Lecture 4:
Kinship testing with Familias

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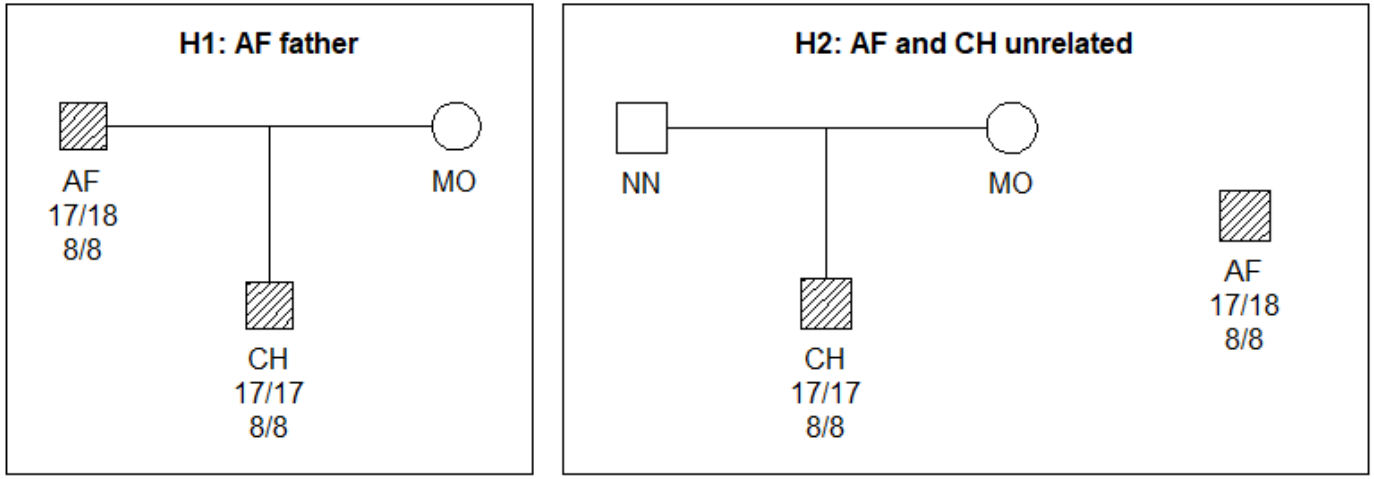
Example used to introduce Familias



$$LR = \text{Likelihood ratio} = \frac{P(\text{data} \mid \text{H1})}{P(\text{data} \mid \text{H2})}$$

$$LR_1 = \frac{2p_{17}p_{18} \cdot \frac{1}{2}p_{17}}{2p_{17}p_{18} \cdot p_{17}^2} = \frac{1}{2p_{17}} = \frac{1}{2 \cdot 0.204} = 2.45,$$

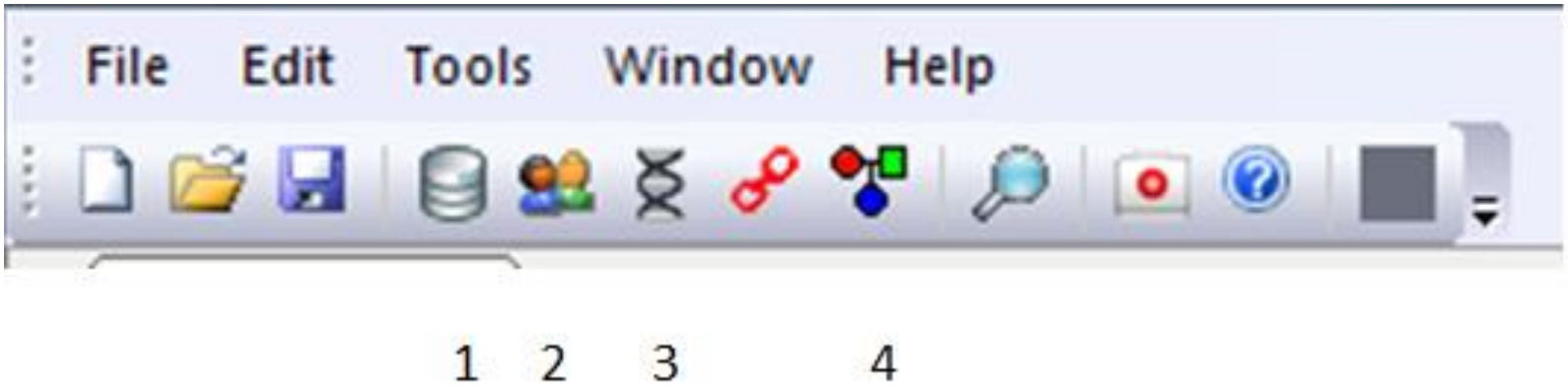
$$LR_2 = \frac{p_8^2 \cdot 1 \cdot p_8}{p_8^2 \cdot p_8^2} = \frac{1}{p_8} = \frac{1}{0.554} = 1.81,$$

$$LR = LR_1 \cdot LR_2 = 2.45 \cdot 1.81 = 4.4.$$

Interpretation: The data is 4.4 times more likely if H1 is true rather than H2.

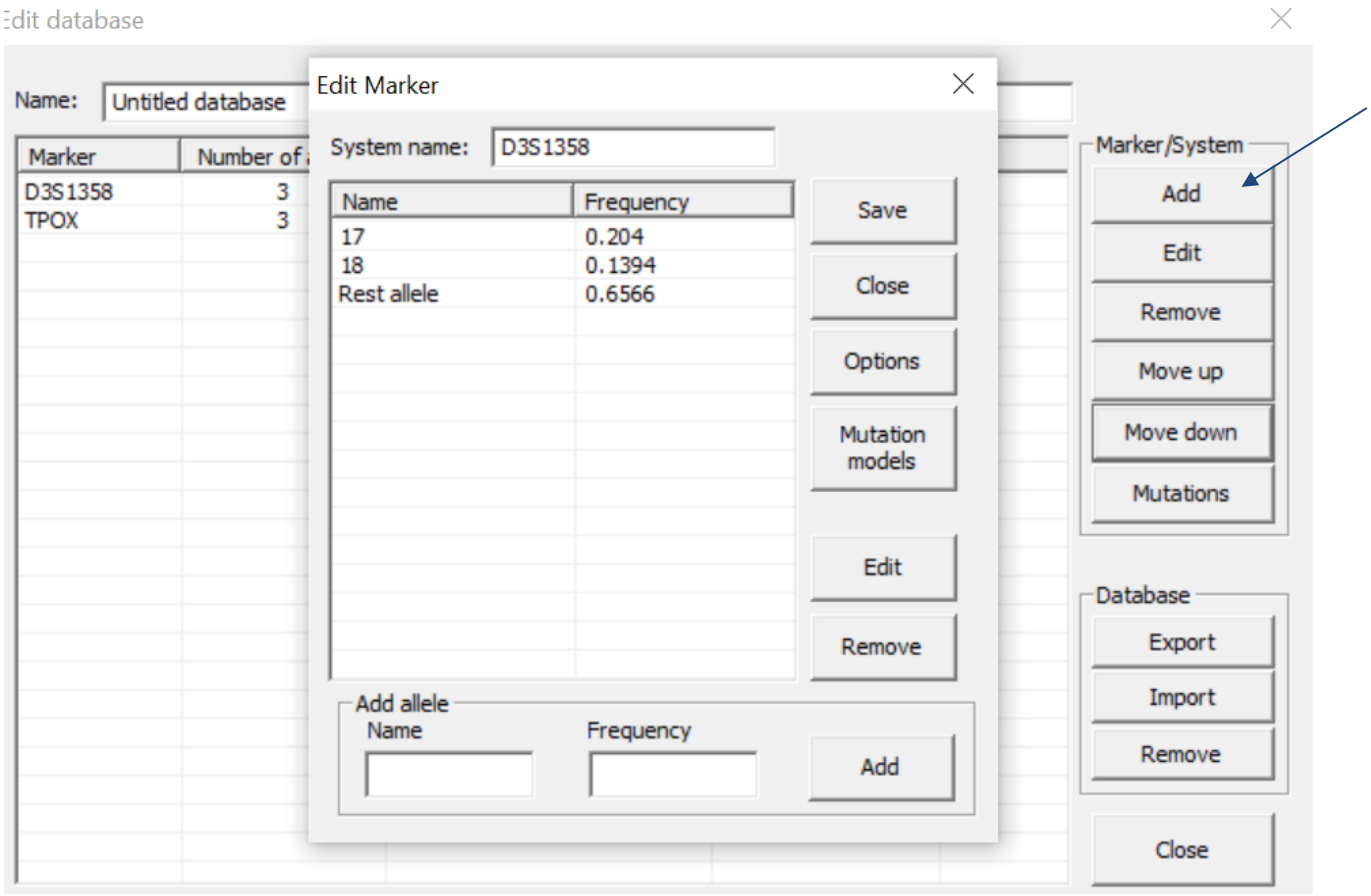
We next explain the steps needed to verify the calculations using Familias.

Four basic steps



1. **General DNA data**. Input of database, i.e., allele frequencies, etc.
2. **Persons**. Individual needed to define pedigrees.
3. **Case DNA data**. Marker data.
4. **Pedigrees**. Define hypotheses and do calculations.

Step1: General DNA data

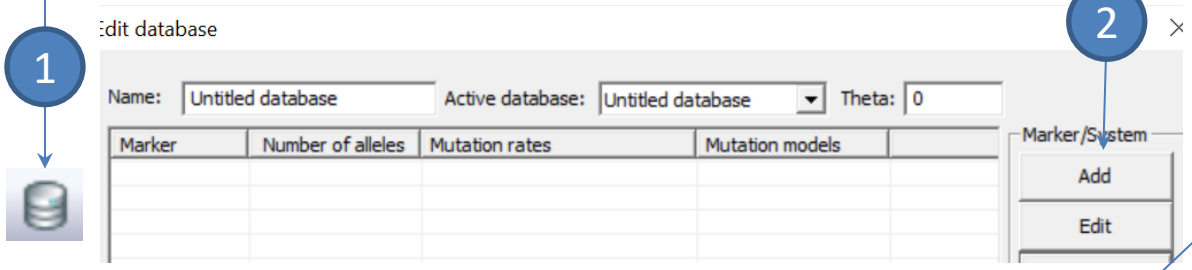


- Click ‘Add’ to enter a marker. In the new window, enter as shown.
- Similarly for next marker TPOX with alleles 8 and 9, frequencies 0.554 and 0.104.
- The order of markers can be modified by using “Move up” or “Move down” buttons.

Details: General DNA data (skipped in presentation)

Click

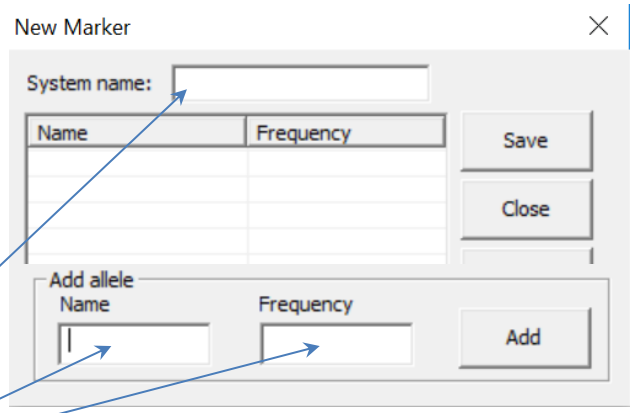
1



Click

2

The “New marker” window opens

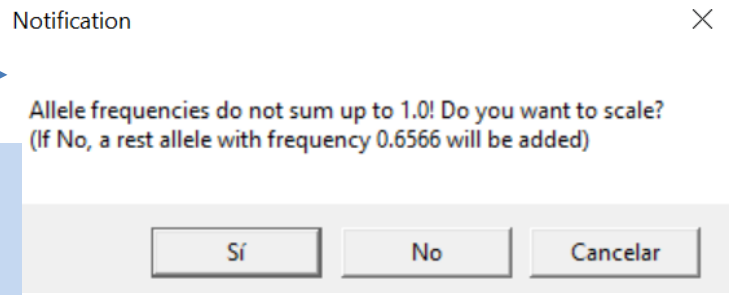


3 Add the name of the first marker (D3S1358 in the example)

4 Add the first allele (17), frequency (0.204) and press ‘Add’

5 Do the same for the second allele (18, freq. 0.1394)

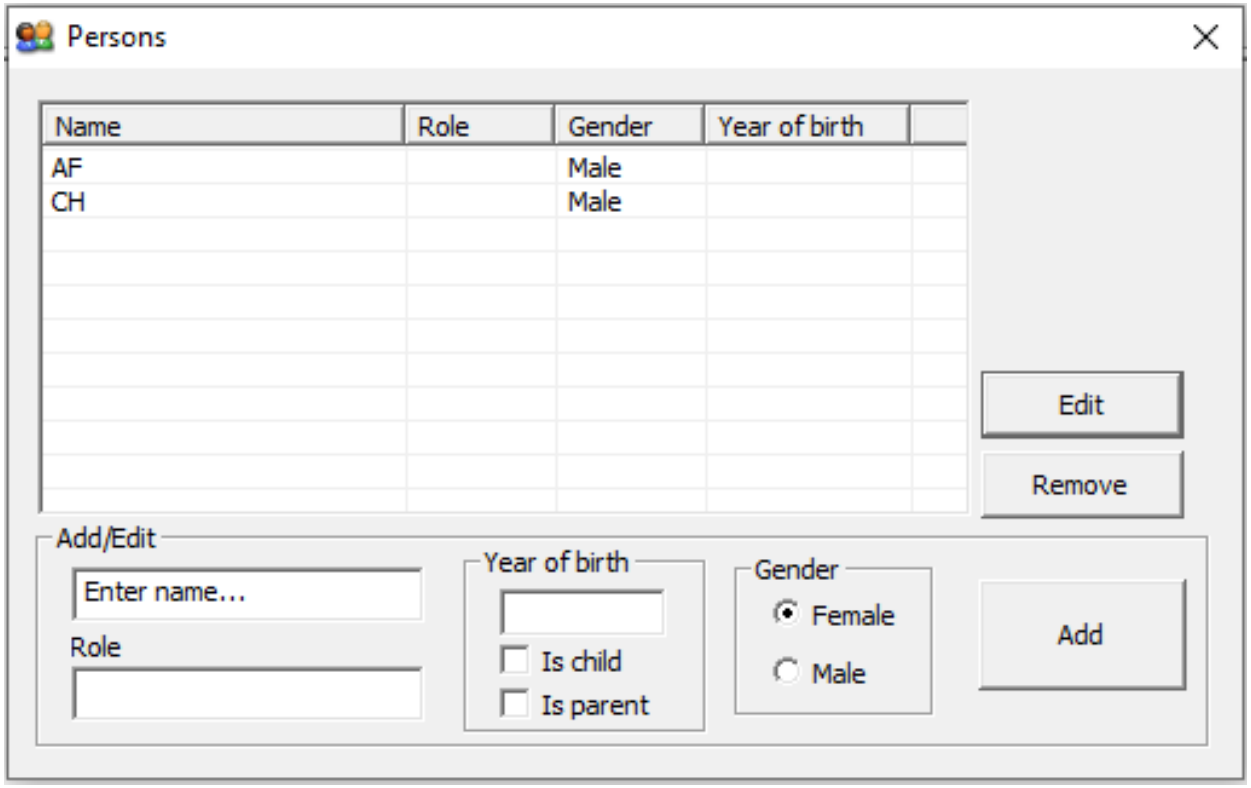
6 Click ‘Save’ and it will appear:



7 For “Scale”, click yes (the freq. of both alleles will change to sum 1)
For “add a rest allele”, click No (a rest allele with freq. 0.6566 will be added)

8 Repeat the process for the second marker (TPOX, in the example)

Step 2. Persons



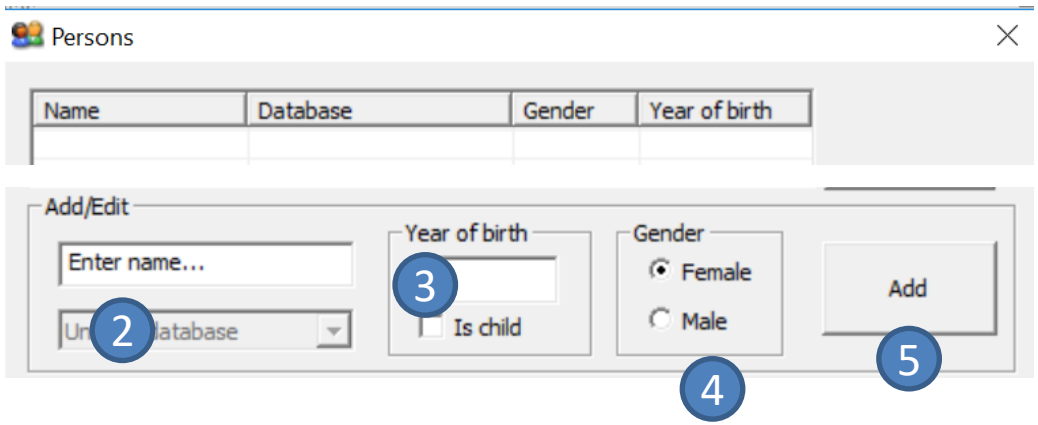
- Enter the persons: AF (alleged father), and CH (child) as shown.
- Information on ‘Role’, ’Year of birth’, ‘Is child’ and ‘Is parent’ are normally not needed nor used.

Step 2 in detail: persons (skipped)

Click

1

The “Persons” window opens



2. Enter the name of the first person (AF)
3. Optional: enter the year of birth
4. Enter the gender
5. Click ‘Add’
6. Do the same with the following person (CH)

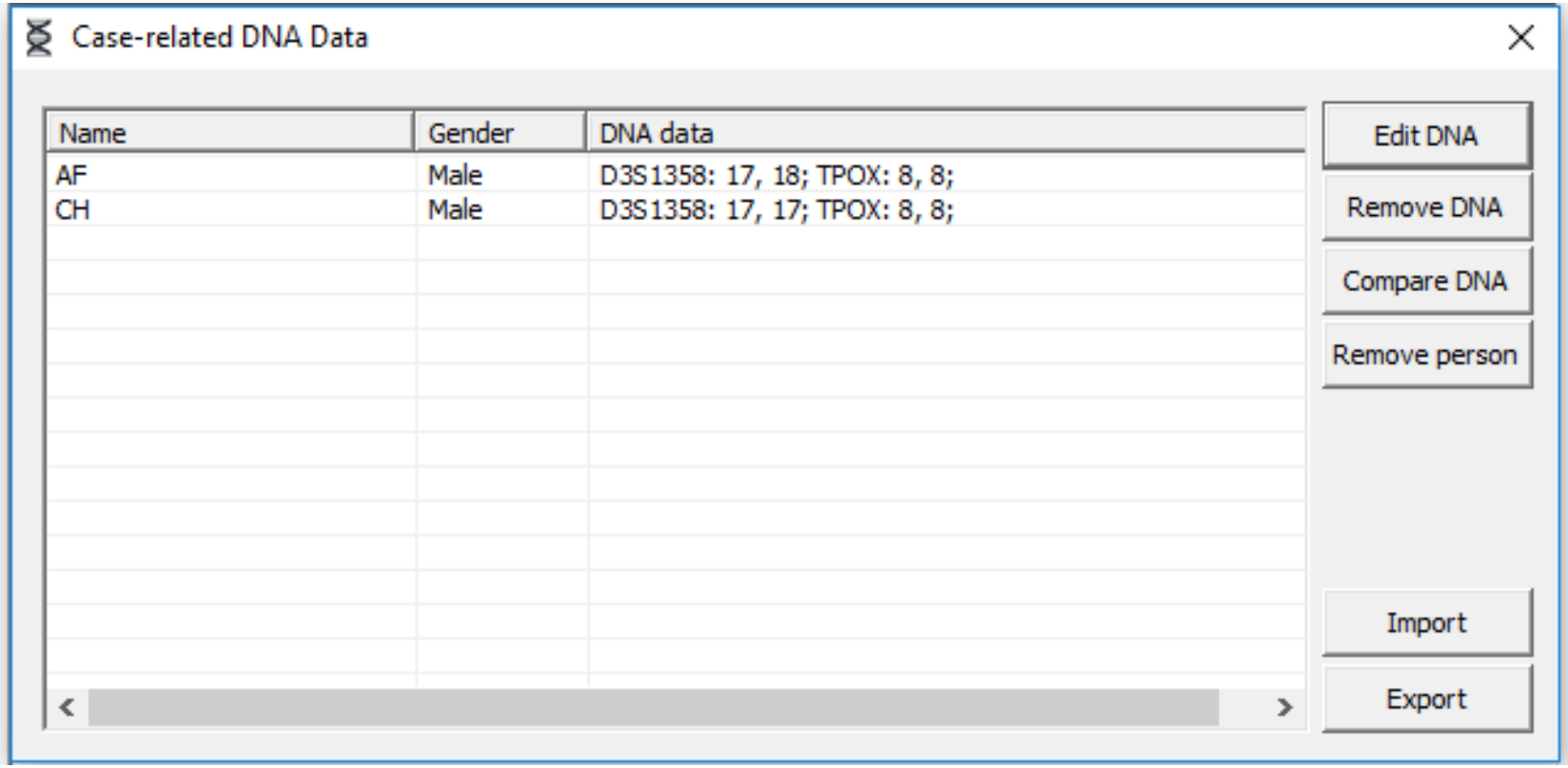
Comment 1

If you enter the year of birth, you make sure that a younger person can not be the parent of an older person (useful to avoid errors in the pedigrees and impossible pedigrees)

Comment 2

If you click the “Is child” box, you make sure that this person cannot have children (useful for the same reasons as before)

Step 3. Case data



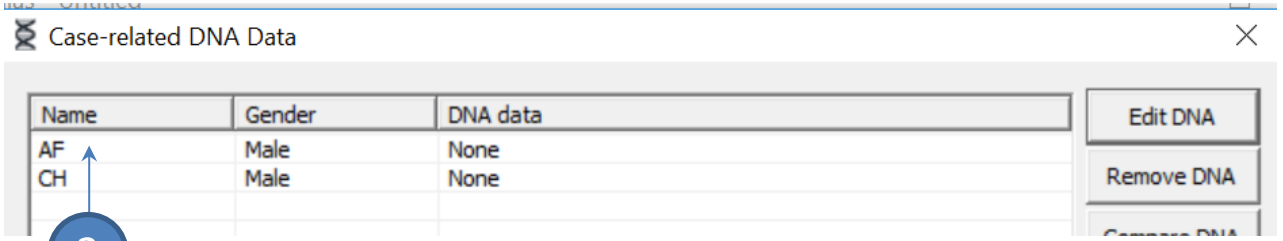
- Double click each person. In the new window select the marker in the pull down menu, press ‘Add’ and ‘OK’, to enter the data as shown.

Step 3 in detail: Case data (skipped)

Click

1

The “Case-related DNA data” window opens

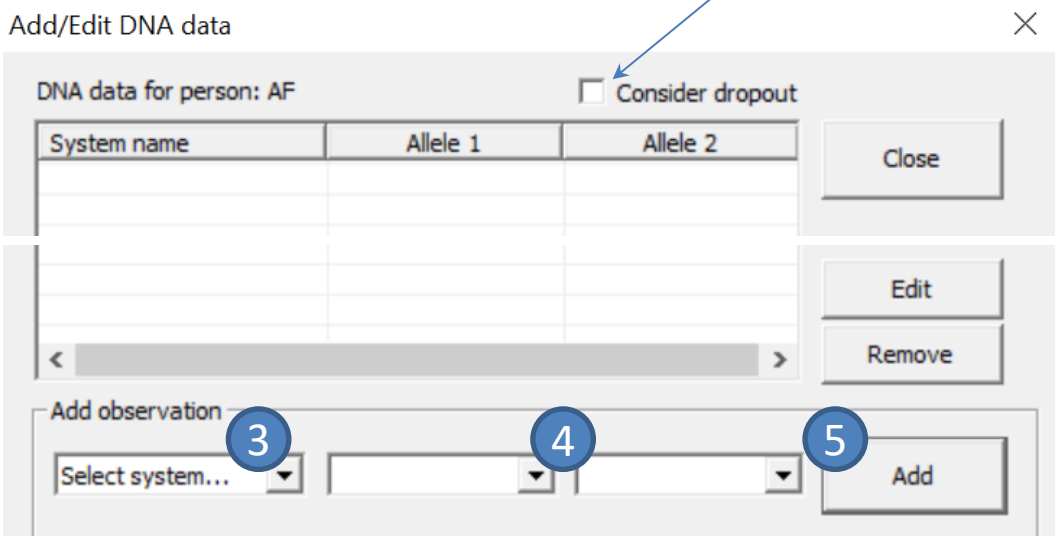


2

Double Click (AF)

Comment
If you want to consider dropout in one specific individual, click the box. See slide 18 to enter the probability of dropout

The “Add/Edit DNA data” window opens



3 Select the marker (D3S1358)

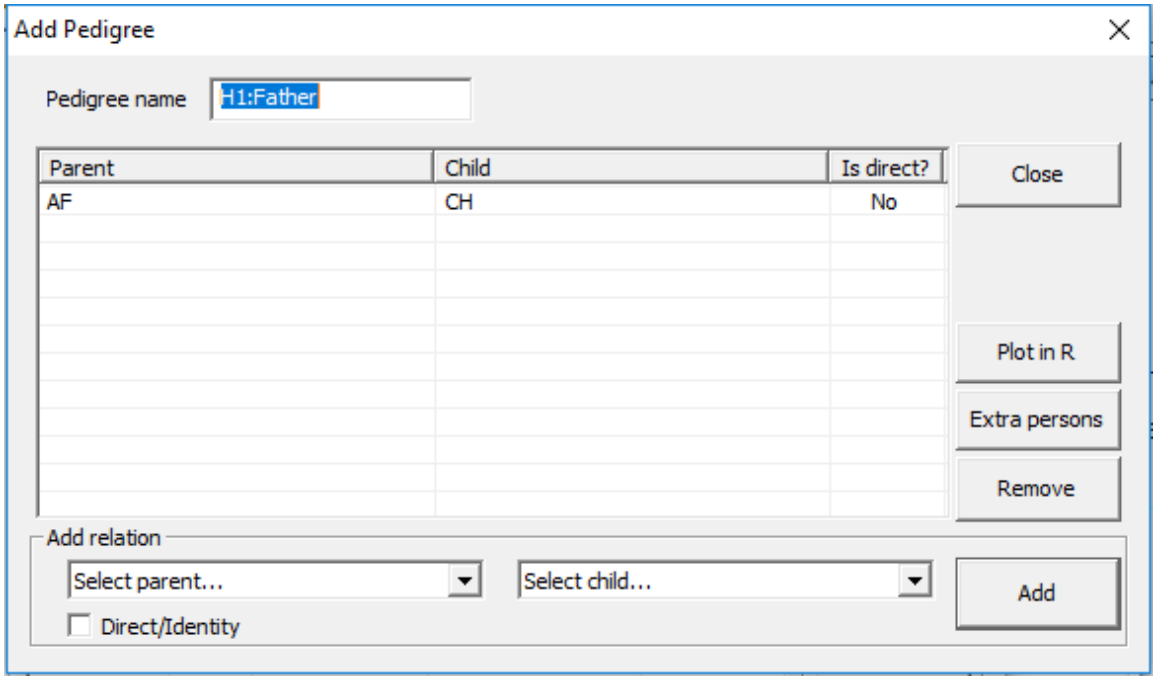
4 Enter the genotype (17-18)

5 Click ‘Add’

6 Do the same for TPOX and then close

7 Repeat the process from 2 for CH

Step 4. Pedigrees



Pedigree	Prior	Posterior	Likelihood Ratio	Ln likelihood
H1:Father	0.5	0.815639396	4.424152332	-6.92145
H2: Unrela...	0.5	0.184360604	1	-8.408529

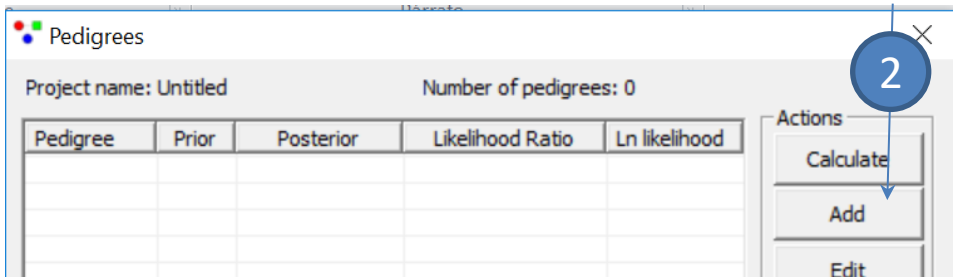
- Click ‘Add’ to enter the hypothesis “H1:Father” as shown (upper panel).
- Enter the pedigree “H2:unrelated”. In this case no relations are added.
- Click ‘Calculate’ to get the output in the lower panel.

Step 4 in detail: Pedigrees (skipped)

Click

1

The “Pedigrees” window opens



Click

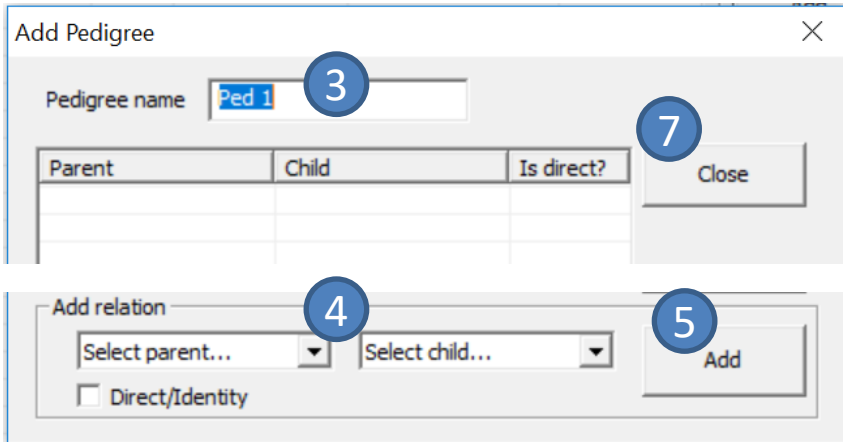
2

Comment

Familias only allows you to define parent-child relationships. If you want to define the relation “2 brothers”, you have to enter a mother and a father and establish that both are sons of them.

In order to define a disputed direct match, e.g. twins, use the Direct/Identity option

The “Add Pedigree” window opens



3 Name the pedigree (e.g., H1: Father)

4 Define the relation (AF father of CH)

5 Click ‘Add’

6 Name the second pedigree (H2: unrelated). You do not have to enter any relation in this case

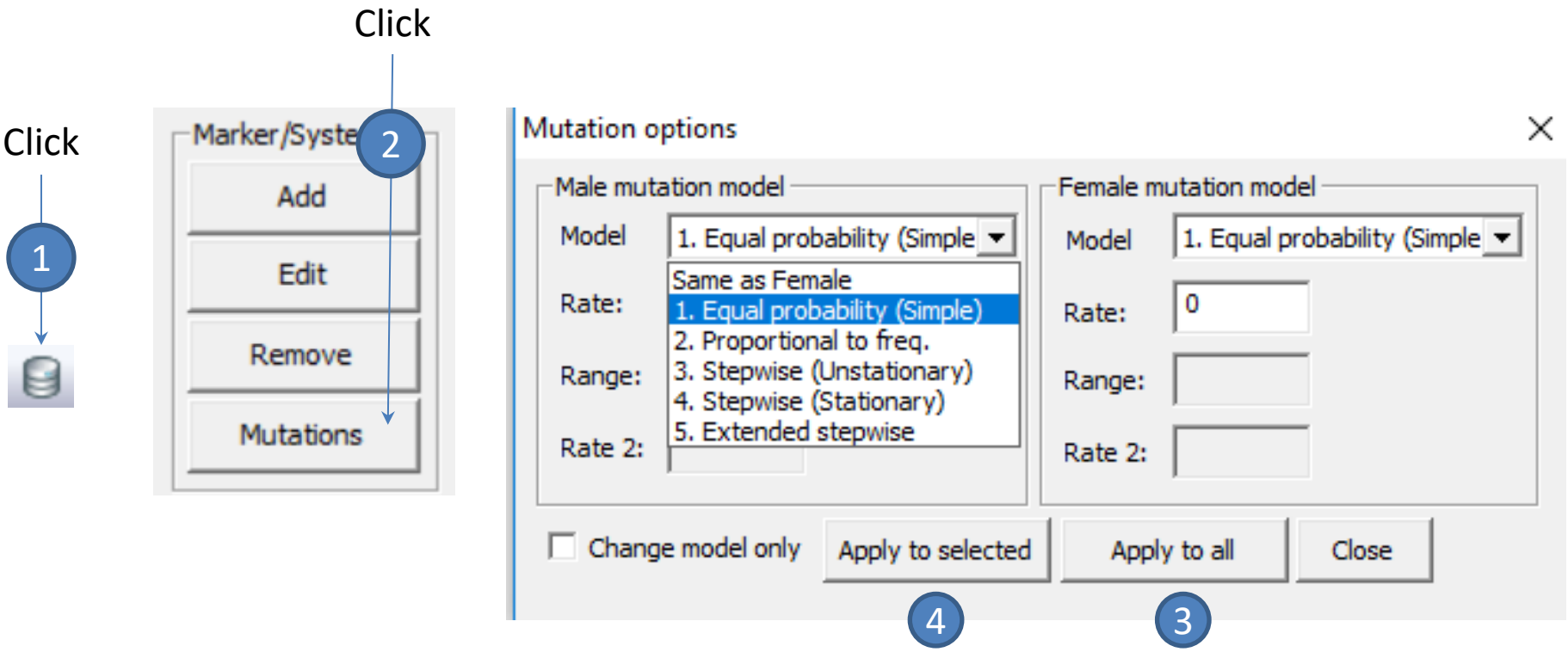
7 Click ‘Close’

8 Then click ‘Calculate’ in the Pedigrees window to obtain:

Pedigree	Prior	Posterior	Likelihood Ratio	Ln likelihood
H1:Father	0.5	0.815639396	4.424152332	-6.92145
H2: Unrela...	0.5	0.184360604	1	-8.408529

2. Complications

Mutations

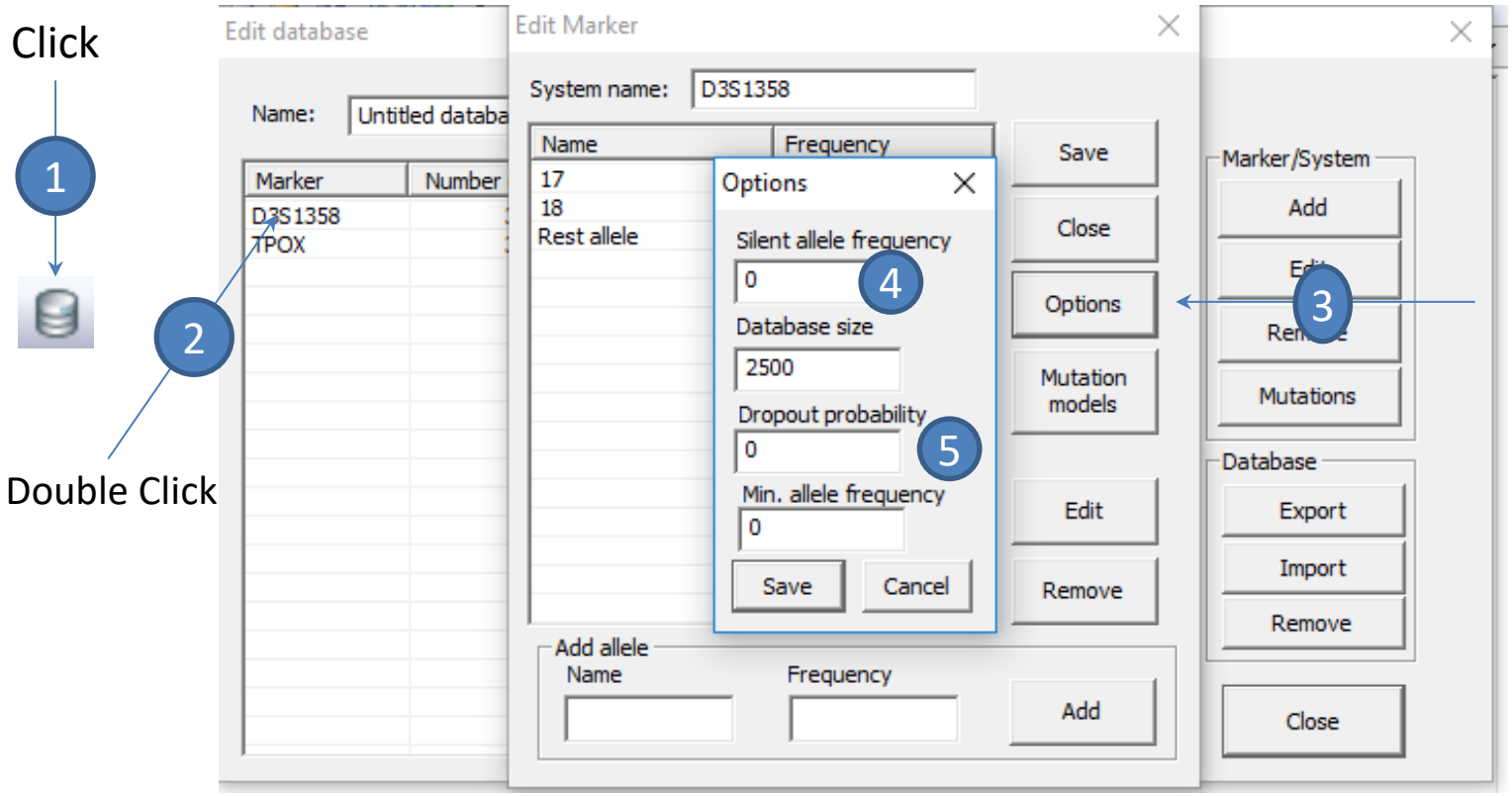


- Enter Step 1 (1), the Database window and press 'Mutations' (2) to get the above window.
- There are five models as shown (see the following slide for more info)
- One can assign the model to all markers (3) or only the ones selected (4) as shown.

Mutation models in Familias

- **Simple model**
  Each mutation has an equal probability of occurring. Appropriate for fast computations (e.g. complicated pedigrees and DVI) as well as for SNP markers.
- **Proportional to frequencies**
  Each mutation has a probability which is proportional to the frequency of the allele we are transitioning to. A low frequency will yield a low mutation probability. Appropriate for testing of statistical properties of calculations.
- **Stepwise model**
  The traditional stepwise model where the probability depends on the number of steps from the original allele to the mutated allele, decreasing probability for longer repeat mutations. Appropriate for STR markers without microvariants.
- **Stepwise stable model**
  The traditional stepwise model where the mutation probabilities have been adjusted to create a stable mutation matrix. Appropriate for testing of statistical properties of calculations.
- **Extended stepwise model (RECOMMENDED)**
  The most complete stepwise model, where both exact repeats as well as microvariants are accounted for. Appropriate for all STR markers.

Silent alleles and Dropout

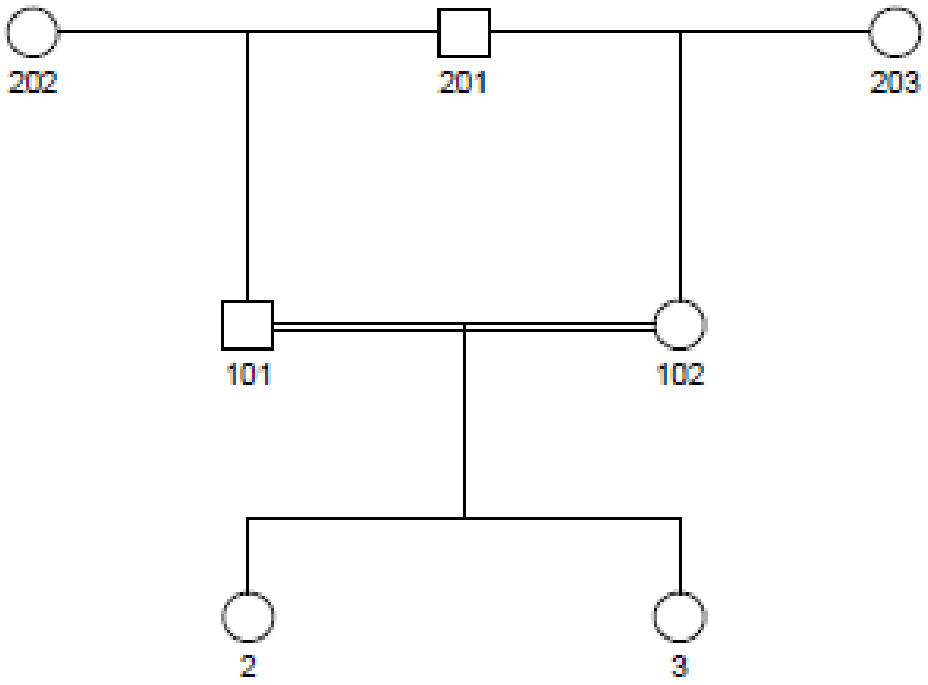


Comment 1
Note that changing the Database size won't affect the results.
Comment 2
Defining a non-zero Min. allele frequency only takes effect once Advanced option is checked

- Enter the Database window (1), double click the marker to edit (2).
- Clicking Options (3) gives the above window where the silent allele frequency (4) and/or Dropout probability (5) can be entered.
- For Dropout , further input is required in the Case DNA to specify the individuals susceptible to dropout (see slide 12).

Inbreeding: Complex pedigrees

- Draw pedigree
- Identify extra persons needed to define the pedigree.
- Enter required persons (Step 2) and pedigrees (Step 4).



Pedigree name : Sisters

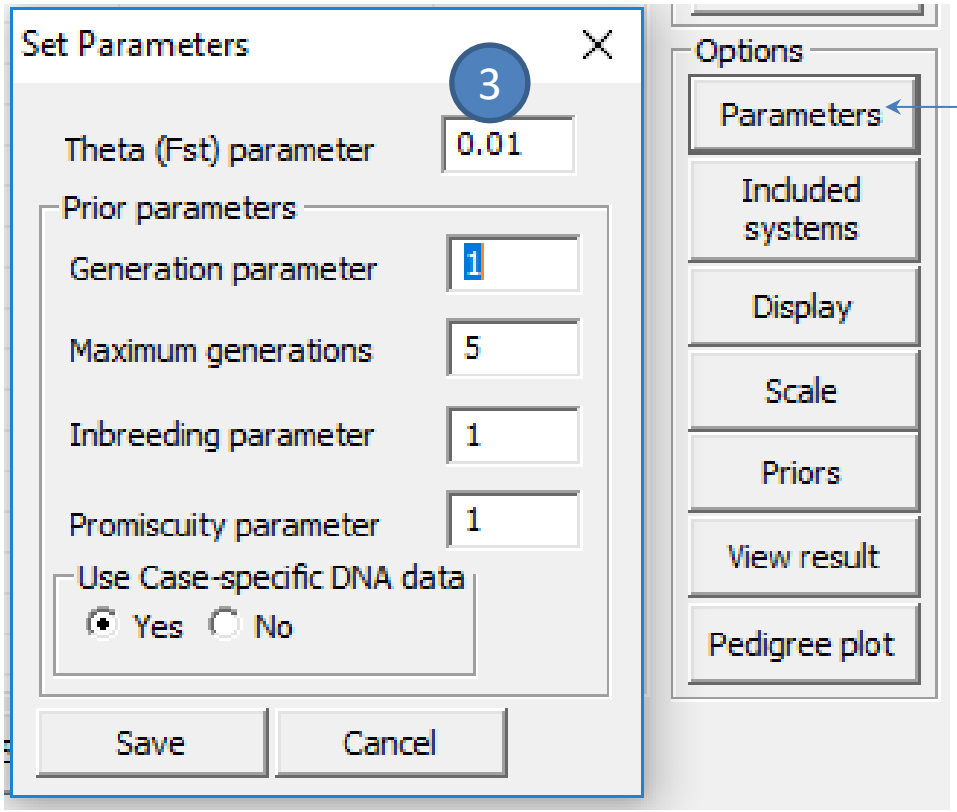
Parent	Child
202	101
201	101
201	102
203	102
101	2
101	3
102	2
102	3

Comment: Persons 202 and 203 above are not needed, but plotting functions will introduce them. The double lines connecting 101 and 102 indicate inbreeding, i.e., parents are related within the pedigree.

Click

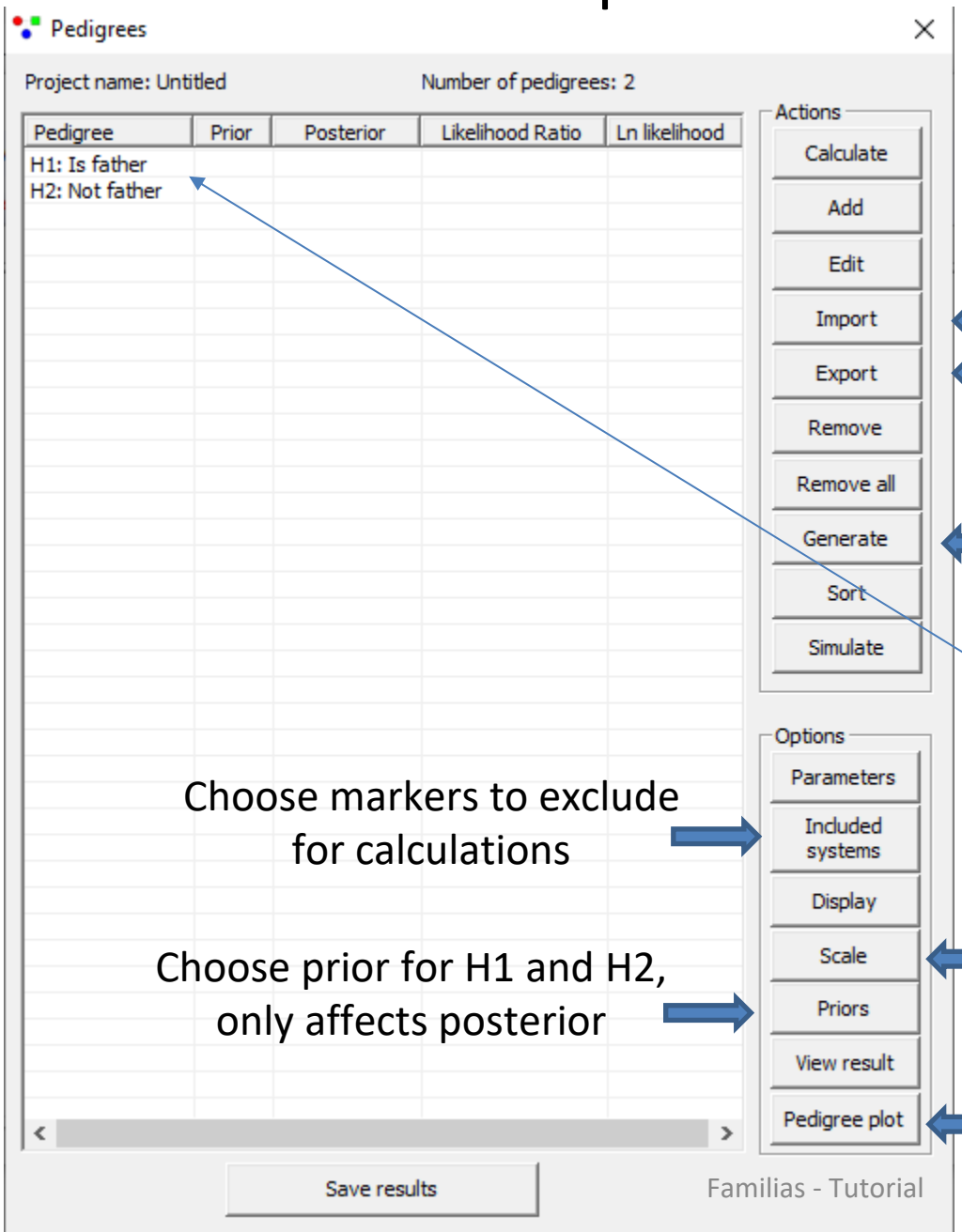
1

Theta correction



- Click ‘Parameters’ in the Pedigrees window (2) . Above the value 0.01 is entered (3).
- ‘Prior parameters’ are virtually never changed: they have no impact on LR, only on the prior (and hence the posterior).

Some further options in the Pedigree window



Imports pedigrees, see next page

Exports pedigree file

Generate pedigrees, see next slides

Choose markers to exclude for calculations

Select denominator of LR: marking H1 and pressing scale gives LR for H2 vs.H1

Choose prior for H1 and H2, only affects posterior

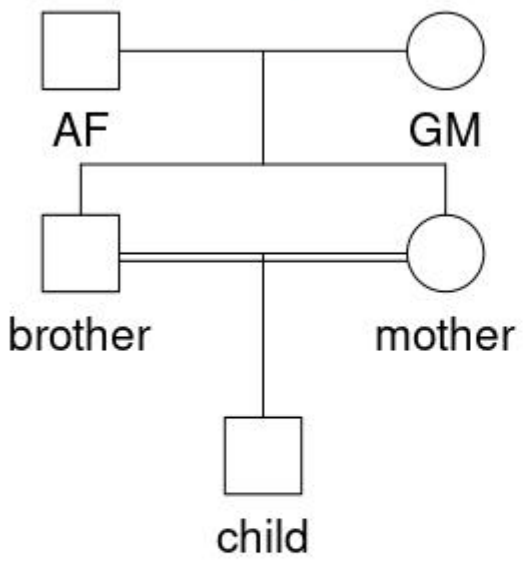
Plots pedigree, see Section 3

Creating pedigrees in QuickPed, import to Familias

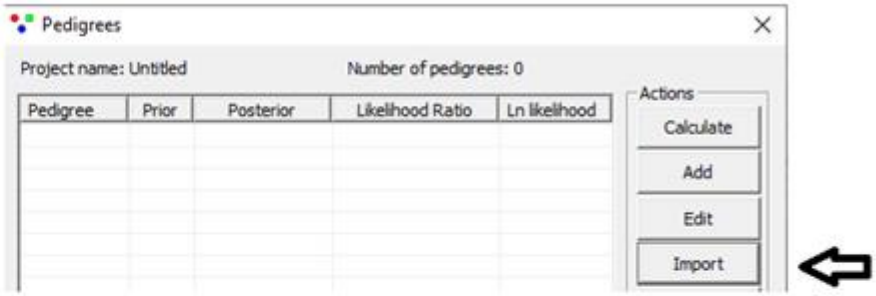
- The next slide shows how the app QuickPed (Vigeland, 2022), an online tool for drawing pedigrees and analysing relatedness, can be used to create pedigrees.
- The pedigrees can be imported to Familias as explained next.

QuickPed: An Interactive Pedigree Creator

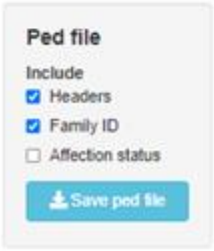
1



4



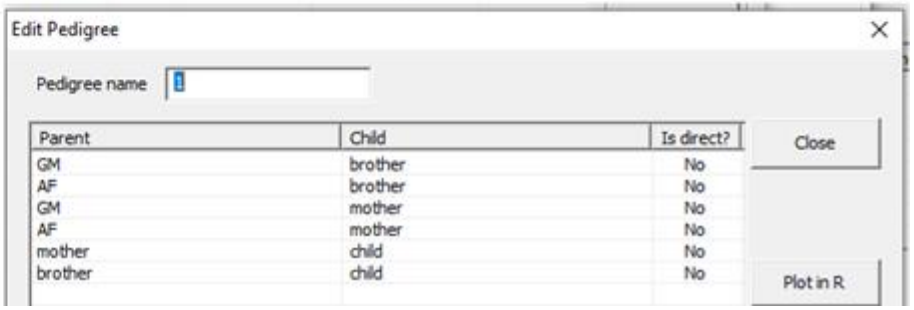
2



3

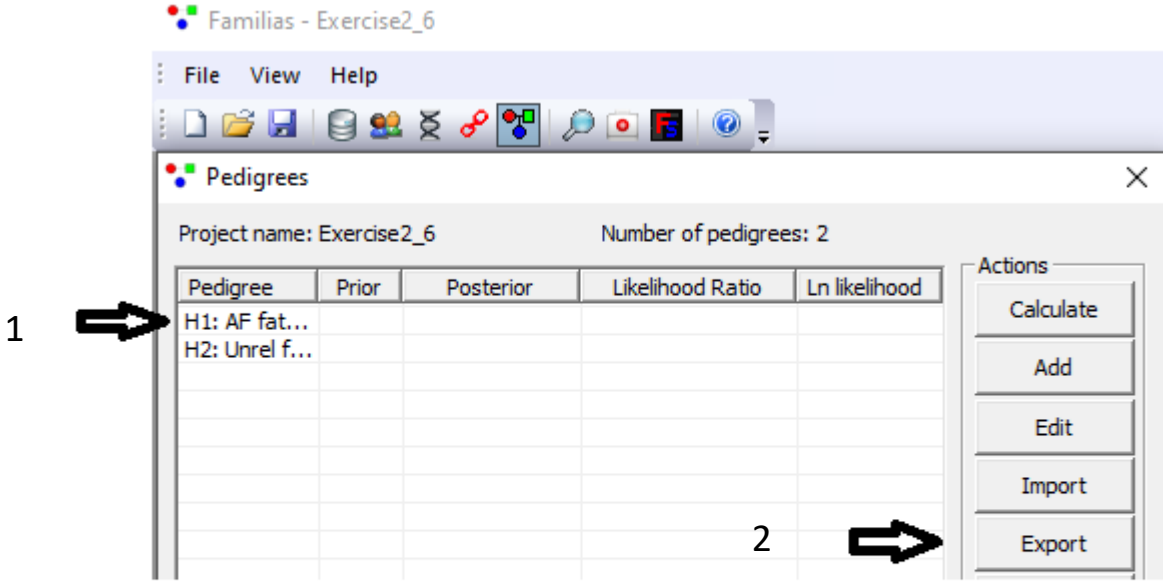
```
famid id fid mid sex
1 AF 0 0 1
1 GM 0 0 2
1 brother AF GM 1
1 mother AF GM 2
1 child brother mother 1
```

5



1. Create pedigree in e.g. QuickPed https://magnusdv.shinyapps.io/quickped/
2. Save ped file from QuickPed
3. Optional look at ped file tutorial.ped
4. Import tutorial.ped to Familias
5. Ped file in Familias

Export from Familias to QuickPed and plot



1. Highlight pedigree. Pedigree must be connected, i.e., none or both parents must be present
2. Hit `Export`
3. `Load file` in QuickPed

Presentation based on Familias tutorial

http://familias.name/tutorial/familias_tutorial_spanish.pdf
http://familias.name/tutorial/familias_tutorial_english.pdf

Daniel Kling, Lourdes Prieto and Thore Egeland