TDT vignette Use of snpStats in family-based studies

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April 26, 2022

Pedigree data

The snpStats package contains some tools for analysis of family-based studies. These assume that a subject support file provides the information necessary to reconstruct pedigrees in the well-known format used in the LINKAGE package. Each line of the support file must contain an identifier of the pedigree to which the individual belongs, together with an identifier of subject within pedigree, and the within-pedigree identifiers for the subject's father and mother. Usually this information, together with phenotype data, will be contained in a dataframe with rownames which link to the rownames of the SnpMatrix containing the genotype data. The following commands read some illustrative data on 3,017 subjects and 43 (autosomal) SNPs¹. The data consist of a dataframe containing the subject and pedigree information (pedData) and a SnpMatrix containing the genotype data (genotypes):

- > require(snpStats)
- > data(families)
- > genotypes

A SnpMatrix with 3017 rows and 43 columns

Row names: id02336 ... id02732 Col names: rs91126 ... rs98918

> head(pedData)

	familyid	${\tt member}$	father	mother	sex	affected
id02336	${\tt fam0005}$	1	NA	NA	1	1
id00695	${\tt fam0005}$	2	NA	NA	2	1
id02750	fam0005	3	1	2	2	2
id01836	fam0005	4	1	2	2	2
id02533	${\tt fam0006}$	1	NA	NA	2	1
id01069	fam0006	2	NA	NA	1	1

¹These data are on a much smaller scale than would arise in genome-wide studies, but serve to illustrate the available tools. Note, however, that execution speeds are quite adequate for genome-wide data.

The first family comprises four individuals: two parents and two sibling offspring. The parents are "founders" in the pedigree, *i.e.* there is no data for their parents, so that their father and mother identifiers are set to NA. This differs from the convention in the LINKAGE package, which would code these as zero. Otherwise coding is as in LINKAGE: sex is coded 1 for male and 2 for female, and disease status (affected) is coded 1 for unaffected and 2 for affected.

Checking for mis-inheritances

The function misinherits counts non-Mendelian inheritances in the data. It returns a logical matrix with one row for each subject who has any mis-inheritances and one column for each SNP which was ever mis-inherited.

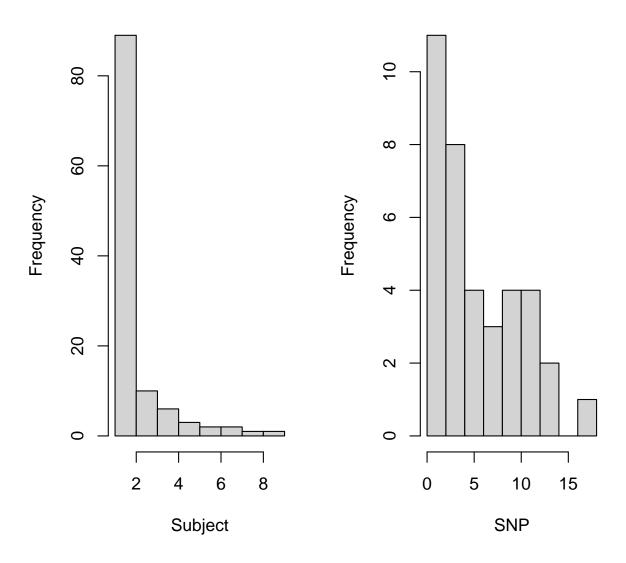
```
> mis <- misinherits(data=pedData, snp.data=genotypes)
> dim(mis)
[1] 114 37
```

Thus, 114 of the subjects and 37 of the SNPs had at least one mis-inheritance. The following commands count mis-inheritances per subject and plot its frequency distribution, and similarly, for mis-inheritances per SNP:

```
> per.subj <- apply(mis, 1, sum, na.rm=TRUE)
> per.snp <- apply(mis, 2, sum, na.rm=TRUE)
> par(mfrow = c(1, 2))
> hist(per.subj,main='Histogram per Subject', xlab='Subject')
> hist(per.snp,main='Histogram per SNP', xlab='SNP')
```

Histogram per Subject

Histogram per SNP



Note that mis-inheritances must be ascribed to offspring, although the error may lie with the parent data. The following commands first extract the pedigree identifiers for mis-inheriting subjects and go on to chart the numbers of mis-inheritances per family:

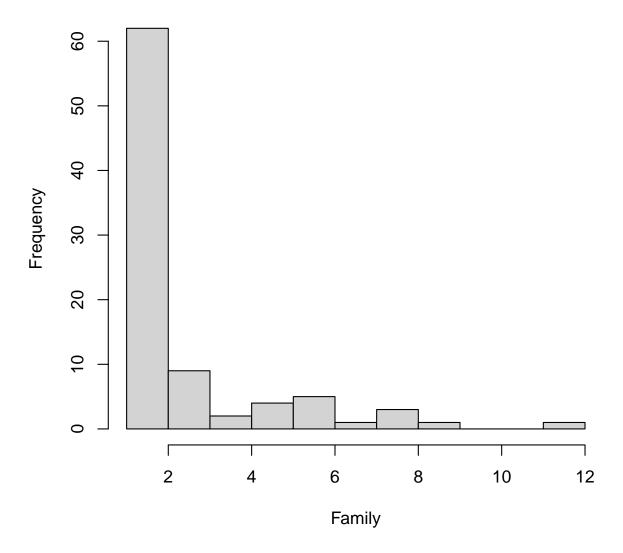
```
> fam <- pedData[rownames(mis), "familyid"]</pre>
```

> per.fam <- tapply(per.subj, fam, sum)</pre>

> par(mfrow = c(1, 1))

> hist(per.fam, main='Histogram per Family', xlab='Family')

Histogram per Family



None of the above analyses suggest serious problems with the data, although there are clearly a few genotyping errors.

TDT tests

At present, the package only allows testing of discrete disease phenotypes in case—parent trios—basically the Transmission/Disequilibrium Test (TDT). This is carried out by the function tdt.snp, which returns the same class of object as that returned by single.snp.tests; allelic (1 df) and genotypic (2 df) tests are computed. The following commands compute

the tests, display the p-values, and plot quantile–quantile plots of the 1 df tests chi-squared statistics:

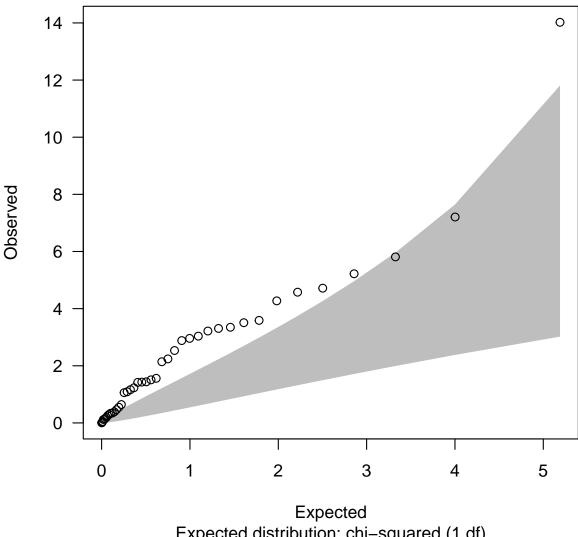
```
> tests <- tdt.snp(data = pedData, snp.data = genotypes)
Analysing 1466 potentially complete trios in 733 different pedigrees
> cbind(p.values.1df = p.value(tests, 1),
        p.values.2df = p.value(tests, 2))
        p.values.1df p.values.2df
rs91126
           0.3034837
                         1.385e-02
rs62927
           0.1113713
                         2.810e-01
rs79960
           0.6942913
                         1.506e-05
rs19348
           0.0895551
                         2.013e-01
                         2.713e-02
rs99786
           0.0072618
rs36984
           0.1434326
                         5.476e-03
           0.9178502
                         2.469e-01
rs52628
rs6699
           0.0001807
                         4.812e-05
rs12373
           0.4590596
                         5.772e-01
                         4.463e-01
rs35215
           0.2115224
rs41229
           0.0159203
                         3.931e-02
rs86267
           0.1344540
                         5.129e-04
rs23261
                         5.535e-03
           0.6174657
rs69208
           0.0854324
                         1.671e-01
rs16483
           0.6603136
                         8.925e-01
rs8558
           0.4961518
                         5.590e-01
rs55762
                         1.913e-01
           0.0689901
rs8124
           0.2336604
                         1.364e-01
rs72056
                         7.391e-02
           0.0298914
rs82369
           0.0813984
                         2.131e-01
rs97686
           0.5612452
                         8.410e-01
rs77065
           0.7236736
                                ΝA
rs53106
           0.9586501
                         5.387e-02
                         8.937e-03
rs37378
           0.2194916
rs83832
           0.8755190
                         8.936e-01
           0.4226781
                         4.597e-01
rs35431
rs61158
           0.5343400
                         5.050e-01
rs32410
           0.0387410
                         5.317e-02
           0.2319977
                         4.759e-01
rs85906
rs83977
           0.2807488
                         2.069e-01
rs24527
           0.2963307
                         3.894e-01
                         9.018e-03
rs73721
           0.0729240
rs36088
           0.0324330
                         3.061e-02
```

```
rs32998
           0.5571397
                        7.510e-01
rs5566
           0.0672924
                        3.919e-02
rs98256
           0.5858278
                        7.995e-01
rs29479
           0.8193228
                        2.904e-01
rs42938
           0.0611009
                        1.147e-05
           0.7280652
                        4.997e-02
rs32018
rs39483
           0.2304232
                        4.391e-03
                        2.496e-01
rs42367
           0.2674484
                        3.507e-02
rs87640
           0.0223276
rs98918
           0.0581770
                        2.983e-04
```

> qq.chisq(chi.squared(tests, 1), df = 1)

N omitted lambda 43.000 0.000 3.401

QQ plot



Expected distribution: chi-squared (1 df)

Since these SNPs were all in a region of known association, the overdispersion of test statistics is not surprising. Note that, because each family had two affected offspring, there were twice as many parent-offspring trios as families. In the above tests, the contribution of the two trios in each family to the test statistic have been assumed to be independent. When there is linkage between the genetic locus and disease trait, this assumption is incorrect and an alternative variance estimate can be used by specifying robust=TRUE in the call. However, in practice, linkage is very rarely strong enough to require this correction.