Mendelian Inheritance

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Genes — Mendelian Inheritance

Gregor Mendel, monk in a monastery in Brünn (now Brno in Czech Republic): Breeding experiments with the garden pea: Flower color and seed shape (phenotypes) are determined by “factors” (now “genes”) that are passed through generations. He formulated two laws of inheritance that he thought were generally valid.

Mendel's Laws

- **First Law**, *Segregation of Characteristics*: Of a pair of characteristics (e.g. blue and brown eye color) only one can be represented in a gamete even though there are two genes in ordinary cells.
- **Second Law**, *Independent Assortment*: For two characteristics, the genes are inherited independently. Today we make use of deviations from this law for statistical gene mapping.

Mendel's paper

Versuche

über

Pflanzen-Hybriden,

von

Gregor Mendel.

Im Verlage des Vereines.

Brünn, 1866.

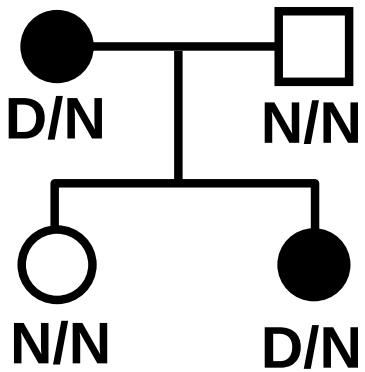
Mendel GJ (1866) Versuche über Pflanzen-Hybriden. *Verh Natur-forsch Ver Brünn* 4:3-47

Ironically, when Mendel's paper was published in 1866, it had little impact. It wasn't until the early 20th century that the enormity of his ideas was realized.

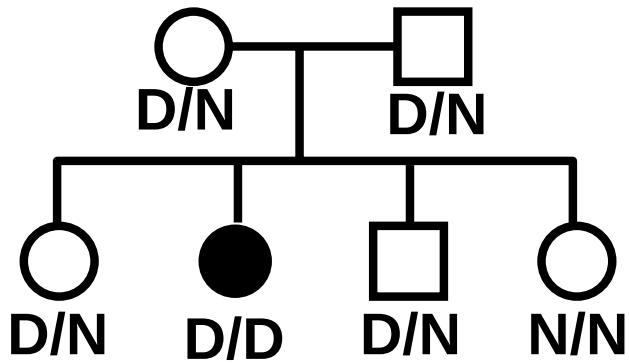
Simple Modes of Inheritance

- Trait due to a single gene
- Examples:
  - Huntington disease (dominant)
  - Cystic fibrosis (recessive)

Dominant

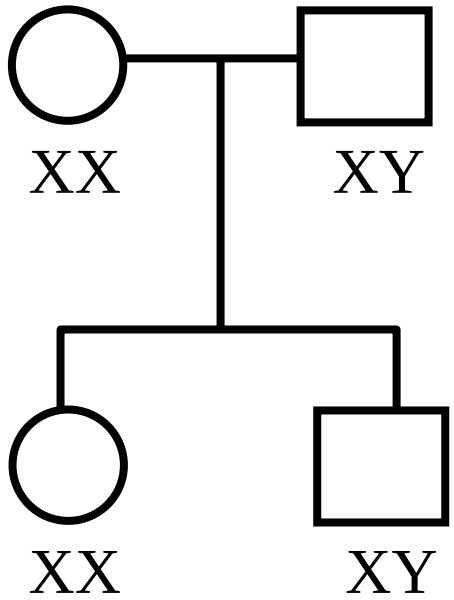


Recessive



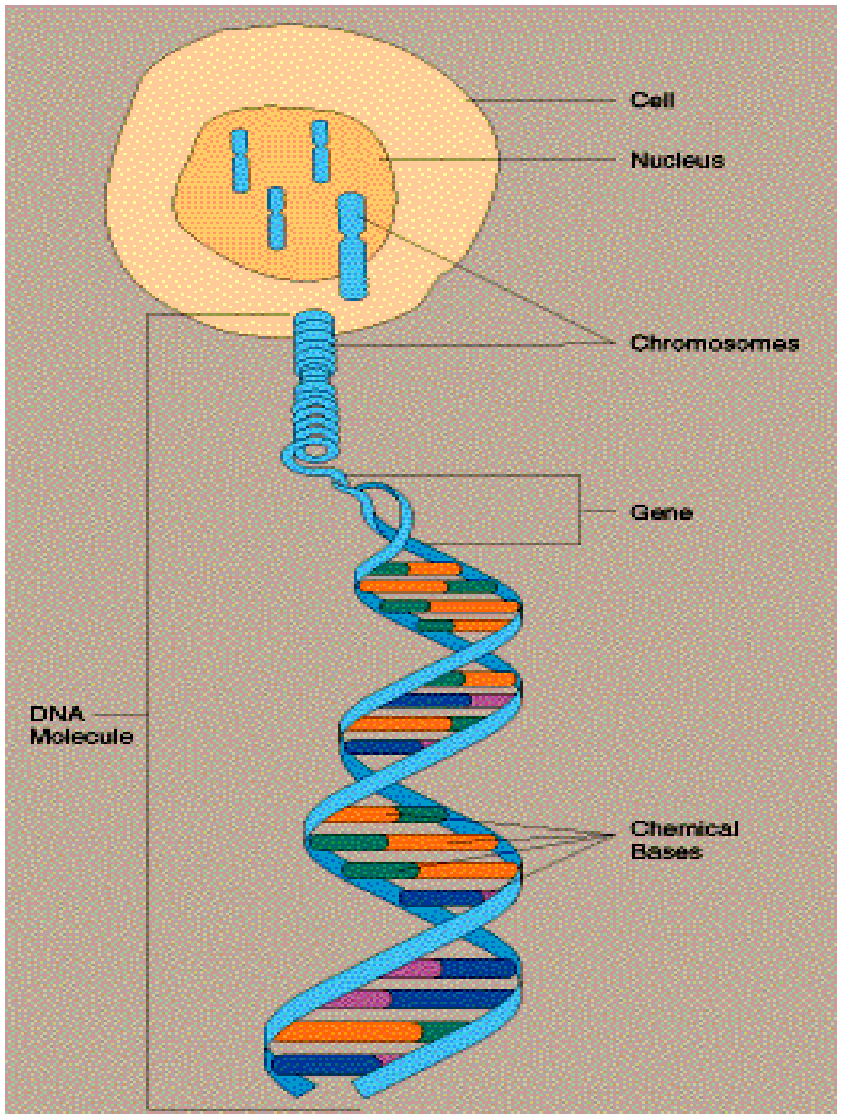
X-Linked Inheritance

- *Female genotypes*: As for autosomal genes
- *Male genotypes*: N/y and D/y (hemizygous)



- Examples (usually recessive): hemophilia, red/green color blindness, Duchenne muscular dystrophy

Genetic Inheritance



- Genes are arranged along chromosomes
- Genes code for enzymes, blood groups, etc.
- Gene defects may cause disease.
- Chromosomes and genes are passed from parents to children.

Genotype and Phenotype

- **Genotype** = set of 2 alleles at a locus (gene) in an individual. *Examples*: A/G (marker alleles), N/A (disease alleles)
- **Phenotype** = “what you see”, expression of this genotype. *Examples*: A/G (marker), affected (disease).

Relation between Genotype and Phenotype

Dominant

Pheno-type	*Genotype*		
	N/N	*A/N*	*A/A*
unaffected	1	0	0
affected	0	1	1

Recessive

Pheno-type	*Genotype*		
	N/N	*A/N*	*A/A*
unaffected	1	1	0
affected	0	0	1

Table entries = penetrances. Usually, only 1 line needed (affected).
Penetrance = conditional probability of phenotype given genotype.
Penetrance = probability of being affected given genotype (diseases).

ABO Blood Types

3 alleles: A, B, 0

Pheno-type	*Genotype*					
	A/A	*A/B*	*A/0*	*B/B*	*B/0*	*0/0*
A	1	0	1	0	0	0
B	0	0	0	1	1	0
AB	0	1	0	0	0	0
0	0	0	0	0	0	1

Generalized mendelian inheritance

Genotype	*NN*	*DN*	*DD*
Frequency	$(1-p)^2$	$2p(1-p)$	p^2
Penetrance	f_1	f_2	f_3

p = population frequency of *D* allele

Prevalence = $(1-p)^2 f_1 + 2p(1-p) f_2 + p^2 f_3$

Penetrance: Cystic fibrosis

p = frequency of disease alleles, 0.025

Genotype	*NN*	*DN*	*DD*
Frequency	0.9506	0.0488	0.0006
Penetrance	0	0	1

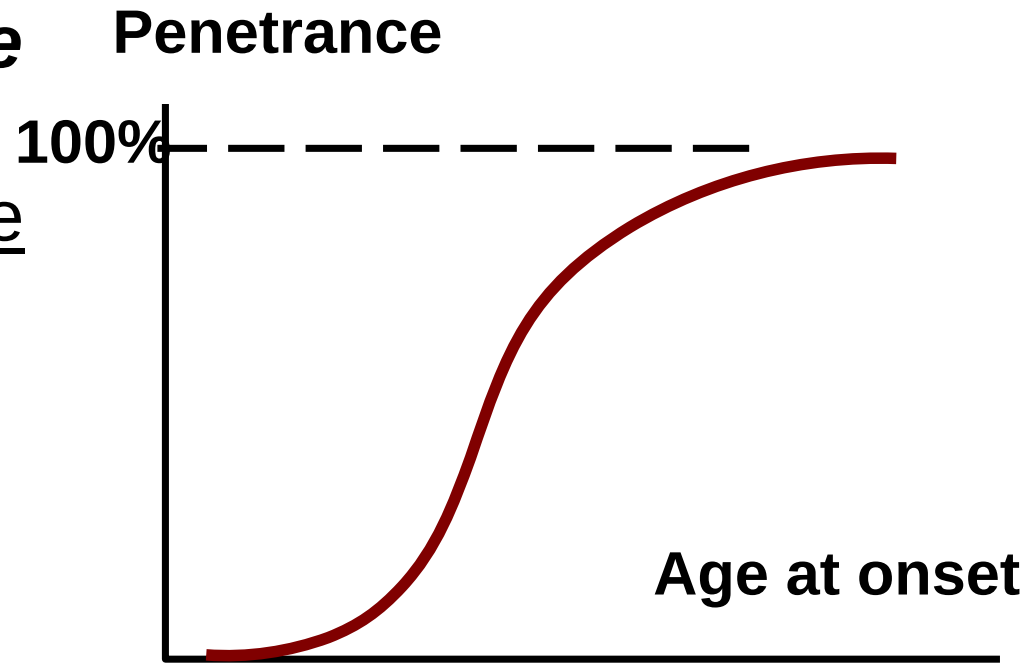
Incidence = Prevalence at birth = 0.0006 = 1/1600

Carrier frequency = 0.0488 ≈ 1/20

Age-dependent penetrance

Huntington disease

Age class	Penetrance
0-15	0.02
16-30	0.33
31-45	0.58
46-60	0.71
61+	0.94



Penetrance = Proportion of susceptible individuals affected by given age

Torsion Dystonia

Median age of onset ≈ 10 years

Penetrance at high age ≈ 30%

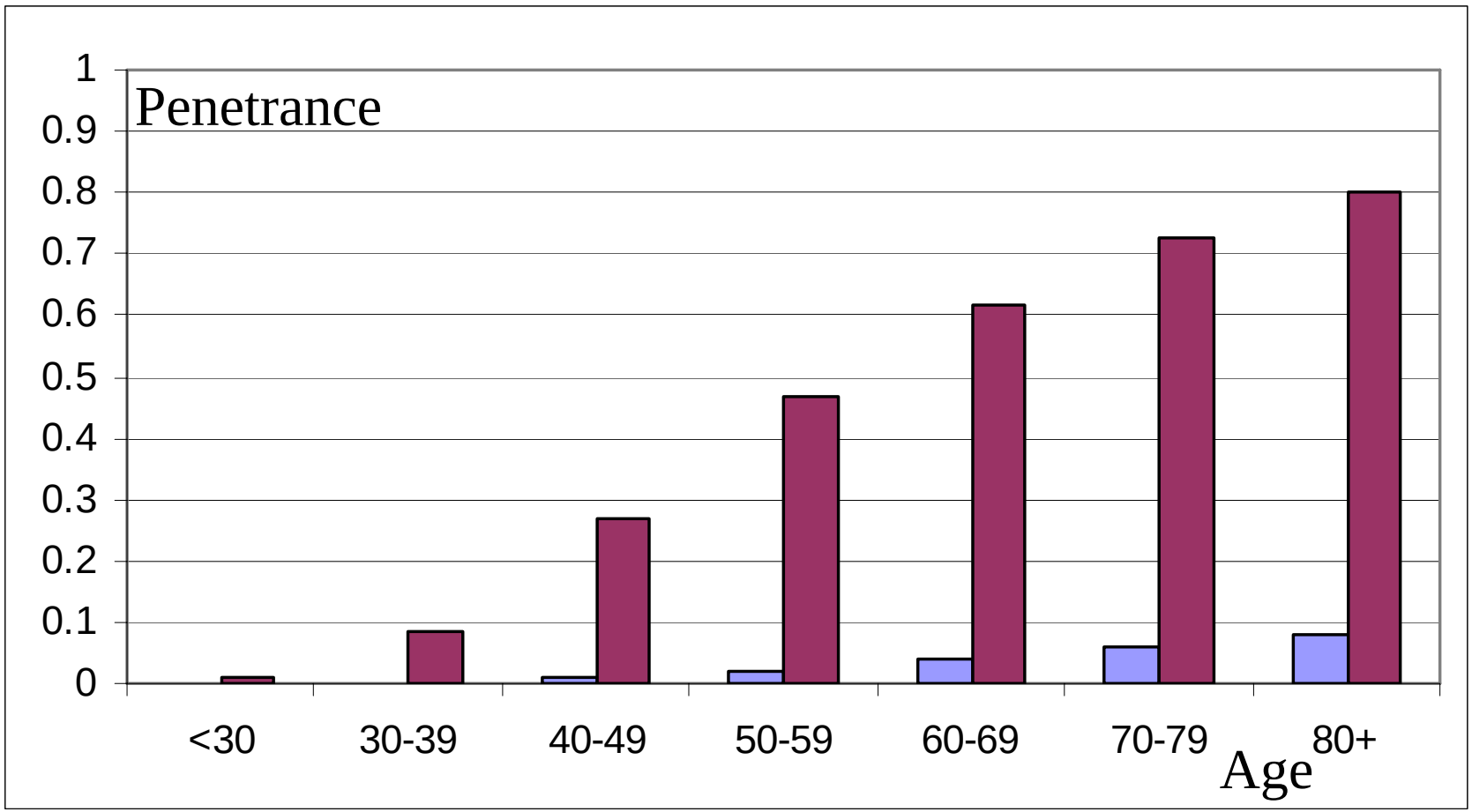
Familial Breast Cancer, BRCA1

Newman et al. (1988) *PNAS* **85**, 3044

Easton et al. (1993) *Am J Hum Genet* **52**, 678

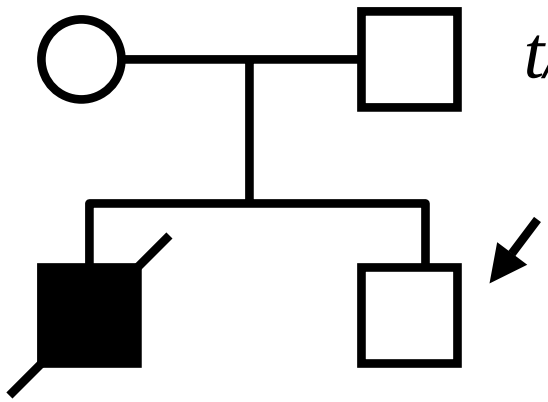
Age group	*P(affected by given age)*		
	dd	*Dd*	*DD*
<30	.00009	.008	.008
30-39	.00146	.083	.083
40-49	.0083	.269	.269
50-59	.021	.469	.469
60-69	.039	.616	.616
70-79	.061	.724	.724
80+	.082	.801	.801

Breast Cancer Penetrances



Cystic fibrosis — 3 mating types

t/n or *r/n*



t/n or *r/n*

Counselee = unaffected child, negative for tested mutations. Carrier? No genetic marker information.

t = tested CF mutations cover 80% of mut.

r = remaining mutations, 20%

Mother	*Father*	
	t/n 0.8	*r/n 0.2*
t/n 0.8	0.64	0.16
r/n 0.2	0.16	0.04

Cystic fibrosis — Calculations

Mating types	Counselee's genotype			
	¼	¼	¼	¼
t/n × t/n 0.64	t/t 0.16	t/n 0.16	t/n 0.16	n/n 0.16
t/n × r/n 0.32	t/r 0.08	t/n 0.08	**r/n** 0.08	n/n 0.08
r/n × r/n 0.04	r/r 0.01	**r/n** 0.01	**r/n** 0.01	n/n 0.01

Risk: $\frac{8+1+1}{8+1+1+16+8+1} = \frac{10}{35} = \frac{2}{7} = 29\%$

Heritability

- Linear model for phenotype:
  - $x = g + c + e$. Heritability = Var(g)/Var(x)
- Gene-environment interactions:
  - CCR5: No effect of mutation without infection
  - Sickle cell anemia: heterozygote advantage in malaria
  - Pima Indians: Obesity, “thrifty gene” hypothesis
- Measure degree of genetic influence by how consistently a trait runs in families

Framingham Study

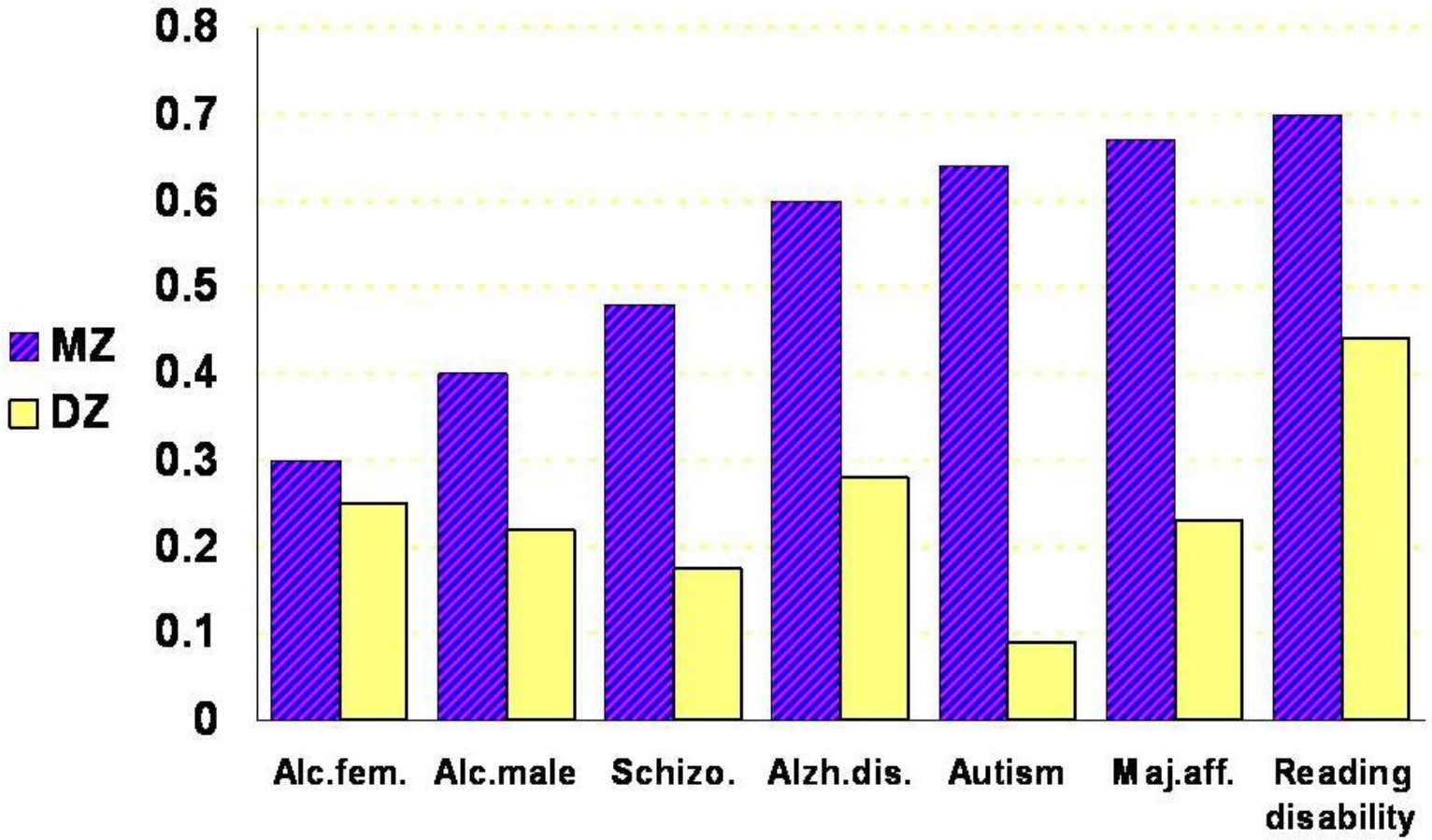
http://www.nhlbi.nih.gov/about/framingham/policies/pagetwelve.htm

Blood Pressure Variable	Families	Subjects	Heritability
Systolic Blood Pressure, adjusted for age	238	2067	0.323 ± 0.043
Systolic Blood Pressure, adjusted for age, BMI	238	2064	0.339 ± 0.043

Lipid Variable	Families	Subjects	Heritability
Total Cholesterol, adjusted	1366	4527	0.462 ± 0.034
HDL Cholesterol, adjusted	1366	4527	0.433 ± 0.034
Log Lp(a), adjusted	902	1832	**0.805** ± 0.064
Log TG, adjusted	1366	4527	0.396 ± 0.033
TC / HDL Ratio, adjusted	1366	4527	0.410 ± 0.032
TG / HDL Ratio, adjusted	1366	4527	0.332 ± 0.031

Twin Concordance Rates "Complex Diseases"

Plomin et al. (1994) *Science* **264**, 1734



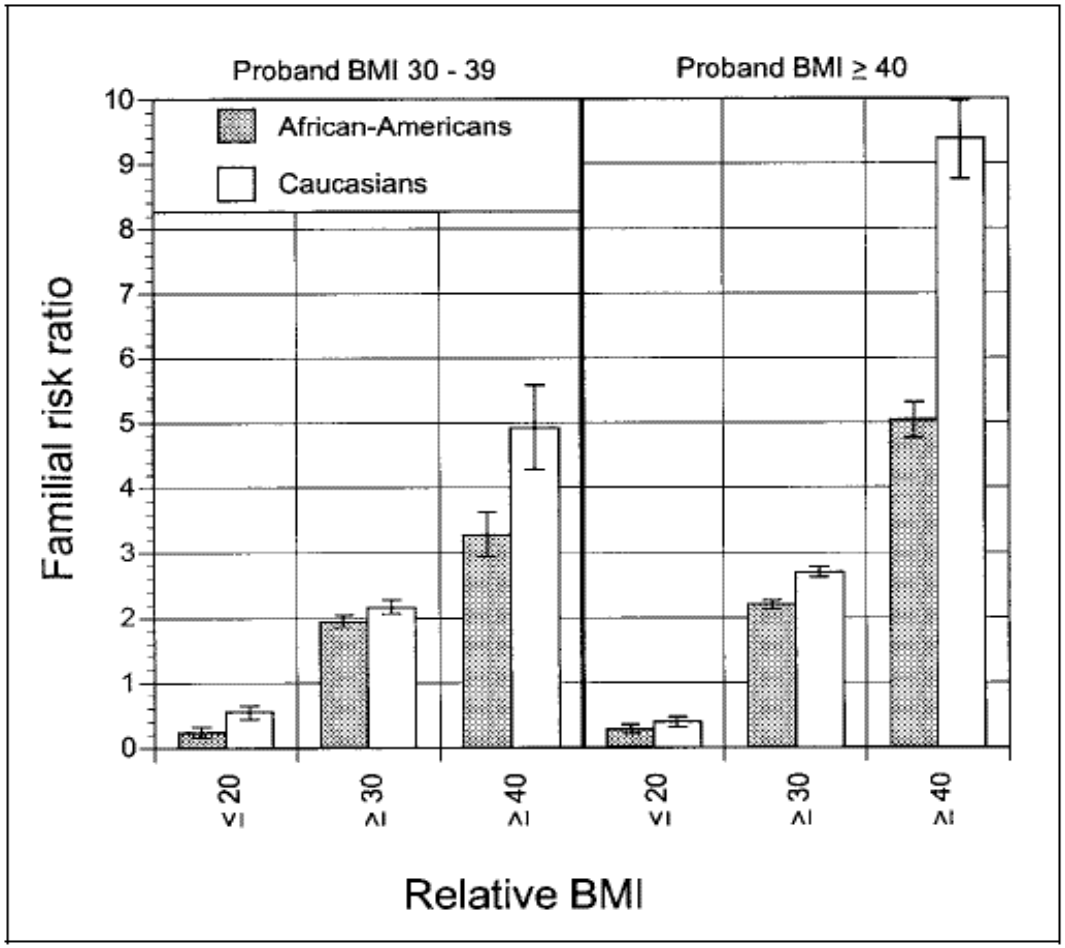
Risch's lambda measure

Risch (1990) *Am J Hum Genet* **46**, 222-228

- Risk, R_r = Prob(relative or type *r* has trait given index case has trait)
- Risk ratio, $\lambda_r = R_r/R_{unrelated} = R_r/K$, K = population prevalence
- Most common: λ_s = risk ratio to a sib
- CF: λ_s = ¼ / 0.0006 = 417

Sib risk ratios for obesity

Price and Lee (2001) *Hum Hered* **51**, 35-40



Risk ratios higher when proband and sibling have high BMI → strong obesity is more heritable than mild obesity.