Software - FamLinkX

DANIEL KLING & ANDREAS TILLMAR

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Teachers

Daniel Kling, PhD

- Forensic Expert
- National Board of Forensic Medicine, Sweden
- Worked in the field for almost 15 years
- Developer of Familias, FamLink and FamLinkX
- Applied biostatistics, relationship inference, genetic genealogy

Andreas Tillmar, PhD

- Forensic geneticist & Associate professor
- National Board of Forensic Medicine, Sweden and Linköping University, Sweden
- Worked in the field for almost 20 years
- Technical leadership mixed with R&D
- Applied biostatistics, relationship inference, population genetics, genetic genealogy

Disclaimer!

Points of view are those of the presenters and do not necessarily represent the official position or policies of the National Board of Forensic Medicine or ISFG. Certain commercial software, instruments, and materials are identified in order to specify experimental procedures as completely as possible. In no case does such identification imply a recommendation or endorsement, nor does it imply that any of the materials, instruments, or equipment identified are necessarily the best available for the purpose.

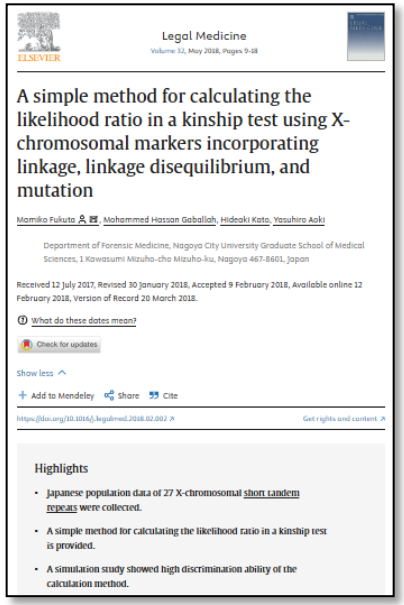
Topics

- Software
- FamLinkX – Demonstration
- Advanced topics
  - Creating pedigrees
  - Advanced settings
  - Simulations
- Validation

SOFTWARE

Software

- Several publications on formulas



Legal Medicine
Volume 32, May 2018, Pages 9-18

A simple method for calculating the likelihood ratio in a kinship test using X-chromosomal markers incorporating linkage, linkage disequilibrium, and mutation

Mamiko Fukuta, Mohammed Hassan Gaballah, Hideaki Kato, Yasuhiro Aoki

Department of Forensic Medicine, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi Mizuho-cho Mizuho-ku, Nagoya 467-8601, Japan

Received 12 July 2017, Revised 30 January 2018, Accepted 9 February 2018, Available online 12 February 2018, Version of Record 20 March 2018.

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Highlights

- Japanese population data of 27 X-chromosomal short tandem repeats were collected.
- A simple method for calculating the likelihood ratio in a kinship test is provided.
- A simulation study showed high discrimination ability of the calculation method.

Forensic Science International: Genetics
Volume 6, Issue 2, March 2012, Pages 198-207

A general method to assess the utility of the X-chromosomal markers in kinship testing

Nádia Pinto, Pedro V. Silva, António Amorim

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https://doi.org/10.1016/j.fsigen.2011.04.014

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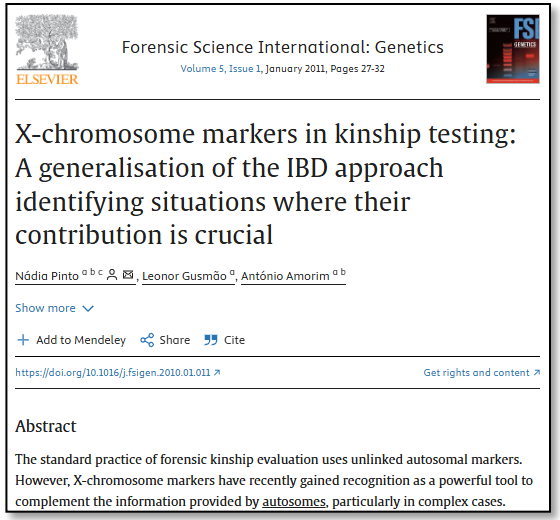
Abstract

In studies involving pedigree reconstruction and kinship estimation, it is acknowledged that some pedigrees have the same algebraic expressions for the joint genotypic probabilities and are, therefore, indistinguishable when considering only genetic information, no matter what the mode of transmission considered. Indeed, although standard forensic practice considers solely unlinked autosomal markers, the existence of pedigrees with the referred theoretical property (that are then said to belong to the same kinship class) is possible when considering any kind of genetic transmission. The research on genetic relatedness has always been linked to the root concept of identity-by-descent (IBD). However, although the basic theoretical core for autosomal transmission has been long formalised, a general method allowing the decision if two



Forensic Science International: Genetics
Volume 5, Issue 1, January 2011, Pages 27-32

X-chromosome markers in kinship testing: A generalisation of the IBD approach identifying situations where their contribution is crucial

Nádia Pinto, Leonor Gusmão, António Amorim

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https://doi.org/10.1016/j.fsigen.2010.01.011

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Abstract

The standard practice of forensic kinship evaluation uses unlinked autosomal markers. However, X-chromosome markers have recently gained recognition as a powerful tool to complement the information provided by autosomes, particularly in complex cases.

Software

- Several publications on formulas

Forensic Science International: Genetics
Volume 5, Issue 1, January 2011, Pages 27-32

X-chromosome markers in kinship testing: A generalisation of the IBD approach identifying situations where their contribution is crucial

Nádia Pinto [a b c], Leonor Gusmão [a], António Amorim [a b]

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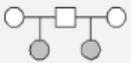
https://doi.org/10.1016/j.fsigen.2010.01.011 Get rights and content

Abstract

The standard practice of forensic kinship evaluation uses unlinked autosomal markers. However, X-chromosome markers have recently gained recognition as a powerful tool to complement the information provided by autosomes, particularly in complex cases.

Box 1. Joint genotypic probabilities for X-markers and two females (Example)

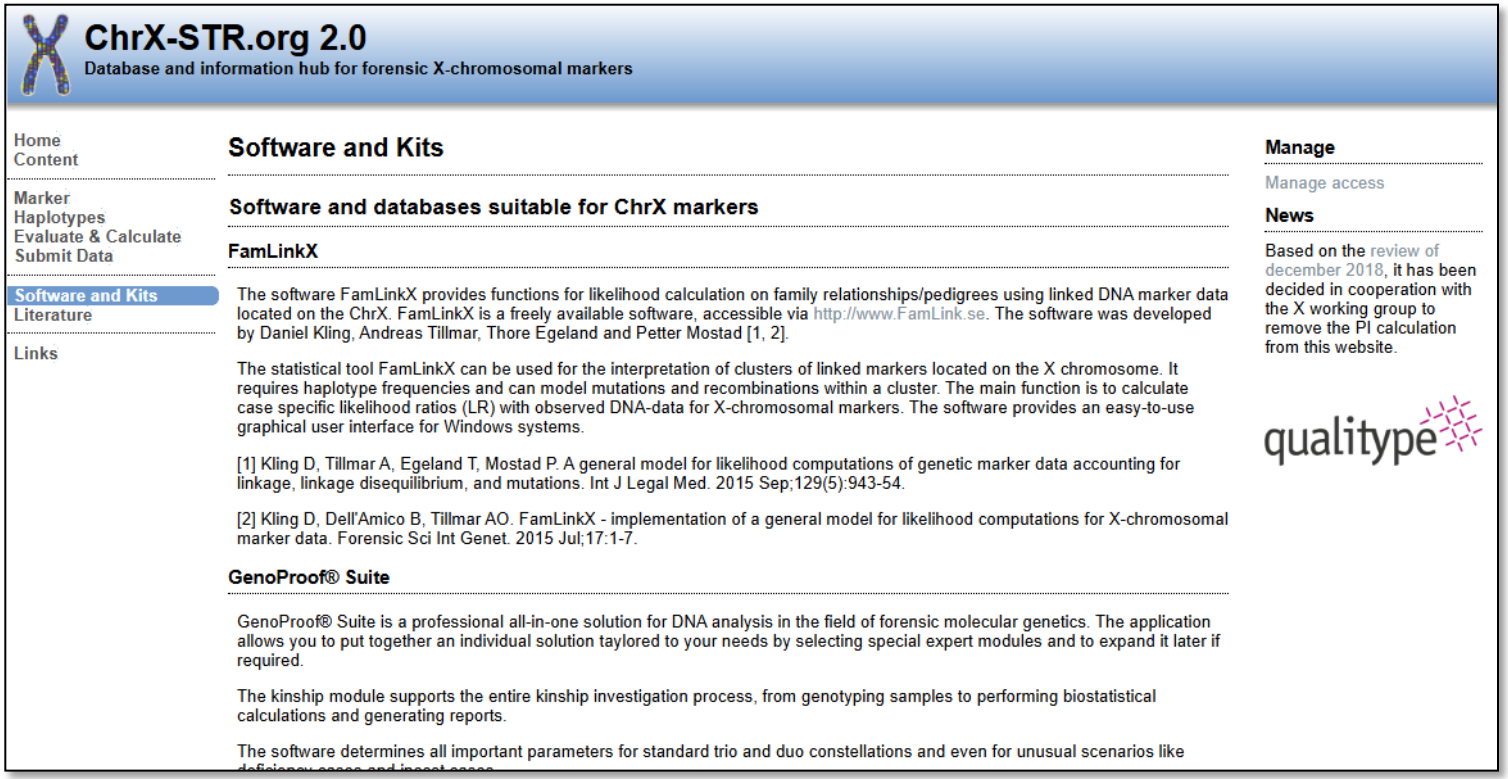
Consider two commonly tested kinships involving two females where the analysis of X-markers seems to be useful: paternal half-sisters and paternal aunt – niece, assuming non-inbred females. Below we present the IBD probabilities associated with these pedigrees, as well as with unrelated X-chromosomal transmission.

Paternal half–sisters	Paternal uncle–niece	Unrelated
		
$x_0^{FF} = 0$ $x_1^{FF} = 1$ $x_2^{FF} = 0$	$x_0^{FF} = 1/2$ $x_1^{FF} = 1/2$ $x_2^{FF} = 0$	$x_0^{FF} = 1$ $x_1^{FF} = 0$ $x_2^{FF} = 0$

Once the IBD probabilities are established we just have to substitute those parameters into the formulas of Table 1 to obtain the joint genotypic probabilities:

Genotypes	Joint genotypic probabilities for X-markers and non-inbred females		
	Paternal half–sisters	Paternal aunt–niece	Unrelated
A_iA_i, A_iA_i	f_i^3	$1/2f_i^3 + 1/2f_i^4$	f_i^4
A_jA_j, A_jA_j	0	$1/2f_i^2f_j^2$	$f_i^2f_j^2$
A_iA_i, A_iA_j	$f_i^2f_j$	$1/2f_i^2f_j + f_i^3f_j$	$2f_i^3f_j$
A_jA_j, A_iA_j	$f_i^2f_j$	$1/2f_i^2f_j + f_i^3f_j$	$2f_i^3f_j$
A_iA_i, A_jA_k	0	$f_i^2f_jf_k$	$2f_i^2f_jf_i$
A_jA_k, A_iA_i	0	$f_i^2f_jf_k$	$2f_i^2f_jf_i$
A_jA_j, A_iA_j	$f_if_j(f_i + f_j)$	$1/2f_if_j(f_i + f_j) + 2f_i^2f_j^2$	$4f_i^2f_j^2$
A_iA_j, A_iA_k	$f_if_jf_k$	$1/2f_if_jf_k + 2f_i^2f_jf_k$	$4f_i^2f_jf_k$
A_jA_j, A_kA_l	0	$2f_jf_jf_kf_l$	$4f_jf_jf_kf_l$

Software



ChrX-STR.org 2.0
Database and information hub for forensic X-chromosomal markers

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Submit Data

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Literature

Links

Software and Kits

Software and databases suitable for ChrX markers

FamLinkX

The software FamLinkX provides functions for likelihood calculation on family relationships/pedigrees using linked DNA marker data located on the ChrX. FamLinkX is a freely available software, accessible via http://www.FamLink.se. The software was developed by Daniel Kling, Andreas Tillmar, Thore Egeland and Petter Mostad [1, 2].

The statistical tool FamLinkX can be used for the interpretation of clusters of linked markers located on the X chromosome. It requires haplotype frequencies and can model mutations and recombinations within a cluster. The main function is to calculate case specific likelihood ratios (LR) with observed DNA-data for X-chromosomal markers. The software provides an easy-to-use graphical user interface for Windows systems.

[1] Kling D, Tillmar A, Egeland T, Mostad P. A general model for likelihood computations of genetic marker data accounting for linkage, linkage disequilibrium, and mutations. Int J Legal Med. 2015 Sep;129(5):943-54.

[2] Kling D, Dell'Amico B, Tillmar AO. FamLinkX - implementation of a general model for likelihood computations for X-chromosomal marker data. Forensic Sci Int Genet. 2015 Jul;17:1-7.

GenoProof® Suite

GenoProof® Suite is a professional all-in-one solution for DNA analysis in the field of forensic molecular genetics. The application allows you to put together an individual solution taylored to your needs by selecting special expert modules and to expand it later if required.

The kinship module supports the entire kinship investigation process, from genotyping samples to performing biostatistical calculations and generating reports.

The software determines all important parameters for standard trio and duo constellations and even for unusual scenarios like

Manage

Manage access

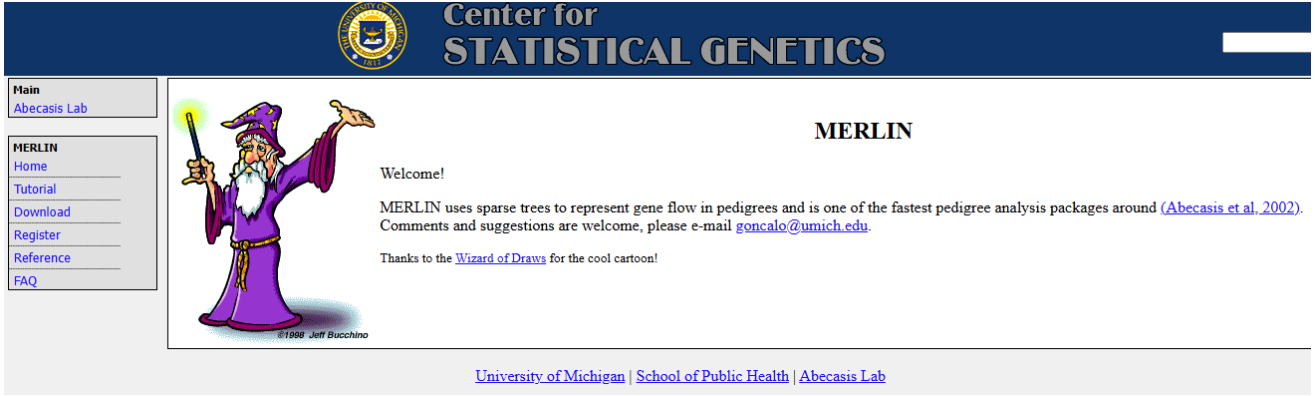
News

Based on the review of december 2018, it has been decided in cooperation with the X working group to remove the PI calculation from this website.

qualitype

Software

Merlin



MINX: Chromosome X Analyses

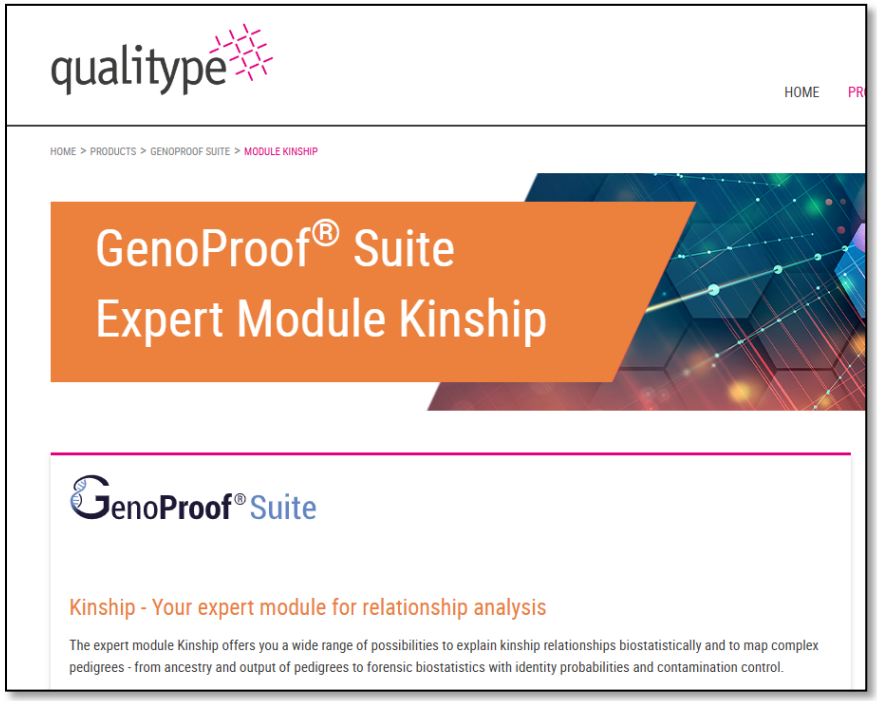
MINX (MERLIN in X) is an X-specific version of Merlin. It is available in distributions of MERLIN version 0.9.1 and later. There is currently no manuscript describing MINX performance and algorithms in detail. Although I believe MINX results to be correct, the methods are unpublished and I would advise using with care.

MINX implements X-chromosome specific versions of the functions provided by the standard Merlin implementation. Males are hemizogous and carry only one X chromosome.

```
D:\>merlin.exe -d markers.dat -m markers.map -f markers.freq -p pedigree.ped --lik --perFamily > results.txt
```

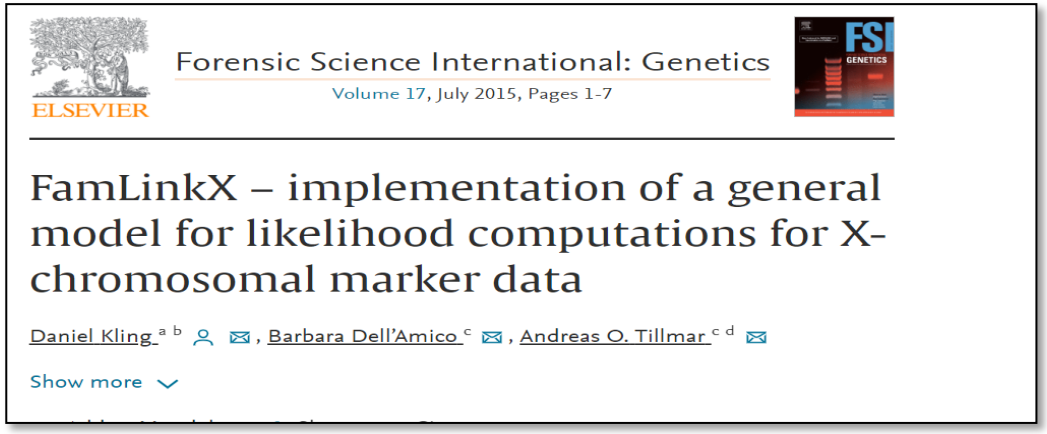
Software

GenoProof



Software

FamLinkX



ELSEVIER

Forensic Science International: Genetics

Volume 17, July 2015, Pages 1-7

FamLinkX – implementation of a general model for likelihood computations for X-chromosomal marker data

Daniel Kling [a b], Barbara Dell'Amico [c], Andreas O. Tillmar [c d]

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FamLinkX

- Windows software (can be run on Macs etc)
- Written in C++
- Works on any marker kit for the X-chromosome
- Developed for the Argus X12 kit (But works just as well with Decaplex or SNPs!)
- Any relationships (e.g. several typed)
- Has a **single** parameter that the user needs to set

FamLinkX

- Algorithm

Home > International Journal of Legal Medicine > Article

A general model for likelihood computations of genetic marker data accounting for linkage, linkage disequilibrium, and mutations

Original Article | Published: 26 November 2014
Volume 129, pages 943–954, (2015) Cite this article

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Daniel Kling, Andreas Tillmar, Thore Egeland & Petter Mostad

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Abstract

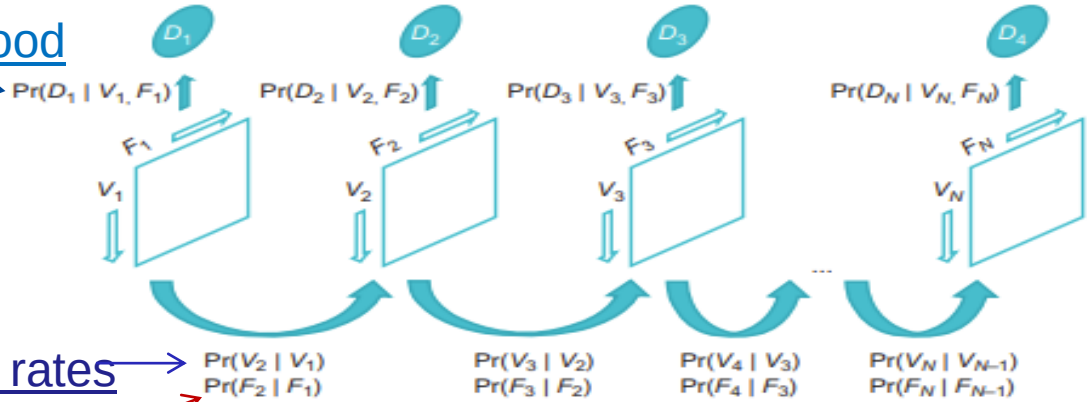
Several applications necessitate an unbiased determination of relatedness, be it in linkage or association studies or in a forensic setting. An appropriate model to compute the joint probability of some genetic data for a set of persons given some hypothesis about the pedigree structure is then required. The increasing number of markers available through high-density SNP microarray typing and NGS technologies intensifies the demand, where using a large number of markers may lead to biased results due to strong dependencies between closely located loci, both within pedigrees (linkage) and in the population (allelic association or linkage disequilibrium (LD)). We present a new general model, based on a Markov chain for inheritance patterns and another Markov chain for founder allele patterns, the latter allowing us to account for LD. We also demonstrate a specific implementation for X chromosomal markers that allows for computation of likelihoods based on hypotheses of alleged relationships and genetic marker data. The algorithm can simultaneously account for linkage, LD, and mutations. We demonstrate its feasibility using simulated examples. The algorithm is implemented in the software FamLinkX,

FamLinkX

- Algorithm

$$\Pr(\text{data} \mid H) = \sum_{V_1} \cdots \sum_{V_N} \sum_{F_1} \cdots \sum_{F_N} \Pr(V_1)\Pr(F_1) \prod_{i=2}^{N} \Pr(V_i \mid V_{i-1}) \prod_{i=2}^{N} \Pr(F_i \mid F_{i-L}, \ldots, F_{i-1}) \prod_{i=1}^{N} \Pr(D_i \mid V_i, F_i), \quad (4.9)$$

Pedigree likelihood



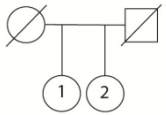
Recombination rates

Haplotype frequencies

FamLinkX

Follows some basic steps (similar to most forensic genetic software)

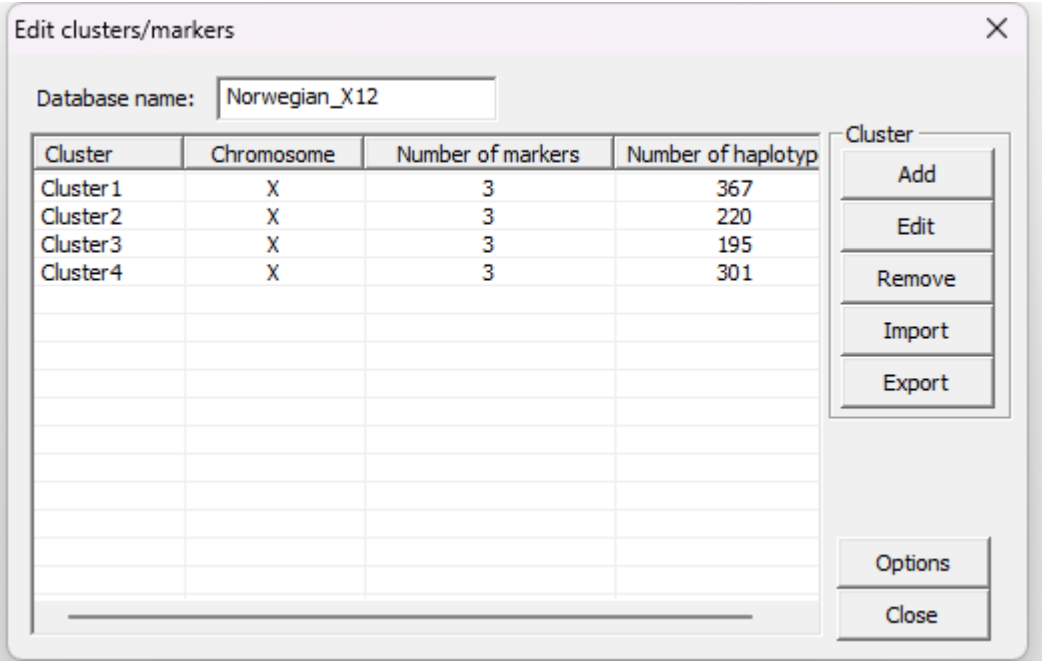
1. Define frequency data (and other parameters)
   a) Alleles and frequencies
   b) Haplotypes
   c) Mutation parameters (rates etc)
   d) Advanced settings
2. Specify pedigree (hypotheses)
   a) Main hypothesis (e.g. Full siblings)
   b) Alternative hypotheses



3. Define case-specific DNA data (STR or SNP data)
4. Compute LR (Different methods)

FamLinkX

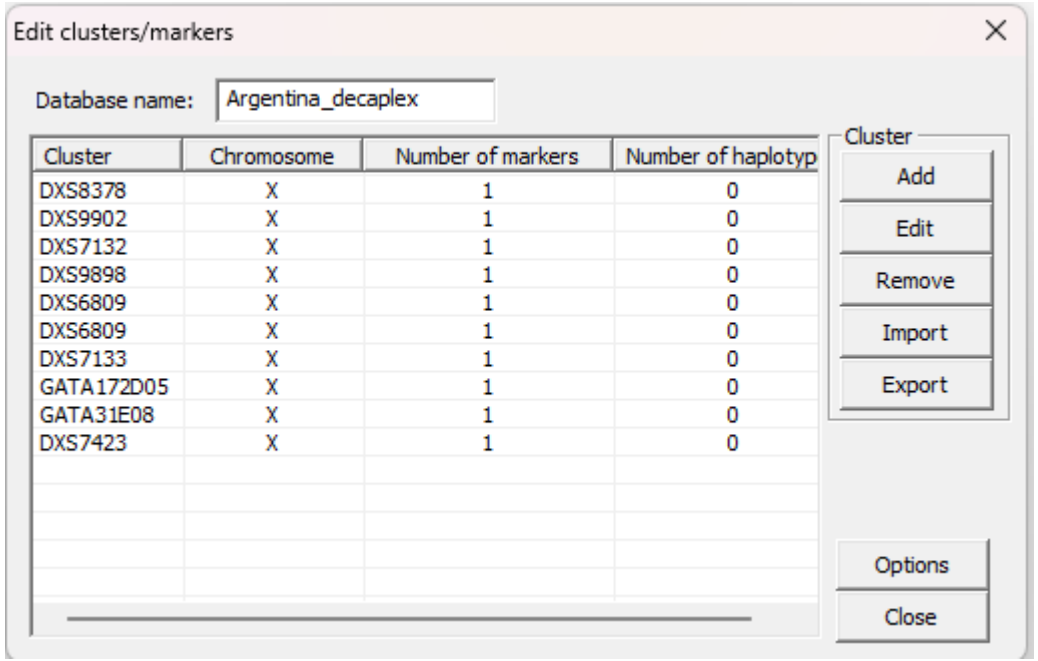
- Define frequency database (Haplotypes if necessary)



Argus X12

FamLinkX

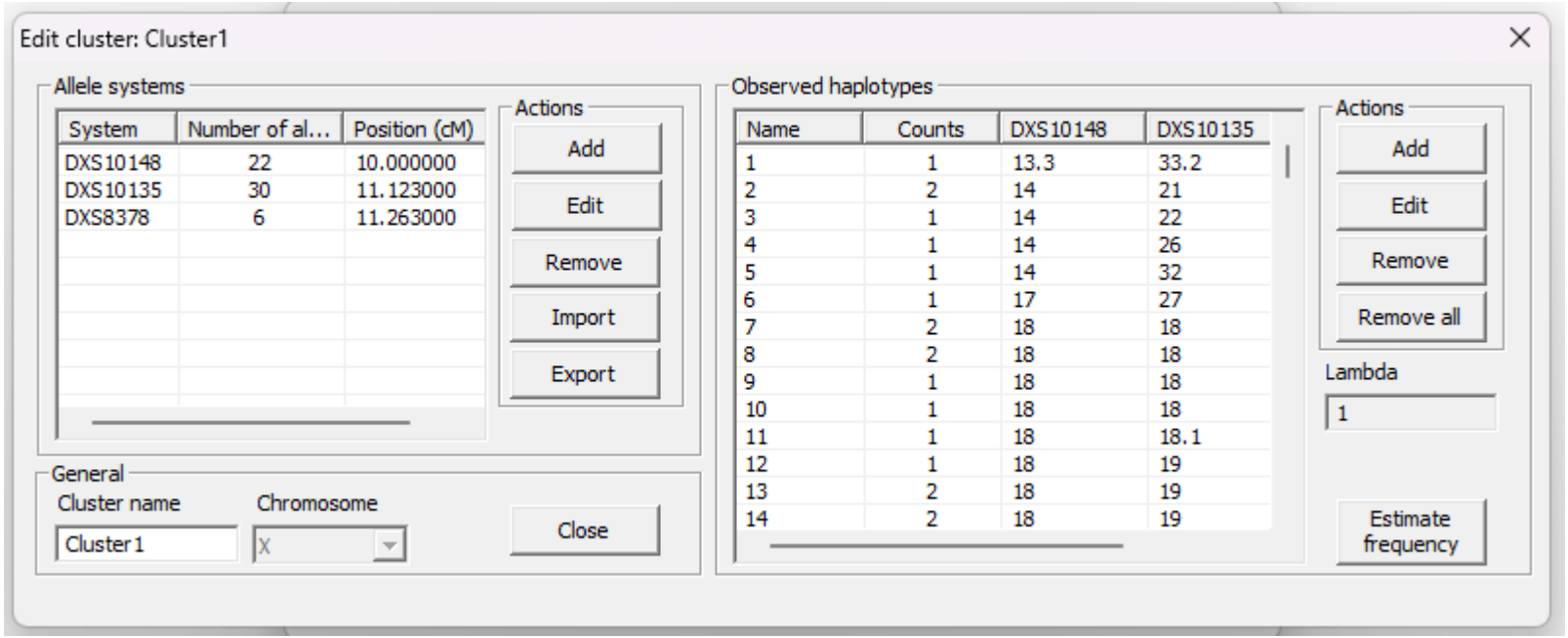
- Define frequency database (Haplotypes if necessary)



Decaplex

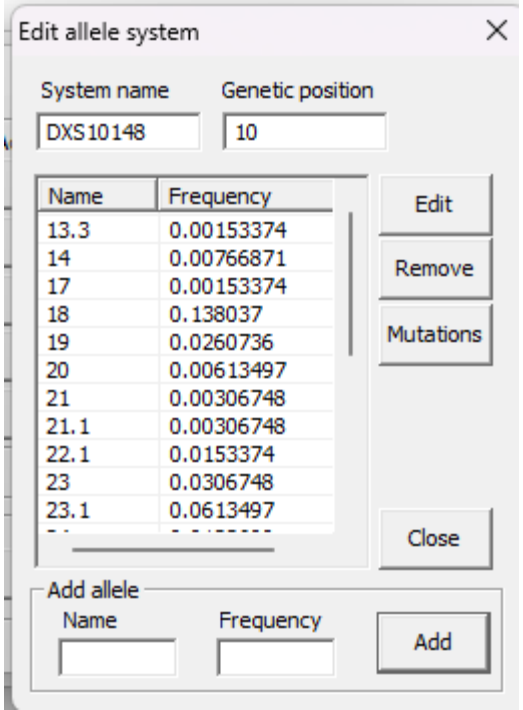
FamLinkX

- Define frequency database (Haplotypes if necessary)



FamLinkX

- Define frequency database (Haplotypes if necessary)



FamLinkX

- Frequency data import format

Allele frequency matrix

ALLELES	DXS10148	DXS10135	DXS8378	DXS7132
7	0,00000	0,00000	0,00000	0,00000
8	0,00000	0,00000	0,00641	0,00000
9	0,00000	0,00000	0,00641	0,00000
10	0,00000	0,00000	0,29487	0,00870
11	0,00000	0,00000	0,36538	0,03478
12	0,00000	0,00000	0,28205	0,12174
13	0,00000	0,00000	0,04487	0,26087
13.3	0,00641	0,00000	0,00000	0,00000
14	0,00000	0,00000	0,00000	0,31304
15	0,00000	0,00641	0,00000	0,18261

FamLinkX

- Frequency data import format

Allele frequency

```
DXS8378
10      0.425925925925926
11      0.296296296296296
12      0.259259259259259
13      0.0185185185185185

DXS9898
8.3     0.0740740740740741
10      0.0185185185185185
11      0.0555555555555556
12      0.333333333333333
13      0.407407407407407
14      0.111111111111111

DXS7133
9       0.5
10      0.222222222222222
11      0.203703703703704
12      0.0740740740740741
```

FamLinkX

- Frequency data import format

Haplotypes

Haplotype	DXS10148	DXS10135	DXS8378	Count
Germa1	13.3	28	12.0	1
Germa2	13.3	29	12.0	1
Germa3	14	27	12.0	1
Germa4	16	22.1	10.0	1
Germa5	16.1	27	10.0	1
Germa6	17	27	12.0	1
Germa7	18	18	11.0	1
Germa8	18	27	11.0	1
Germa9	18	27	11.0	1
Germa10	18	27	11.0	1
Germa11	18	27	12.0	1

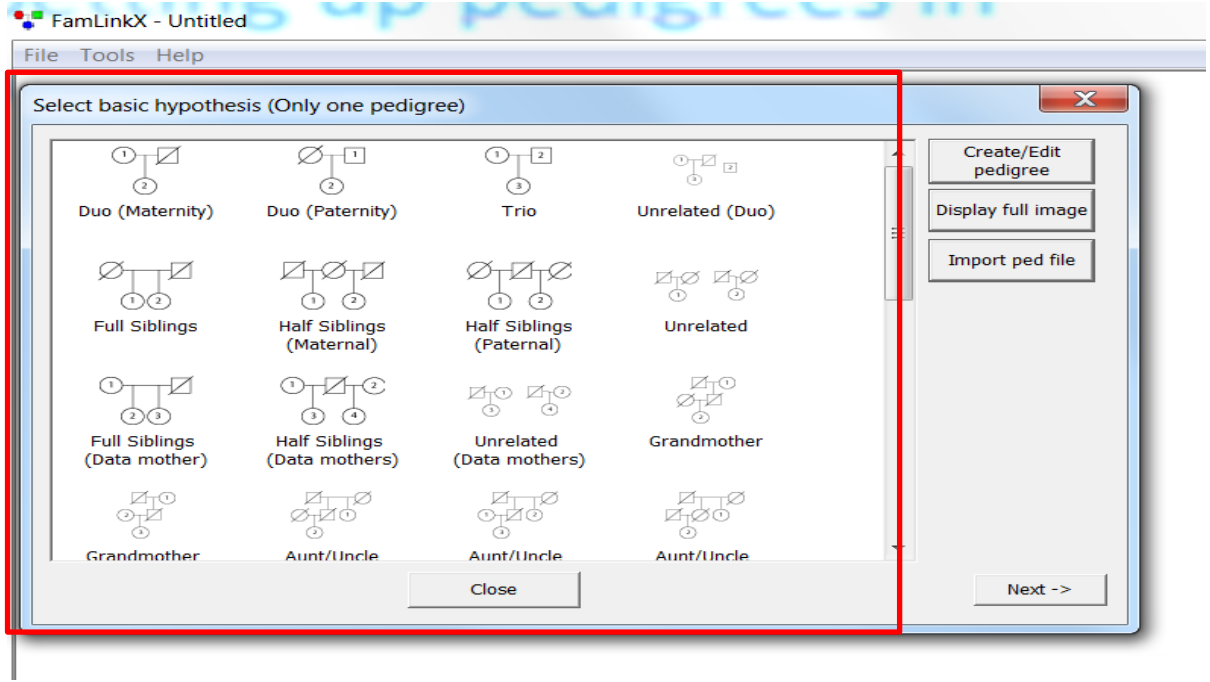
FamLinkX

- Specify hypotheses

Standard set of pedigrees

Total of 50

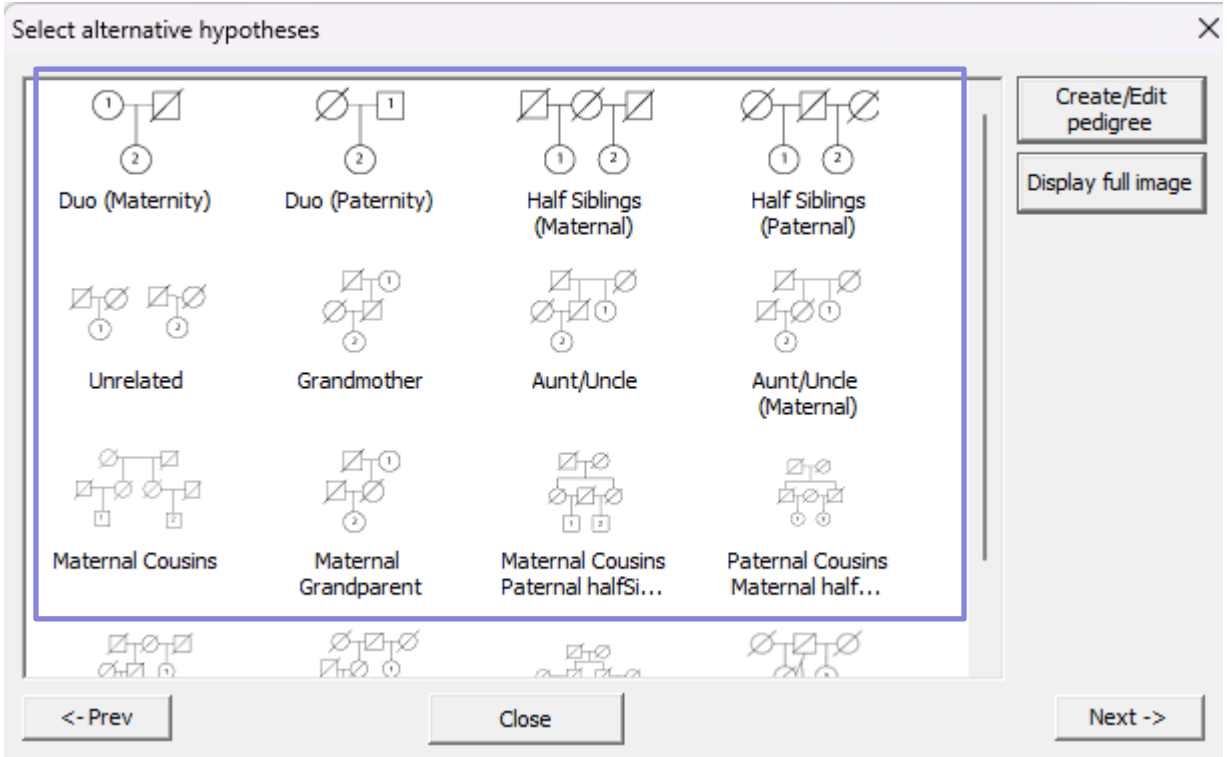
Full model



FamLinkX

- Specify hypotheses

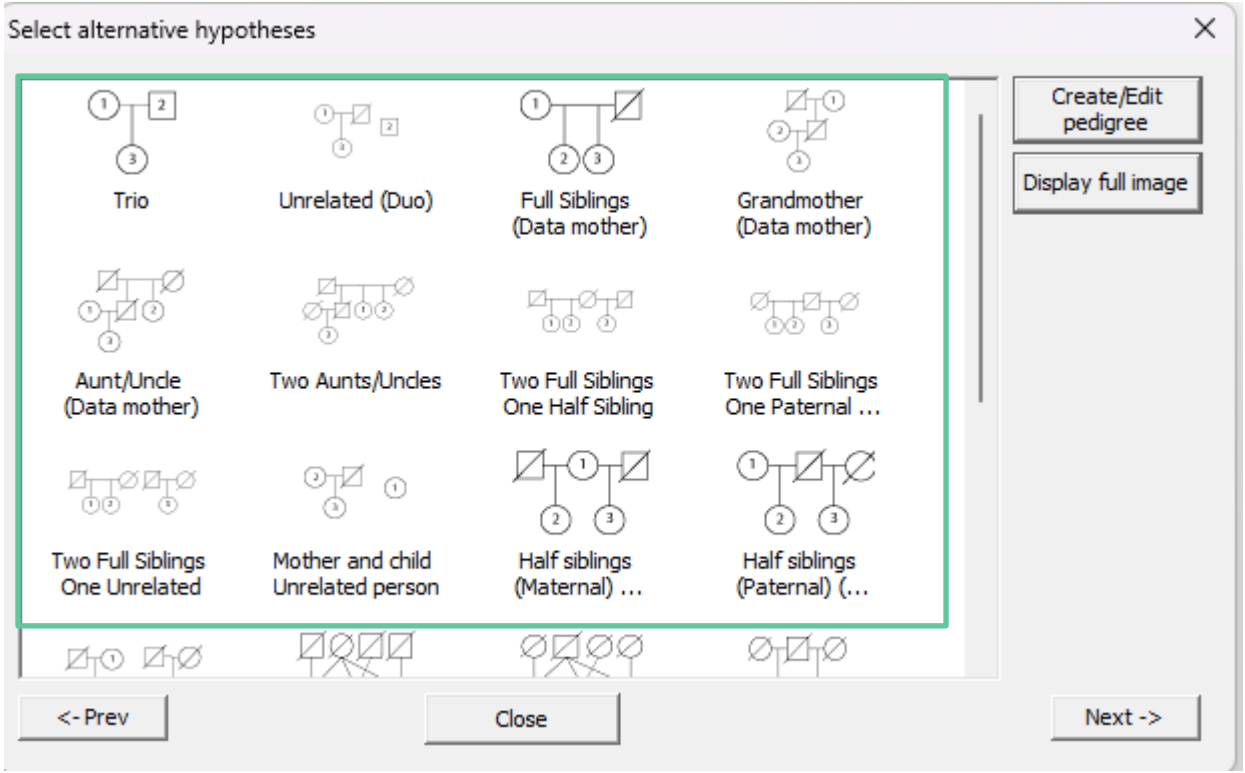
Two typed individuals



FamLinkX

- Specify hypotheses

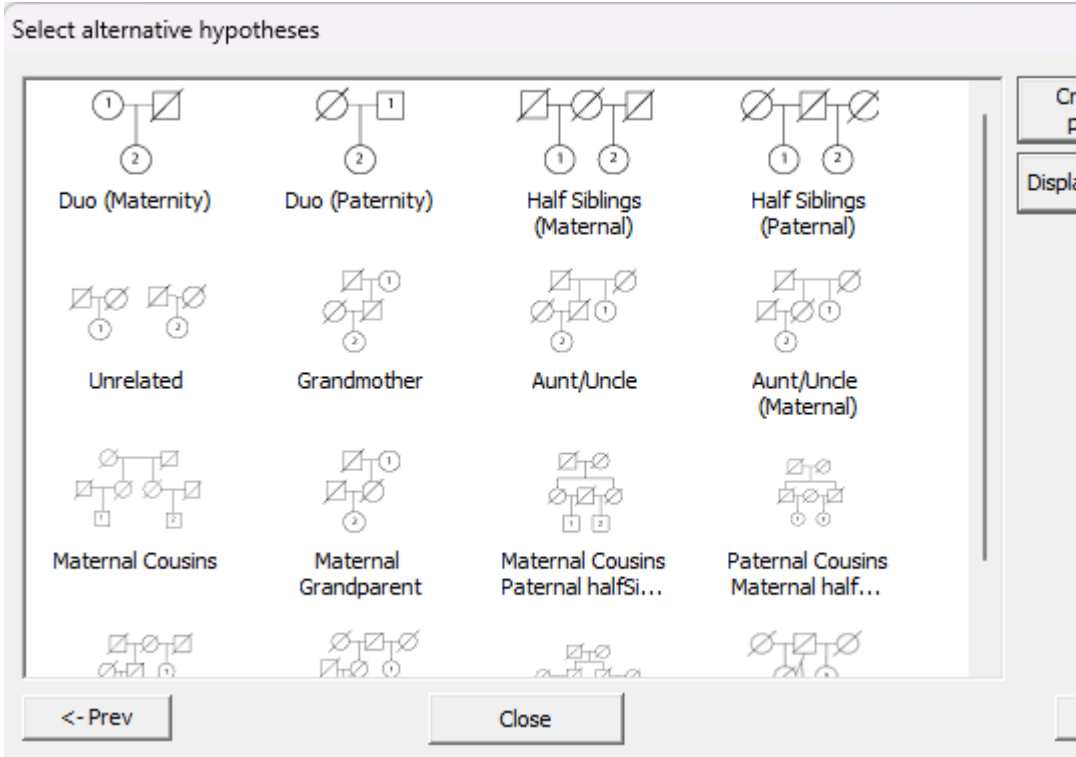
Three typed individuals



FamLinkX

- Specify hypotheses

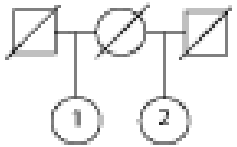
Genders can be changed in most pedigrees!



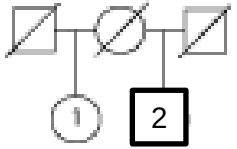
FamLinkX

- Specify hypotheses

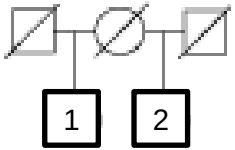
Genders can be changed in most pedigrees!



Half Siblings
(Maternal)



Half Siblings
(Maternal)



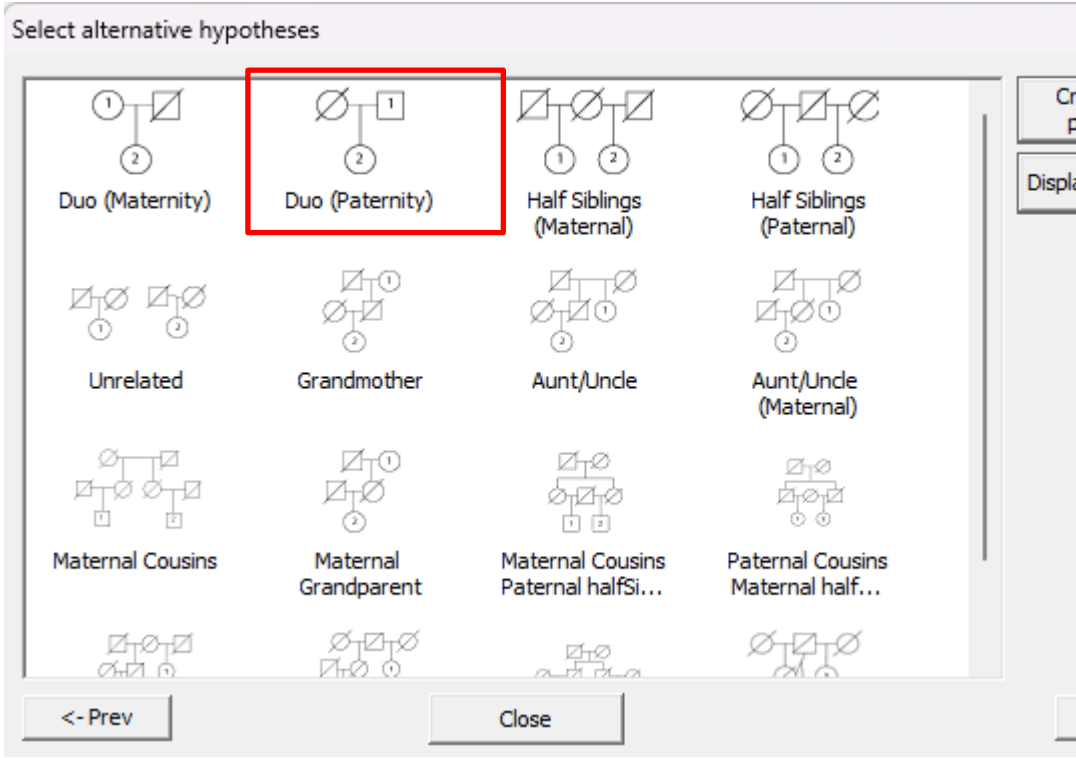
Half Siblings
(Maternal)

FamLinkX

- Specify hypotheses

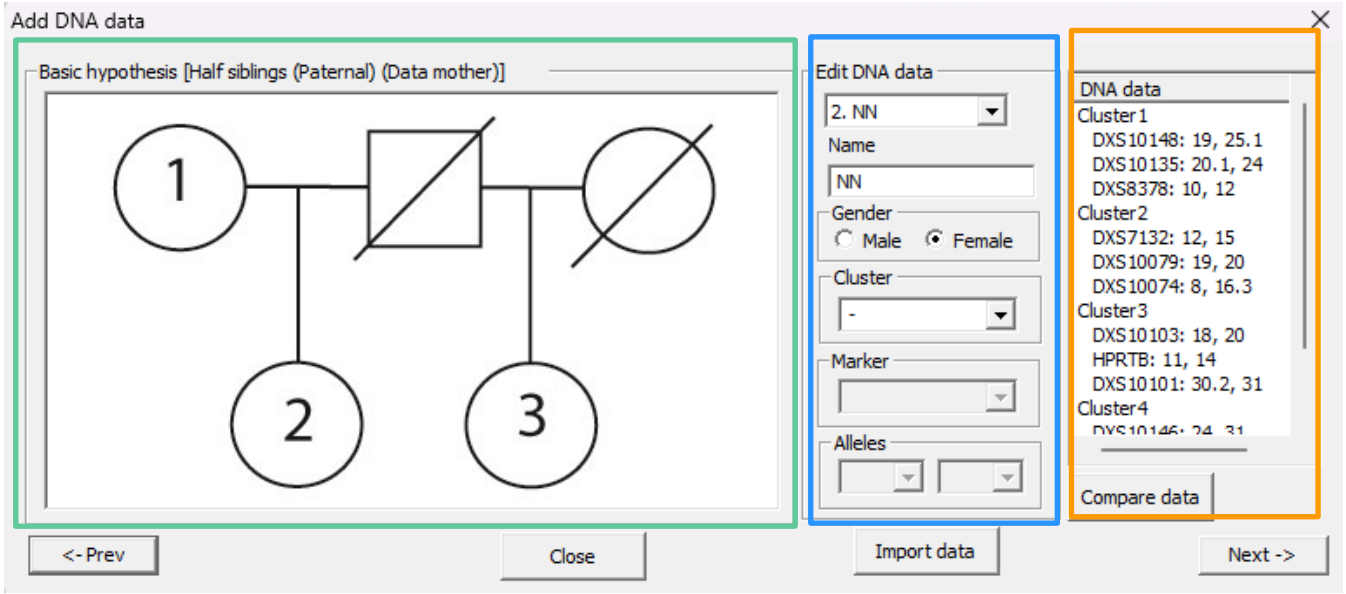
Genders can be changed in most pedigrees!

Not in all!



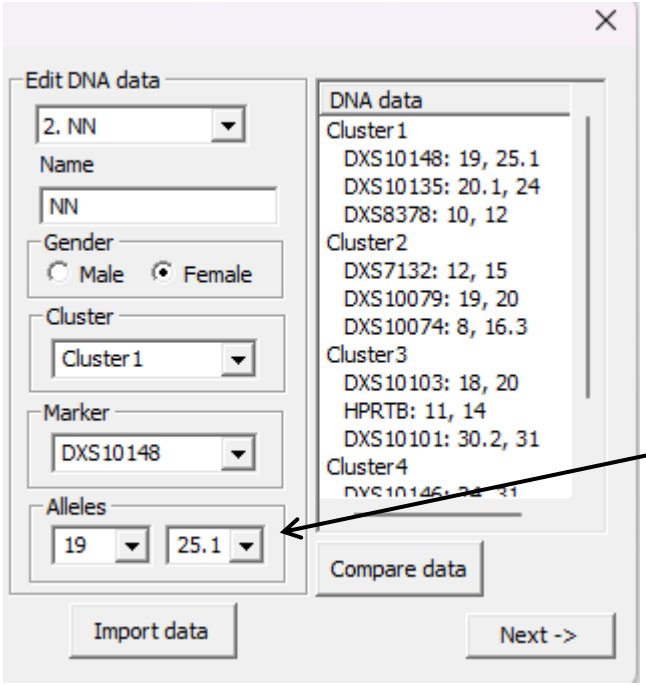
FamLinkX

- Import case-related DNA data



FamLinkX

- Import case-related DNA data



FamLinkX

- Import format for case-specific DNA data

”Familias-like” format

Sample name:	Ameloger	Ameloger	DXS10148	DXS10148	DXS10135	DXS10135	DXS8378 1	DXS8378
Mother	X	X	22.1	27.1	24	25	10	1
Child	X	X	25.1	27.1	24	25	11	1

xml (CODIS-like) format

Genemapper-like format

FamLinkX

- Import format for case-specific DNA data

”Familias-like” format

xml (CODIS-like) format

Genemapper-like format

```
<?xml version="1.0" encoding="UTF-8"?>
<CODISImportFile xmlns="urn:CODISImportFile-schema">
    <SPECIMEN>
        <SPECIMENID>Mother</SPECIMENID>
        <SPECIMENCATEGORY>Mother</SPECIMENCATEGORY>
        <SPECIMENNATIONALITY>Europe</SPECIMENNATIONALITY>
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            <ALLELE>
                <ALLELEVALUE>12</ALLELEVALUE>
                <ALLELEHEIGHT>1274</ALLELEHEIGHT>
            </ALLELE>
        </LOCUS>
```

FamLinkX

- Import format for case-specific DNA data

”Familias-like” format

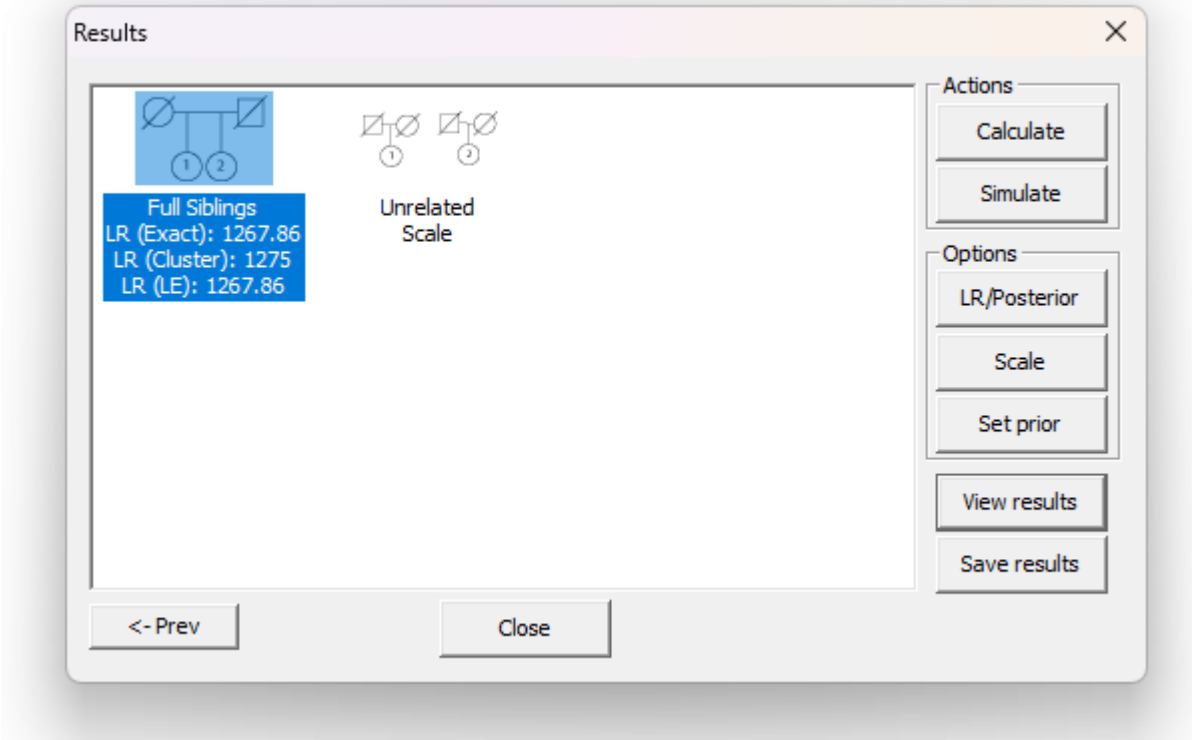
xml (CODIS-like) format

Genemapper-like format

Sample	Marker	Allele 1	Allele 2
Mother	DXS10135	14	16
Mother	DXS7123	20	23

FamLinkX

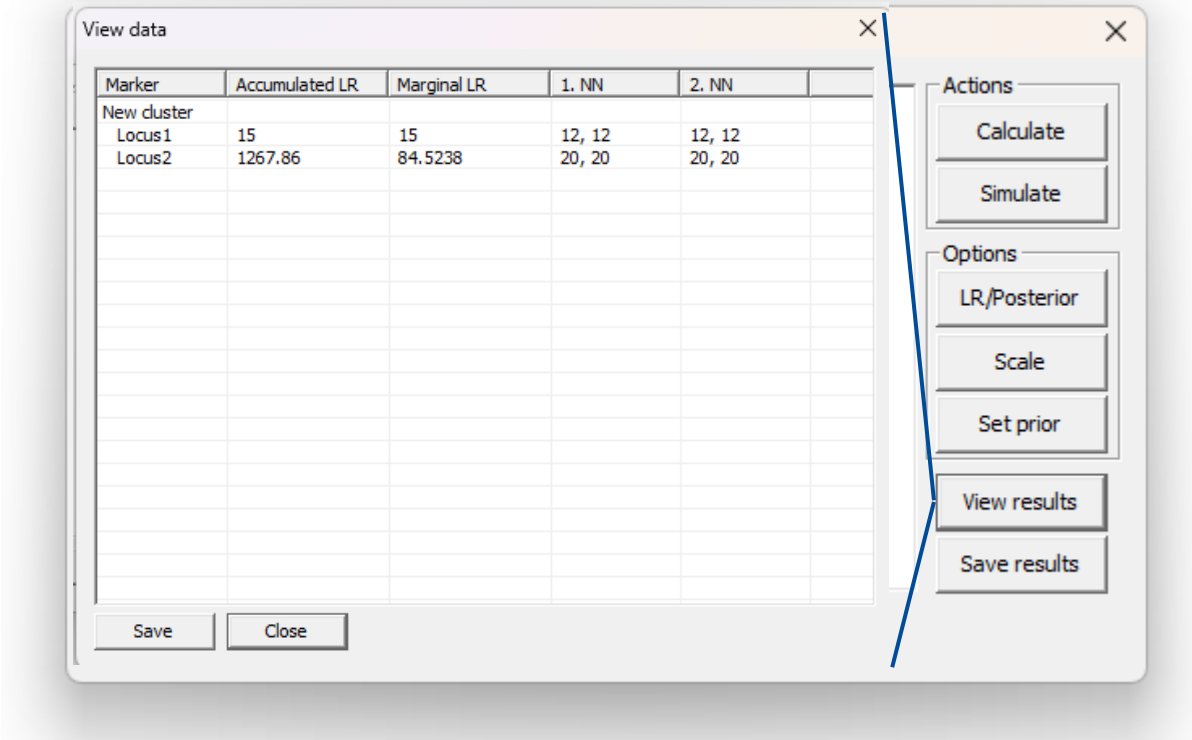
- Calculate LR



Three different methods to compute LR (more later)

FamLinkX

- Calculate LR

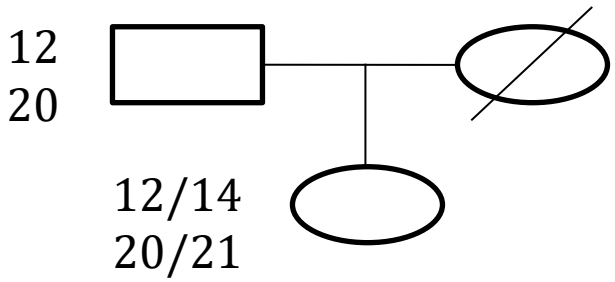


Individual marker LRs

FamLinkX – Basics

DEMONSTRATION 1

Demonstration



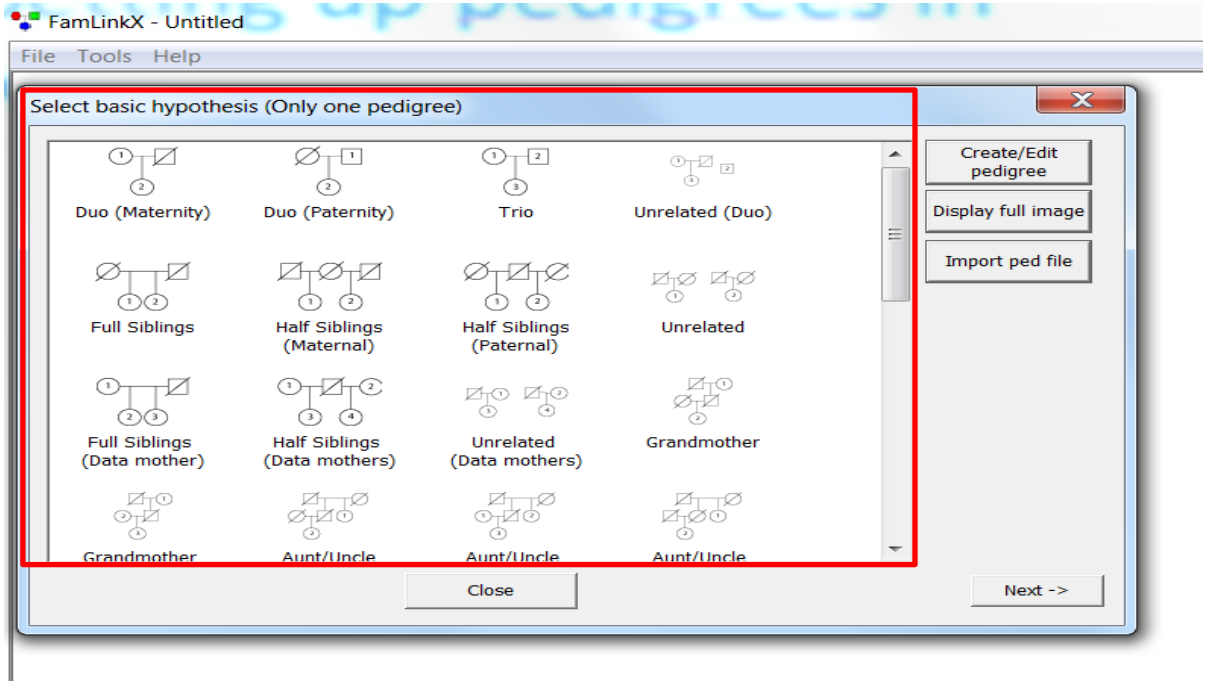
$LR=1/2p_{12} * 1/2p_{20}=5*5=\underline{25}$

Marker	Position (cM)	Alleles	Frequencies
DXS10148	19.84	12, 14	0.1, 0.9
DXS10135	20.03	20, 21	0.1, 0.9

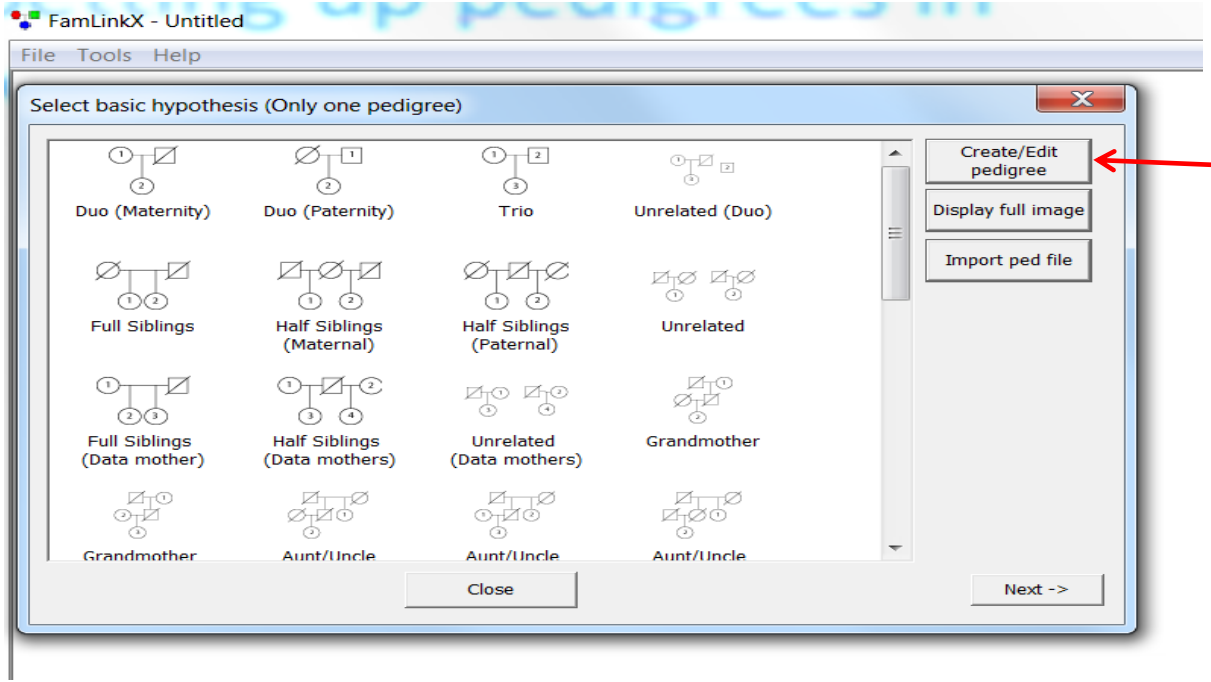
ADVANCED TOPICS

Creating pedigrees in FamLinkX

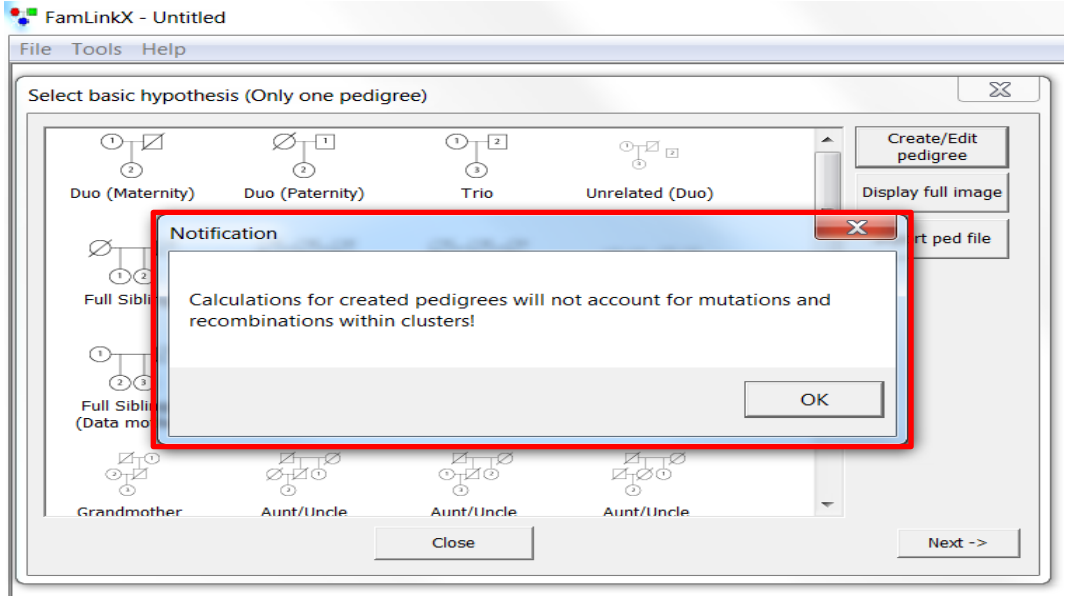
Standard set of pedigrees



Creating pedigrees in FamLinkX



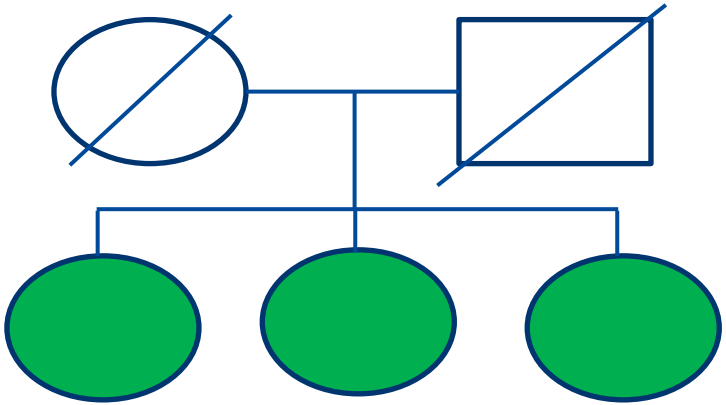
Creating pedigrees in FamLinkX



Created pedigrees will use Merlin for computations and mutations will not be considered!

Creating pedigrees in FamLinkX

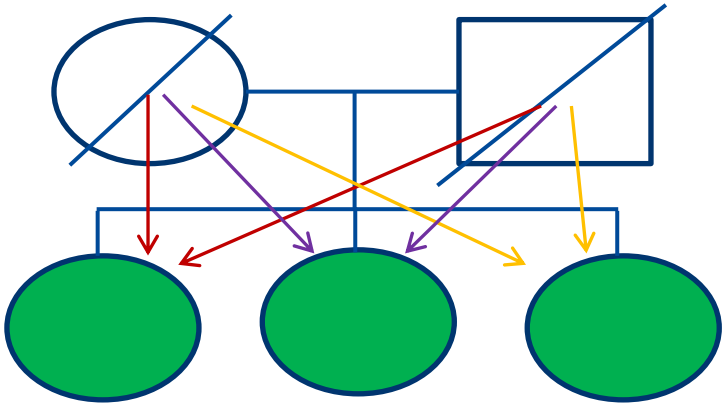
We first need to define the persons involved



2 untyped parents
3 typed children

Creating pedigrees in FamLinkX

Next identify relations

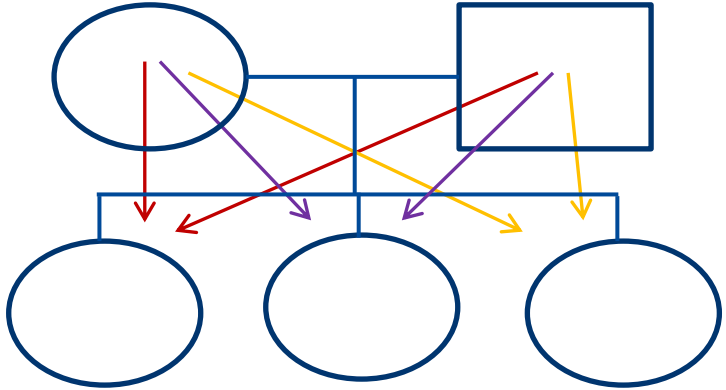


6 relations in total

Creating pedigrees in FamLinkX

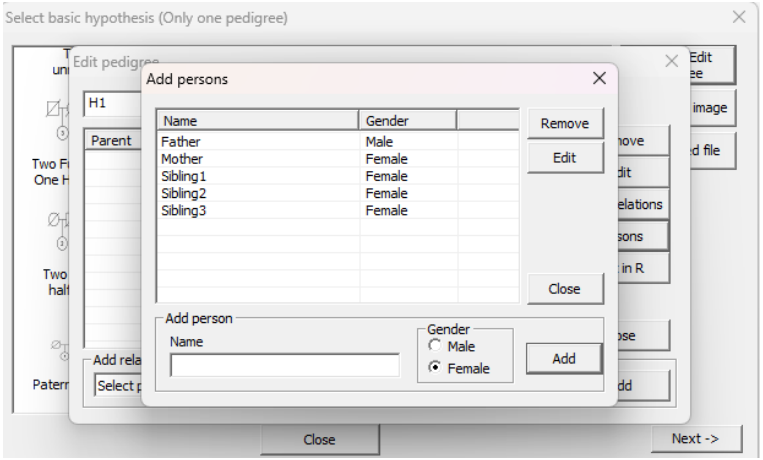
General recipe

1. Identify persons
2. Identify the parents of each person
3. Known relations
4. Pedigree specific relations

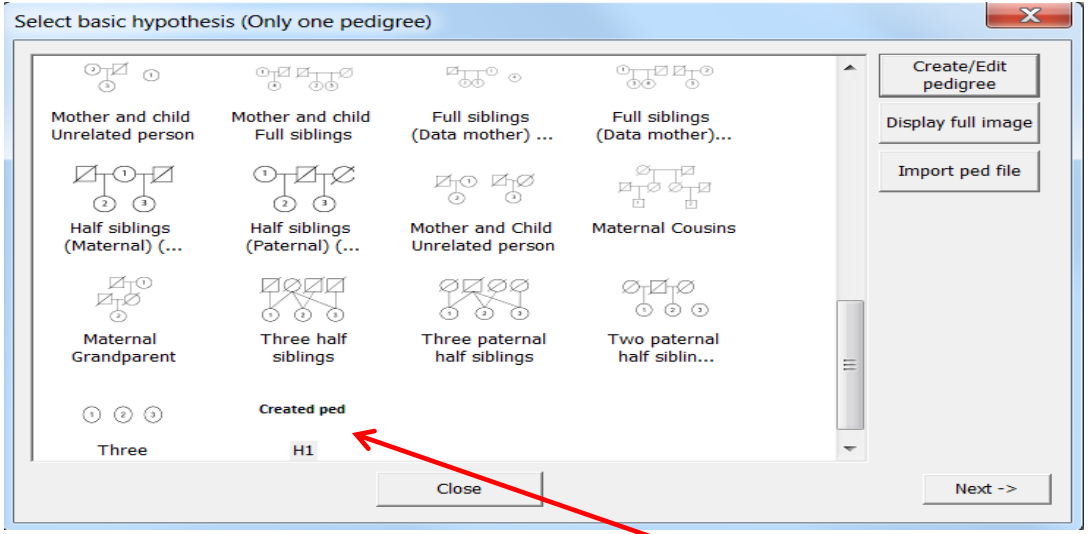


Six relations

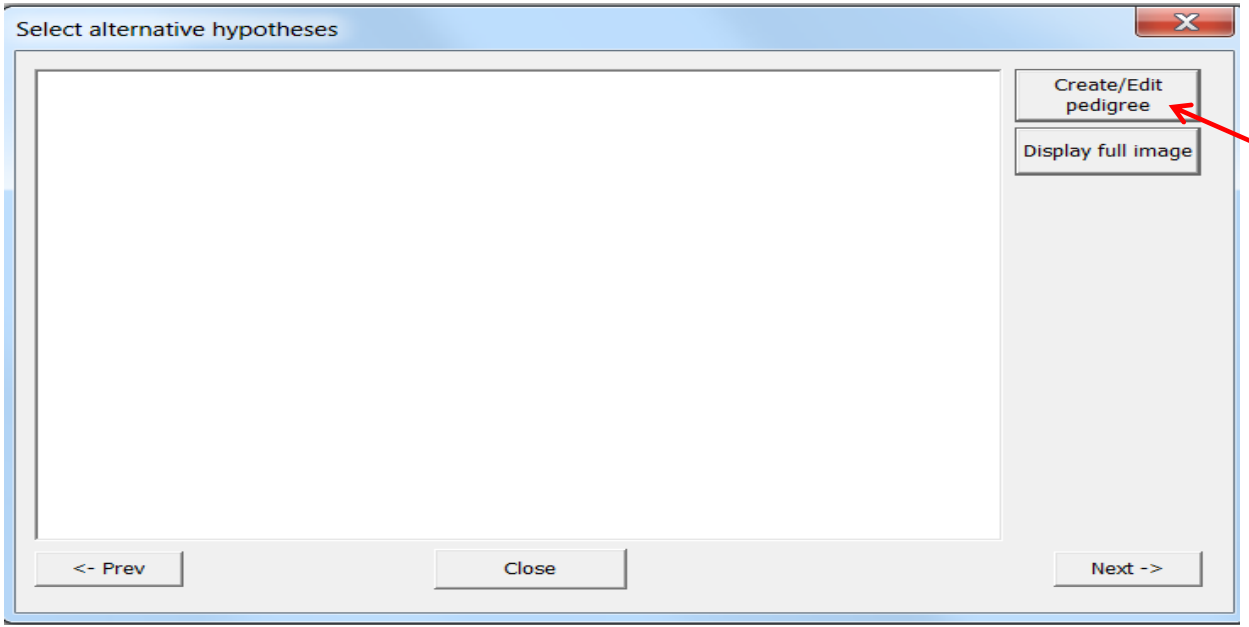
Creating pedigrees in FamLinkX



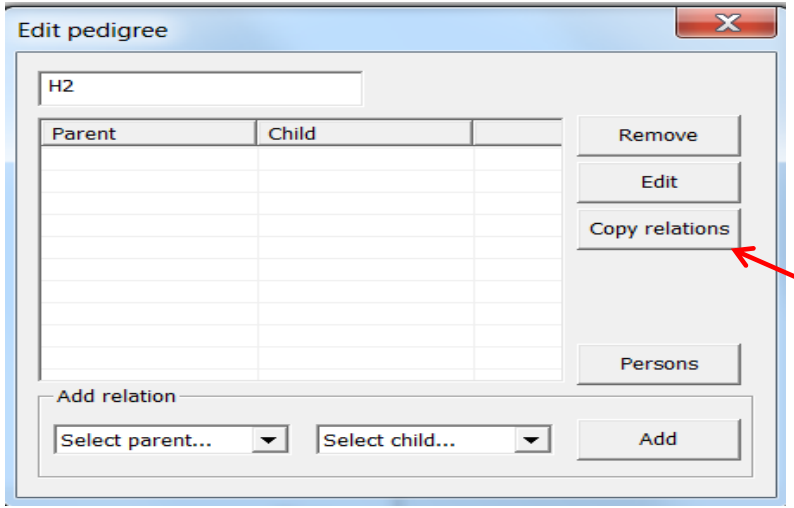
Creating pedigrees in FamLinkX



Creating pedigrees in FamLinkX

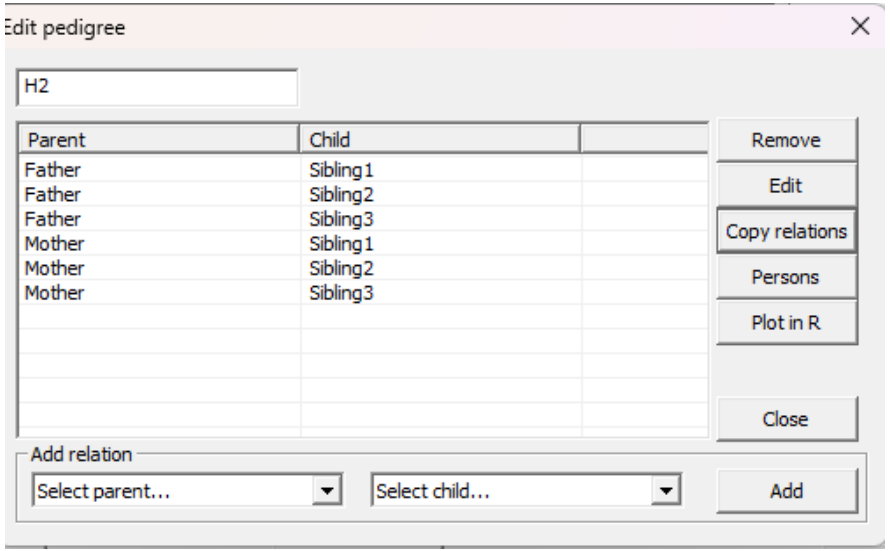


Creating pedigrees in FamLinkX



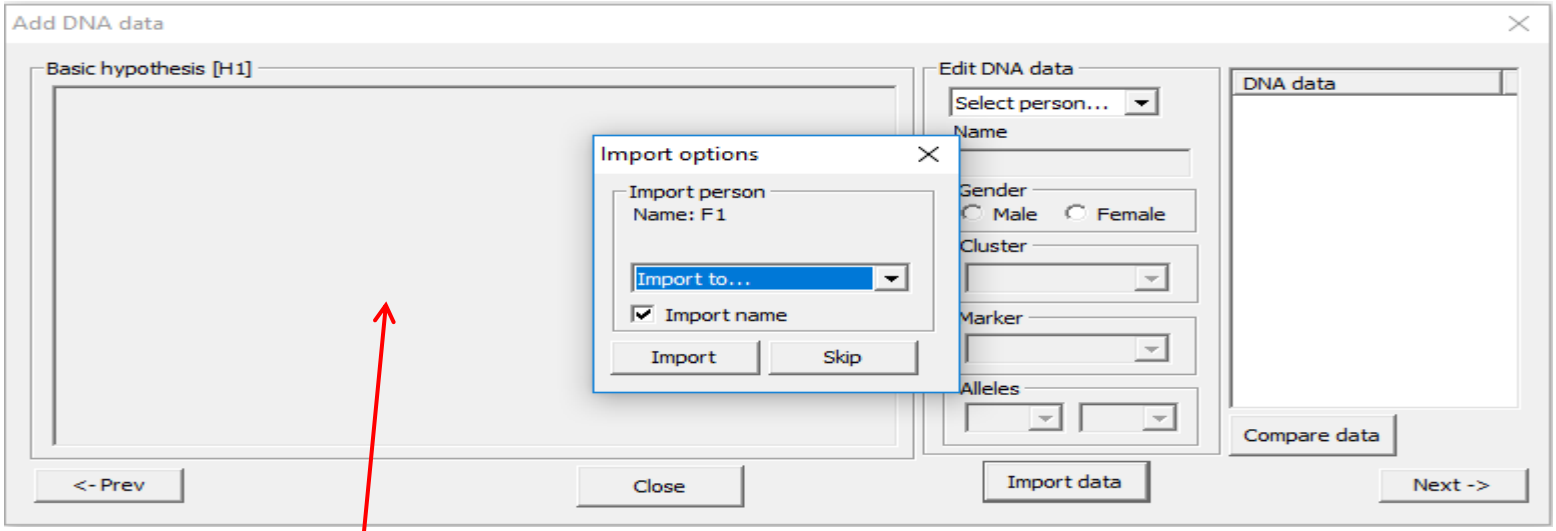
Copy all relations from first pedigree (H1)

Creating pedigrees in FamLinkX



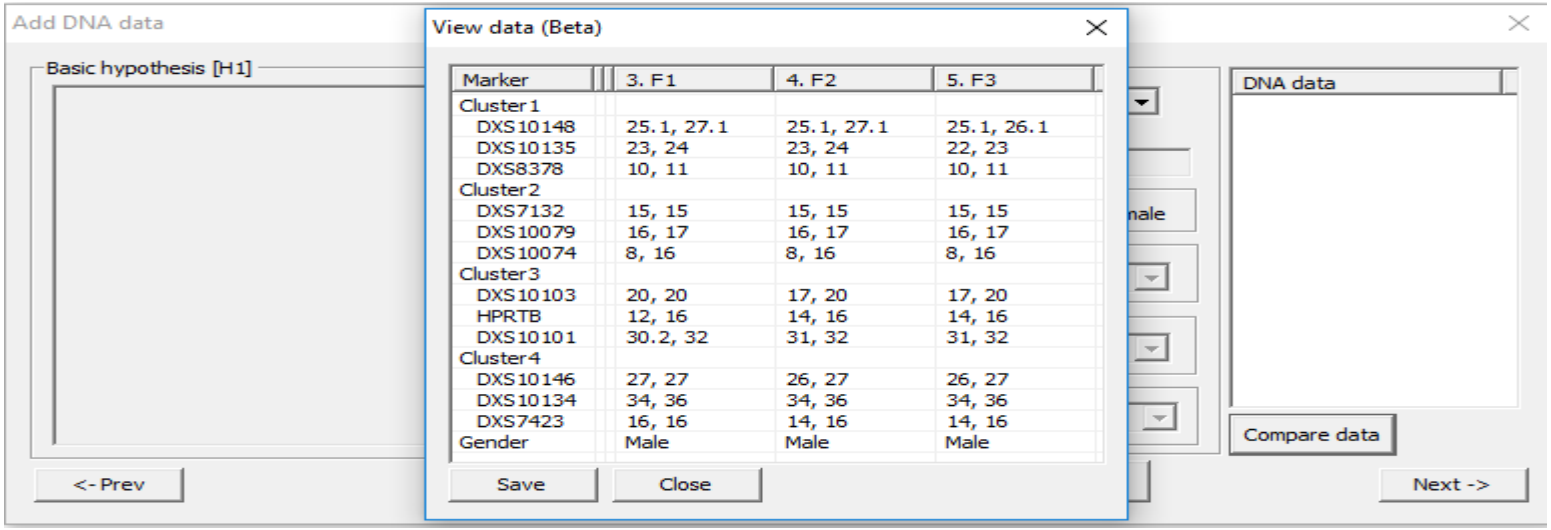
Copy all relations from first pedigree (H1)

Creating pedigrees in FamLinkX



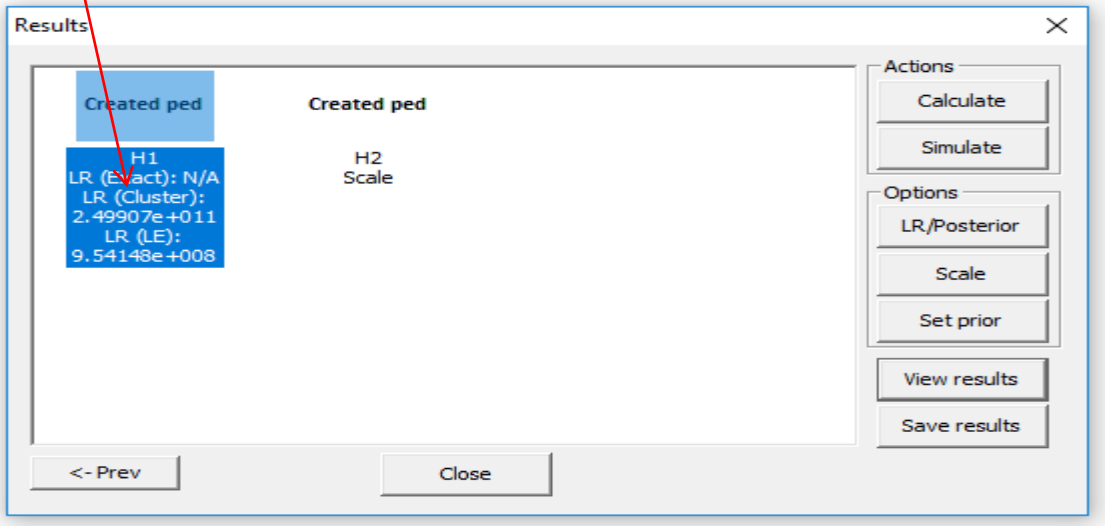
No illustration! (More later)

Creating pedigrees in FamLinkX



Creating pedigrees in FamLinkX

We should use LR (Cluster)



Creating pedigrees in FamLinkX

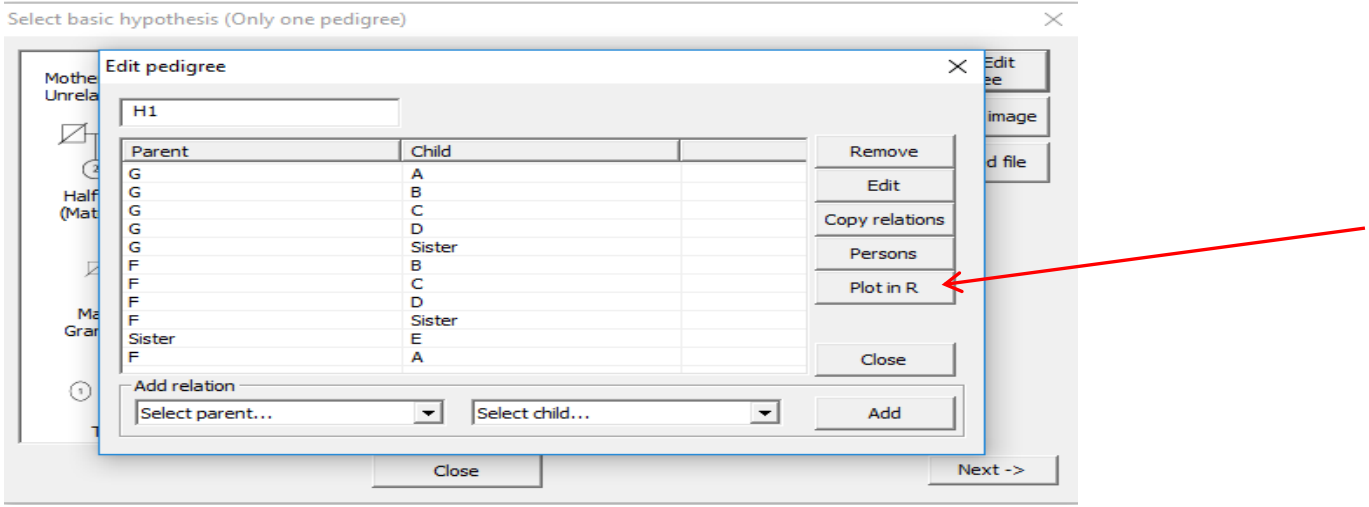
Why does the LR become 0? (or infinity)

- Check pedigree (possible errors)
- Check genders of all persons
- Check for potential mutations
- Advanced users may check the temporary output from Merlin via

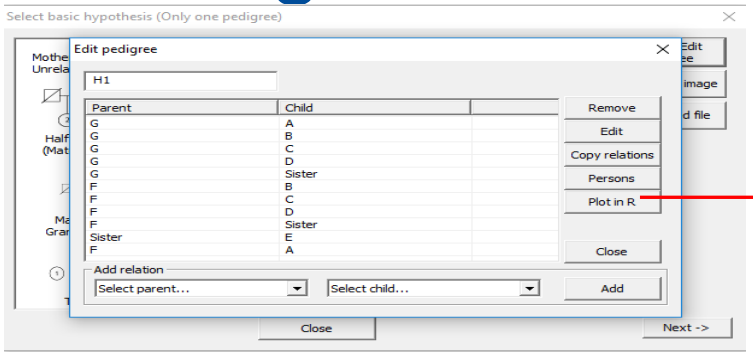
C:\Program files (x86)\FamLinkX\temp\tempResults.txt

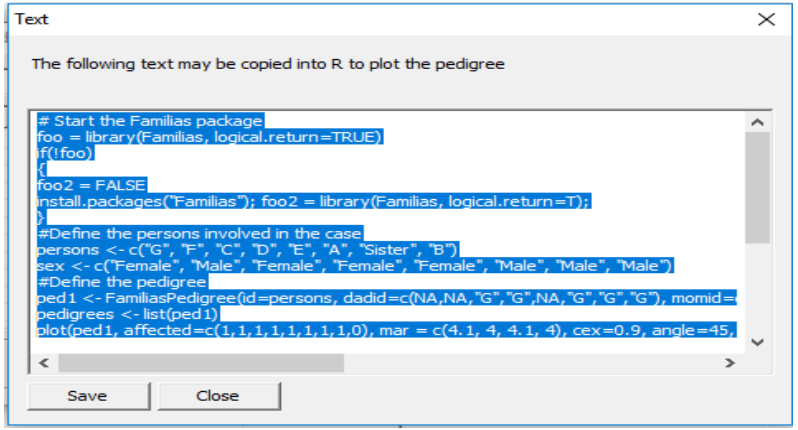
Plotting in FamLinkX

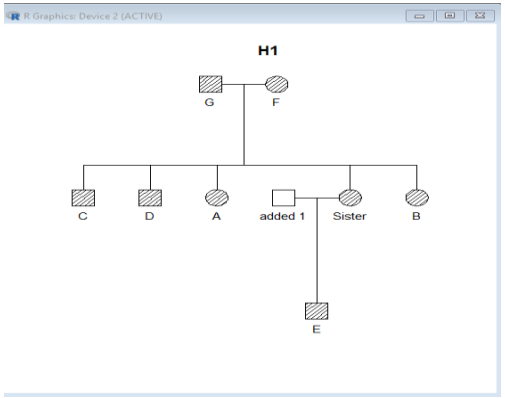
- Similar as in Familias – requires R
- Available since version 2.8



Plotting in FamLinkX

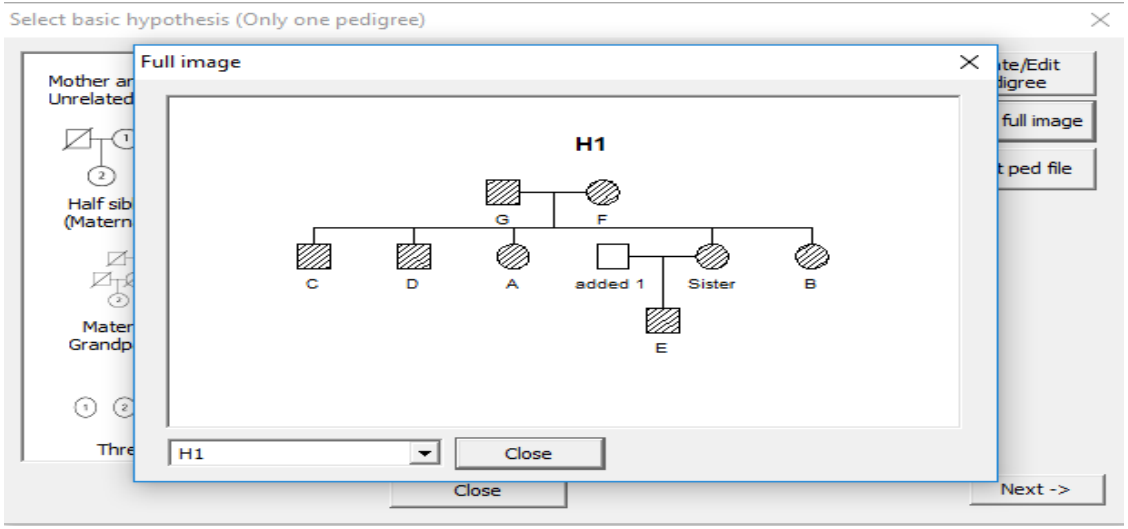






Plotting in FamLinkX

- Once plotted, it can be viewed in FamLinkX and automatically inserted into report!

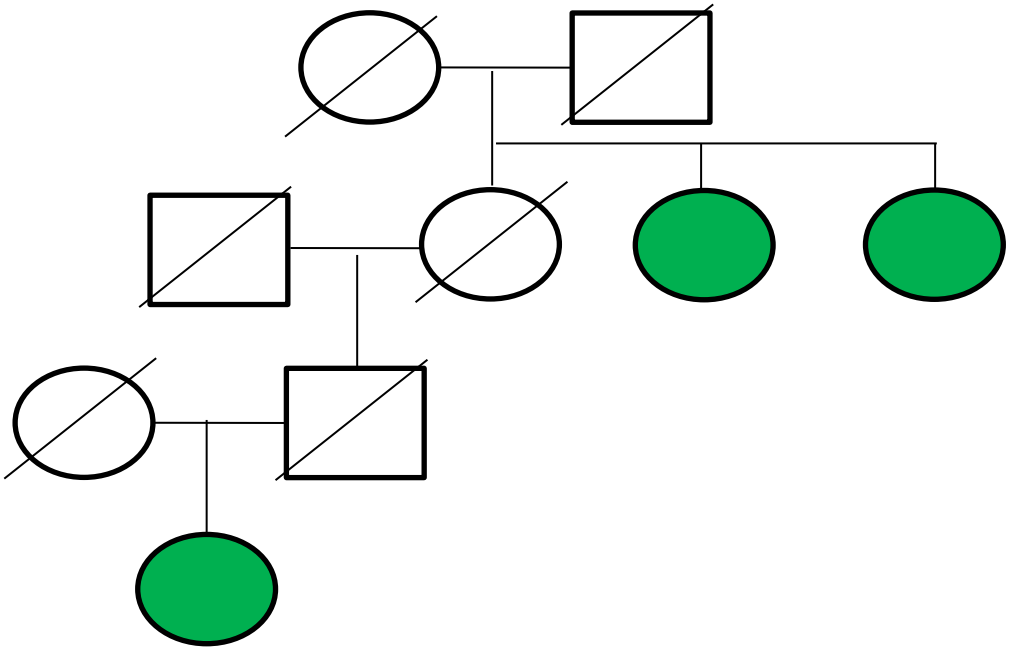


FamLinkX – Creating pedigrees and plotting

DEMONSTRATION 2

Demonstration

- Pedigree



UNDERSTANDING THE RESULTS

Understanding the results

- FamLinkX computes three different LRs

1. LR (Exact) – Uses the published method in Kling et al.
2. LR (Cluster) – Uses the cluster function in Merlin
3. LR (LE) – Considers the LE model in Merlin (linkage still modelled!)

- Why do we present all?

Understanding the results

- FamLinkX computes three different LRs

1. LR (Exact) – Uses the published method in Kling et al.
2. LR (Cluster) – Uses the cluster function in Merlin
3. LR (LE) – Considers the LE model in Merlin (linkage still modelled!)

- Why do we present all?
  a) Validation purposes
  b) 2 and 3 only available for created peds

Understanding the results

Comparison

	LR (Exact)	LR (Cluster)	LR (LE)	LR (Single marker)
Linkage	Yes	Yes	Yes	No
LD (Haplotypes)	Yes	Yes	No	No
Mutations	Yes	No	No	No
Recombinations within clusters	Yes	No	Yes	NA
Lambda model	Yes	Yes	No	No

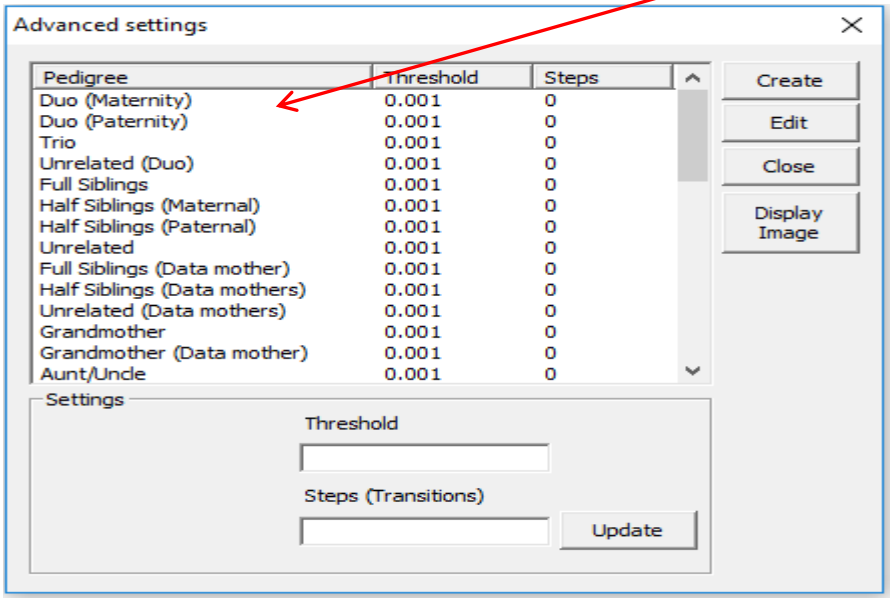
Understanding the results

- LR (Cluster) will, in many cases, gives similar results as the LR (Exact)
- LR (LE) will give the same results as the other two when lambda approaches infinity or for Decaplex and similar kits
- If mutations -> Only LR (Exact) will give results
- If recombinations within clusters are necessary -> LR (Exact) and LR (LE) will give results
- If created pedigrees -> Only LR (Cluster) and LR (LE) will give results

ADVANCED SETTINGS

Advanced settings

Lists all pre-defined pedigrees



Two parameters

Threshold – Decides what likelihoods should be computed.

Steps – Decides what alleles should be included in the likelihood calculations, ref. stepwise mutation model

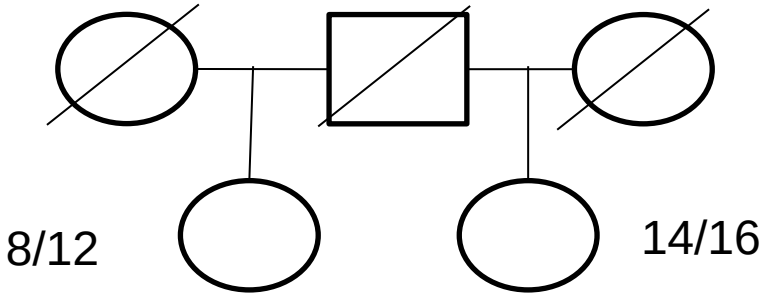
Advanced settings

- Example 1

Threshold=0.1, Steps=0

Since steps=0, shared father must have one of the alleles of the daughters. Threshold is high thus discarding low likelihoods, i.e. two step mutations.

LR=0



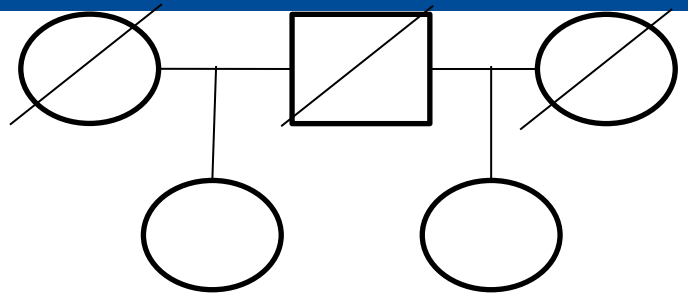
Threshold=0.000001, Steps=1

Since steps=1, shared father can be 13/13. Threshold allows low likelihoods corresponding to two step mutations as well as double mutations.

LR=0.0035

Advanced settings

- Example 2



Threshold=0.001, Steps=0

View data (Beta)

Marker	Accumulated LR	Marginal LR	Single mark...
KG1			
DXS10148	1.96658	1.96658	
DXS10135	7.95526	4.04521	
DXS8378	25.5163	3.20747	
KG2			
DXS7132	59.5996	2.33575	
DXS10079	221.873	3.72273	
DXS10074	1448.59	6.5289	
KG3			
DXS10103	3403.55	2.34956	
HPRT	6222.76	1.82832	
DXS10101	0	0	
KG4			
DXS10146	0	-1.#IND	
DXS10134	0	-1.#IND	
DXS7423	0	-1.#IND	
	0	-1.#IND	1.59541e+...

Save Close

Threshold=0.00001, Steps=0

View data (Beta)

Marker	Accumulated LR	Marginal LR	Single mark...
KG1			
DXS10148	1.97093	1.97093	
DXS10135	7.96409	4.04078	
DXS8378	25.5253	3.20505	
KG2			
DXS7132	59.7143	2.33942	
DXS10079	222.298	3.7227	
DXS10074	1451.48	6.52943	
KG3			
DXS10103	3410.35	2.34956	
HPRT	6244.7	1.8311	
DXS10101	20.0605	0.0032124	
KG4			
DXS10146	27.7779	1.38471	
DXS10134	121.174	4.36225	
DXS7423	323.422	2.66907	
	323.422	323.422	1.59541e+...

Save Close

Advanced settings

- Keep the steps parameter at zero. Higher values will slow down computations.
- Use a threshold of 0.00001 thus allowing single step mutations.
- Both should be same for all pedigrees and fixed in database. Can be changed if necessary.
- Works on individual markers -> threshold does not have to be extremely low if mutations in different markers.

Other topics (covered later)

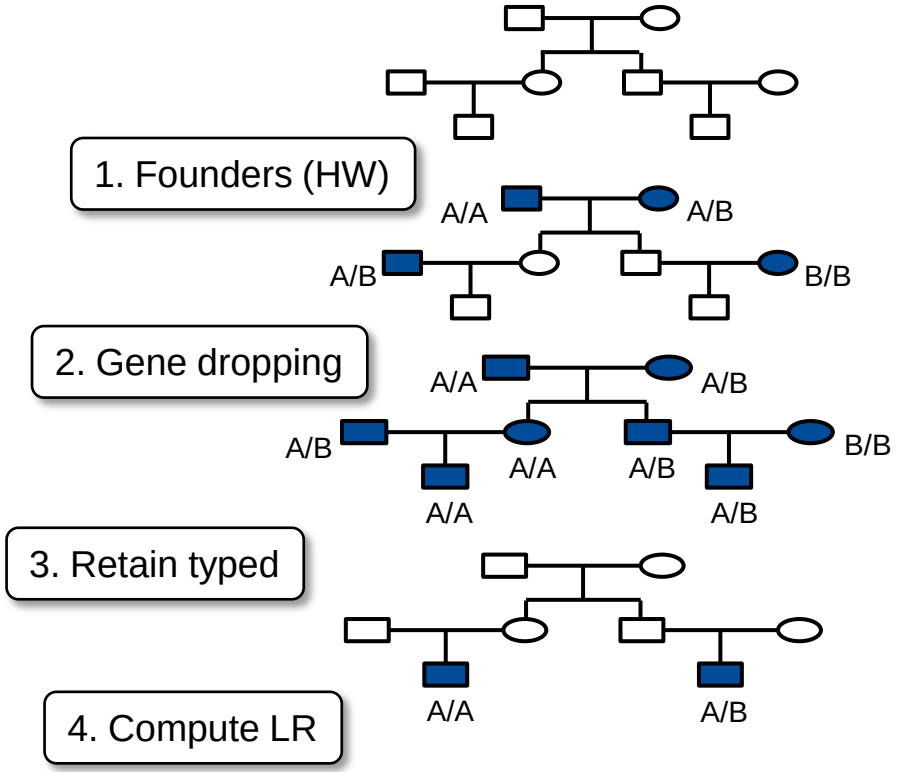
- Haplotype frequency model (Lambda)
- Pseuo-counts
- Estimating Lambda from data
- Frequency databases etc.

SIMULATIONS

Simulations in FamLinkX

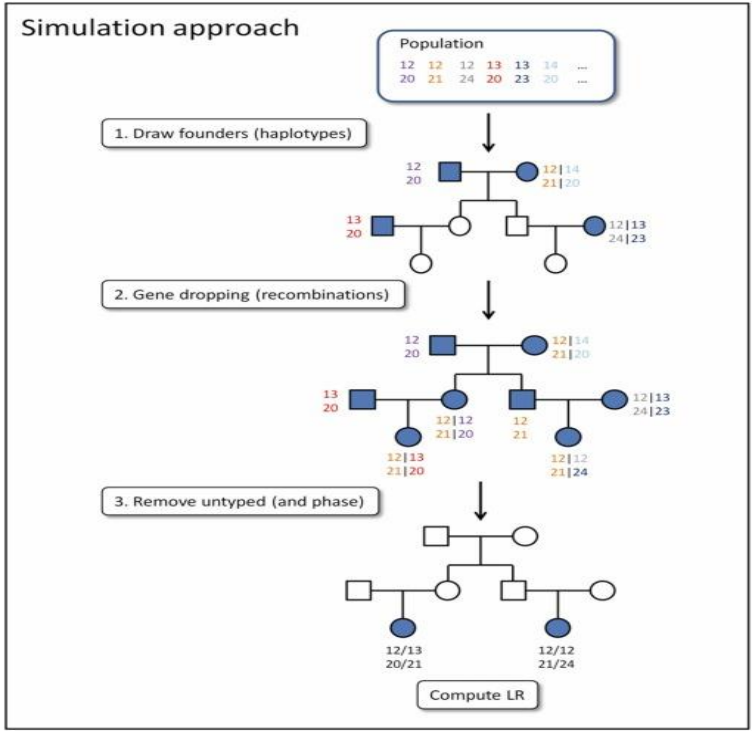
- Similar to Familias
- Gene dropping
- More advanced approach

Simulations – Simple example



A/A	A/B	B/B
0.25	0.5	0.25

Simulations – Full example



Simulations – Output

Simulation	LR (Half sisters)	LR(Unrelated)
1	1000	0.0001
2	100	0.02
3	600	0.1
4	0.1	0.0000001
5	10000	1.5
6	5000	0.01
…	…	…

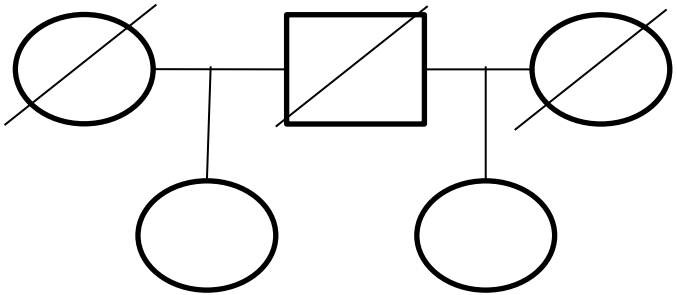
Conclusion?

FamLinkX – Simulations

DEMONSTRATION 3

Demonstration

- Background

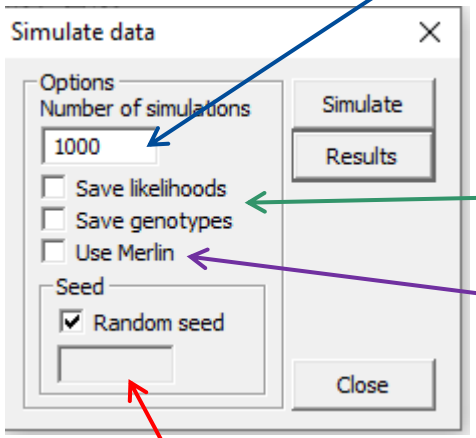


Decaplex data

Simulations in FamLinkX

- Settings

#Simulations (at least 100 is recommended)



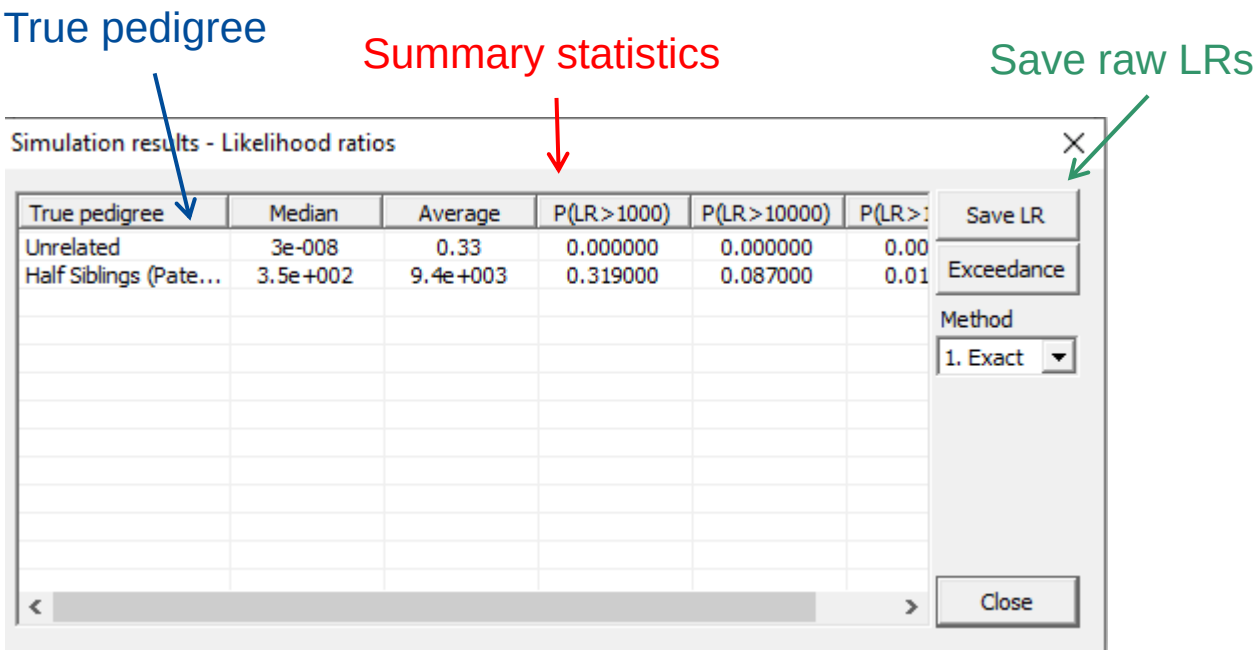
Save settings

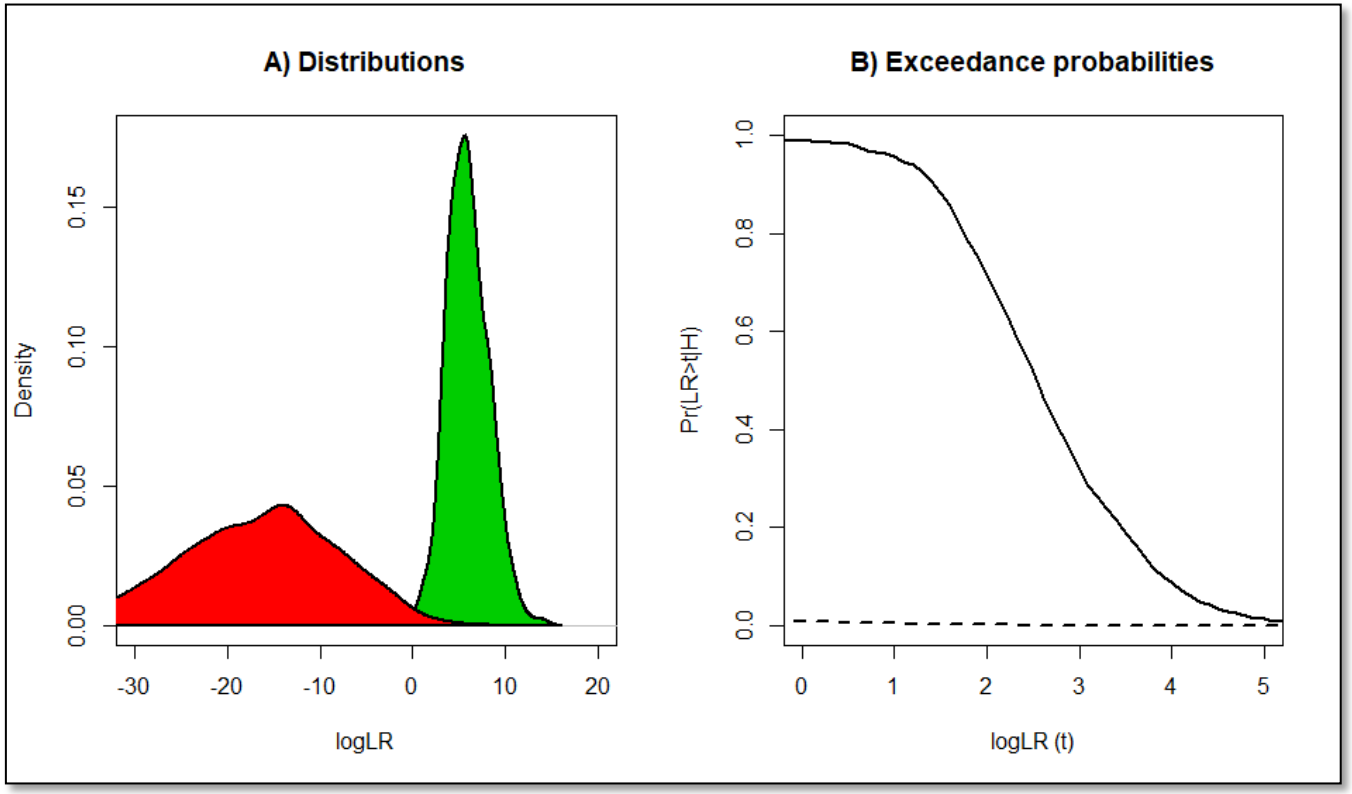
Much faster for Argus X12 (no mutations!)

Set a seed (random)

Simulations in FamLinkX

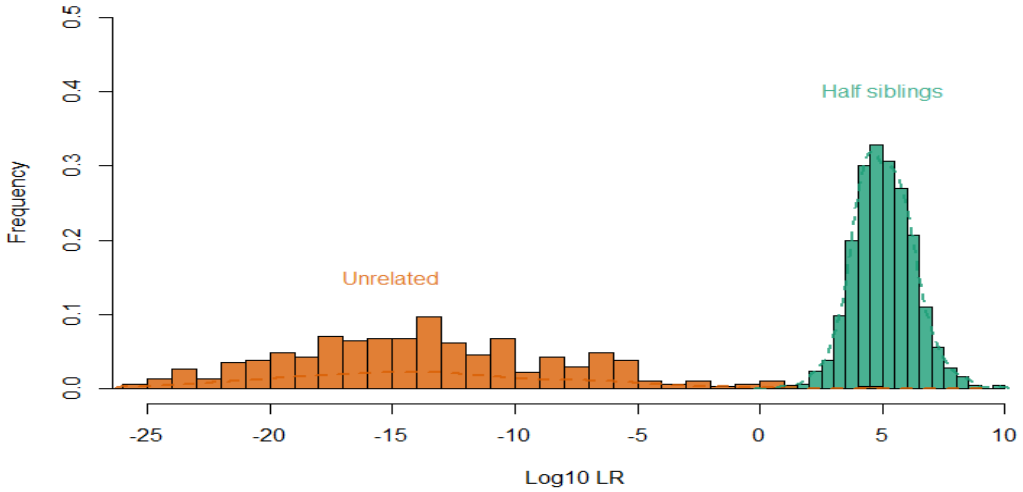
- Results




A) Distributions
Density
0.00
0.05
0.10
0.15
-30
-20
-10
0
10
20
logLR
B) Exceedance probabilities
Pr(LR>t|H)
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
logLR (t)

Simulations wth Argus X12

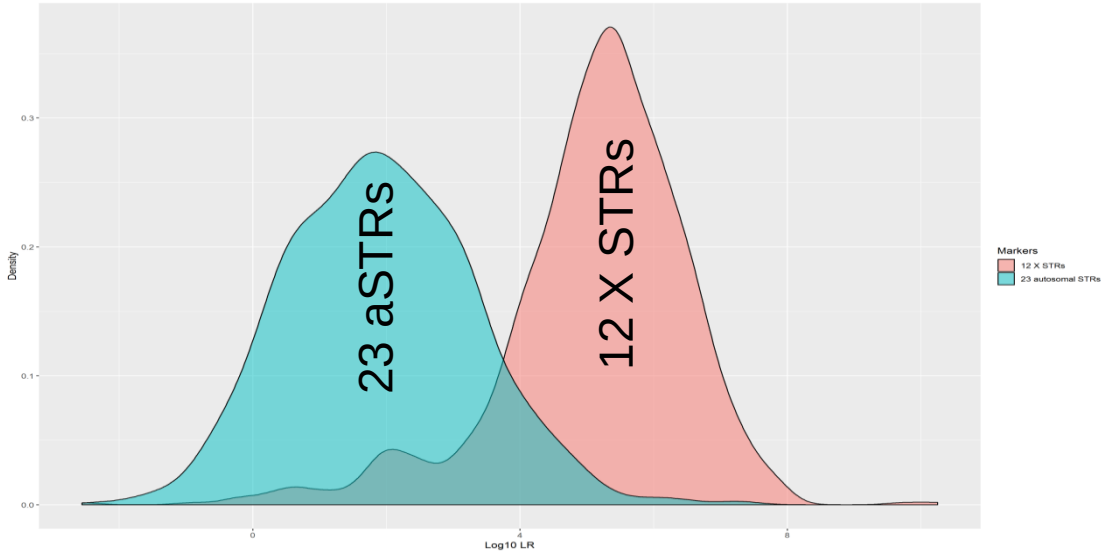
Paternal half sisters (Histogram of 1000 simulations)



Paternal half siblings can be distinguished from unrelated

Autosomal markers vs Argus X12

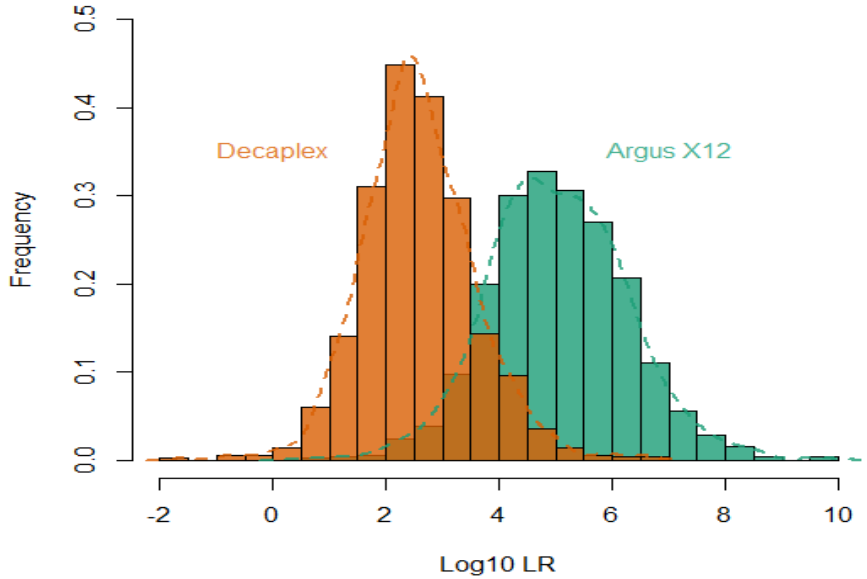
Paternal half sisters



X-STRs is more powerful for some cases

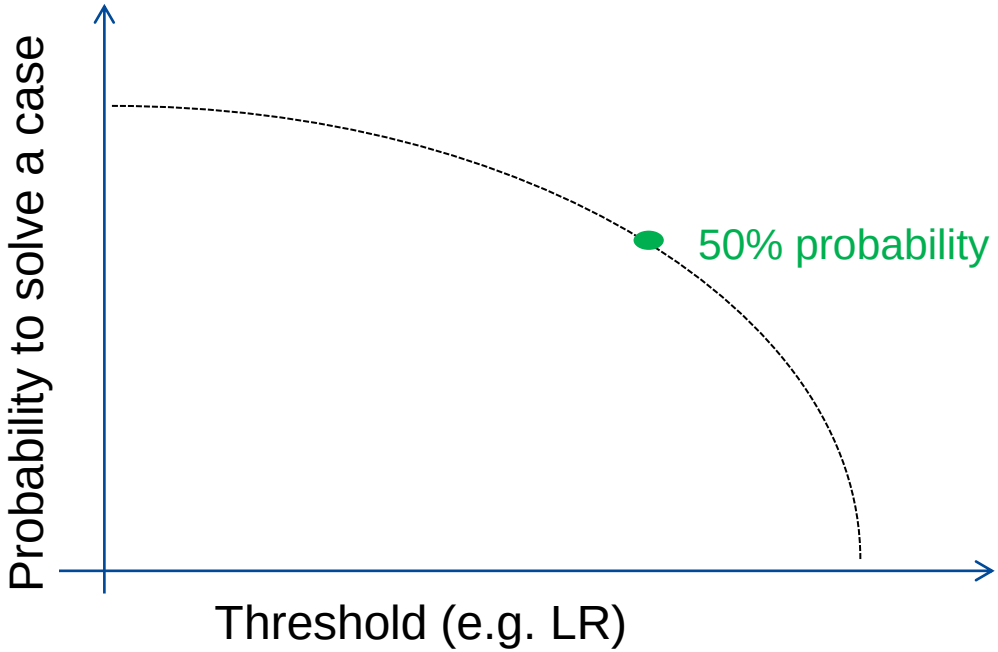
Argus X12 versus Decaplex

Paternal half sisters

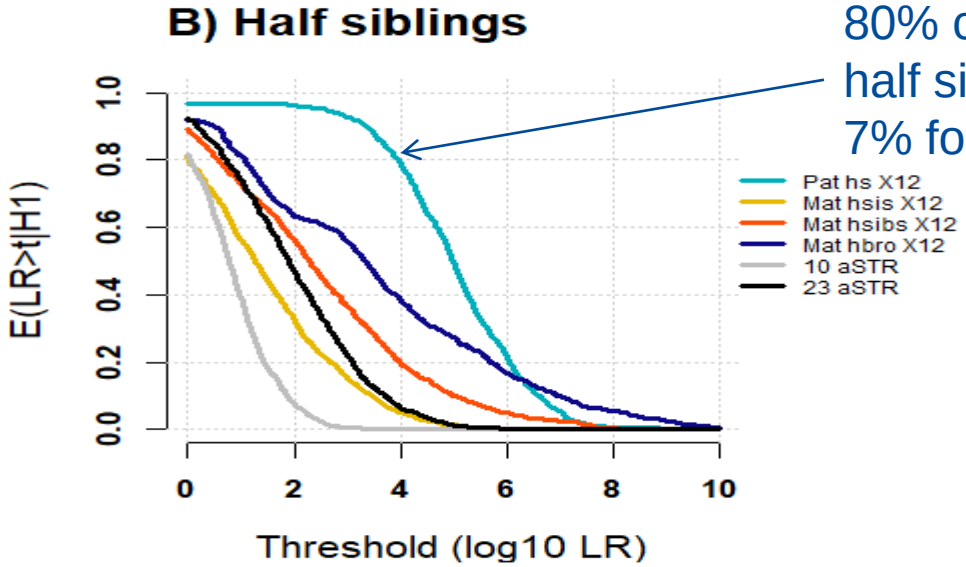


Argus X12 is more powerful than Decaplex

Exceedance plots



Utility of simulations (Argus X12)

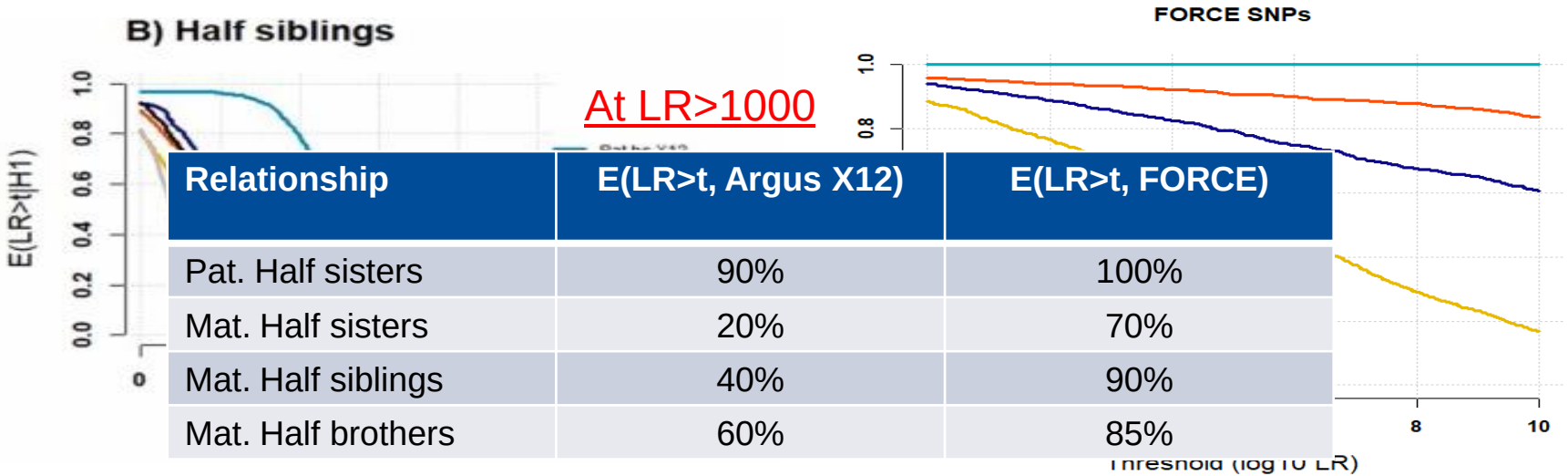


80% chance to solve paternal half siblings with X12 but only 6-7% for 23 aSTR if LR=10,000

Probability that we can solve a case with the given threshold

FORCE X-SNPs

242 SNPs (only linkage, no LD)



At LR>1000

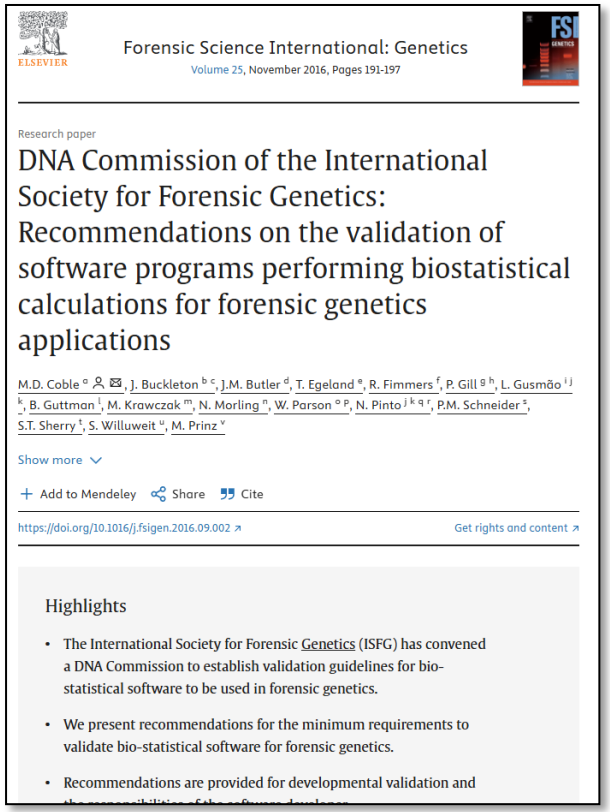
Relationship	E(LR>t, Argus X12)	E(LR>t, FORCE)
Pat. Half sisters	90%	100%
Mat. Half sisters	20%	70%
Mat. Half siblings	40%	90%
Mat. Half brothers	60%	85%

From Bergseth et al. 2022

Power increased substantially

VALIDATION

Guidelines



ELSEVIER

Forensic Science International: Genetics

Volume 25, November 2016, Pages 191-197

Research paper

DNA Commission of the International Society for Forensic Genetics: Recommendations on the validation of software programs performing biostatistical calculations for forensic genetics applications

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Highlights

- The International Society for Forensic Genetics (ISFG) has convened a DNA Commission to establish validation guidelines for bio-statistical software to be used in forensic genetics.
- We present recommendations for the minimum requirements to validate bio-statistical software for forensic genetics.
- Recommendations are provided for developmental validation and

Unfortunately not open access

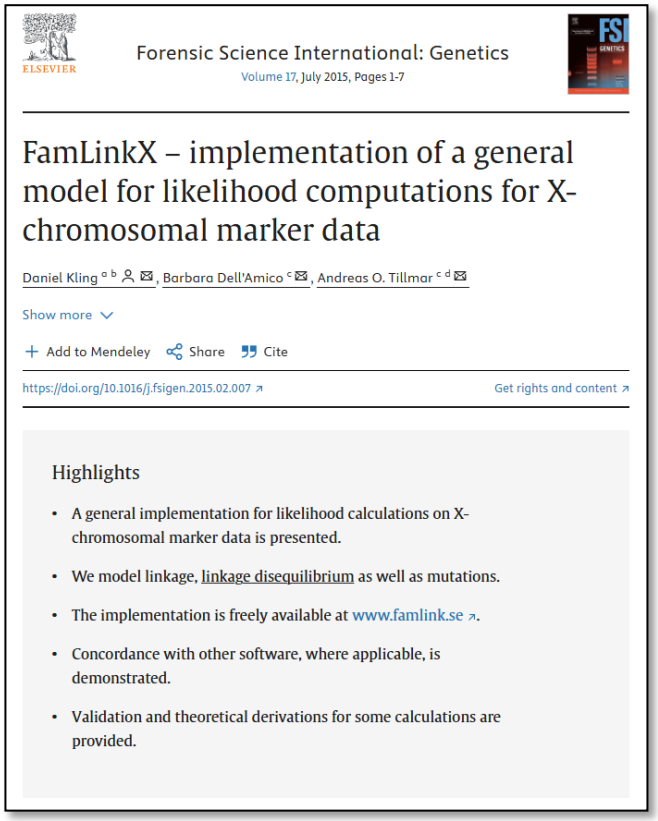
Guidelines

1. Scientific paper
2. Developmental validation with freely available data
3. Version control
4. Instruction for how to validate (internal validations)
5. User manual
6. Training and education
7. Open source/algorithms
8. Updates/bug fixes etc

Guidelines

9. Randomness (MCMC etc)
10. Plan for internal validation – which tests to perform etc
11. Test the software on in-house data from real samples
12. Samples to include
13. Consistent with previous results (e.g. other software)
14. Standard operating procedure (SOP)
15. In-house training
16. Public repository

Guidelines



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FamLinkX – implementation of a general model for likelihood computations for X-chromosomal marker data

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Highlights

- A general implementation for likelihood calculations on X-chromosomal marker data is presented.
- We model linkage, linkage disequilibrium as well as mutations.
- The implementation is freely available at www.famlink.se.
- Concordance with other software, where applicable, is demonstrated.
- Validation and theoretical derivations for some calculations are provided.

Unfortunately not open access. Ask us for a copy!

Guidelines for FamLinkX

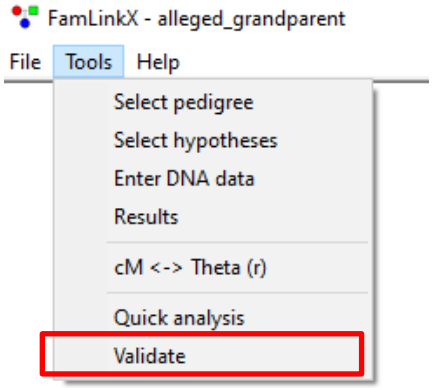
1. Import of data
   a) Importing frequencies
   b) Importing haplotypes
   c) Importing case-specific DNA data (new alleles)
2. Test parameters (value of lambda)
3. Test all relevant cases (hypotheses/pedigrees)
4. Report (output)
5. Save/Open projects with same results
6. Identify sources/points where errors can arise

Guidelines for FamLinkX

7. Create pedigrees
8. Training and education

Simulation does not generally need to be validated

Self-validation in FamLinkX



Will test the pre-defined pedigrees through

1. Two genetic markers (no mutations)
2. 100 simulations
3. Compare results with Merlin

FamLinkX

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