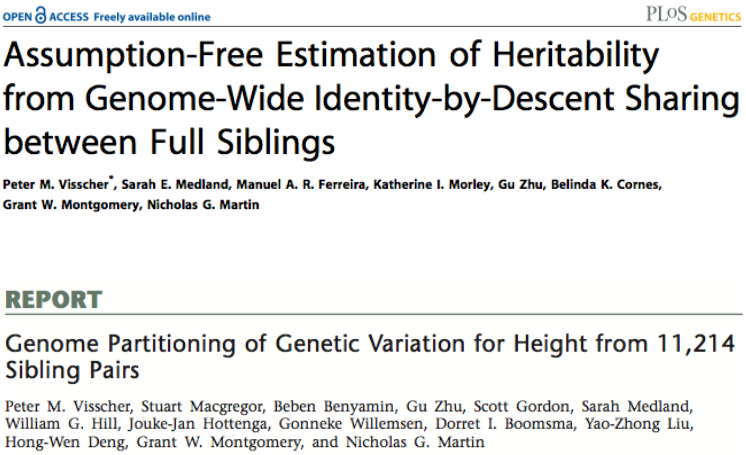
Practical 2 - Estimating genetic variance within families

In this practical we will be using the QTDT software from <http://csg.sph.umich.edu/abecasis/QTDT/> (Abecasis et al., 2000). This software was developed for family based tests of linkage disequilibrium between a marker and a complex trait (i.e., family based association mapping). We will use it to estimate variance components where our marker is the whole genome or a chromosome.

Data

The data used today is real family data and was used in the following studies Visscher et al. (2006) and Visscher et al. (2007). If you are interested take a quick look at these papers and look at the data and conclusions made.



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Assumption-Free Estimation of Heritability from Genome-Wide Identity-by-Descent Sharing between Full Siblings

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REPORT

Genome Partitioning of Genetic Variation for Height from 11,214 Sibling Pairs

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QTDT software

Using `QTDT`

The `QTDT` software uses a similar command parsing system to `pedstats`, with options again called by a `-flag` system. For example, `QTDT` allows for customised variance-covariance matrices, with the null and variance structure stipulated with the `-w` and alternative `-v` options. Using observed marker genotypes `QTDT` can implement different association models using the `-a` option. `QTDT` can also deal with an identity by descent (IBD) matrix generated from other programs, which we will make use of in this practical.

The two variance component flags `-w` and `-v` are coupled with the following letter flags to implement different models. These include

- `e` - non-shared environment
- `g` - polygenic compoennts
- `a` - additive major gene effect
- `t` - twin environment
- `c` - common environment

For example, the `-w` flag, which specifies variances under the null, coupled with the `e` option specifies that only environmental effects are modelled. The `-v` flag specifies variances under the alternative, for example, the option combination`-veg` models environment and polygenic effects.

To estimate heritability, `QTDT` requires the disabling of the association model via `-a-` and requires the specification of two models for variance. A typical command line execution of `QTDT` heritability estimation would look like

```
$ qtdt -d example.dat -p example.ped -a- -we -veg
```

Listing 1 Example run of heritability using QTDT

`QTDT` prints the summary output to the screen and saves the variance component estimates to the `regress.tbl` file.

`QTDT` estimates linkage via again disabling the association flag `-a-`, specifying the null and alternative as `-weg` and `-vega`, and providing an IBD file via `-i ibd_file.ibd`. A typical execution at the command line looks like

```
$ qtdt -d example.dat -p example.ped -i example.ibd -a- -weg -vega
```

Listing 2 Example run of linkage with QTDT

File requirements

The file requirements for this practical include the aptly named `data.txt` file that contains the pre-calculated chromosomal (1-22, X) estimates $\hat{\pi}_a$ (additive coefficient of relationship) and $\hat{\pi}_d$ (coefficient of fraternity). Let's have a look at these data using R.

```
> # Read data.txt file
> data <- read.table("practical_2/data/data.txt", header = T)
> dim(data)
  11214    59
> # Look at the pi_hat_a for the autosomes and X chromosome
> data[1:2, 1:24]
  pairID    chr1_pi chr2_pi chr3_pi chr4_pi chr5_pi
  800301112  0.3025  0.4413  0.4603  0.3322  0.4801
  801101112  0.5184  0.3173  0.4297  0.6732  0.5803
  chr6_pi chr7_pi chr8_pi chr9_pi chr10_pi chr11_pi
  0.2045  0.6479  0.1674  0.3484   0.4224   0.4550
  0.4266  0.3382  0.6611  0.4706   0.3917   0.4542
  chr12_pi chr13_pi chr14_pi chr15_pi chr16_pi chr17_pi
  0.2969   0.5484   0.2646   0.6484   0.7575   0.5294
  0.4342   0.3589   0.4113   0.4557   0.7145   0.6257
  chr18_pi chr19_pi chr20_pi chr21_pi chr22_pi chrx_pi
  0.7745   0.6430   0.6818   0.8810   0.5376  0.4681
  0.6315   0.8907   0.6510   0.3921   0.4344  0.7597
> # Investigate the pi_hat_d values for the autosomes and X chromosome
> data[1:2, 25:47]
  chr1_ibd chr2_ibd chr3_ibd chr4_ibd chr5_ibd chr6_ibd
  0.0146   0.1576   0.1428   0.0201   0.2047   0.0102
  0.1987   0.0300   0.1771   0.5068   0.3305   0.1260
  chr7_ibd chr8_ibd chr9_ibd chr10_ibd chr11_ibd chr12_ibd
  0.4009   0.0318   0.0458    0.1916    0.1324    0.1090
  0.0731   0.4637   0.2977    0.1373    0.2333    0.1679
  chr13_ibd chr14_ibd chr15_ibd chr16_ibd chr17_ibd chr18_ibd
  0.4508    0.0107    0.3754    0.5247    0.2466    0.5560
  0.0037    0.0597    0.3768    0.4518    0.3782    0.3355
  chr19_ibd chr20_ibd chr21_ibd chr22_ibd chrx_ibd
  0.3028    0.3735    0.7689    0.1238   0.4681
  0.7852    0.3151    0.0176    0.0309   0.7597
> # Take a look at the rest of the data matrix
> data[1:2, 48:59]
  gw_pi      gw_ibd    sex_sib1 age_sib1 ht_sib1  zht_sib1
  0.4920500 0.2361227        1       16   178.0  0.47048173
  0.5118773 0.2498455        1       16   174.5 -0.05328332s
  sex_sib2 age_sib2 ht_sib2  zht_sib2 sex_pair pop
   1        16      166      -1.325284      1   2
   1        16      185       1.518012      1   2
```

Listing 3 Contents of `data.txt`

In listing 3 the columns 49-59 have the following information, column 48 contains the genome-wide $\hat{\pi}_a$, column 49 contains the genome-wide $\hat{\pi}_d$, column 50 contains the sex (1 = male), column 51 contains the age (years), column 52 contains the height (cm), column 53 contains the z-score of height, columns 54-57 contain the same as 50-53 but for sibling 2, column 58 contains the sex code for the sibling pair, and column 59 contains the country code.

For the $\hat{\pi}_a$ estimates on chromosome 1-22, the estimates are equal to the mean probability of $\pi_a = k_1/2 + k_2$, where k_1 and k_2 are the IBD probabilities for sharing 1 or 2 alleles, across all markers. For the X sex chromosome the expected π_a estimates are 1/2 for male-male pairs, 3/4 for female-female pairs, and 1/4 for male-female pairs. The $\hat{\pi}_d$ estimates for all chromosomes, including the sex chromosome, are equal to the mean probability of $\pi_d = k_2$ across all markers on that chromosome. Further outline of the can be found in the lectures or (Lynch et al., 1998) chapter 7.

Exercise 1

Calculate the sample mean and SD of $\hat{\pi}_a$ and $\hat{\pi}_d$

- for each autosome
- genome-wide
- plot genome-wide $\hat{\pi}_a$ against $\hat{\pi}_d$ for each sibling pair
- regress genome-wide $\hat{\pi}_d$ values on genome-wide $\hat{\pi}_a$

```
> # Row means over a matrix can be calculated with the below function
> rowMeans(data[, 2:23])
> # A similar function does not exist for row standard deviations and thus we
> # must appeal to the apply function
> apply(data[, 2:23], 1, sd)
> pihat.mean  <- rowMeans(data[, 2:23])
> pihat.sd    <- apply(data[, 2:23], 1, sd)
> ibd.mean    <- rowMeans(data[, 25:46])
> ibd.sd      <-  apply(data[, 25:46], 1, sd)
> plot(pihat.mean, ibd.mean, pch = 20,
     col = 4, ylab = "Dominance relationship (mean IBD2 sharing)", xlab = "Additive relationship (mean IBD
         sharing)")
> # Regress IBD2 on pi-hat. Use the lm function un R. Try ?lm if you are interested
> reg <- lm(ibd.mean ~ pihat.mean)
> abline(reg, lwd = 2.5)
```

Listing 4 Hints for exercise 1

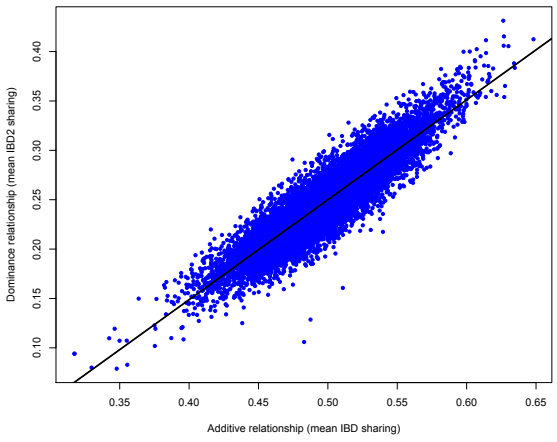

Figure 1 Plot of genome-wide $\hat{\pi}_a$ versus genome-wide $\hat{\pi}_d$. This highlights the dependance between genome wide π_d and π_a.

```
> # Regress IBD on pi-hat. Use the lm function un R. Try ?lm if you are interested
> summary(lm(ibd.mean ~ pihat.mean))
  Call:
  lm(formula = ibd.mean ~ pihat.mean)

  Residuals:
        Min         1Q     Median         3Q        Max
  -0.126745 -0.011290  0.000044  0.011251  0.066568

  Coefficients:
               Estimate Std. Error t value Pr(>|t|)
  (Intercept) -0.256023   0.002184  -117.2   <2e-16 ***
  pihat.mean   1.011945   0.004362   232.0   <2e-16 ***
  ---
  Signif. codes:  0  ***  0.001  **  0.01  *  0.05  .  0.1     1

  Residual standard error: 0.01709 on 11212 degrees of freedom
  Multiple R-squared:  0.8276,  Adjusted R-squared:  0.8276
  F-statistic: 5.382e+04 on 1 and 11212 DF,  p-value: < 2.2e-16
```

Listing 5 Hints for exercise 1 cont.

Quick look at **QTDT .ped .dat** files

Let's read into R the `.ped` and `.dat` files that we will use in the following exercises and see what they consist of.

```
> # Read in .ped and .dat files
> ped <- read.table("practical_2/data/qtdt.ped")
> dat <- read.table("practical_2/data/qtdt.dat")
> ibd <- read.table("practical_2/data/qtdt.ibd")
> # The head of the .ped file. Two columns have been cut to fit in the listing
> head(ped)
  1  1  0  0  1 X  X  X 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2
  1  2  0  0  2 X  X  X 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2
  1  3  1  2  1 0.47  1 16. 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1 1/1
  1  4  1  2  1 -1.33 1 16. 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2 2/2
  2  1  0  0  1 X  X  X 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2
  2  2  0  0  2 X  X  X 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2 1/2
> dat
   T   Y
   C SEX
   C AGE
  S2  C1
  S2  C2
  S2  C3
  S2  C4
  S2  C5
  S2  C6
  S2  C7
  S2  C8
  S2  C9
  S2 C10
  S2 C11
  S2 C12
  S2 C13
  S2 C14
  S2 C15
  S2 C16
  S2 C17
  S2 C18
  S2 C19
  S2 C20
  S2 C21
  S2 C22
   M   G
> head(ibd)
  V1 V2 V3 V4     V5     V6     V7
   1  3  4 C1 0.4096 0.5758 0.0146
   1  3  4 C2 0.2750 0.5674 0.1576
   1  3  4 C3 0.2222 0.6350 0.1428
   1  3  4 C4 0.3557 0.6242 0.0201
   1  3  4 C5 0.2445 0.5508 0.2047
   1  3  4 C6 0.6012 0.3886 0.0102
```

Listing 6 `QTDT .ped, .dat,` and `.ibd` files

In listing 6 the first five columns of the `.ped` file contain a pedigree similar to the `pedstats` format from practical 1. The next three columns of the `.ped` file contain the information specified in the first three rows of the `.dat` file. These include the trait - Y, covariate 1 - sex, and covariate 2 - age. The following columns of the `.ped` contain dummy information for each of the chromosomes 1-22. The `s2` command tells `QTDT` to skip the next 2 columns. The final row specifies that we want to model `M` the whole genome `G`.

The columns of the `.ibd` file contain family, person 1, person 2, marker, and the last three columns are the probabilities that person 1 and person 2 share 0, 1, or 2 alleles IBD at the marker locus. The dummy variables in the `.ped` file are adequate as we only use these as flags and in combination with the `.ibd` file.

Exercise 2

- Using R, estimate the sibling correlation for the standardised z-scores (hint: `zht_sib1` and `zht_sib2`)
- Why should we use the z-scores?

IMPORTANT- before executing any binaries at the command line please export the path to your binaries by using the below line

```
export PATH=$PATH:~/Desktop/SISG_AQG_2015/bin
```

Listing 7 Hints for exercises 2 and 3

Exercise 3

- Estimate the heritability using QTDT and `.dat` and `.ped` files
- Estimate the additive variance from genome wide $\hat{\pi}_a$.

This will require the use of the following `QTDT` commands

```
qtdt_mac -d practical_2/data/qtdt.dat -p practical_2/data/qtdt.ped -a- -we -veg
qtdt_mac -d practical_2/data/qtdt.dat -p practical_2/data/qtdt.ped -i practical_2/data/qtdt.ibd
          -a- -weg -vega
```

Listing 8 Hints for exercises 2 and 3

- Estimate the additive variance for a specific chromosome
- Need to edit the .dat file and change one S2 to an M!

References

GR Abecasis, LR Cardon, and WOC Cookson. A general test of association for quantitative traits in nuclear families. *The American Journal of Human Genetics*, 66(1):279–292, 2000.

Michael Lynch, Bruce Walsh, et al. *Genetics and analysis of quantitative traits*, volume 1. Sinauer Sunderland, MA, 1998.

Peter M Visscher, Sarah E Medland, MA Ferreira, Katherine I Morley, Gu Zhu, Belinda K Cornes, Grant W Montgomery, and Nicholas G Martin. Assumption-free estimation of heritability from genome-wide identity-by-descent sharing between full siblings. *PLoS Genet*, 2(3):e41, 2006.

Peter M Visscher, Stuart Macgregor, Beben Benyamin, Gu Zhu, Scott Gordon, Sarah Medland, William G Hill, Jouke-Jan Hottenga, Gonneke Willemsen, Dorret I Boomsma, et al. Genome partitioning of genetic variation for height from 11,214 sibling pairs. *The American Journal of Human Genetics*, 81(5):1104–1110, 2007.