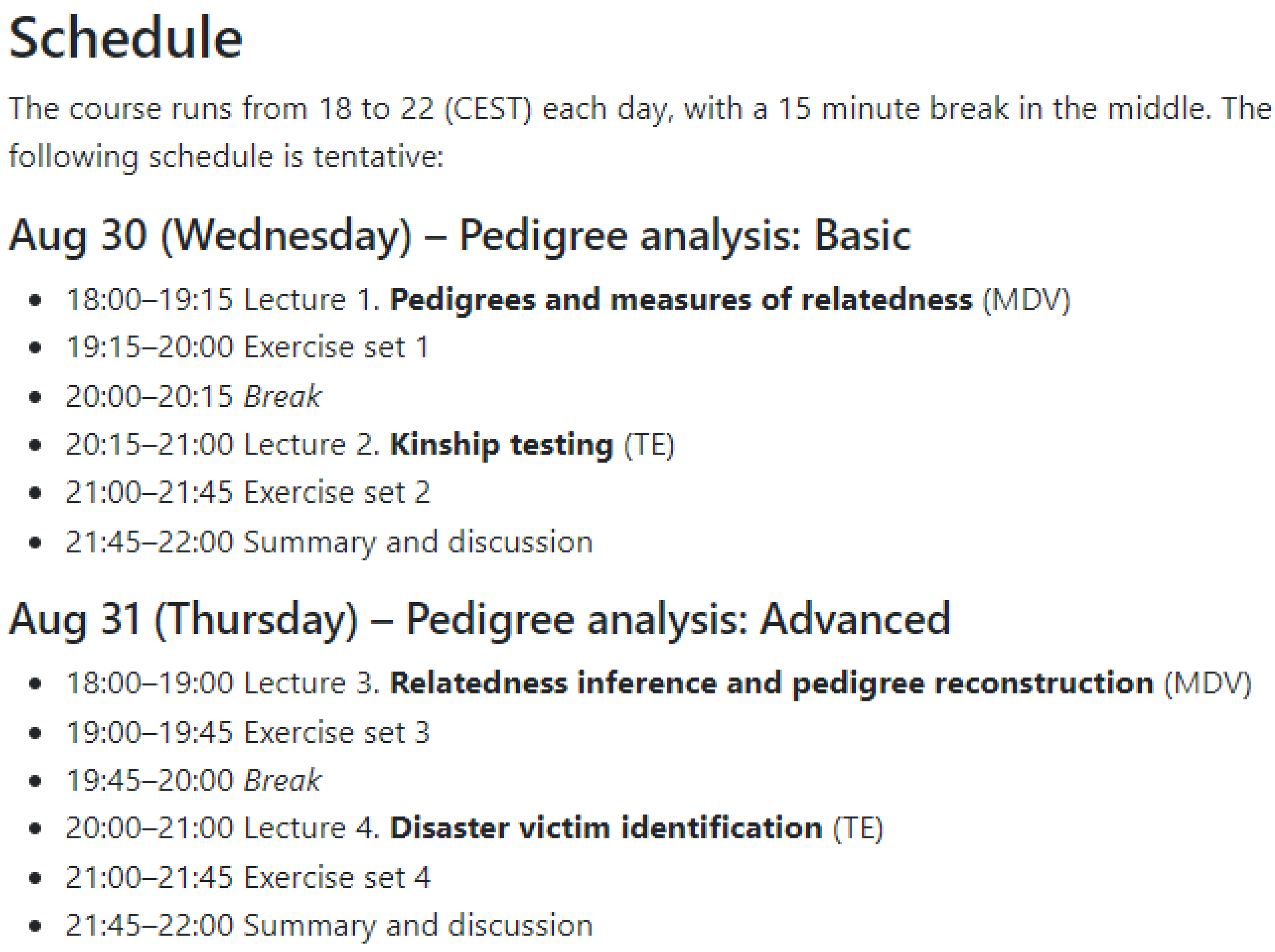
ISFG Summer School - Virtual Edition 2023

Pedigree analysis in R

Teachers:
Thore Egeland
Magnus Dehli Vigeland



Schedule

The course runs from 18 to 22 (CEST) each day, with a 15 minute break in the middle. The following schedule is tentative:

Aug 30 (Wednesday) – Pedigree analysis: Basic

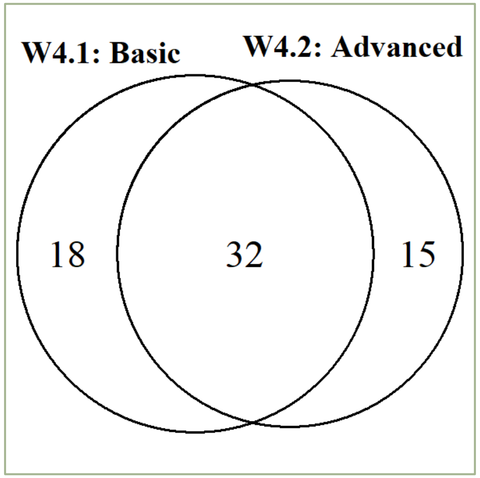
- 18:00–19:15 Lecture 1. **Pedigrees and measures of relatedness** (MDV)
- 19:15–20:00 Exercise set 1
- 20:00–20:15 *Break*
- 20:15–21:00 Lecture 2. **Kinship testing** (TE)
- 21:00–21:45 Exercise set 2
- 21:45–22:00 Summary and discussion

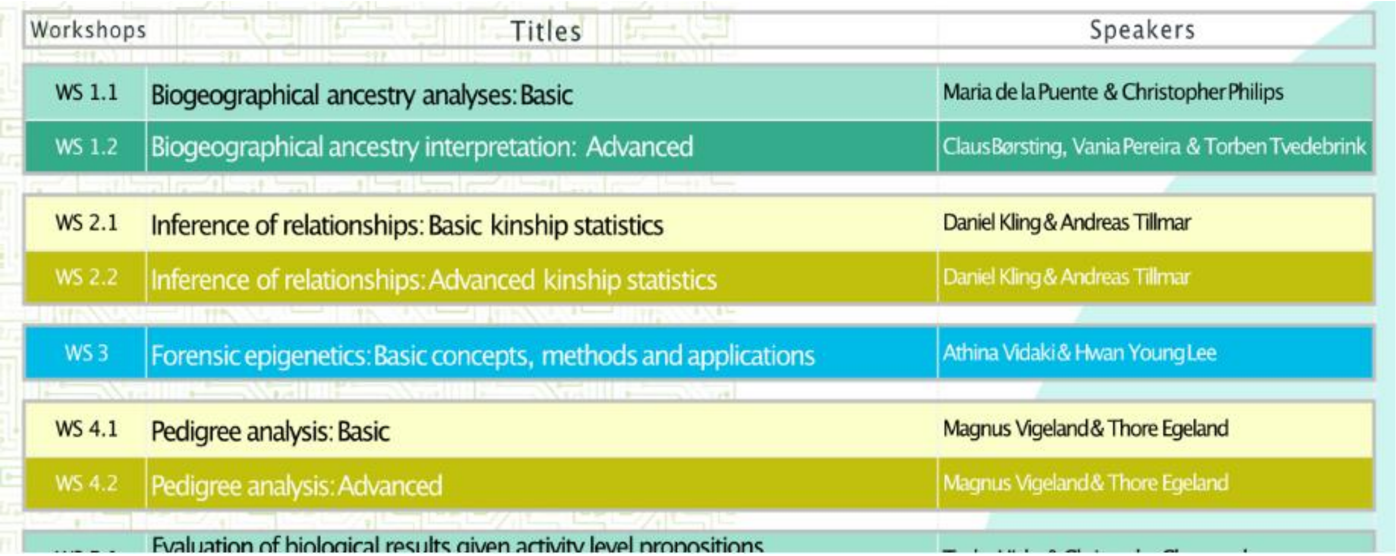
Aug 31 (Thursday) – Pedigree analysis: Advanced

- 18:00–19:00 Lecture 3. **Relatedness inference and pedigree reconstruction** (MDV)
- 19:00–19:45 Exercise set 3
- 19:45–20:00 *Break*
- 20:00–21:00 Lecture 4. **Disaster victim identification** (TE)
- 21:00–21:45 Exercise set 4
- 21:45–22:00 Summary and discussion

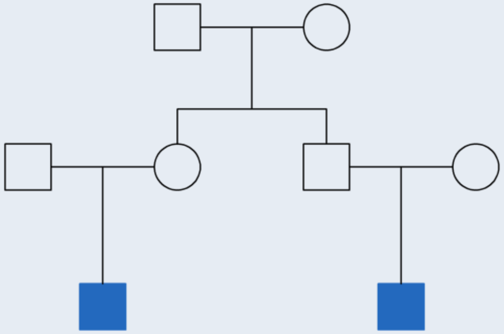
Home page

https://magnusdv.github.io/pedsuite/articles/web_only/course-isfg2023.html





Workshops	Titles	Speakers
WS 1.1	Biogeographical ancestry analyses: Basic	Maria de la Puente & Christopher Philips
WS 1.2	Biogeographical ancestry interpretation: Advanced	Claus Børsting, Vania Pereira & Torben Tvedebrink
WS 2.1	Inference of relationships: Basic kinship statistics	Daniel Kling & Andreas Tillmar
WS 2.2	Inference of relationships: Advanced kinship statistics	Daniel Kling & Andreas Tillmar
WS 3	Forensic epigenetics: Basic concepts, methods and applications	Athina Vidaki & Hwan Young Lee
WS 4.1	Pedigree analysis: Basic	Magnus Vigeland & Thore Egeland
WS 4.2	Pedigree analysis: Advanced	Magnus Vigeland & Thore Egeland
	Evaluation of biological results given activity level propositions	



Lecture 1:
Pedigrees and measures of relatedness

ISFG Summer School 2023. Workshop 4.1

Pedigree analysis: Basic

Magnus Dehli Vigeland

Outline

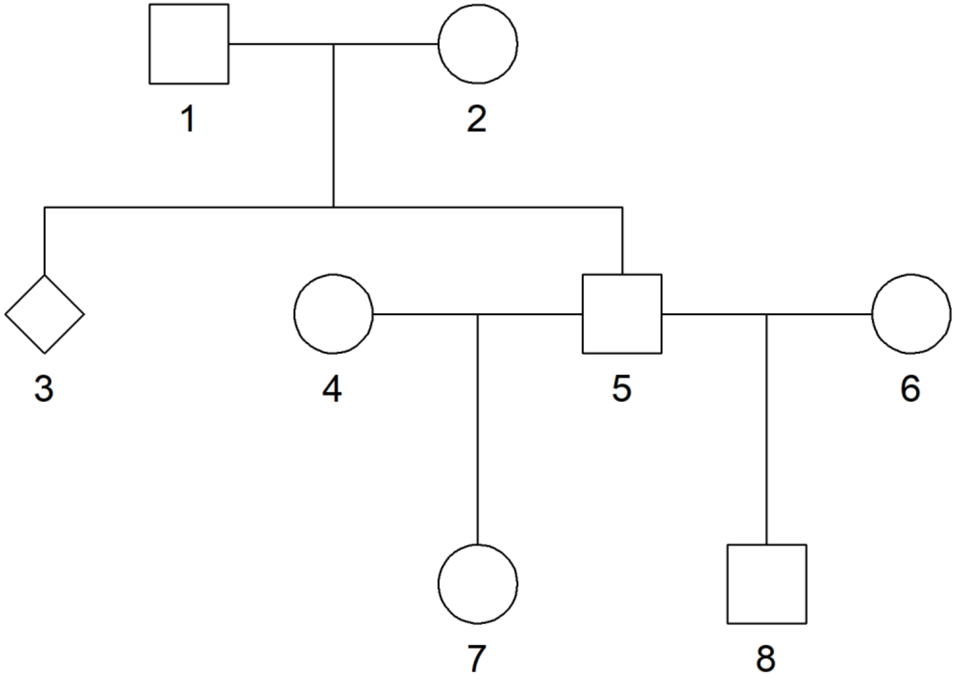
- Part I: *Pedigrees*
  - Conventions and terminology
  - QuickPed

- Part II: *Measures of relatedness*
  - Identity by descent (IBD)
  - Kinship/inbreeding coefficients
  - Kappa coefficients
  - IBD triangle
  - Realised relatedness

- Part III: Crash course in R

Part I: Pedigrees

Conventions and terminology

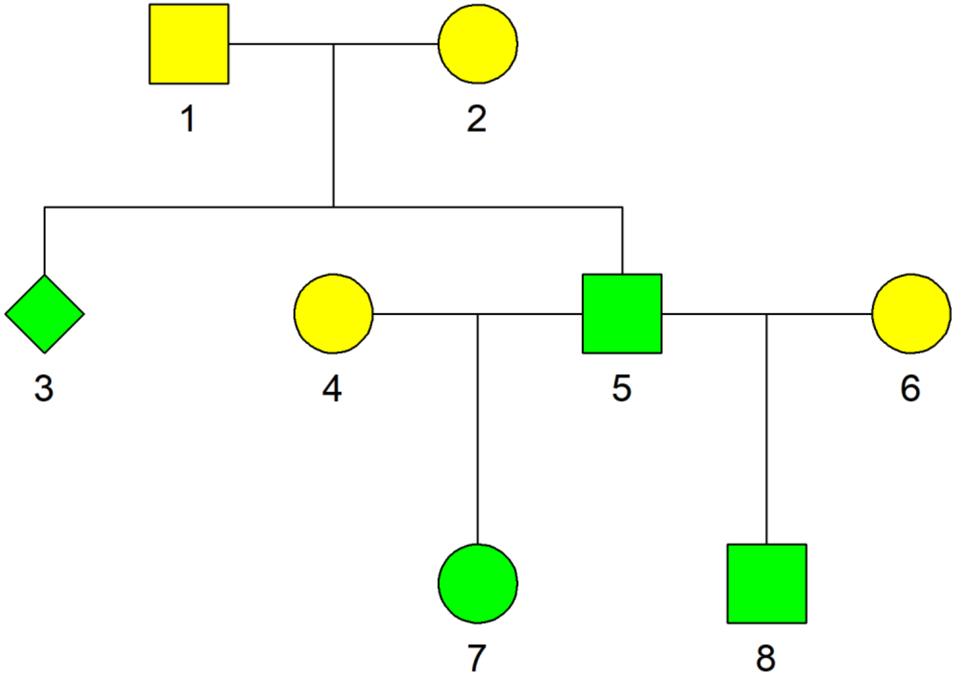


□ = male

○ = female

◇ = unknown

Conventions and terminology



□ = male

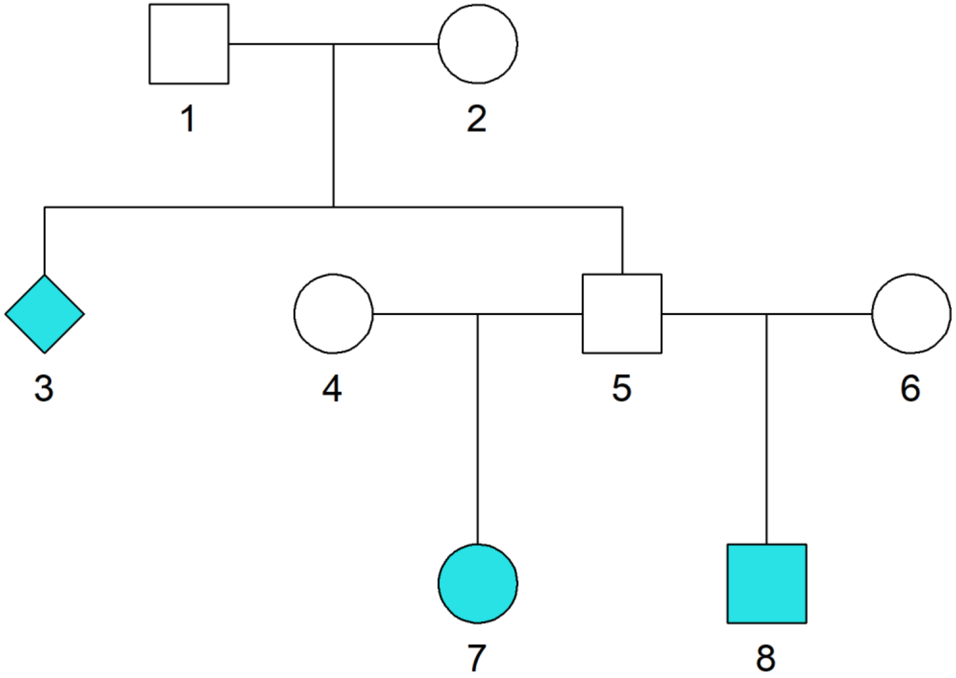
○ = female

◇ = unknown

Founders
No parents included in the pedigree

Nonfounders
Parents are included

Conventions and terminology



□ = male

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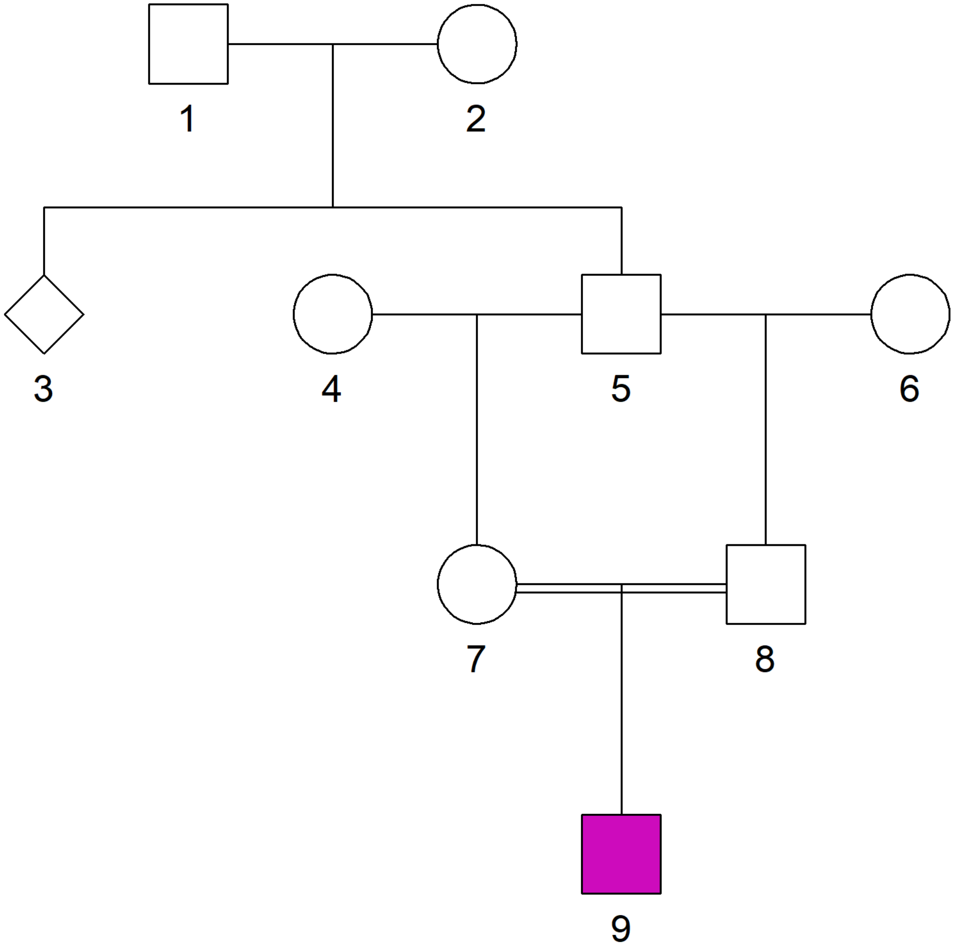
Founders
No parents included in the pedigree

Nonfounders
Parents are included

Leaves
No children included

Conventions and terminology



□ = male

○ = female

◇ = unknown

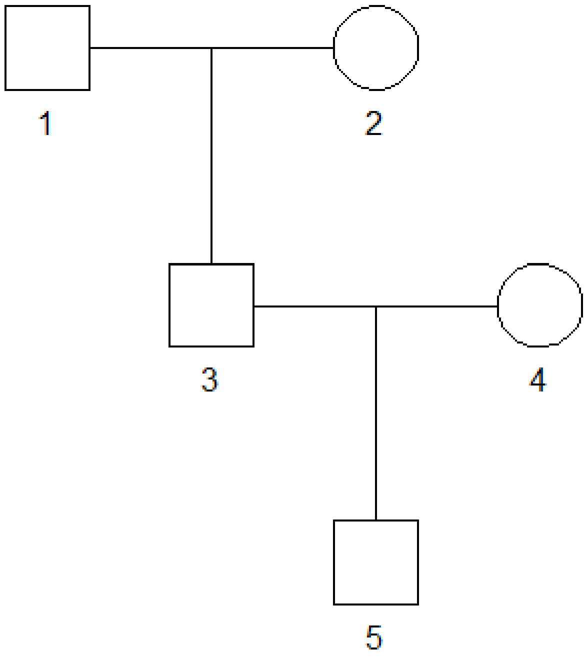
Founders
No parents included in the pedigree

Nonfounders
Parents are included

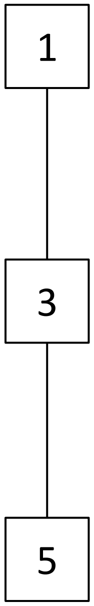
Leaves
No children included

Inbred
Children of related parents

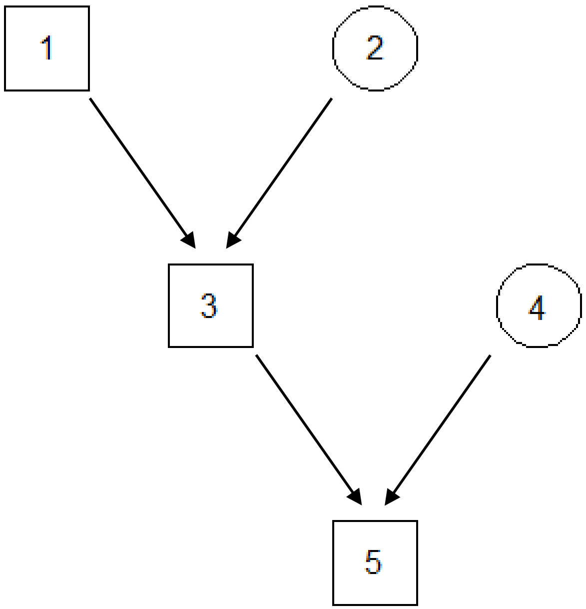
Alternative ways of drawing pedigrees



Standard



Simplified

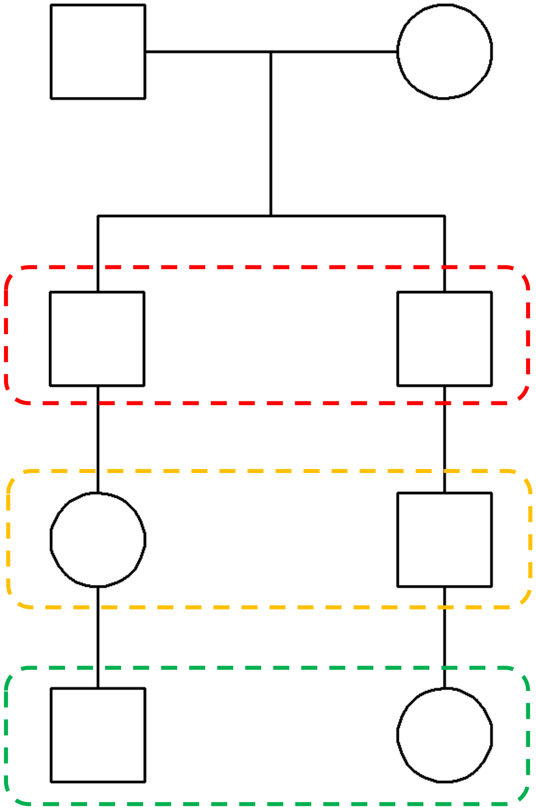


Directed acyclic graph

Some common relationships

(and some less common...)

Cousin relationships

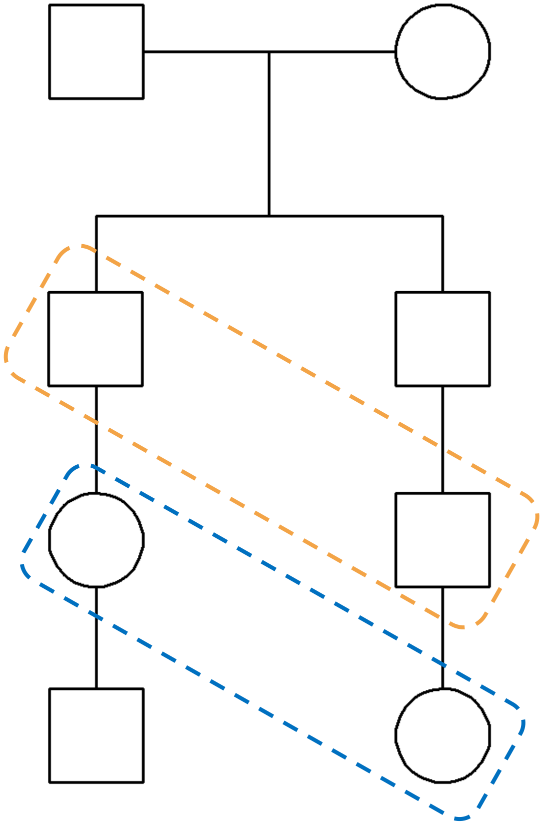


Full siblings

First cousins

Second cousins

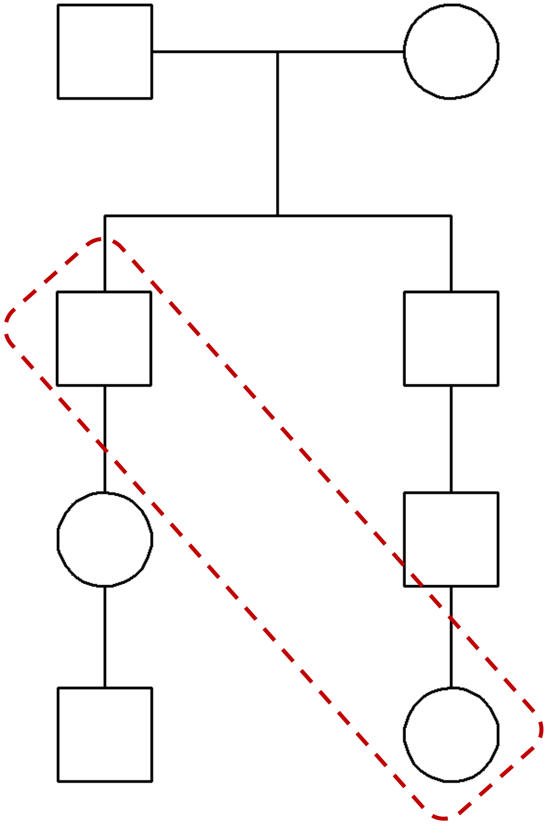
Cousin relationships



Uncle - nephew
(*avuncular*)

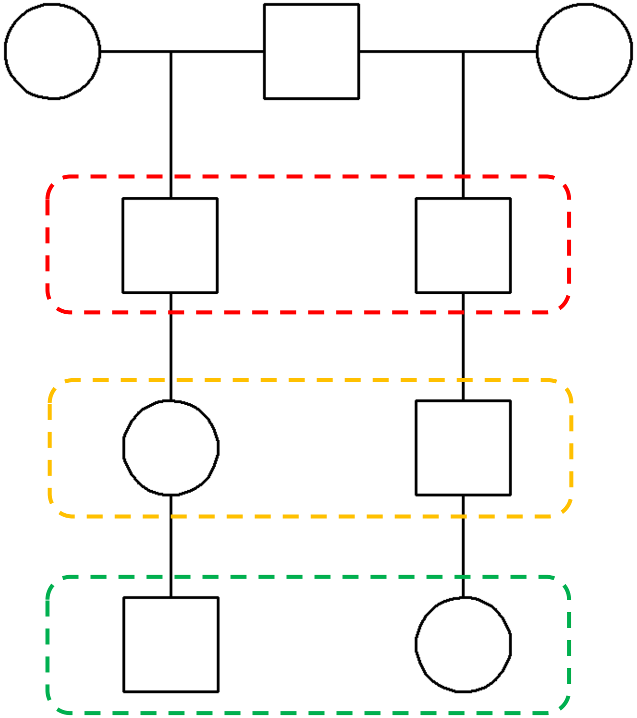
First cousins
once removed

Cousin relationships



Grand-uncle
(or *great uncle*)

Half cousin relationships

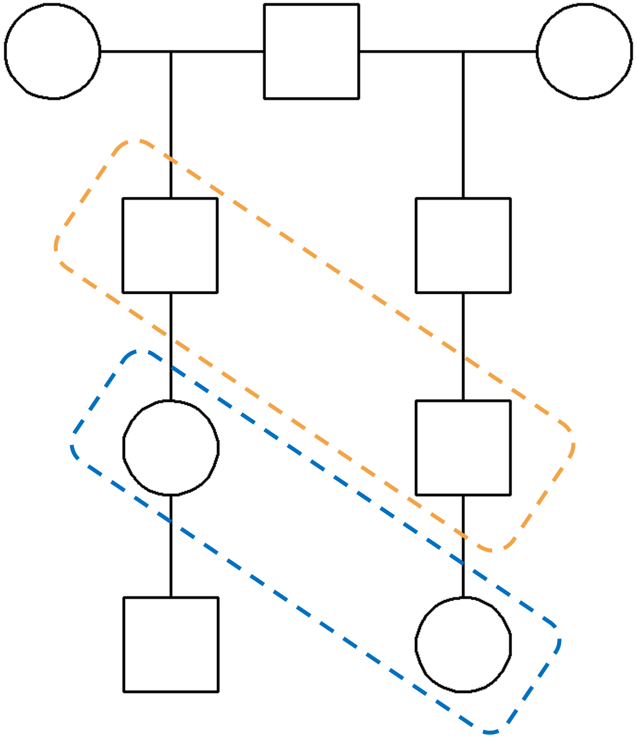


Half siblings

Half first cousins

Half second cousins

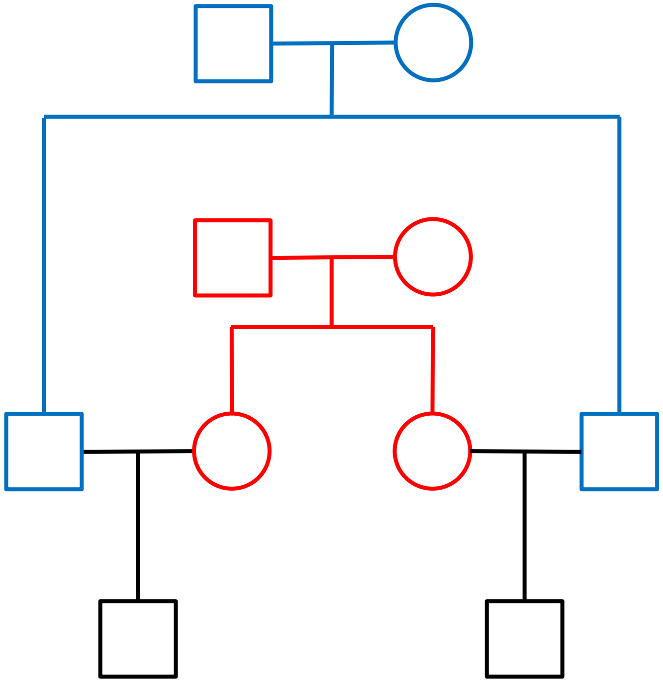
Half cousin relationships



Half-uncle - half-nephew
(*half avuncular*)

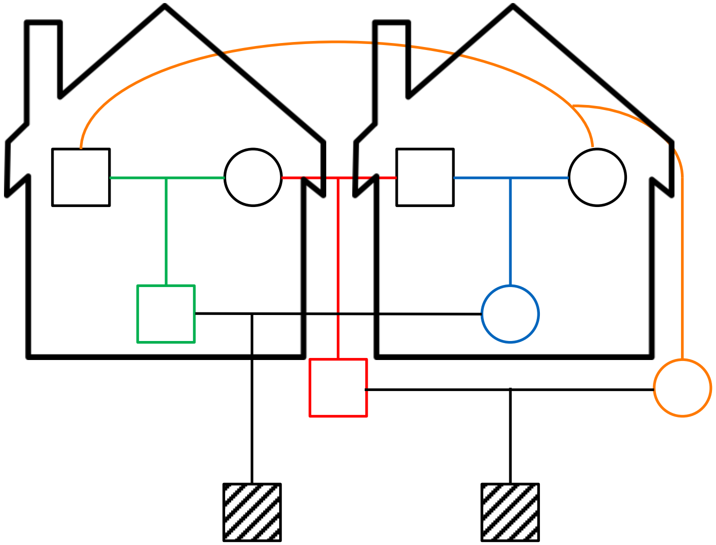
Half first cousins
once removed

Double relationships



Double first cousins

The connoisseur's favourite



Quadruple half first cousins!

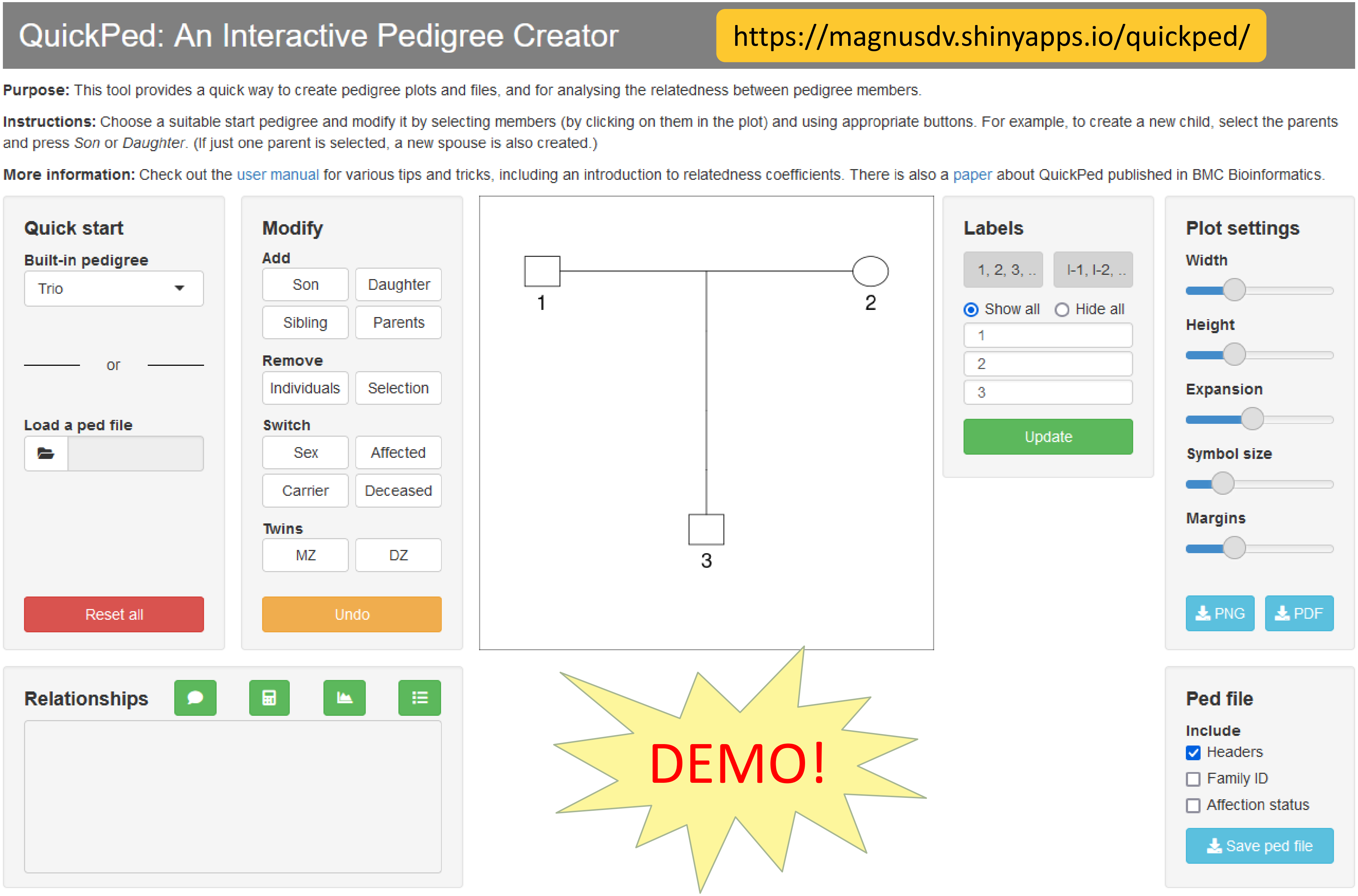
What software exists to create pedigrees?

It depends!

- medical genetics
- forensic genetics
- animal pedigrees
- amateur genealogy

In this course:

- QuickPed
- R



QuickPed: An Interactive Pedigree Creator

https://magnusdv.shinyapps.io/quickped/

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.

Built-in pedigree: Trio

Labels: 1, 2, 3

Ped file – Include: ☑ Headers ☐ Family ID ☐ Affection status

DEMO!

Part II: Measures of relatedness

Typical responses

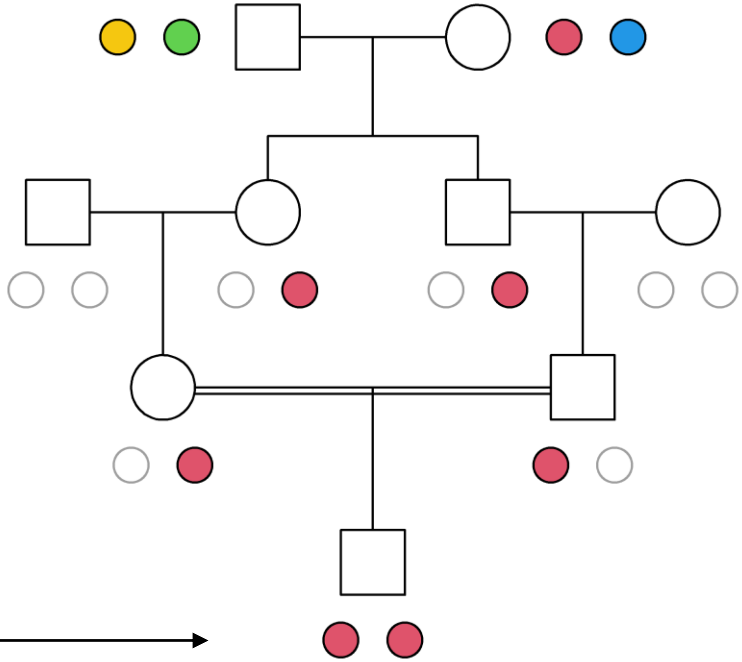
- being connected by family
- having a common ancestor...
  (not too far back)

- sharing DNA ...
  (more than unrelated people)

To make this precise, we need some terminology!

IBD and autozygosity

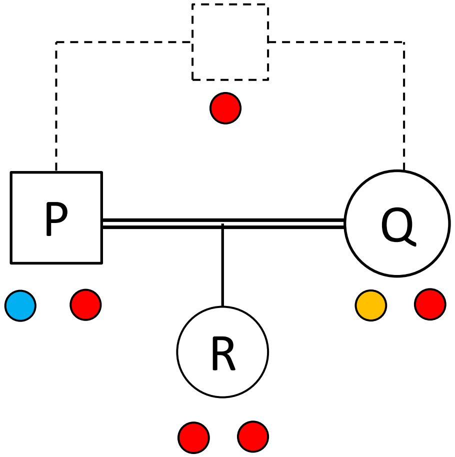
- identity by descent (IBD)
  - when alleles have a common origin **in the given pedigree**
- autozygous
  - homozygous; alleles are IBD →

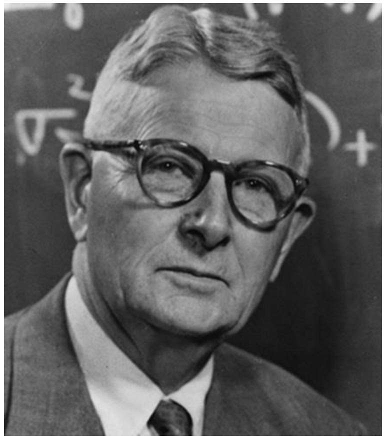


Inbreeding coefficient

$f = Pr(autozygosity)$

Coefficient of kinship/inbreeding





Sewall Wright
(1889 - 1988)

- Wright (1921): The kinship coefficient φ

$\varphi_{P,Q}$ = *Pr*(P and Q emit IBD alleles)

= *Pr*(R is autozygous)

= f_R

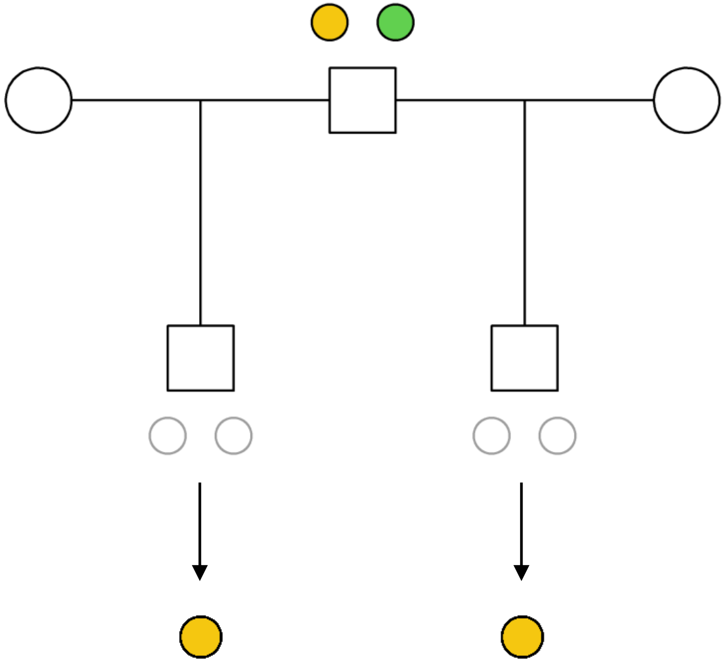
Kinship of parents = inbreeding of child

P and Q related

⇕

$\varphi_{P,Q} > 0$

Example: Kinship coefficient of half siblings



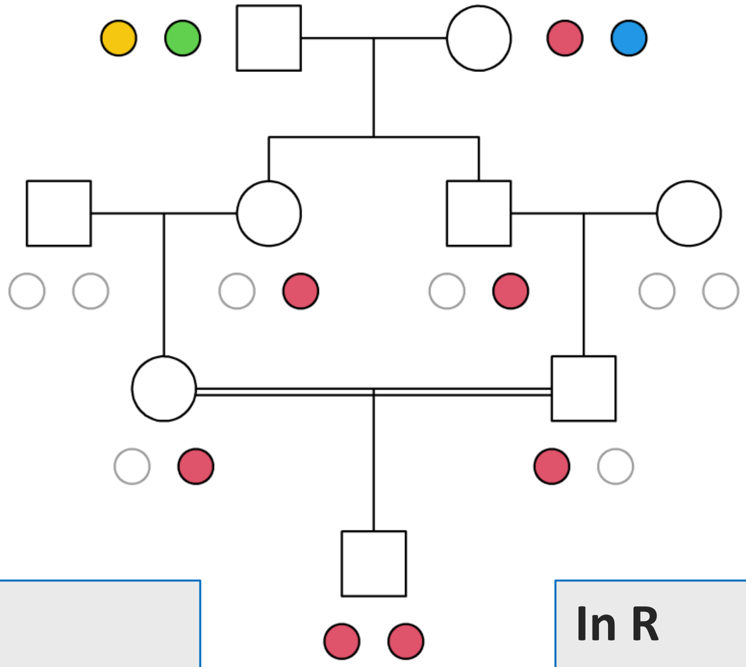
Kinship coefficient

$$\begin{aligned}\varphi &= P(\text{🟡 from both}) \cdot \underset{\overset{\uparrow}{\text{green}}}{2} \\ &= 0.5^4 \cdot 2 \\ &= 1/8\end{aligned}$$

Inbreding coefficient: Example

Wright's path formula:

$$\varphi_{P,Q} = \sum_{A} \sum_{v} \left(\frac{1}{2}\right)^{|v|+1} (1 + f_A)$$



By hand

$$f = P(\bullet\ \text{autozygous}) \cdot 4$$
$$= 0.5^6 \cdot 4$$
$$= 1/16$$

↑ other colors

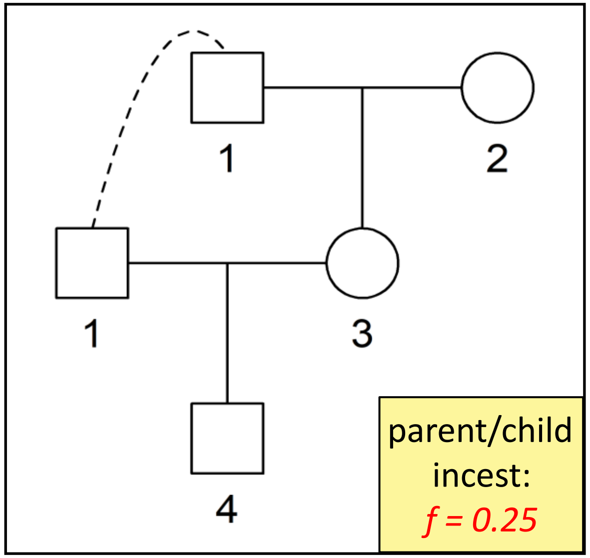
In R

```
>   library(pedsuite)

>   x = cousinPed(1, child = T)
>   inbreeding(x, ids = 9)
[1] 0.0625
```

More kinship & inbreeding coefficients

Relationship	kinship φ = f of child
Parent-child	1/4
Full siblings	1/4
Half siblings	1/8
Grandparent-grandchild	1/8
Avuncular (uncle/aunt)	1/8
1st cousins	1/16
2nd cousins	1/64
3rd cousins	1/256

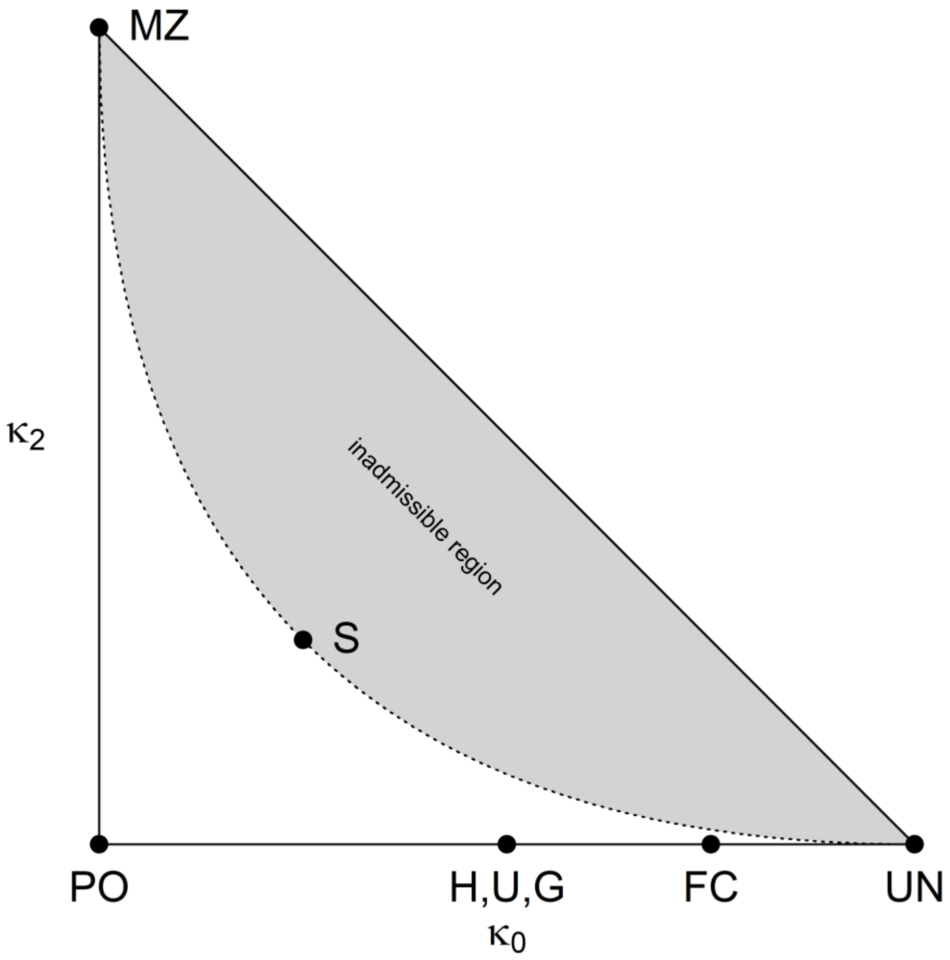
Challenge
Different relationships
with the same kinship!



parent/child incest: $f = 0.25$

```
>  x = nuclearPed(1, sex = 2) |>
     addSon(parents = c(1, 3))

>  kinship(x, ids = c(1, 3))
[1] 0.25
>  inbreeding(x, id = 4)
[1] 0.25
```

The IBD triangle



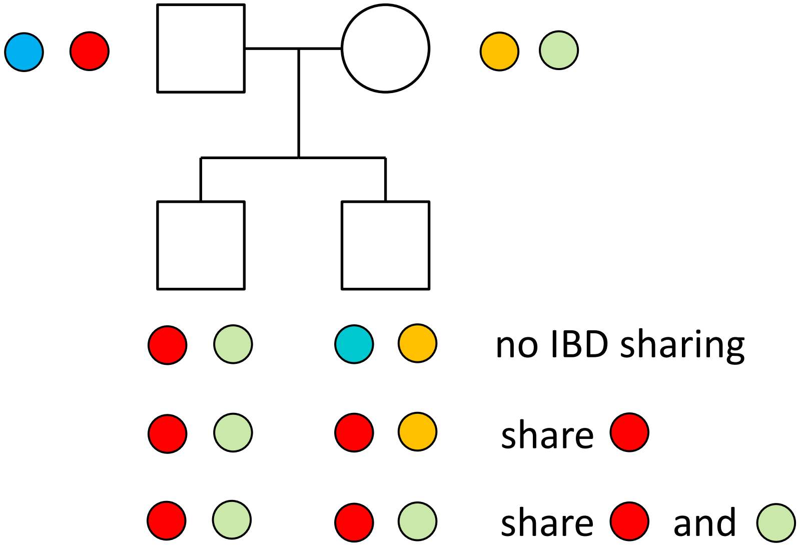
Charles Cotterman
(1914-1989)

Elisabeth Thompson
(1949 -)

IBD coefficients

- Summary so far:
  - Two individuals are related if they can have IBD alleles
  - Their kinship coefficient meassures the amount of IBD sharing

- Natural generalisation:
  - How *many* alleles are IBD in each locus?

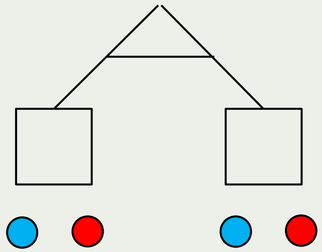


Definition

- $\kappa_0 = Pr(0 \text{ alleles IBD})$
- $\kappa_1 = Pr(1 \text{ alleles IBD})$
- $\kappa_2 = Pr(2 \text{ alleles IBD})$

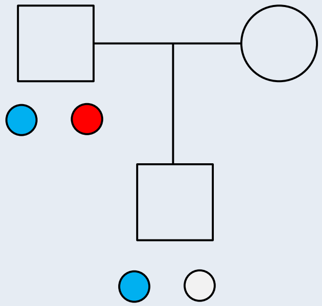
(at random autosomal locus)

Three trivial relationships



Monozygotic twins (MZ)

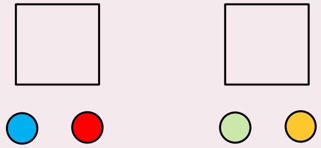
$(\kappa_0, \kappa_1, \kappa_2) = (0,0,1)$



Parent-offspring (PO)

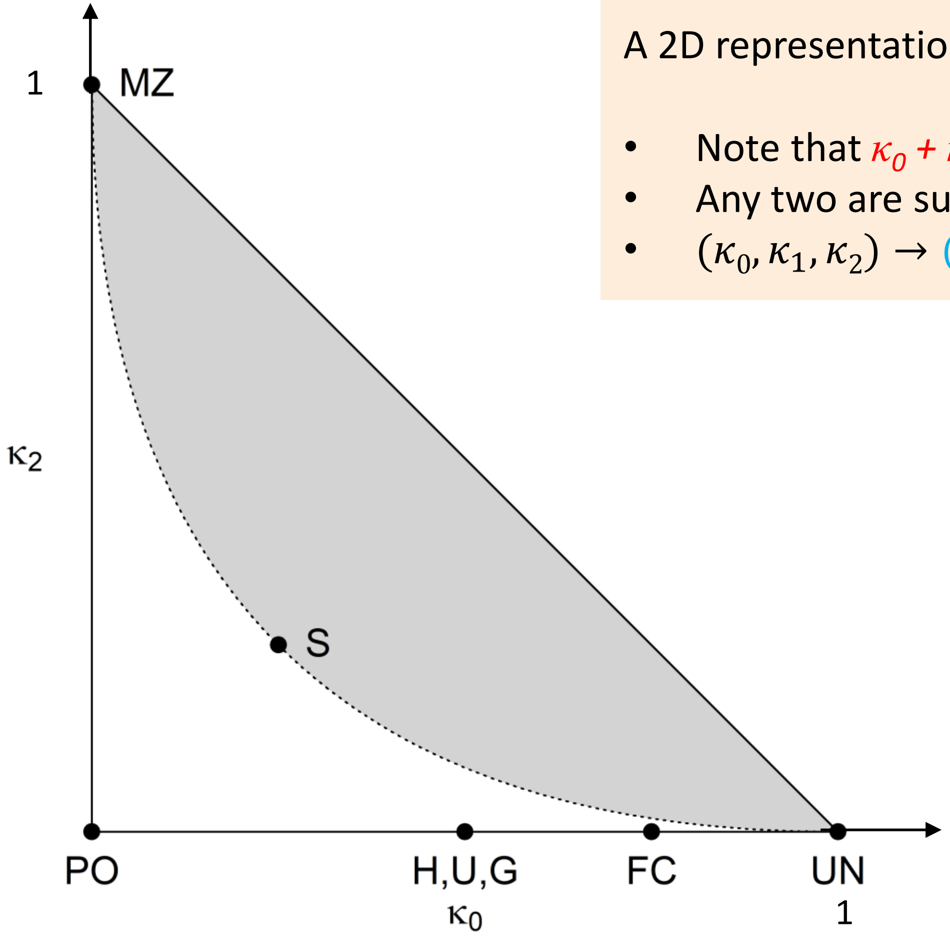
$(\kappa_0, \kappa_1, \kappa_2) = (0,1,0)$

Unrelated (UN)



$(\kappa_0, \kappa_1, \kappa_2) = (1,0,0)$

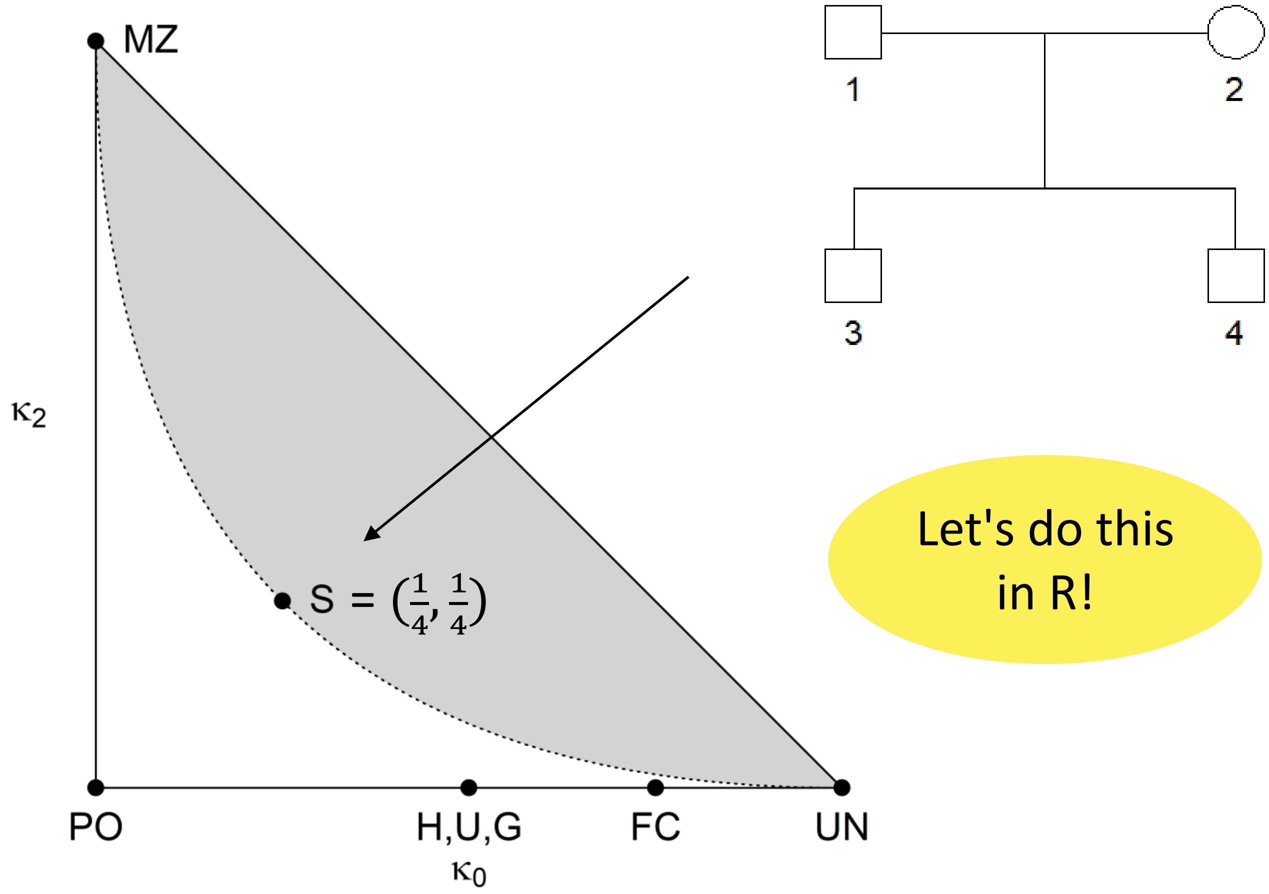
The relatedness triangle



A 2D representation of $(\kappa_0, \kappa_1, \kappa_2)$

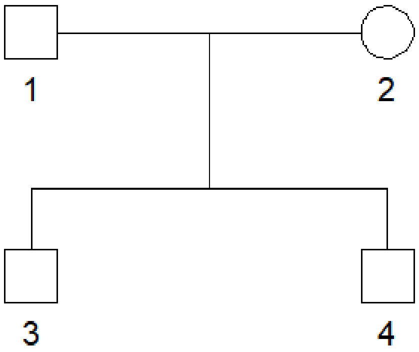
- Note that $\kappa_0 + \kappa_1 + \kappa_2 = 1$
- Any two are sufficient
- $(\kappa_0, \kappa_1, \kappa_2) \rightarrow (\kappa_0, \kappa_2)$

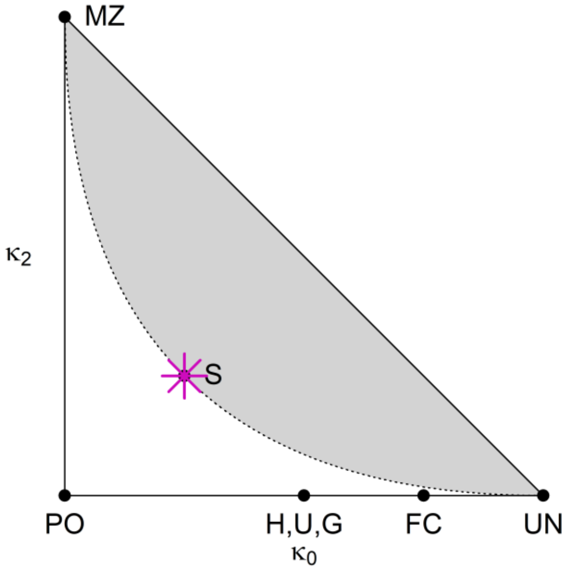
What are the coefficients of full sibs?



Let's do this in R!

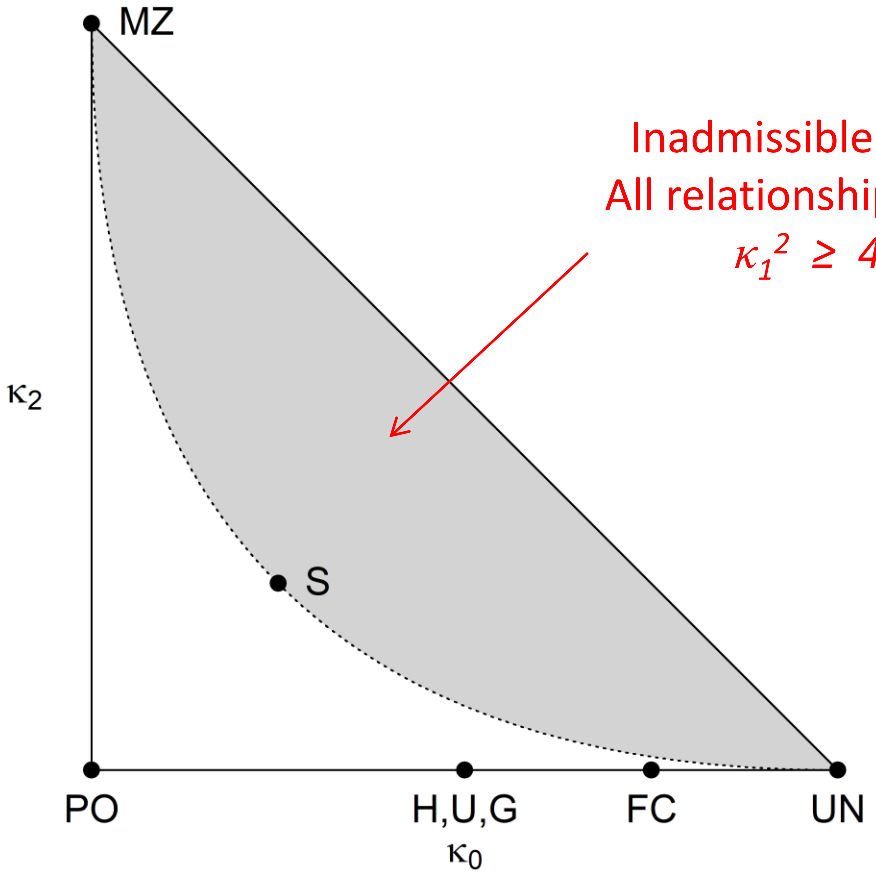
ribd: Pedigree-based relatedness coefficients





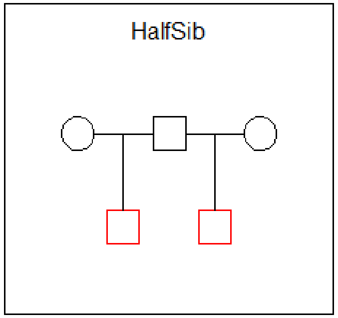
```
>   library(pedsuite)

>   x = nuclearPed(2)
>   plot(x)

>   kinship(x, ids = 3:4)
[1] 0.25

>   kappaIBD(x, ids = 3:4)
[1] 0.25 0.50 0.25

>   k = kappaIBD(x, ids = 3:4)
>   showInTriangle(k)
```

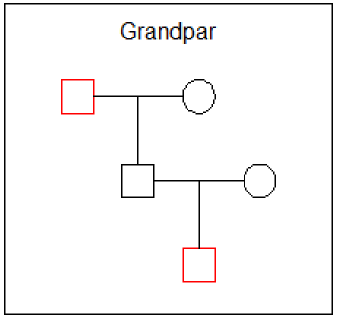
The relatedness triangle

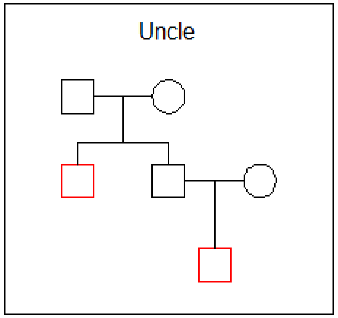


Inadmissible region!
All relationships satisfy
$\kappa_1^2 \geq 4\kappa_0\kappa_2$

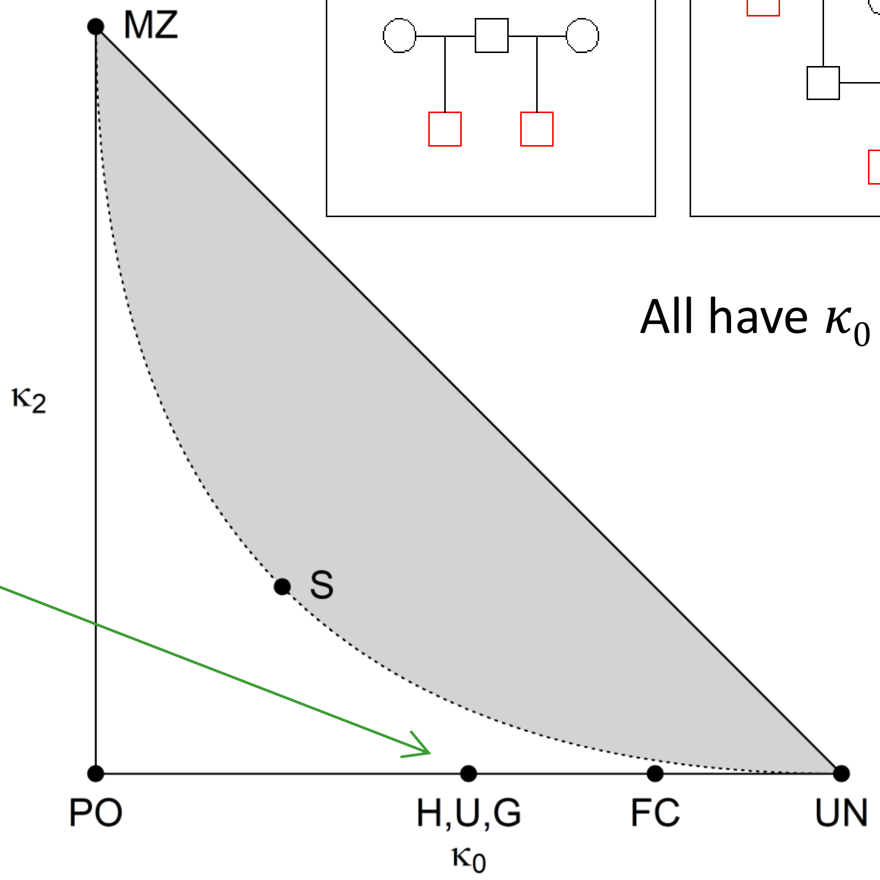
The relatedness triangle





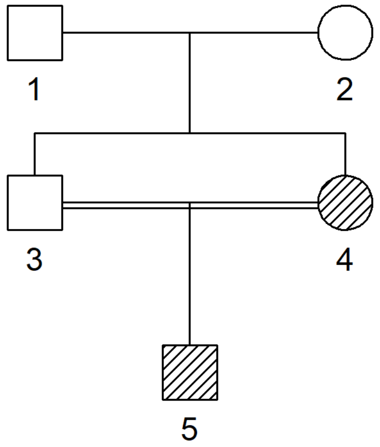


All have $\kappa_0 = \kappa_1 = \frac{1}{2}$



Some relationships coincide!

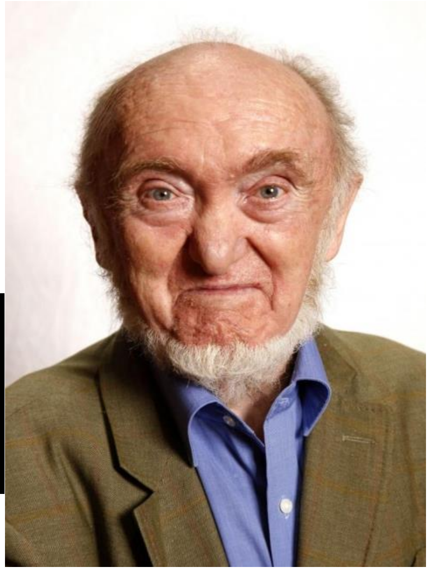
A word of caution



κ is only defined for non-inbred individuals.
For the whole story, we need 9 coefficients!

Jacquard's identity coefficients

Not suitable for a basic course ...

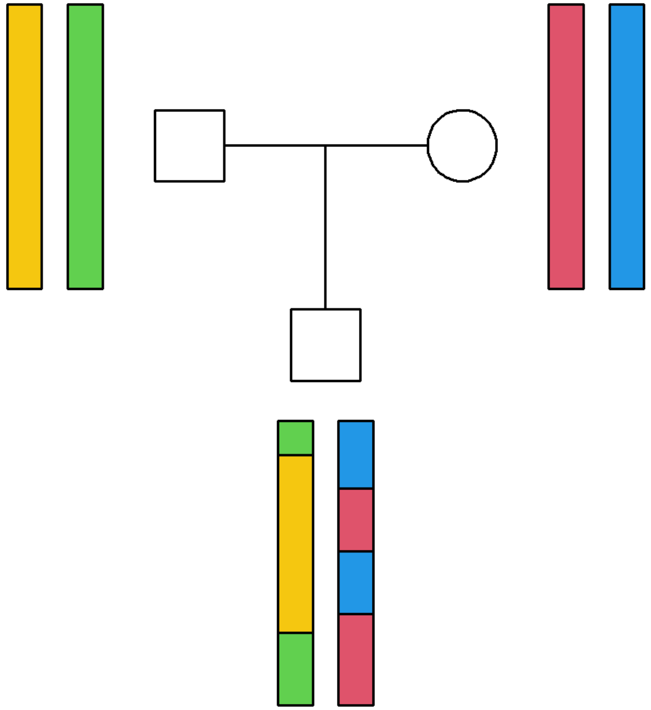


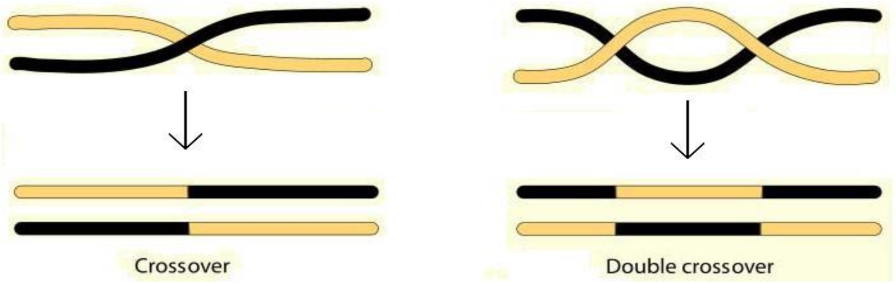
Albert Jacquard
(1925 - 2013)

Part II: Measures of relatedness

Realised relatedness

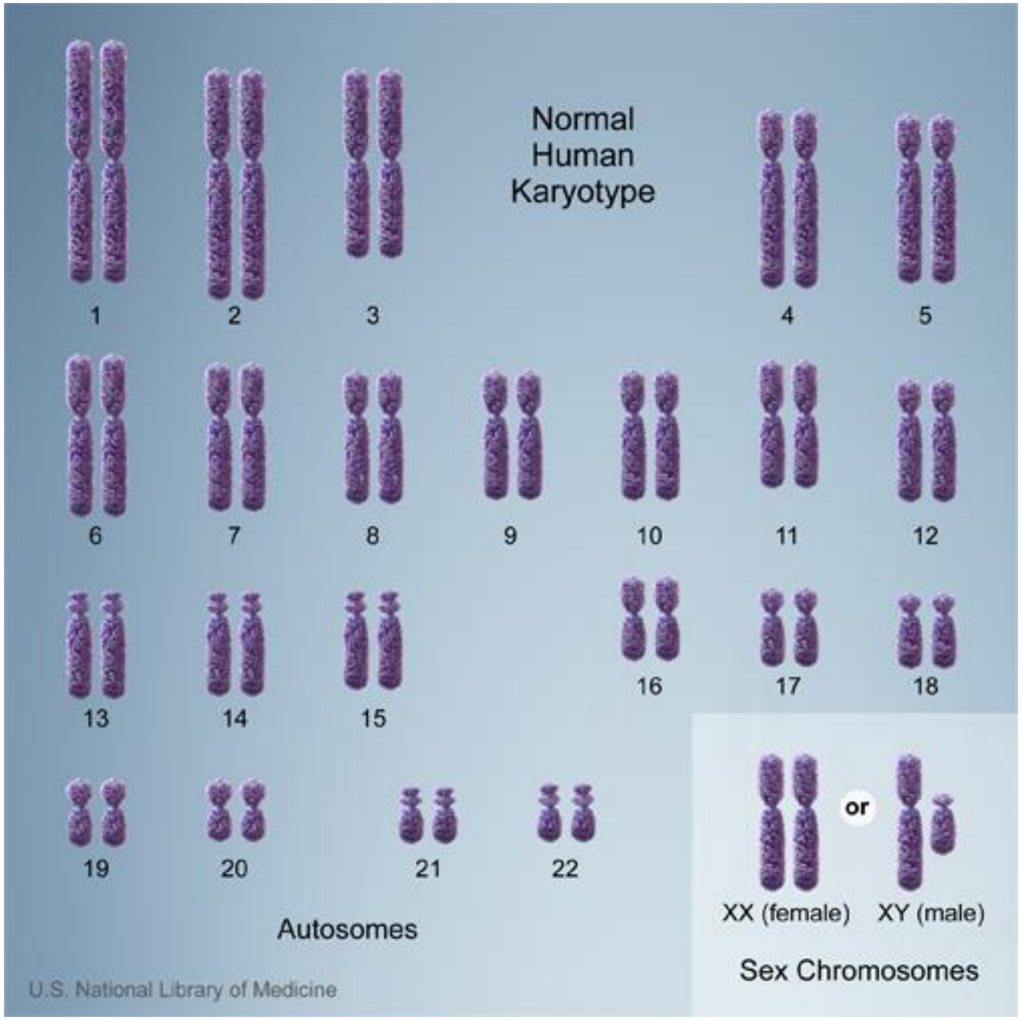
Meiotic recombination



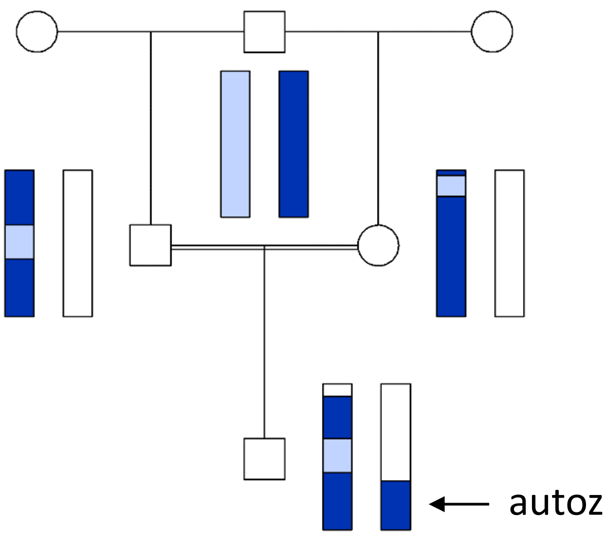


- Genetic distance between two loci: = average # crossovers/ meiosis
- Units:
  - 1 Morgan (M) = 1 crossover per meiosis
  - 1 centiMorgan (cM) = 0.01 M
- The human genome: Ca 30 Morgan

Rule of thumb: One crossover per chromosome arm

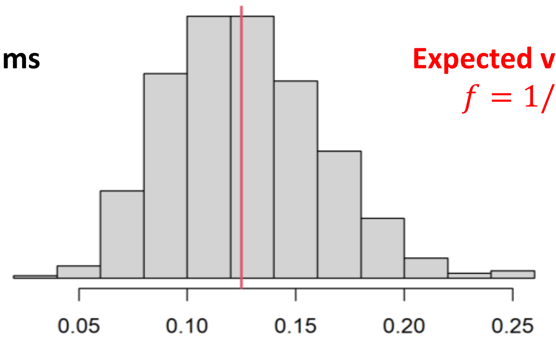


Realised inbreeding

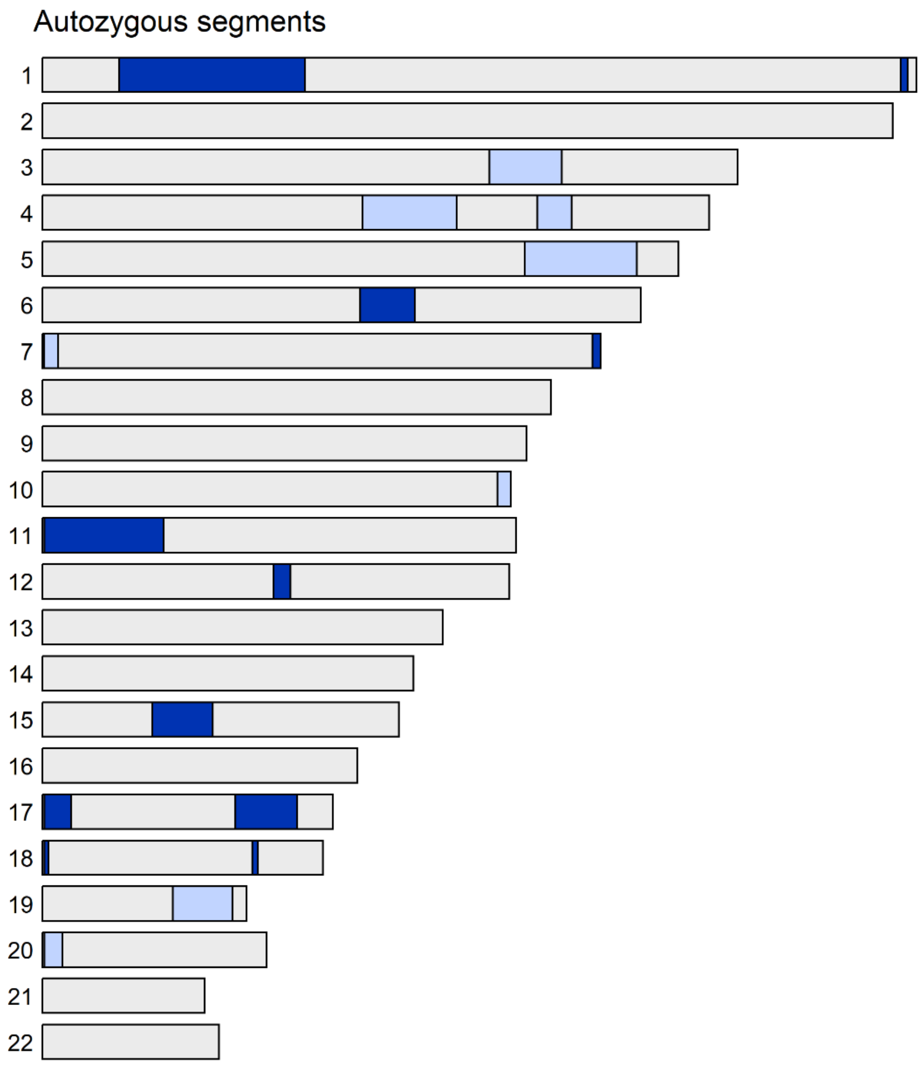


f_R = autozygous fraction of genome

500 sims

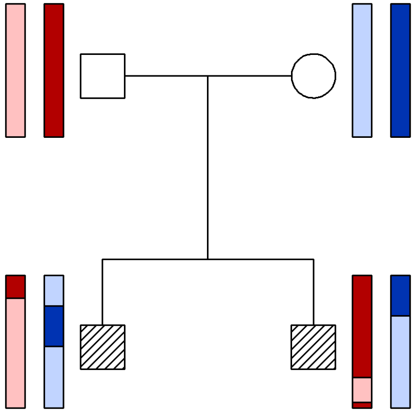


Expected value:
$f = 1/8$

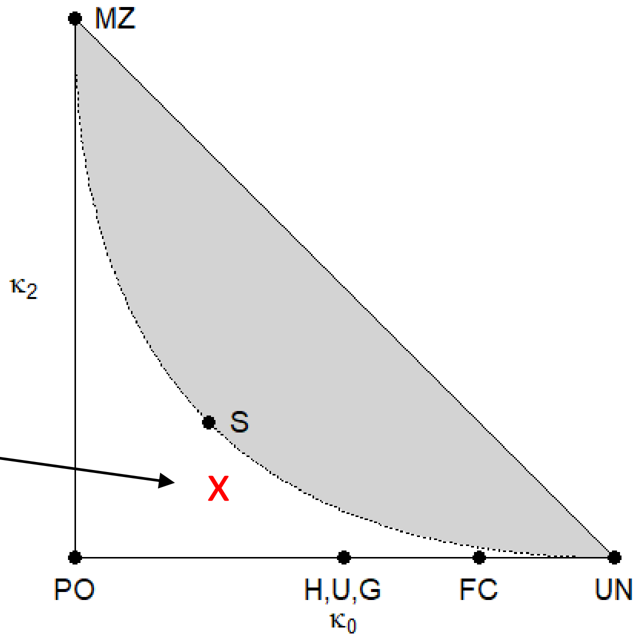


Realised IBD coefficients

1000 simulations

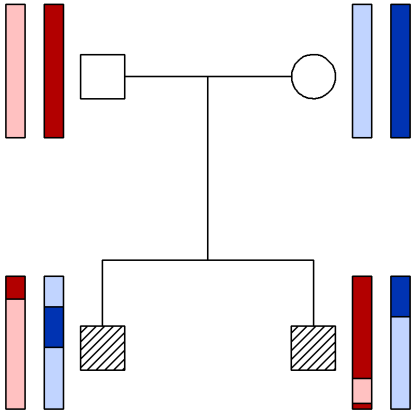


Realised IBD coefficients:
Proportions of genome with IBD = 0, 1, 2

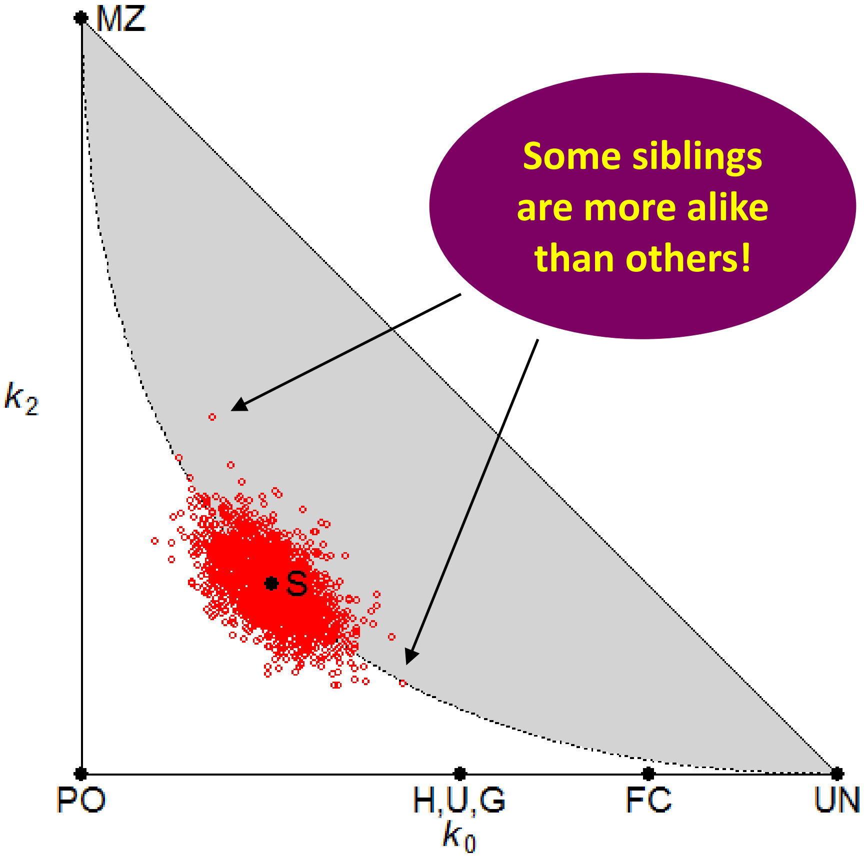


Variation in realised IBD coefficients

1000 simulations



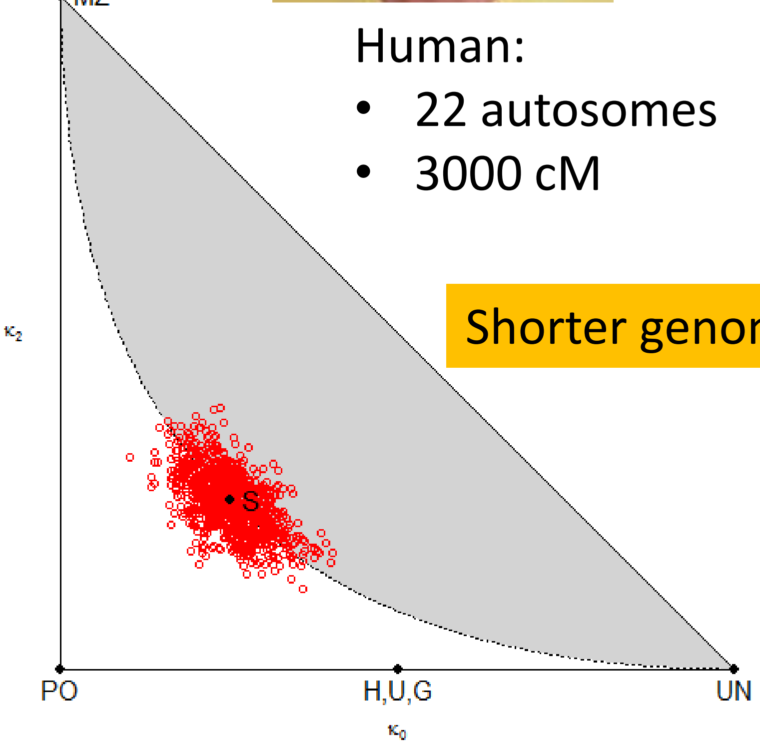
```
>  library(ibdsim2)

>  x = nuclearPed(2)
>  s = ibdsim(x, N = 1000)
>  k = realisedKappa(s, ids = 3:4)

>  ribd::showInTriangle(k)
```



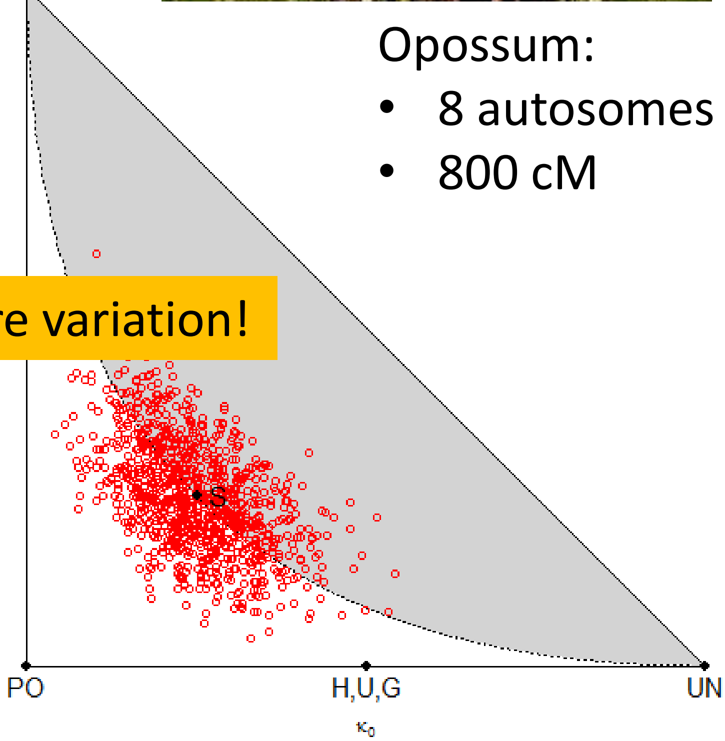
Some siblings are more alike than others!

Variation depends on the genome

Human:
- 22 autosomes
- 3000 cM

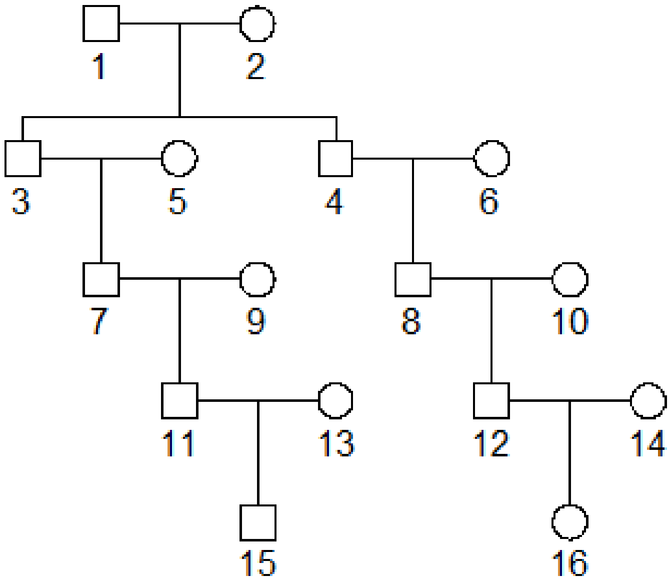


Opossum:
- 8 autosomes
- 800 cM



Shorter genome = more variation!

The probability of zero IBD



N'th cousins	*P*(zero IBD)
first	0.0 %
second	0.0 %
third	1.5 %
fourth	28 %
fifth	67 %

Third cousins

Expected fraction with IBD = 1:

$$k_1 = \frac{1}{64}$$

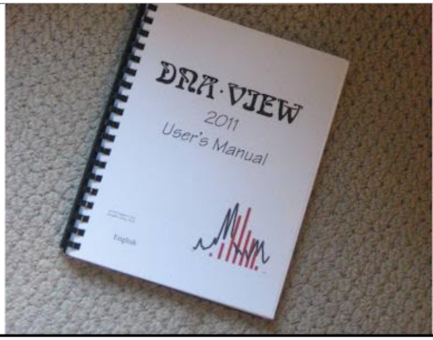
Two individuals can have a common ancestor without being genetically related

Part III: Crash course in R

What is R? (And why should you care?)

- A framework for statistical computing
  - calculator
  - data handling and numerical analysis
  - flexible plotting
  - programming language
  - external packages
    - anyone can make one
    - thousands!

Familias.no



BONAPARTE

Designed, built and proven for real world case work

Pros
- free!
- very widely used
- anything is possible (but not always easy)
- scripting --> reproducibility

Cons
- learning curve
- packages come and go

Oh boy, that
sounds great!

I which I knew R ...

Don't worry!

It's not that hard.

Here is a quick intro to R that contains most of what you need

Basic calculations

```
>   2 + 3
[1] 5
>   2+      3
[1] 5
>   (1 + 2) * 3
[1] 9
>   4^2
[1] 16
>   log(100)
[1] 4.60517
>   log(100, base = 10)
[1] 2
>   log10(100)
[1] 2
```

Spaces don't matter

$e^{4.60517} \approx 100$

Variables

I use this

Two (mostly synonymous) ways to assign values: **=** or **<-**

```
>   a = 5      or    a <- 5
>   b = 2      or    b <- 2
>   a
[1]  5
>   a - 2*b
[1]  1
```

Changing a variable:

```
>   a = a+1
>   a
[1]  6
```

Common beginners' mistake:
forgetting to assign after change

Creating new variables from old:

```
>   newVar = a^b
>   newVar
[1]  36
```

Most programmers stick to either
camelCase or **snake_case**
when naming their variables

Vectors

```
>   c(3, 2, 6, -1)
[1]  3  2  6 -1
>   4:20
[1]  4  5  6  7  8  9 10 11 12
[10] 13 14 15 16 17 18 19 20
>   5:7 - 4
[1] 1  2  3
>   c(10,20,30,40) + c(1,3,8,0)
[1] 11 23 38 40
>   seq(from = 2, to = 15, by = 3)
[1]  2  5  8 11 14
```

The **c()** operator!

The **':'** operator
(shortcut for consecutive numbers)

There is a help page
for every function!
`> ?seq`

Character vectors:

```
>   c("Alice", "Bob")
```

Logical vectors:

```
>   c(TRUE, FALSE, T, F)
[1] TRUE FALSE TRUE FALSE
```

Built-in logcial constants:
TRUE   short form: **T**
FALSE short form: **F**

Matrix-like containers

Data frames: Collects vectors of the same length

```
>   x = data.frame(Name   = c("Ali", "Bob", "Joe"),
                   Weight = c(75, 81, 70))
>   x
  Name Weight
1  Ali     75
2  Bob     81
3  Joe     70
```

Use **$** to refer to columns: **`x$Name`**

Matrices:

```
>   x = matrix(1:12, nrow = 3, ncol = 4)
>   x
     [,1] [,2] [,3] [,4]
[1,]    1    4    7   10
[2,]    2    5    8   11
[3,]    3    6    9   12
```

Note: No **$** for matrices!

First column: **`x[, 1]`**
First row: **`x[1, ]`**

Faster, but less flexible. Good for all-numeric (or all-character) data

Lists

```
>   a = list(good = 1:3, bad = 0)
>   a
$good
[1] 1  2  3

$bad
[1] 0
>   a$good
[1] 1  2  3
```

Alternative to **$**:
`a[["good"]]`

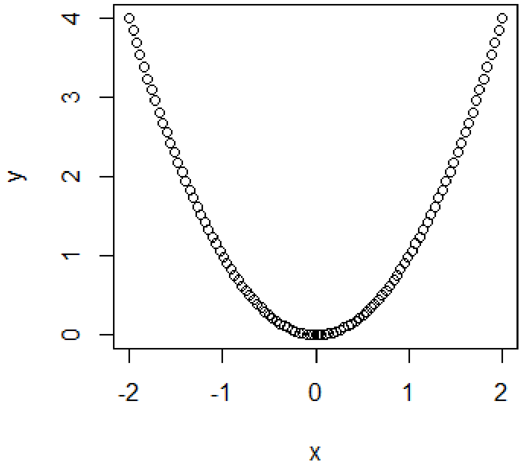
Easy to change lists:

```
>   a$bad = NULL              (delete item)
>   a$ok = -1                 (add new item)
>   a$good = c(a$good, 10)    (modify item)
>   a
$good
[1] 1  2  3  10

$ok
[1] -1
```

Basic plots

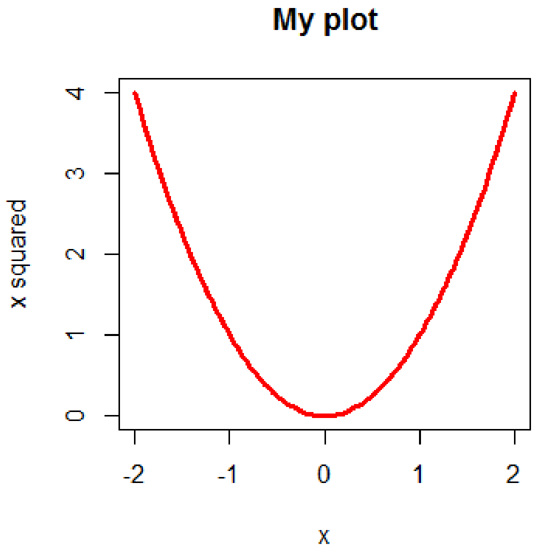
Let's plot the graph of $y = x^2$!

```
>   x = seq(-2, 2, length = 100)
>   y = x^2
>   plot(x, y)
```

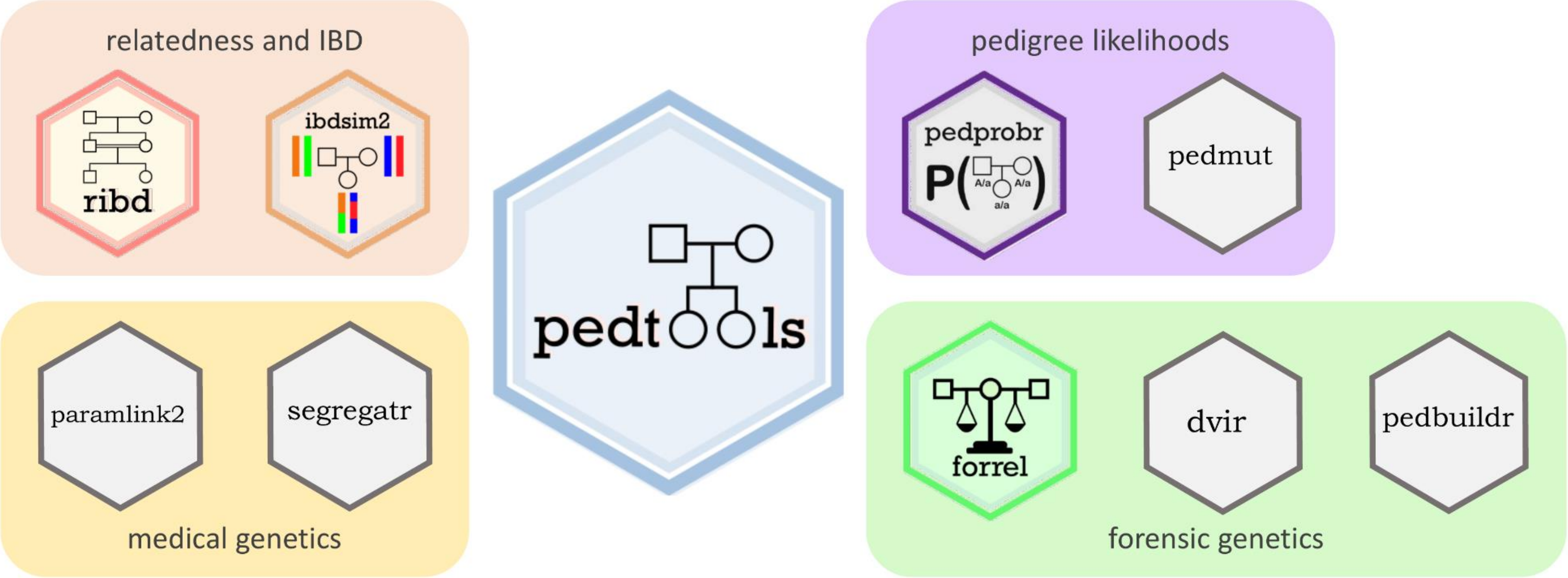


Many options to play with…

```
>   plot(x, y, type="l", lwd = 3, col = "red",
         ylab = "x squared", main = "My plot!")
```



The *pedsuite* packages

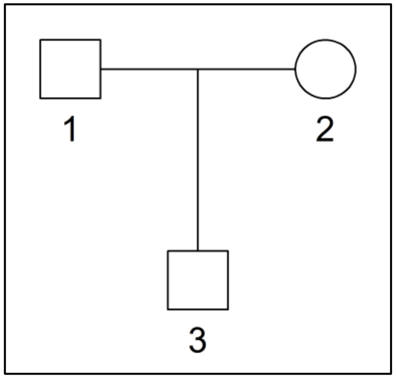


Home page:
https://magnusdv.github.io/pedsuite

Source code available on GitHub:
https://github.com/magnusdv

Your first pedigree

```
>   library(pedsuite)

>   x = nuclearPed()
>   plot(x)
```



Some useful functions

Create: basic

- singleton
- nuclearPed
- linearPed
- halfSibPed
- cousinPed
- halfCousinPed

Member subsets

- founders
- nonfounders
- leaves
- males
- females
- typedMembers
- untypedMembers

Create: complex

- ancestralPed
- doubleCousins
- quadHalfFirstCousins
- fullSibMating
- randomPed

Relatives

- father
- mother
- children
- siblings
- grandparents
- spouses

- ancestors
- descendants
- unrelated

Manipulate

- addSon
- addDaugher
- addParents
- addChildren

- swapSex
- relabel
- removeIndividuals

- branch
- subset

- mergePed
- breakLoops

Another example

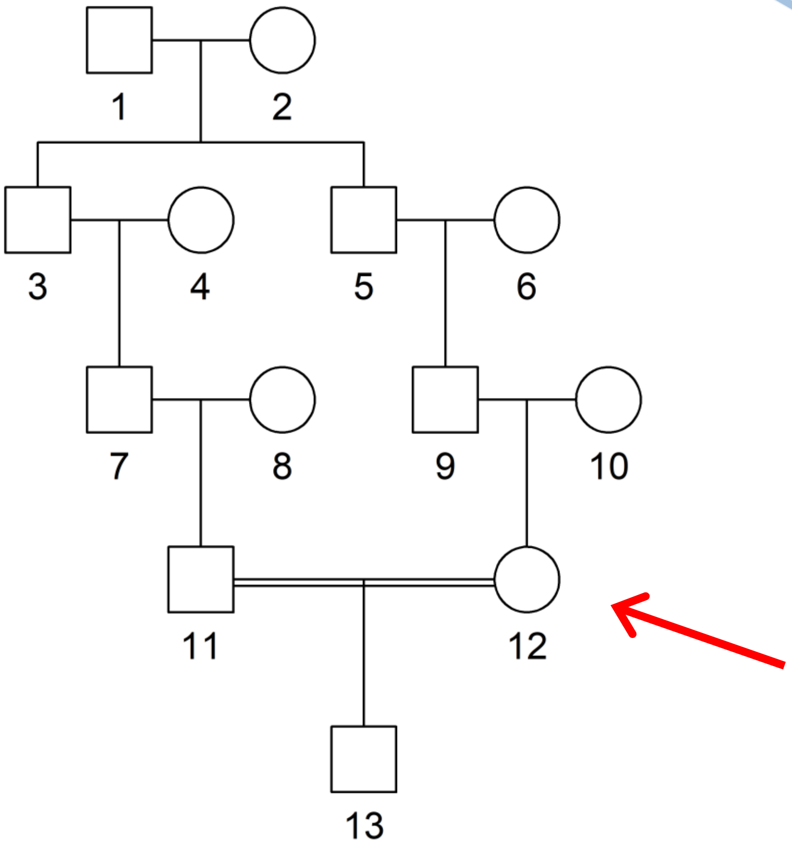
```
>   x = cousinPed(2)
>   plot(x)
```

Change gender:

```
>   x = swapSex(x, 12)
>   plot(x)
```

Add inbred child

```
>   x = addSon(x, parents = 11:12)
>   plot(x)
```



Remember

- Store the result after each change!
- It is OK to use the same name
  (if you don't need the previous object)

Shortcut command for this pedigree

```
> x = cousinPed(2, child = TRUE)
```

The pipe |>

Introduced in R 4.1

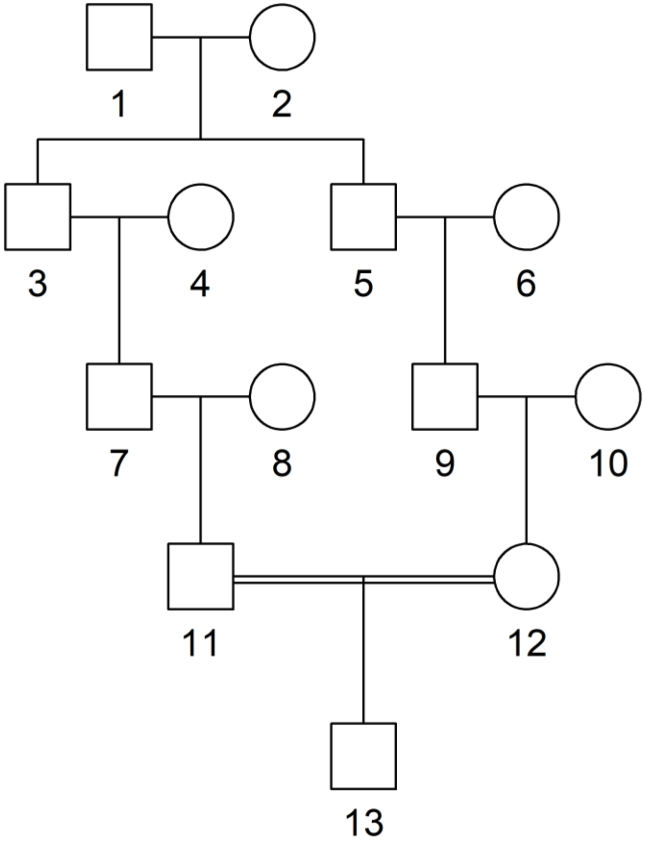
Instead of ...

```
>   x = cousinPed(2)
>   x = swapSex(x, 12)
>   x = addSon(x, parents = 11:12)
```

... we can write

```
>   x = cousinPed(2) |>
      swapSex(12) |>
      addSon(parents = 11:12)
```

Feeds the previous result into the next function!



R stuff skipped in this brief introduction

- User-defined functions
- Loops, **`apply()`**, **`lapply()`**, etc.
- Basic statistics, linear models + +
- Random numbers
- The "tidyverse" for data science
- ... and LOTS of other things...

Your turn: Exercises!