

TDT vignette

Use of `snpStats` in family-based studies

David Clayton

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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 | member | father | mother | sex | affected |
|---------|----------|--------|--------|--------|-----|----------|
| id02336 | fam0005 | 1 | NA | NA | 1 | 1 |
| id00695 | fam0005 | 2 | NA | NA | 2 | 1 |
| id02750 | fam0005 | 3 | 1 | 2 | 2 | 2 |
| id01836 | fam0005 | 4 | 1 | 2 | 2 | 2 |
| id02533 | 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"]  
> per.fam <- tapply(per.subj, fam, sum)  
> 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 |
| rs99786 | 0.0072618 | 2.713e-02 |
| rs36984 | 0.1434326 | 5.476e-03 |
| rs52628 | 0.9178502 | 2.469e-01 |
| rs6699 | 0.0001807 | 4.812e-05 |
| rs12373 | 0.4590596 | 5.772e-01 |
| rs35215 | 0.2115224 | 4.463e-01 |
| rs41229 | 0.0159203 | 3.931e-02 |
| rs86267 | 0.1344540 | 5.129e-04 |
| rs23261 | 0.6174657 | 5.535e-03 |
| rs69208 | 0.0854324 | 1.671e-01 |
| rs16483 | 0.6603136 | 8.925e-01 |
| rs8558 | 0.4961518 | 5.590e-01 |
| rs55762 | 0.0689901 | 1.913e-01 |
| rs8124 | 0.2336604 | 1.364e-01 |
| rs72056 | 0.0298914 | 7.391e-02 |
| rs82369 | 0.0813984 | 2.131e-01 |
| rs97686 | 0.5612452 | 8.410e-01 |
| rs77065 | 0.7236736 | NA |
| rs53106 | 0.9586501 | 5.387e-02 |
| rs37378 | 0.2194916 | 8.937e-03 |
| rs83832 | 0.8755190 | 8.936e-01 |
| rs35431 | 0.4226781 | 4.597e-01 |
| rs61158 | 0.5343400 | 5.050e-01 |
| rs32410 | 0.0387410 | 5.317e-02 |
| rs85906 | 0.2319977 | 4.759e-01 |
| rs83977 | 0.2807488 | 2.069e-01 |
| rs24527 | 0.2963307 | 3.894e-01 |
| rs73721 | 0.0729240 | 9.018e-03 |
| 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 |
| rs32018 | 0.7280652 | 4.997e-02 |
| rs39483 | 0.2304232 | 4.391e-03 |
| rs42367 | 0.2674484 | 2.496e-01 |
| rs87640 | 0.0223276 | 3.507e-02 |
| rs98918 | 0.0581770 | 2.983e-04 |

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

| | N omitted | lambda |
|--|-----------|-------------|
| | 43.000 | 0.000 3.401 |



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.