Genetics: history and context

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April 2007

Proof: There IS a gene that makes you fat

By FIONA MACRAE

Scientists have discovered a rogue gene behind the obesity epidemic.

They say the genetic make-up of one in six Britons increases their risk of becoming dangerously overweight by 70 per cent and their chance of developing diabetes by a half.

The study, led by geneticists from Oxford University and the Peninsula Medical School in Exeter, could lead to ways of treating and even preventing the condition that blights the health of millions.

It could pave the way for tests for people to find out if they carried the gene. One day, couples could even choose to have babies free of ?fat? genes.

The findings may also help explain why some people find it harder to lose weight than others.

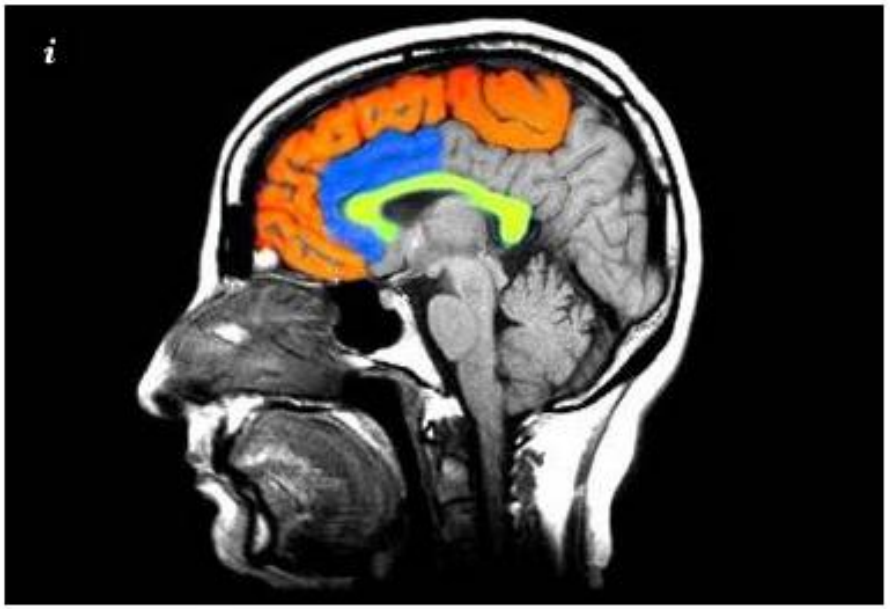
The INDEPENDENT

Unlocked: the secrets of schizophrenia

Scientific breakthrough offers hope of new treatments for mental condition

BY STEVE CONNOR, SCIENCE EDITOR | THURSDAY 02 JULY 2009

July 2009



Scientists have discovered a remarkable similarity between the genetic faults behind both schizophrenia and manic depression in a breakthrough that is expected to open the way to new treatments for two of the most common mental illnesses, affecting millions of people.

Previously doctors had assumed that the two conditions were quite separate. But new research shows for the first time that both have a common genetic basis that leads people to develop one or other of the two illnesses.

Suggested Topics

- Schizophrenia
- Research
- Aberdeen
- The Brain

Sept 2010

The Telegraph

ADHD 'caused by genetic faults'

A genetic basis for Attention Deficit Hyperactivity Disorder (ADHD) has been discovered by British scientists, who say their research explodes the myth that it is just an excuse for bad parenting.

By **Stephen Adams**, Medical Correspondent
6:30AM BST 30 Sep 2010

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Children with the condition, thought to affect one in 50, are more likely to carry particular faulty sections of genetic code than those without it.

Researchers at Cardiff University made their conclusions after studying the DNA of 366 children diagnosed with ADHD and more than 1,000 children without it.

BBC Mobile NEWS

Page last updated at 08:50 GMT, Friday, 14 November 2008

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India battles diabetes 'epidemic'

By Adam Mynott
BBC News, Chennai, India

Inside an Indian mobile diabetes clinic

The latest figures for the prevalence of diabetes are two years old and by common medical consent hopelessly out of date.

It is estimated that up to three million people die from the disease every year, and over a quarter of a billion people are affected.

nature genetics

Genome-wide association study in individuals of South Asian ancestry identifies six new type 2 diabetes susceptibility loci

Jaspal S Kooner[1–3,46], Danish Saleheen[4,5,46], Xueling Sim[6,46], Joban Sehmi[1,2,46], Weihua Zhang[7,46], Philippe Frossard[4,46], Latonya F Been[8], Kee-Seng Chia[6,9], Antigone S Dimas[10,11], Neelam Hassanali[12], Tazeen Jafar[13,14], Jeremy B M Jowett[15], Xinzhong Li[1], Venkatesan Radha[16], Simon D Rees[17,18], Fumihiko Takeuchi[19], Robin Young[5], Tin Aung[20,21], Abdul Basit[22], Manickam Chidambaram[16], Debashish Das[2], Elin Grundberg[23], Åsa K Hedman[11], Zafar I Hydrie[22], Muhammed Islam[13], Chiea-Chuen Khor[6,21,24], Sudhir Kowlessur[25], Malene M Kristensen[15], Samuel Liju[16], Wei-Yen Lim[6], David R Matthews[12], Jianjun Liu[24], Andrew P Morris[11], Alexandra C Nica[10], Janani M Pinidiyapathirage[26], Inga Prokopenko[11], Asif Rasheed[4], Maria Samuel[4], Nabi Shah[4], A Samad Shera[27], Kerrin S Small[23,28], Chen Suo[6], Ananda R Wickremasinghe[26], Tien Yin Wong[20,21,29], Mingyu Yang[30], Fan Zhang[30], DIAGRAM[31], MuTHER[31], Goncalo R Abecasis[32], Anthony H Barnett[17,18], Mark Caulfield[33], Panos Deloukas[34], Timothy M Frayling[35], Philippe Froguel[36], Norihiro Kato[19], Prasad Katulanda[12,37], M Ann Kelly[17,18], Junbin Liang[30], Viswanathan Mohan[16,38], Dharambir K Sanghera[8], James Scott[1], Mark Seielstad[39], Paul Z Zimmet[15], Paul Elliott[7,40,46], Yik Ying Teo[6,9,24,41,42,46], Mark I McCarthy[11,12,43,46], John Danesh[5,46], E Shyong Tai[9,44–46] & John C Chambers[2,3,7,46]

Six new genes found that trigger diabetes

Pushpa Narayan, TNN Aug 29, 2011, 05.50am IST

Tags: science

CHENNAI: Scientists have found six new genes that trigger diabetes mellitus in South Asians. These genes are responsible for the early onset of diabetes in South Asians, including Indians. Scientists from the UK collaborated with doctors in India, Singapore, Pakistan, Mauritius and Sri Lanka on the study.

This is the first time studies have been conducted in South Asia, where more than 55 million people have diabetes, a majority of them from India and China. So far, scientists have discovered 42 genes associated with diabetes but all these studies were done on Europeans.

Aug 2011

Aims of Genetic Epidemiology

- Quantify the genetic contribution to a disease or trait
  - "Nature vs Nurture"
- Find the gene(s) that cause a disease

- Measure the effect of each gene
  - Within groups of relatives
  - Compare between populations
  - Interactions with environmental factors

How can genetics help us?

- Understanding disease
  - Etiology – what are the biological pathways to disease?
  - Distribution – which groups of people are at greater risk?
  - Control – how could we limit the impact of disease?
- New targets for treatment
  - Drug targets in novel pathways
  - Distribution & evolution of pathogens
- Personalised Medicine
  - Which treatments work on which people
  - Preventing adverse drug reactions
  - Predicting disease risks much earlier in life
- Forensics
- Genealogy

Genetic vs Mainstream Epidemiology

- A gene is an “exposure” / “treatment” / “intervention” / etc
- How do genes differ from variables that are usually studied?

Genetic vs Mainstream Epidemiology

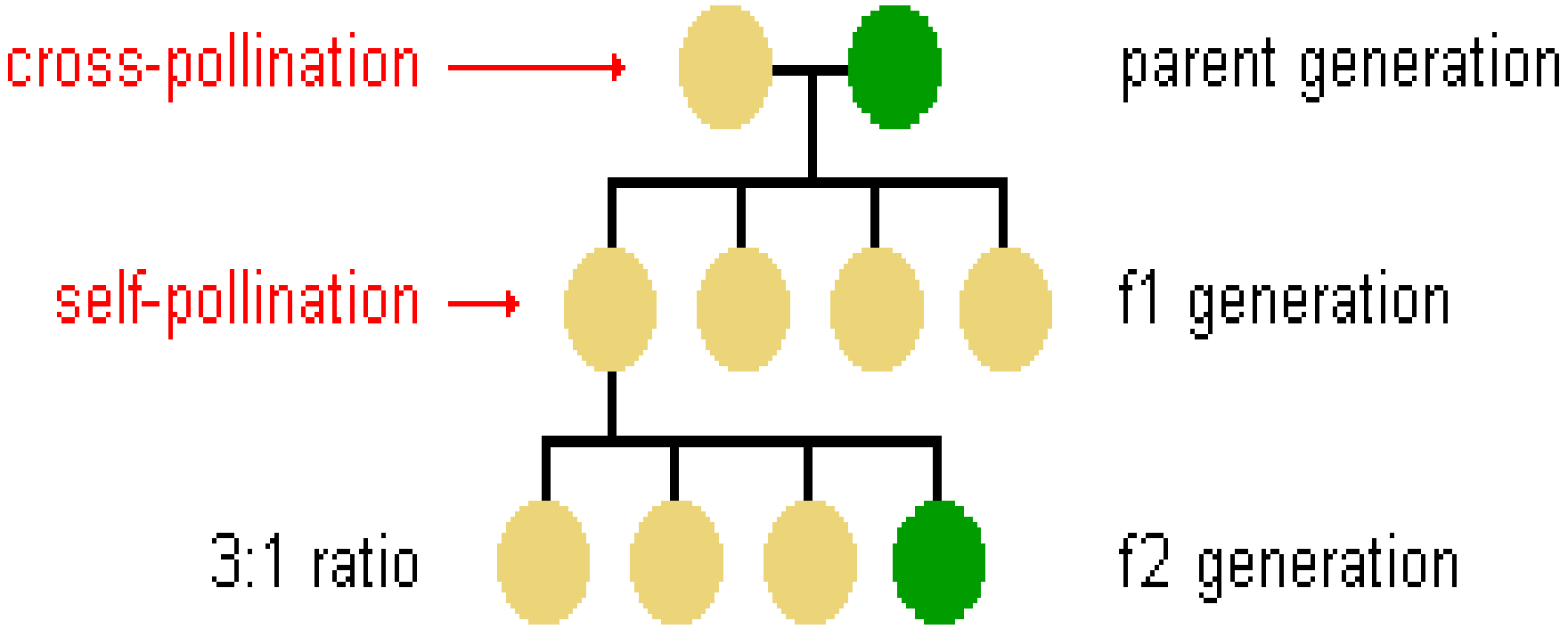
- A gene is an “exposure” / “treatment” / “intervention” / etc
- How do genes differ from variables that are usually studied?
  - Not modifiable: can only intervene on downstream effects
  - Fixed at conception
    - Can measure after disease has occurred
    - Clear causal path from gene to disease
  - Easy to measure
    - Selection bias & confounding less of a problem

Gregor Mendel (1822-1884)

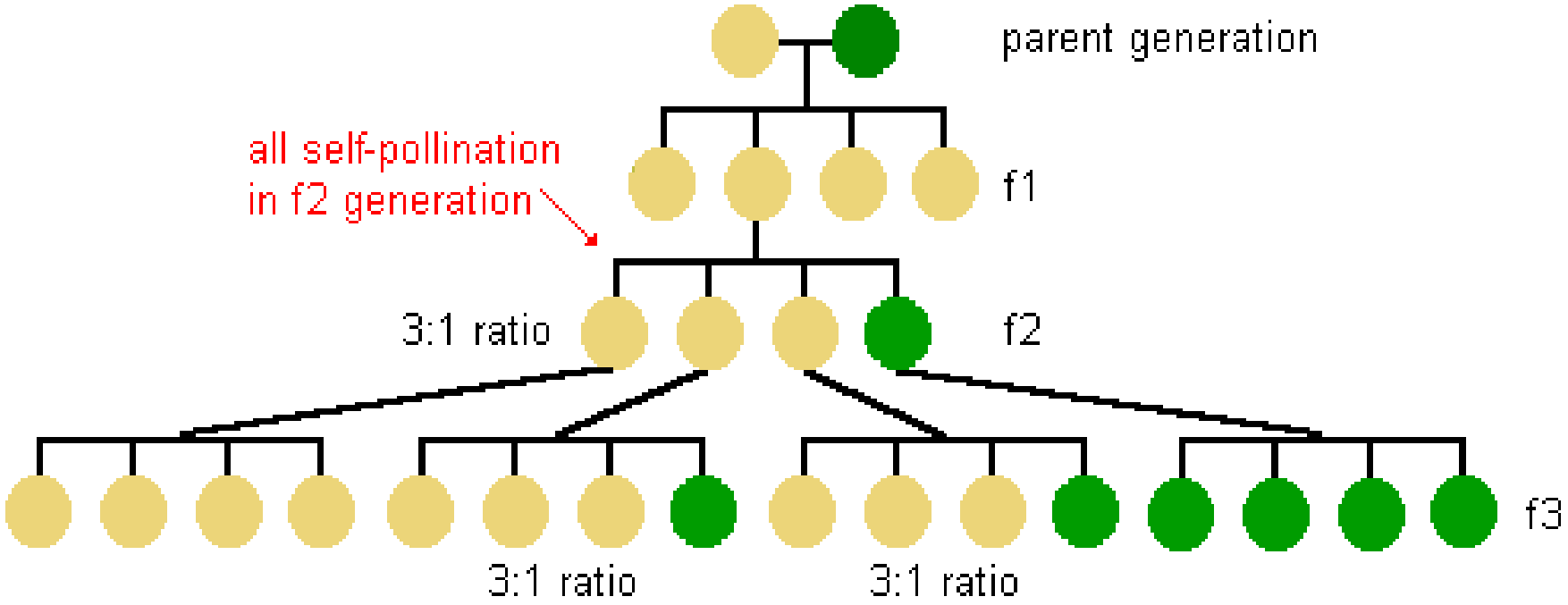
- In 1860 developed theory for inheritance based on statistical analysis of data collected for garden pea plant

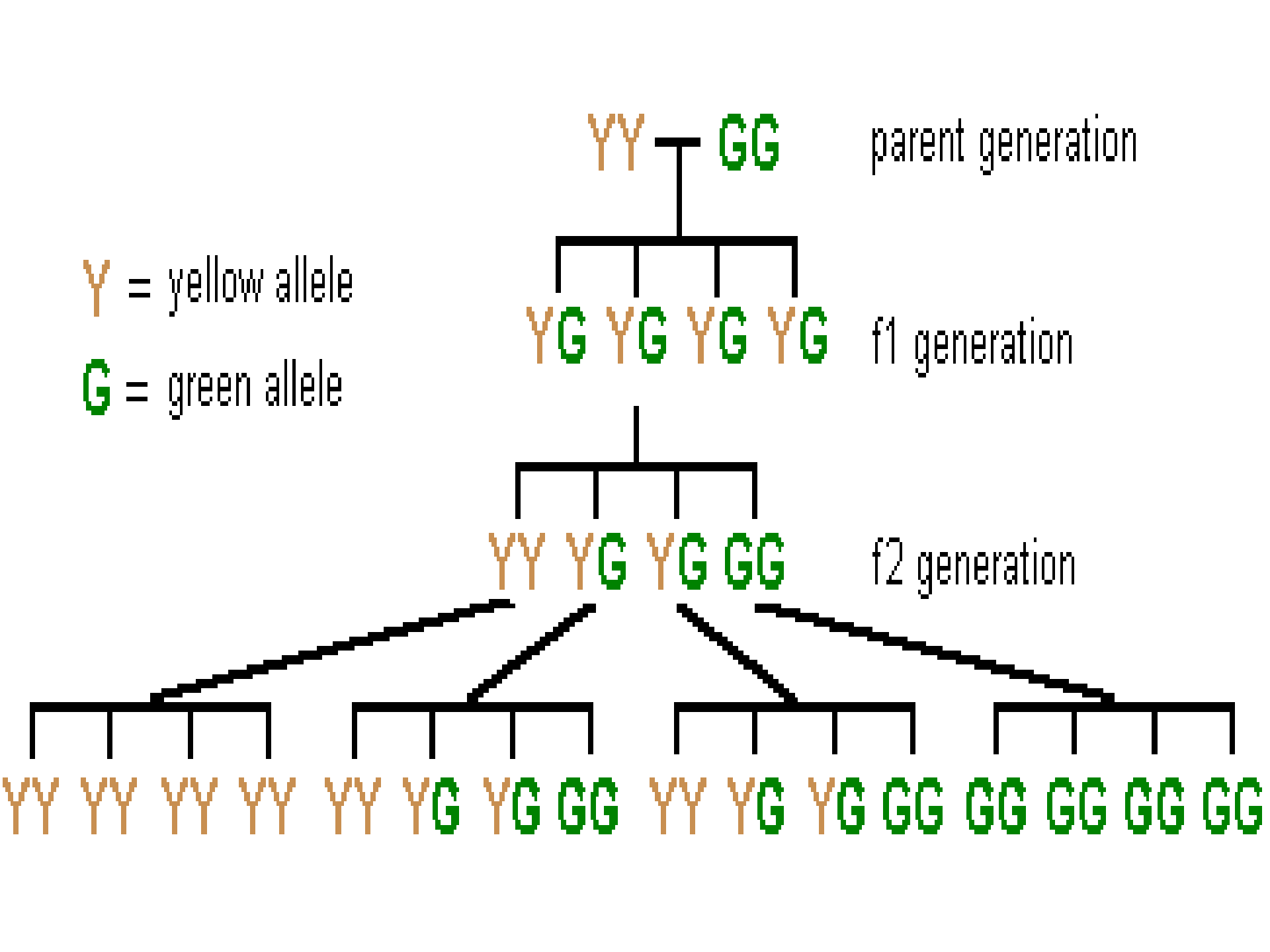
- Mendel's cross pollination used statistical approach to reveal effects of crossing different strains of the common garden pea

Mendel: Experiments on Plant Hybridization



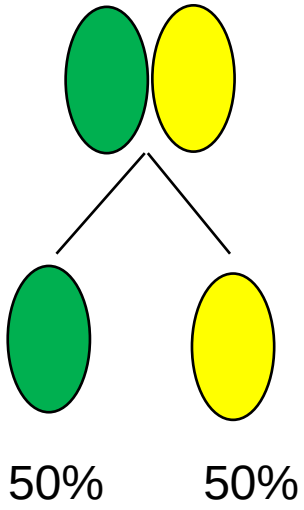
Mendel: Experiments on Plant Hybridization




Y = yellow allele
G = green allele
YY GG
parent generation
YG YG YG YG
f1 generation
YY YG YG GG
f2 generation
YY YY YY YY YY YG YG GG YY YG YG GG GG GG GG GG

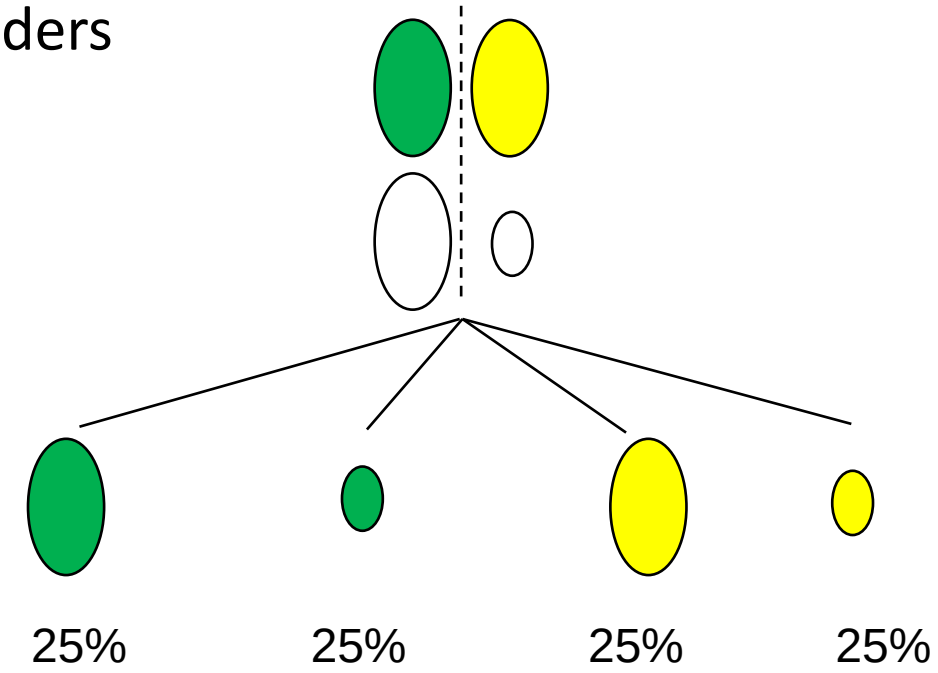
Mendel's first law

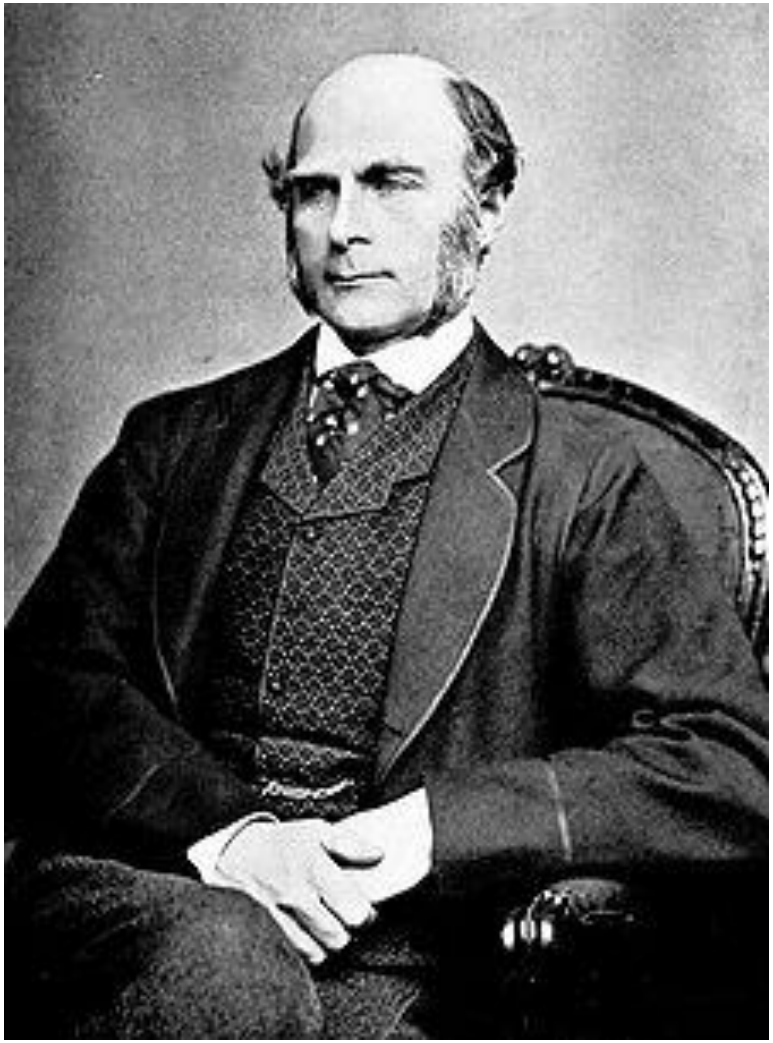
- *Law of segregation:* Two copies of a gene have an equal probability of being transmitted (*segregating*) to an offspring



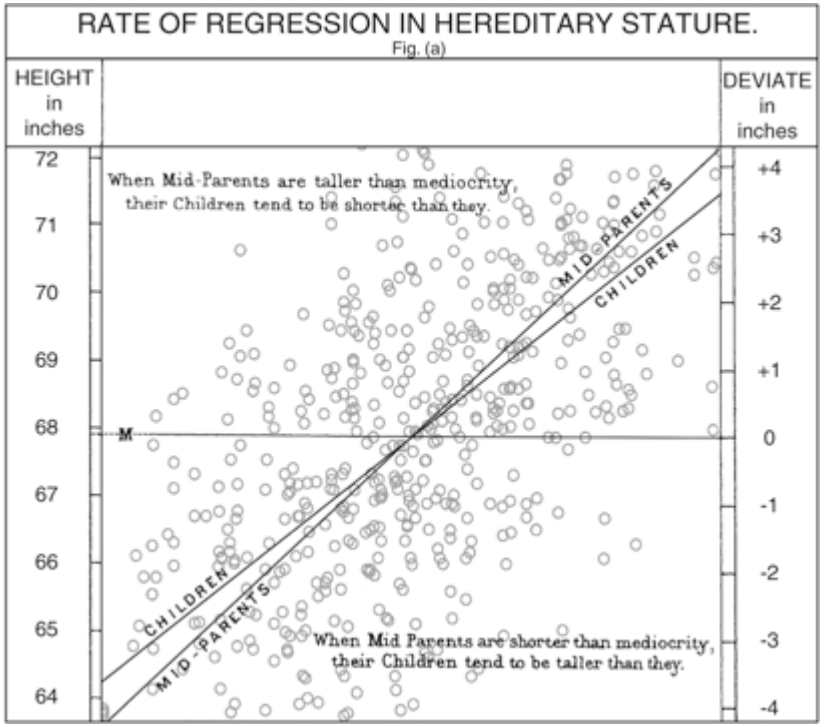
Mendel's second law

- *Law of independent assortment:* each gene is distributed randomly and independently from genes for other characteristics
  - "Random allocation at conception" independent of confounders





Francis Galton (1822 – 1911)



- Studied continuous traits, like height
- Child height well predicted by average of parents
- Child between mid-parents and population mean

Galton vs Mendel

Mendel	Galton
Discrete traits	Continuous traits
Genes inherited intact with dominant/recessive action	Traits inherited directly from parents
Trait could skip a generation	“Blending” of traits from parents
Medical genetics	Quantitative/behavioural genetics
Experimental genetics	Genetic epidemiology

R. A. Fisher (1890 – 1962)

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.)

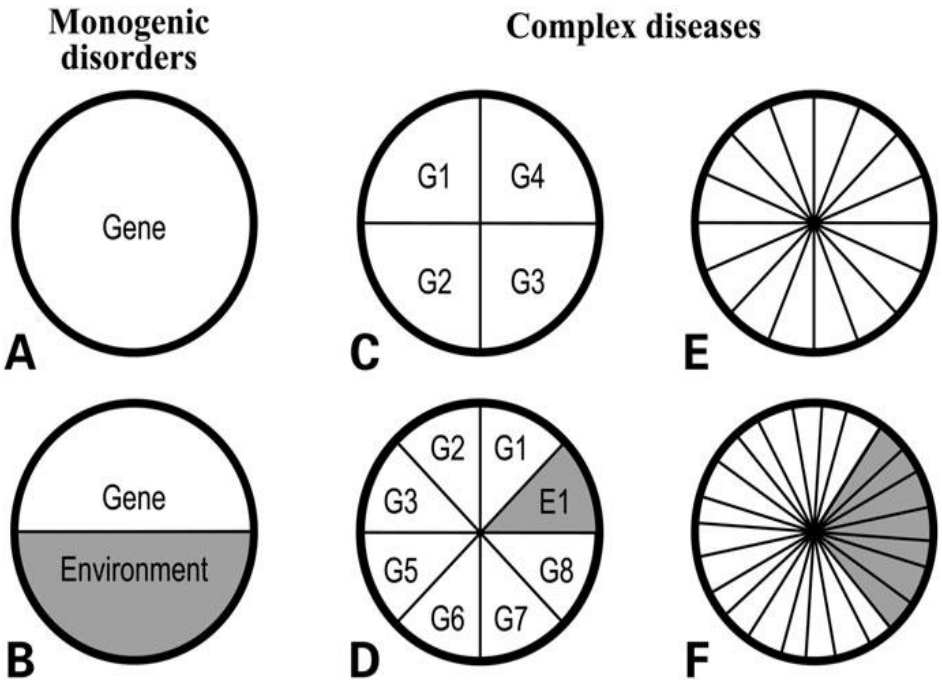
uniformity measured by the standard deviation corresponding to the square root of the mean square error. When there are two independent causes of variability capable of producing in an otherwise uniform population distributions with standard deviations σ_1 and σ_2, it is found that the distribution, 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

Biometrical model

- Fisher showed that continuous traits can arise from combination of multiple "*genes*" inherited in Mendelian fashion
- Also known as *polygenic model*, especially when applied to disease traits (with continuous *risk* or *liability*)
- Introduced the term "*variance*" which has genetic and environmental *components*
- Reconciles Mendel vs Galton

Classes of genetic disease

- Monogenic
  - Clear phenotype
  - Mendelian
- Oligogenic
  - Variable phenotype
  - Genetic heterogeneity
- Polygenic
  - ‘continuous’ phenotype
  - Complex traits
  - Multifactorial
  - extensive heterogeneity



Janssens A. and van Duijn C, Hum Mol Genet 2008
Figure 3. Complete cause models or sufficient causes of disease development.
Complete causal models for (A) Huntington Disease; (B) Phenylketonuria;
(C–F) Hypothetical examples for complex diseases. White areas refer to
genetic factors and grey areas to environmental factors.

Study Design in Genetic Epidemiology

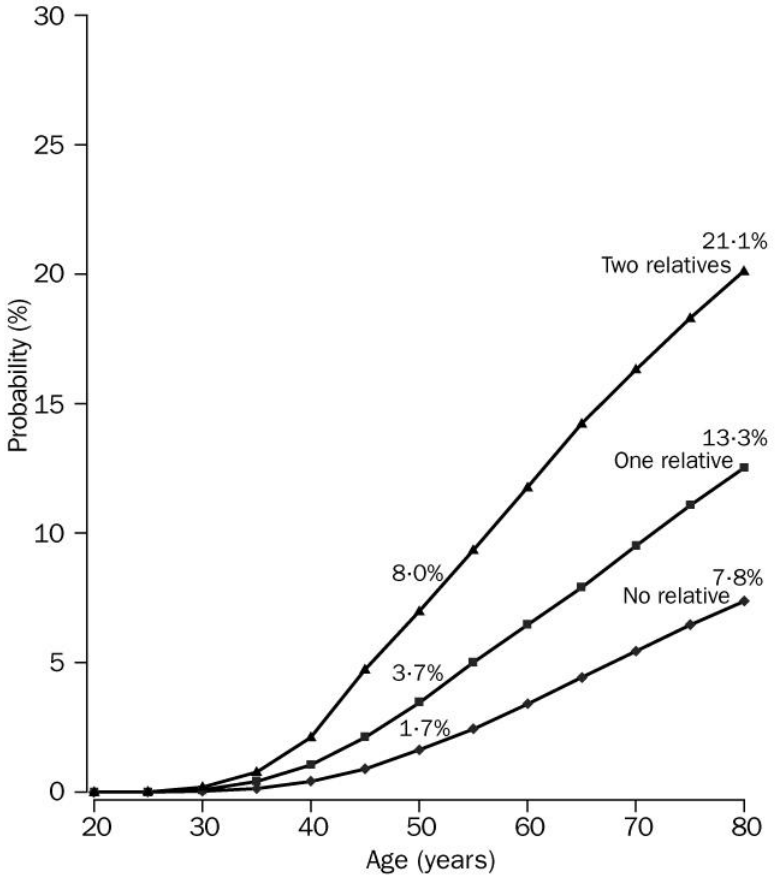
Familial Risk/Heritability

- Families, Twin studies, Migrant, Half Sibling, Adoption studies

Mapping

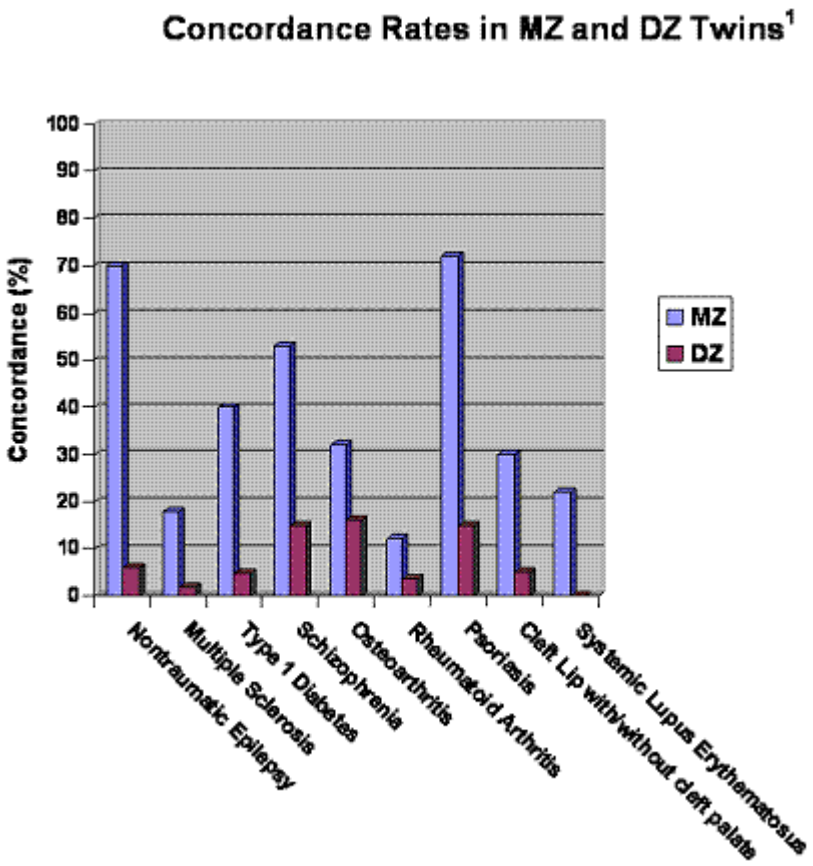
- Families with multiple affected
- Case/control, cohort, parent-child “trios”

Family history and risk of breast cancer



Collaborative Group on Hormonal factors in Breast Cancer, Lancet, 2001

Twin concordances



Similarities → genetic
Differences → environment

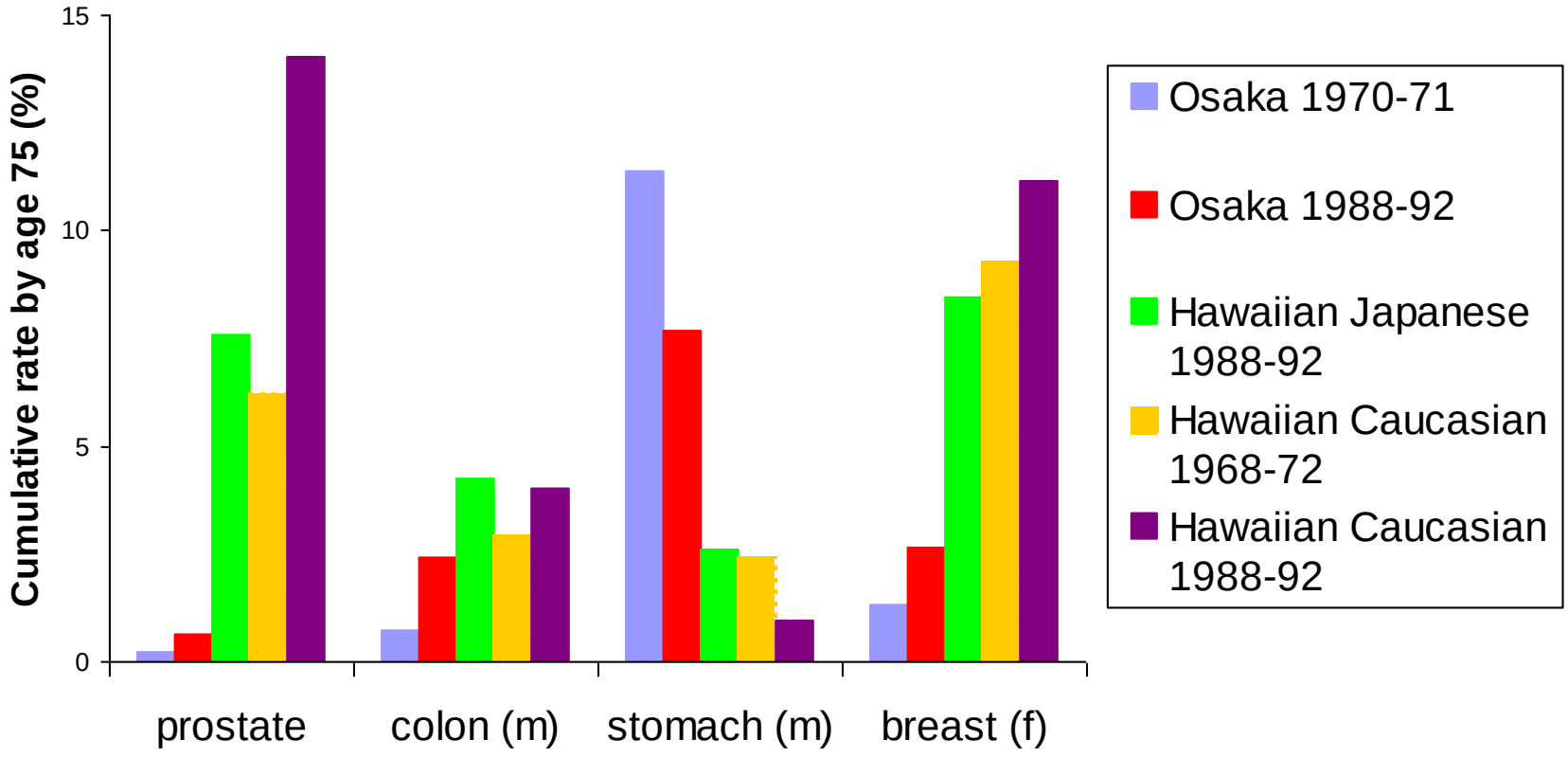
MZ

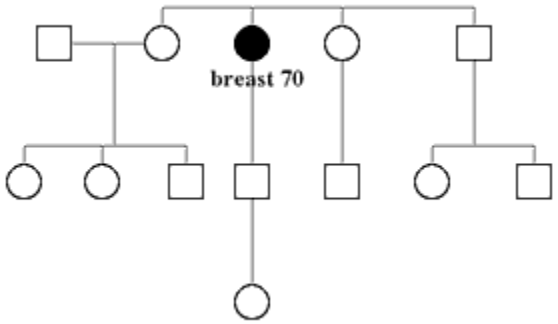
more similar than

DZ

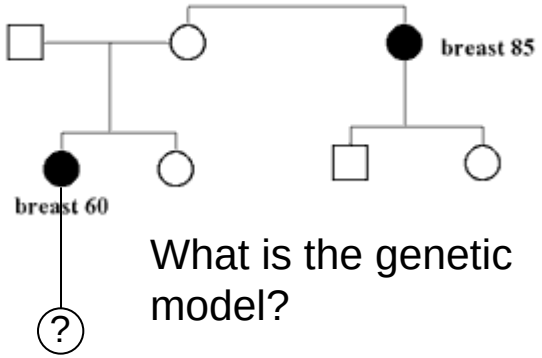
[1] Nussbaum, R. L., McInnes, R. R., & Willard, H.F. (2004). Genetics of Disorders with Complex Inheritance. In Thompson & Thompson (Eds.), Genetics in Medicine. 6th edition.(p.293) Philadelphia : Saunders.

Cancer rates in Japanese migrants become similar to those in the local US population





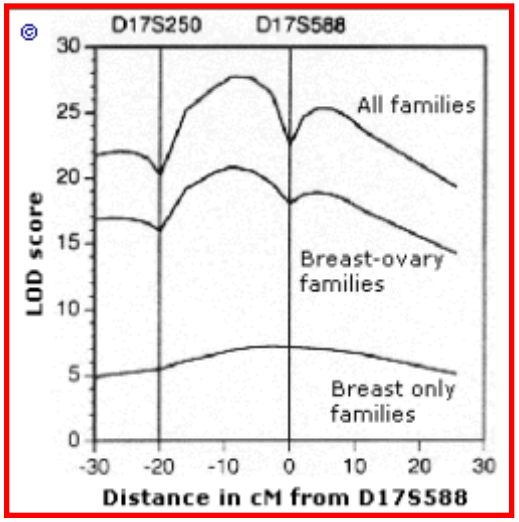
Sporadic or genetic?



What is the genetic model?

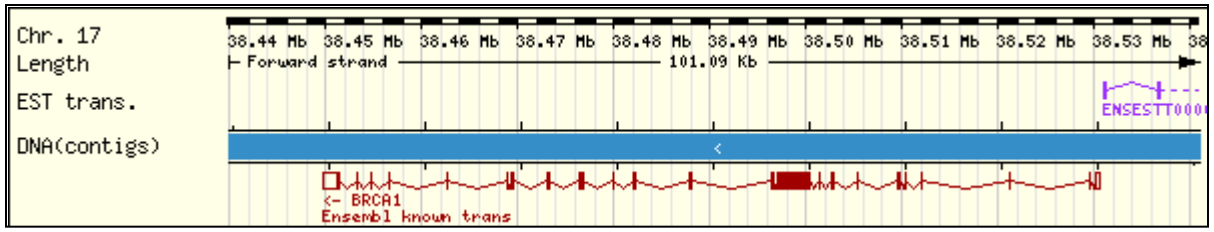
Where in the genome is the disease locus?

Fine-map the locus.

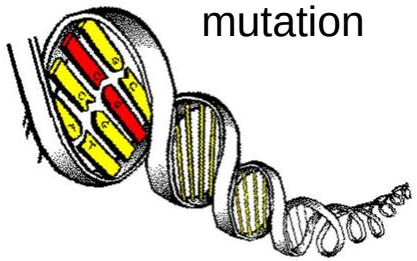


The path to gene discovery in human genetic disease

Identify the gene

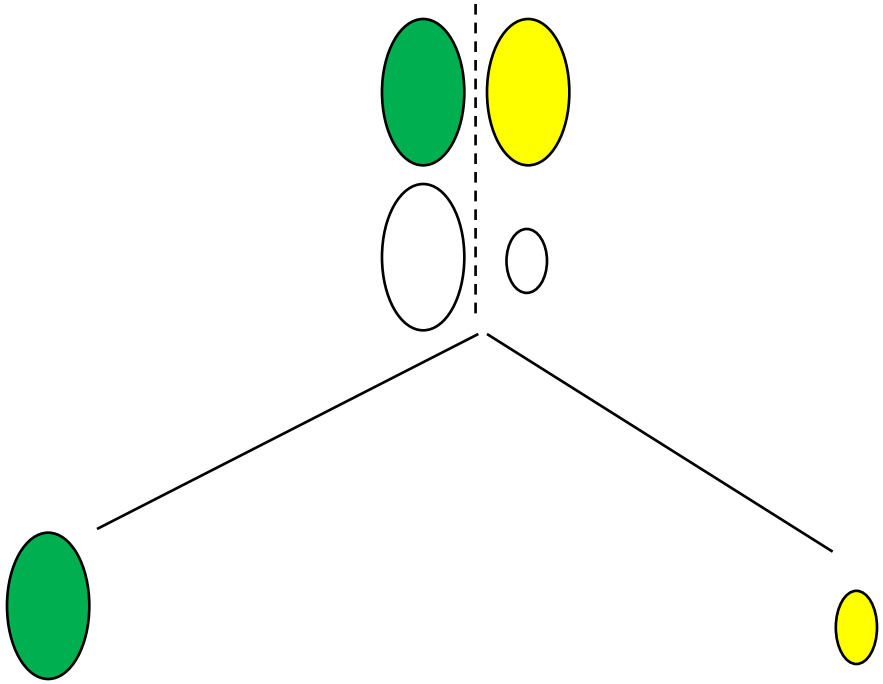


Find the mutation

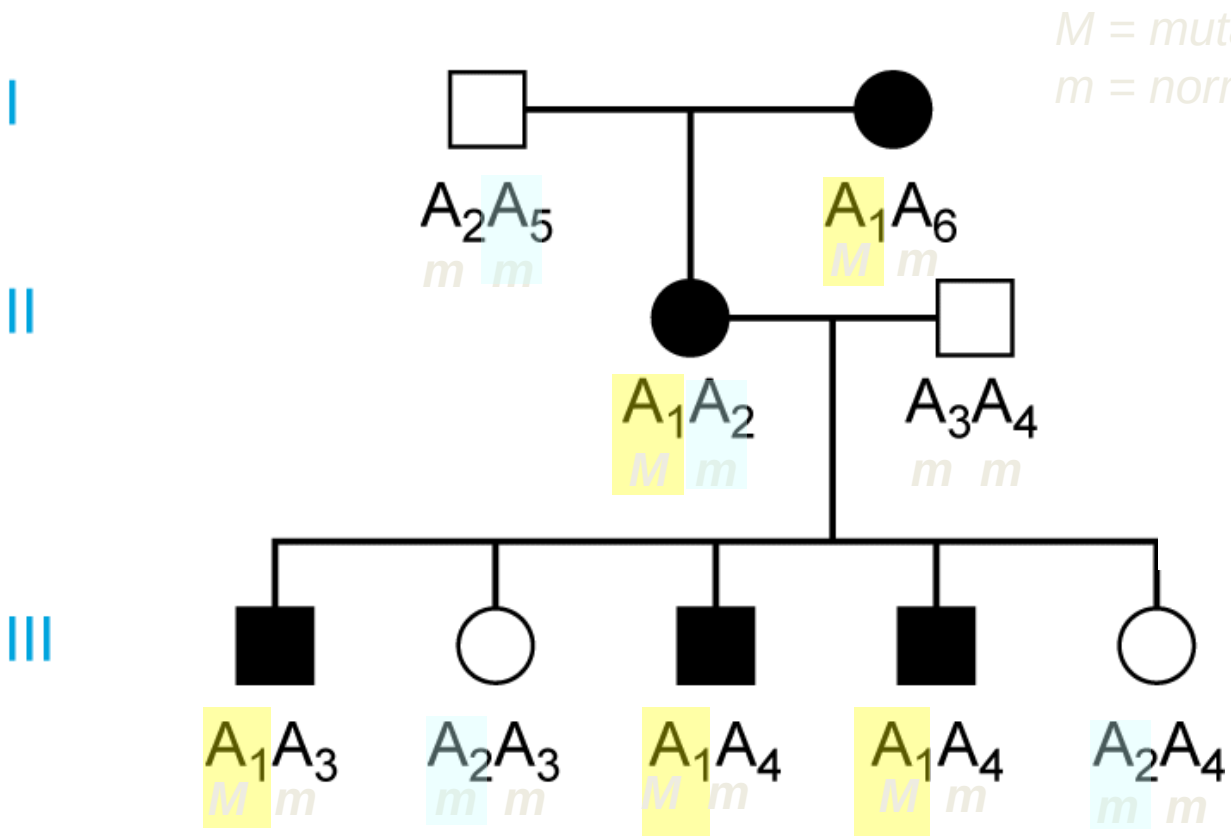


Linkage

- Sometimes two traits don't follow Mendel's 2nd law
- These traits – or the genes for them – are said to be *linked*
- They are inherited together within families



Linkage analysis



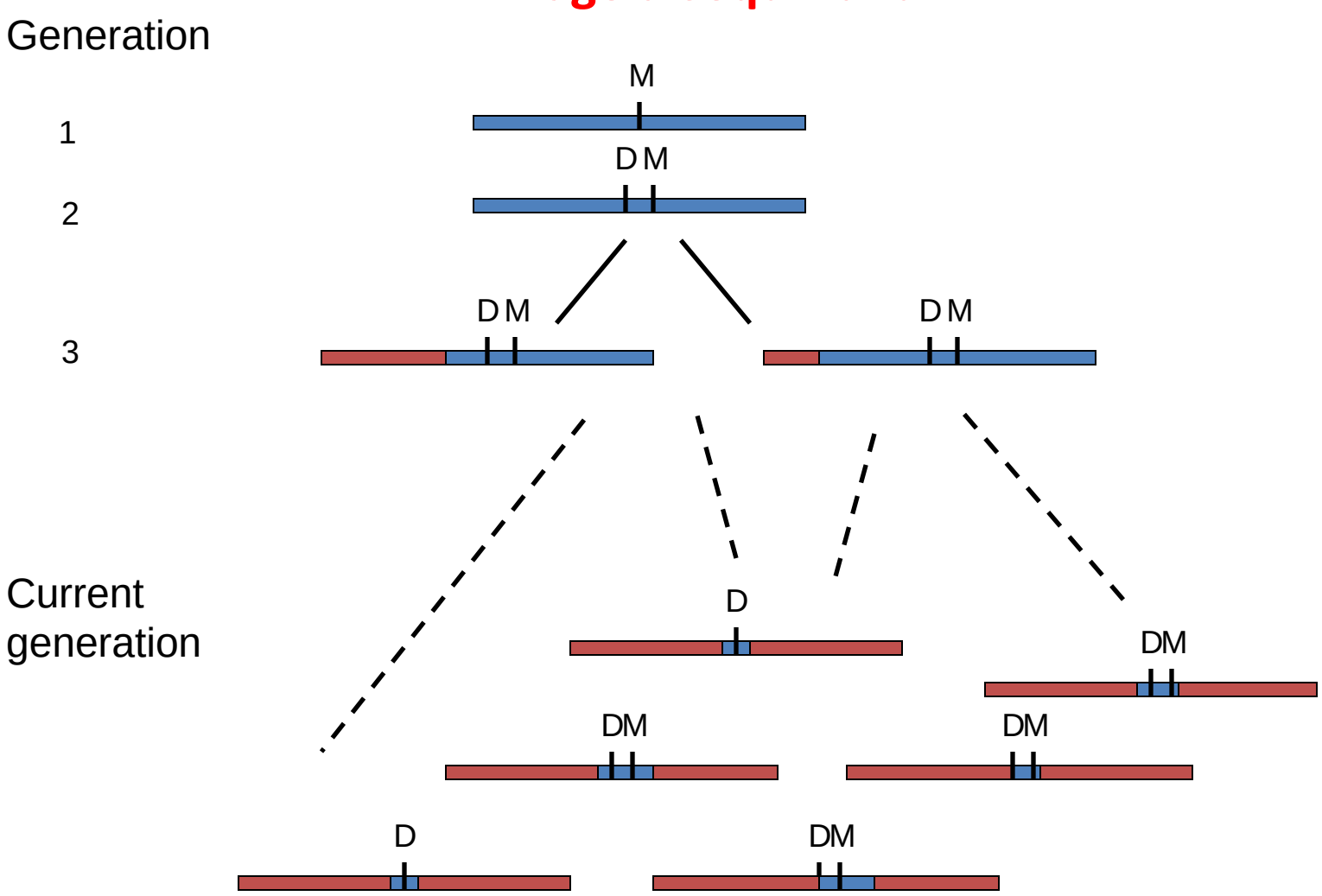
Is the co-segregation of the marker allele A_1 with the disease phenotype due to random chance* or is the marker linked to the disease locus?

*probability, p-values etc

Finding disease genes

- Linkage analysis worked well for monogenic Mendelian diseases
- Not so good for complex diseases
  - Diabetes, heart disease, schizophrenia etc
- For complex diseases, it is better to use association analysis based on **linkage disequilibrium (LD)**
- Genes that are close on a chromosome tend to be correlated in the population
- Standard tests of association for genes and disease
  - Chi-squared tests, linear regression etc

Linkage disequilibrium

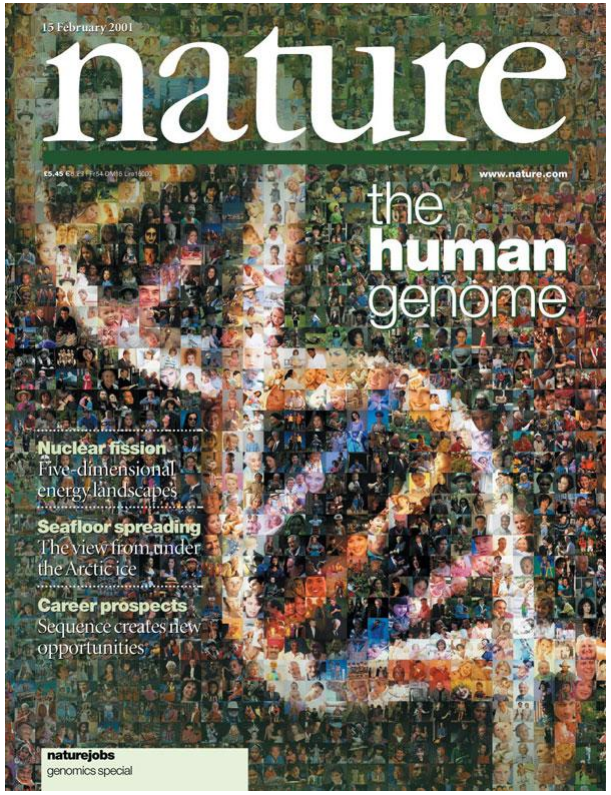


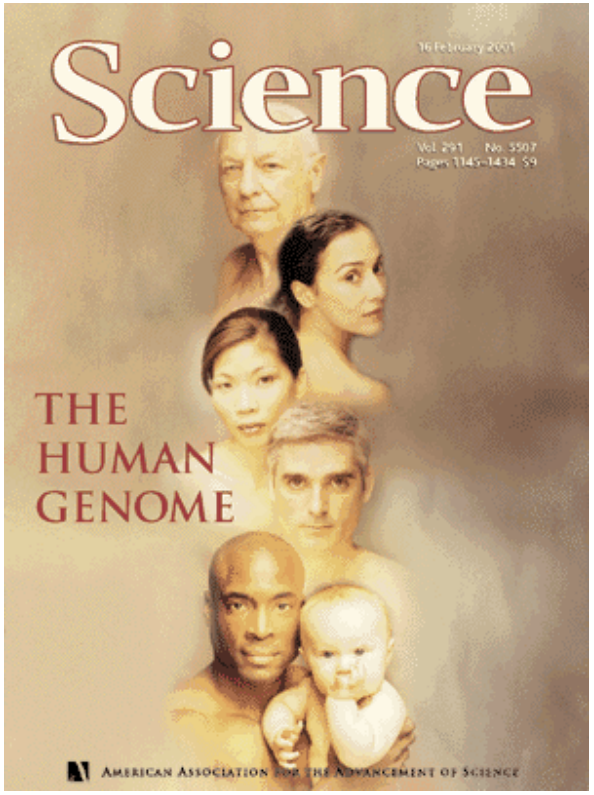
Common ancestry leads to present-day correlation at short ranges
Association between disease and genetic marker → marker is close to disease gene

Genomewide association scan (GWAS)

- A single nucleotide polymorphism (**SNP**) is a DNA "letter" which varies between individuals
- Ideally we would test every SNP for association to disease, but this is too expensive
- Instead we select a subset of SNPs in the hope that causal variants will be in *linkage disequilibrium* with them
- Current GWAS use 1M SNPs
  - At least 10M SNPs in the human genome

Draft human genome in 2001





Tells us about an “average” human

Doesn’t tell us about differences between humans

- Particularly why some get disease when others don’t

HapMap in 2005

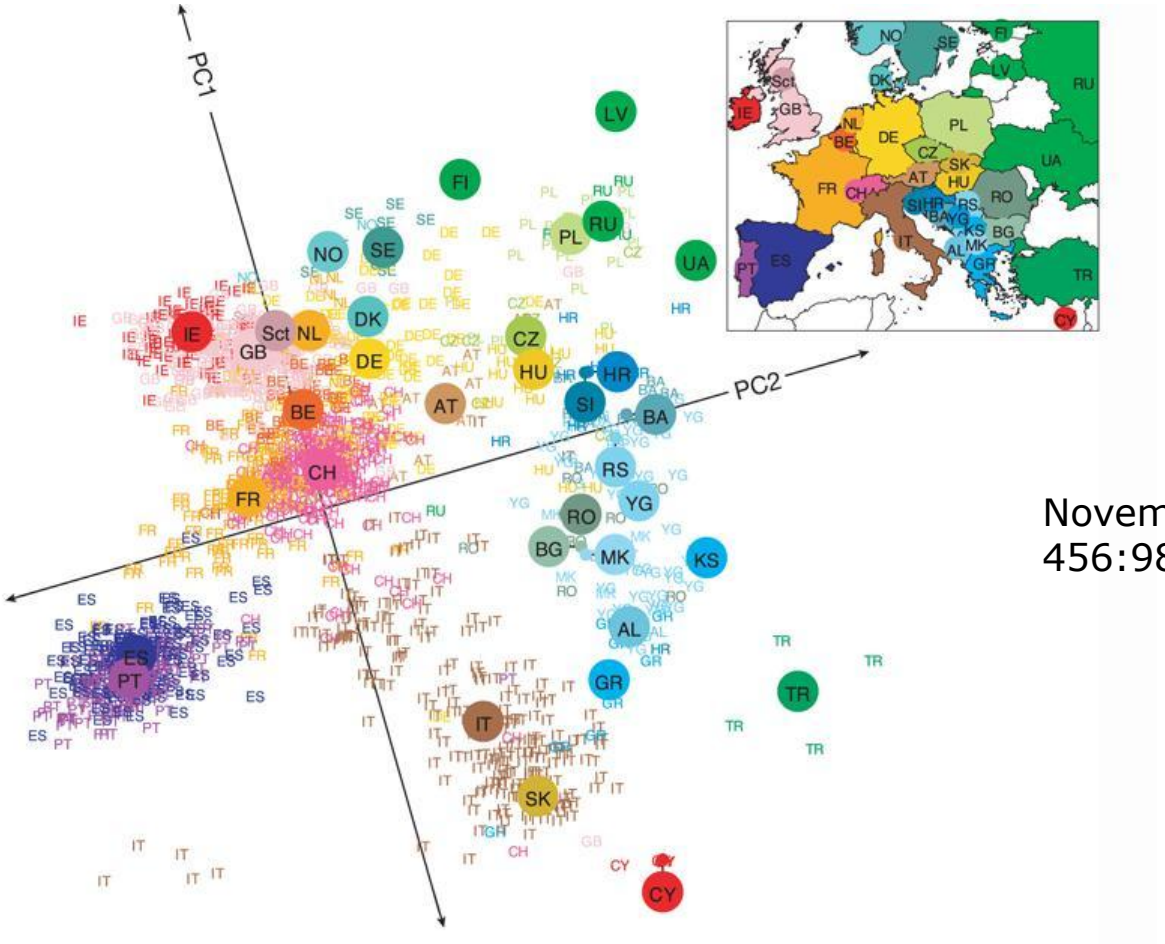
Catalogue of genetic variation in 4 populations

Allows design of genomewide panel of markers for association studies

Ongoing: now 11 populations

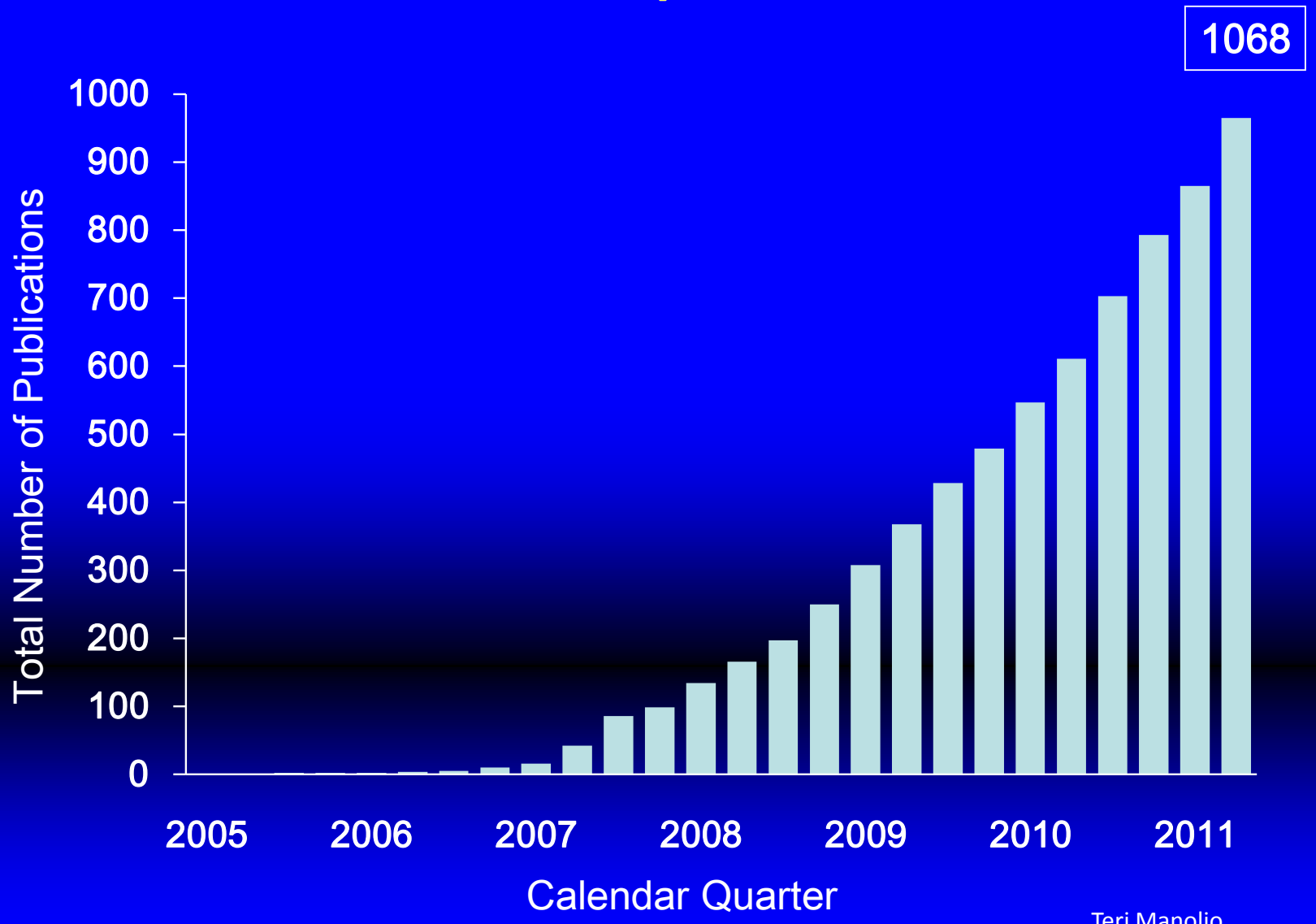
www.hapmap.org

Genome-wide variation is a rich source of information



Novembre et al., Nature 456:98-101 (2008)

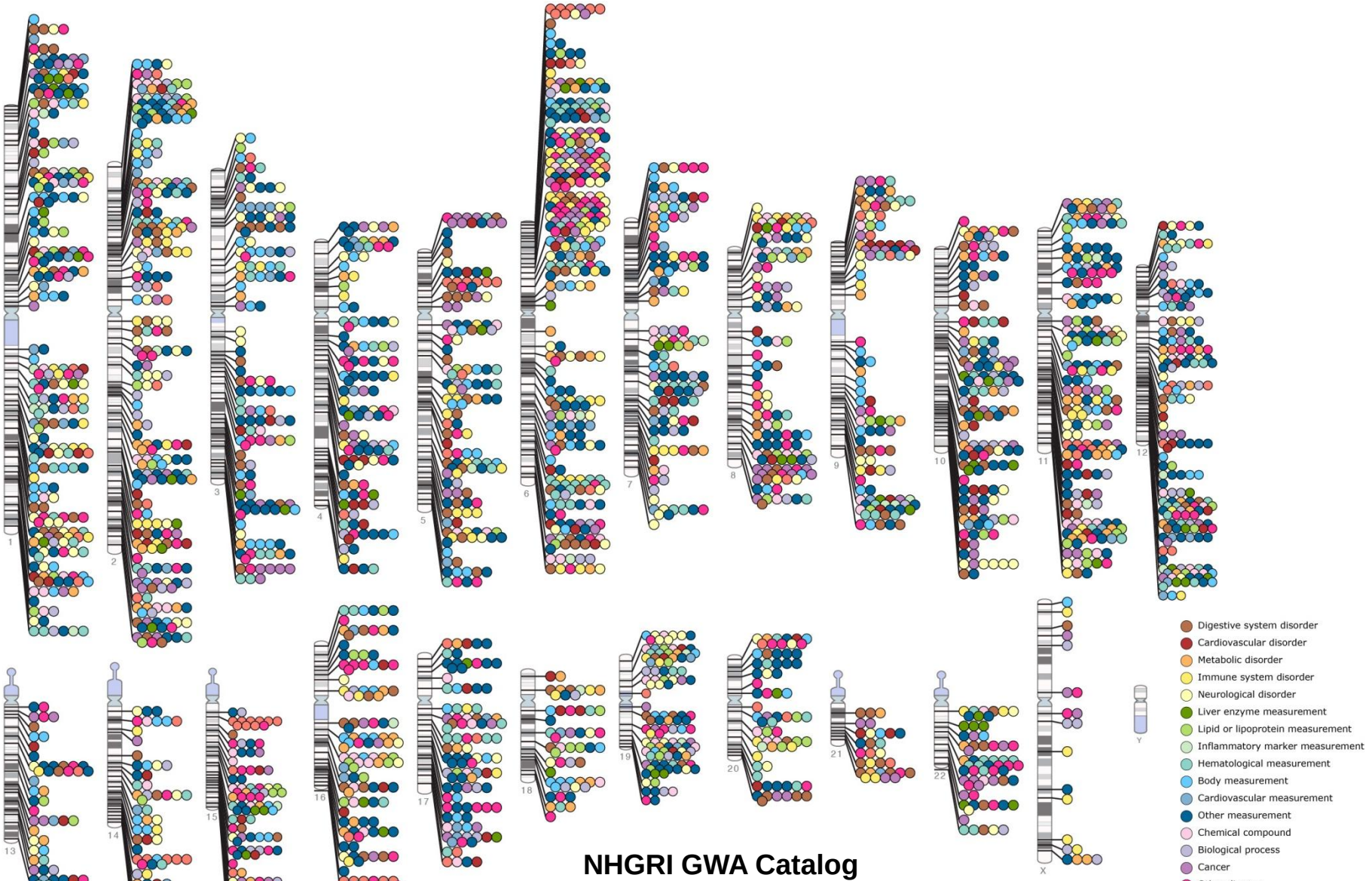
Published GWA Reports, 2005 – 9/2011



Through 9/30/10 postings

Teri Manolio

Published Genome-Wide Associations through 07/2012
Published GWA at p≤5X10^{-8} for 18 trait categories



NHGRI GWA Catalog
www.genome.gov/GWAStudies
www.ebi.ac.uk/fgpt/gwas/

National Human Genome Research Institute

EMBL-EBI

Coming soon

April 2008

nature news

James Watson's genome sequenced at high speed

New-generation technology takes just four months and costs a fraction of old method.

Meredith Wadman

The first full genome to be sequenced using next-generation rapid-sequencing technology is published today (see page 872)[1], marking another milestone in the extraordinarily fastmoving field of human genome sequencing.

It took just four months, a handful of scientists and less than US$1.5 million to sequence the 6 billion base pairs of DNA pioneer James Watson. The achievement is first proof of principle that

Genomewide Association
Complex disease
- Type-2 diabetes
- Heart Disease
- Schizophrenia

Linkage mapping
Mendelian disease
- Huntingdon's
- Haemophilia

Whole genome linkage scan
- Type-1 diabetes

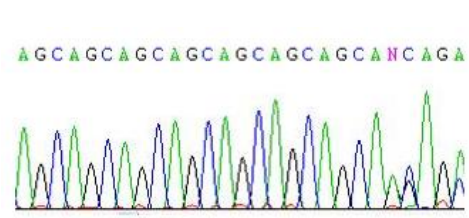
Fine mapping
- Cystic Fibrosis

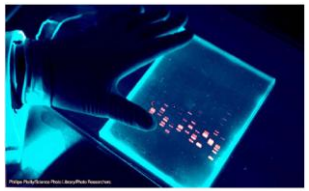
Human Genome Project

HapMap

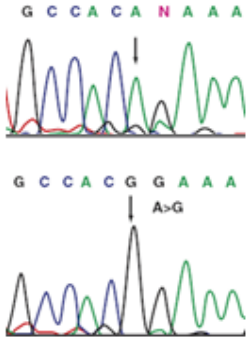
Sequencing

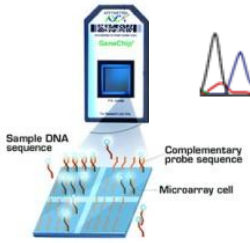
1970 1980 1990 2000 2010





STRs





SNPs

Summary

- In the last 20 years, genetics has evolved from “difficult” analyses of pedigrees to “standard” epidemiological methods
  - This resulted from rapid advances in genotyping technology and knowledge of the human genome

- Currently enormous effort & expenditure on finding the hundreds of genes that explain common diseases

- These discoveries will lead to better understanding of disease etiology, more accurate population screening, and opportunities for personalised medicine