Tutorial: Using *GeneticsBase*

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```
> options(width = 90)
```

1 Introduction

This vignette was created as a tutorial for the 2007 BioConductor User's Conference held in Seattle, WA, USA during August 2007, and was presented by Dr. Warnes and Dr. Lazarus. The material is structured as a tutorial with a small example data set (8184 Markers x 180 Subjects belonging to 50 Families) .

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3 Preliminaries

3.1 Install RGenetics packages and depenedencies

For MS-Windows it is necessary to manually install dependencies from CRAN

```
> install.packages(c("xtable", "combinat", "gdata", "gplots", "mvtnorm"),
+     dep = TRUE)
```

Now to install the necessary packages:

```
> repos <- c("http://www.warnes.net/bioc2007/", "http://cran.fhcrc.org")
> install.packages(c("GeneticsBase", "GeneticsDesign", "fbat"), repos = repos,
+     type = "source", dep = TRUE)
```

3.2 Load the libraries

```
> library(GeneticsBase)
> library(GeneticsDesign)
> library(fbat)
```

4 Loading Data

4.1 Read data from files

Load the full data:

```
> hm.a <- readGenes(gfile = "hmCEU_YRI_chr22_ALLfbat.ped", gformat = "fbat")

Reading 8184 markers and 180 subjects from ` hmCEU_YRI_chr22_ALLfbat.ped ' ...
generating 'geneSet' object...

100 200 300 400 500 600 700 800 900 1000
1100 1200 1300 1400 1500 1600 1700 1800 1900 2000
2100 2200 2300 2400 2500 2600 2700 2800 2900 3000
3100 3200 3300 3400 3500 3600 3700 3800 3900 4000
4100 4200 4300 4400 4500 4600 4700 4800 4900 5000
5100 5200 5300 5400 5500 5600 5700 5800 5900 6000
6100 6200 6300 6400 6500 6600 6700 6800 6900 7000
7100 7200 7300 7400 7500 7600 7700 7800 7900 8000
8100 Successfully read the pedigree file ` hmCEU_YRI_chr22_ALLfbat.ped '.

Number of Markers:  8184
Number of Subjects: 180
Number of Families: 50

> print(hm.a)

geneSet object
------------------

Number of Markers:      8184
Number of Observations: 180
```

```
Sample variables: family, pid, father, mother, sex, affected

Genetic data:

                      1334.1 1334.10 1334.11 1334.12 1334.13 1334.2     74.3 77.1 77.2
22_14884399_rs4911642 4/4    4/4     4/4     4/4     4/4     4/4    ... 4/4  4/4  2/4
22_15298335_rs2027653 2/2    2/4     2/4     4/4     2/4     4/4    ... 4/4  2/4  2/2
22_15412698_rs5747620 2/2    2/2     2/2     2/4     2/4     4/4    ... 2/4  2/4  2/2
22_15434720_rs9605903 4/4    4/4     4/4     2/4     4/4     2/4    ... 4/4  4/4  4/4
22_15447504_rs5747968 3/4    4/4     3/4     3/4     4/4     3/4    ... 4/4  4/4  4/4
22_15452483_rs2236639 3/3    3/3     3/3     3/3     3/3     3/3    ... 3/3  3/3  3/3
                       .      .       .       .       .       .      .   .    .    .
                       .      .       .       .       .       .      .   .    .    .
                       .      .       .       .       .       .      .   .    .    .
22_49497339_rs5770820 1/3    <NA>    1/1     3/3     3/3     3/3    ... 3/3  3/3  3/3
22_49498590_rs6010061 2/4    2/2     4/4     2/2     2/2     2/2    ... 2/4  2/4  4/4
22_49510004_rs715586  2/2    2/2     2/2     2/2     2/2     2/2    ... 2/2  2/2  2/2
22_49512530_rs8137951 1/3    1/3     1/1     3/3     3/3     3/3    ... 3/3  1/3  1/3
22_49518559_rs756638  3/3    3/3     3/3     1/3     3/3     3/3    ... 1/3  3/3  1/3
22_49522492_rs3810648 1/1    1/1     1/1     1/1     1/1     1/1    ... 1/3  1/1  1/1
                      77.3 9.1  9.2
22_14884399_rs4911642 2/4  <NA> 2/4
22_15298335_rs2027653 4/4  4/4  4/4
22_15412698_rs5747620 4/4  2/4  4/4
22_15434720_rs9605903 4/4  4/4  4/4
22_15447504_rs5747968 4/4  4/4  4/4
22_15452483_rs2236639 3/3  3/3  3/3
                       .    .    .
                       .    .    .
                       .    .    .
22_49497339_rs5770820 3/3  3/3  3/3
22_49498590_rs6010061 2/4  4/4  4/4
22_49510004_rs715586  2/2  2/2  2/2
22_49512530_rs8137951 1/3  1/1  1/3
22_49518559_rs756638  3/3  1/3  1/3
22_49522492_rs3810648 1/1  1/3  1/1
```

We'll also need just the founders later:

```
> hm.f <- readGenes(gfile = "hmCEU_YRI_chr22_Foundersfbat.ped", gformat = "fbat")
```

```
Reading 8184 markers and 120 subjects from ` hmCEU_YRI_chr22_Foundersfbat.ped ' ...
generating 'geneSet' object...

100 200 300 400 500 600 700 800 900 1000
1100 1200 1300 1400 1500 1600 1700 1800 1900 2000
2100 2200 2300 2400 2500 2600 2700 2800 2900 3000
3100 3200 3300 3400 3500 3600 3700 3800 3900 4000
4100 4200 4300 4400 4500 4600 4700 4800 4900 5000
5100 5200 5300 5400 5500 5600 5700 5800 5900 6000
6100 6200 6300 6400 6500 6600 6700 6800 6900 7000
7100 7200 7300 7400 7500 7600 7700 7800 7900 8000
8100 Successfully read the pedigree file ` hmCEU_YRI_chr22_Foundersfbat.ped '.
```

```
Number of Markers:  8184
Number of Subjects: 120
Number of Families: 50
```

For the purpose of speeding execution of examples, we'll also create a smaller subset of 100 markers from the original file.

```
> hm.a2 <- hm.a[1:100, ]
```

4.2 Error check the loaded data

Count frequencies of missing genotypes (requires 26 seconds on my MacBook Pro)

Number of missing genotypes per subject:

```
> mG <- missGFreq(hm.a2, founderOnly = TRUE, quiet = FALSE)
```

```
converting geneSet object to numerical matrix...
counting frequencies of missing genotypes...
```

```
> head(mG$nMissSubjects)
```

```
         00 0* *0
subject2  3  0  0
subject3  2  0  0
subject4  4  0  0
subject5  0  0  0
subject8  1  0  0
subject9  3  0  0
```

Column headers:

00 missing both alleles

0* 1st allele missing while the 2nd allele is not missing

*0 1st allele is not missing while the 2nd allele is missing

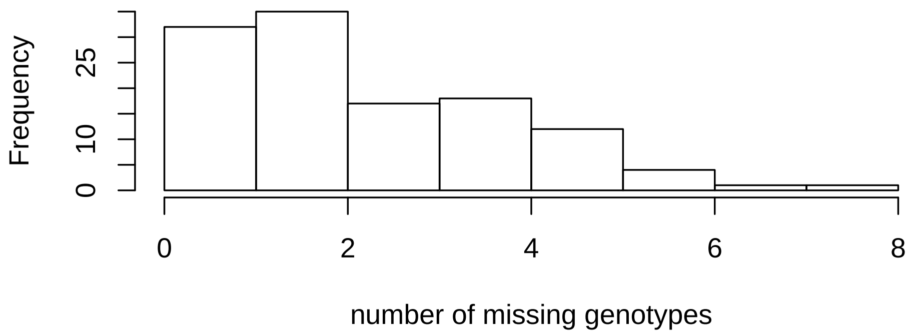
Number of missing genotypes per marker:

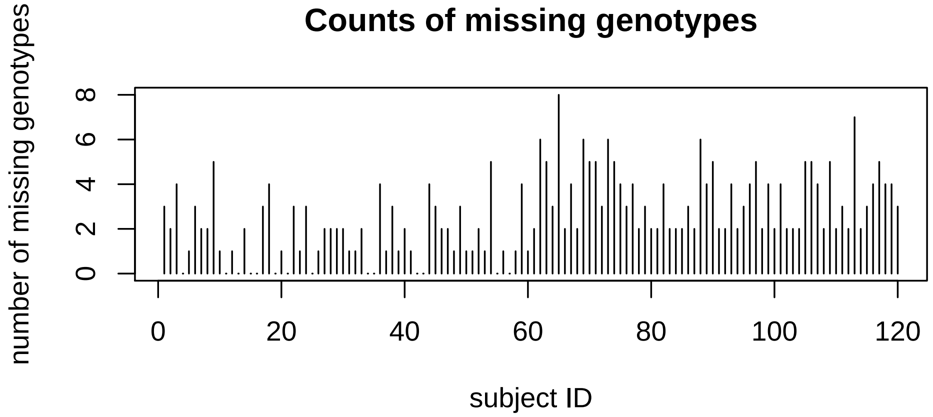
```
> head(mG$nMissMarkers)
```

```
                      00 0* *0
22_14884399_rs4911642 13  0  0
22_15298335_rs2027653  1  0  0
22_15412698_rs5747620  0  0  0
22_15434720_rs9605903  0  0  0
22_15447504_rs5747968  0  0  0
22_15452483_rs2236639  0  0  0
```

Plot counts of missing genotypes:

```
> par(mfrow = c(2, 1))
> hist(mG$nMissSubjects[, 1], main = "", xlab = "number of missing genotypes")
> plot(1:nrow(mG$nMissSubjects), mG$nMissSubjects[, 1], xlab = "subject ID",
+     ylab = "number of missing genotypes", type = "h")
> title("Counts of missing genotypes")
> par(mfrow = c(1, 1))
```





5 Descriptive Statistics

1. Summary of allele/genotyope frequency
2. HWE test
3. Visualize Disequilbrium

Basic data quality checks for markers. Column headings are:

ObsHET observed proportion of heterozygous genotypes per marker

PredHET predicted proportion of heterozygous genotypes per marker

HWpval pvalues of Hardy-Weinberg test per marker

pGeno percentage of non-missing genotypes for markes

MAF minor allele frequencies. missing allele are excluded from calculation

Rating 1 if passes HW test; 0 if failed HW test.

```
> cM <- checkMarkers(hm.a2)
> head(cM)
```

```
                                           Name Position     ObsHET   PredHET     HWpval
22_14884399_rs4911642 22_14884399_rs4911642        ? 0.30841121 0.2608525 0.05930340
22_15298335_rs2027653 22_15298335_rs2027653        ? 0.34453782 0.3892734 0.20997430
22_15412698_rs5747620 22_15412698_rs5747620        ? 0.50000000 0.4994444 0.99027790
22_15434720_rs9605903 22_15434720_rs9605903        ? 0.16666667 0.2061111 0.03604633
22_15447504_rs5747968 22_15447504_rs5747968        ? 0.23333333 0.2665278 0.17246954
22_15452483_rs2236639 22_15452483_rs2236639        ? 0.09166667 0.1171875 0.01704962
                          pGeno       MAF Rating
22_14884399_rs4911642  89.16667 0.1542056      1
22_15298335_rs2027653  99.16667 0.2647059      1
22_15412698_rs5747620 100.00000 0.4833333      1
22_15434720_rs9605903 100.00000 0.1166667      0
22_15447504_rs5747968 100.00000 0.1583333      1
22_15452483_rs2236639 100.00000 0.0625000      0
```

Check Mendelian errors:

```
> cMend <- checkMendelian(hm.a2, quiet = FALSE)
```

```
converting geneSet object to numerical matrix...
checking Mendelian errors ...
checking compatibility ...
```

Number of Mendelian errors per marker:

```
> head(cMend$nMerrMarker)
```

```
22_14884399_rs4911642 22_15298335_rs2027653 22_15412698_rs5747620 22_15434720_rs9605903
                    8                     1                     0                     0
22_15447504_rs5747968 22_15452483_rs2236639
                    0                     0
```

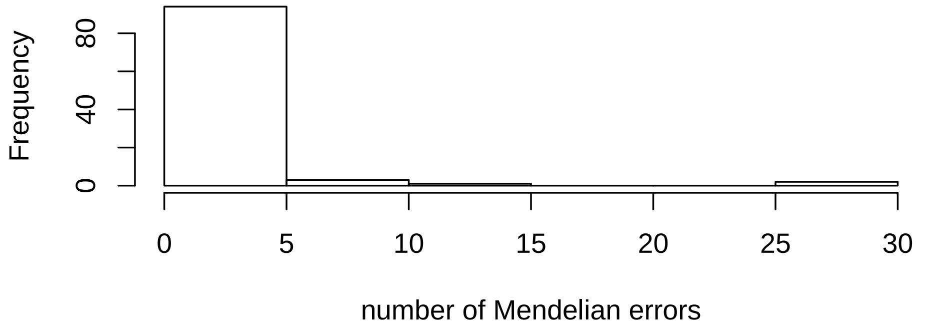
Number of Mendelian errors per family:

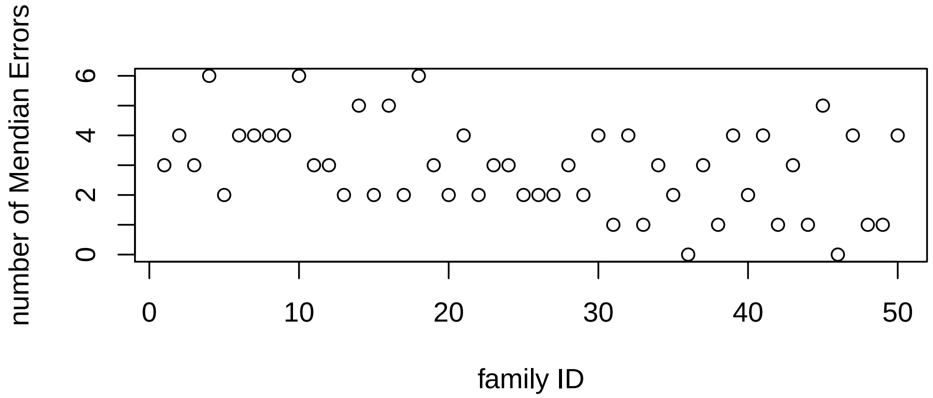
```
> head(cMend$nMerrFamily)
```

```
family1 family2 family3 family4 family5 family6
      3       4       3       6       2       4
```

Plot counts of Mendelian errors

```
> par(mfrow = c(2, 1))
> hist(cMend$nMerrMarker, main = "", xlab = "number of Mendelian errors")
> plot(1:length(cMend$nMerrFamily), cMend$nMerrFamily, xlab = "family ID",
+     ylab = "number of Mendian Errors")
> par(mfrow = c(1, 1))
```





5.1 Summary of allele/genotype frequency based on GeneticsBase functions

Allele summary, including allele counts, allele frequencies, 95% CI of allele frequencies:

```
> t1 <- alleleSummary(hm.a2[1:10])
> t1
```

```
 Gene Marker                  Position Group Allele Count  Freq  CI-Lower CI-Upper
 ALL  22_14884399_rs4911642  ?        ALL   2         48 0.151 0.113    0.192
                                      ALL   4        270 0.849 0.808    0.887

      22_15298335_rs2027653  ?        ALL   2         94 0.264 0.219    0.312
                                      ALL   4        262 0.736 0.688    0.781

      22_15412698_rs5747620  ?        ALL   2        169 0.469 0.417    0.522
                                      ALL   4        191 0.531 0.478    0.583

      22_15434720_rs9605903  ?        ALL   2         43 0.119 0.086    0.153
                                      ALL   4        317 0.881 0.847    0.914
      22_15447504_rs5747968  ?        ALL   3           59 0.164 0.128    0.203
                                      ALL   4          301 0.836 0.797    0.872

      22_15452483_rs2236639  ?        ALL   1           26 0.072 0.047    0.100
                                      ALL   3          334 0.928 0.900    0.953

      22_15455353_rs5747999  ?        ALL   1          225 0.625 0.575    0.675
                                      ALL   2          135 0.375 0.325    0.425

      22_15467656_rs11089263 ?        ALL   1          219 0.608 0.558    0.658
                                      ALL   2          141 0.392 0.342    0.442

      22_15474749_rs2096537  ?        ALL   1           80 0.231 0.188    0.277
                                      ALL   2          266 0.769 0.723    0.812

      22_15479107_rs9604959  ?        ALL   2          249 0.808 0.763    0.851
                                      ALL   4           59 0.192 0.149    0.237

Footer:
          Confidence intervals width is 95%, computed using
          the exact quantiles for the binomial
          distribution.
```

Same for genotypes:

```
> t2 <- genotypeSummary(hm.a2[1:10], founderOnly = TRUE)
> t2
```

```
 Gene Marker                 Position Group Genotype Count  Freq  CI-Lower CI-Upper
 ?    22_14884399_rs4911642  ?        ALL   2/2           0 0.000
                                            2/4          33 0.308 0.224    0.402
                                            4/4          74 0.692 0.598    0.776
                                            NA           13

 ?    22_15298335_rs2027653  ?        ALL   2/2          11 0.092 0.042    0.151
                                            2/4          41 0.345 0.261    0.429
                                            4/4          67 0.563 0.471    0.655
                                            NA            1

 ?    22_15412698_rs5747620  ?        ALL   2/2          28 0.233 0.158    0.308
                                            2/4          60 0.500 0.408    0.592
                                            4/4          32 0.267 0.192    0.350
                                            NA            0

 ?    22_15434720_rs9605903  ?        ALL   2/2           4 0.033 0.008    0.067
                                            2/4          20 0.167 0.100    0.233
                                            4/4          96 0.800 0.725    0.867
                                            NA            0

 ?    22_15447504_rs5747968  ?        ALL   3/3           5 0.042 0.008    0.083
                                            3/4          28 0.233 0.158    0.308
                                            4/4          87 0.725 0.642    0.800
                                            NA            0
```

```
?    22_15452483_rs2236639  ?        ALL   1/1            2 0.017 0.000    0.042
                                           1/3           11 0.092 0.042    0.150
                                           3/3          107 0.892 0.833    0.942
                                           NA             0

?    22_15455353_rs5747999  ?        ALL   1/1           49 0.408 0.325    0.500
                                           1/2           54 0.450 0.358    0.542
                                           2/2           17 0.142 0.083    0.208
                                           NA             0

?    22_15467656_rs11089263 ?        ALL   1/1           46 0.383 0.300    0.475
                                           1/2           52 0.433 0.342    0.525
                                           2/2           22 0.183 0.117    0.258
                                           NA             0

?    22_15474749_rs2096537  ?        ALL   1/1            0 0.000
                                           1/2           51 0.440 0.353    0.534
                                           2/2           65 0.560 0.466    0.647
                                           NA             4

?    22_15479107_rs9604959  ?        ALL   2/2           68 0.642 0.547    0.736
                                           2/4           36 0.340 0.255    0.434
                                           4/4            2 0.019 0.000    0.047
                                           NA            14

Expected Obs-Exp HWE X^2 P-value
2.544    -2.544  3.557   0.0626
27.911   5.089
76.544   -2.544


8.338    2.662   1.572   0.228
46.324   -5.324
64.338   2.662


28.033   -0.033  0.000   1
59.933   0.067
32.033   -0.033


1.633    2.367   4.395   0.0623
24.733   -4.733
93.633   2.367


3.008    1.992   1.861   0.302
31.983   -3.983
85.008   1.992
```

```
 0.469    1.531   5.691   0.0499
 14.062   -3.062
 105.469  1.531


 48.133   0.867   0.116   0.847
 55.733   -1.733
 16.133   0.867


 43.200   2.800   1.134   0.34
 57.600   -5.600
 19.200   2.800


 5.606    -5.606  9.210   0.0041
 39.789   11.211
 70.606   -5.606


 69.774   -1.774  1.266   0.354
 32.453   3.547
 3.774    -1.774


Footer:
          Confidence intervals width is 95%, computed using
          the exact quantiles for the binomial
          distribution. As the true distribution is
          multinomial this is only approximately correct.
```

HWE test:

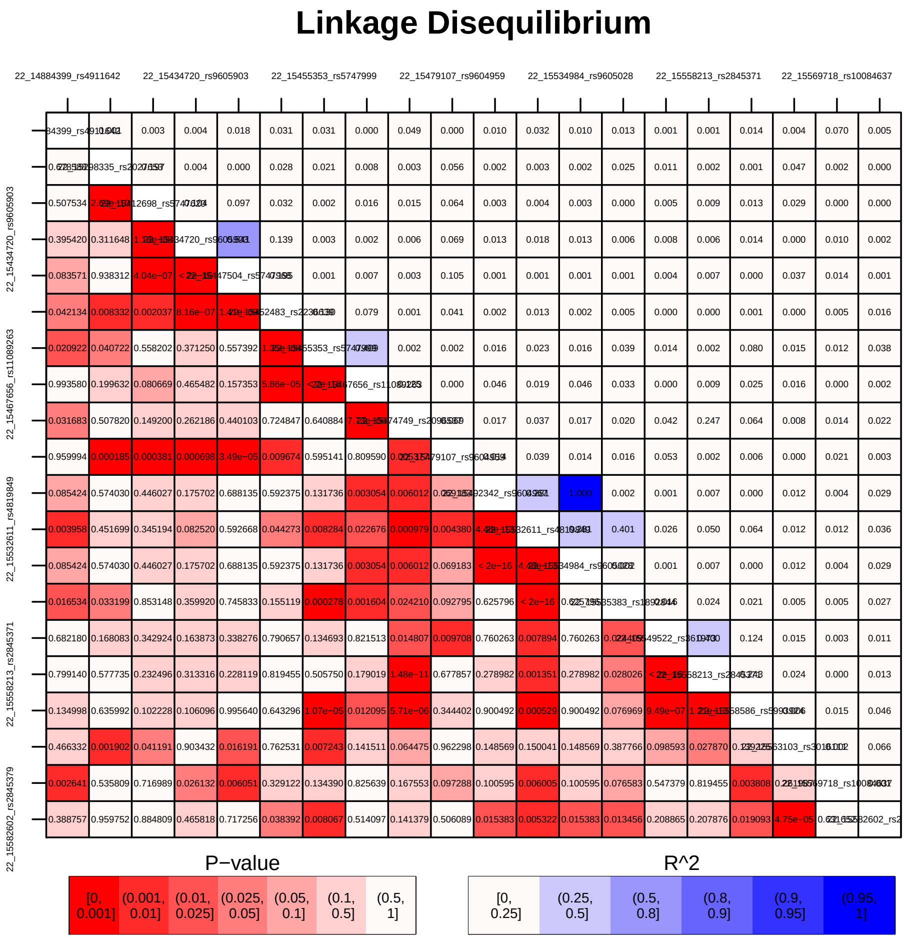
```
> hwe <- HWE(hm.a2[1:10])
> hwe
```

```
[[1]]
[1] "diseq"

$call
HWE(object = hm.a2[1:10])

$D
                                Est        2.5%        97.5%   n      P-value
22_14884399_rs4911642   0.022783909  0.01427950 0.0344230845 159 2.602556e-02
22_15298335_rs2027653  -0.025785886 -0.05345758 0.0051129908 178 8.267860e-02
22_15412698_rs5747620  -0.001844136 -0.03876543 0.0338271605 180 1.000000e+00
22_15434720_rs9605903  -0.019066358 -0.04061728 0.0011111111 180 2.387117e-02
22_15447504_rs5747968  -0.023140432 -0.05073302 0.0002777778 180 2.881018e-02
22_15452483_rs2236639  -0.005895062 -0.02036265 0.0048225309 180 2.254611e-01
22_15455353_rs5747999   0.012847222 -0.01906636 0.0456790123 180 5.265022e-01
22_15467656_rs11089263 -0.018819444 -0.05111111 0.0145138889 180 2.780714e-01
```

```
22_15474749_rs2096537   0.053459855  0.03749708 0.0722459822 173 7.796707e-06
22_15479107_rs9604959   0.010720611 -0.01045708 0.0315504301 154 6.010626e-01

$`D'`
                                Est       2.5%       97.5%   n      P-value
22_14884399_rs4911642   0.177777778  0.1357143 0.227799228 159 2.602556e-02
22_15298335_rs2027653  -0.369850611 -0.7977528 0.026923077 178 8.267860e-02
22_15412698_rs5747620  -0.008368054 -0.1840108 0.135576447 180 1.000000e+00
22_15434720_rs9605903  -1.336398053 -2.8939968 0.012500000 180 2.387117e-02
22_15447504_rs5747968  -0.861534042 -1.8195087 0.002178649 180 2.881018e-02
22_15452483_rs2236639  -1.130177515 -4.0000000 0.074626866 180 2.254611e-01
22_15455353_rs5747999   0.054814815 -0.1458333 0.196013289 180 5.265022e-01
22_15467656_rs11089263 -0.122679946 -0.3568736 0.060915185 180 2.780714e-01
22_15474749_rs2096537   0.300751880  0.2401434 0.367588933 173 7.796707e-06
22_15479107_rs9604959   0.069226057 -0.2819979 0.201709296 154 6.010626e-01

$r
                                Est         2.5%       97.5%   n      P-value
22_14884399_rs4911642  -0.177777778 -0.227799228 -0.13571429 159 2.602556e-02
22_15298335_rs2027653   0.132694494 -0.026923077  0.27663280 178 8.267860e-02
22_15412698_rs5747620   0.007404195 -0.135576447  0.15545129 180 1.000000e+00
22_15434720_rs9605903   0.181277969 -0.012500000  0.36507937 180 2.387117e-02
22_15447504_rs5747968   0.168872121 -0.002178649  0.34864850 180 2.881018e-02
22_15452483_rs2236639   0.087977890 -0.074626866  0.28742577 180 2.254611e-01
22_15455353_rs5747999  -0.054814815 -0.196013289  0.08349715 180 5.265022e-01
22_15467656_rs11089263  0.078985718 -0.060915185  0.21855922 180 2.780714e-01
22_15474749_rs2096537  -0.300751880 -0.367588933 -0.24014337 173 7.796707e-06
22_15479107_rs9604959  -0.069226057 -0.201709296  0.06563078 154 6.010626e-01

$`X^2`
                                Est 2.5% 97.5%   n      P-value
22_14884399_rs4911642  0.0316049383   NA    NA 159 2.602556e-02
22_15298335_rs2027653  0.0176078288   NA    NA 178 8.267860e-02
22_15412698_rs5747620  0.0000548221   NA    NA 180 1.000000e+00
22_15434720_rs9605903  0.0328617022   NA    NA 180 2.387117e-02
22_15447504_rs5747968  0.0285177933   NA    NA 180 2.881018e-02
22_15452483_rs2236639  0.0077401092   NA    NA 180 2.254611e-01
22_15455353_rs5747999  0.0030046639   NA    NA 180 5.265022e-01
22_15467656_rs11089263 0.0062387437   NA    NA 180 2.780714e-01
22_15474749_rs2096537  0.0904516931   NA    NA 173 7.796707e-06
22_15479107_rs9604959  0.0047922469   NA    NA 154 6.010626e-01
```

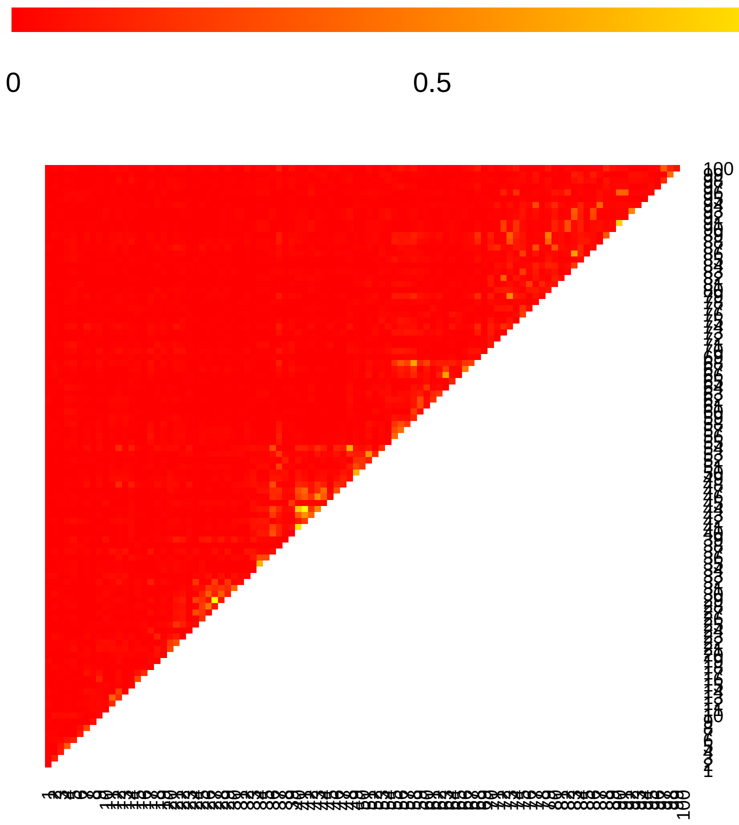
Defatult graphical display of LD:

```
> ld.small <- LD(hm.a2[1:20])
> plot(ld.small)
```



Alternative graphical display of LD:

```
> ld <- LD(hm.a2)
> LDView(ld@"X^2")
```



6 Hypothesis Testing

6.1 Armitage test

For the following examples, suppose 'A' is the minor allele, and 'a' is the major allele.

Armitage test using additive model to code genotype:

genotype	coding
AA	2
Aa	1
aa	0

```
> res.A <- Armitage(hm.a2, method = "A")
> head(res.A)

                              stat       pvalue
22_14884399_rs4911642  4.38726430 3.620837e-02
22_15298335_rs2027653  8.62689991 3.312348e-03
22_15412698_rs5747620  0.01107079 9.162030e-01
22_15434720_rs9605903 34.00571358 5.495048e-09
22_15447504_rs5747968 35.11899027 3.101613e-09
22_15452483_rs2236639  2.43861135 1.183810e-01
```

Armitage test using recessive model to code genotype:

genotype	coding
AA	1
Aa	0
aa	0

```
> res.R <- Armitage(hm.a2, method = "R")
> head(res.R)
```

```
                              stat      pvalue
22_14884399_rs4911642           NA          NA
22_15298335_rs2027653 1.6258677 0.202275552
22_15412698_rs5747620 0.1285714 0.719917853
22_15434720_rs9605903 6.2068966 0.012725353
22_15447504_rs5747968 9.4736842 0.002084403
22_15452483_rs2236639 0.0000000 1.000000000
```

Armitage test using dominant model to code genotype:

genotype	coding
AA	1
Aa	1
aa	0

```
> res.D <- Armitage(hm.a2, method = "D")
> head(res.D)
```

```
                               stat       pvalue
22_14884399_rs4911642  4.3872643 3.620837e-02
22_15298335_rs2027653 10.0936094 1.487844e-03
22_15412698_rs5747620  0.2462380 6.197365e-01
22_15434720_rs9605903 37.0478170 1.152676e-09
22_15447504_rs5747968 35.8892308 2.088600e-09
22_15452483_rs2236639  3.0769231 7.941063e-02
```

6.2 Logistic regression

First, we need to construct some synthetic covariates on the founders

```
> sampleInfo(hm.f)$race <- sampleInfo(hm.f)$affected
> raceval <- sampleInfo(hm.f)$race - 1
> sampleInfo(hm.f)$Norm0.0 <- rnorm(nobs(hm.f), mean = 0 * raceval)
> sampleInfo(hm.f)$Norm0.5 <- rnorm(nobs(hm.f), mean = 0.5 * raceval)
> sampleInfo(hm.f)$Norm1.0 <- rnorm(nobs(hm.f), mean = 1 * raceval)
> sampleInfo(hm.f)$Norm1.5 <- rnorm(nobs(hm.f), mean = 1.5 * sampleInfo(hm.f)$race)
> doSample <- function(raceval, mult) {
+     prob <- c(0.33 - raceval * mult, 0.33 + (raceval * mult)/2, 0.33 +
+         (raceval * mult)/2)
+     factor(sample(x = c("Red", "Green", "Blue"), size = 1, p = prob,
+         rep = T))
+ }
> sampleInfo(hm.f)$Cat0.0 <- sapply(raceval, doSample, mult = 0)
> sampleInfo(hm.f)$Cat0.1 <- sapply(raceval, doSample, mult = 0.1)
> sampleInfo(hm.f)$Cat0.2 <- sapply(raceval, doSample, mult = 0.2)
> sampleInfo(hm.f)$Cat0.3 <- sapply(raceval, doSample, mult = 0.3)
```

Now, construct a function to fit the regression model and return the parameters and statistics that are of interest.

```
model <- function( markerName )
  {
    # extract requested genetic marker
    genotype <- genotypes(hm.f,marker=markerName)

    # get data frame to use for fitting the model
    mframe <- model.frame(race ~ sex + Norm0.0 + Norm0.5 + Norm1.0 + Norm1.5 + genotype,
                          data=sampleInfo(hm.f) )

    # To test significance of a term, best method is to do anova of
    # the full model against a submodel omitting the particular term.
    # This avoids issues with changes in names of factor levels,
    # presence or absence of covaraiates, etc.
    result <- try(
                  {
  fit.with    <- glm( race==1 ~ sex + Norm0.0 + Norm0.5 + Norm1.0 + Norm1.5 + as.factor(genotype),
                     data=mframe, family="binomial")
  fit.without <- glm( race==1 ~ sex + Norm0.0 + Norm0.5 + Norm1.0 + Norm1.5,
                     data=mframe, family="binomial")
                    anova(fit.with, fit.without, test="Chisq")$"P(>|Chi|)"[2]
                  }
                  )

    if(class(result)=="try-error")
      return(NA)  # or return(result) to see the error messages
    else

      result # full result.  Usually we want to specify exactly which
             # parameters and stats get returned so the format is consistent
             # across all markers.
  }
```

```
> model <- function(markerName) {
+     genotype <- genotypes(hm.f, marker = markerName)
+     mframe <- model.frame(race ~ sex + Norm0.0 + Norm0.5 + Norm1.0 +
+         Norm1.5 + genotype, data = sampleInfo(hm.f))
+     result <- try({
+         fit.with <- glm(race == 1 ~ sex + Norm0.0 + Norm0.5 + Norm1.0 +
+             Norm1.5 + as.factor(genotype), data = mframe, family = "binomial")
+         fit.without <- glm(race == 1 ~ sex + Norm0.0 + Norm0.5 + Norm1.0 +
+             Norm1.5, data = mframe, family = "binomial")
+         anova(fit.with, fit.without, test = "Chisq")$"P(>|Chi|)"[2]
+     })
+     if (class(result) == "try-error")
+         return(NA)
+     else result
+ }
```

Fit to a subset of 50, then 100 and use this information to compute the expected run time for all markers:

```
> t1 <- unix.time(fits <- sapply(markerNames(hm.f)[1:50], model))[3]
> t1
```

```
elapsed
   3.11
```

(This takes 5.365 seconds on my MacBook Pro, R 2.4.1)

```
> t2 <- unix.time(fits <- sapply(markerNames(hm.f)[1:100], model))[3]
> t2
```

```
elapsed
   6.07
```

(This takes 11.878 seconds on my MacBook Pro, R 2.4.1)

Estimate total time to complete, in minutes

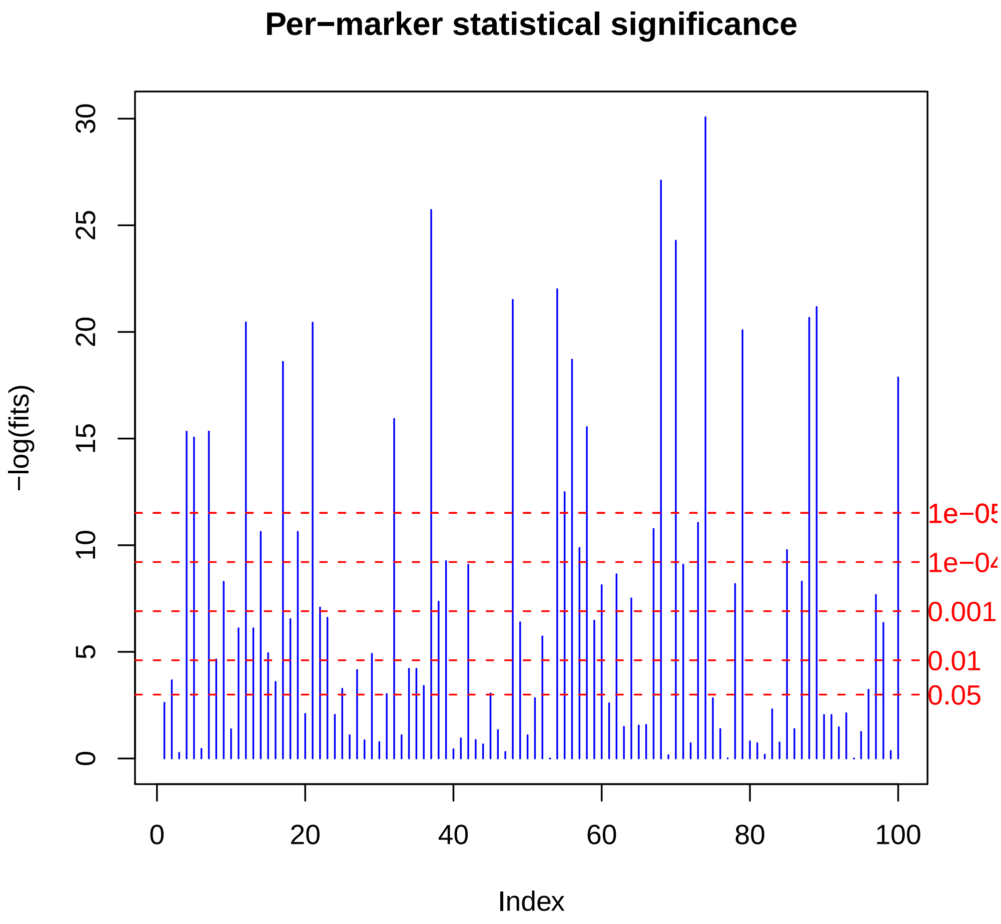
```
> t1 + (t2 - t1)/50 * (nmarker(hm.f) - 50)/60
```

```
 elapsed
11.13555
```

(This yields 23.02 minutes on my MacBook Pro, R 2.4.1)

Plot the p-values for the first 100 markers

```
> fits.sorted <- sort(fits)
> plot(-log(fits), type = "h", col = "blue")
> labels <- c(0.05, 0.01, 0.001, 1e-04, 1e-05, 1e-05)
> abline(h = -log(labels), lty = 2, col = "red")
> mtext(text = as.character(labels), side = 4, at = -log(labels), col = "red",
+     las = 1)
> title("Per-marker statistical significance")
```



6.3 Family-Based Associaton Test ('fbat')

Do the fbat calculations:

```
> f <- fbat(hm.a2)
```

Show the p-values:

```
> summaryPvalue(f)
```

```
****************************
                             chisq rank     pvalue
22_14884399_rs4911642  1.66666667    1 0.19670560
22_15298335_rs2027653  0.06666667    1 0.79625341
22_15412698_rs5747620  0.57142857    1 0.44969180
22_15434720_rs9605903  1.00000000    1 0.31731051
22_15447504_rs5747968  1.00000000    1 0.31731051
22_15452483_rs2236639  0.00000000    1 1.00000000
22_15455353_rs5747999  1.05882353    1 0.30348366
22_15467656_rs11089263 4.50000000    1 0.03389485
22_15474749_rs2096537  0.75757576    1 0.38408825
```

```
22_15479107_rs9604959  2.77777778    1 0.09558070
22_15492342_rs9604967  1.00000000    1 0.31731051
22_15532611_rs4819849  1.00000000    1 0.31731051
22_15534984_rs9605028  1.00000000    1 0.31731051
22_15535383_rs1892844  0.00000000    0 0.00000000
22_15549522_rs361973   0.80645161    1 0.36917142
22_15558213_rs2845371  0.04761905    1 0.82725935
22_15558586_rs5993924  0.20000000    1 0.65472085
22_15563103_rs3016111  0.00000000    0 0.00000000
22_15569718_rs10084637 0.69230769    1 0.40538056
22_15582602_rs2845379  4.16666667    1 0.04122683
22_15583103_rs2845380  0.00000000    0 0.00000000
22_15594252_rs2845346  0.00000000    1 1.00000000
22_15608796_rs17433377 0.00000000    0 0.00000000
22_15634399_rs2190742  1.08695652    1 0.29714653
22_15636231_rs5748614  3.76923077    1 0.05220364
22_15644565_rs5748622  3.57142857    1 0.05878172
22_15644904_rs9605145  3.57142857    1 0.05878172
22_15645124_rs5748623  3.60000000    1 0.05777957
22_15645194_rs9605146  5.14285714    1 0.02334220
22_15647006_rs759235   0.60000000    1 0.43857803
22_15649076_rs2108585  2.90909091    1 0.08808151
22_15653728_rs9606468  0.00000000    1 1.00000000
22_15655394_rs5748636  0.36000000    1 0.54850624
22_15658762_rs4819535  0.69230769    1 0.40538056
22_15660822_rs5748648  0.69230769    1 0.40538056
22_15661931_rs738045   0.60000000    1 0.43857803
22_15665949_rs2385714  0.00000000    0 0.00000000
22_15668988_rs2072467  0.00000000    0 0.00000000
22_15669118_rs2072466  1.00000000    1 0.31731051
22_15674251_rs7291429  0.00000000    1 1.00000000
22_15681217_rs874835   0.03703704    1 0.84738966
22_15681843_rs874836   2.46153846    1 0.11666446
22_15684246_rs175139   2.46153846    1 0.11666446
22_15684887_rs983305   0.03703704    1 0.84738966
22_15686104_rs175140   0.66666667    1 0.41421618
22_15690741_rs175149   1.28571429    1 0.25683926
22_15692596_rs9606481  0.61538462    1 0.43276758
22_15695102_rs17363716 0.00000000    0 0.00000000
22_15695503_rs165757   0.11764706    1 0.73160059
22_15697233_rs175152   0.80645161    1 0.36917142
22_15698150_rs165611   0.92592593    1 0.33592381
22_15699156_rs165778   1.00000000    1 0.31731051
22_15706181_rs165810   0.00000000    0 0.00000000
22_15706432_rs2075120  0.00000000    0 0.00000000
22_15775610_rs737936   1.00000000    1 0.31731051
22_15776612_rs7288841  0.00000000    0 0.00000000
22_15777875_rs9606534  2.00000000    1 0.15729921
22_15778508_rs7292561  3.00000000    1 0.08326452
22_15778800_rs7293026  0.80645161    1 0.36917142
22_15778812_rs13058496 3.00000000    1 0.08326452
```

```
22_15779211_rs8136206  0.80000000    1 0.37109337
22_15785173_rs759081   1.00000000    1 0.31731051
22_15787349_rs5992587  1.80000000    1 0.17971249
22_15787566_rs11703901 2.66666667    1 0.10247043
22_15789897_rs12485066 3.00000000    1 0.08326452
22_15790373_rs5748744  3.85714286    1 0.04953461
22_15791899_rs9306242  3.24000000    1 0.07186064
22_15792216_rs9605179  4.00000000    1 0.04550026
22_15792806_rs5992590  0.61538462    1 0.43276758
22_15794103_rs5994097  2.13043478    1 0.14439979
22_15794640_rs9618937  0.50000000    1 0.47950012
22_15795572_rs5748748  0.69230769    1 0.40538056
22_15806401_rs5748755  2.66666667    1 0.10247043
22_15807037_rs2385785  2.00000000    1 0.15729921
22_15809384_rs1981707  5.53846154    1 0.01860293
22_15809434_rs1981708  1.60000000    1 0.20590321
22_15813210_rs4819923  2.46153846    1 0.11666446
22_15813888_rs5994105  0.40000000    1 0.52708926
22_15814084_rs5748760  1.00000000    1 0.31731051
22_15816846_rs2385786  0.12500000    1 0.72367361
22_15821524_rs5994110  1.00000000    1 0.31731051
22_15822154_rs17733785 0.33333333    1 0.56370286
22_15823131_rs7287116  0.20000000    1 0.65472085
22_15825502_rs5748765  0.03030303    1 0.86180443
22_15826157_rs1541529  0.00000000    0 0.00000000
22_15826914_rs5748766  0.81818182    1 0.36571230
22_15830515_rs2041607  0.69230769    1 0.40538056
22_15832966_rs757630   0.00000000    0 0.00000000
22_15842185_rs4819932  1.00000000    1 0.31731051
22_15847411_rs4819934  0.22222222    1 0.63735189
22_15847684_rs4819936  0.22222222    1 0.63735189
22_15850779_rs9618954  1.60000000    1 0.20590321
22_15855921_rs2399152  2.27272727    1 0.13166802
22_15868195_rs5748798  0.00000000    0 0.00000000
22_15869577_rs7291404  0.06666667    1 0.79625341
22_15869890_rs11913227 0.18181818    1 0.66981536
22_15870932_rs5994128  0.14285714    1 0.70545699
22_15872203_rs5994129  1.50000000    1 0.22067136
22_15872452_rs917838   0.18181818    1 0.66981536
22_15872533_rs2192155  0.00000000    0 0.00000000
***************************
```

Look at the fit details for a specific marker:

```
> viewstat(f, "22_14884399_rs4911642")
```

```
****************************************
50  pedigree  180  persons
13  informative families at marker  22_14884399_rs4911642
The alleles of marker  22_14884399_rs4911642  >>
[1] 1 2
Score for marker  22_14884399_rs4911642  >>
[1]  5 21
```

```
Expected score for marker  22_14884399_rs4911642  >>
[1]  7.5 18.5
Covariance matrix of the score for marker  22_14884399_rs4911642  >>
      [,1]  [,2]
[1,]  3.75 -3.75
[2,] -3.75  3.75
Moore-Penrose generalized inverse of covariance matrix
            [,1]        [,2]
[1,]  0.06666667 -0.06666667
[2,] -0.06666667  0.06666667
test statistics for marker  22_14884399_rs4911642  >>
    chisq      rank    pvalue
1.6666667 1.0000000 0.1967056
*****************************************
```

7 Study planning tools (GeneticsDesign package)

7.1 Power to detect a low-frequencty allele

Compute the probability of missing an allele with frequency 0.15 when 20 genotypes are sampled:

```
> gregorius(freq = 0.15, N = 20)

$call
gregorius(freq = 0.15, N = 20)

$method
[1] "Compute missprob given N and freq"

$freq
[1] 0.15

$N
[1] 20

$missprob
[1] 0.1938351
```

Determine what sample size is required to observe all alleles with true frequency 0.15 with probability 0.95

```
> gregorius(freq = 0.15, missprob = 1 - 0.95)

$call
gregorius(freq = 0.15, missprob = 1 - 0.95)

$method
[1] "Determine minimal N given missprob and freq"

$freq
[1] 0.15

$N
```

```
[1] 29

$missprob
[1] 0.04520557
```

7.2 Power for a genetics study using a quantitative outcome

Calculate power for genetics study using a quantitative outcome:

```
> GeneticPower.Quantitative.Numeric(N = 50, freq = 0.1, minh = "recessive",
+     alpha = 0.05)
```

```
[1] 0.0600883
```

```
> GeneticPower.Quantitative.Factor(N = 50, freq = 0.1, minh = "recessive",
+     alpha = 0.05)
```

```
[1] 0.08666032
```

For a range of sample sizes:

```
> power.range <- function(N, ...) {
+     sapply(N, function(n) GeneticPower.Quantitative.Numeric(N = n, ...))
+ }
> power.range(N = c(25, 50, 100, 200, 500), freq = 0.1, minh = "recessive",
+     alpha = 0.05)
```

```
[1] 0.05492509 0.06008830 0.07049383 0.09160716 0.15665828
```

Create a power table:

```
> fun <- function(p) power.range(freq = p, N = seq(100, 1000, by = 100),
+     alpha = 0.05, minh = "recessive")
> m <- sapply(X = seq(0.1, 0.9, by = 0.1), fun)
> colnames(m) <- seq(0.1, 0.9, by = 0.1)
> rownames(m) <- seq(100, 1000, by = 100)
> print(round(m, 2))
```

```
      0.1  0.2  0.3  0.4  0.5  0.6  0.7  0.8  0.9
100  0.07 0.20 0.47 0.76 0.93 0.98 0.99 0.99 0.97
200  0.09 0.35 0.77 0.97 1.00 1.00 1.00 1.00 1.00
300  0.11 0.49 0.91 1.00 1.00 1.00 1.00 1.00 1.00
400  0.13 0.61 0.97 1.00 1.00 1.00 1.00 1.00 1.00
500  0.16 0.70 0.99 1.00 1.00 1.00 1.00 1.00 1.00
600  0.18 0.78 1.00 1.00 1.00 1.00 1.00 1.00 1.00
700  0.20 0.84 1.00 1.00 1.00 1.00 1.00 1.00 1.00
800  0.22 0.88 1.00 1.00 1.00 1.00 1.00 1.00 1.00
900  0.24 0.92 1.00 1.00 1.00 1.00 1.00 1.00 1.00
1000 0.27 0.94 1.00 1.00 1.00 1.00 1.00 1.00 1.00
```

7.3 Power calculator for genetic linear trend association studies.

The power is for the test that disease is associated with a marker, given high risk allele frequency ('A'), disease prevalence, genotype relative risk ('Aa'), genotype relative risk ('AA'), LD measure (D' or R^2), marker allele frequency ('B'), number of cases, control:case ratio, and probability of the Type I error. The linear trend test (Cochran 1954; Armitage 1955) is used.

Using R^2 as the measuer of LD:

```
> res1 <- GPC(pA = 0.05, pD = 0.1, RRAa = 1.414, RRAA = 2, r2 = 0.9, pB = 0.06,
+     nCase = 500, ratio = 1, alpha = 0.05, quiet = FALSE)

 Case-control parameters>>
                                         [,1]
Number of cases                  500.00000000
Number of controls               500.00000000
High risk allele frequency (A)     0.05000000
Prevalence                         0.10000000
Genotypic relative risk Aa         1.41400000
Genotypic relative risk AA         2.00000000
Genotypic risk for aa (baseline)   0.09598495

 Marker locus B>>
                                       [,1]
High risk allele frequency (B)   0.06000000
Linkage disequilibrium (D')      0.99723021
Penetrance at marker genotype bb 0.09599596
Penetrance at marker genotype Bb 0.12902094
Penetrance at marker genotype BB 0.17344738
Genotypic odds ratio Bb          1.39498627
Genotypic odds ratio BB          1.97612611

 Expected allele frequencies>>
       Case    Control
B 0.07901192 0.05788756
b 0.92098808 0.94211244

 Expected genotype frequencies>>
          Case     Control
BB 0.006244106 0.003306210
Bb 0.145535624 0.109162708
bb 0.848220271 0.887531081

 Case-control statistics>>
 Alpha      Power
 0.100 0.58900688
 0.050 0.46393515
 0.010 0.23992694
 0.001 0.07762229
 0.050 0.46393515

 power (alpha= 0.05 )= 0.4639352  ncp= 3.494199
```

Using D' as the measure of LD:

```
> res2 <- GPC.default(pA = 0.05, pD = 0.1, RRAa = 1.414, RRAA = 2, Dprime = 0.9,
+     pB = 0.06, nCase = 500, ratio = 1, alpha = 0.05, quiet = FALSE)

 Case-control parameters>>
                                         [,1]
Number of cases                  500.00000000
Number of controls               500.00000000
```

```
High risk allele frequency (A)     0.05000000
Prevalence                         0.10000000
Genotypic relative risk Aa         1.41400000
Genotypic relative risk AA         2.00000000
Genotypic risk for aa (baseline)   0.09598495

 Marker locus B>>
                                       [,1]
High risk allele frequency (B)   0.06000000
Linkage disequilibrium (D')      0.90000000
Penetrance at marker genotype bb 0.09638274
Penetrance at marker genotype Bb 0.12624798
Penetrance at marker genotype BB 0.16539976
Genotypic odds ratio Bb          1.35463248
Genotypic odds ratio BB          1.85798248

 Expected allele frequencies>>
        Case    Control
B 0.07715825 0.05809353
b 0.92284175 0.94190647

 Expected genotype frequencies>>
          Case     Control
BB 0.005954391 0.003338401
Bb 0.142407718 0.109510254
bb 0.851637891 0.887151345

 Case-control statistics>>
 Alpha      Power
 0.100 0.52110203
 0.050 0.39631201
 0.010 0.18968278
 0.001 0.05549084
 0.050 0.39631201

 power (alpha= 0.05 )= 0.396312  ncp= 2.878885
```

The End.