THE INTERNATIONAL HAPMAP PROJECT

A community resource for disease gene discovery

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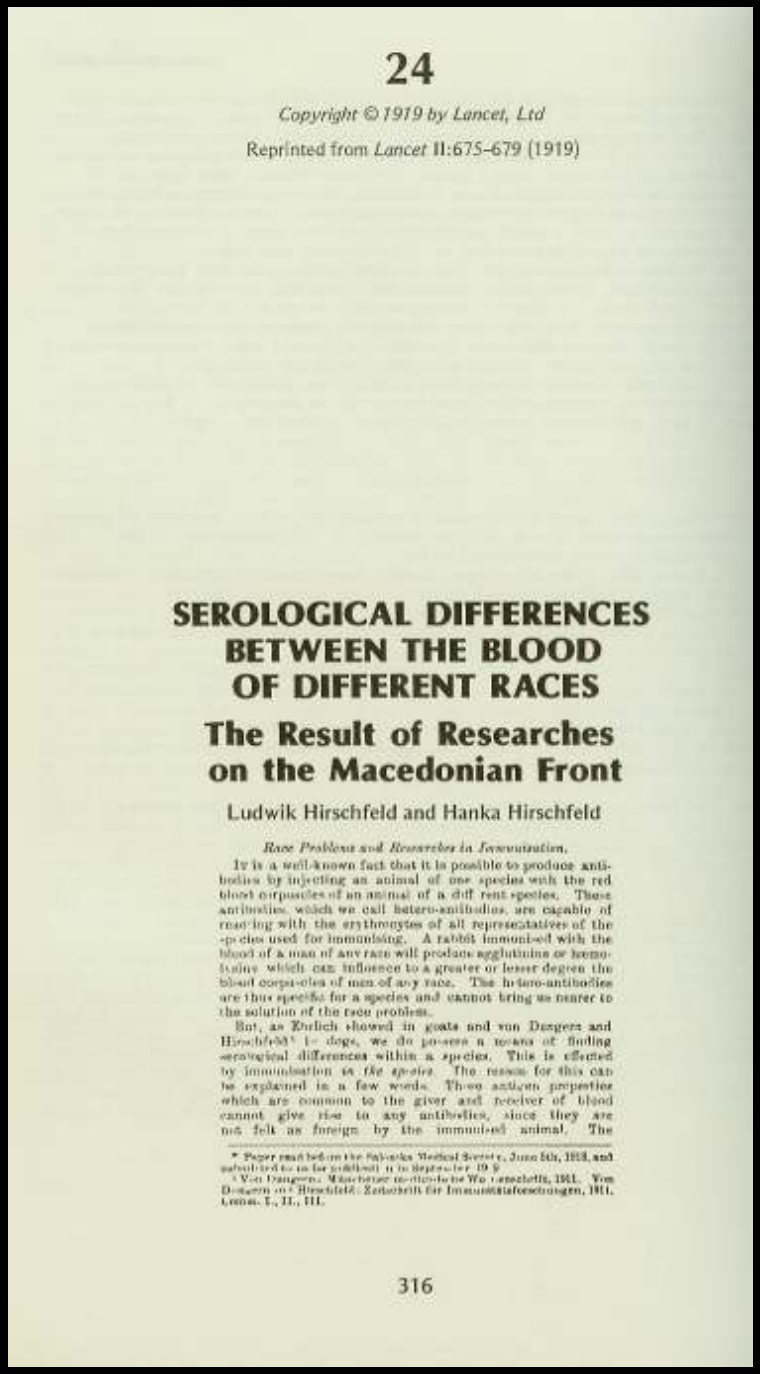
Whenever a mutation has a single origin it can be identified through its association with nearby markers

linkage disequilibrium (LD mapping)

LD mapping is not just for isolated populations anymore !

Genetics is pointing the way to personalized medicine…
the practice of medicine that embraces human genetic individuality

The HapMap Project is essential to defining this individuality including that for disease susceptibility and drug response



24

Reprinted from *Lancet* II:675–679 (1919)

SEROLOGICAL DIFFERENCES BETWEEN THE BLOOD OF DIFFERENT RACES

The Result of Researches on the Macedonian Front

Ludwik Hirschfeld and Hanka Hirschfeld

Race Problems and Researches in Immunization.

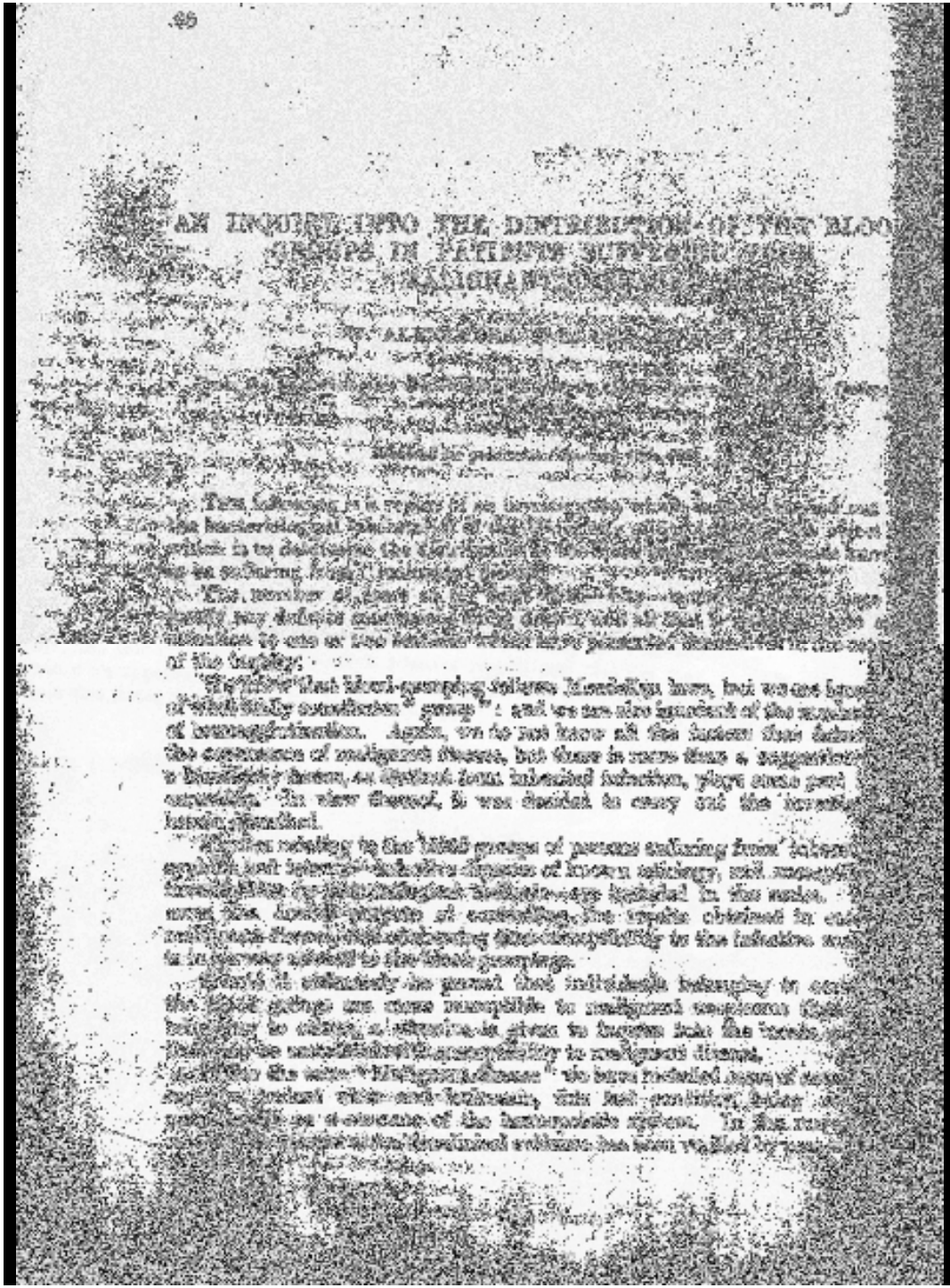
It is a well-known fact that it is possible to produce antibodies by injecting an animal of one species with the red blood corpuscles of an animal of a different species. These antibodies, which we call hetero-antibodies, are capable of reacting with the erythrocytes of all representatives of the species used for immunising. A rabbit immunised with the blood of a man of any race will produce agglutinins or haemolysins which can influence to a greater or lesser degree the blood corpuscles of men of any race. The hetero-antibodies are thus specific for a species and cannot bring us nearer to the solution of the race problem.

But, as Ehrlich showed in goats and von Dungern and Hirschfeld[1] in dogs, we do possess a means of finding serological differences within a species. This is effected by immunisation *in the species*. The reason for this can be explained in a few words. The antigen properties which are common to the giver and receiver of blood cannot give rise to any antibodies, since they are not felt as foreign by the immunised animal. The

* Paper read before the Salonika Medical Society, June 5th, 1918, and published for the first time in September 1919.

[1] Von Dungern u. Hirschfeld: Zeitschrift für Immunitätsforschungen, 1911, Orig. I., II., III.

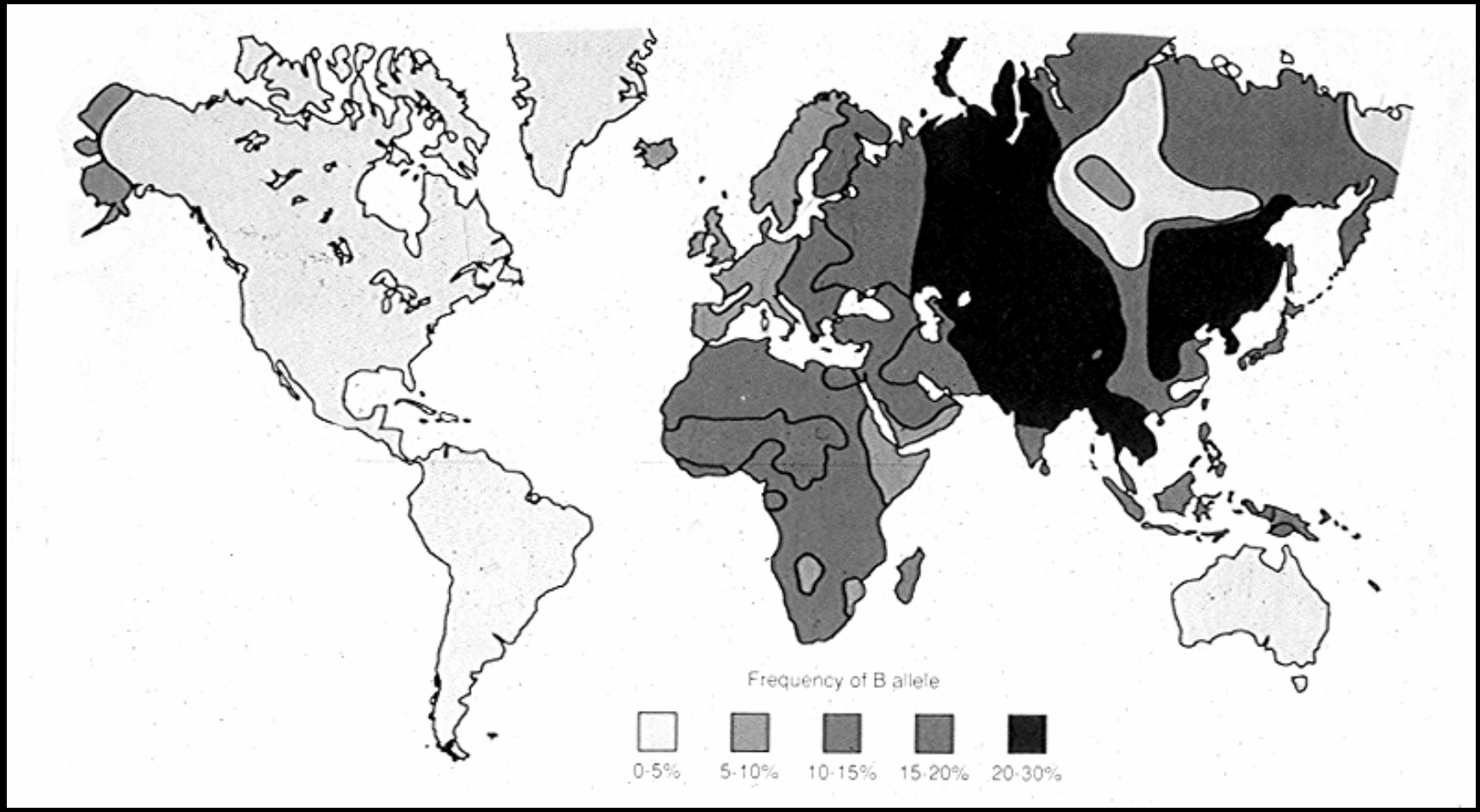
The first demonstration of world-wide differences in human *A*, *B* & *O* allele frequencies (1919)

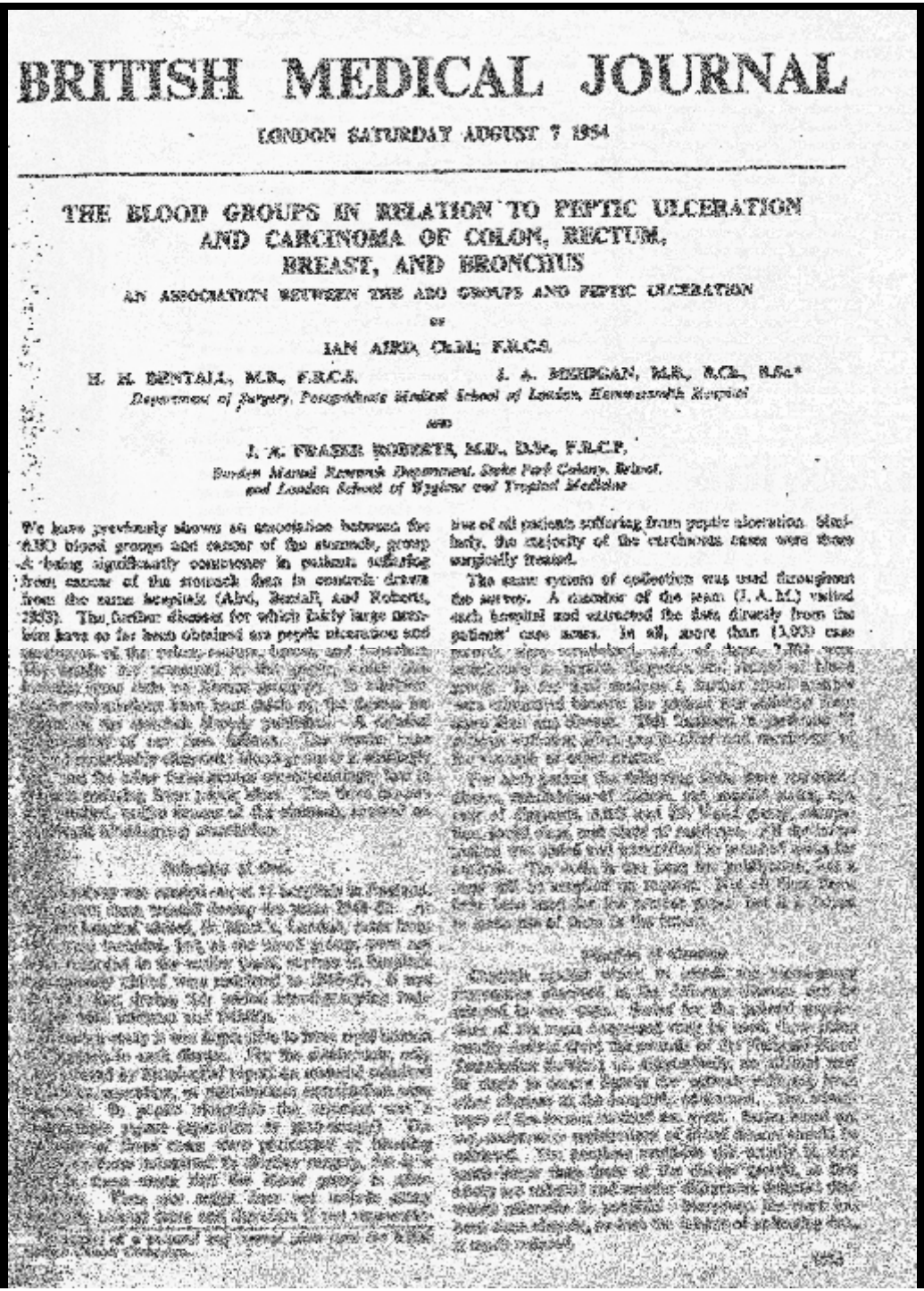


The first use of A, B & O allele frequencies in a case-control association study !

Br J Exp Path
2: 66-69 (1921)

World-wide distribution of the I^B (ABO) allele





BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 7 1954

THE BLOOD GROUPS IN RELATION TO PEPTIC ULCERATION AND CARCINOMA OF COLON, RECTUM, BREAST, AND BRONCHUS

AN ASSOCIATION BETWEEN THE ABO GROUPS AND PEPTIC ULCERATION

BY

IAN AIRD, C.B.E., F.R.C.S.

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Burden Mental Research Department, Stoke Park Colony, Bristol, and London School of Hygiene and Tropical Medicine

We have previously shown an association between the ABO blood groups and cancer of the stomach, group A being significantly commoner in patients suffering from cancer of the stomach than in controls drawn from the same hospitals (Aird, Bentall, and Roberts, 1953). The further diseases for which fairly large series have so far been obtained are peptic ulceration and

The same system of collection was used throughout the survey. A member of the team (I. A. H.) visited each hospital and extracted the data directly from the patients' case notes. In all, more than [illegible] case

The first replicated A,B & O association study

Mechanism: ABO blood group binding adhesin *BabA* in *H. pylori*

Br Med J
2: 315-321 (1954)

Common Gene Variation in Complex Disease

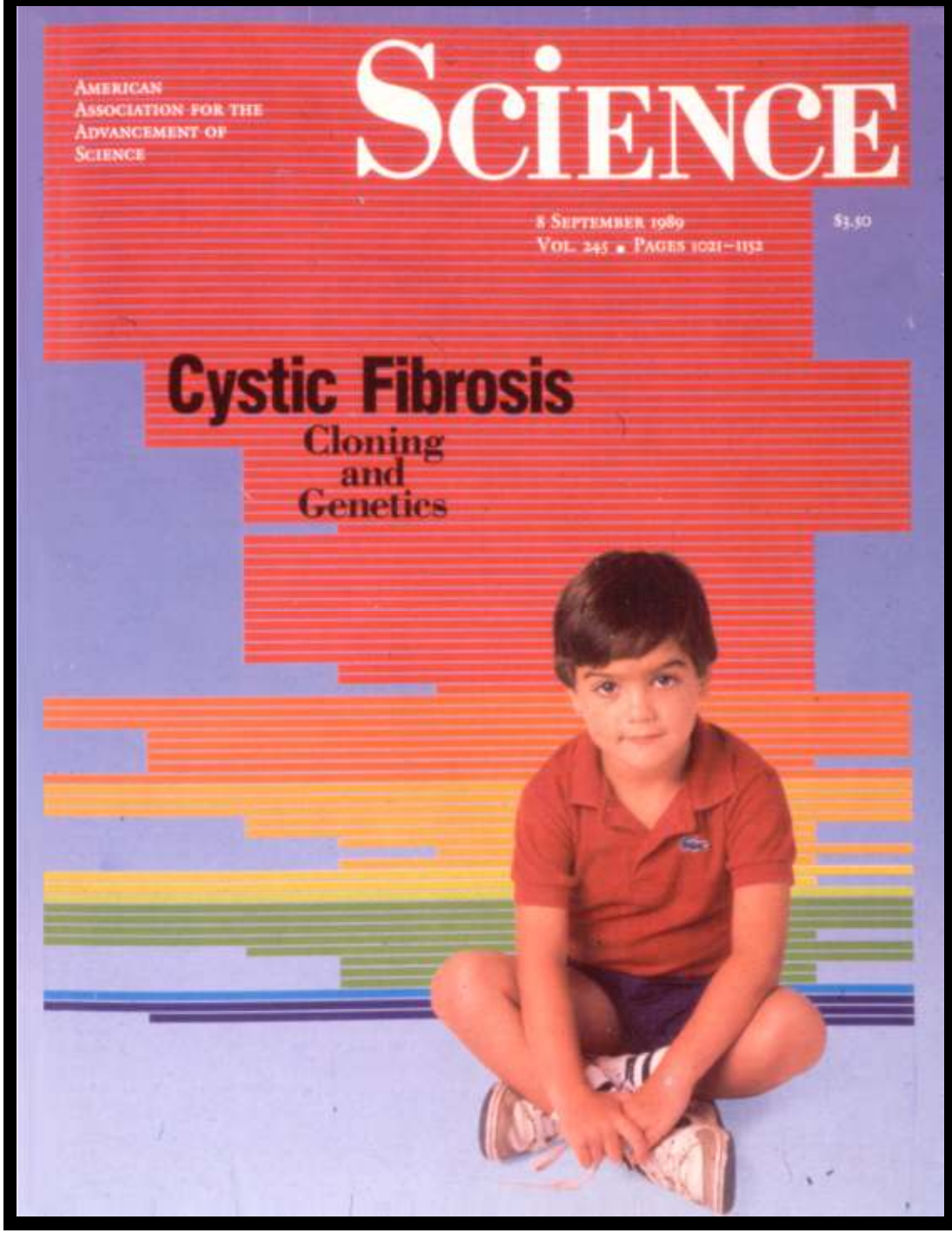
- Case-control studies, comparing the frequencies of common gene variants can identify susceptibility and protective alleles
- Some have multiple identified genes (*)

Phenotype	Gene	Variant
Peptic ulcer	ABO	B
IDDM*	HLA	DR3,4
Alzheimer dementia	APOE	E4
Deep venous thrombosis	F5	Leiden
Falciparum malaria*	HBBE	β^S
AIDS*	CCR5	Δ32
Colorectal cancer	APC	3920A
NIDDM	PPARγ	12A

Positional Cloning of the CF Gene (1987-1989)

The entry of population genetics into the world of the molecular geneticist

- In the mid 1980's the conventional wisdom was that chromosomal aberrations were needed to clone genes for mendelian defects
- CF is a common mendelian disorder with heterozygote advantage
- There is likely one major common (2%) mutation arisen recently
- Linkage disequilibrium between this mutation and nearby markers is expected on mutant chromosomes



CFTR cloning assisted by LD Mapping

ΔF508 ~ 70% of all mutants

ΔF508 modifies the pancreatic sufficiency phenotype

The NEW ENGLAND JOURNAL of MEDICINE

OCTOBER 6, 2005

Genetic Modifiers of Lung Disease in Cystic Fibrosis

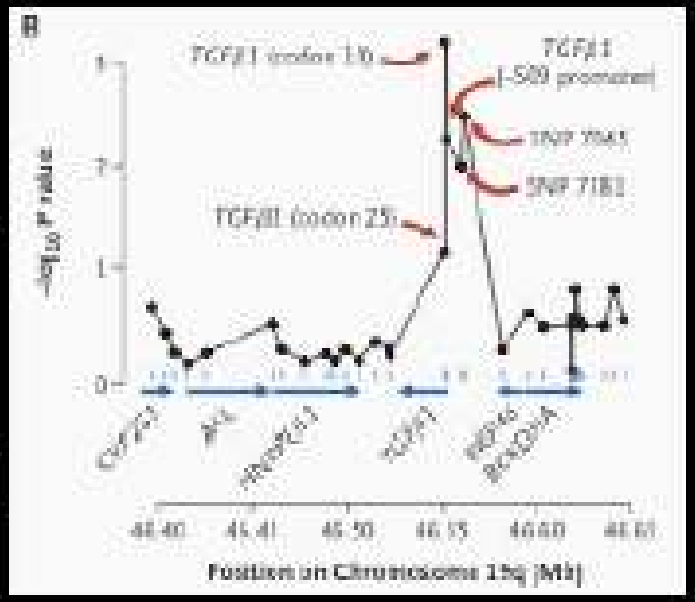
Mitchell L. Drumm, Ph.D., Michael W. Konstan, M.D., Mark D. Schluchter, Ph.D., Albert Handler, R.N., Rhonda Pace, B.S., Fei Zou, Ph.D., Makrooni Zariwala, Ph.D., David Fargo, Ph.D., Aiping Xu, M.D., John M. Dunn, M.S., Rebecca J. Darrah, M.S., Rufan Durfee, Ph.D., Andrew J. Sandford, Ph.D., Mary Corey, Ph.D., Julian Zielenski, Ph.D., Peter Durie, M.D., Katrina Goddard, Ph.D., James R. Yankaskas, M.D., Fred A. Wright, Ph.D., and Michael R. Knowles, M.D., for the Gene Modifier Study Group*

BACKGROUND

Polymorphisms in genes other than the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene may modify the severity of pulmonary disease in patients with cystic fibrosis.

CONCLUSIONS

Genetic variation in the 5′ end of *TGFB1* or a nearby upstream region modifies disease severity in cystic fibrosis.



Haplotype Map of the Human Genome

Goals:

- Define patterns of genetic variation across human genome
- Guide selection of SNPs efficiently to "tag" common variants
- Public release of all data (assays, genotypes)

Phase I: 1.3 M markers in 269 people
Phase II: +2.8 M markers in 270 people

There is much more exciting but hard work ahead: Proving Causality from Association

Even trained statisticians often fail to appreciate the extent to which statistics are vitiated by the unrecorded assumptions of their interpreters... It is easy to prove that the wearing of tall hats and the carrying of umbrellas enlarges the chest, prolongs life, and confers comparative immunity from disease.... A university degree, a daily bath, the owning of thirty pairs of trousers, a knowledge of Wagner's music, a pew in church, anything, in short, that implies more means and better nurture ... can be statistically palmed off as a magic-spell conferring all sorts of privileges..... The mathematician whose correlations would fill a Newton with admiration, may, in collecting and accepting data and drawing conclusions from them, fall into quite crude errors by just such popular oversights as I have been describing.

George Bernard Shaw, Preface,
The Doctors Dilemma (1906)