Statistical methods in genetic relatedness and pedigree analysis

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Exercise set VIII. Segregation analysis for variant interpretation

Before starting, load the core **pedsuite** packages and the specialised package **segregatr**.

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

Exercise VIII-1

Consider the following pedigree, affected with an autosomal dominant disease with reduced penetrance. A potentially causal variant is detected in some members. The disease allele has frequency 0.001.
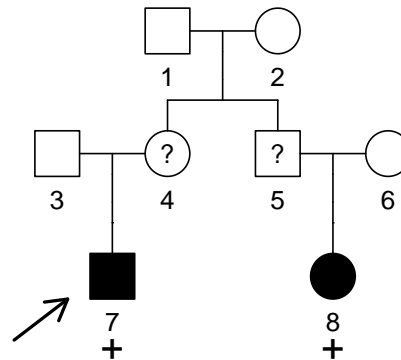
Note: Each question below, after the first, is a continuation of the previous.

a) Who are affected? Who are carriers of the variant? What does the arrow mean? What do the question marks mean?

b) Create the pedigree in R with the following code:

```
x = cousinPed(1) |>
  swapSex(c(3,8)) |>
  relabel("asPlot")
```

(Bonus exercise: Use `plotSegregation()` to reproduce the plot shown above.)

c) Initially we assume that the penetrance vector is $(f_0, f_1, f_2) = (0.05, 0.7, 0.7)$. What do the numbers mean? What is the phenocopy rate and penetrance for this disease?

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

```
FLB(x,
    affected = ,
    carriers = ,
    proband = ,
    unknown = ,
    freq = ,
    penetrances = )
```

What is the strength of the segregation evidence?

e) Suppose that after a clinical examination, individuals 4 and 5 are found to be affected. Change the arguments to `FLB()` accordingly and re-run the analysis. What is the FLB now?

f) Suppose further that individuals 4 and 5 are carriers of the rare allele in question. Compute the FLB with the new information.

g) Adjust the penetrance values to those of a fully penetrant dominant disease with no phenocopies, and compute FLB again. Explain why the answer is undefined (`NaN`) in this case.

h) Set individuals 1 and 2 to have unknown affection status. What is FLB then?

Exercise VIII-2

In this exercise we go back to the original situation of the previous exercise, and examine the effect of including additional affected relatives. Each question below is a continuation of the previous.

a) It is brought to light that individual 8 has a brother, who is also affected - but not yet genotyped. How do you think this affects FLB. Modify the pedigree and check your intuition.
   Hint: Recreate the pedigree as in part a of Exercise VIII-1, and add `x = addSon(x, parents = 5:6)`.

b) The brother is subsequently genotyped. Find the new FLB in both scenarios: (i) if he carries the variant, and (ii) if he does not carry the variant. In the following we assume that he is a carrier.

c) Individuals 4 and 5 have a half sister, who is also affected, and who also carries the variant. Compute the FLB and classify the evidence according to the thresholds given in class.

Exercise VIII-3

This exercise is based on a real case. The family shown below, slightly modified for anonymity purposes, is affected with a rare, dominant form of hereditary spastic paraplegia (HSP).
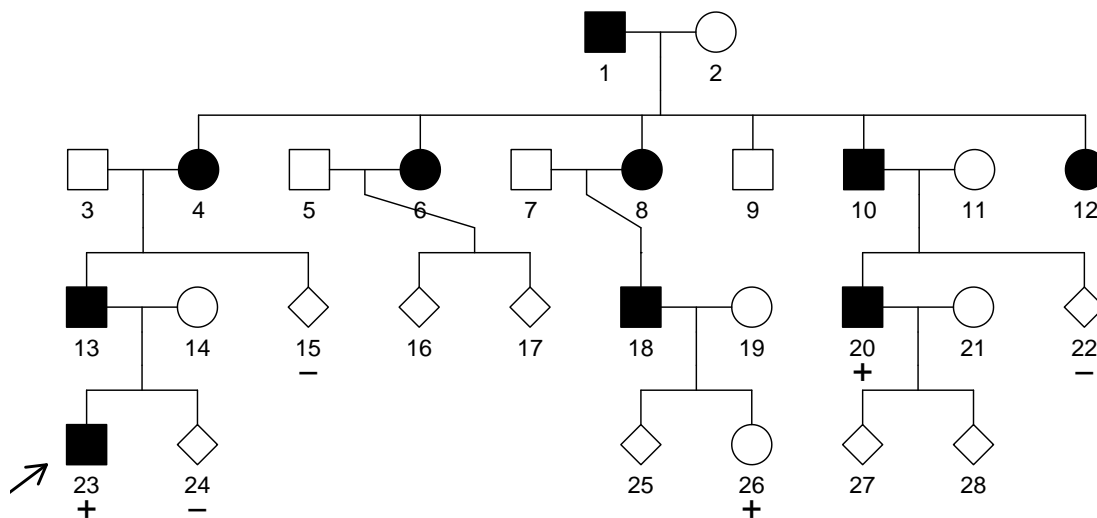
A potential genetic cause was identified in the family. The plus and minus signs indicate known carriers/non-carriers.

a) Explain that the variant does not segregate perfectly with the disease.

b) Load the pedigree:

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

c) Assume that the disease has penetrance of 90% and no phenocopies, and allele frequency 0.00001. Compute the FLB and give a conclusion.