An Introduction to Statistical Genetics

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Planning for Statistical Genetics part of the BSG course

1. Introduction to statistical genetics
2. Hardy-Weinberg equilibrium
3. Linkage disequilibrium
4. Haplotype estimation
5. Population substructure
6. Genetic association analysis
7. Relatedness analysis (allele sharing)

Statistical genetics

- Statistical genetics is a branch of statistics that deals with the analysis of inherited traits and genetic data.
- Nowadays genetic data arises in different forms (sequences, markers, ...)
- The size of the genetic databases has grown enormously over the years.

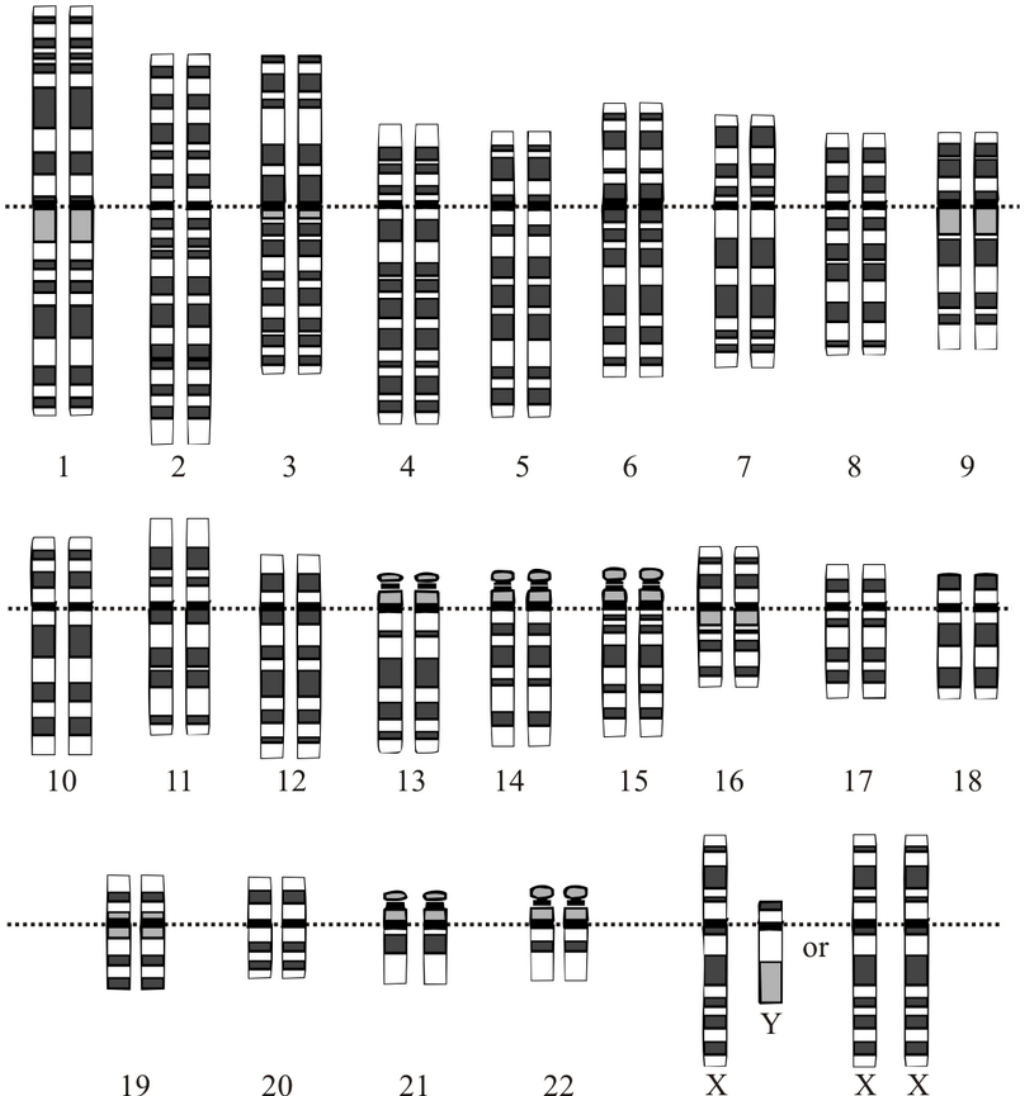
Type of studies in statistical genetics

- Population based studies (unrelated individuals)
- Family based studies (related individuals)

Some basic terminology

- A human being has 46 chromosomes in the nucleus of each cell, coming in 23 homologous pairs (22 pairs of autosomes and 1 pair of sex chromosomes (X/Y)).
- Of each pair one chromosome comes from the mother and one from the father.
- All genetic information of an individual together constitutes his/her genome.
- Homologous pairs split during the formation of reproductive cells (meiosis).
- Reproductive cells have one copy of the genome and are haploid. Body cells of any individual are diploid.
- A gene correspondes to a piece of a chromosome, a stretch of DNA.
- The location of a gene in the genome is called its locus.
- Each individual inherits two copies of each gene, one from the father and one from the mother.
- The different forms of a gene are called alleles, if there are two often indicated by `A` and a, A_1 and A_2, or `A` and `B`.
- The genetic makeup of an individual is called his/her genotype. For a gene with two alleles, this can be `AA`, `Aa` or aa.
- Alleles can be dominant, recessive or codominant.
- An individual that inherits the same allele from father and mother is homozygous (`AA` or aa).
- An individual with a different allele on each chromosome of a pair is heterozygous (`Aa`).

The Human genome



Traits and markers

- In many studies in statistical genetics, some trait (e.g. yield or disease status) of an organism is considered to depend on one or more genetic variables.
- The position of genetic factors affecting a trait is often unknown.
- A marker is a genetic variable that shows variation over individuals, and has a known locus.
- The study of associations between markers and trait can be helpful in identifying the genetic factors that affect the trait.

Markers and polymorphisms

- A genetic marker that consists only of homozygotes for one particular allele is called monomorphic.
- Whether a marker varies or not depends on sample size.
- In population genetics, the term polymorphism is sometimes reserved for marker where the most common allele has a frequency below 99%.
- The terms marker, variant and polymorphism are often used interchangeably.

Markers

There are many different markers of which we consider

- RFLPs (Restriction Fragment Length Polymorphism)
- SNPs (Single Nucleotide Polymorphism)
- Microsatellites or STRs (Short Tandem Repeat)
- indels (insertion/deletion polymorphism)
- ...

RFLPs (Restriction Fragment Length Polymorphism)

- A large number of restriction enzymes has been discovered that cut DNA at a specific motif.
- E.g. enzyme BamHI cuts DNA at the recognition sequence GGATCC/CCTAGG
- By digesting DNA with a restriction enzyme DNA fragments of variable length arise.
- These can be separated on a gel in the laboratory, and presence/absence of restriction sites can be inferred.
- Produces binary data.

Microsatellites or STRs (Short Tandem Repeat, 1/2)

- Microsatellites consist of short sequences (e.g. ATT) that repeat a certain number of times (e.g. ATTATTATTATT).
- A small (2-6) number of base pairs is repeated.
- Individuals vary in the number of repeats they have.
- Produces count data, with a limited number of outcomes.
- Microsatellites have many alleles.

Microsatellites or STRs (Short Tandem Repeat, 2/2)

- STRs can be coded in different ways:
  - reporting the number of repeats an individual has on each chromosome.
  - reporting the total size of the repeating sequences as the number of base pairs on each chromosome.
- Example:
  - a tri-nucleotide STR: ATT.
  - an individual has the DNA sequences (ATTATTATT,ATTATTCAA)
  - can be coded as (3/2) (repeats)
  - (9/6) (total size)
- In the statistical analysis mostly treated as categorical.

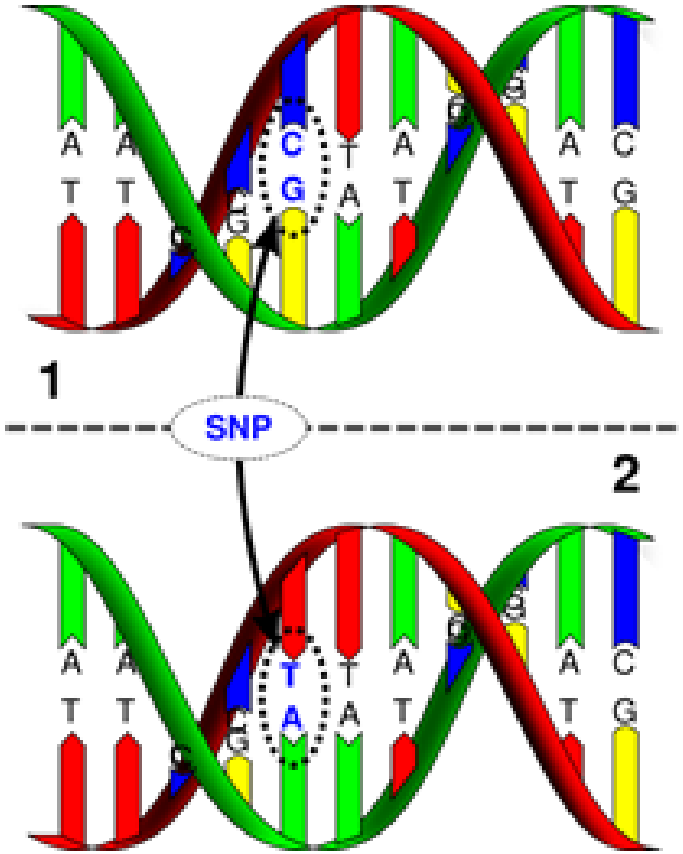
A glance at a STR database

	Id	STR1	STR2	STR3	STR4	STR5	STR6	STR7	STR8	STR9	···
1	794	129	264	142	156	157	171	205	183	196	···
2	794	155	292	146	156	166	179	205	187	196	···
3	795	145	288	138	168	157	171	205	195	196	···
4	795	150	292	142	172	166	175	210	203	196	···
5	796	155	292	138	156	157	167	205	183	184	···
6	796	155	300	142	156	169	171	205	199	196	···
7	797	150	264	142	156	157	171	205	187	196	···
8	797	155	292	146	176	163	175	205	187	196	···
9	798	150	292	138	156	157	171	205	183	187	···
10	798	155	300	146	160	166	171	205	207	190	···
11	799	155	296	146	152	157	167	205	179	196	···
12	799	155	296	146	176	157	171	210	183	196	···
13	800	145	264	138	156	157	163	205	187	190	···
14	800	160	296	146	156	157	171	210	199	196	···
15	801	155	264	142	156	157	175	205	183	196	···
16	801	155	292	146	184	166	179	209	199	199	···
17	802	145	292	138	176	157	159	193	183	187	···
18	802	155	296	142	180	166	171	201	187	187	···
19	803	155	280	142	172	166	163	205	183	196	···
20	803	155	300	142	176	169	175	213	187	196	···
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	

Single Nucleotide Polymorphism

- A Single Nucleotide Polymorphism (SNP) corresponds to the position of one base pair in the DNA chain.
- There are four nucleotides (A,T,G and C).
- In theory, a SNP is a categorical variable with 10 possible categories (genotypes).
- In practice, the vast majority of SNPs is bi-allelic, so that only three genotypes occur.
- E.g. we may have a A/T polymorphism, with AA, AT and TT individuals.
- SNPs have become the most popular genetic markers.

Single Nucleotide Polymorphism



A glance at a SNP database

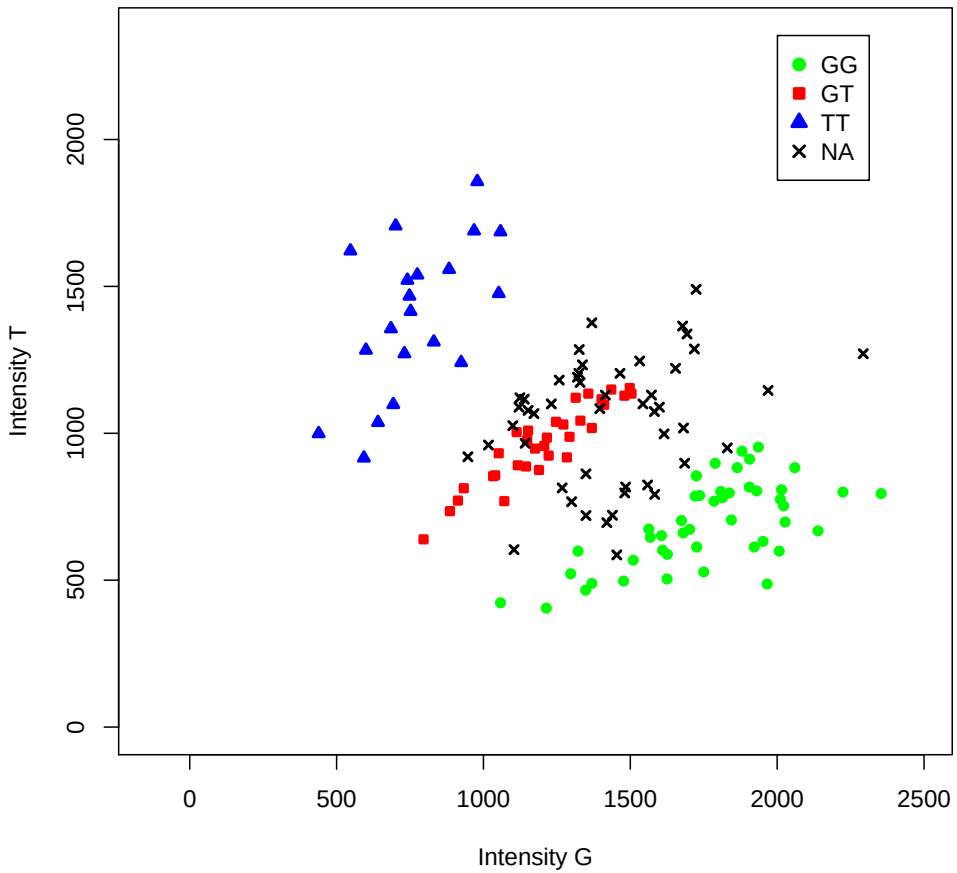
Id	SNP1	SNP2	SNP3	SNP4	SNP5	SNP6	SNP7	SNP8	SNP9	SNP10	···
NA18524	CC	CC	TT	TT	AT	AC	CC	AC	CT	GG	···
NA18526	CC	CC	CT	TT	AT	CC	CC	AC	CT	GG	···
NA18529	CC	CC	TT	TT	TT	AC	CG	AC	CT	GG	···
NA18532	CC	CC	TT	TT	TT	AC	CG	AC	CT	GG	···
NA18537	CC	CC	TT	TT	AT	CC	CC	AC	CT	GG	···
NA18540	CC	CC	CT	TT	AT	CC	CG	AC	CT	GG	···
NA18542	CC	CC	TT	TT	TT	CC	CG	AC	CT	GG	···
NA18545	CC	CC	CT	TT	AT	CC	CC	AC	CT	GG	···
NA18547	CC	CC	CT	TT	AT	CC	CC	AC	CT	GG	···
NA18550	CC	CC	CT	TT	AT	CC	CC	AC	CT	GG	···
NA18552	CC	CC	TT	TT	TT	CC	CG	AC	CT	GG	···
NA18555	CC	CC	TT	TT	TT	CC	CG	AC	CT	GG	···
NA18558	CC	NA	CC	TT	TT	CC	CG	CC	CT	GG	···
NA18561	CC	CC	TT	TT	TT	AC	CC	AC	CT	GG	···
NA18562	CC	CC	TT	TT	AT	AC	CG	AC	CT	GG	···
NA18563	CC	CC	CT	TT	AA	CC	CC	AA	CT	GG	···
NA18564	CC	CC	TT	TT	TT	AC	CC	AC	CT	GG	···
NA18566	CC	CC	TT	TT	TT	AC	CC	AC	CT	GG	···
NA18570	CC	CC	TT	TT	AT	AC	CC	AC	CT	GG	···
NA18571	CC	CC	TT	TT	AT	AC	CC	AC	CT	GG	···
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	

SNP data

Note that:

- Missing data is a common problem (10% missing not unusual).
- SNP data is multivariate categorical data.
- SNPs occur about once in every 300 base pairs.
- Approximately 10 million SNPs in the human genome.
- Genotypes determined by a classification/clustering algorithm that use allele intensities.

Example of a Call plot



Elements of the descriptive analysis of one genetic marker

- Number and percentage of missing values (NA)
- Number of alleles
- Genotype frequencies
- Allele frequencies
- Heterozygosity
- Minor and major allele
- Minor allele frequency (MAF)

Some notation (bi-allelic markers)

- Allele frequencies: $p_A + p_B = 1$
- MAF: $\min(p_A, p_B)$
- Genotype frequencies: $f_{AA} + f_{AB} + f_{BB} = 1$
- Observed heterozygosity: $H_o = f_{AB}$
- Expected heterozygosity: $H_e = 1 - \sum_{i=1}^{K} p_i^2$

Notes:

- Note that for a genetic marker with K alleles there will be $\frac{1}{2}K(K+1)$ genotypes.
- Mind the difference between population parameters and sample estimates.

Reading genetic data in R

```
load("c:/data/Chromosome1_CHBPopSubset.rda")
install.packages("genetics")
library(genetics)
Ysub[Ysub=="NN"] <- NA
Ysub[,1:5]
Ysub[,3]
Geno <- genotype(Ysub[,3],sep="")
Geno
summary(Geno)
```

Summarizing a genetic marker in R

```
> Geno
 [1] "T/T" "T/C" "T/T" "T/T" "T/T" "T/C" "T/T" "T/C" "T/C" "T/C" "T/T" "T/T"
[13] "C/C" "T/T" "T/T" "T/C" "T/T" "T/T" "T/T" "T/T" "T/C" "T/T" "T/T" "T/T"
[25] "T/C" "T/T" "T/C" NA    "T/C" "T/C" "T/T" "T/T" "T/T" "T/T" "T/T" "T/T"
[37] "T/T" NA    "T/T" "T/T" "T/C" "T/T" "T/T" "T/T" "T/T" "C/C" "T/T" "T/C"
Alleles: T C
> summary(Geno)

Number of samples typed: 46 (95.8%)

Allele Frequency: (2 alleles)
   Count Proportion
T     75       0.82
C     17       0.18
NA     4         NA


Genotype Frequency:
    Count Proportion
T/T    31       0.67
T/C    13       0.28
C/C     2       0.04
NA      2         NA

Heterozygosity (Hu)  = 0.3045867
Poly. Inf. Content   = 0.2558924
>
```

Public resources

The 1000 genomes project: http://www.internationalgenome.org

References

- Foulkes, A.S. (2009) *Applied statistical genetics with R*. Springer.
- Laird, N.M. & Lange, C. (2011) *The fundamentals of modern statistical genetics*. Springer.
- Weir, B.S. (1996) *Genetic Data Analysis II*, Sinauer Associates, Massachusetts.

Computer exercise: SNPs

1. Load http://www-eio.upc.es/~jan/data/bsg/Chromosome1_CHBPopSubset.rda
2. Install the `genetics` package
3. Determine # SNPs and # individuals in the database
4. Change all NN for NA
5. Describe the first 3 SNPs with the `summary` command
6. Compute the % of missings per individual and plot these
7. Compute the % of missings per SNP and plot these
8. Are there any individuals/SNPs with an exceptional amount of missing data?
9. Compute the allele frequencies of SNP3 from the genotype frequencies
10. Compute the MAF for all SNPs in the database, and make a histogram. What do you observe?

Computer exercise: STRs

1. Load http://www-eio.upc.es/~jan/data/bsg/JapaneseSTRs.rda
2. Determine # STRs and # individuals in the database.
3. Change all -9 for NA.
4. Determine the number of alleles of the first STR.
5. Determine the allele counts for the first STR.
6. Determine the genotype counts for the first STR.
7. How many different genotypes are observed?
8. How many different genotypes are theoretically possible?
9. Determine the number of alleles for each STR, and make a barplot of the number of alleles.