19th International Workshop on Methodology of Twin and Family Studies: Introductory course

- Mike Neale (director) 🇬🇧🇺🇸
- Hermine Maes 🇧🇪🇺🇸
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- Ben Neale 🇬🇧🇺🇸🇭🇰
- Fruhling Rijsdijk 🇸🇷🇳🇱🇬🇧
- Dorret Boomsma 
- Danielle Posthuma 
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- John Hewitt (host) 🇬🇧🇺🇸
- Jeff Lessem 🇺🇸
- Stacey Cherny 🇨🇦🇺🇸🇬🇧
- Nick Martin 🇦🇺
- Sarah Medland 🇳🇿🇦🇺🇺🇸
- Manuel Ferreira 🇵🇹🇦🇺
- Kate Morley 🇦🇺

History of International Methodology Workshops

	Year	**Location**	**Type**	**#Faculty**	**# Students**
TC1	1987	Leuven	Introductory	10	24
TC2	1989	Leuven	Introductory	11	41
TC3	1990	Boulder	Introductory	11	28
TC4	1991	Leuven	Introductory	14	49
			Advanced	12	55
TC5	1993	Boulder	Introductory	13	49
TC6	1994	Boulder	Introductory	16	43
TC7	1995	Helsinki	Introductory	10	29
TC8	1996	Boulder	Introductory	10	49
TC9	1997	Boulder	Introductory	10	55
TC10	1998	Boulder	Introductory	12	57
TC11	1998	Leuven	Introductory	10	55
			Advanced	13	62
TC12	1999	Boulder	Advanced	12	37
TC13	2000	Boulder	Introductory	12	63
TC14	2001	Boulder	Advanced	18	65
TC15	2002	Boulder	Introductory	18	95
TC16	2003	Boulder	Advanced	15	82
TC17	2004	Boulder	Introductory	16	93
TC18	2005	Boulder	Advanced	18	64

Attendance at International Methodology Workshops

Frequency	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**16**	**17**	**19**	**20**	
Faculty	8	4	3	2	5	2	3	1	2	3	1	1	3	3	**41**
Student	507	171	32	14	5	4		1							**734**
	# of 'Unique' Students														

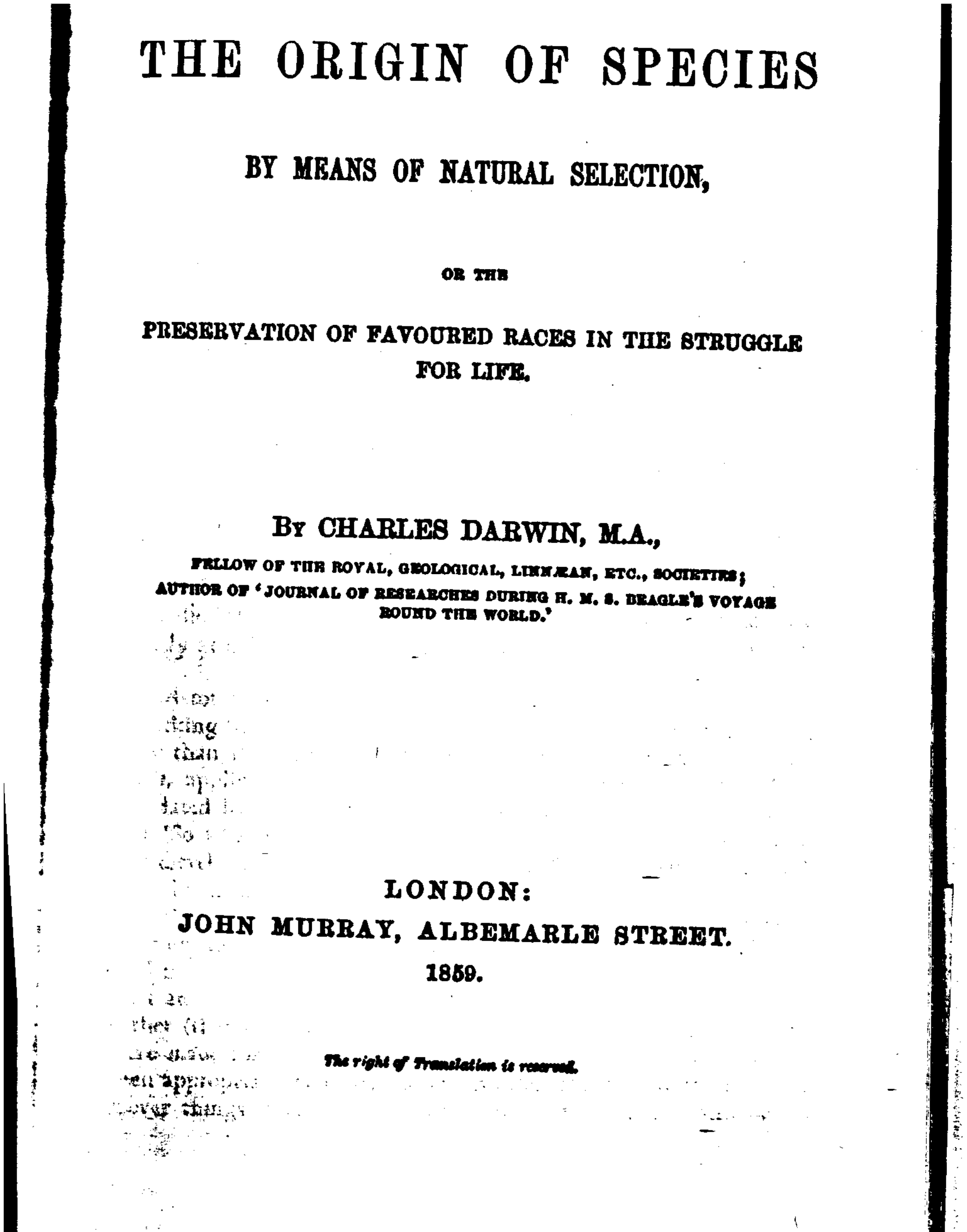
Introductory	**Workshop # of Students**	**730**
Advanced	**Workshop # of Students**	**365**
Total		**1095**

Causes of Human Variation

Nick Martin

Queensland Institute of Medical Research

Boulder workshop: March 6, 2006



THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

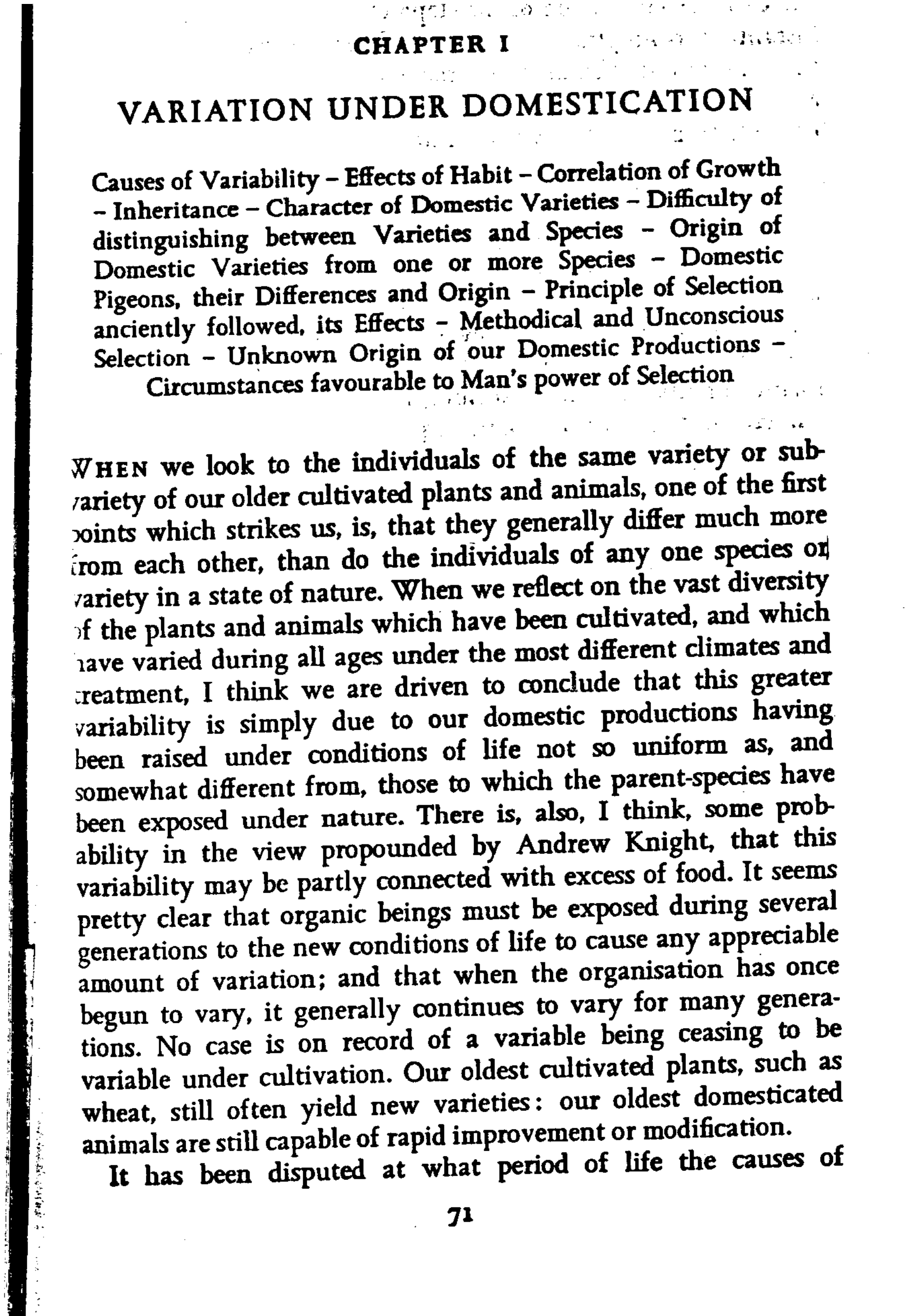
PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

BY CHARLES DARWIN, M.A.,

FELLOW OF THE ROYAL, GEOLOGICAL, LINNÆAN, ETC., SOCIETIES;
AUTHOR OF 'JOURNAL OF RESEARCHES DURING H. M. S. BEAGLE'S VOYAGE ROUND THE WORLD.'

LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1859.

The right of Translation is reserved.



CHAPTER I

VARIATION UNDER DOMESTICATION

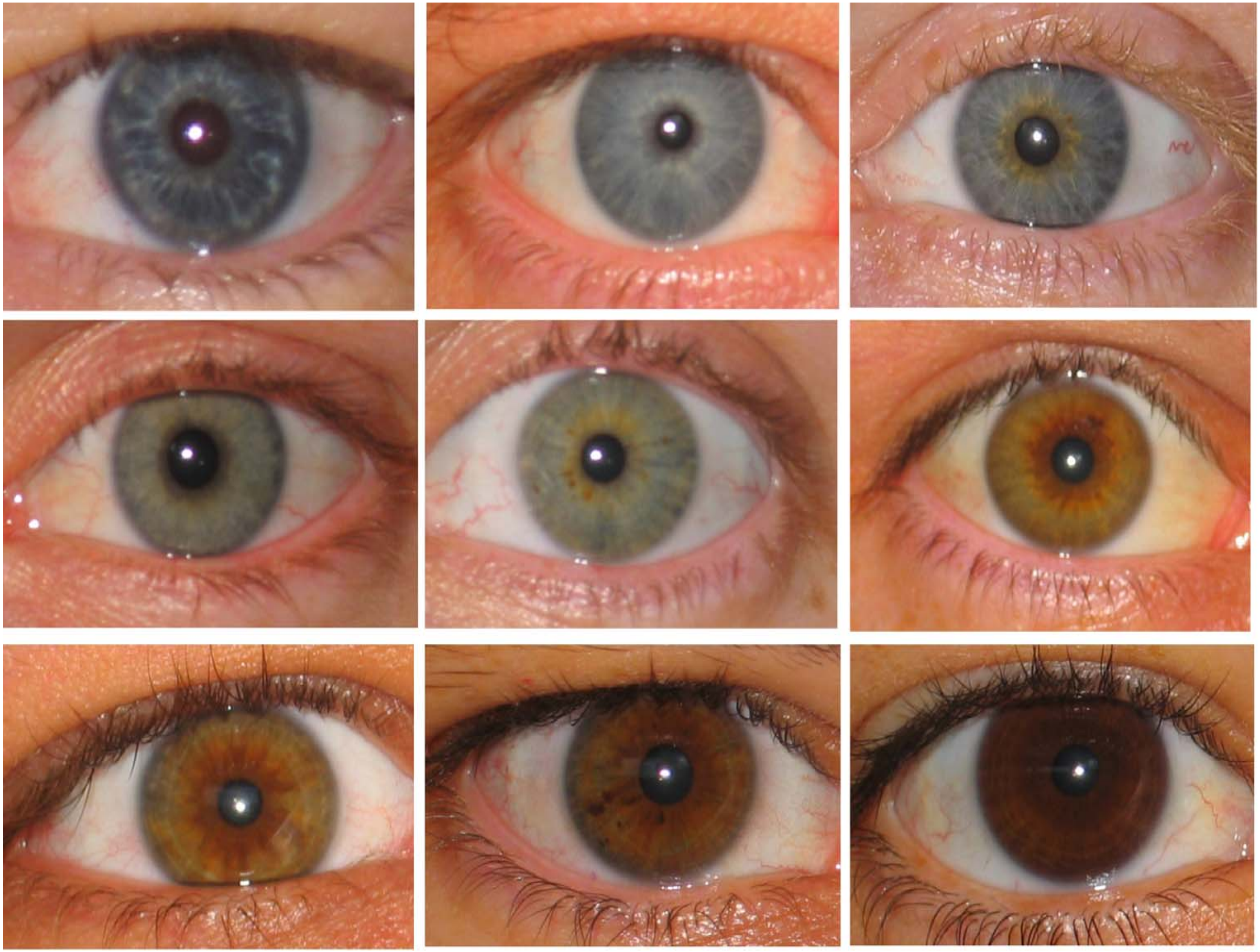
Causes of Variability – Effects of Habit – Correlation of Growth – Inheritance – Character of Domestic Varieties – Difficulty of distinguishing between Varieties and Species – Origin of Domestic Varieties from one or more Species – Domestic Pigeons, their Differences and Origin – Principle of Selection anciently followed, its Effects – Methodical and Unconscious Selection – Unknown Origin of our Domestic Productions – Circumstances favourable to Man's power of Selection

WHEN we look to the individuals of the same variety or sub-ariety of our older cultivated plants and animals, one of the first oints which strikes us, is, that they generally differ much more rom each other, than do the individuals of any one species or ariety in a state of nature. When we reflect on the vast diversity f the plants and animals which have been cultivated, and which ave varied during all ages under the most different climates and reatment, I think we are driven to conclude that this greater variability is simply due to our domestic productions having been raised under conditions of life not so uniform as, and somewhat different from, those to which the parent-species have been exposed under nature. There is, also, I think, some probability in the view propounded by Andrew Knight, that this variability may be partly connected with excess of food. It seems pretty clear that organic beings must be exposed during several generations to the new conditions of life to cause any appreciable amount of variation; and that when the organisation has once begun to vary, it generally continues to vary for many generations. No case is on record of a variable being ceasing to be variable under cultivation. Our oldest cultivated plants, such as wheat, still often yield new varieties: our oldest domesticated animals are still capable of rapid improvement or modification.

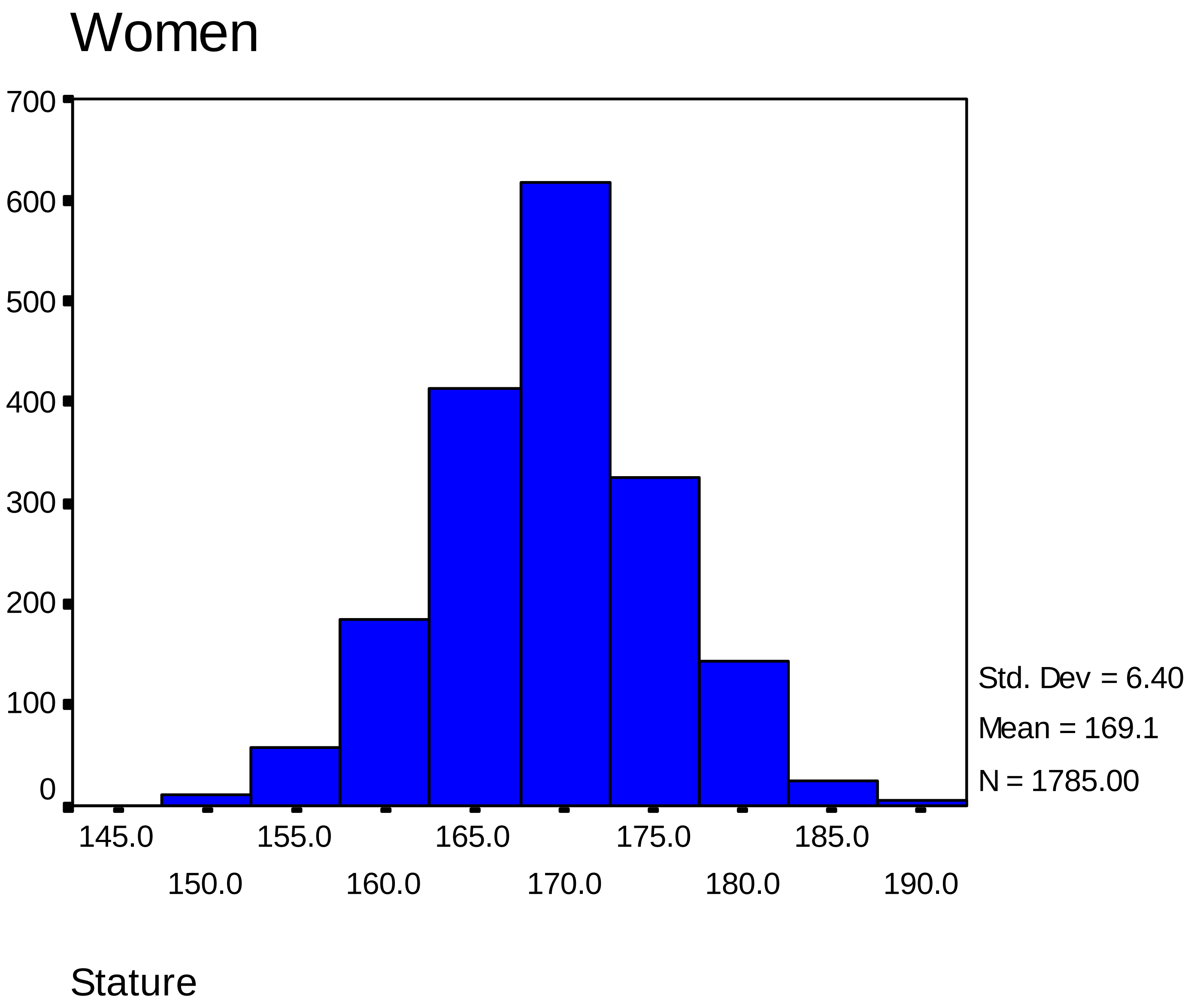
It has been disputed at what period of life the causes of

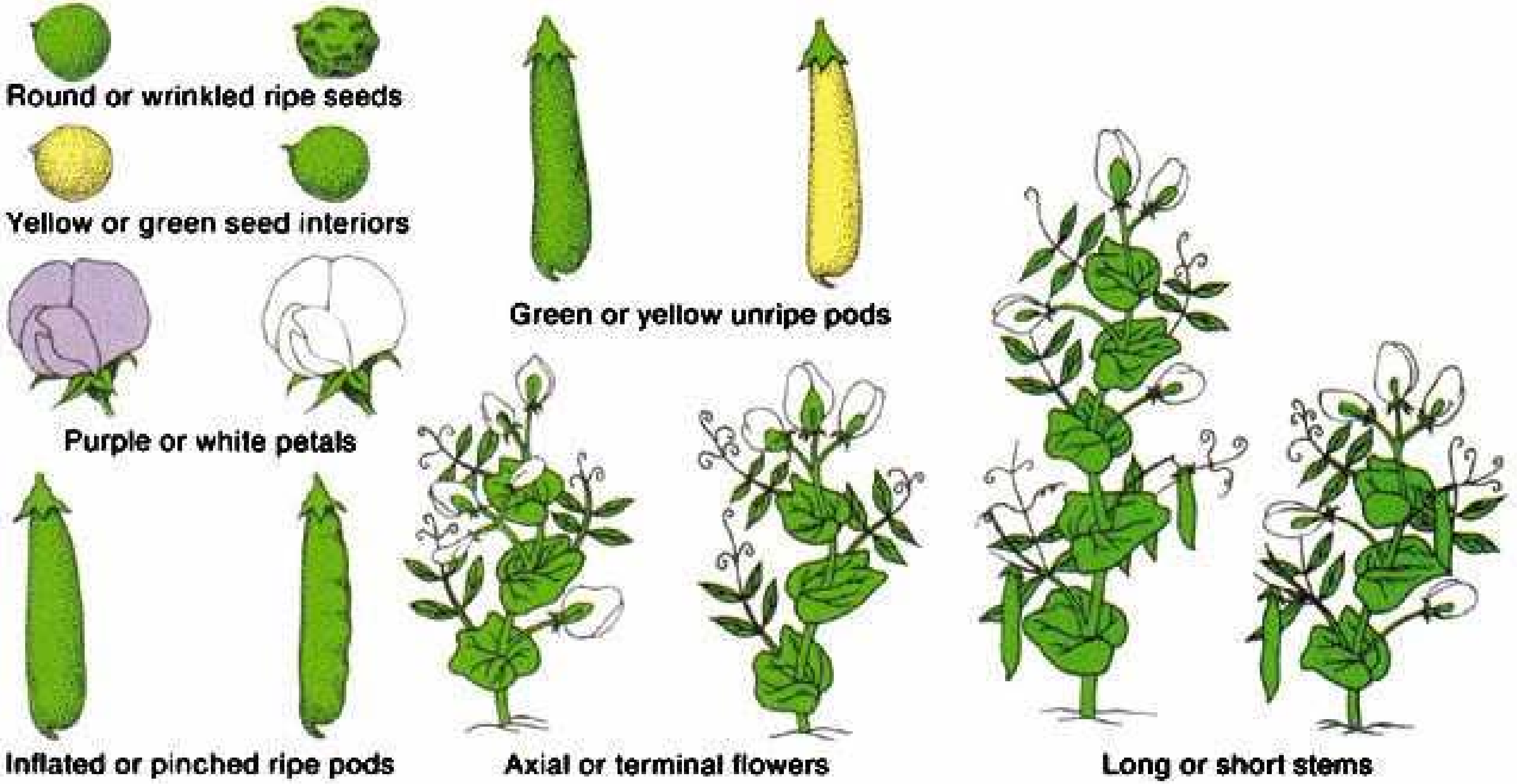
71

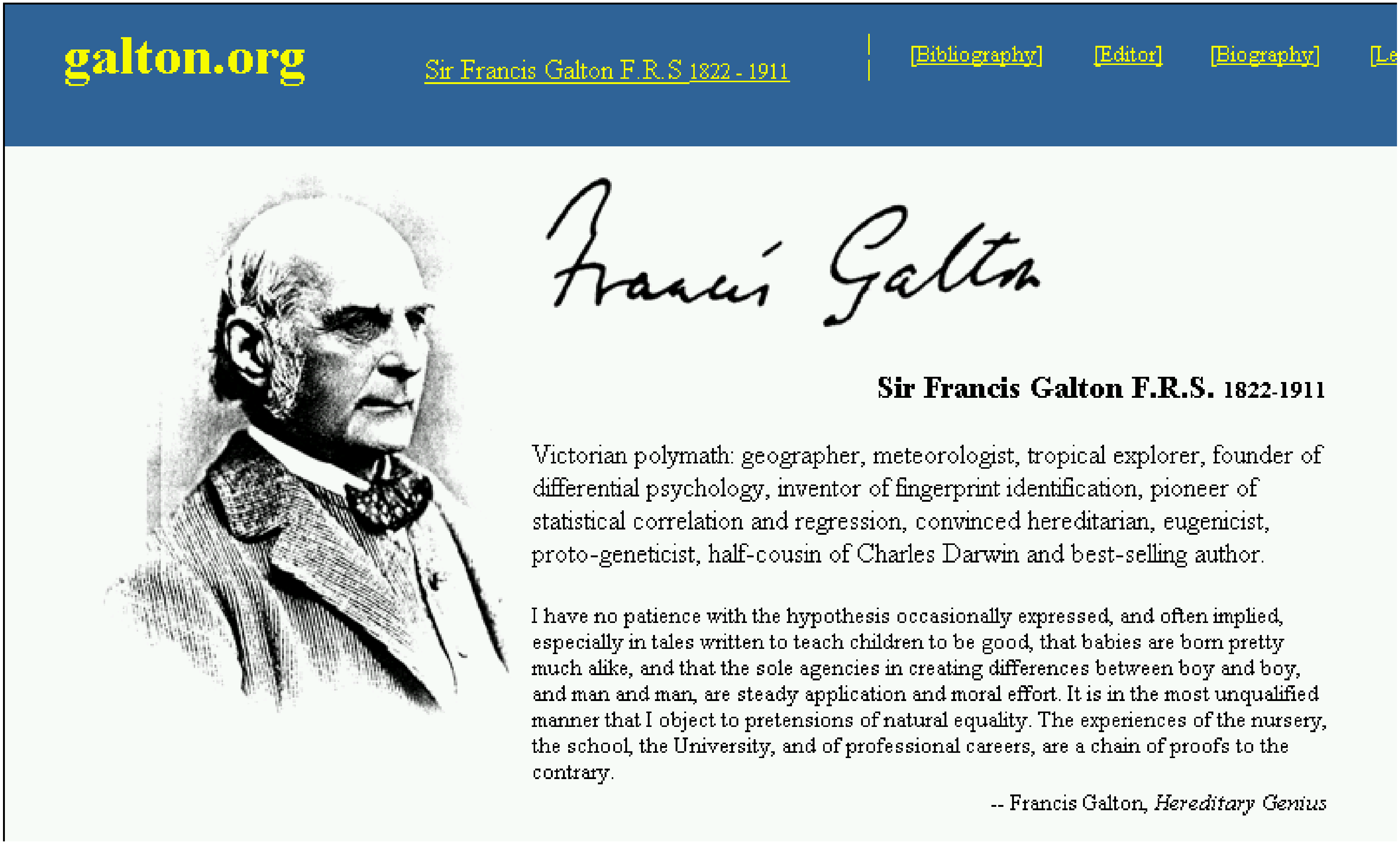
It's all about genetic variation …



Stature in adolescent twins




Round or wrinkled ripe seeds
Yellow or green seed interiors
Purple or white petals
Inflated or pinched ripe pods
Green or yellow unripe pods
Axial or terminal flowers
Long or short stems



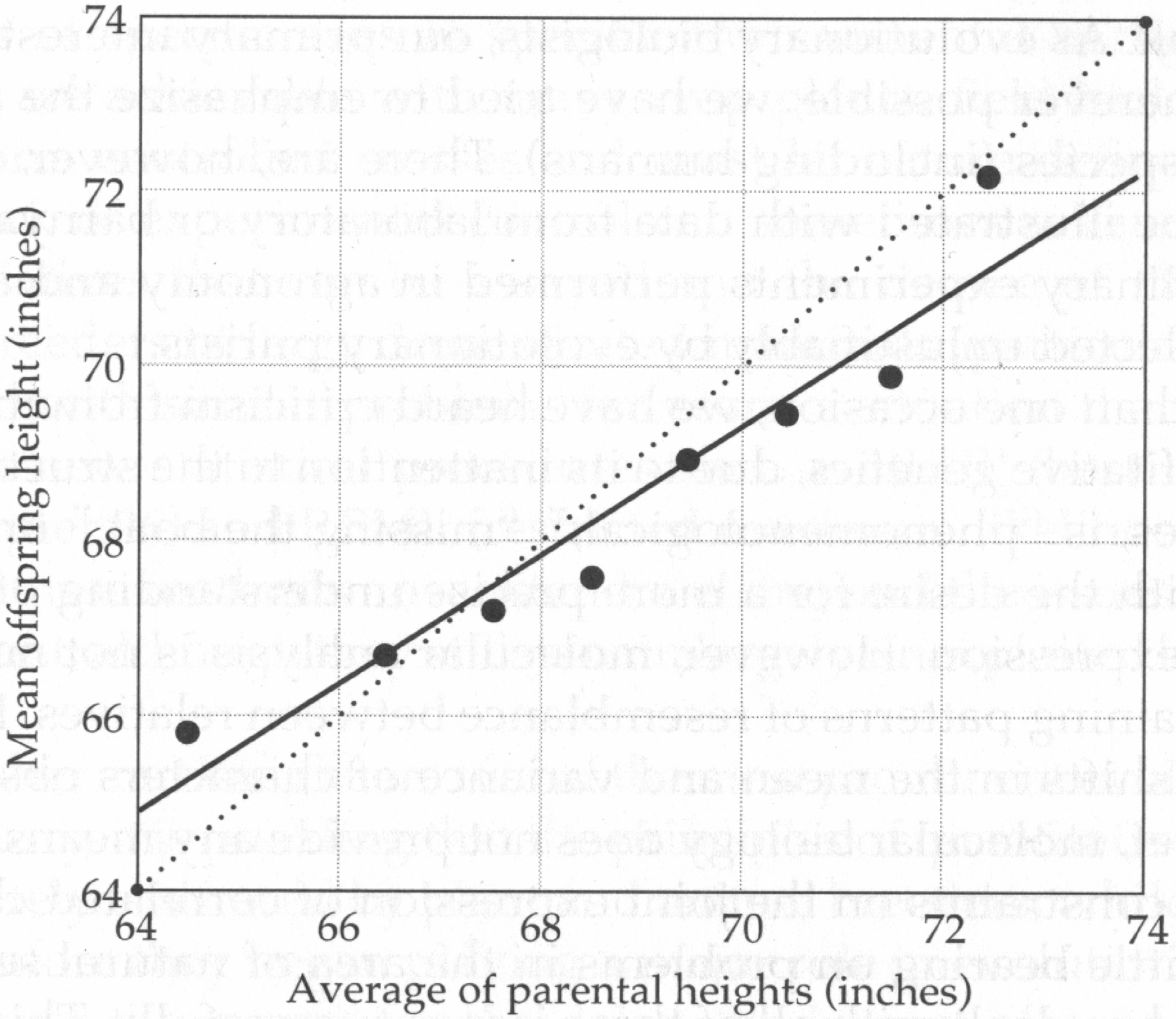
Francis Galton

Sir Francis Galton F.R.S. 1822-1911

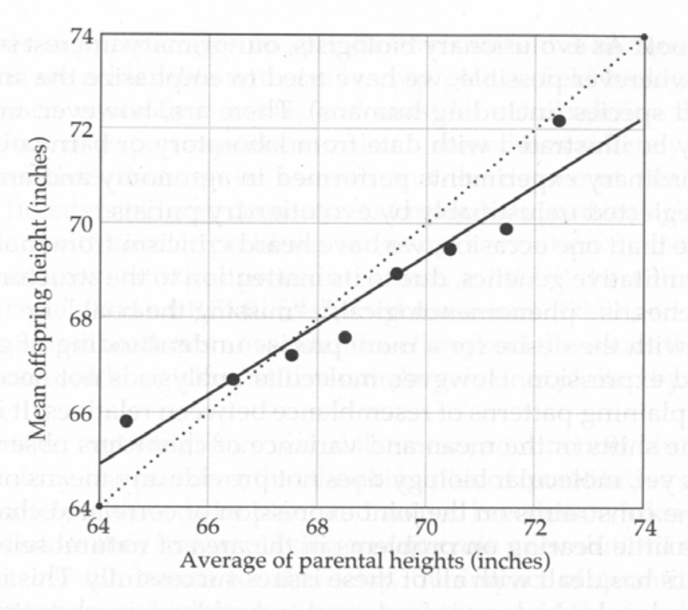
Victorian polymath: geographer, meteorologist, tropical explorer, founder of differential psychology, inventor of fingerprint identification, pioneer of statistical correlation and regression, convinced hereditarian, eugenicist, proto-geneticist, half-cousin of Charles Darwin and best-selling author.

I have no patience with the hypothesis occasionally expressed, and often implied, especially in tales written to teach children to be good, that babies are born pretty much alike, and that the sole agencies in creating differences between boy and boy, and man and man, are steady application and moral effort. It is in the most unqualified manner that I object to pretensions of natural equality. The experiences of the nursery, the school, the University, and of professional careers, are a chain of proofs to the contrary.

-- Francis Galton, *Hereditary Genius*


Mean offspring height (inches)
Average of parental heights (inches)
64
66
68
70
72
74
64
66
68
70
72
74

[Galton, 1889]



The height vs. pea debate (early 1900s)

Biometricians

Mendelians

Do quantitative traits have the same hereditary and evolutionary properties as discrete characters?

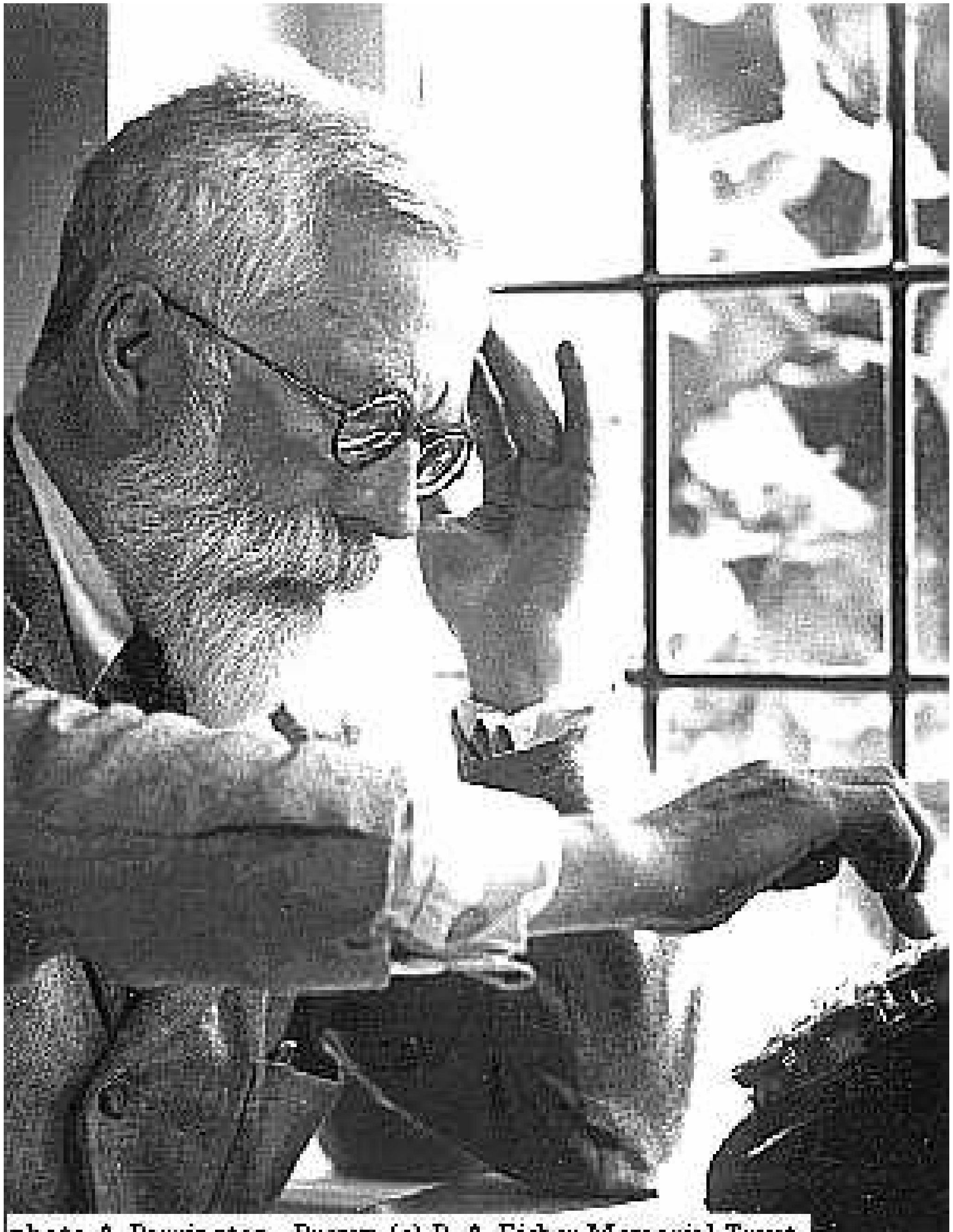
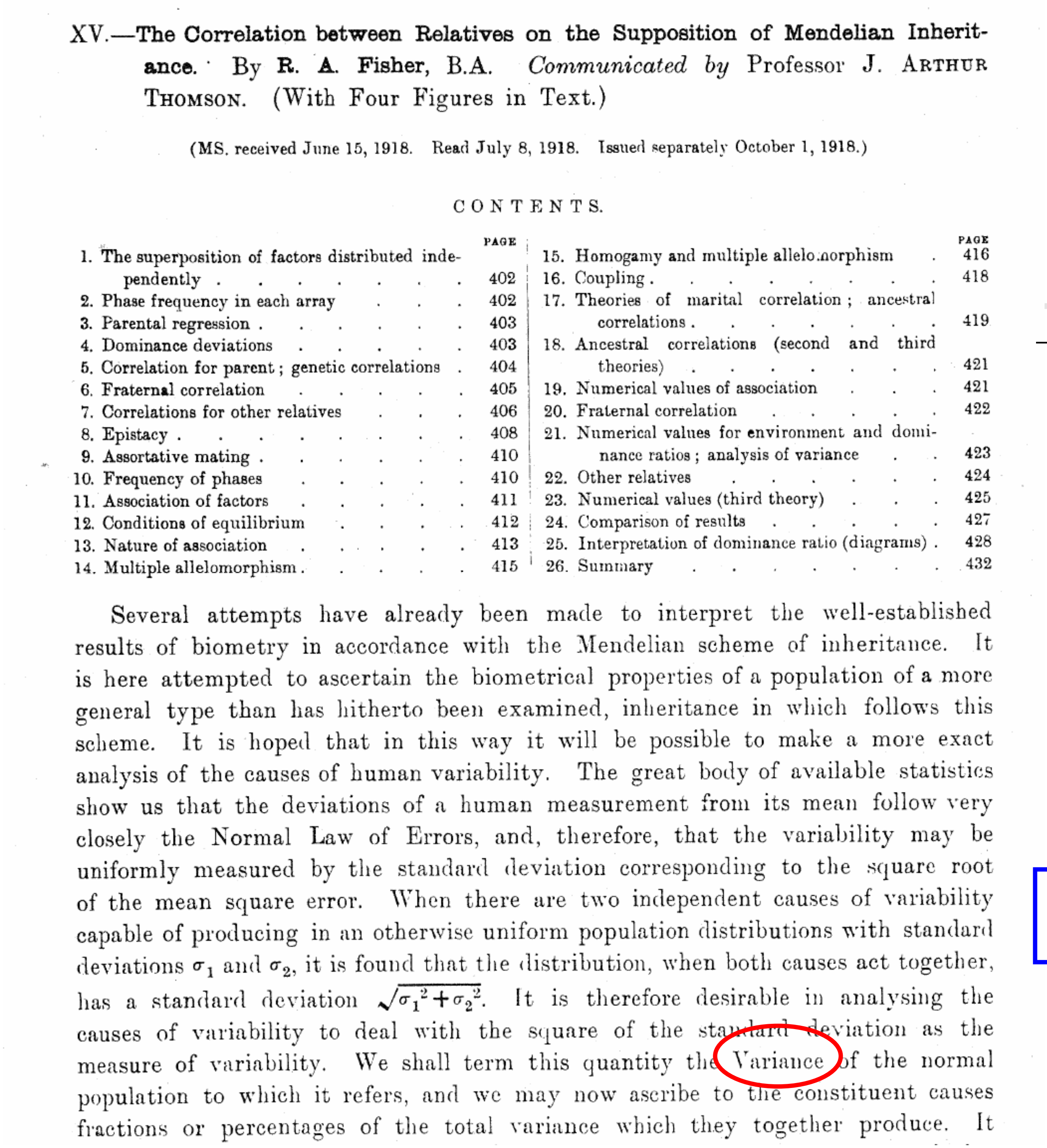


photo A.Barrington– Brown (c) R.A.Fisher Memorial Trust.

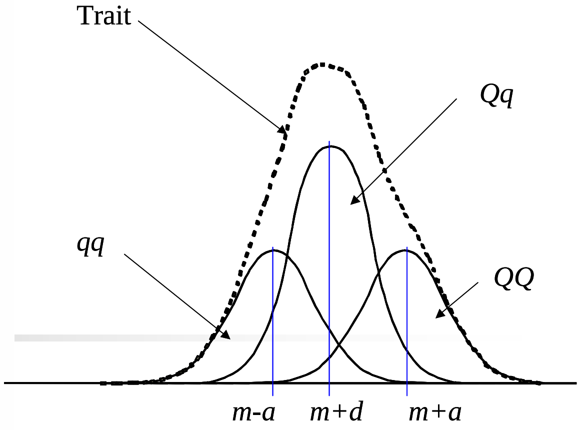


XV.—The Correlation between Relatives on the Supposition of Mendelian Inheritance. By R. A. Fisher, B.A. *Communicated by* Professor J. Arthur Thomson. (With Four Figures in Text.)

(MS. received June 15, 1918. Read July 8, 1918. Issued separately October 1, 1918.)

CONTENTS.

Several attempts have already been made to interpret the well-established results of biometry in accordance with the Mendelian scheme of inheritance. It is here attempted to ascertain the biometrical properties of a population of a more general type than has hitherto been examined, inheritance in which follows this scheme. It is hoped that in this way it will be possible to make a more exact analysis of the causes of human variability. The great body of available statistics show us that the deviations of a human measurement from its mean follow very closely the Normal Law of Errors, and, therefore, that the variability may be uniformly measured by the standard deviation corresponding to the square root of the mean square error. When there are two independent causes of variability capable of producing in an otherwise uniform population distributions with standard deviations σ_1 and σ_2, it is found that the distribution, when both causes act together, has a standard deviation $\sqrt{\sigma_1^2+\sigma_2^2}$. It is therefore desirable in analysing the causes of variability to deal with the square of the standard deviation as the measure of variability. We shall term this quantity the Variance of the normal population to which it refers, and we may now ascribe to the constituent causes fractions or percentages of the total variance which they together produce. It



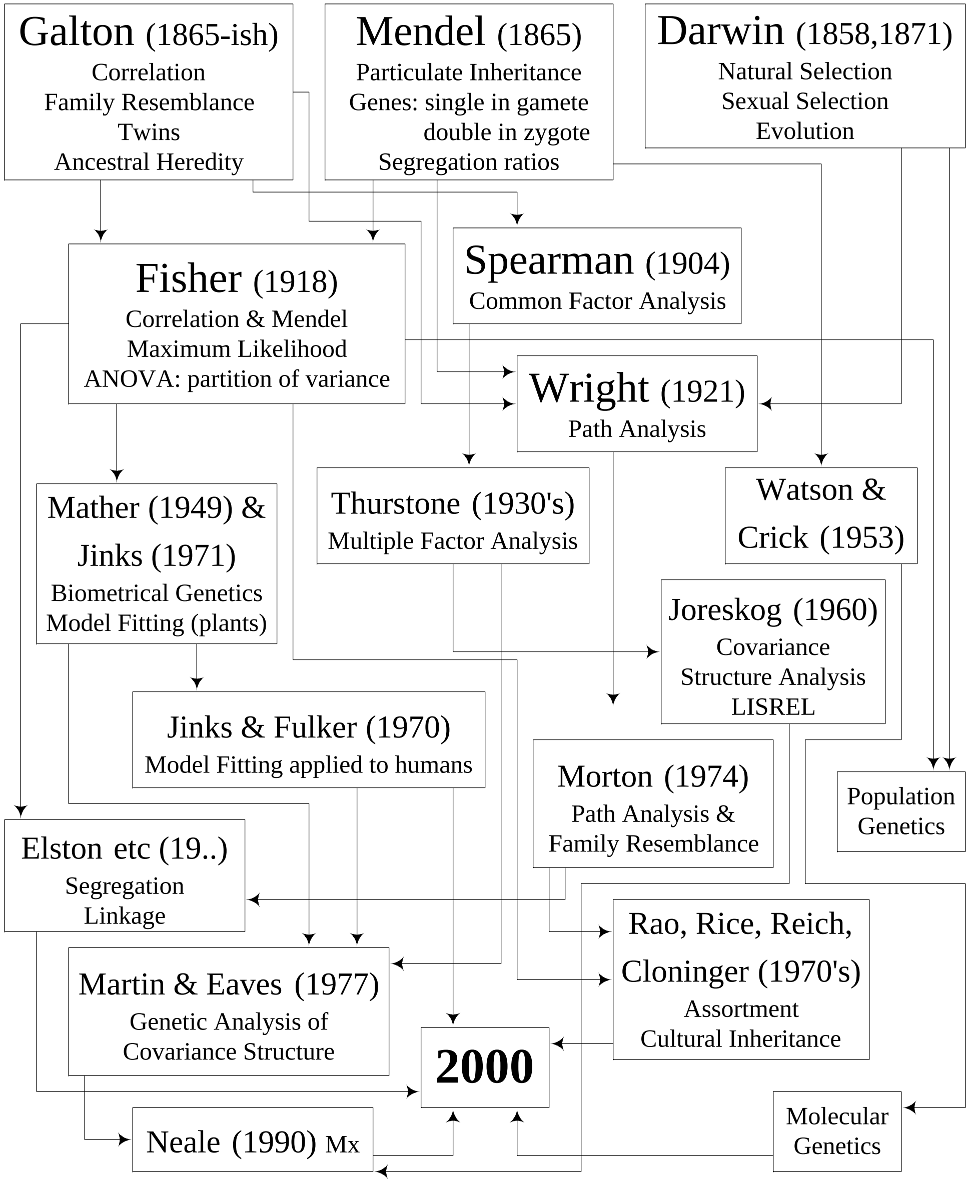
RA Fisher (1918). *Transactions of the Royal Society of Edinburgh* **52**: 399-433.

$$\boxed{\mathrm{var}(A)=2p(1-p)\alpha^2}$$

Kenneth Mather 1911-1990

John Jinks 1929-1987

People and Ideas



Galton (1865-ish)
Correlation
Family Resemblance
Twins
Ancestral Heredity

Mendel (1865)
Particulate Inheritance
Genes: single in gamete
double in zygote
Segregation ratios

Darwin (1858,1871)
Natural Selection
Sexual Selection
Evolution

Fisher (1918)
Correlation & Mendel
Maximum Likelihood
ANOVA: partition of variance

Spearman (1904)
Common Factor Analysis

Wright (1921)
Path Analysis

Mather (1949) & Jinks (1971)
Biometrical Genetics
Model Fitting (plants)

Thurstone (1930's)
Multiple Factor Analysis

Watson & Crick (1953)

Joreskog (1960)
Covariance
Structure Analysis
LISREL

Jinks & Fulker (1970)
Model Fitting applied to humans

Morton (1974)
Path Analysis &
Family Resemblance

Population
Genetics

Elston etc (19..)
Segregation
Linkage

Rao, Rice, Reich, Cloninger (1970's)
Assortment
Cultural Inheritance

Martin & Eaves (1977)
Genetic Analysis of
Covariance Structure

2000

Neale (1990) Mx

Molecular
Genetics

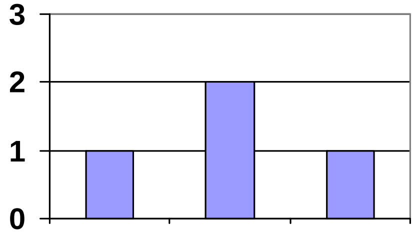
Polygenic Traits

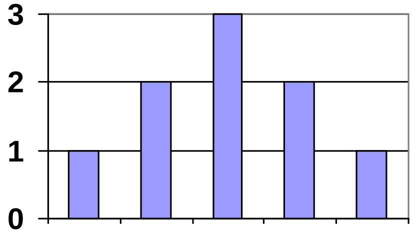
1 Gene
→ 3 Genotypes
→ 3 Phenotypes

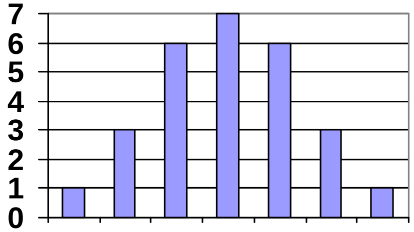
2 Genes
→ 9 Genotypes
→ 5 Phenotypes

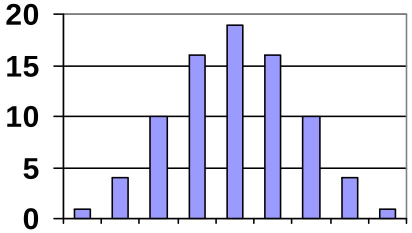
3 Genes
→ 27 Genotypes
→ 7 Phenotypes

4 Genes
→ 81 Genotypes
→ 9 Phenotypes



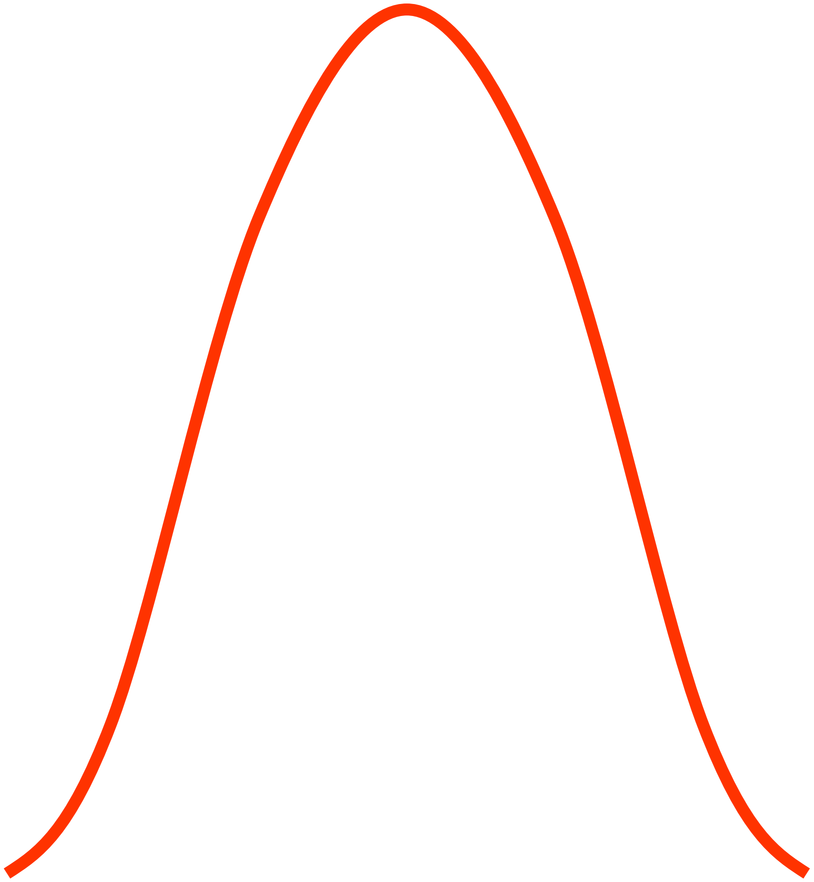






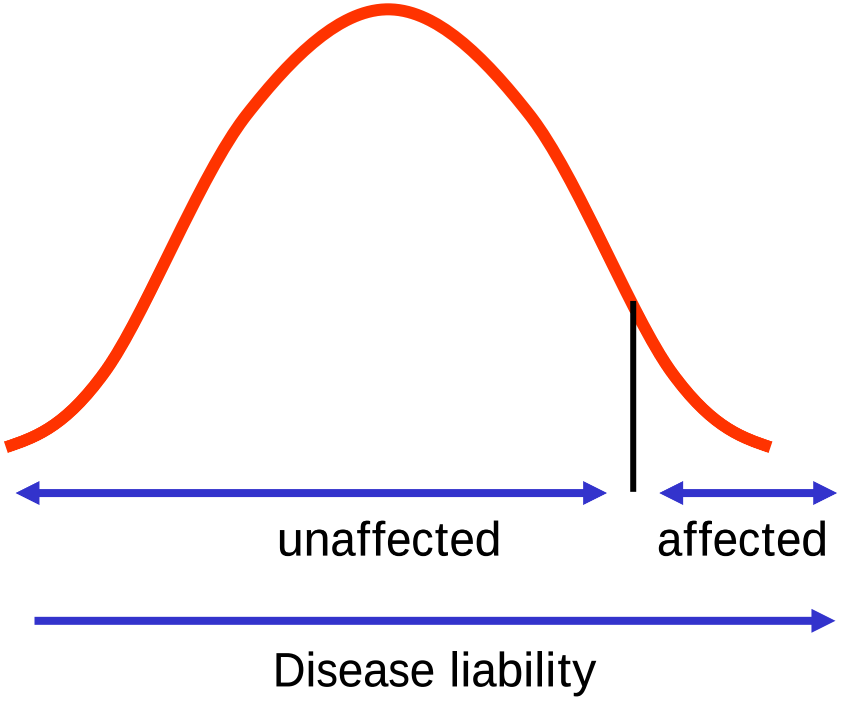
Central Limit Theorem

The normal distribution is to be expected whenever variation is produced by the addition of a large number of effects.

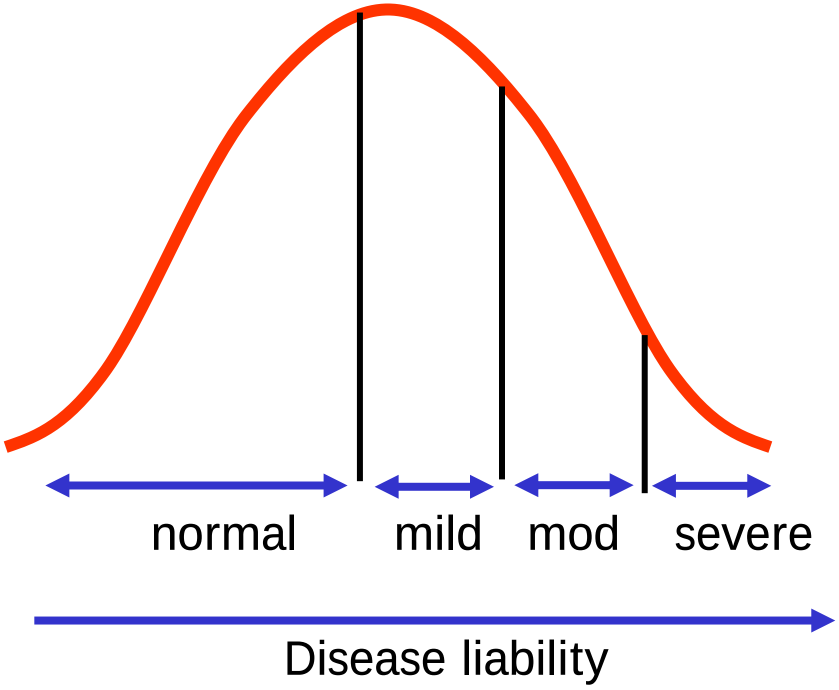


Multifactorial Threshold Model of Disease

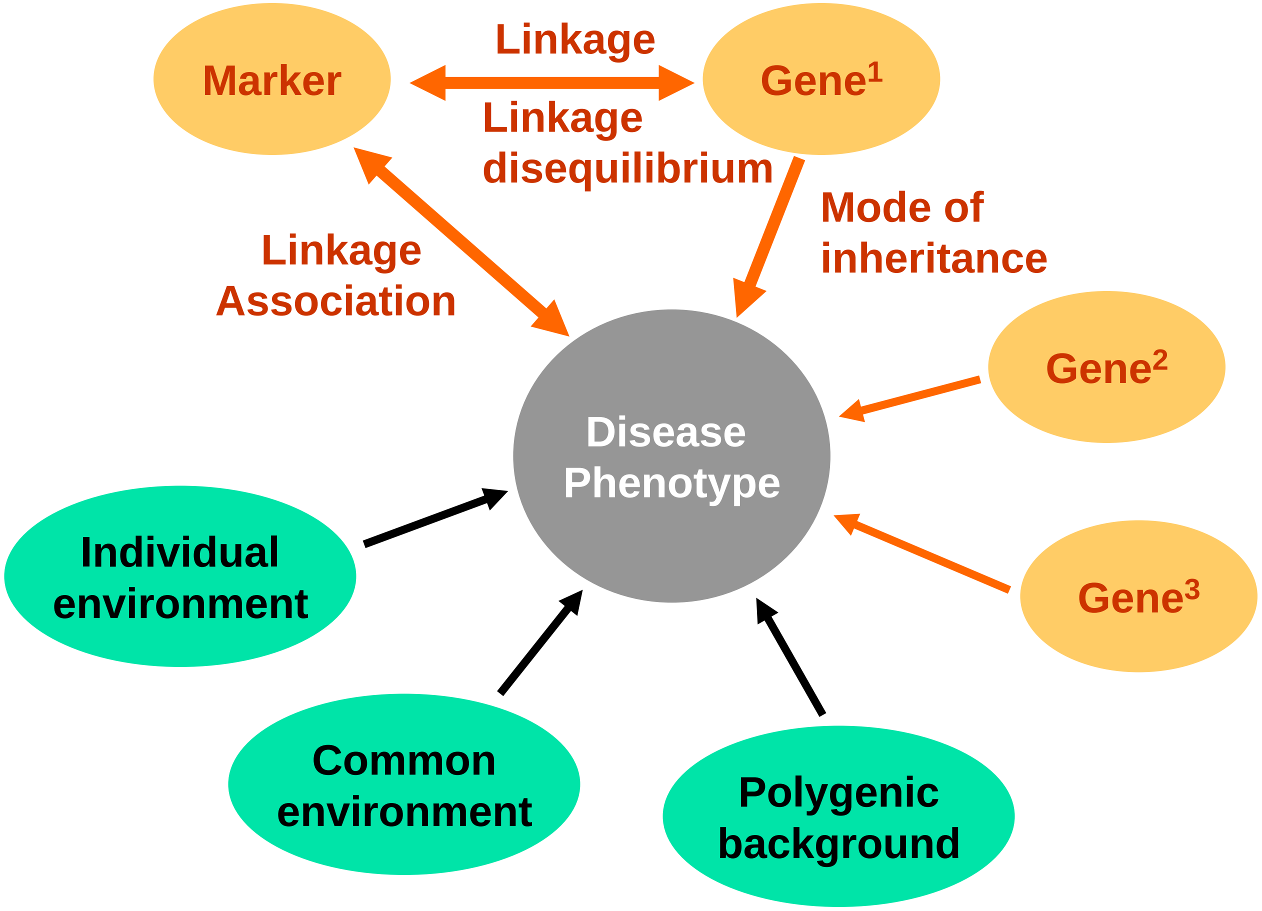
Single threshold



Multiple thresholds



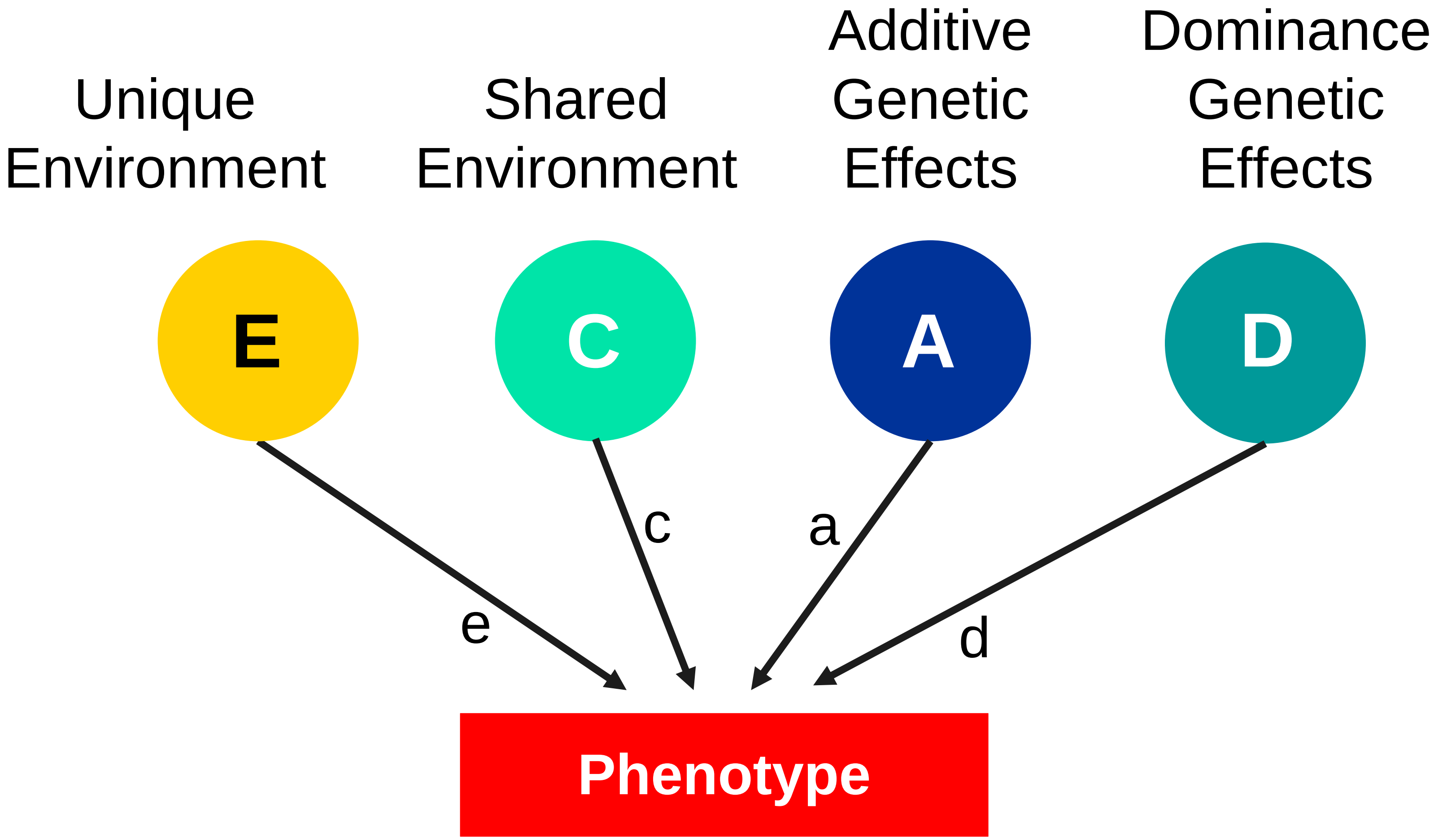
Complex Trait Model



3 Stages of Genetic Mapping

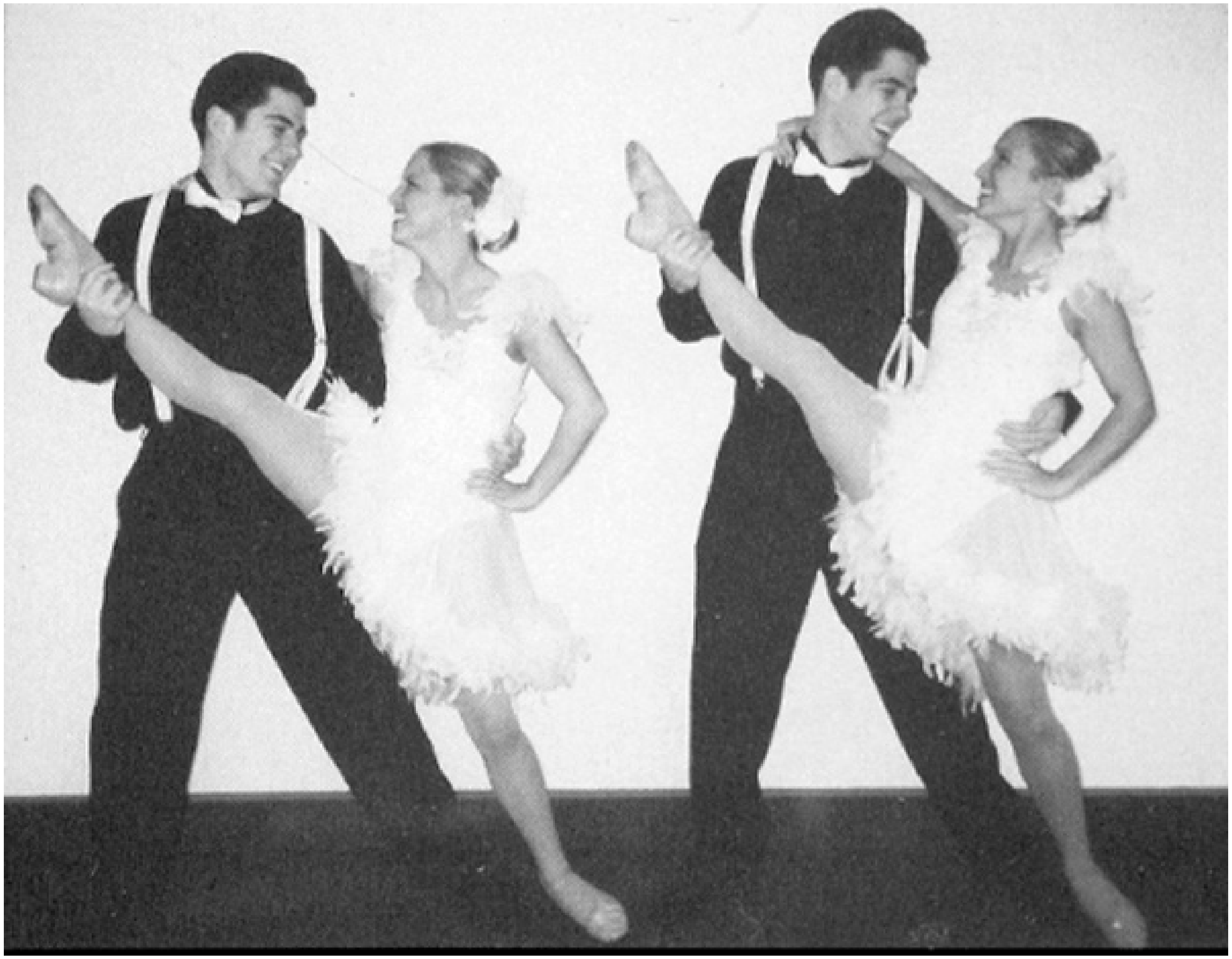
- Are there genes influencing this trait?
  - Genetic epidemiological studies
- Where are those genes?
  - Linkage analysis
- What are those genes?
  - Association analysis

Variance components



$$P = eE + aA + cC + dD$$

Controversy: nature vs nurture



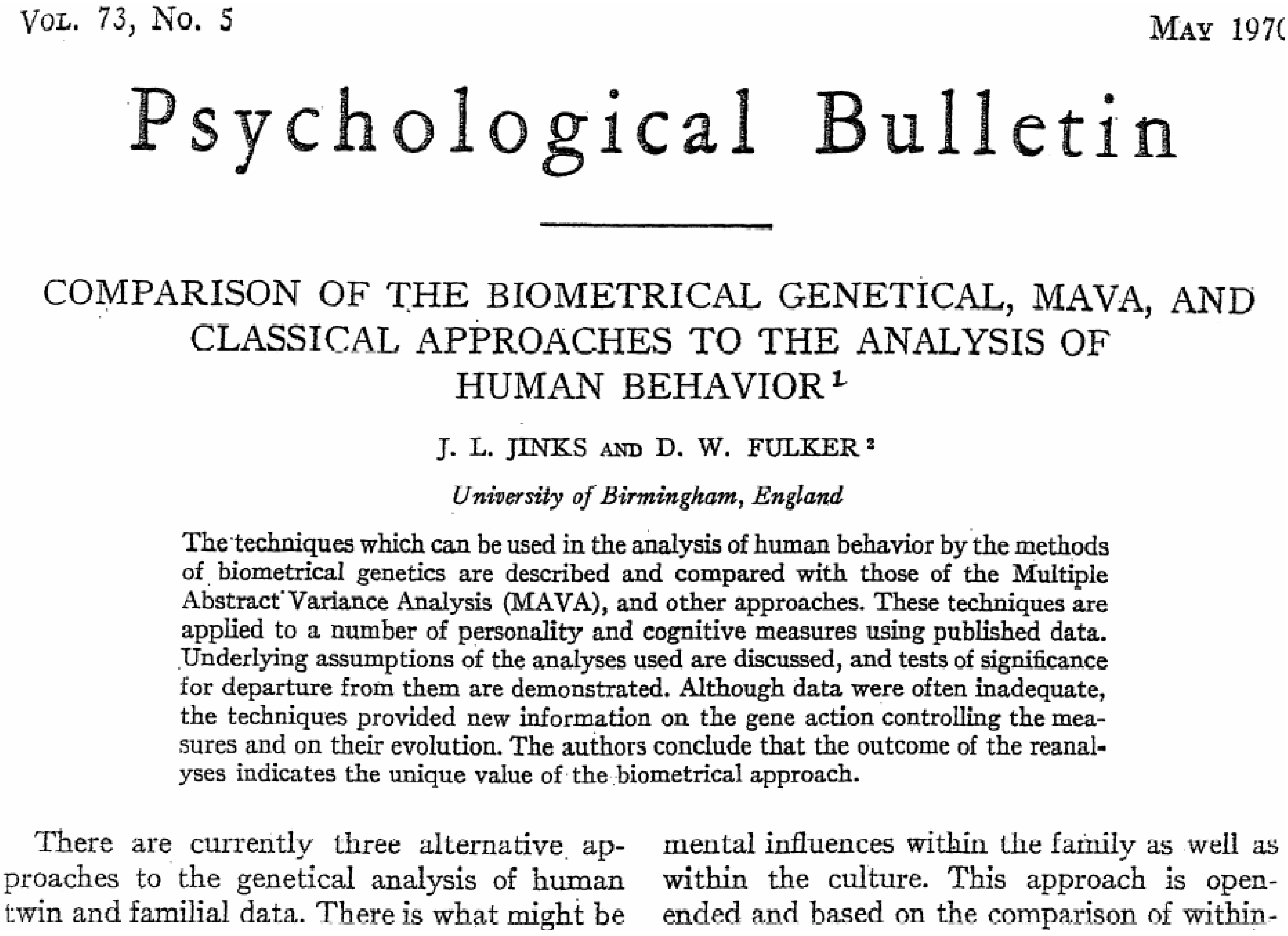
Designs to disentangle G + E

Resemblance between relatives caused by:

- shared Genes (G = A + D)
- environment Common to family members (C)

Differences between relatives caused by:

- nonshared Genes
- Unique environment (U or E)



VOL. 73, No. 5 MAY 197

Psychological Bulletin

COMPARISON OF THE BIOMETRICAL GENETICAL, MAVA, AND CLASSICAL APPROACHES TO THE ANALYSIS OF HUMAN BEHAVIOR[1]

J. L. JINKS AND D. W. FULKER[2]

University of Birmingham, England

The techniques which can be used in the analysis of human behavior by the methods of biometrical genetics are described and compared with those of the Multiple Abstract Variance Analysis (MAVA), and other approaches. These techniques are applied to a number of personality and cognitive measures using published data. Underlying assumptions of the analyses used are discussed, and tests of significance for departure from them are demonstrated. Although data were often inadequate, the techniques provided new information on the gene action controlling the measures and on their evolution. The authors conclude that the outcome of the reanalyses indicates the unique value of the biometrical approach.

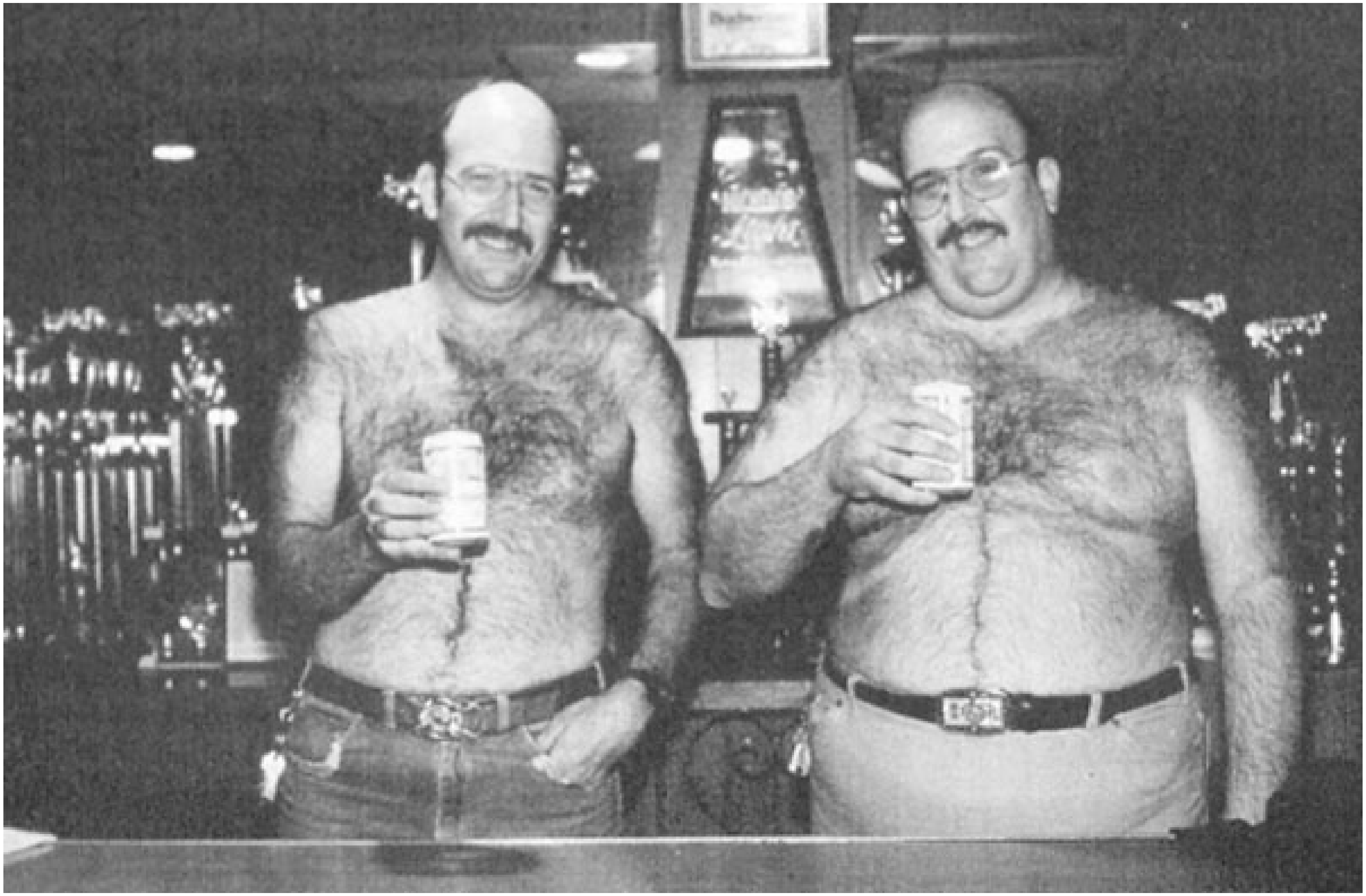
There are currently three alternative approaches to the genetical analysis of human twin and familial data. There is what might be

mental influences within the family as well as within the culture. This approach is open-ended and based on the comparison of within-

http://genepi.qimr.edu.au/staff/classicpapers.html

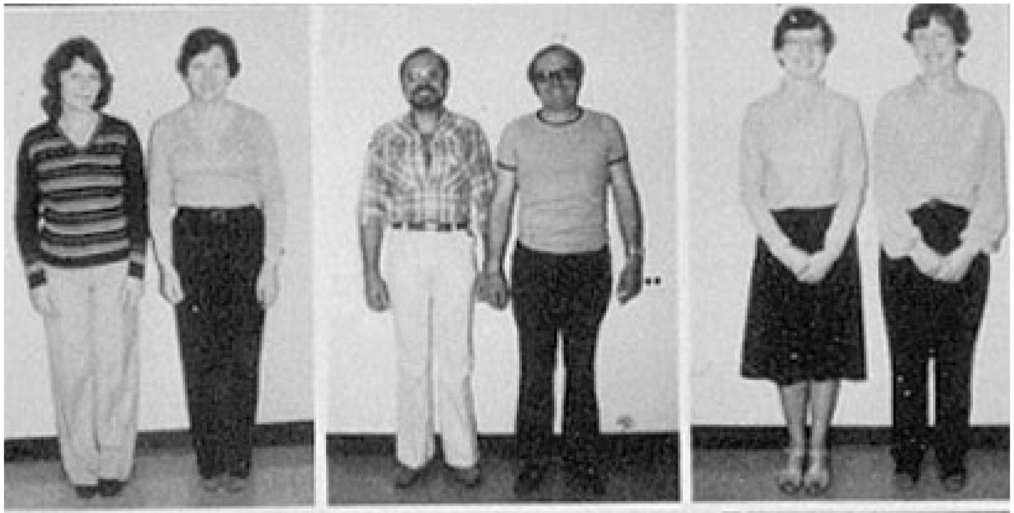
Designs to disentangle G + E

- Family studies – G + C confounded
- MZ twins alone – G + C confounded
- MZ twins reared apart – rare, atypical, selective placement ?
- Adoptions – increasingly rare, atypical, selective placement ?
- MZ and DZ twins reared together
- Extended twin design



MZ twins reared apart - note the same way of supporting their cans of beer

Body postures of MZ twins reared apart



Body postures of DZ twins reared apart

American
Association for the
Advancement of
Science

Science

6 June 1997 $7.00
Vol. 276 • Pages 1465–1612

Designs to disentangle G + E

- Family studies – G + C confounded
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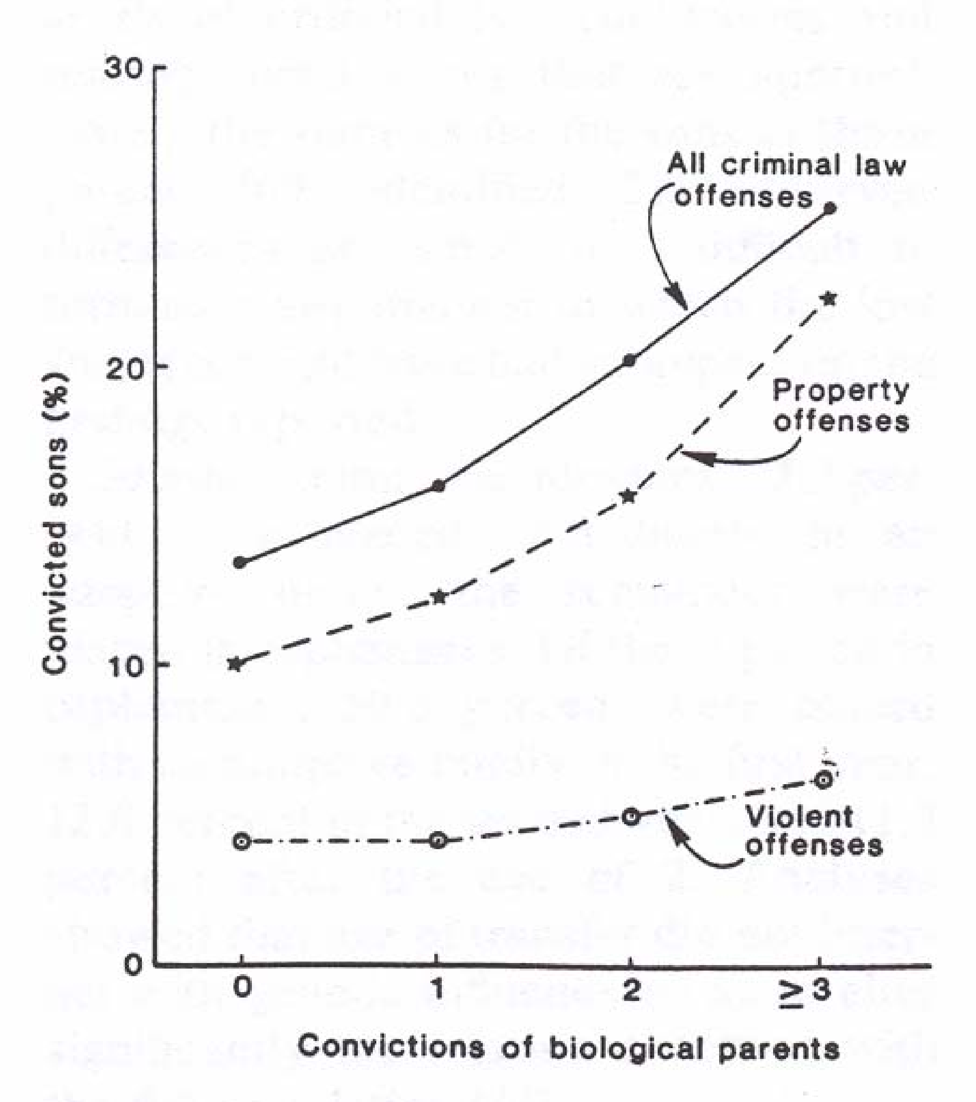
- Adoptions – increasingly rare, atypical, selective placement ?
- MZ and DZ twins reared together
- Extended twin design

Percentage of adoptees convicted of violent and property offenses by biological parents’ convictions



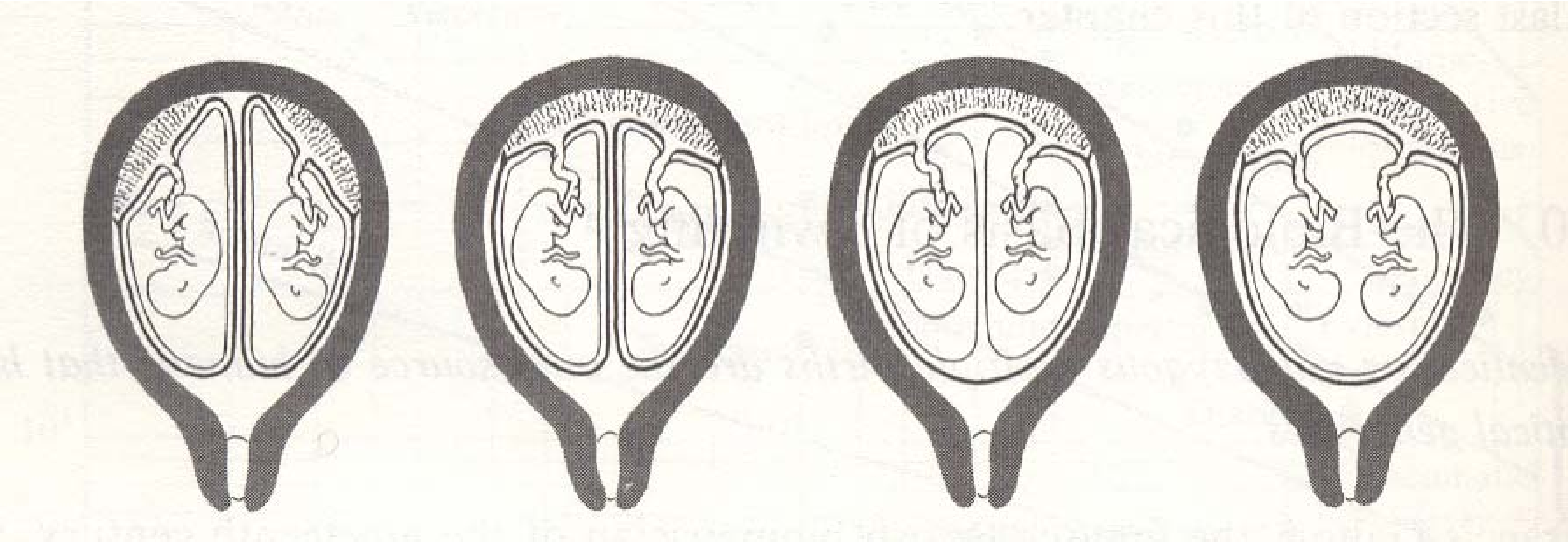
- Denmark
- 14,427 nonfamilial adoptions 1927-47
- Court convictions available for biological and adoptive parents

- Mednick et al (1984) Science 224:891-4

Designs to disentangle G + E

- **Family studies – G + C confounded**
- **MZ twins alone – G + C confounded**
- **MZ twins reared apart – rare, atypical, selective placement ?**
- **Adoptions – increasingly rare, atypical, selective placement ?**
- **MZ and DZ twins reared together**
- **Extended twin design**

Placentation and zygosity

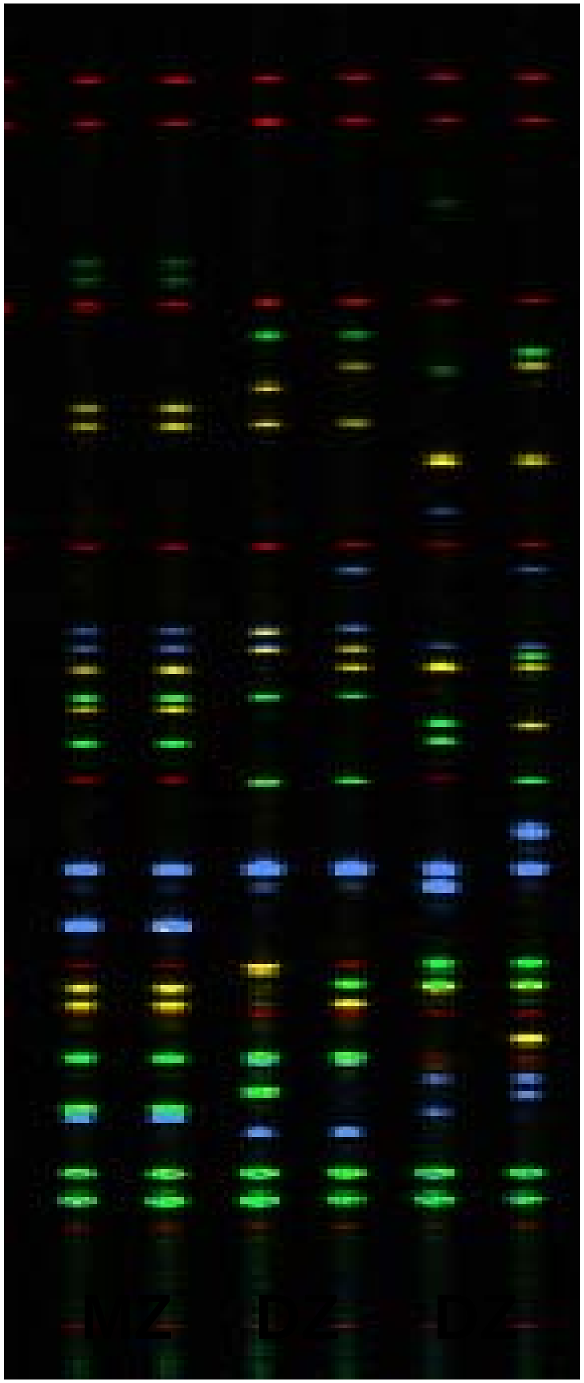


Dichorionic
Two placentas
MZ 19%
DZ 58%

Dichorionic
Fused placentas
MZ 14%
DZ 42%

Monochorionic
Diamniotic
MZ 63%
DZ 0%

Monochorionic
Monoamniotic
MZ 4%
DZ 0%



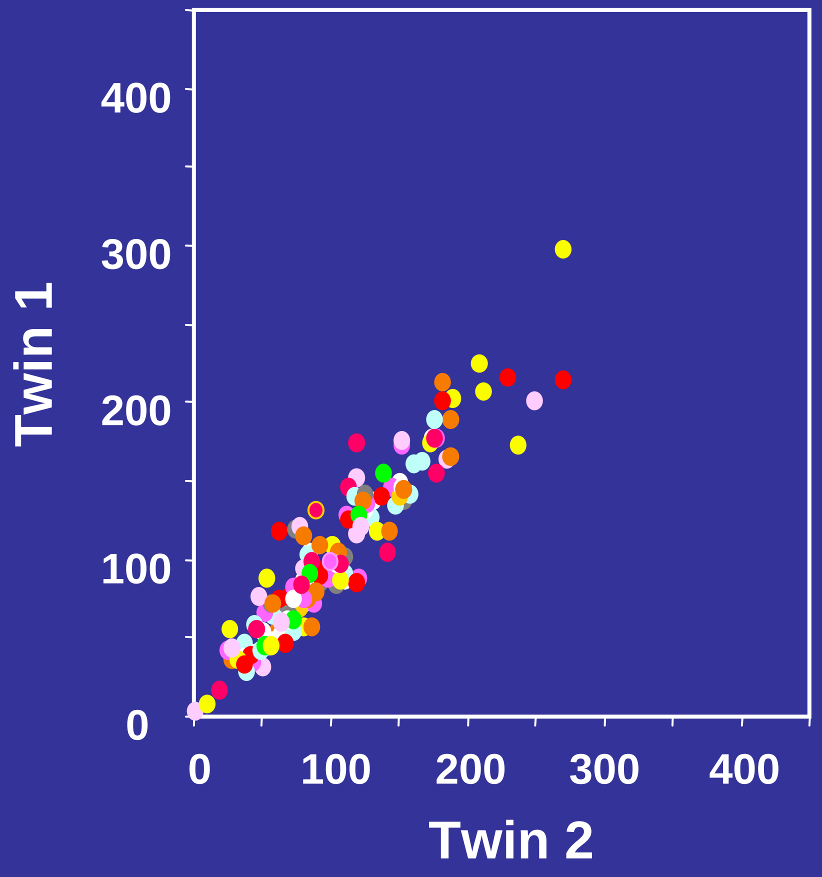
Identity at marker loci - except for rare mutation

MZ and DZ twins: determining zygosity using ABI Profiler™ genotyping

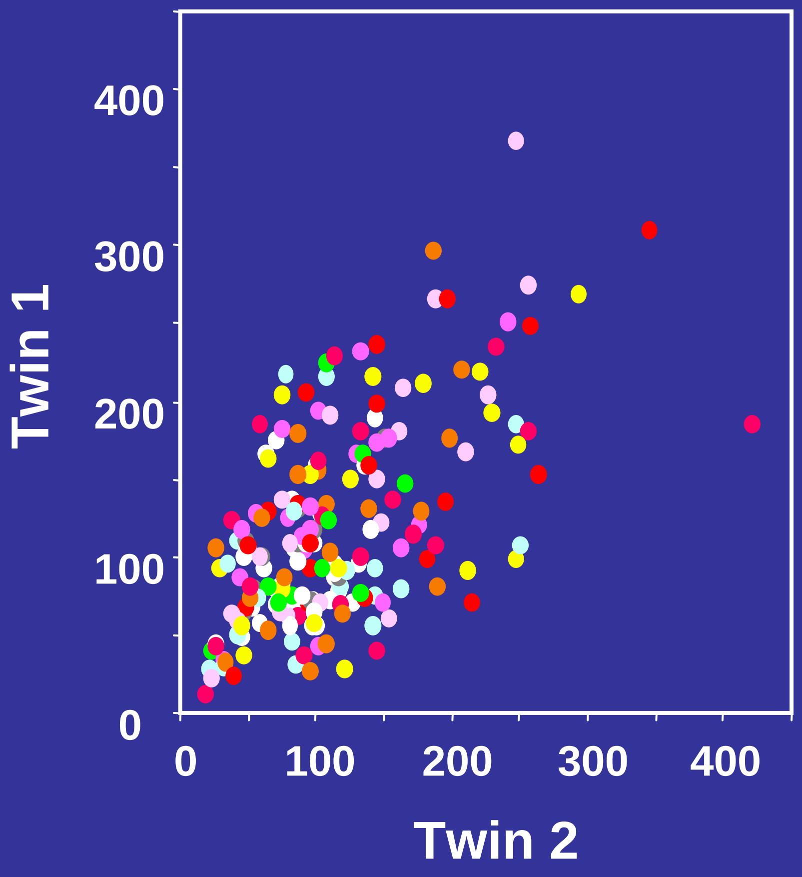
(9 STR markers + sex)

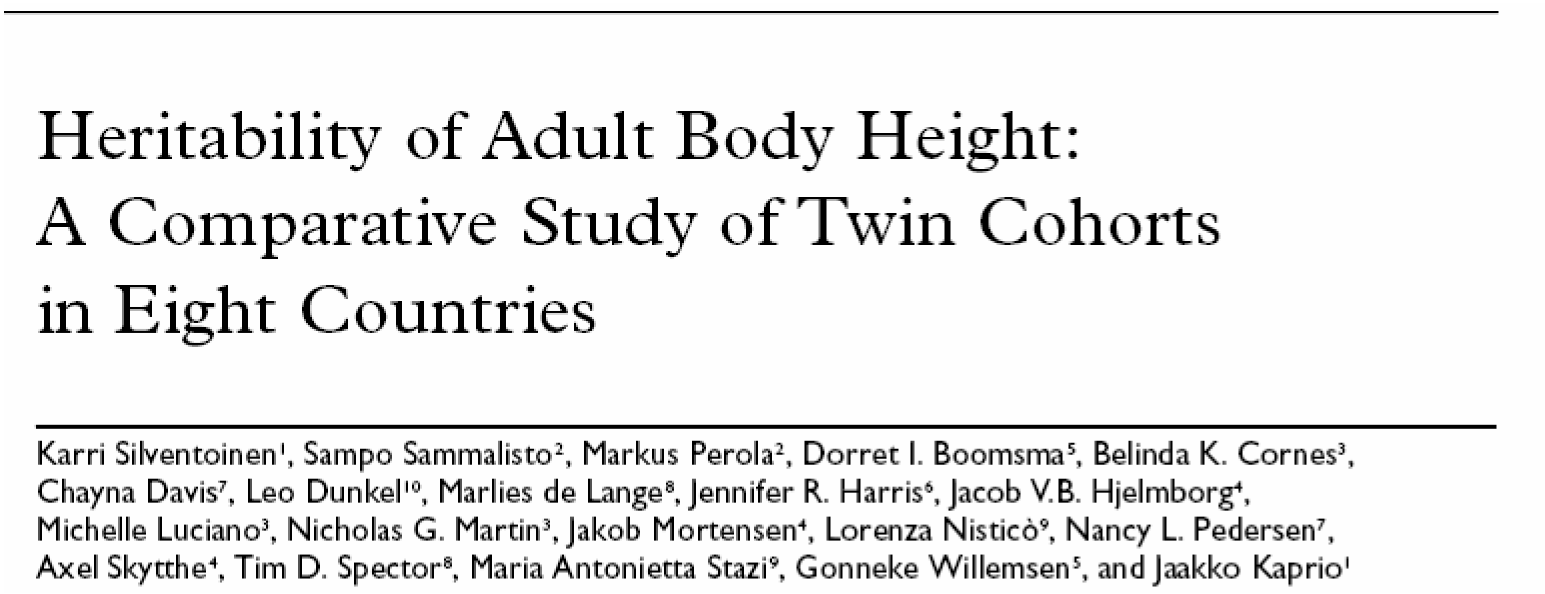
Total mole count for MZ and DZ twins

MZ twins - 153 pairs, r = 0.94



DZ twins - 199 pairs, r = 0.60





Heritability of Adult Body Height: A Comparative Study of Twin Cohorts in Eight Countries

Karri Silventoinen[1], Sampo Sammalisto[2], Markus Perola[2], Dorret I. Boomsma[5], Belinda K. Cornes[3], Chayna Davis[7], Leo Dunkel[10], Marlies de Lange[8], Jennifer R. Harris[6], Jacob V.B. Hjelmborg[4], Michelle Luciano[3], Nicholas G. Martin[3], Jakob Mortensen[4], Lorenza Nisticò[9], Nancy L. Pedersen[7], Axel Skytthe[4], Tim D. Spector[8], Maria Antonietta Stazi[9], Gonneke Willemsen[5], and Jaakko Kaprio[1]

Twin Research 6: 399-408

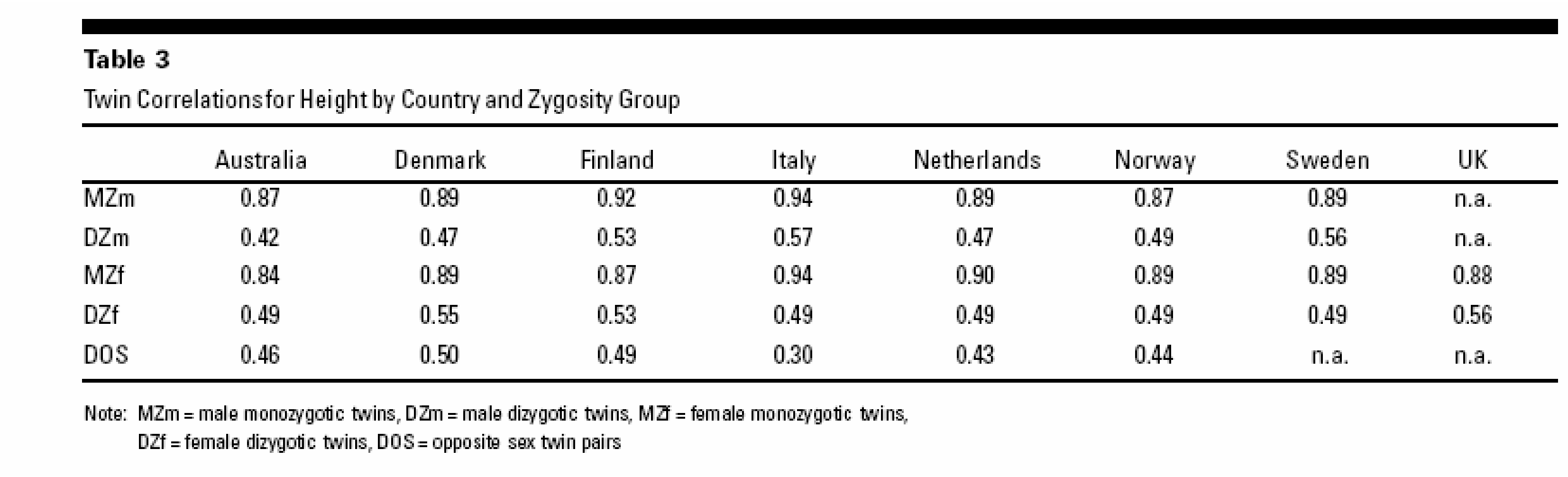


Table 3

Twin Correlations for Height by Country and Zygosity Group

	Australia	Denmark	Finland	Italy	Netherlands	Norway	Sweden	UK
MZm	0.87	0.89	0.92	0.94	0.89	0.87	0.89	n.a.
DZm	0.42	0.47	0.53	0.57	0.47	0.49	0.56	n.a.
MZf	0.84	0.89	0.87	0.94	0.90	0.89	0.89	0.88
DZf	0.49	0.55	0.53	0.49	0.49	0.49	0.49	0.56
DOS	0.46	0.50	0.49	0.30	0.43	0.44	n.a.	n.a.

Note: MZm = male monozygotic twins, DZm = male dizygotic twins, MZf = female monozygotic twins, DZf = female dizygotic twins, DOS = opposite sex twin pairs

Table 4

Estimates of Variance Components and Heritabilities for Height

	Men							Women						
	Model	Va	Vc	Ve	Vp	h^2	$\Delta\chi^2_1$	Model	Va	Vc	Ve	Vp	h^2	$\Delta\chi^2_1$
Australia	ACE	40.26	0.00	6.30	46.60	0.87	—	ACE	33.80	6.00	7.60	47.40	0.71	—
	AE	40.26		6.30	46.60	0.87	0.00	AE	39.27		7.47	46.74	0.84	4.86*
Denmark	ACE	37.20	1.90	5.00	44.20	0.84	—	ACE	29.50	6.60	4.20	40.30	0.73	—
	AE	38.80		5.00	43.80	0.89	0.55	AE	35.20		4.20	39.40	0.89	13.38***
Finland	ACE	34.28	6.98	3.77	45.03	0.76	—	ACE	24.30	6.10	4.30	34.70	0.70	—
	AE	40.10		3.71	43.81	0.89	3.51	AE	29.61		4.25	33.86	0.87	5.25*
Italy	ACE	37.48	12.90	3.29	53.67	0.70	—	ACE	25.57	4.39	2.31	32.27	0.79	—
	AE	48.31		3.25	51.56	0.94	2.60	AE	29.34		2.30	31.64	0.93	0.99
Netherlands	ACE	38.71	5.49	5.66	49.86	0.78	—	ACE	33.49	2.23	3.94	39.65	0.84	—
	AE	43.66		5.62	49.28	0.89	1.20	AE	35.50		3.92	39.42	0.90	0.58
Norway	ACE	33.32	4.47	5.47	43.26	0.77	—	ACE	30.00	3.34	4.28	37.66	0.79	—
	AE	37.17		5.40	42.57	0.87	2.47	AE	32.95		4.25	37.19	0.89	2.33
Sweden	ACE	29.80	4.10	5.00	38.90	0.77	—	ACE	25.94	1.08	3.48	30.50	0.85	—
	AE	33.32		4.94	38.26	0.87	14.44***	AE	26.90		3.50	30.40	0.89	1.87
UK	ACE							ACE	26.96	8.16	4.56	39.68	0.68	—
	AE							AE	33.89		4.34	38.23	0.89	8.21**

Note: Va = additive genetic variance, Vc = shared environmental variance, Ve = specific environmental variance, Vp = total phenotypic variance,
h^2 = heritability estimate, $\Delta\chi^2$ = change in the χ^2-values between AE and ACE models
*$p < .05$, **$p < .01$, ***$p < .001$

Genetic covariance between relatives

$\mathrm{cov}_G(y_i, y_j) = a_{ij}\sigma_A^2 + d_{ij}\sigma_D^2$

a = additive coefficient of relationship
= 2 * coefficient of kinship (= $E(\pi)$)

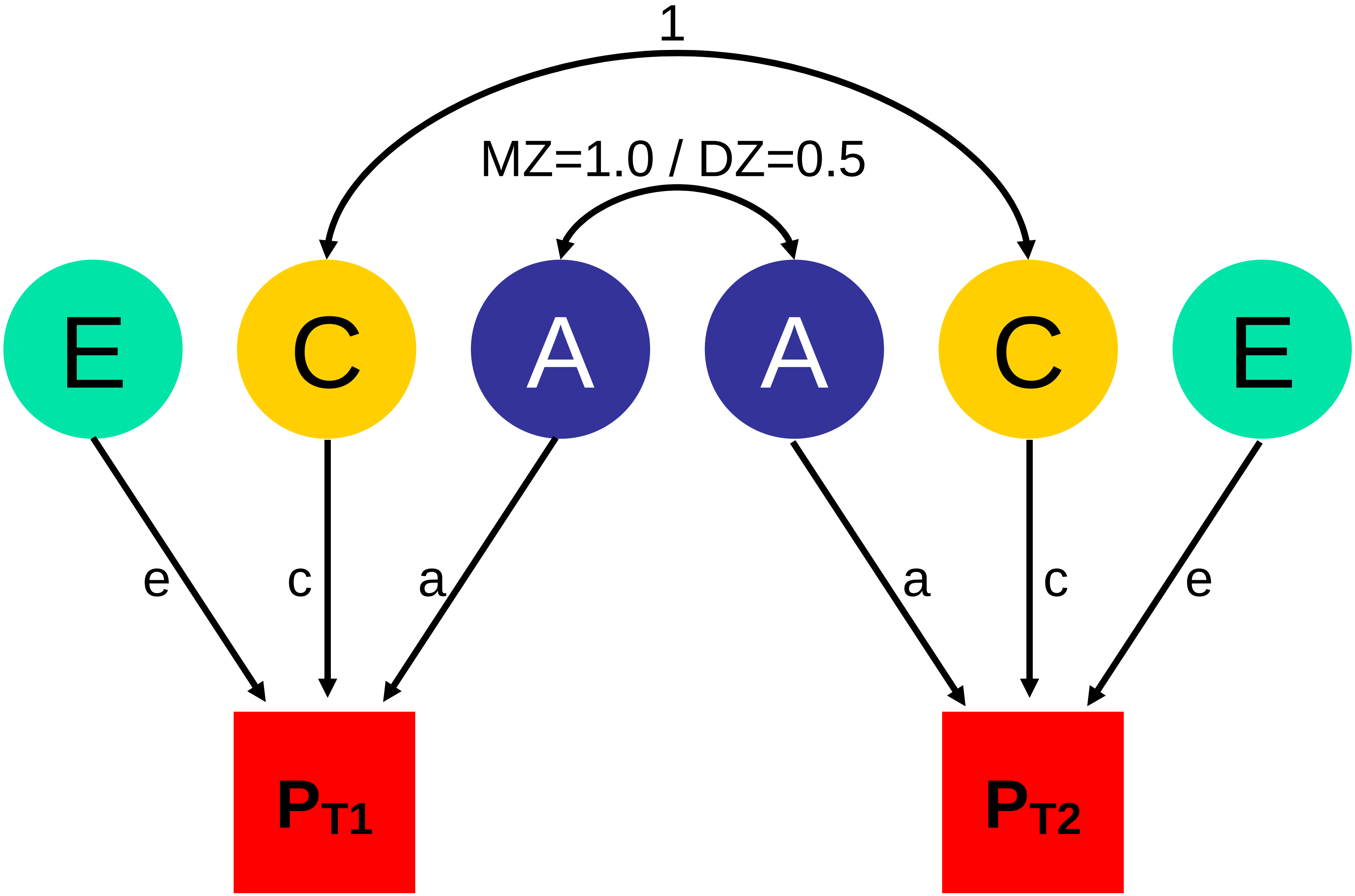
d = coefficient of fraternity
= Prob(2 alleles are IBD)

Examples

Relatives	**a**	**d**
Parent-offspring	½	0
MZ twins	1	1
Fullsibs	½	¼
Double first cousins	¼	$^{1}/_{16}$

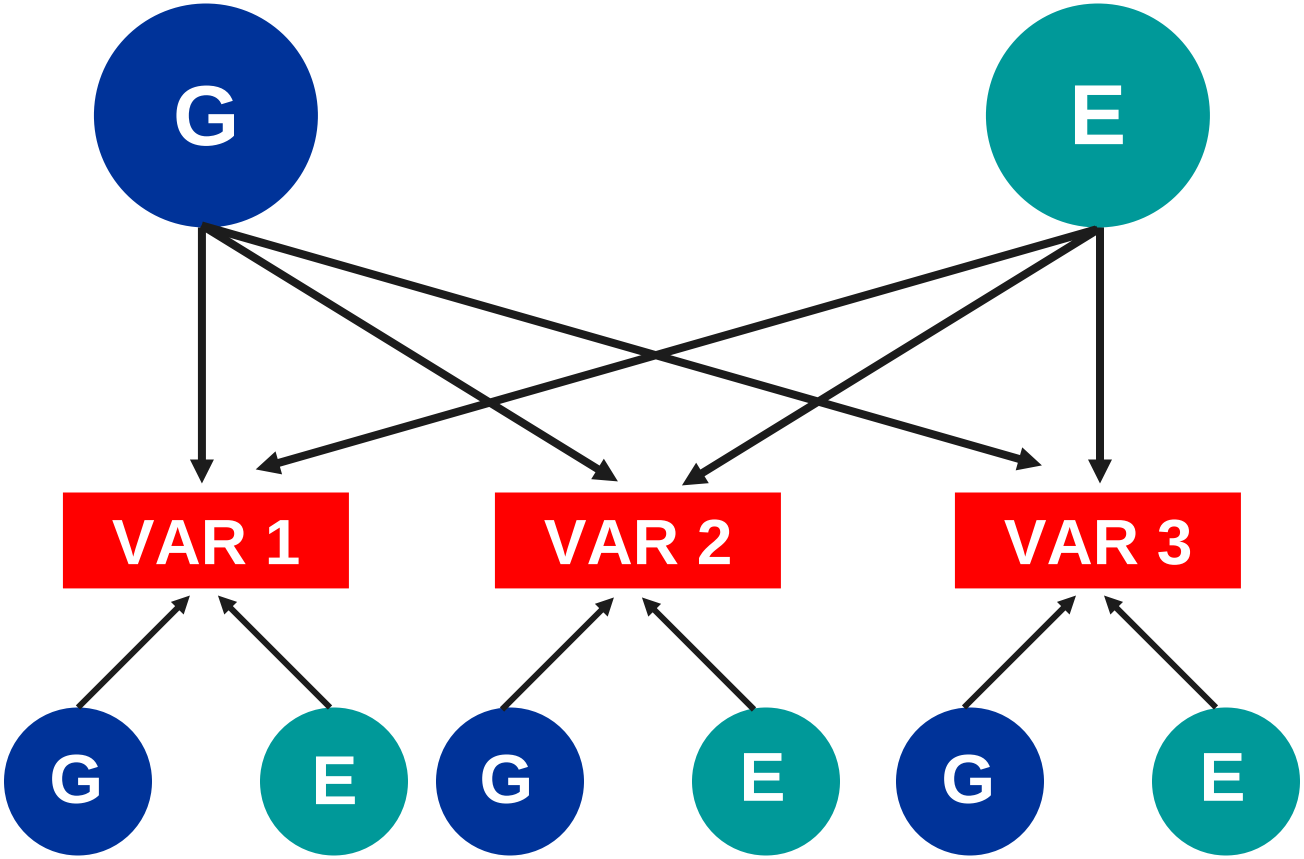
[Lynch & Walsh 1998]

ACE Model for twin data

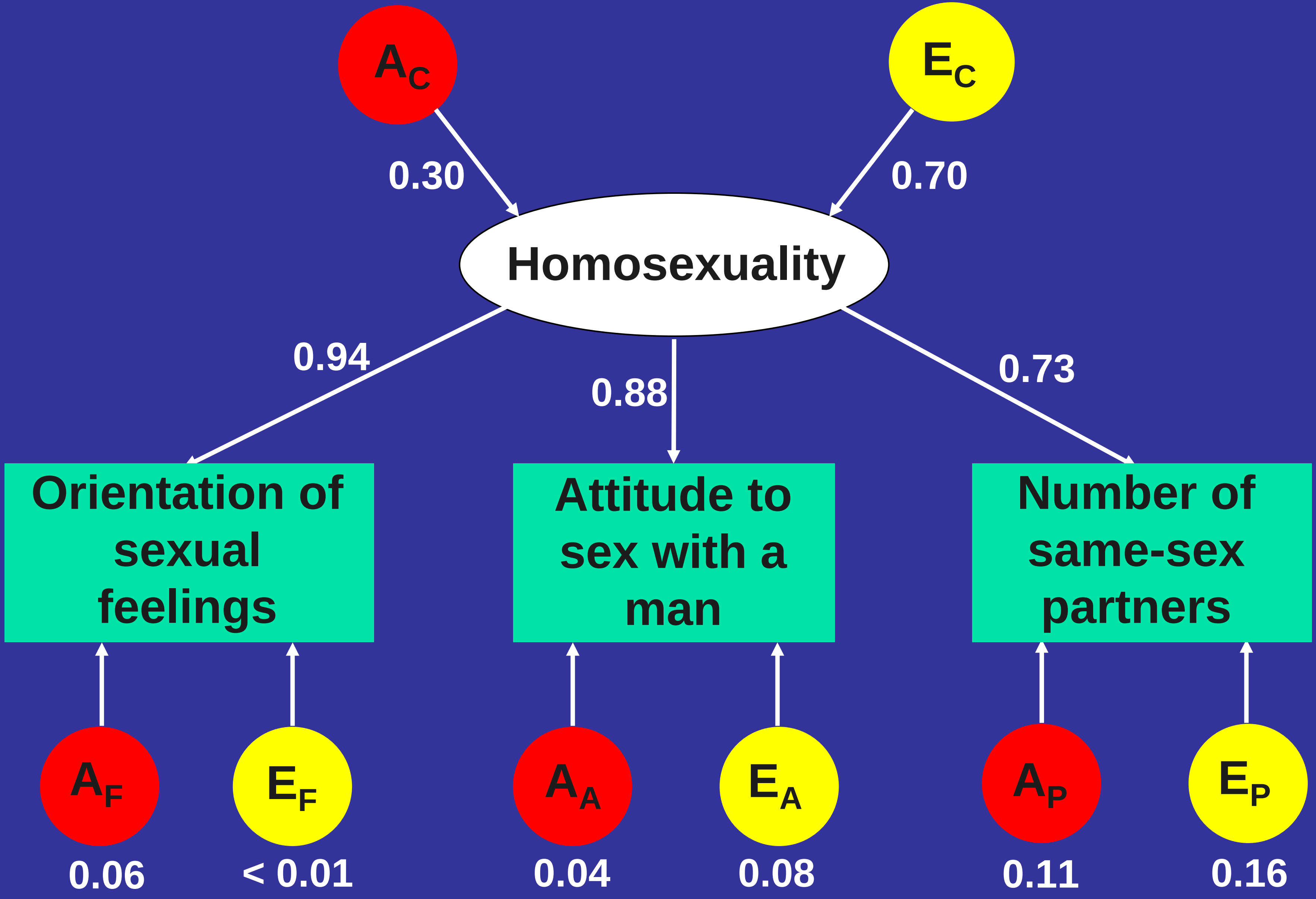


Structural equation modeling

- Both continuous and categorical variables
- Systematic approach to hypothesis testing
- Tests of significance
- Can be extended to:
  - More complex questions
  - Multiple variables
  - Other relatives

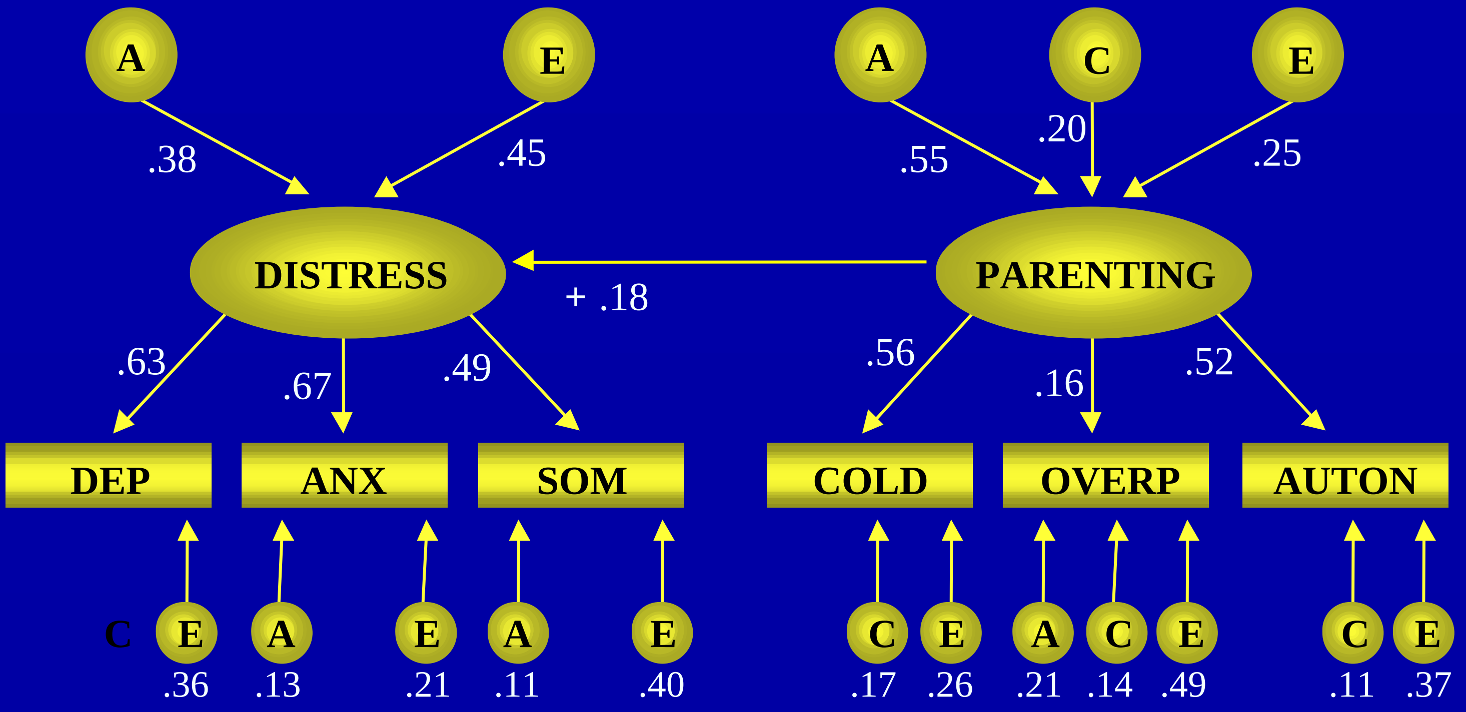

G
E
VAR 1
VAR 2
VAR 3
G
E
G
E
G
E

Sources of variation in male sexual orientation



Direction of causation modeling with cross-sectional twin data

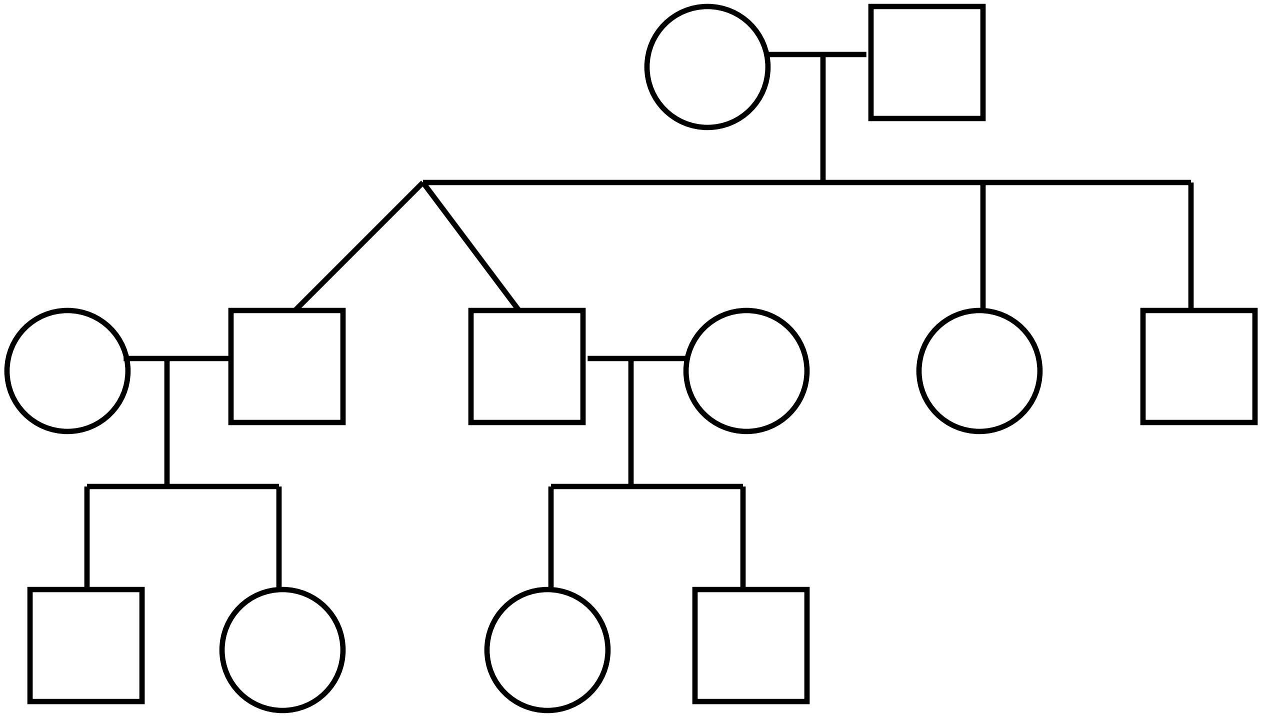
Model	χ^2	df	$\Delta\chi^2$	AIC
Full Bivariate	145.66	107		-69.34
Reciprocal	146.00	108	.34	-70.00
Distress → Parenting	161.74	109	16.08	-56.26
Parenting → Distress	146.71	109	1.05	-71.29
No causation	376.29	110	230.63	156.29
Final	**151.26**	**116**	**5.60**	**-80.74**



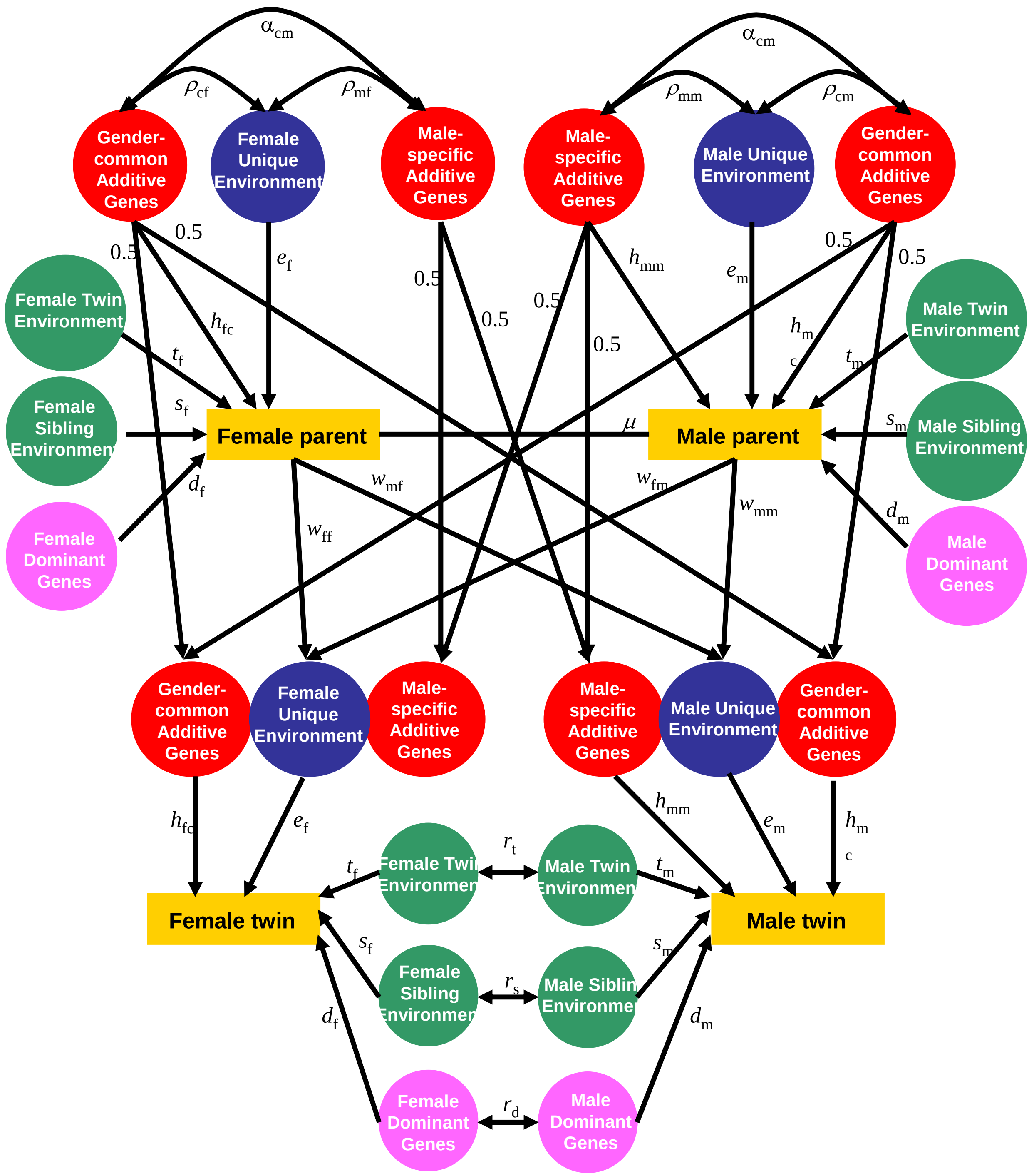
Designs to disentangle G + E

- **Family studies – G + C confounded**
- **MZ twins alone – G + C confounded**
- **MZ twins reared apart – rare, atypical, selective placement ?**
- **Adoptions – increasingly rare, atypical, selective placement ?**
- **MZ and DZ twins reared together**
- **Extended twin design**

Extended Twin Design



Truett, et al (1994) Behavior Genetics, 24: 35-49



Extended kinship model

- twins
- siblings
- parents
- children
- grandparents
- aunts, uncles
- cousins

Estimated contributions of sources of variation to differences in stature and conservatism

	Proportion of total variation (%)			
	Stature		Conservatism	
Source	Males	Females	Males	Females
Genetic				
Additive	55.8	59.6	35.5	19.8
Assortment	16.1	17.2	22.2	12.4
Dominance	9.4	6.9	6.7	12.5
"Total genetic"	83.9	86.7	64.4	44.7
Environment				
Maternal	0.0	0.2	1.5	1.0
Paternal	0.0	0.2	0.0	0.1
Twin	4.7	7.6	0.1	4.2
Sibling	0.0	1.6	0.0	5.2
Within-family	0.0	1.4	17.5	32.4
"Error"	15.3	13.1	22.9	4.1
G-E covariance	−1.2	−7.9	−6.2	8.1

Finding QTLs

- Linkage
- Association

We also run a journal

twin research and human genetics

Volume 8 Number 1

February 2005

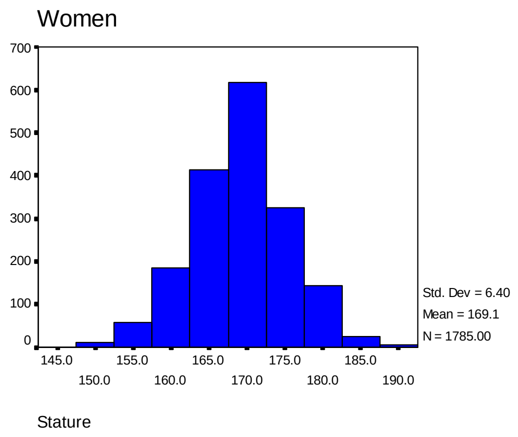
Editor

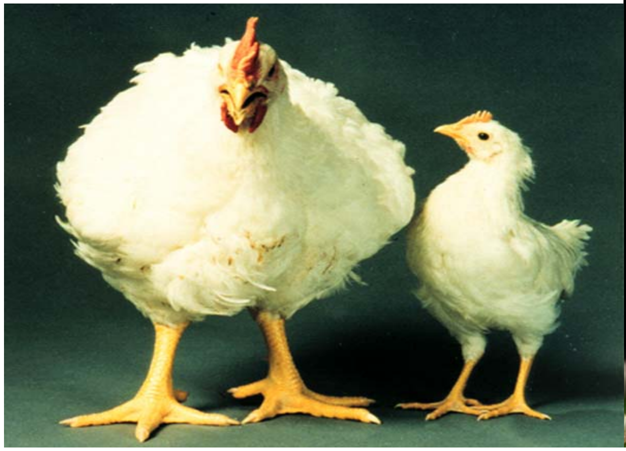
Nicholas G. Martin

- Editor: Nick Martin
- Editorial assistant + subscriptions: Marisa Grimmer
- Publisher: Australian Academic Press
- Fully online
- http://www.ists.qimr.edu.au/journal.html

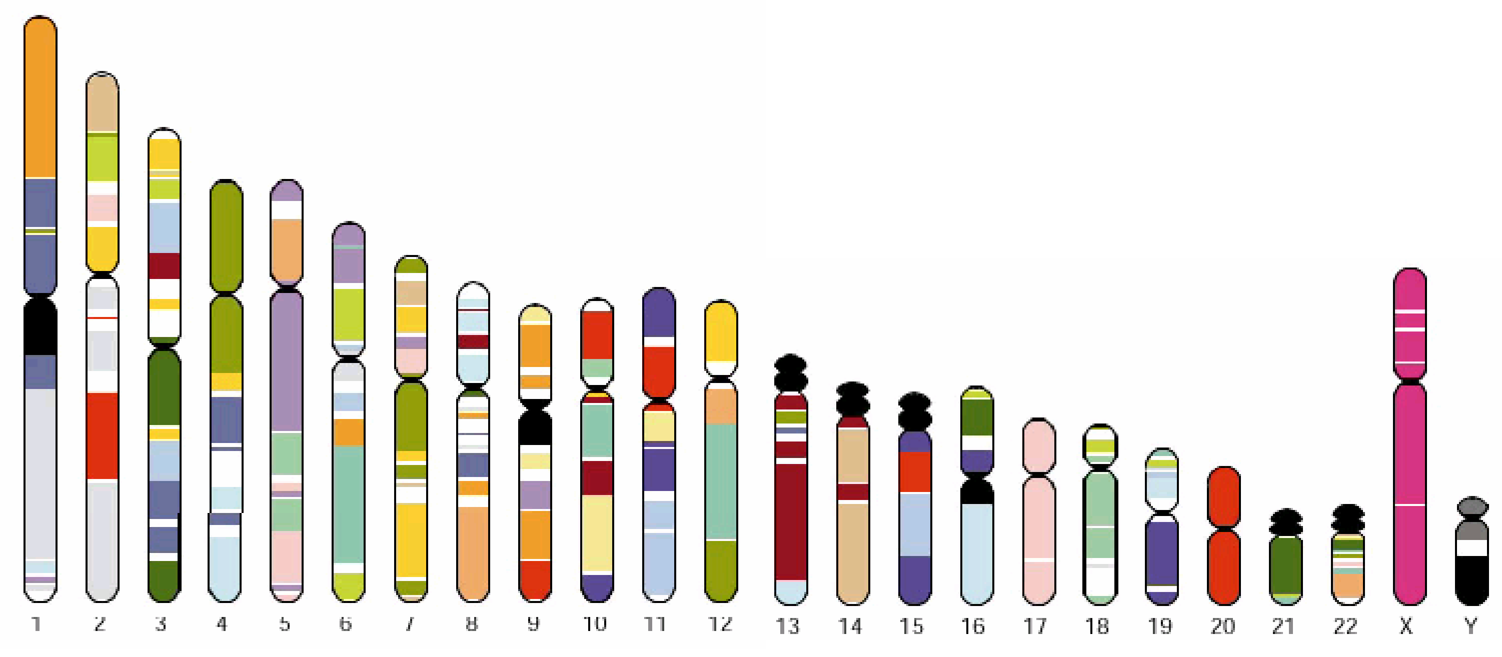
Rationale for QTL analysis

- QTL = quantitative trait locus
- Biology: Understanding genetic variation by dissecting complex traits
  - basic biology
  - applications in agriculture
  - applications in medicine

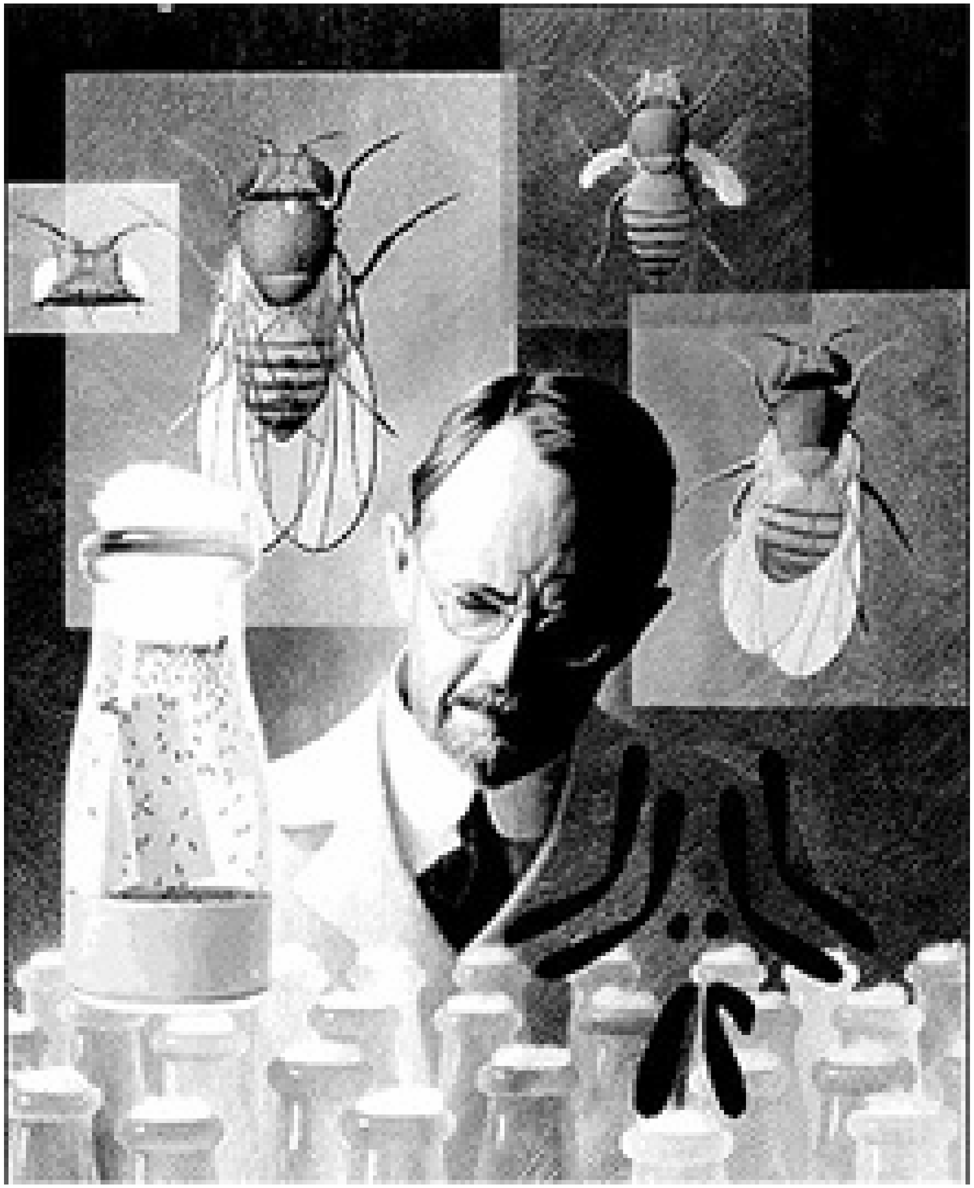




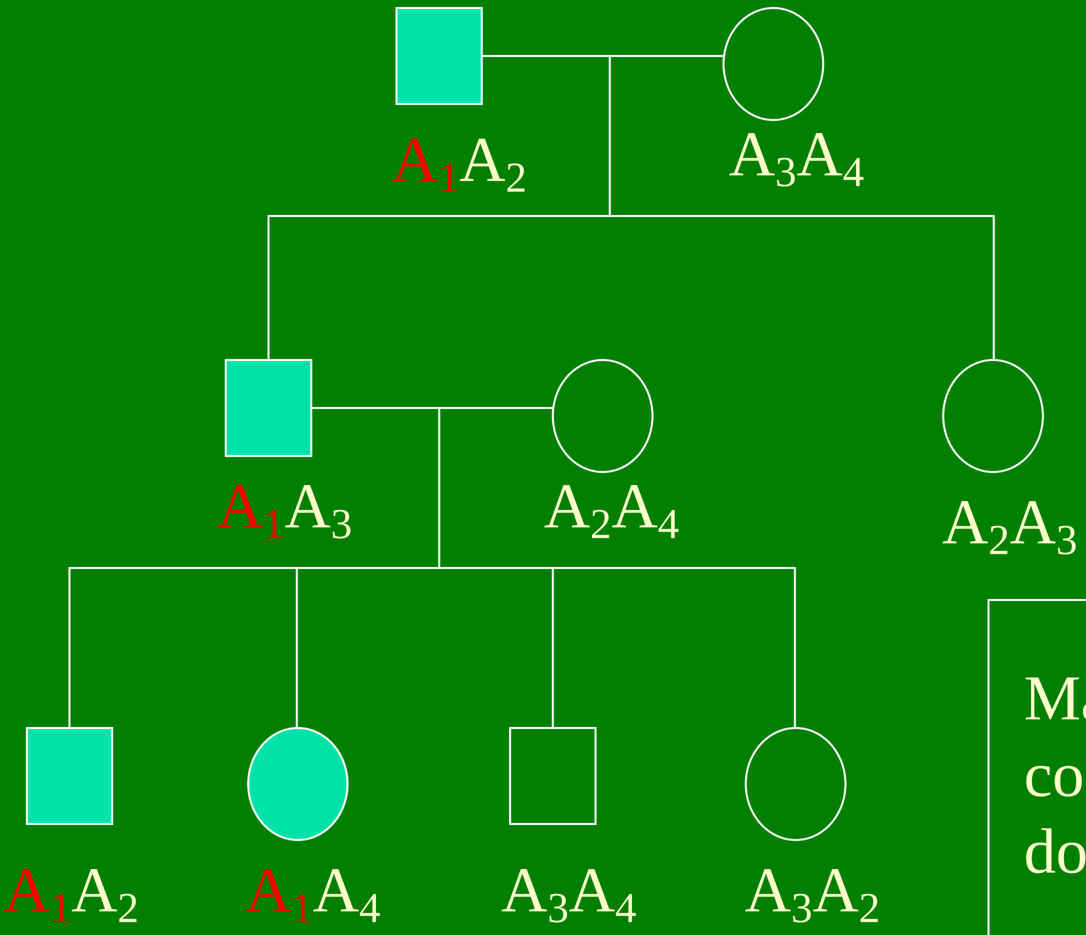
Linkage analysis



Thomas Hunt Morgan – discoverer of linkage

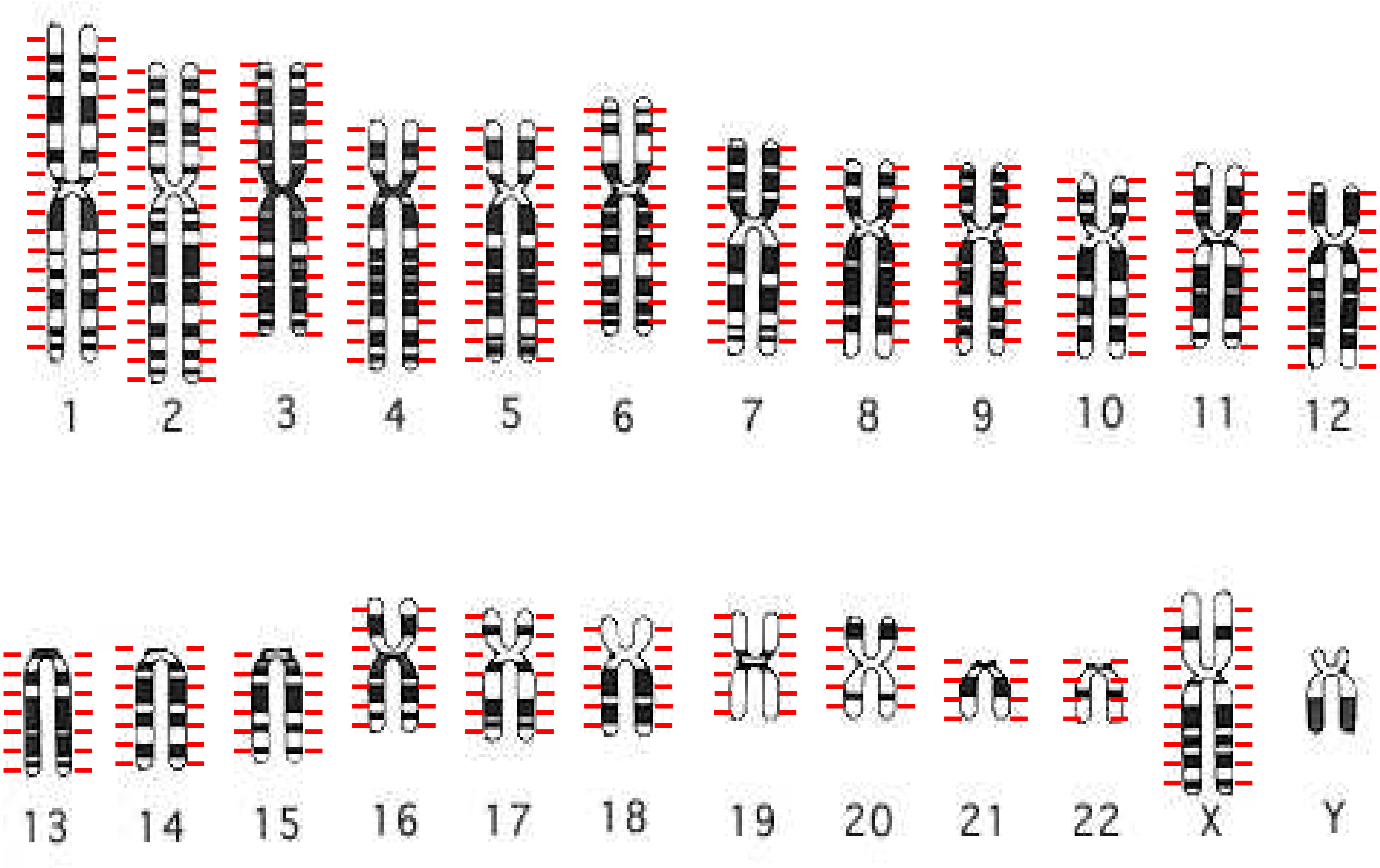


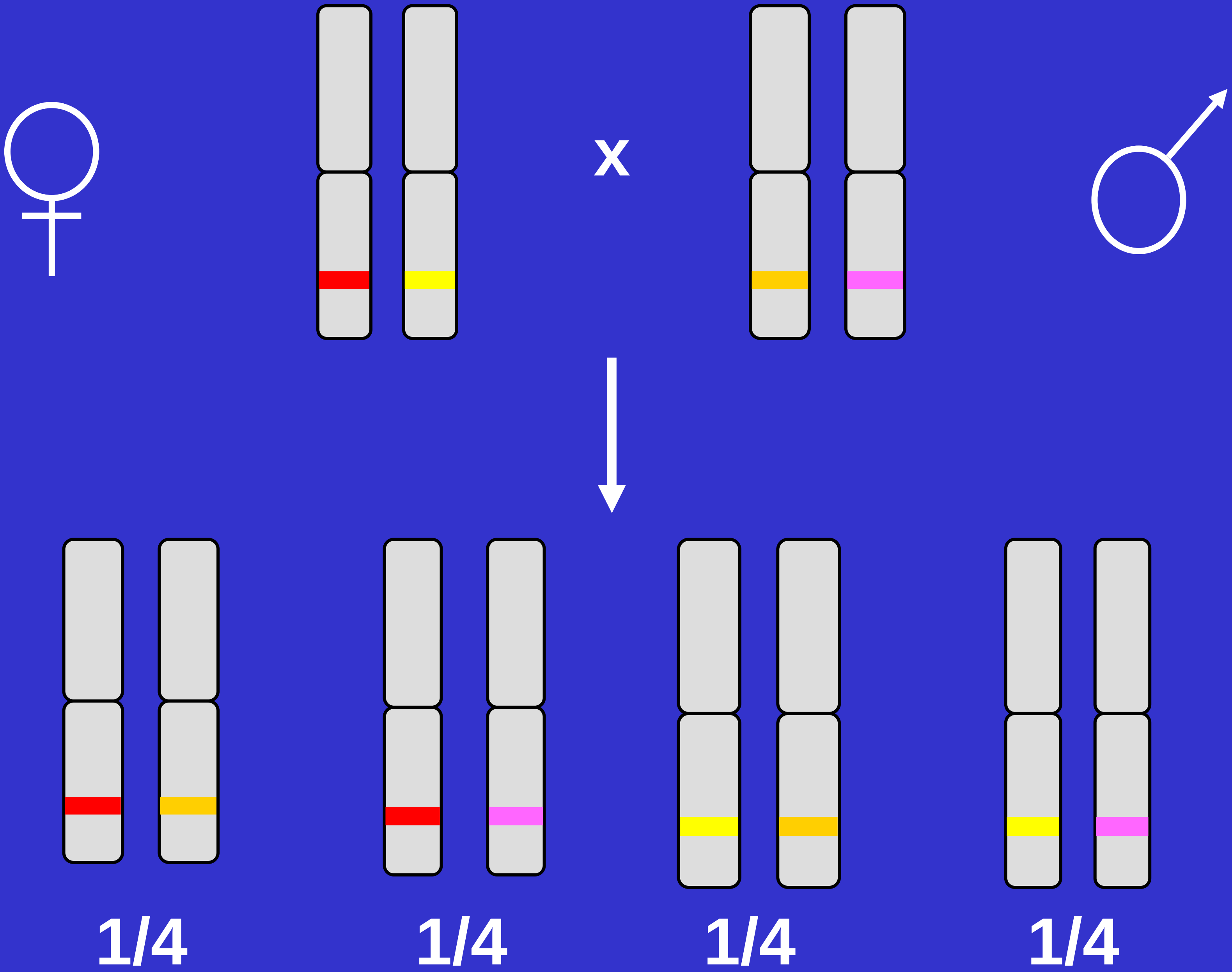
Linkage = Co-segregation



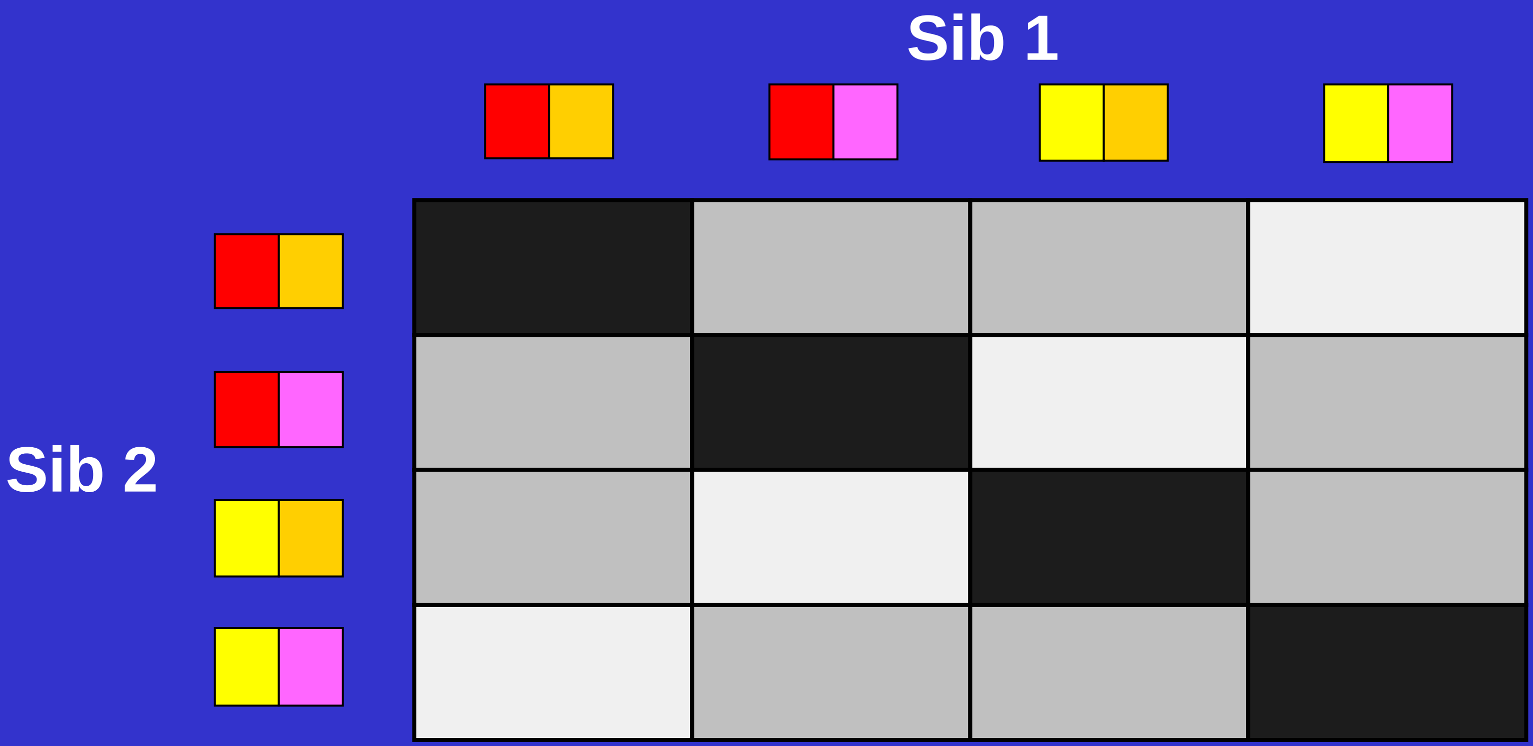
Marker allele A_1 cosegregates with dominant disease 🟩

Linkage Markers…




♀
x
♂
1/4
1/4
1/4
1/4

IDENTITY BY DESCENT



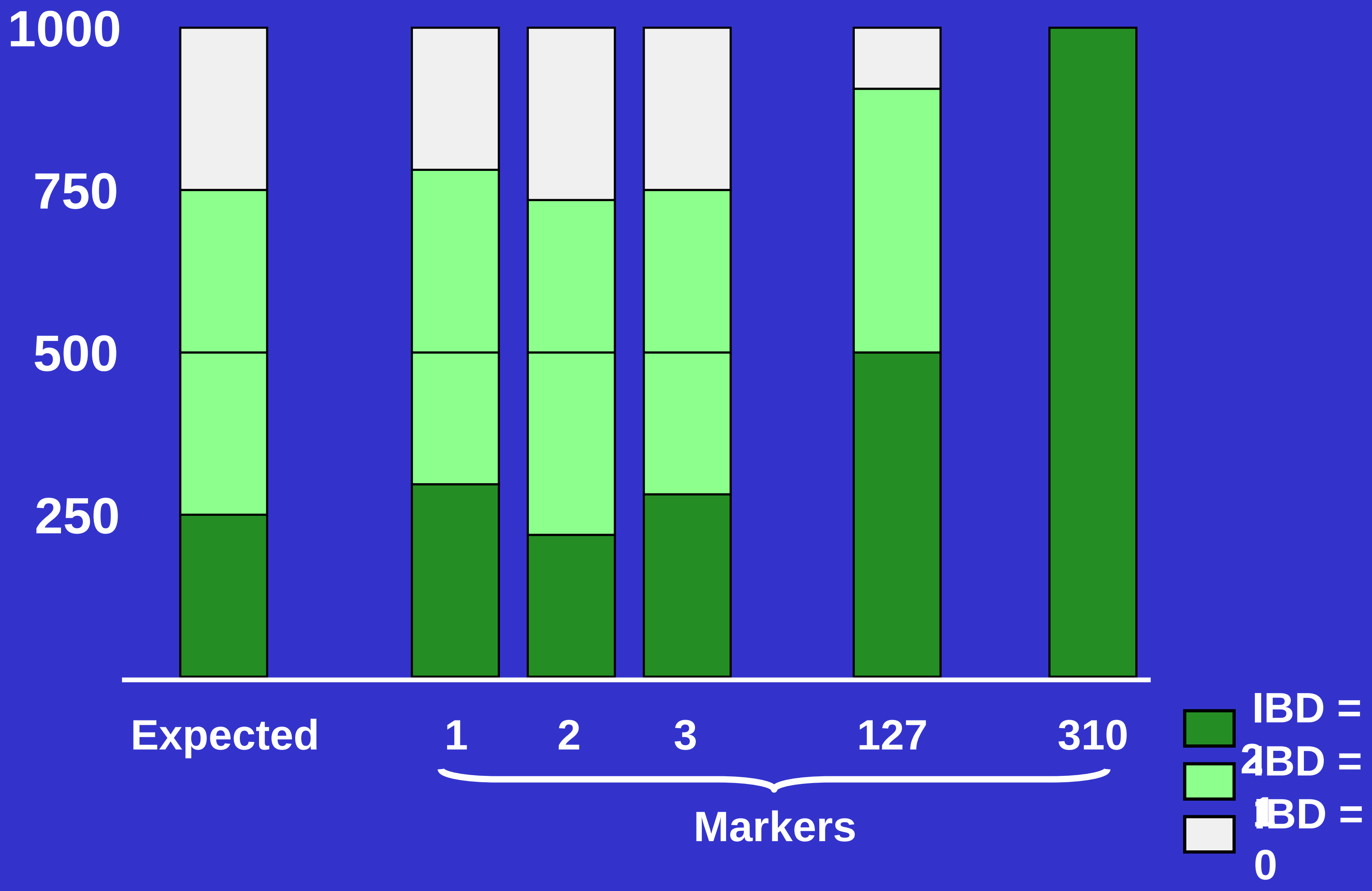
■ 4/16 = 1/4 sibs share BOTH parental alleles IBD = 2

▨ 8/16 = 1/2 sibs share ONE parental allele IBD = 1

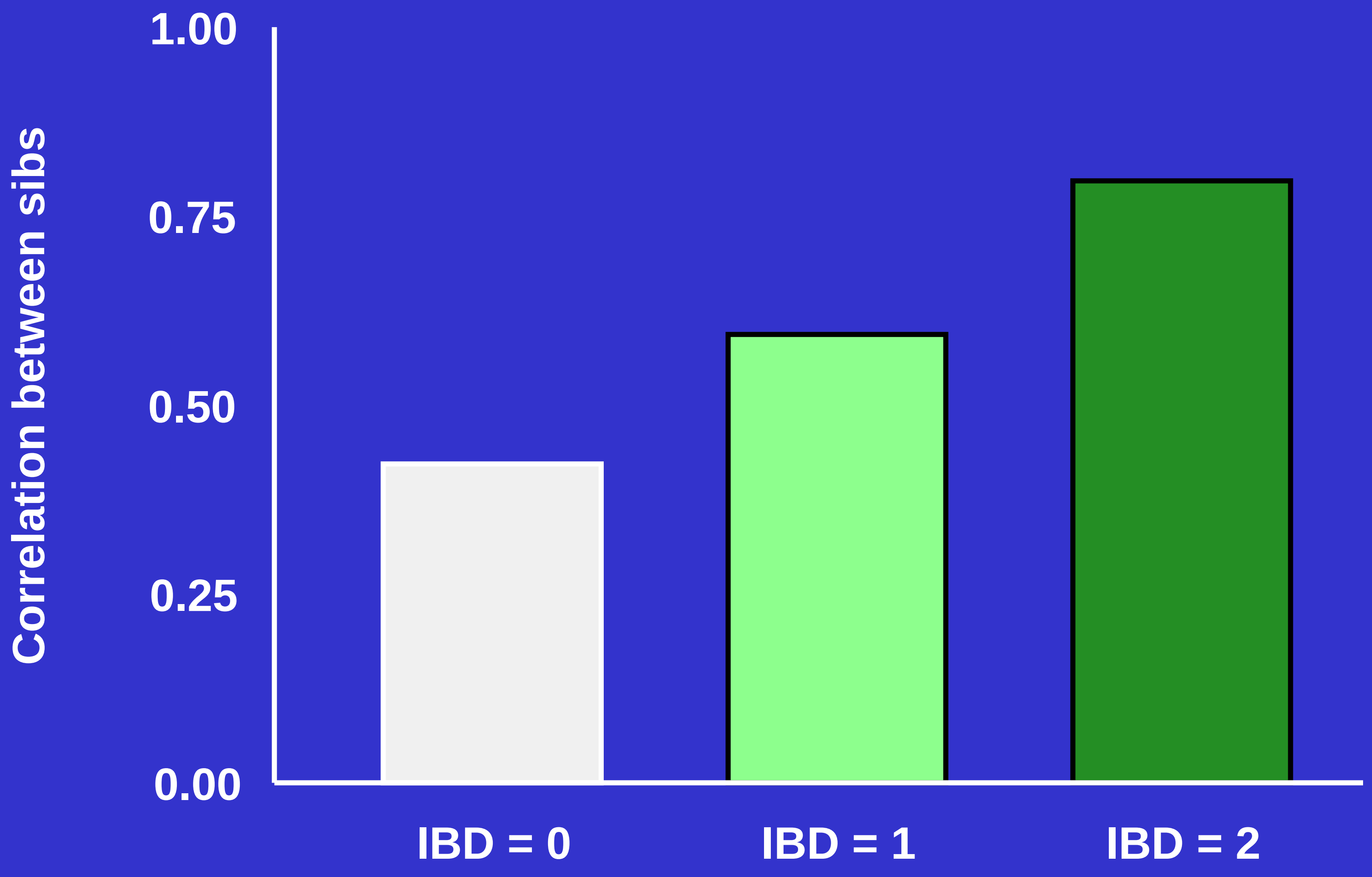
□ 4/16 = 1/4 sibs share NO parental alleles IBD = 0

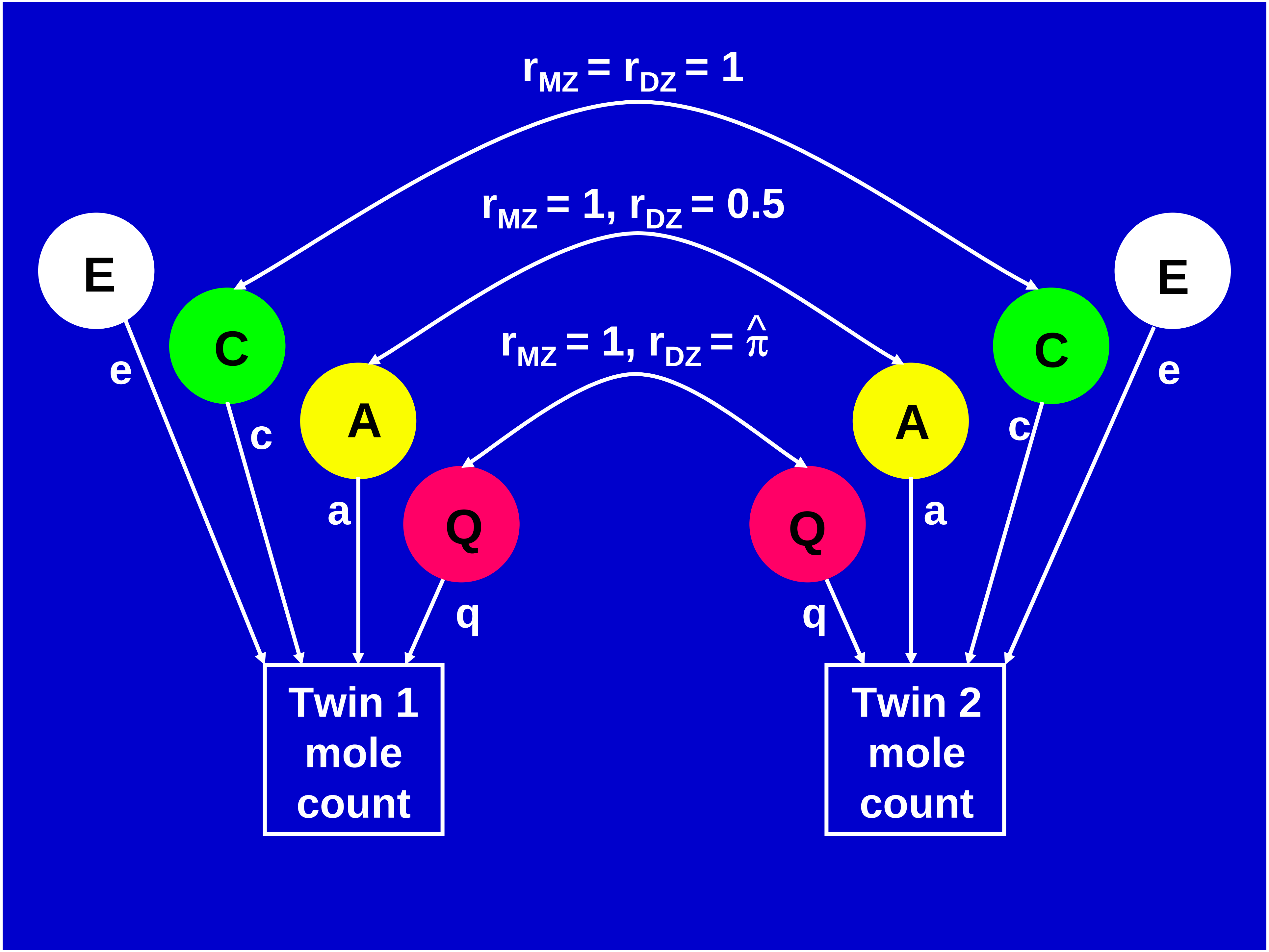
For disease traits (affected/unaffected)

Affected sib pairs selected



For continuous measures
Unselected sib pairs





$r_{MZ} = r_{DZ} = 1$

$r_{MZ} = 1, r_{DZ} = 0.5$

$r_{MZ} = 1, r_{DZ} = \hat{\pi}$