

Methods in Genetic Epidemiology

Lindon Eaves

VIPBG

March 2006

Link to basic genetics

[http://psych-www.colorado.edu/
hgss/hgssfigures/hgssfigures.htm#Chapter10](http://psych-www.colorado.edu/hgss/hgssfigures/hgssfigures.htm#Chapter10)

“Epidemiology”

Identification of “causes from clusters”

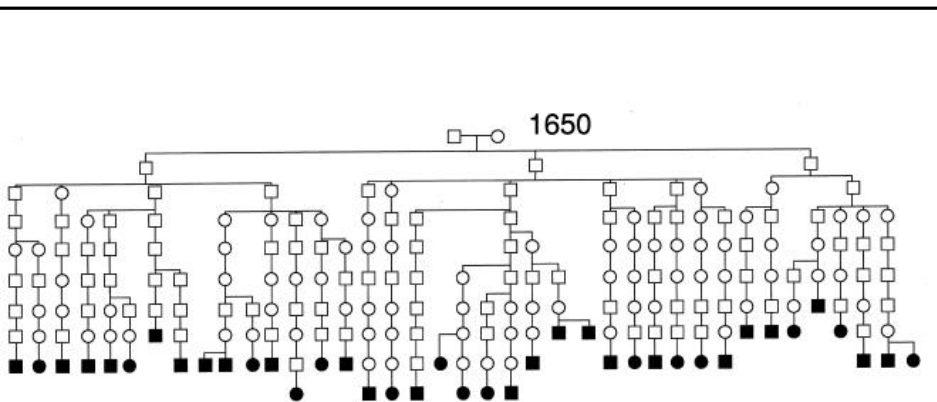
Clusters and Causes

- Sources of water (cholera)
- Insect vectors (malaria)
- Working in mines (silicosis)
- Toxic waste (some cancers)
- Hypertension (ethnicity)

- Etc.

THE "FAMILY"

A primary cluster



Large pedigree from the isolate with a founder couple born in approximately 1650.
Circles represent females; squares represent males.
Blackened circles and squares represent individuals with at least two children affected with schizophrenia.

Am J Hum Genet. October 1999; 65(4): 1114-1124.
Published online September 3, 1999.
Copyright © 1999 by The American Society of Human Genetics. All rights reserved.

Insert Kuru pedigree here!

Draw your own pedigree

<http://www.genesoc.com/nutrition/pedigree.htm>

Familial disorders

- Familial hypercholesterolemia
- Bovine spongiform encephalopathy
- Schizophrenia
- Kuru
- Colon cancer
- Mental retardation
- Breast cancer
- Etc. etc. etc.

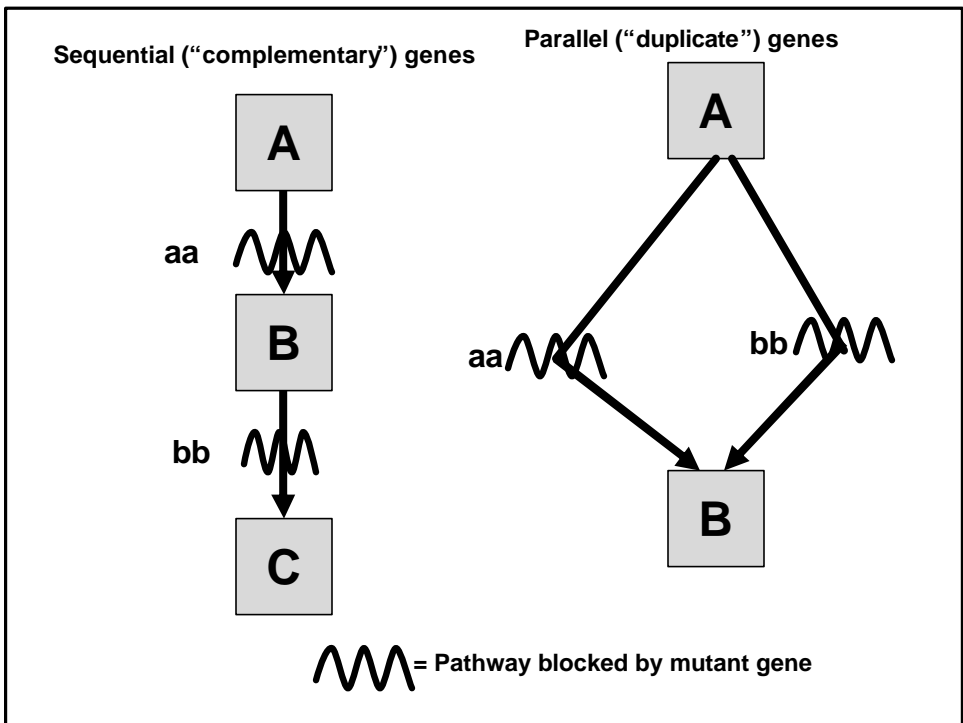
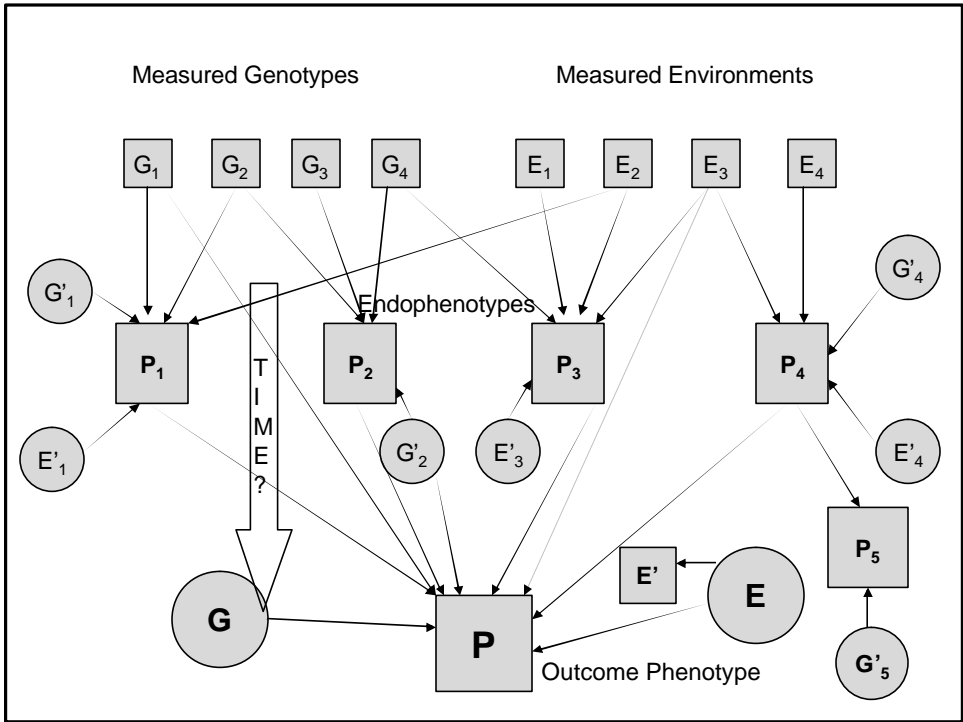
Family clustering may be genetic or
environmental

“Genetic Epidemiology”

Systematic use of familial clustering to resolve and identify genetic and environmental causes of disease

Questions in GE

- Is “it” familial?
- Is it “genetic” (G), “environmental” (E) or both (G+E)?
- What are relative contributions of G and E?
- What kinds of genetic effects are there (one, few, many, additive/epistatic)?
- Effects of population structure, ethnicity, stratification, mate selection?
- What is role of E? Which? GxE interaction?
- Which specific genes are involved?



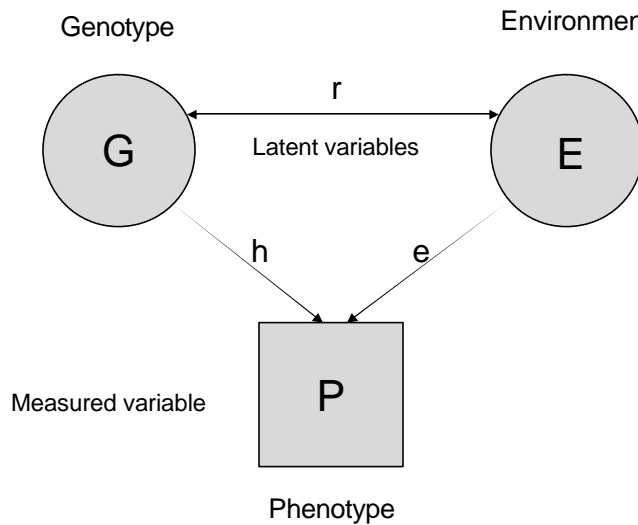
Answering the questions: some approaches

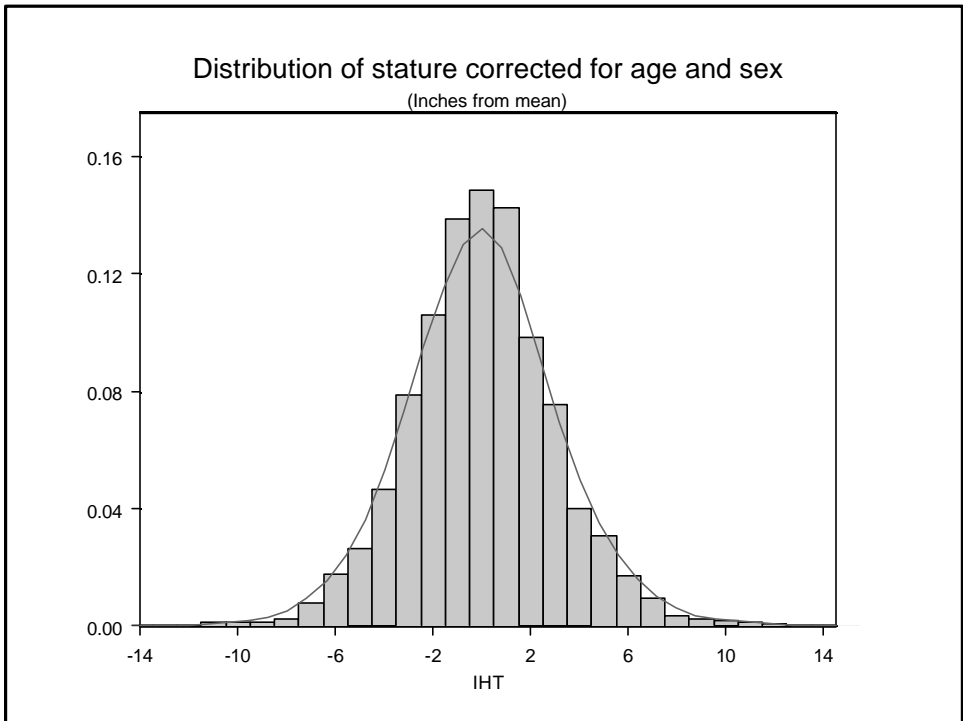
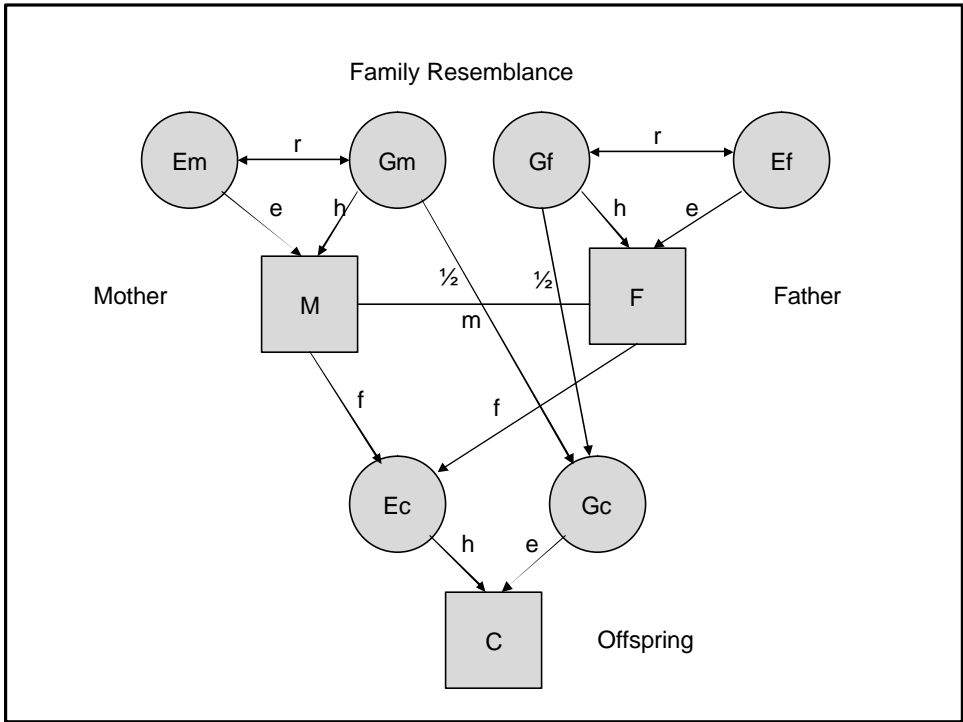
Is it familial?

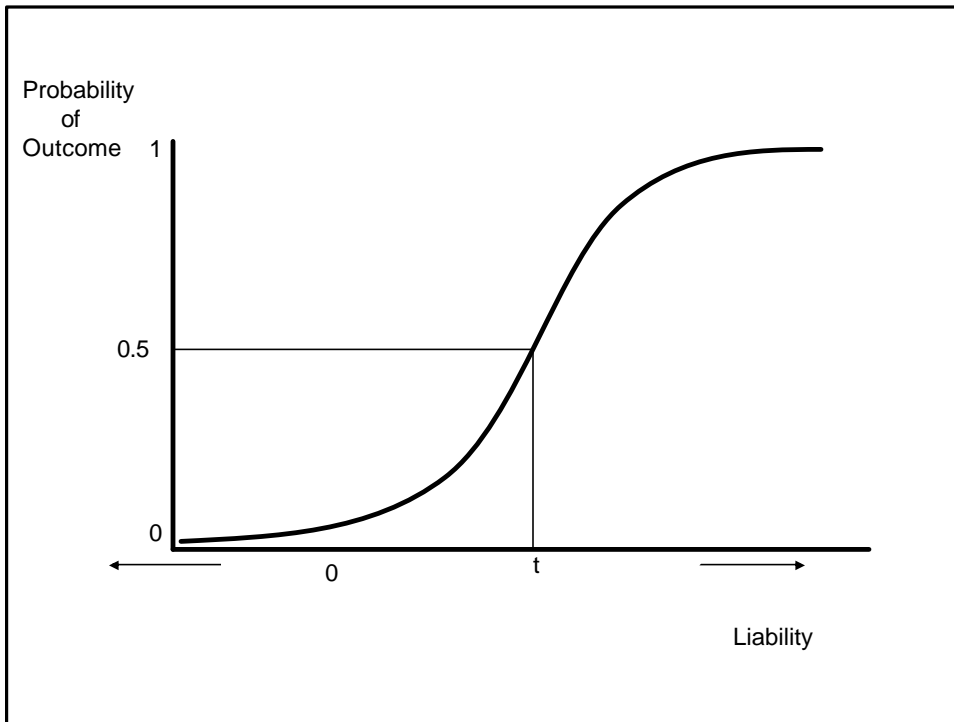
- Risk to relatives (schizophrenia, colorectal cancer, mental retardation, hypertension)
- Correlation between relatives (IQ, diastolic blood pressure)
- Same trait may be category or dimension (hypertension = $DBP > 90\text{mmHg}$)

Causes of Family Resemblance

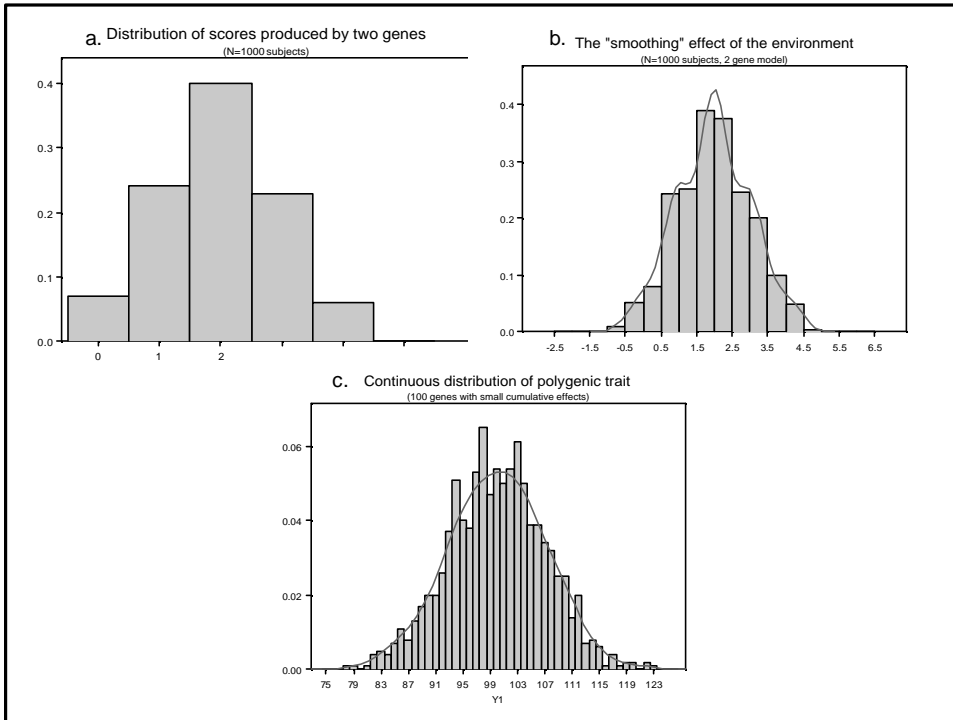
Path diagram for the effects of genes and environment on phenotype







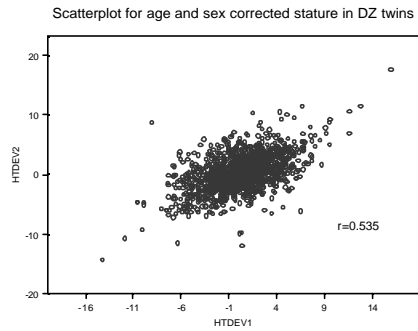
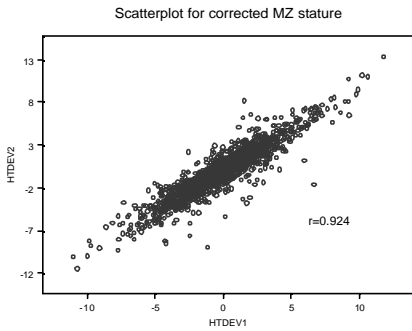
Polygenic Inheritance (Fisher, 1918)



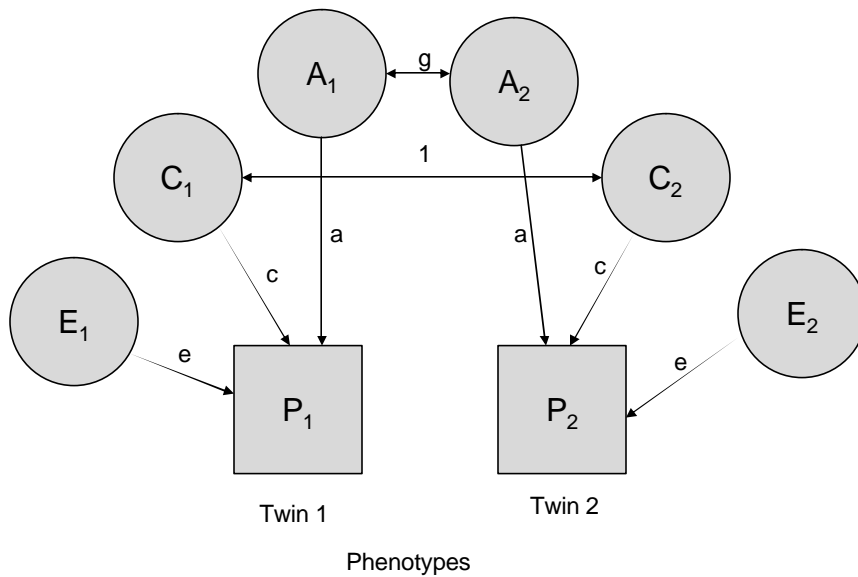
Estimating G and E (1)

Twin Studies (Galton 1865)

Stature in Twins

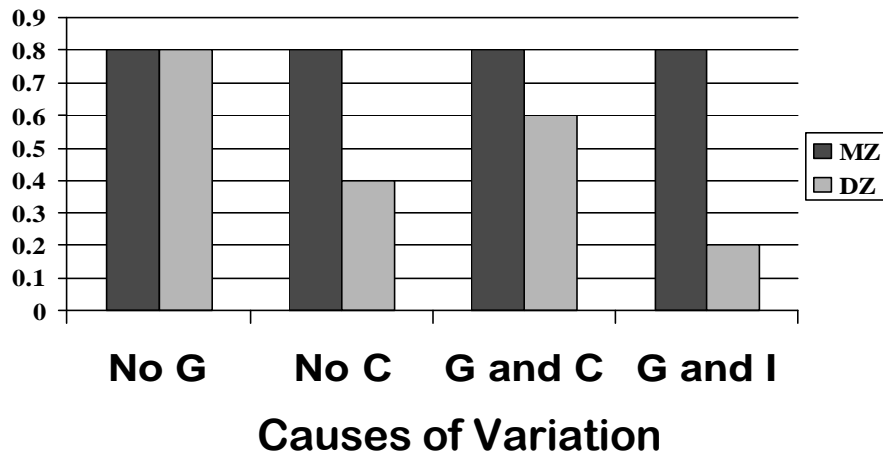


Path diagram for twin resemblance



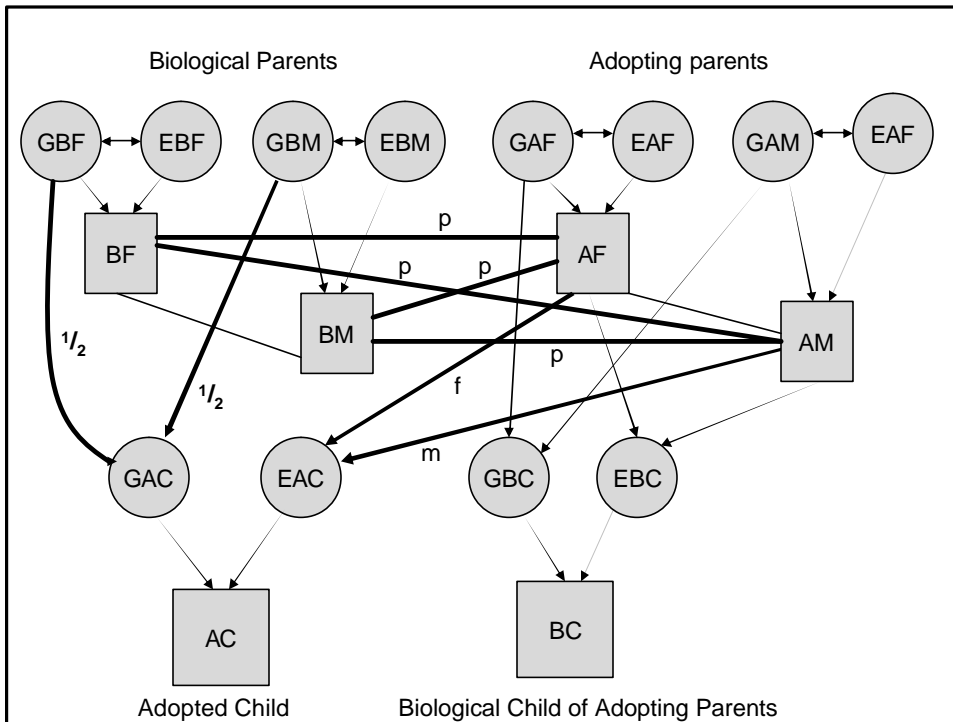
Four scenarios

Twin
Correlation



Estimating G and E (2)

Adoption studies



Other approaches

- Separated Twins (e.g. Shields, 1966)
- Twins and parents
- Children of Twins
- Extended twin kinships
- Combinations of Methods

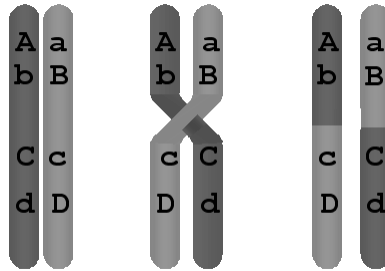
Identifying environments

Measure environment in family, twin or adoption study (e.g. twins discordant for exposure, characteristics of foster parents etc.)

Finding the genes

- Linkage studies – extended pedigrees, sib pairs
- Association studies (case-control, family-based – e.g. TDT, sib-pair)

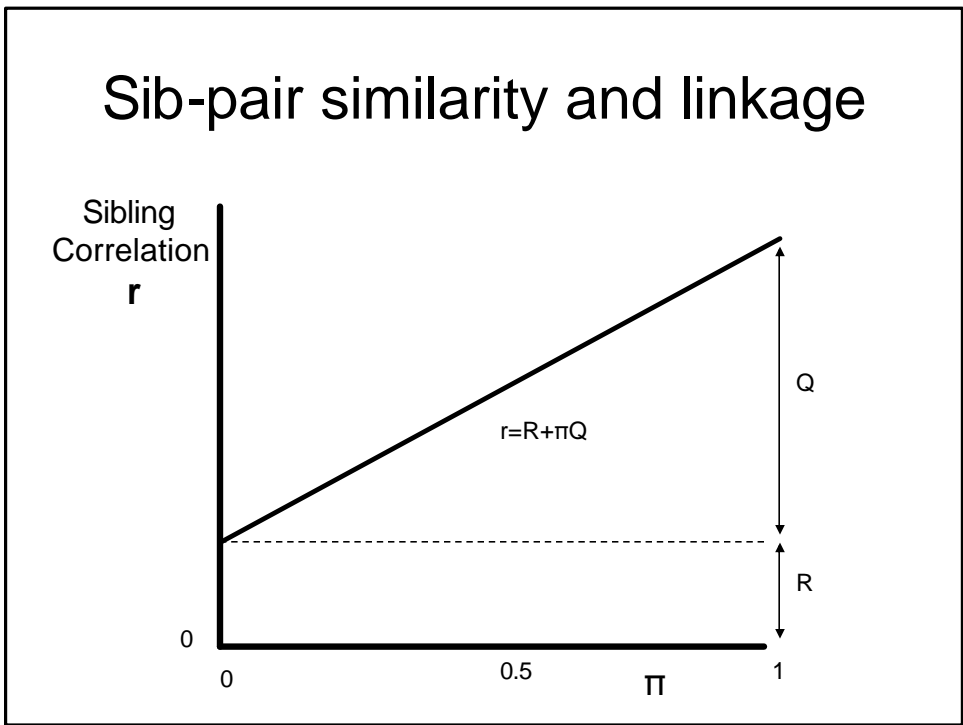
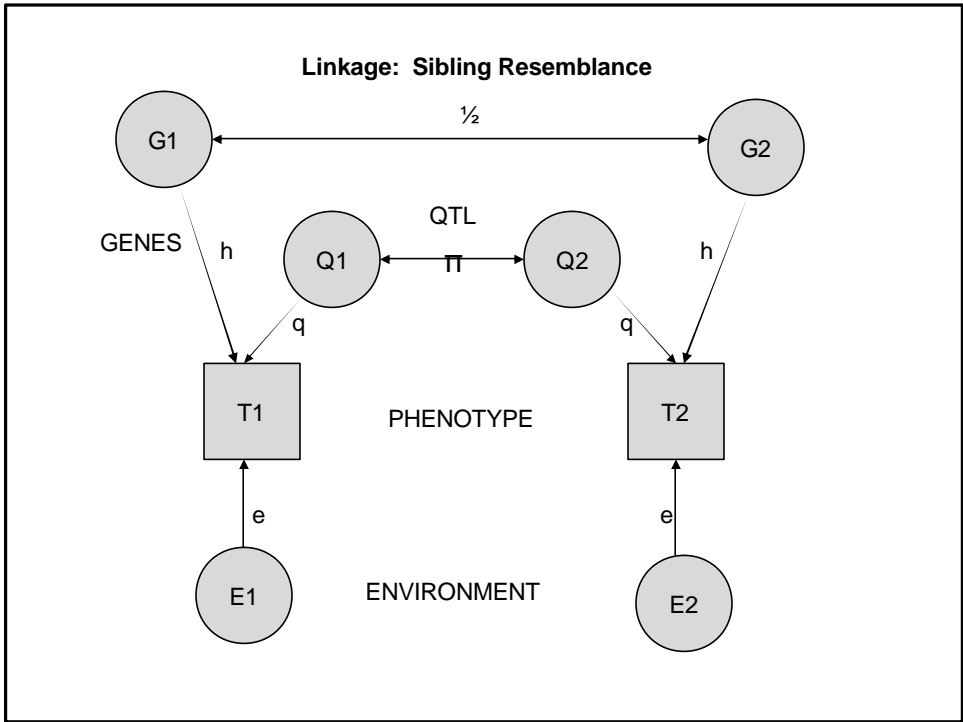
“Linkage”



Genes that start together stay together –
the closer they are, the more they stay together

Linkage

Are relatives who are more alike
for a “marker” more alike in their
phenotypes?



Linkage – plusses and minuses

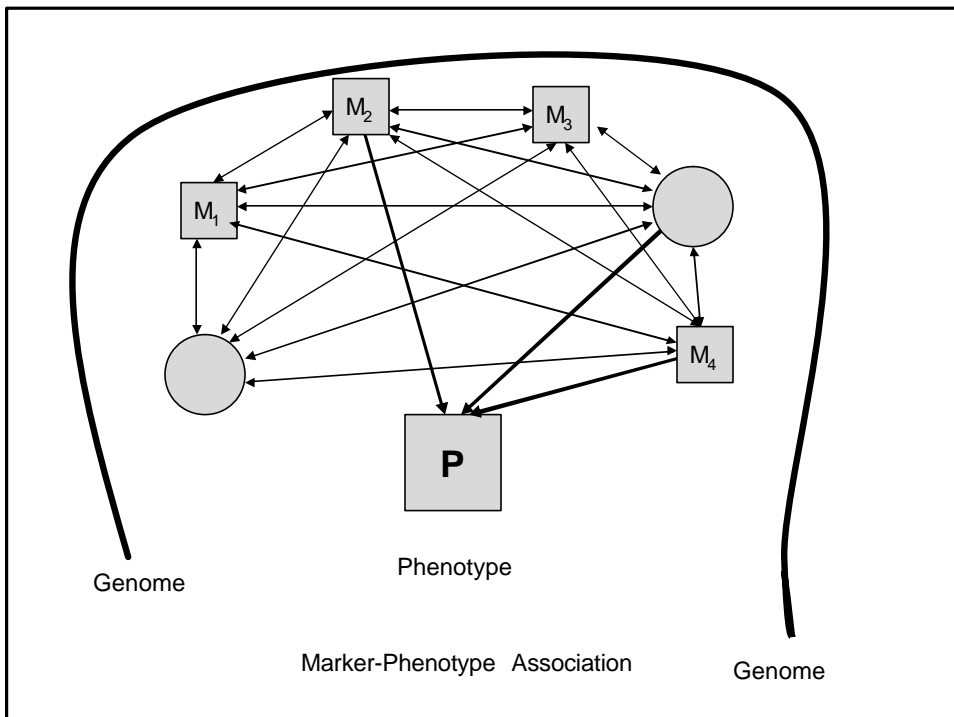
- PLUSES
- Depends only on marker location, not effect of marker on phenotype
- Doesn't require many markers to cover genome (100s)
- Hard to “invent” linkage - robust
- MINUSES
- Works best for simple (few-gene) traits
- Gene effects need to be big
- Specific localization poor (i.e. many genes under linkage “peak”)

Association

Do different forms of gene (“alleles”) have different phenotypes?

Association: Pluses and Minuses

- PLUSES
 - Statistical power
 - “Tight” localization
 - Can use “candidate genes”
- MINUSES
 - Association may not be causal (e.g. “linkage disequilibrium”, population stratification) – but can control/eliminate
 - Needs large number of markers for genome-wide study (?500,000+)



Controlling for stratification

- Analyze within strata (ethnicity, SES etc)
- Use random genes to test, characterize and eliminate
- Family-based association – TDT, sib-pairs etc.

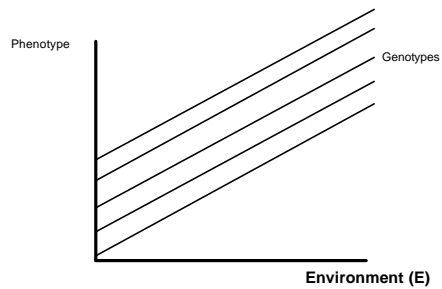
Complications – can't always do genetics without environment

- GxE Interaction
- G-E correlation
- G x Age interaction

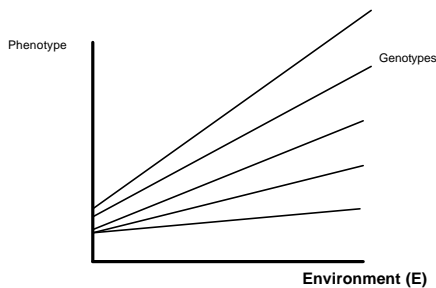
GxE Interaction

- Genes control sensitivity to the environment (some environments only affect particular genotypes)
- Environments modulate expression of genes (some genes only expressed in particular environments)

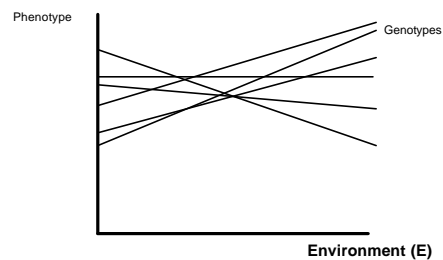
a. No GxE



b. "Scalar" GxE



c. "Non-scalar" GxE



Analyzing GxE

- Family resemblance depends on environmental exposure
- Effect of gene contingent on environment (or vice-versa)

Genetic Variance and Shared Life Events in Adolescent Females (Silberg et al., 1999)

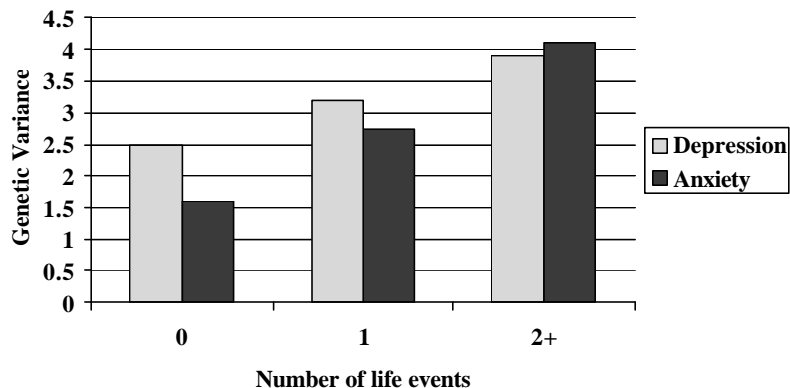
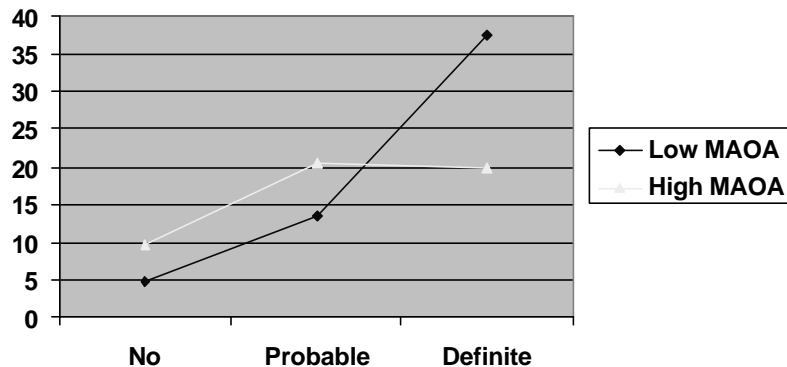


Figure: Prevalence of Conduct Disorder as a function of MAOA activity and exposure to environmental adversity (Foley et al, 2004)



G-E Correlation: Environmental exposure caused/influenced by genes

- “Active/Evocative” - environment depends directly on genes of individual (e.g. own smoking”)
- “Passive” – environment depends on genes of relatives (e.g. parental smoking)

Analyzing rGE

- Include environmental measures in twin, adoption and family studies – build and test path models.

G x Age Interaction

- Genetic control of age of onset
 - Different genes expressed at different ages
 - Rates of growth/change depend on genes
- A bit like GxE in some ways.