QTL mapping in humans

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Linkage vs association

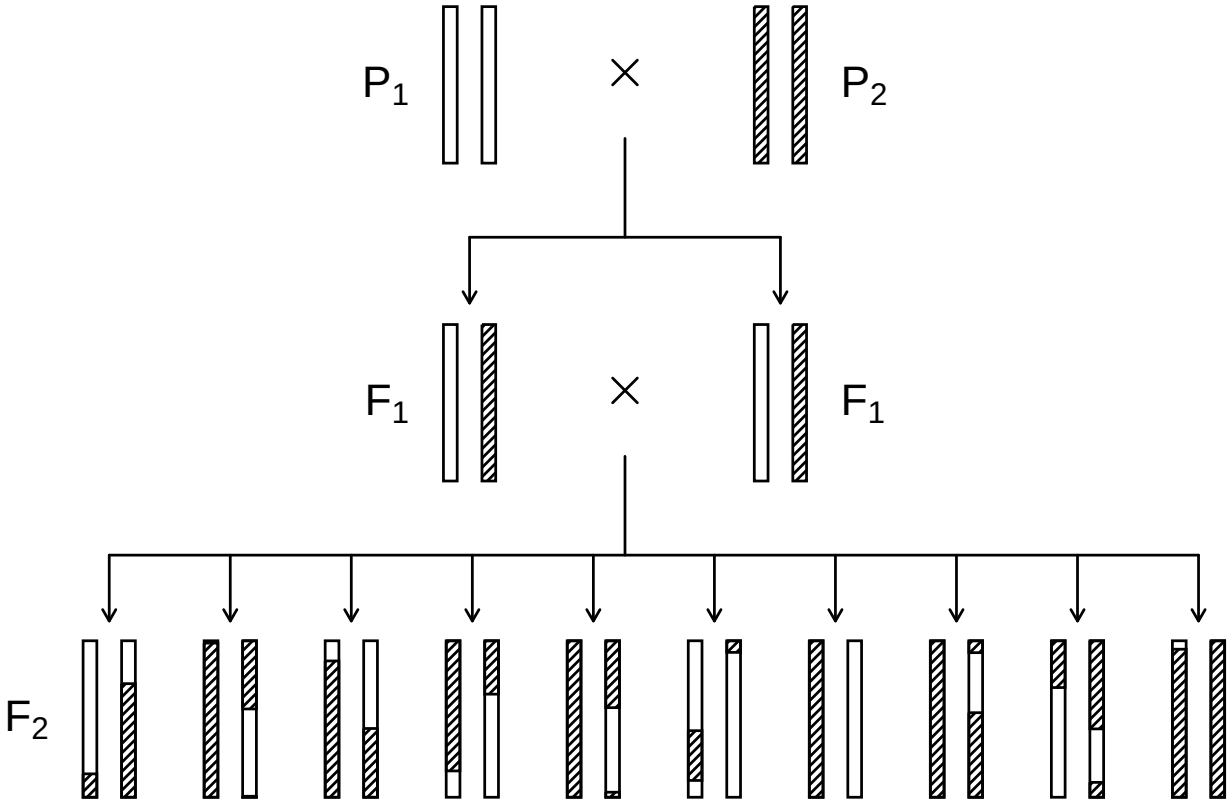
Advantages

+ If you find something, it is real
+ Power with limited genotyping
+ Numerous rare variants okay

Disadvantages

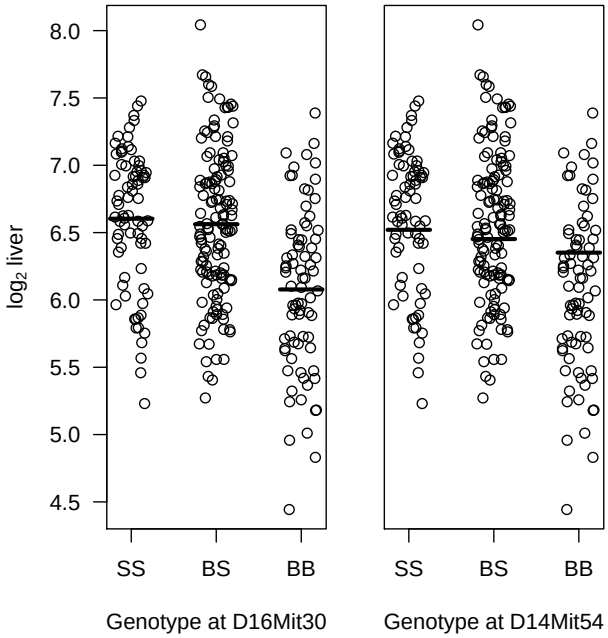
– Need families
– Lower power if common variant and lots of genotyping
– Low precision of localization

Intercross

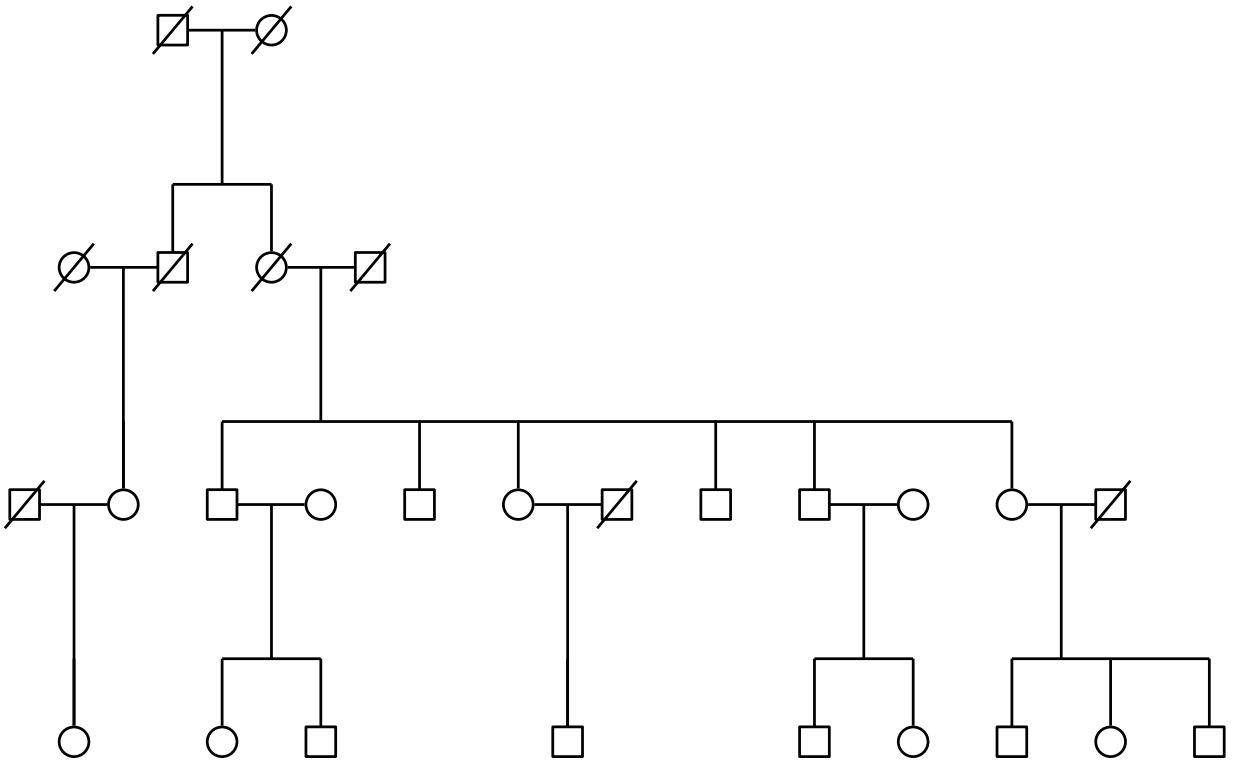


ANOVA at marker loci

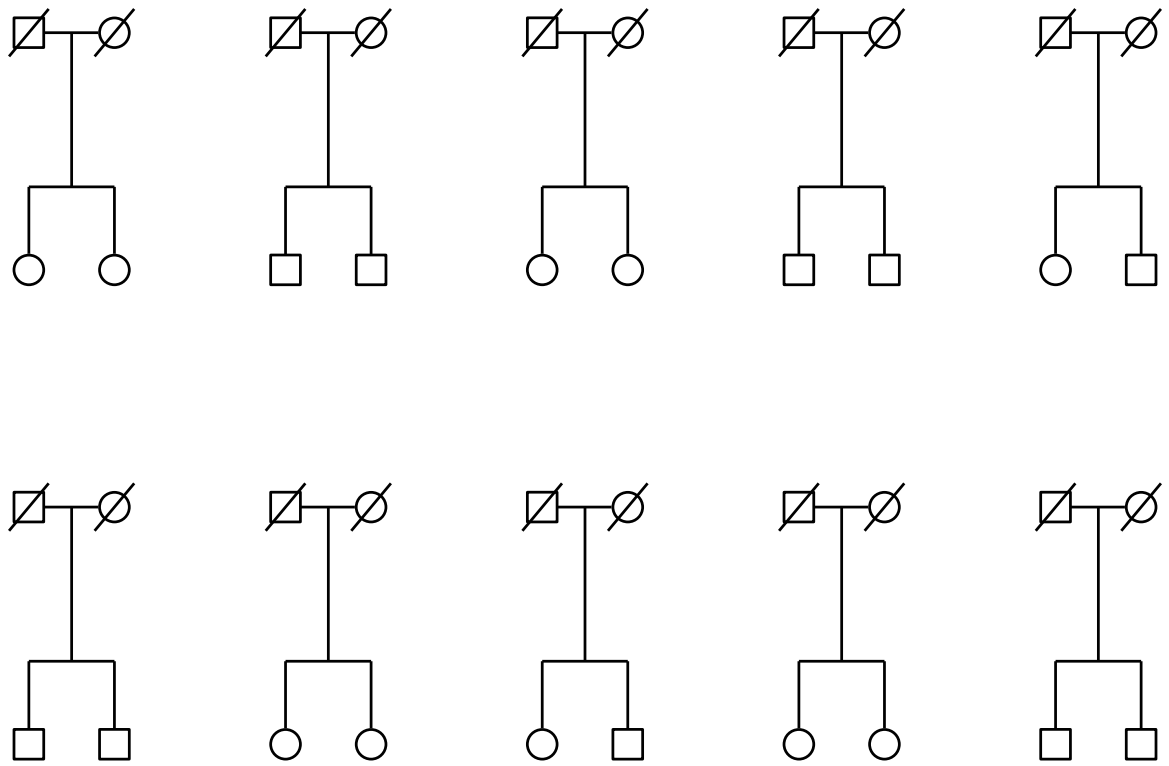
- Split mice into groups according to genotype at a marker.
- Do a t-test / ANOVA.
- Repeat for each marker.



Human pedigree



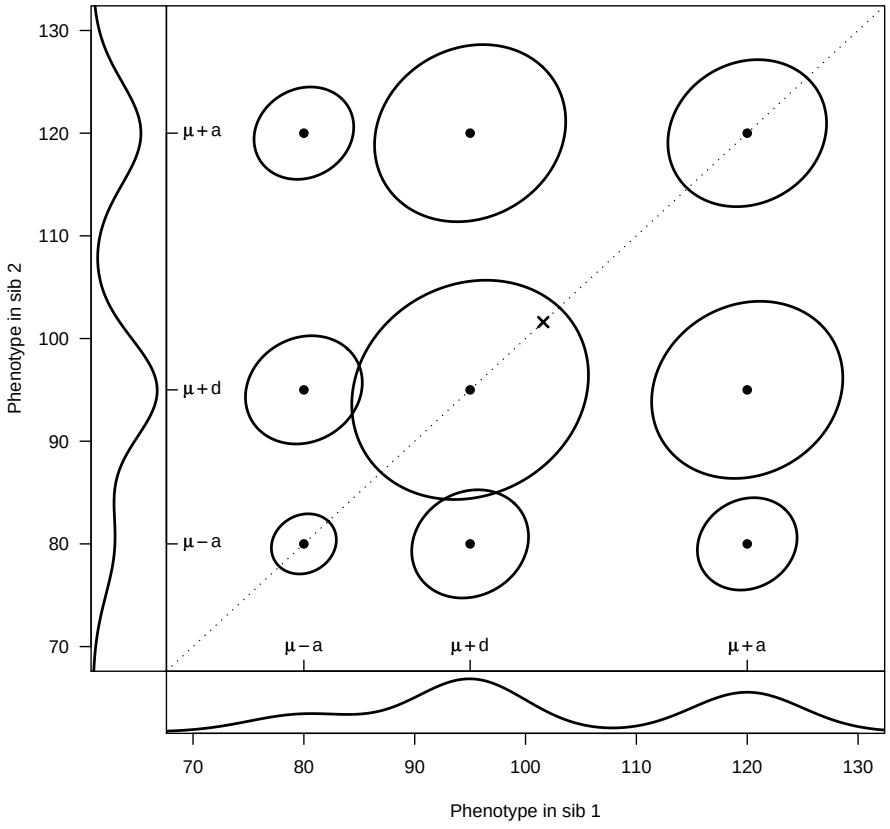
Sibling pairs



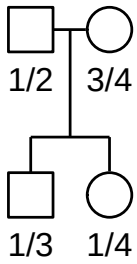
Humans vs mice

- More than two alleles
- Unknown phase
- Parents may be homozygous
- Markers not fully informative
- Varying environment

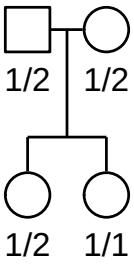
Diallelic QTL



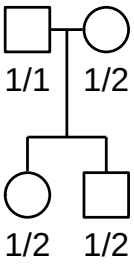
Identity by descent



IBD = 1

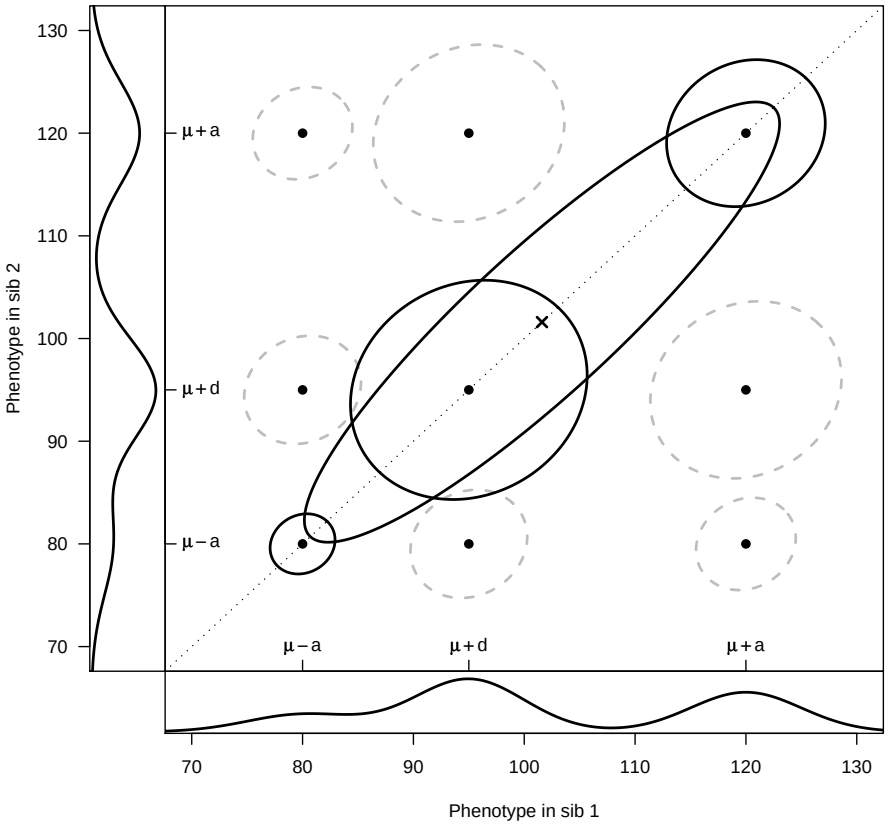


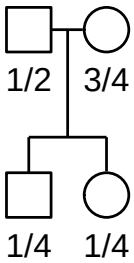
IBD = 1



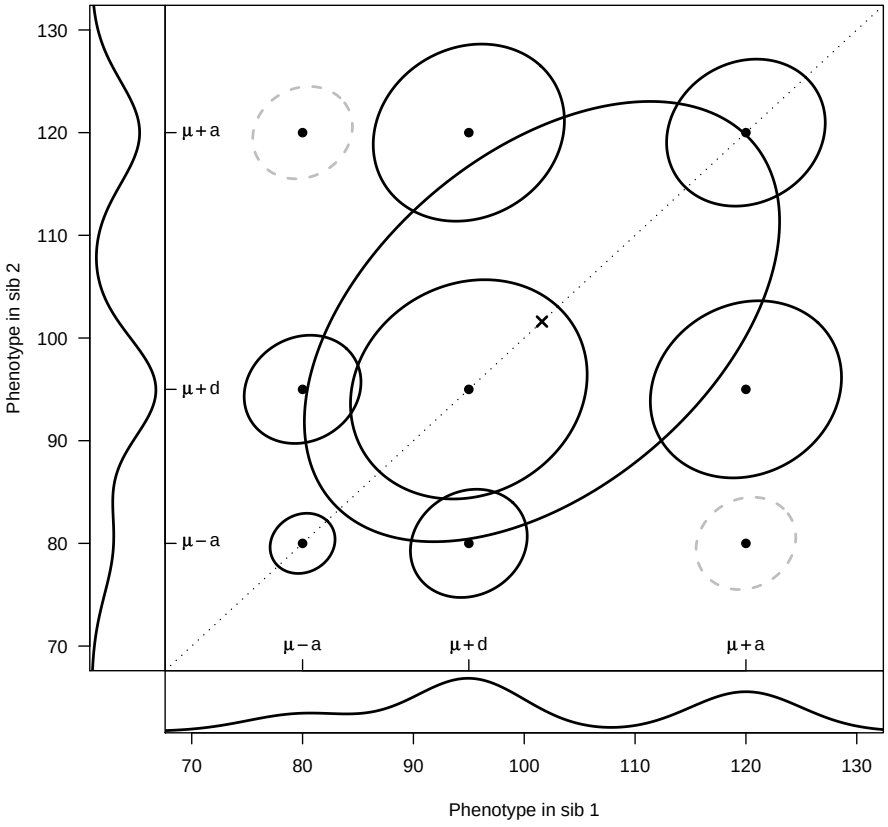
IBD = 1 or 2

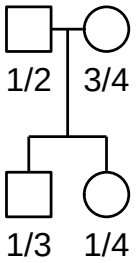
IBD = 2



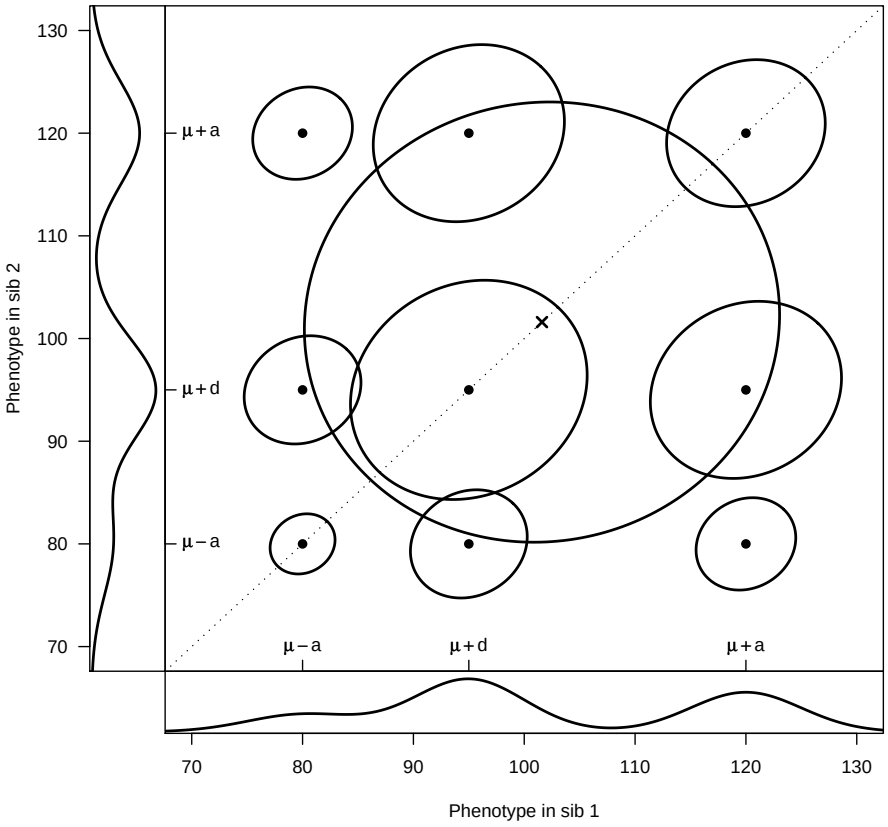


IBD = 1


Phenotype in sib 2
Phenotype in sib 1
μ+a
μ+d
μ−a
130
120
110
100
90
80
70


1/2
3/4
1/3
1/4

IBD = 0


Phenotype in sib 2
Phenotype in sib 1
μ+a
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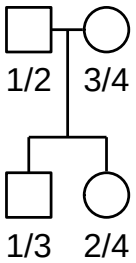
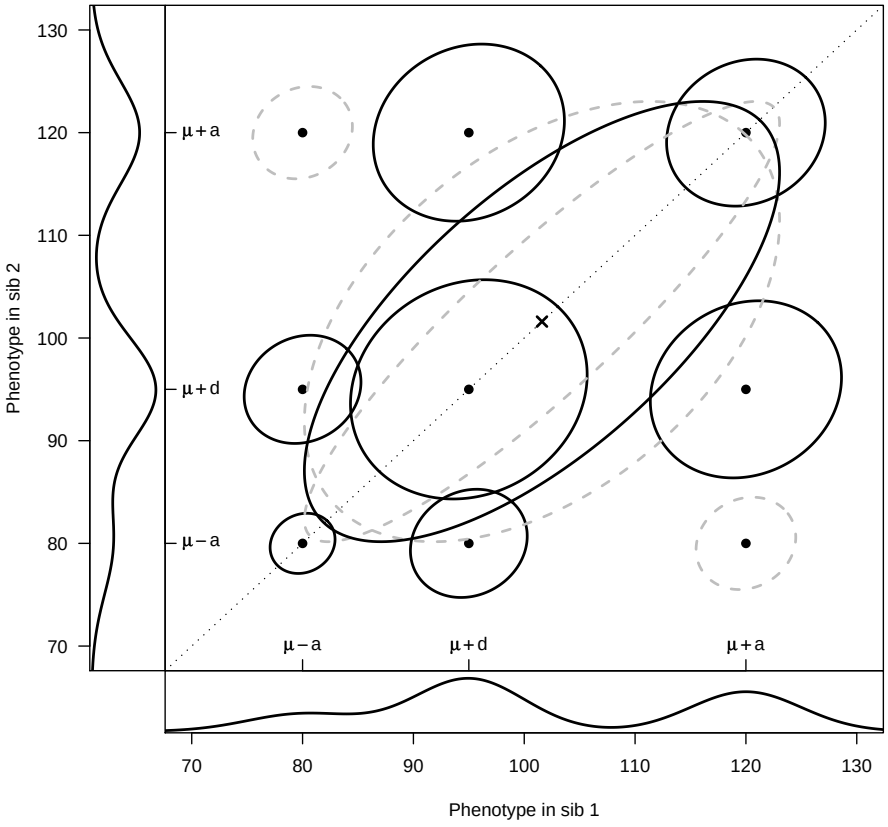
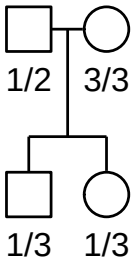

1/2
3/4
1/3
2/4

IBD = 1 or 2





Challenges

- Non-normality
- Genetic heterogeneity
- Environmental covariates
- Multiple QTL
- Multiple phenotypes
- Complex ascertainment
- Precision of mapping