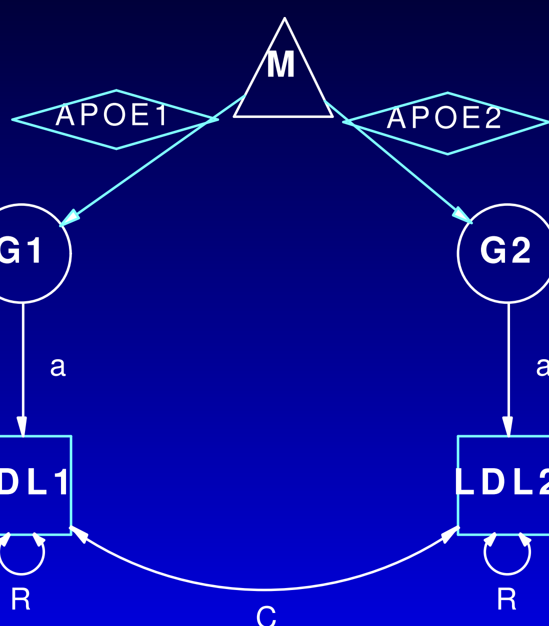
Association Analysis

Using sib pairs to control for stratification

Michael Neale   Boulder Workshop 2001

Association Model

Each sib pair i has different MEANS



Features of Association Model

Attractive

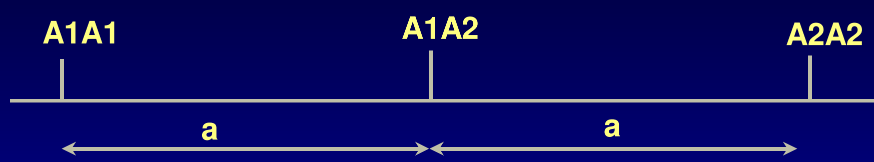
- Residual variances & covariances (R & C)
  - change
  - could use linkage model for joint analysis
- Can be extended to multiple alleles, loci, phenotypes and larger pedigrees
- But assumes no population stratification

Fulker association model

- Separate associated mean differences
  - between sib pairs
  - within sib pairs
- Between = within if genuine allelic effect
- Derive cunning model

Allelic effects

Assuming additivity, unnecessarily



Call contributions to pair sum b's
Call contributions to pair diffs w's

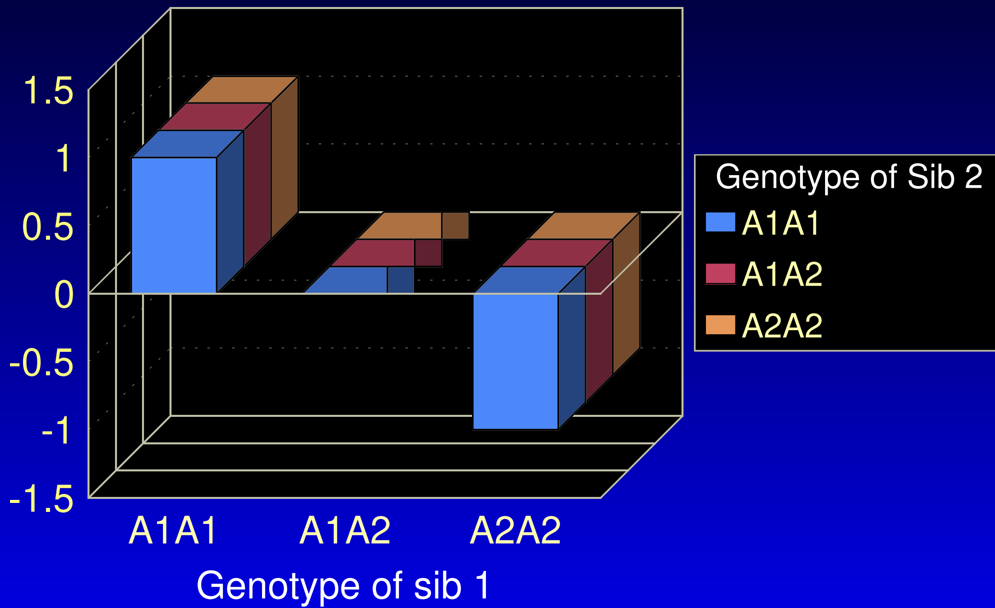
Pair means & differences

G Sib1	G Sib2	Pair Sum/2	Pair Diff/2	Mean Sib1	Mean Sib2
A1A1	A1A1	b	0	b	b
A1A1	A1A2	b/2	w/2	b/2+w/2	b/2-w/2
A1A1	A2A2	0	w	w	-w
A1A2	A1A1	b/2	-w/2	b/2-w/2	b/2+w/2
A1A2	A1A2	0	0	0	0
A1A2	A2A2	-b/2	w/2	w/2-b/2	-b/2-w/2
A2A2	A1A1	0	-w	-w	w
A2A2	A1A2	-b/2	-w/2	-b/2-w/2	-b/2+w/2
A2A2	A2A2	-b	0	-b	-b

Within pair distance between homozygote = w ; between pairs it is b

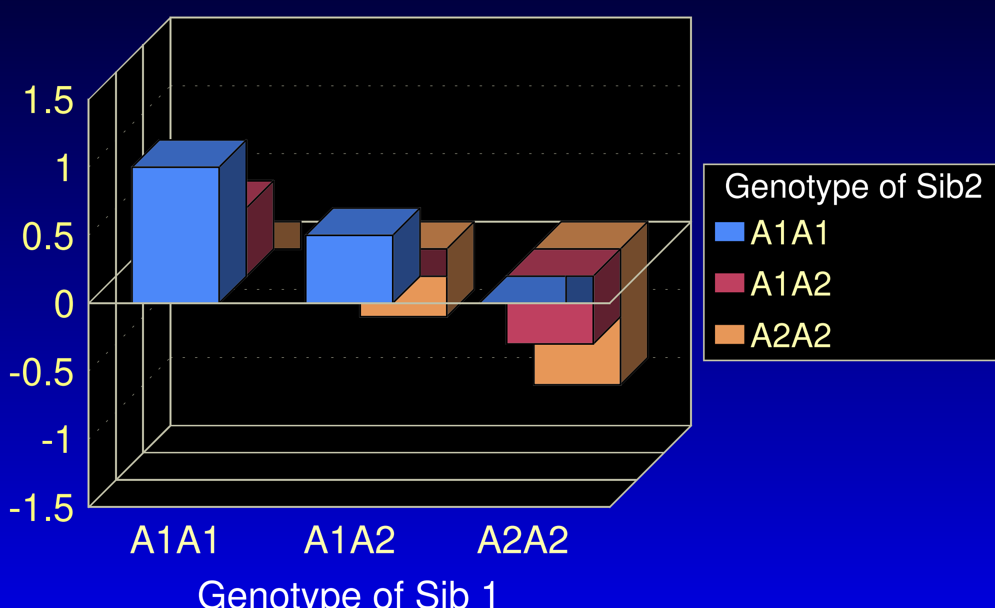
Mean of sib 1

b=w (no stratification)



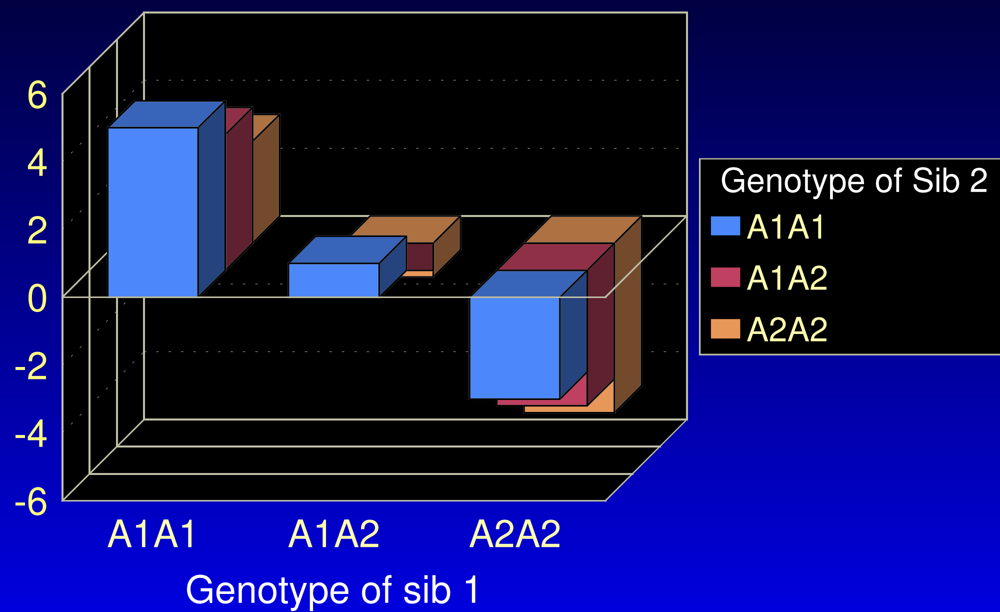
Mean of sib 1

No w (all stratification)



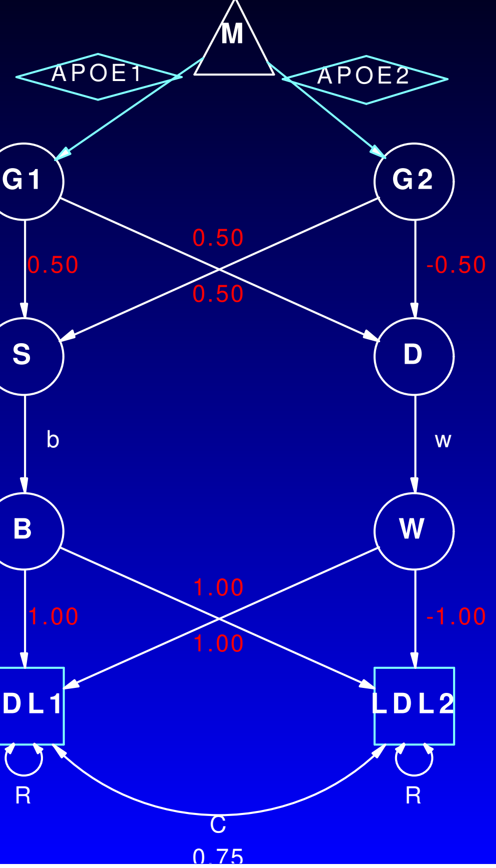
Mean of sib 1

b=5 w=4 (some of each)



Fulker Association Model

Multilevel model for the means



Cat's cradle

Conclusion

Association analysis

- Easy method to control for stratification
- Sibling samples are readily available
- Extensions straightforward:
  - Multivariate
  - Multiallelic
  - Multiple sibs