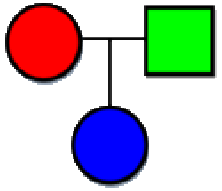
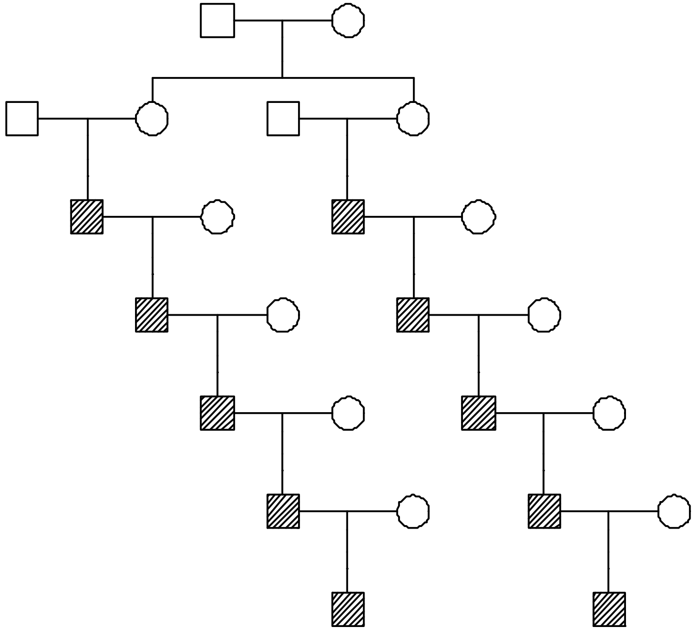
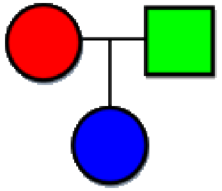


What does it mean to be related?



Thore Egeland
ISFG 2022
Norwegian University of Life Sciences (NMBU)
Department of Forensic Sciences, Oslo University Hospital



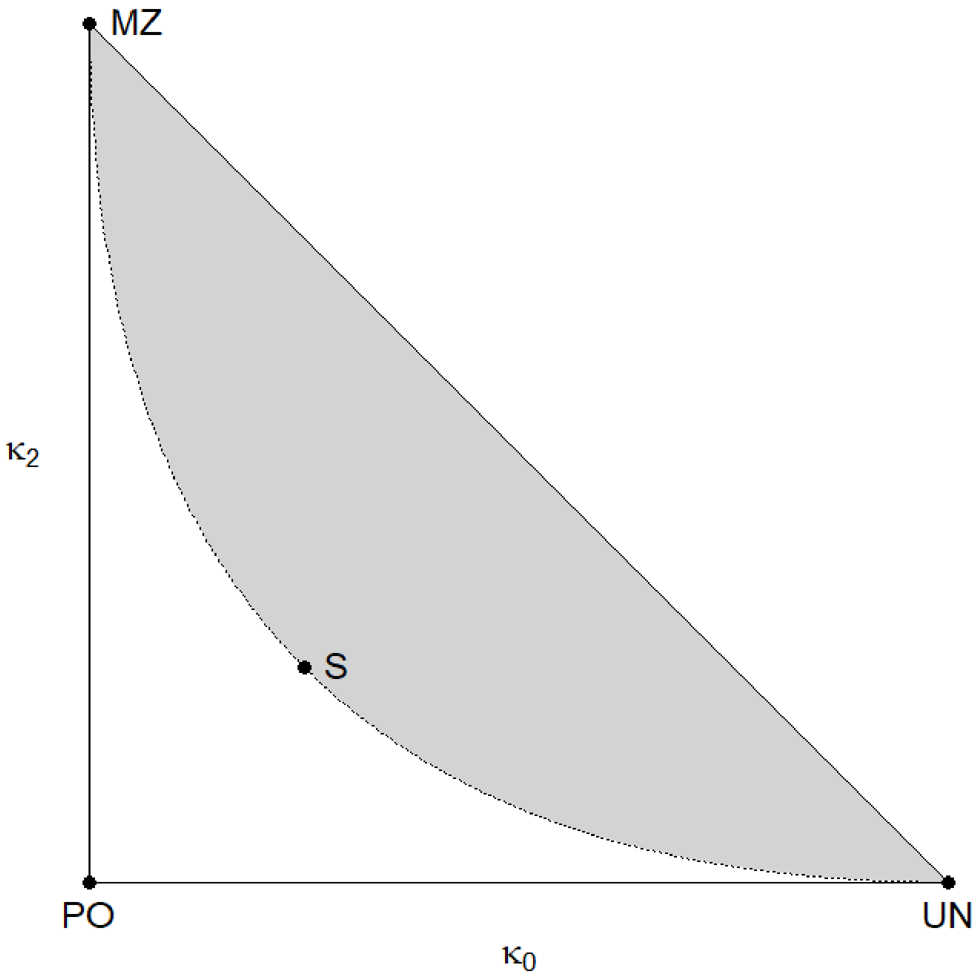
What does it mean to be *unrelated*?

Thore Egeland

Norwegian University of Life Sciences (NMBU)
Department of Forensic Sciences, Oslo University Hospital

Contents

- Non-genetic definitions
- Concepts of genetic relatedness
  - Identity By Descent (IBD)
  - Coefficients of relatedness
  - The relatedness triangle
  - Realised relatedness
- What does it mean to be related?
- Inferring relatedness
  - By pedigree likelihoods
  - By IBD sharing



The relatedness triangle

Adapted from Thompson (1975)

Defining relatedness

- Dictionary:

  Connected by common ancestry or sometimes by marriage

  Merriam-Webster

- Legal:

  Associated through birth, adoption, marriage or common-law agreement

  https://www.lawinsider.com/dictionary/legally-related

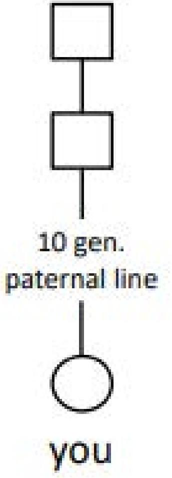
- Anthropology:

  Those who see themselves as related

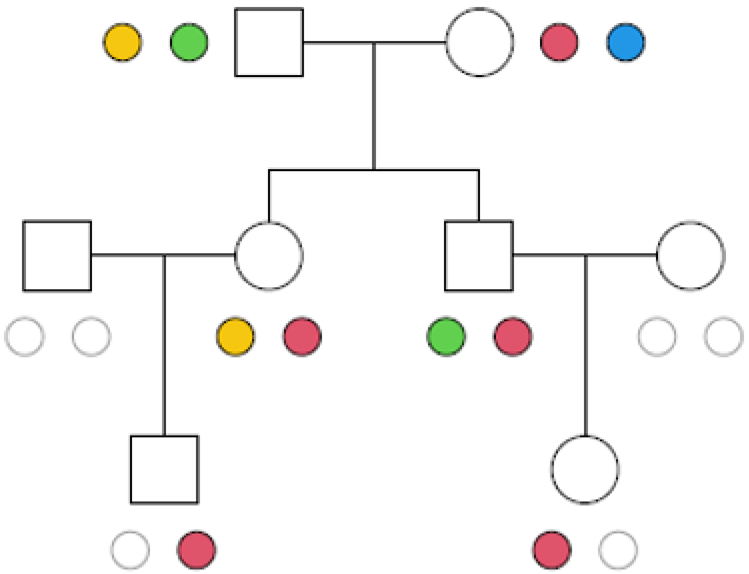
  Anthropological perspectives on kinship, L Holy, University of Alberta

What does it mean to be *genetically* related?

Napoleon Bonaparte (1769 - 1821)



Key concept: Identical By Descent (IBD)

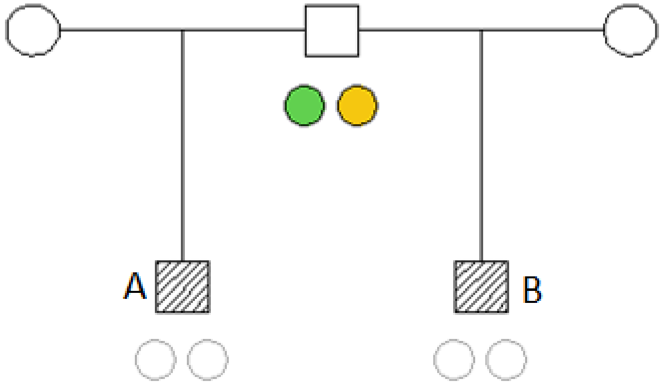


- Red alleles are IBD, originate from grandmother
- Definitions are with respect to a given pedigree

Kinship coefficient

- **Definition:**
  φ = P (Random allele from A and random allele from B are IBD)

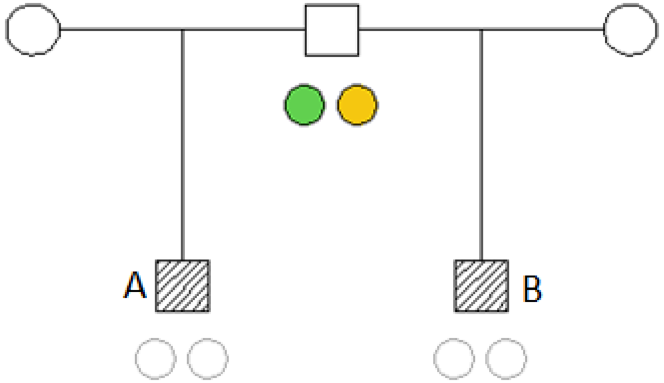
- Half siblings A and B
  $\varphi = \frac{1}{2}\frac{1}{4} = \frac{1}{8}$.



IBD coefficients

- Definition:

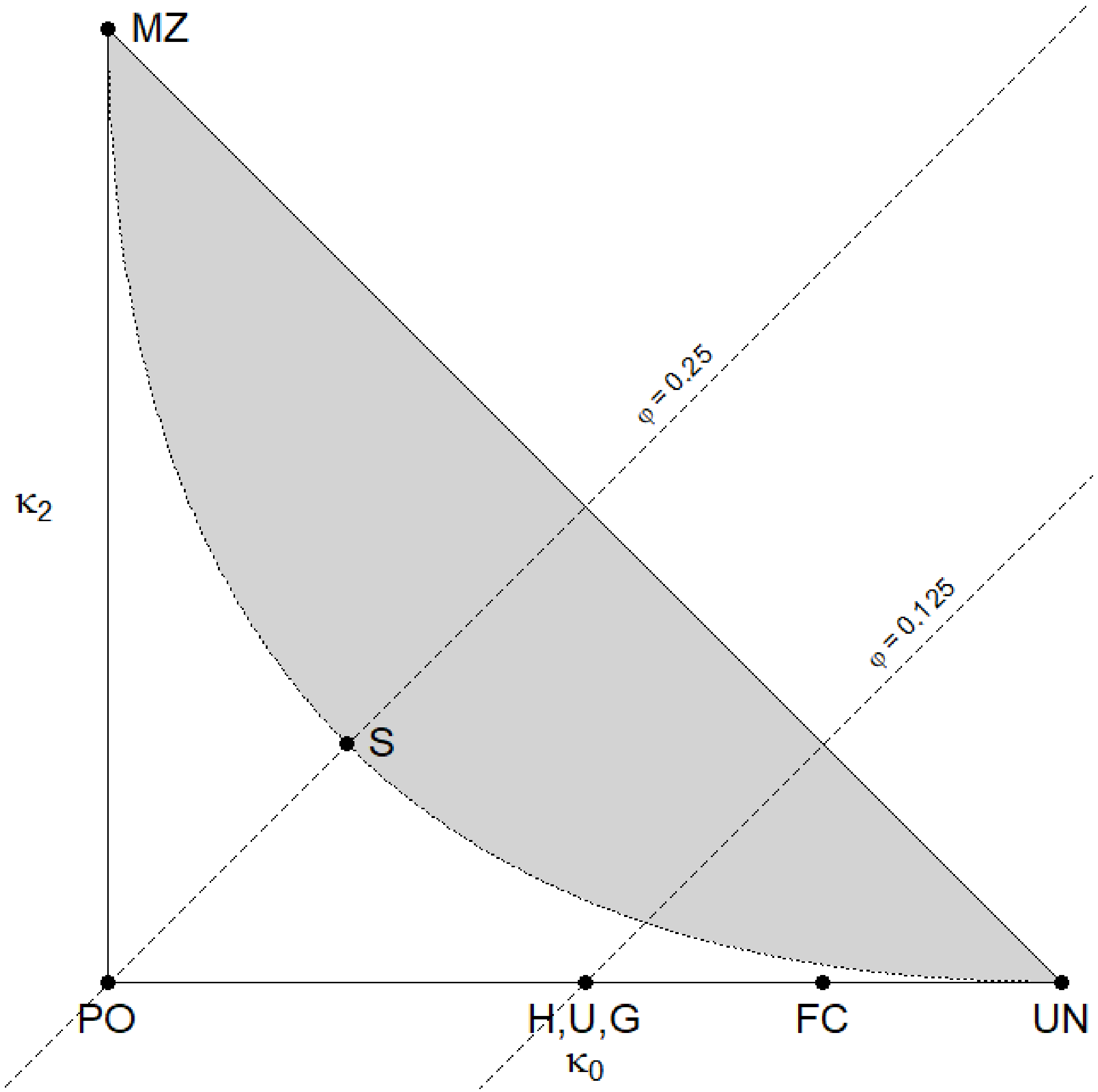
$$\kappa_0 = P(A \text{ and } B \text{ share 0 alleles IBD}),$$
$$\kappa_1 = P(A \text{ and } B \text{ share 1 allele IBD}),$$
$$\kappa_2 = P(A \text{ and } B \text{ share 2 alleles IBD}).$$



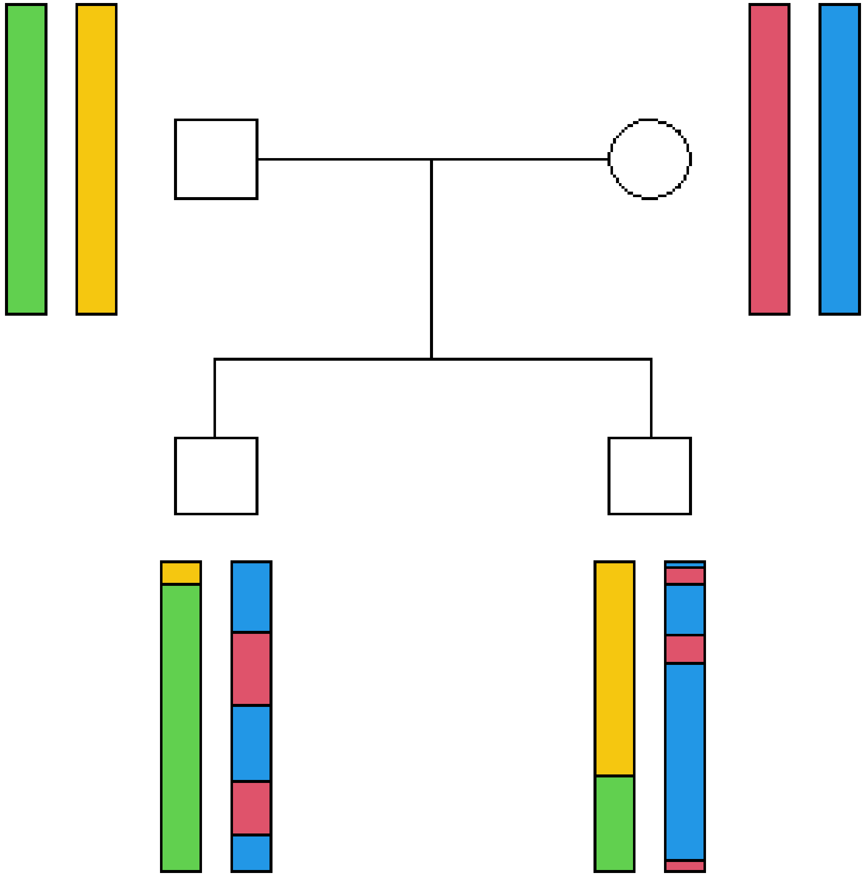
- Half siblings A and B:
  κ_0= 0.5, κ_1= 0.5, κ_2= 0

The relatedness triangle

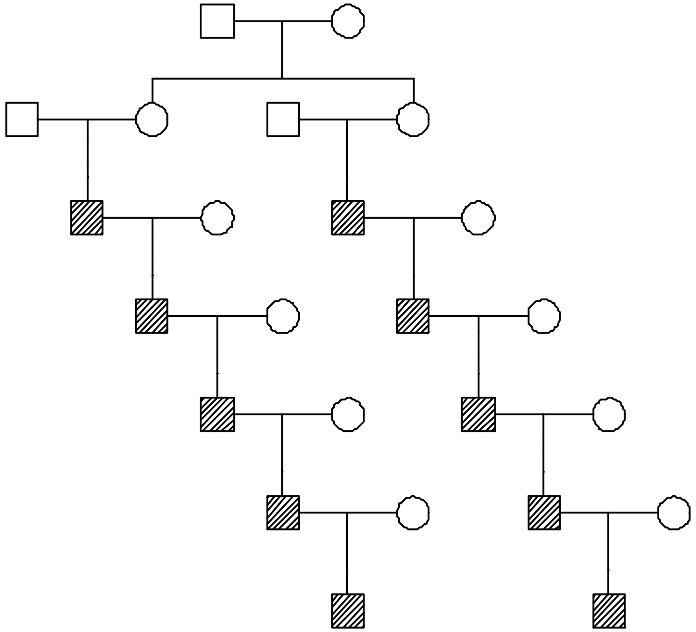
Label	Relationship	φ	κ_0	κ_1	κ_2
UN	Unrelated	0	1	0	0
PO	Parent–offspring	1/4	0	1	0
MZ	Monozygotic twins	1/2	0	0	1
S	Full siblings	1/4	1/4	1/2	1/4
H	Half siblings	1/8	1/2	1/2	0
U	Uncle–niece, etc.	1/8	1/2	1/2	0
G	Grandparent–grandchild	1/8	1/2	1/2	0
FC	First cousins	1/16	3/4	1/4	0



Realised sharing between siblings



The probability of zero IBD



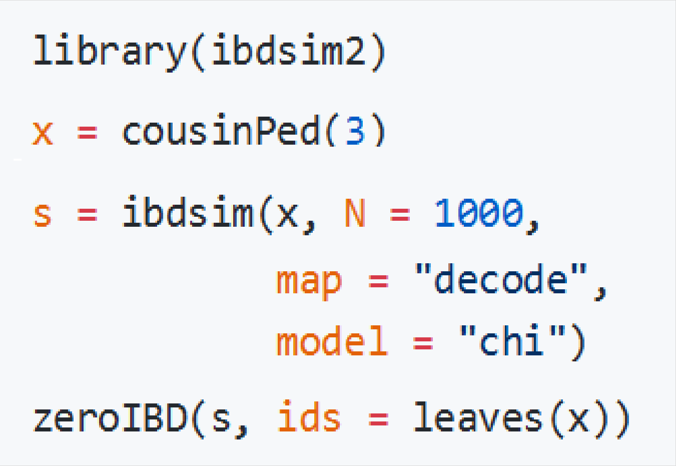
k'th cousins	P(no IBD)
1	0.000
2	0.000
3	0.029
4	0.332
5	0.724

May have common ancestor without IBD sharing

5th cousins:
Usually no sharing!

Simulations in R (package: ibdsim2)

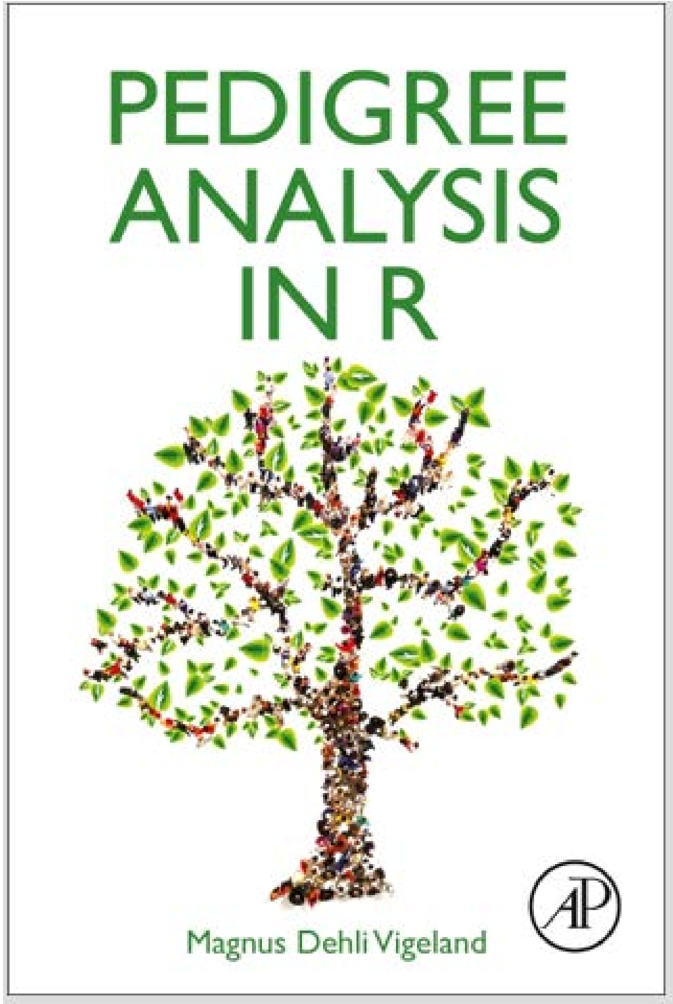
Example: $P(No\ \text{IBD}\ between\ 3rd\ cousins)$



```
library(ibdsim2)

x = cousinPed(3)

s = ibdsim(x, N = 1000,
           map = "decode",
           model = "chi")

zeroIBD(s, ids = leaves(x))
```

Result: $P = 0.029\ (se = 0.005)$

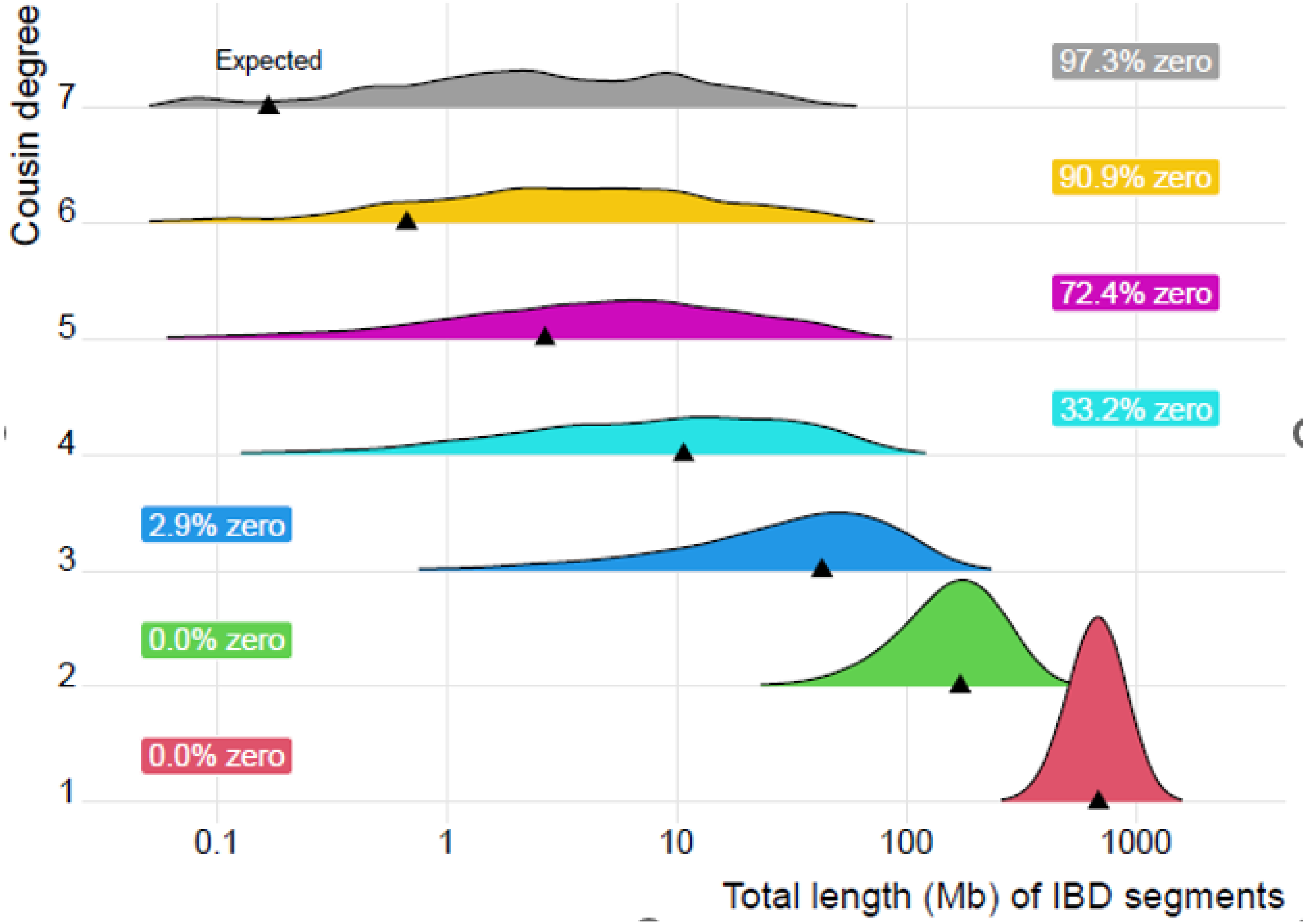
- Genetic map
  - Decode (2019): Fine-scale recombination map
- Recombination model
  - χ^2 waiting times between crossovers



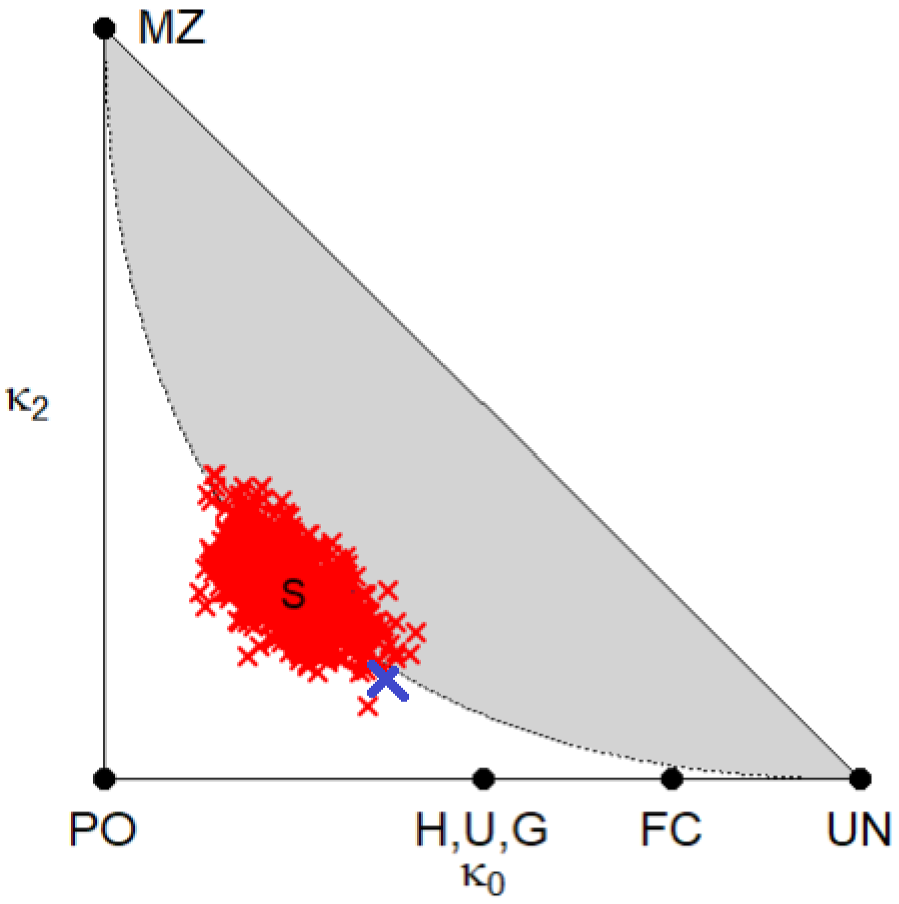
PEDIGREE
ANALYSIS
IN R

Magnus Dehli Vigeland

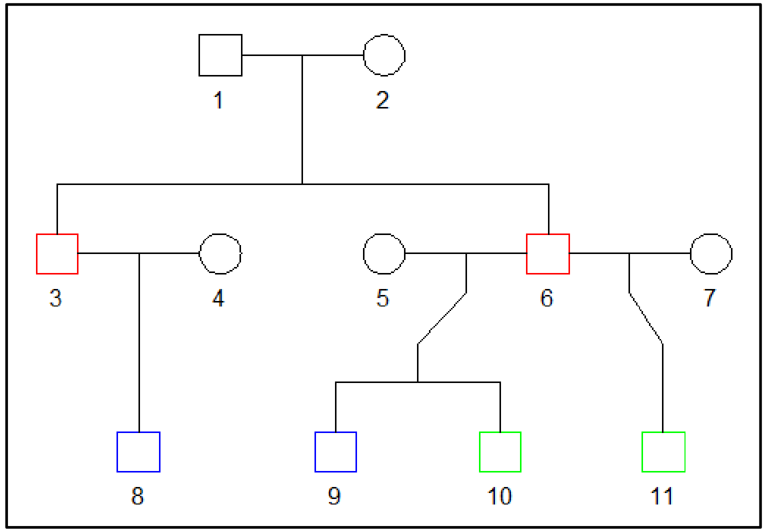
Distant cousins share either nothing or quite a bit

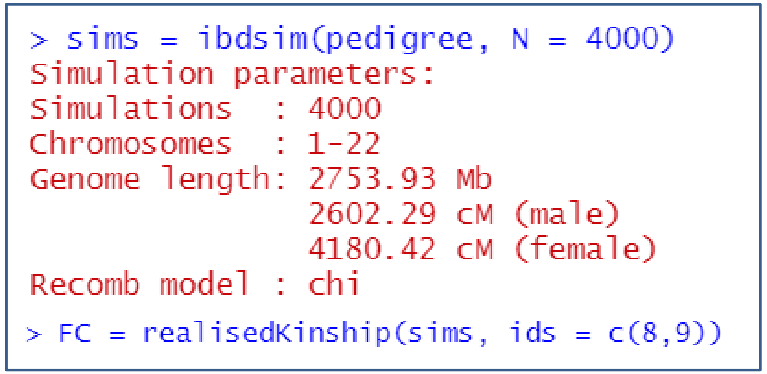


Realised relatedness, full siblings

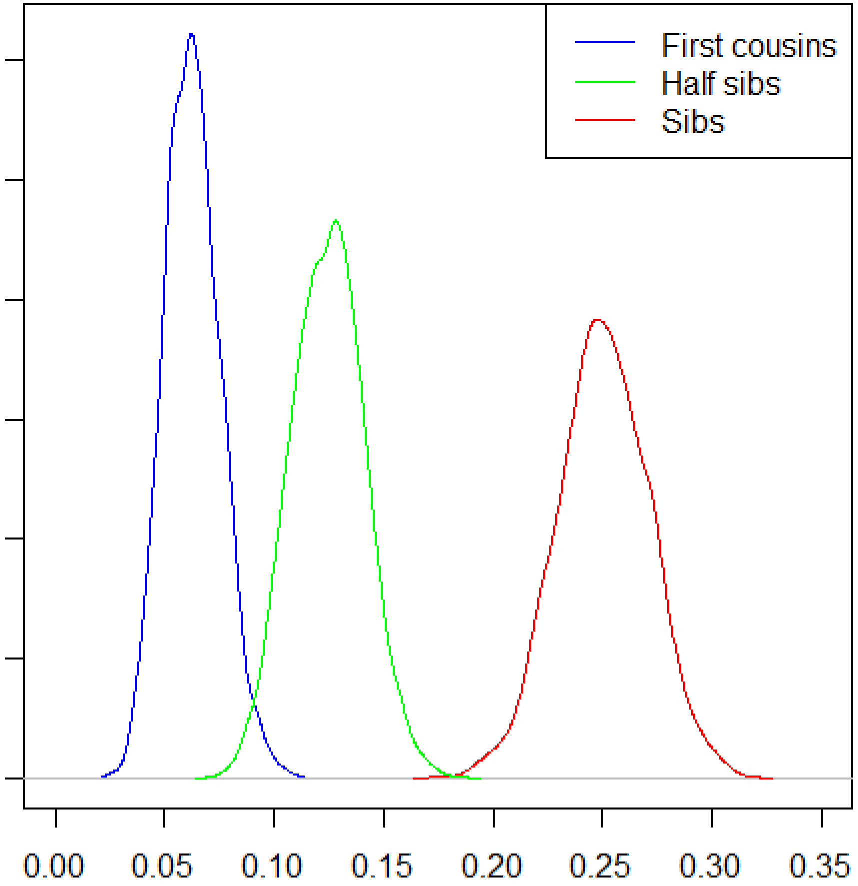


Realised kinship coefficients





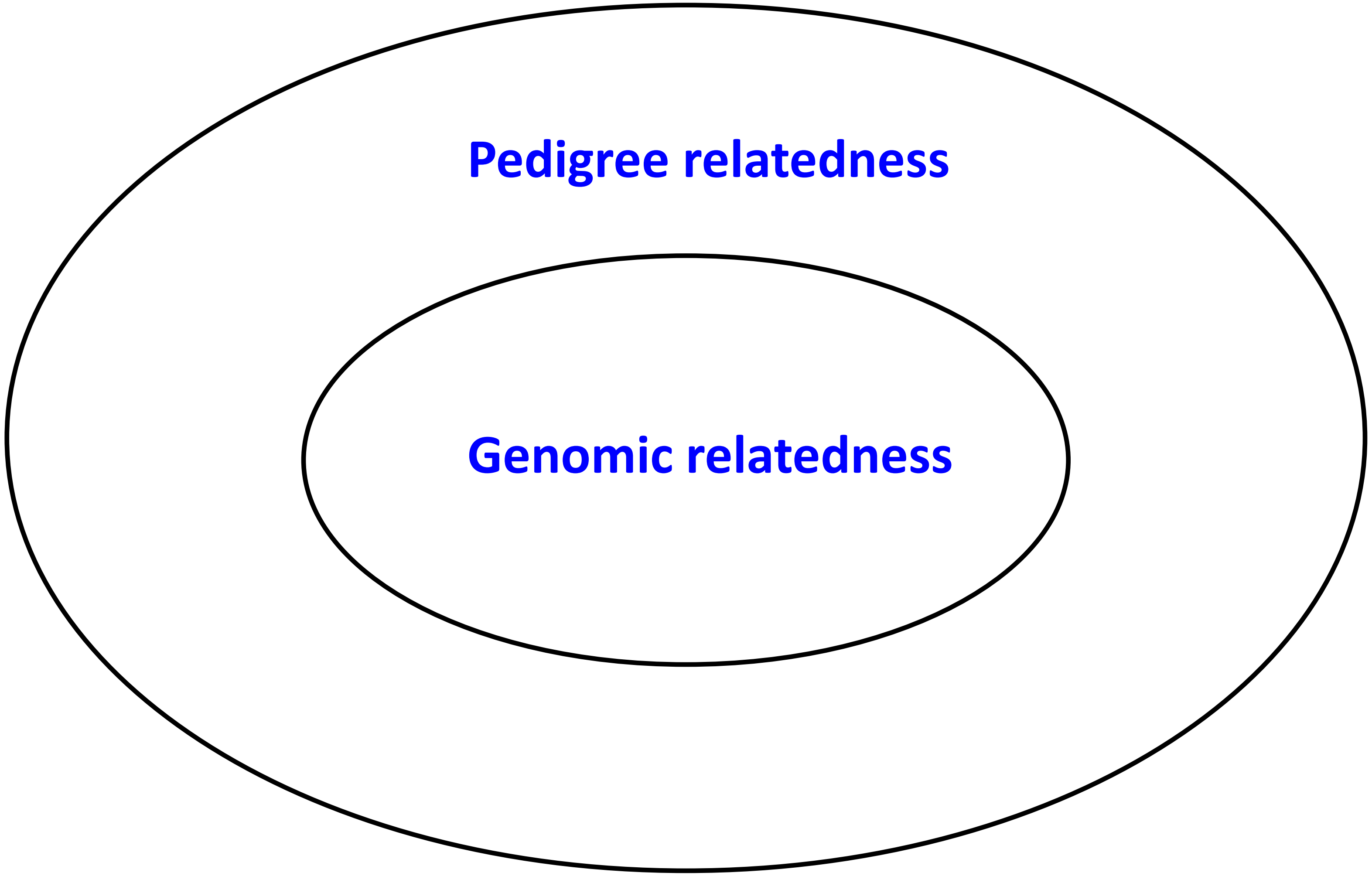
```
> sims = ibdsim(pedigree, N = 4000)
Simulation parameters:
Simulations  : 4000
Chromosomes  : 1-22
Genome length: 2753.93 Mb
               2602.29 cM (male)
               4180.42 cM (female)
Recomb model : chi

> FC = realisedKinship(sims, ids = c(8,9))
```



So... what does it mean to be *related*?

- Pedigree relatedness: Kinship coefficient $\boldsymbol{\varphi} > \mathbf{0}$
  - Potentially having alleles IBD
  - Relevance
    - Forensics
    - Pedigree based comparisons
    - Expected relatedness
- Genomic relatedness: Realised kinship coefficient $\boldsymbol{\varphi_R} > \mathbf{0}$
  - Actually having alleles IBD
  - Relevance
    - Animal genetics, breeding
    - Clinical genetics
    - Observed relatedness

Genomic relatedness implies Pedigree relatedness



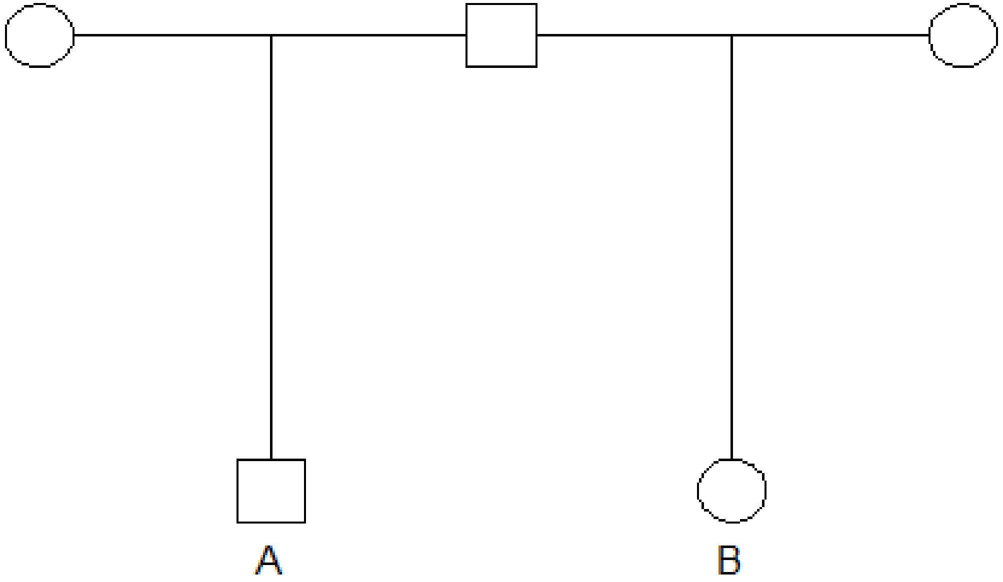
Pedigree relatedness

Genomic relatedness

And what does it mean to be *inbred*?

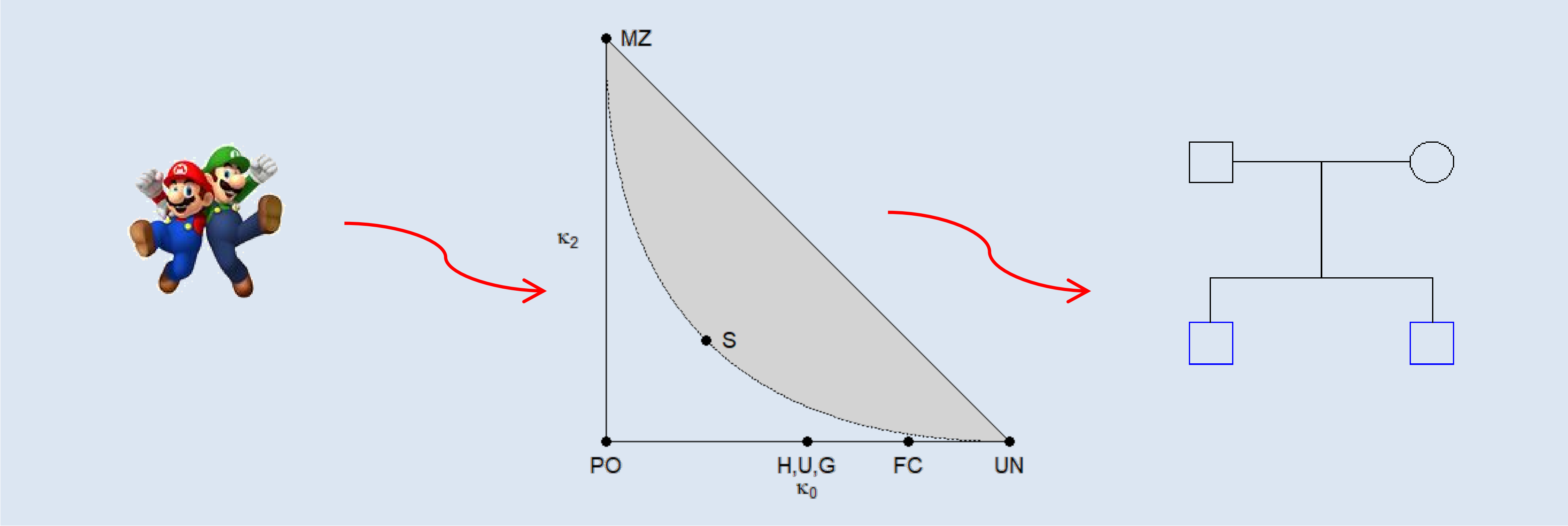
- Pedigree inbreeding: Inbreeding coefficient $f > 0$
  - Individual potentially having alleles IBD
  - Relevance:
    - Legal contexts
    - Define incest
    - Expected inbreeding
- Genomic inbreeding: Realised inbreeding coefficient $f_R > 0$
  - Individual actually having alleles IBD
  - Relevance:
    - Clinical genetics, e.g., recessive diseases
    - Breeding programs
    - Observed inbreeding

Genomic relatedness *vs* mode of inheritance



Paternal half sibs genomically unrelated for X, Y and mtDNA!

Inferring relatedness



METRO

HOME NEWS SPORT ENTERTAINMENT LIFES

UK WORLD WEIRD TECH

Let's not forget – Prince Harry and Meghan Markle are actually (very distant) cousins

Richard Hartley-Parkinson for Metro.co.uk Monday 27 Nov 2017 11:35 am

18.8k

FASHION

CULTURE

FASHION BEAUTY GIFT GUIDE

Ou, Awkward...Meghan Markle and Prince Harry are Apparently Related

By Meghan McKenna Date November 2, 2017

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ousins!

Brigitte

SPIELE NEWSLETTER VIDEO GEWINNSPIELE FORUM F-MAG ACADEMY SHOPPING ABC

Aktuell Mode Beauty Rezepte Gesund Liebe Familie Leben Horo

Brigitte → Aktuell → Stars und TV → *Meghan Markle und Prinz Harry sind "verwandt"*

Stammbaum erforscht: Prinz Harry und Meghan Markle sind Cousins!

1.1K shares

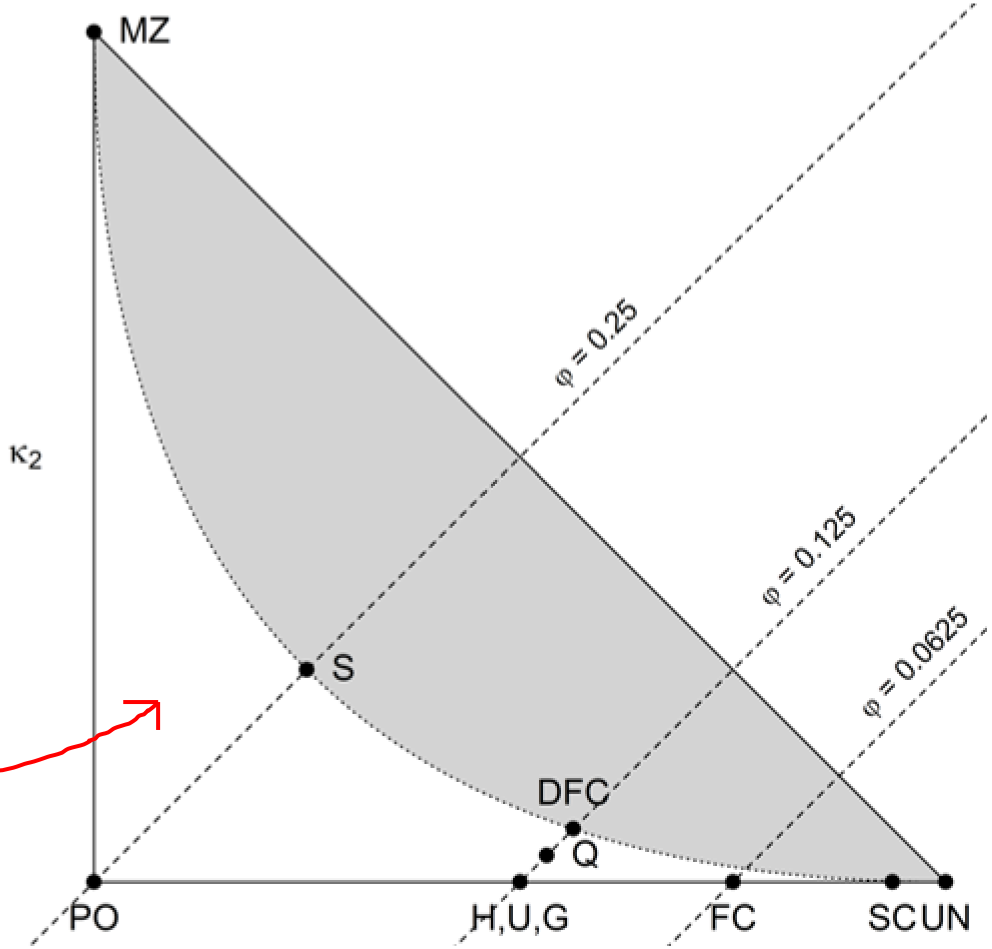
View c

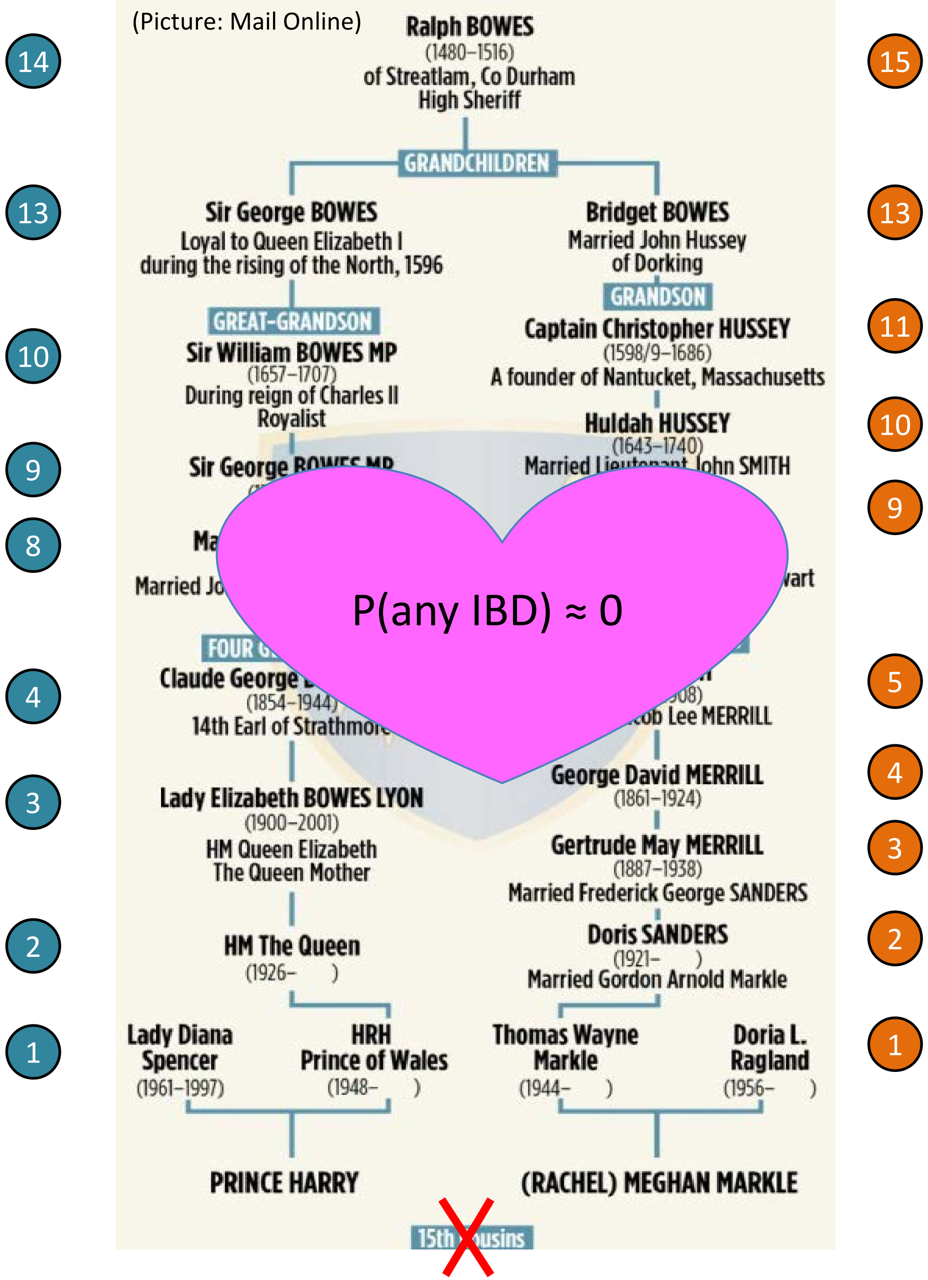
STJERNEPAR: Meghan Markle og prins Harry viser endelig kjærligheten sin offentlig, etter å ha holdt forholdet svært privat i lang tid. Nå kommer det frem at paret, som er fra to forskjellige kontinenter, faktisk er i slekt. Foto: NTB scanpix

Prins Harry er i slekt med kjæresten

SE OG HØR

where??




(Picture: Mail Online)

P(any IBD) ≈ 0

13th cousins once removed

Inferring relatedness: two approaches

1. Maximum likelihood estimation from marker data

2. Classification based on IBD segments

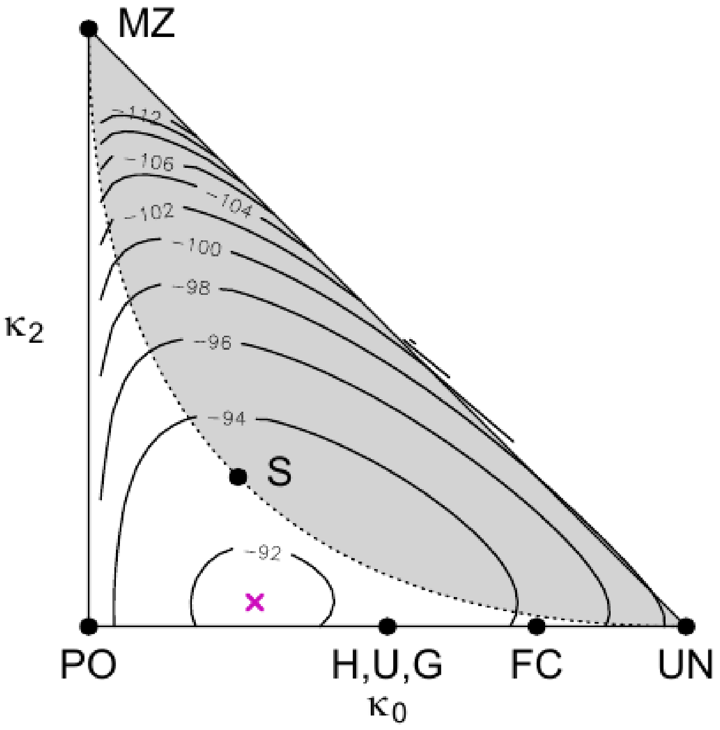
1. Maximum likelihood estimation of $\kappa = (\kappa_0, \kappa_1, \kappa_2)$

- Thompson (1975)
  - Given: marker genotypes for two individuals
  - The likelihood function

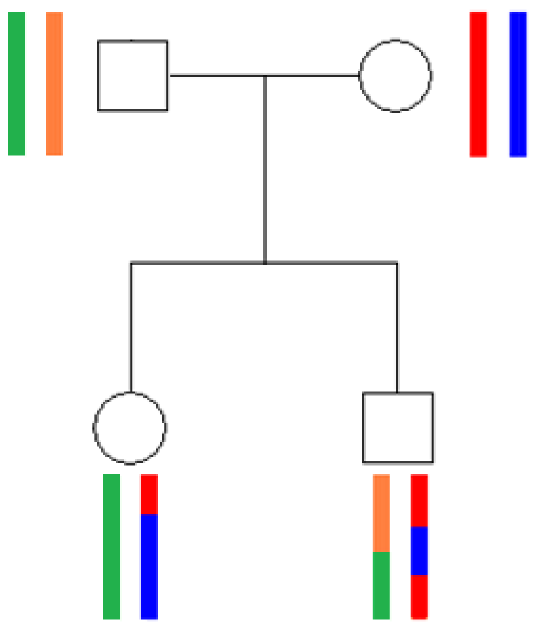
$$L(\kappa) = P(genotypes \mid \kappa)$$

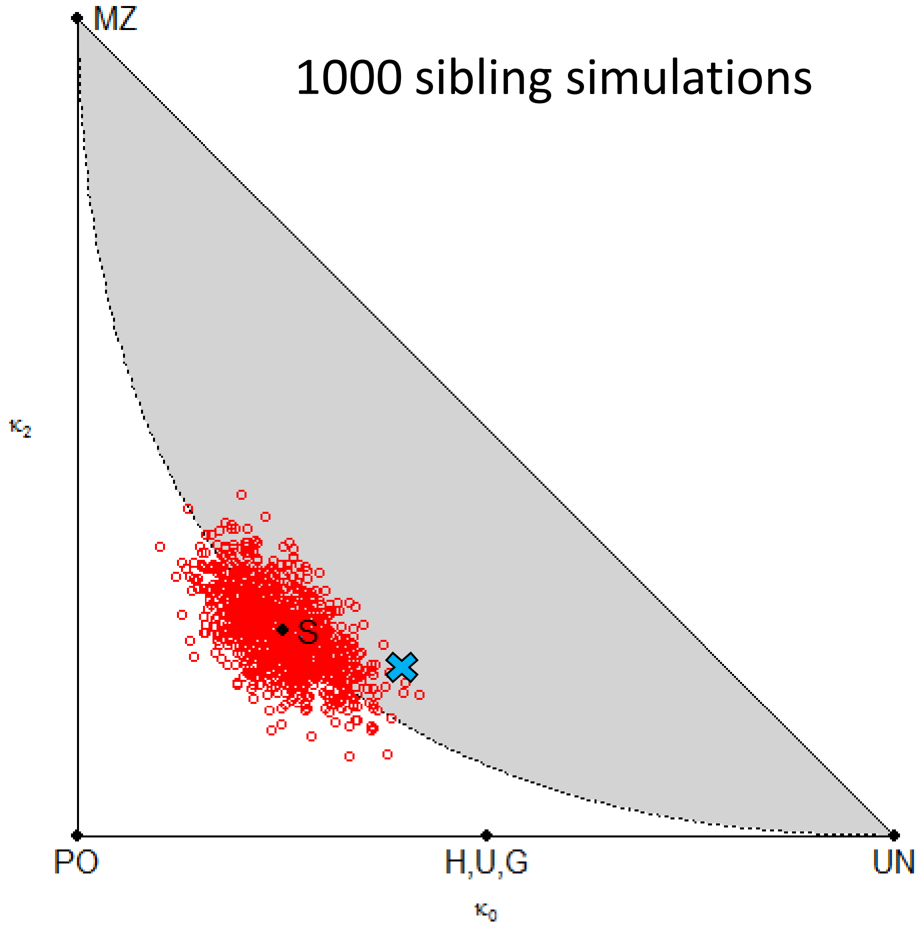
- Find the point which maximizes *L*!
  - Called the <u>maximum likelihood estimate</u> (MLE)

- Assumptions:
  - known allele freqs
  - HWE
  - no inbreeding



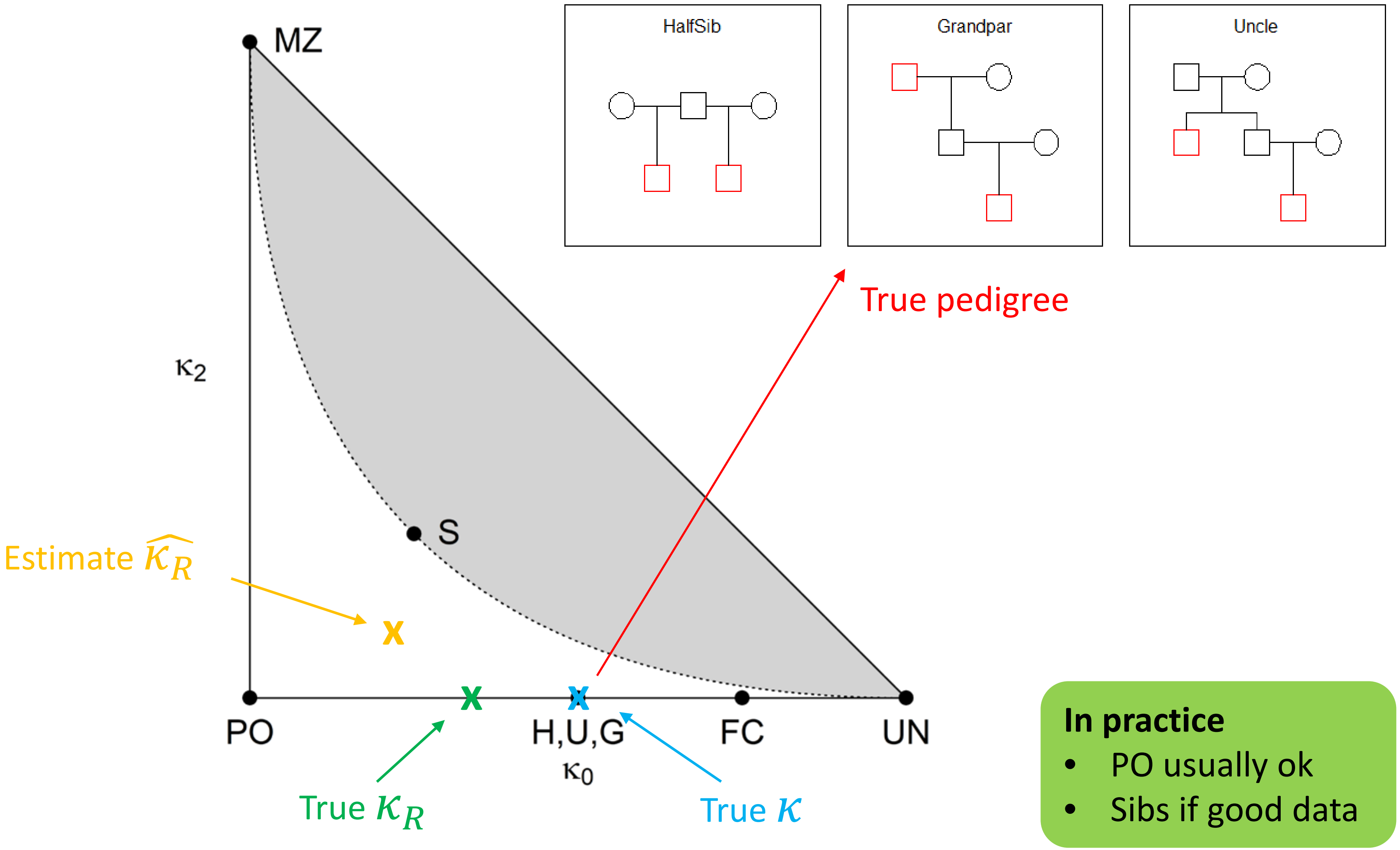
What are we estimating?





Answer: The *realised* coefficients!

Can we recover the pedigree?



True pedigree

Estimate $\widehat{\kappa_R}$

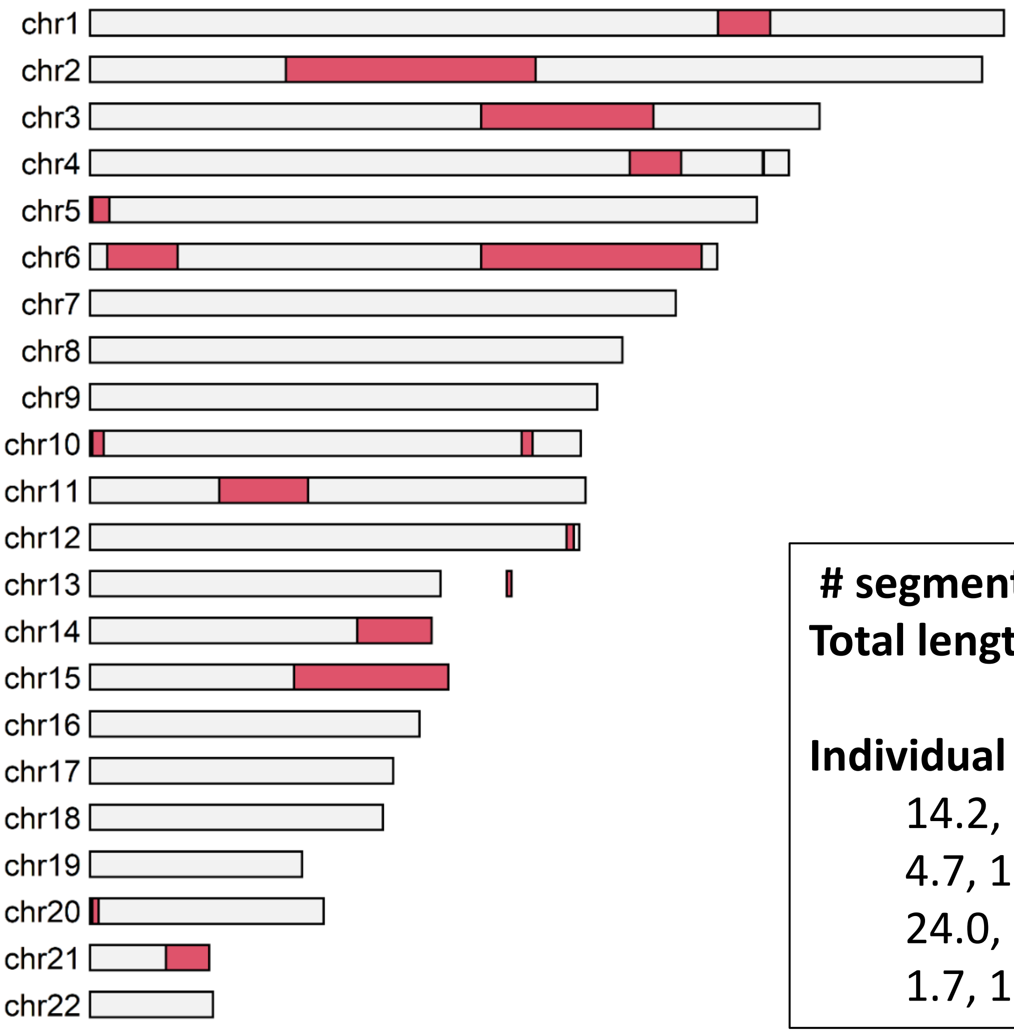
True κ_R

True κ

In practice

- PO usually ok
- Sibs if good data

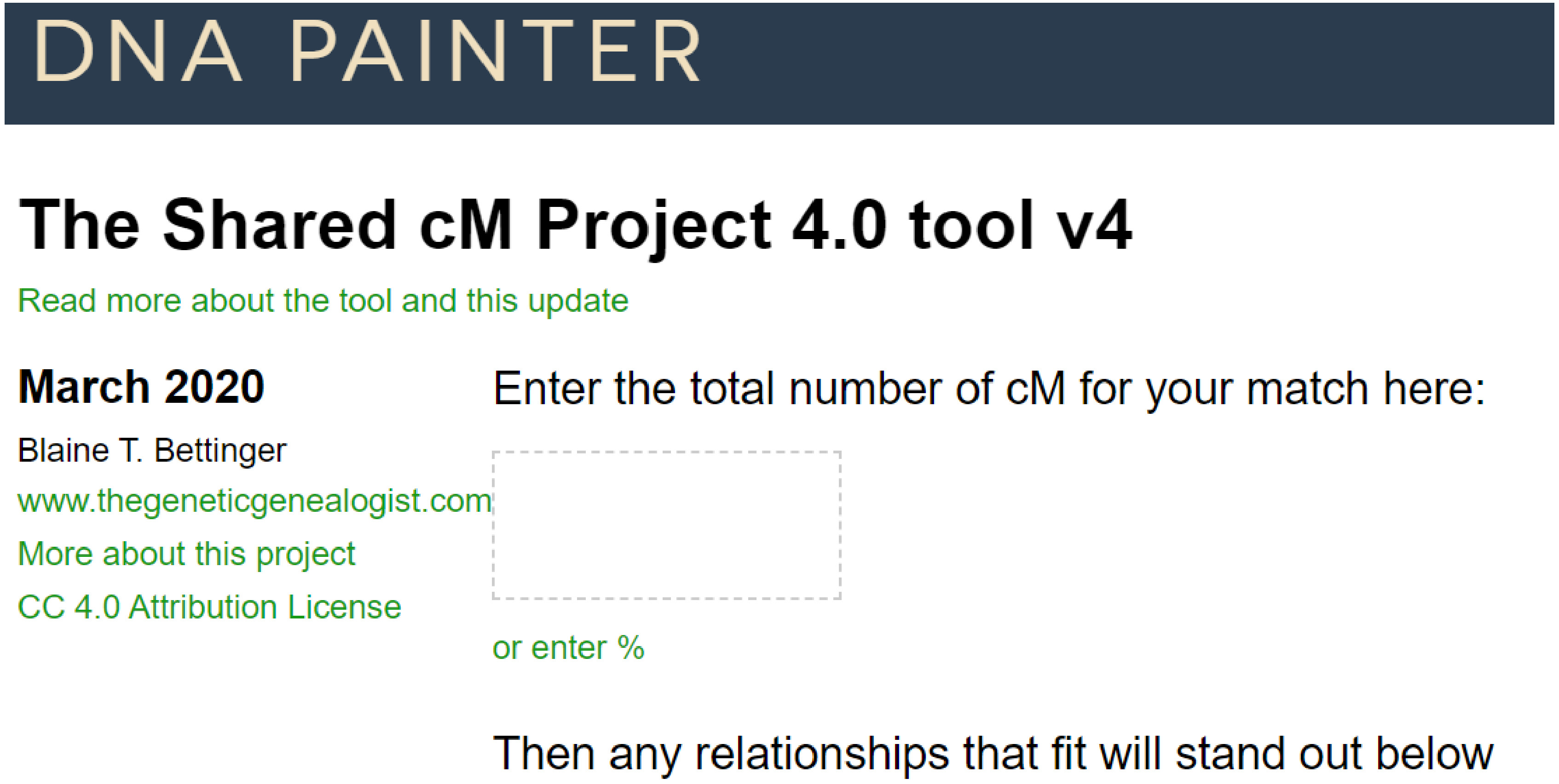
2. IBD segments



 # segments: 17
Total length: 334 cM

Individual lengths:
14.2, 67.6, 46.6, 13.9, 0.3, 4.7, 19.0, 59.6, 3.1, 2.9, 24.0, 1.9, 1.3, 20.1, 41.6, 1.7, 11.7

2. Classification based on IBD segments



DNA PAINTER

The Shared cM Project 4.0 tool v4

Read more about the tool and this update

March 2020

Blaine T. Bettinger

www.thegeneticgenealogist.com

More about this project

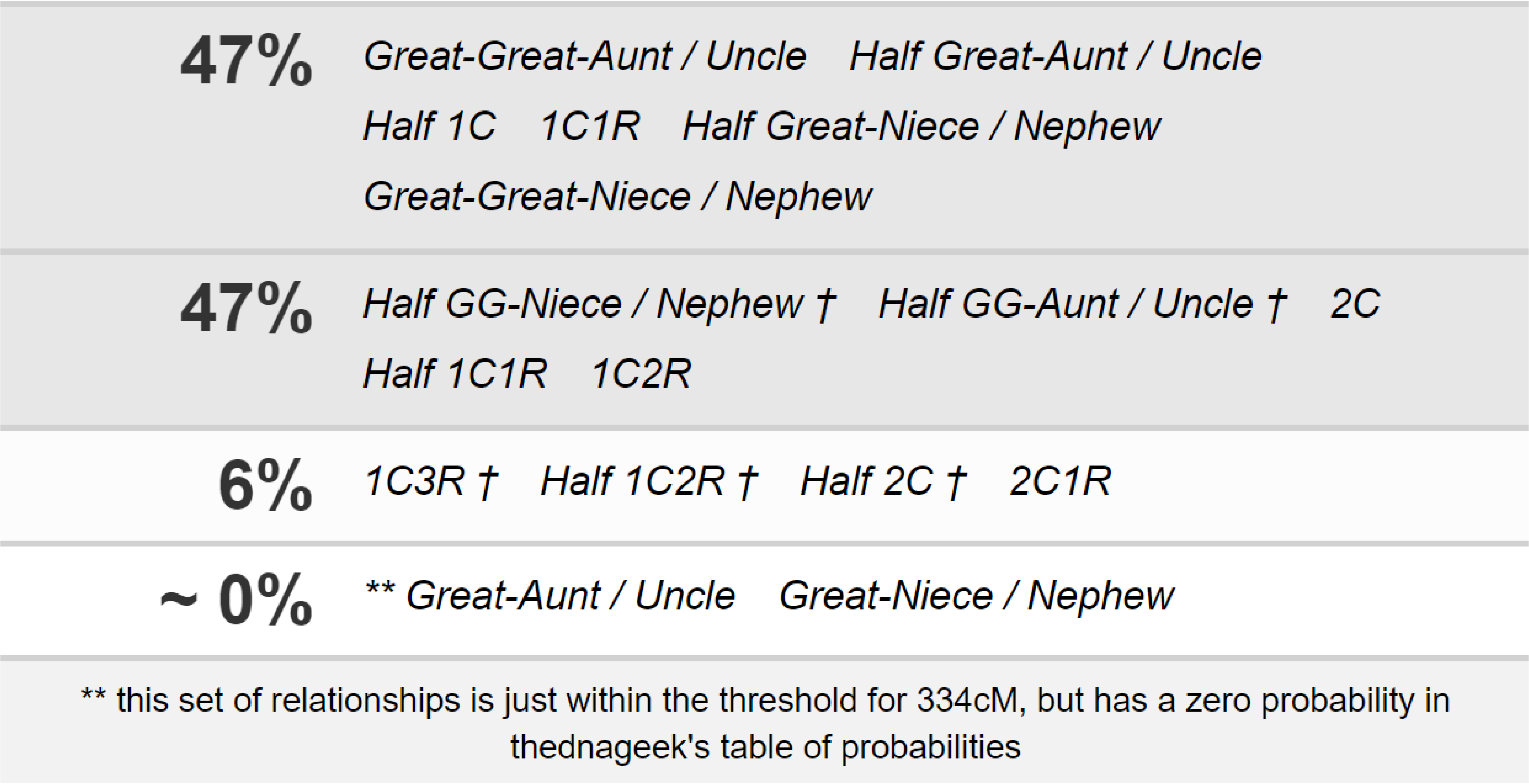
CC 4.0 Attribution License

Enter the total number of cM for your match here:

or enter %

Then any relationships that fit will stand out below

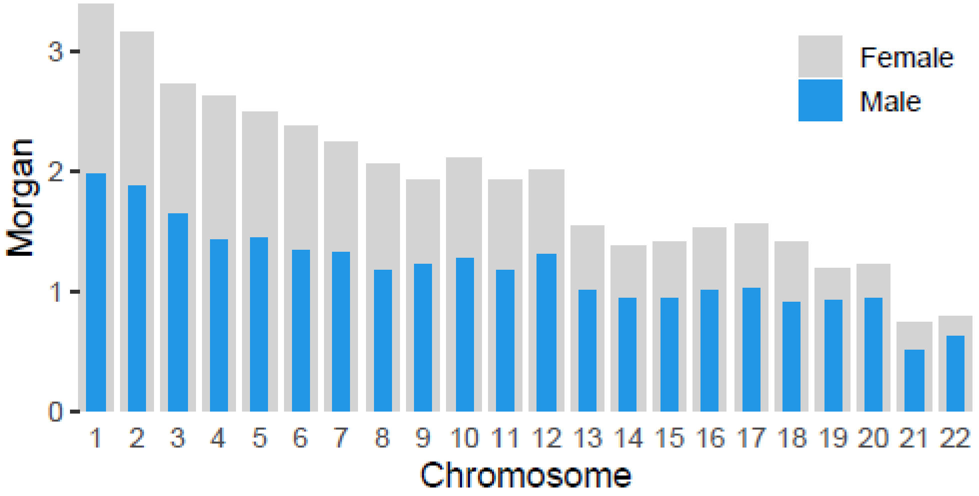
334 cM



47%	*Great-Great-Aunt / Uncle* *Half Great-Aunt / Uncle* *Half 1C* *1C1R* *Half Great-Niece / Nephew* *Great-Great-Niece / Nephew*
47%	*Half GG-Niece / Nephew †* *Half GG-Aunt / Uncle †* *2C* *Half 1C1R* *1C2R*
6%	*1C3R †* *Half 1C2R †* *Half 2C †* *2C1R*
~ 0%	*** Great-Aunt / Uncle* *Great-Niece / Nephew*

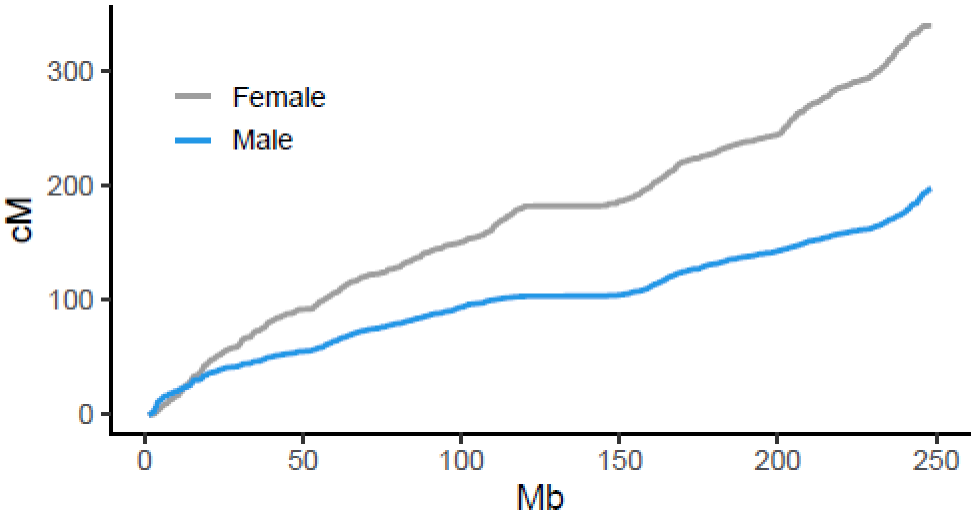
** this set of relationships is just within the threshold for 334cM, but has a zero probability in thednageek's table of probabilities

The importance of sex

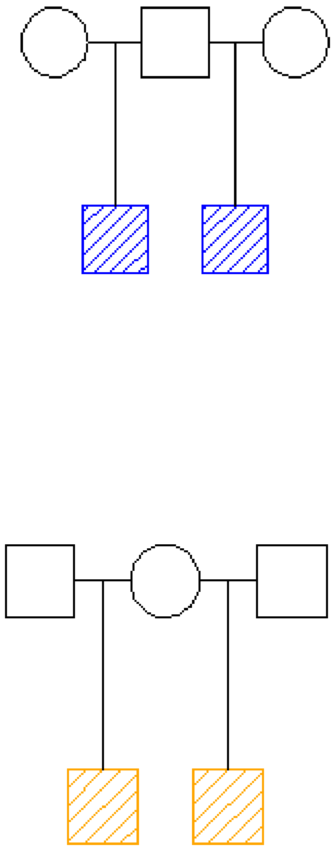


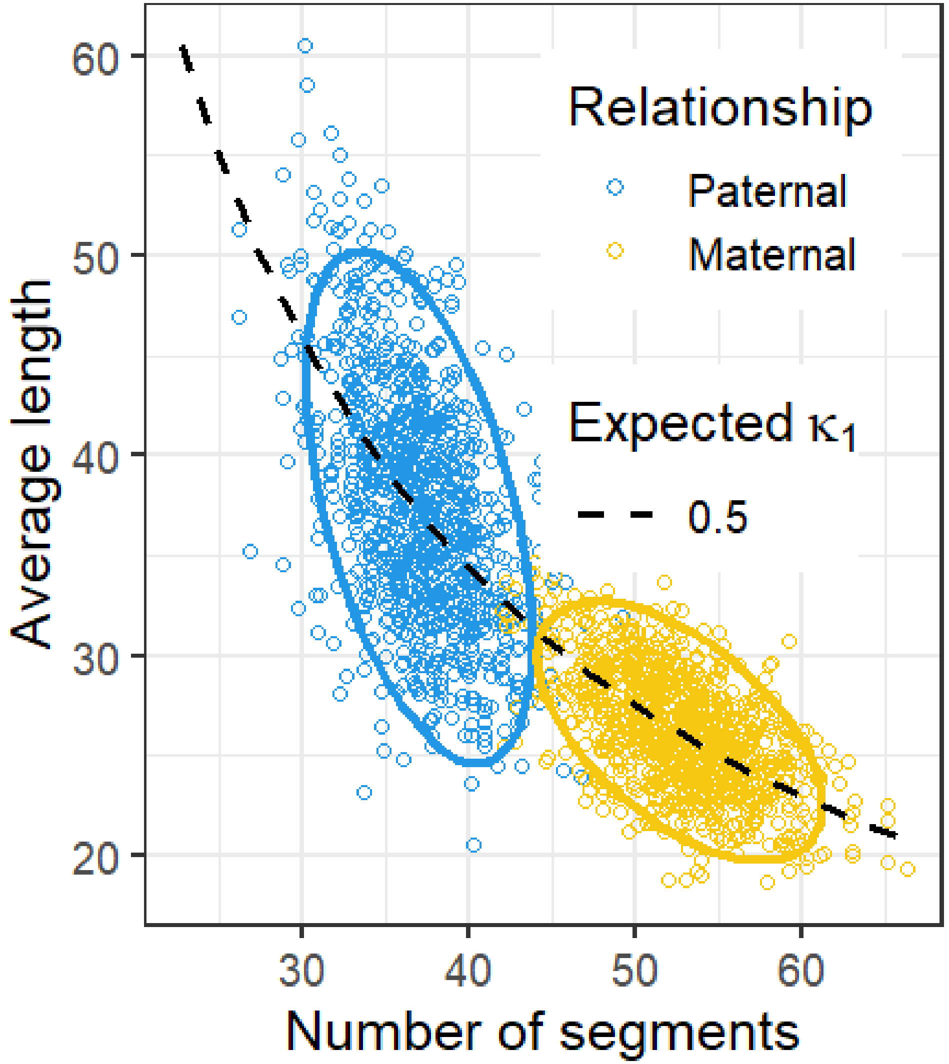
```
decode = loadMap("decode19")
decode
```

```
## Genome map consisting of 22 chromosomes
## Physical range: 2753.93 Mb
## Male length   : 2602.29 cM
## Female length : 4180.42 cM
```



Maternal and paternal half sibs





Jane Austen 1775 - 1817

Napoleon 1769 -1821

10 gen

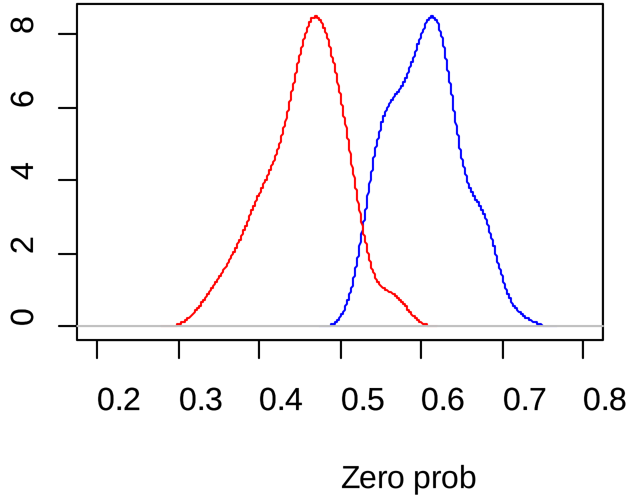
mat line

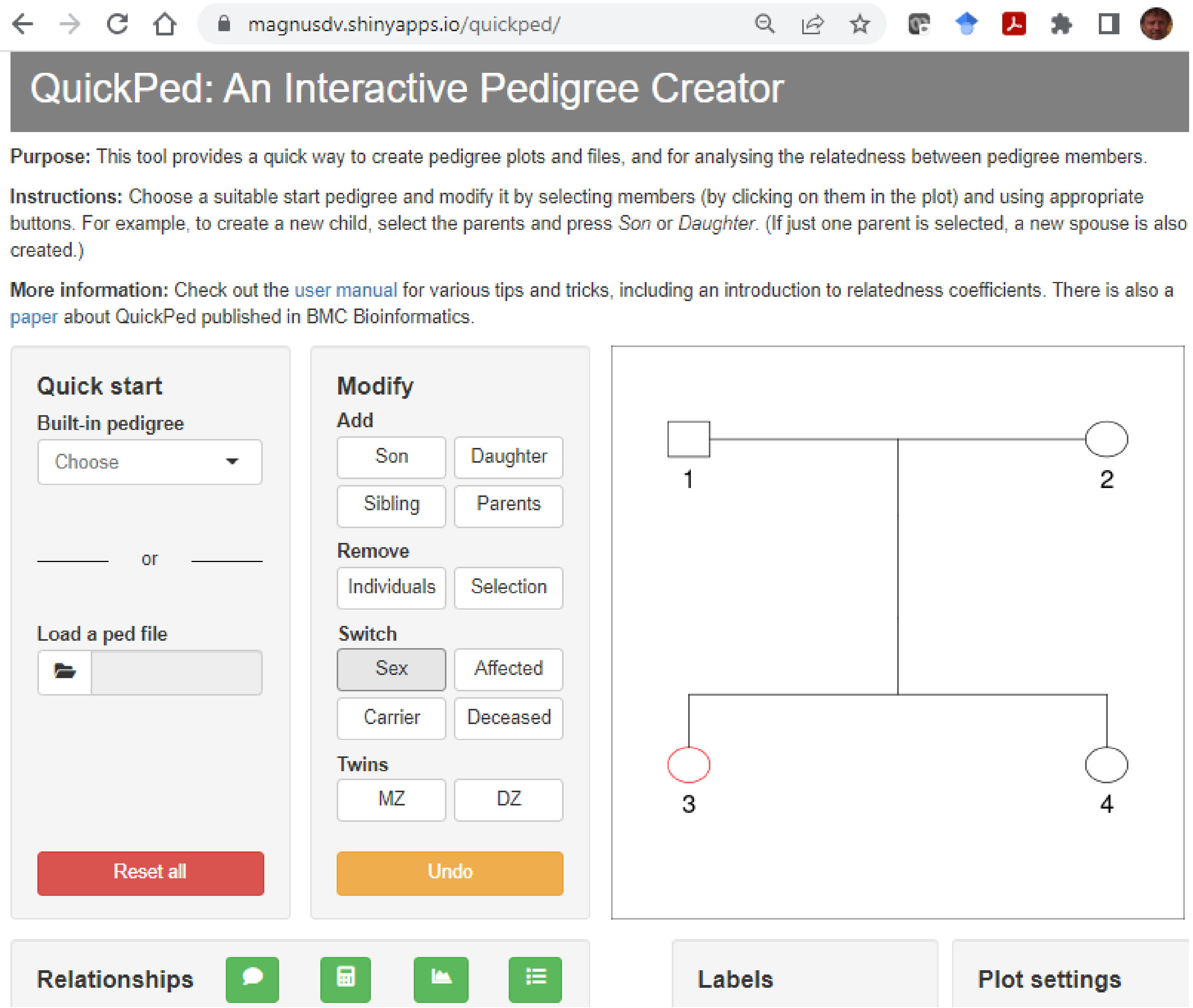
you

10 gen

pat line

you





QuickPed: An Interactive Pedigree Creator

Purpose: This tool provides a quick way to create pedigree plots and files, and for analysing the relatedness between pedigree members.

Instructions: Choose a suitable start pedigree and modify it by selecting members (by clicking on them in the plot) and using appropriate buttons. For example, to create a new child, select the parents and press *Son* or *Daughter*. (If just one parent is selected, a new spouse is also created.)

More information: Check out the user manual for various tips and tricks, including an introduction to relatedness coefficients. There is also a paper about QuickPed published in BMC Bioinformatics.

Summary

- Pedigree definition: $\varphi > 0$
  - *Potentially* having alleles IBD

- Genomic definition (realised relatedness): $\varphi_R > 0$
  - *Actually* having alleles IBD

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  - *The estimation of pairwise relationships.* Ann. Hum. Genet. 39.
- Vigeland (2021)
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