# Statistical methods in genetic relatedness and pedigree analysis

NORBIS course, Oslo, June 2022

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## Solutions for exercise set VIII

*Note:* Some answers are given in the exercise and therefore omitted here.

```
library(pedsuite)
library(segregatr)
```

### Exercise VIII-1

a) 7 and 8 are affected, and carry the variant. The arrow points to the proband (the patient originally investigated). The individuals with question marks have unknown disease status.

b) The plot was produced with the command

```
plotSegregation(x, aff = 7:8, carriers = 7:8, unknown = 4:5, proband = 7)
```

c) For $i = 0, 1, 2$, the parameter $f_i$ is the probability of being affected, for a person with $i$ copies of the disease allele. In this case the phenocopy rate ($f_0$) is 0.05 and the penetrance ($f_1$) is 0.7.

d) Compute the full-likelihood Bayes factor (FLB) by completing and running this command:

```
FLB(x,
    affected = 7:8,
    carriers = 7:8,
    proband = 7,
    unknown = 4:5,
    freq = 0.001,
    penetrances = c(0.05, 0.7, 0.7))
```

```
## [1] 5.278084
```

The FLB is neutral, i.e., not high enough to be supporting evidence.

e)
```
FLB(x,
    affected = c(4:5, 7:8),
    carriers = 7:8,
    proband = 7,
    freq = 0.001,
    penetrances = c(0.05, 0.7, 0.7))
```

```
## [1] 7.297385
```

If 4 and 5 are affected, the FLB increases (even though we haven't added any genotype information!).

f)
```
FLB(x,
    affected = c(4:5, 7:8),
    carriers = c(4:5, 7:8),
    proband = 7,
    freq = 0.001,
    penetrances = c(0.05, 0.7, 0.7))
```

```
## [1] 7.369795
```

Adding the variant genotypes of 4 and 5 had very little effect on the FLB. The reason is that they are (almost) forced carriers.

g) The phrase *fully penetrant dominant with no phenocopies* means that $(f_0, f_1, f_2) = (0, 1, 1)$. Hence we get:

```
FLB(x,
    affected = c(4:5, 7:8),
    carriers = c(4:5, 7:8),
    proband = 7,
    freq = 0.001,
    penetrances = c(0, 1, 1))
```

```
## [1] NaN
```

The FLB is undefined in this case, because the data has probability 0 under both models. With the new assumption, it is impossible for healthy parents (1 and 2() to have affected children (3 and 4).

h)
```
FLB(x,
    affected = c(4:5, 7:8),
    unknown = 1:2,
    carriers = c(4:5, 7:8),
    proband = 7,
    freq = 0.001,
    penetrances = c(0, 1, 1))
```

```
## [1] 7.968096
```

Finally we reached (or close enough) the threshold FLB = 8 indicating *supporting evidence*.

**Exercise VIII-2**

a) The new pedigree:

```
x = cousinPed(1) |>
  swapSex(c(3,8)) |>
  relabel("asPlot") |>
  addSon(parents = 5:6)
```

```
FLB(x,
    affected = 7:9,
    carriers = 7:8,
    proband = 7,
    unknown = 4:5,
    freq = 0.001,
    penetrances = c(0.05, 0.7, 0.7))
```

```
## [1] 7.004912
```

The presence of another affected relative increases the FLB.

b) If 9 is a carrier:

```
FLB(x,
    affected = 7:9,
    carriers = 7:9,
    proband = 7,
    unknown = 4:5,
```

```
    freq = 0.001,
    penetrances = c(0.05, 0.7, 0.7))
```

```
## [1] 13.0475
```

If he is a non-carrier:

```
FLB(x,
    affected = 7:9,
    carriers = 7:8,
    noncarriers = 9,
    proband = 7,
    unknown = 4:5,
    freq = 0.001,
    penetrances = c(0.05, 0.7, 0.7))
```

```
## [1] 0.9351207
```

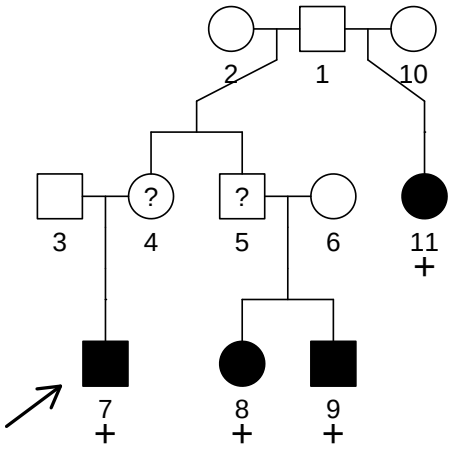
c) Adding a half sister to 4 and 5:

```
x = addDaughter(x, parent = 1)
```

Assuming that 9 (from previous question) is a carrier, we find this FLB:

```
FLB(x,
    affected = c(7:9,11),
    carriers = c(7:9,11),
    proband = 7,
    unknown = 4:5,
    freq = 0.001,
    penetrances = c(0.05, 0.7, 0.7),
    plot = TRUE)
```

```
## [1] 43.87842
```




This gives a classification as *strong evidence* (FLB $> 32$).

**Exercise VIII-3**

a) The problem is individual 26, who is unaffected but carries the variant.

b) (Answer omitted.)

c) Complete code:

```
y = readPed("data/segregation-hsp.ped")

aff = c(1,4,6,8,10,12,13,18,20,23)
carr = c(20,23,26)
noncarr = c(15,22,24)
proband = 23
freq = 0.00001
penet = c(0, 0.9, 0.9)

FLB(y, aff = aff, carr = carr, noncarr = noncarr, proband = proband,
    freq = freq, penetrances = penet)
```

```
## [1] 69.923
```

The output indicates *strong evidence* in favour of pathogenicity!