     0     2     0     1     0     0     0     1     0
5     0     0     0     0     0     0     1     0     0     1     0     1     2
6     0     2     0     0     1     0     1     1     0     0     0     2     0
  snp28 snp29 snp30 snp31 snp32 snp33 snp34 snp35 snp36 snp37 snp38 snp39 snp40
1     0     1     0     0     0     0     0     0     1     1     0     0     1
2     1     2     0     0     0     1     2     1     2     0     1     1     0
3     0     0     0     0     0     0     1     1     1     2     2     0     0
4     2     0     0     0     1     2     2     0     1     1     1     1     0
5     0     0     0     0     0     1     1     0     0     1     1     0     0
6     0     0     0     0     0     1     0     1     1     0     0     2     0
  snp41 snp42 snp43 snp44 snp45 snp46 snp47 snp48 snp49 snp50 snp51 snp52 snp53
1     0     0     1     0     0     0     0     1     1     0     0     0     1
2     1     0     0     1     0     0     0     2     0     1     0     1     0
3     0     1     0     1     0     2     1     1     1     0     0     0     1
4     0     0     1     1     0     0     1     1     2     0     1     0     2
5     2     2     0     0     0     1     2     1     0     0     0     0     1
6     1     1     2     0     0     0     1     1     1     0     0     1     1
  snp54 snp55 snp56 snp57 snp58 snp59 snp60 snp61 snp62 snp63 snp64 snp65 snp66
1     1     1     1     1     0     0     0     0     1     1     0     1     1
```

```
2     2     1     0     1     0     0     0     1     0     1     2     2     1
3     2     1     0     0     0     0     0     0     0     1     0     0     1
4     1     1     0     0     0     0     2     1     0     1     0     0     2
5     1     1     1     0     0     0     2     1     1     0     0     1     1
6     0     1     1     0     0     0     0     0     0     0     1     2     1
  snp67 snp68 snp69 snp70 snp71 snp72 snp73 snp74 snp75 snp76 snp77 snp78 snp79
1     1     0     1     1     2     1     1     1     0     0     2     1     1
2     1     0     1     0     1     0     0     0     0     1     1     2     1
3     1     0     1     2     1     0     1     1     0     0     0     0     1
4     1     0     0     1     1     1     0     0     0     0     0     1     0
5     0     0     1     1     0     0     1     0     1     0     0     1     0
6     1     0     0     0     0     0     1     1     1     1     1     1     2
  snp80 snp81 snp82 snp83 snp84 snp85 snp86 snp87 snp88 snp89 snp90 snp91 snp92
1     1     0     1     1     0     1     1     0     0     0     1     0     1
2     1     2     0     0     0     1     2     0     2     1     0     0     2
3     1     0     0     0     0     2     0     0     2     0     0     0     0
4     1     2     0     1     0     1     2     0     0     0     0     0     0
5     2     0     1     0     0     2     0     0     0     0     1     0     0
6     1     0     0     1     0     0     0     0     2     0     1     0     0
  snp93 snp94 snp95 snp96 snp97 snp98 snp99 snp100
1     1     0     0     0     1     0     1      1
2     1     0     0     0     0     1     1      2
3     1     1     0     0     1     2     0      0
4     1     0     0     0     1     0     0      0
5     1     0     0     1     1     2     1      1
6     0     0     0     1     1     0     1      1
...

Covariates:
          COV1
1 -0.612463927
2 -0.464158885
3  0.006153597
4 -0.732109468
5 -0.223530136
6 -0.744903822


Results:

$Qstatistic
        Q1       Q2       Q3
1 2.012625 3.761859 2.012625

$p.value
       p.Q1      p.Q2      p.Q3
1 0.1559952 0.8258796 0.2895166
```

5 Meta-analysis

```
> library(rqt)
> data1 <- read.table(system.file("extdata/phengen2.dat",package="rqt"), skip=1)
> obj1 <- rqtClass(phenotype=data1[,1], genotype=data1[, 2:dim(data1)[2]])
> data2 <- read.table(system.file("extdata/phengen3.dat",package="rqt"), skip=1)
> obj2 <- rqtClass(phenotype=data2[,1], genotype=data2[, 2:dim(data2)[2]])
> data3 <- read.table(system.file("extdata/phengen.dat",package="rqt"), skip=1)
> obj3 <- rqtClass(phenotype=data3[,1], genotype=data3[, 2:dim(data3)[2]])
> res.meta <- rQTestMeta(list(obj1, obj2, obj3))
> print(res.meta)

$final.pvalue
[1] 0.004276623

$pvalueList
[1] 0.000858092 0.367634896 0.245240026

$df
[1] 6

$chi.comb
[1] 18.93396
```

6 Session information

```
> sessionInfo()

R version 3.2.4 (2016-03-10)
Platform: x86_64-apple-darwin13.4.0 (64-bit)
Running under: OS X 10.12.1 (unknown)

locale:
[1] C

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

other attached packages:
[1] rqt_0.99.0     ropls_1.2.14   plyr_1.8.4     pls_2.5-0      glmnet_2.0-5
[6] foreach_1.4.3  Matrix_1.2-7.1

loaded via a namespace (and not attached):
[1] CCP_1.1            parallel_3.2.4     tools_3.2.4        Rcpp_0.12.8
[5] codetools_0.2-15   grid_3.2.4         iterators_1.0.8    CompQuadForm_1.4.1
[9] lattice_0.20-34
```

7 References

References

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[2] Li, B. and Leal, S.M. (2008) Methods for Detecting Associations with Rare Vari-ants for Common Diseases: Application to Analysis of Sequence Data. The American Journal of Human Genetics, 83, 311-321.

[3] Liu D., Leal S. (2010) A Novel Adaptive Method for the Analysis of Next-Generation Sequencing Data to Detect Complex Trait Associations with Rare Variants Due to Gene Main Effects and Interactions, PLoS Genet., 6(10).

[4] Madsen, B.E, Browning, S.R. (2009) A Groupwise Association Test for Rare Mutations Using a Weighted Sum Statistic, PLoS Genet., 5(2).

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[6] Tibshirani, R. (1996) Regression shrinkage and selection via the lasso. J. Royal. Statist. Soc B., Vol. 58, No. 1, pages 267-288.