

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

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 iso-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 Denigern and Hirschfeld¹ 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. These 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

¹ Paper read before the Pathologic Medical Society, June 5th, 1913, and published in its proceedings in September, 1913.

² Von Denigern, *Monatsh. naturforsch. Ver. Basel*, 1911. Von Denigern and Hirschfeld, *Zeitschrift für Immunitätsforschungen*, 1911, volume I, II, III.

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

AN INQUIRY INTO THE DISTRIBUTION OF THE BLOOD GROUPS IN PATIENTS SUFFERING FROM MALIGNANT DISEASE

This following is a review of the literature which deals with the distribution of the blood groups in patients suffering from malignant disease. It is to be noted that the distribution of the blood groups in patients suffering from malignant disease is a subject which has been the subject of many investigations. The number of cases in the literature is so large that it is not possible to give a complete list of the references. It is to be noted that the distribution of the blood groups in patients suffering from malignant disease is a subject which has been the subject of many investigations. The number of cases in the literature is so large that it is not possible to give a complete list of the references.

The first of the blood-grouping systems, Mendelian inheritance, but we are aware of the fact that the "group" is not the only factor in the causation of leucogranuloma. Again, we do not know all the factors that enter into the causation of malignant disease, but there is more than a suggestion that the blood-grouping system, as distinct from inherited factors, plays some part in the causation. In view thereof, it was decided to carry out the investigation.

After relating to the blood groups of persons suffering from various types of malignant disease, the distribution of known antigens, and the distribution of the blood groups in patients suffering from malignant disease, the results obtained in the investigation of the distribution of the blood groups in patients suffering from malignant disease are given in the following table.

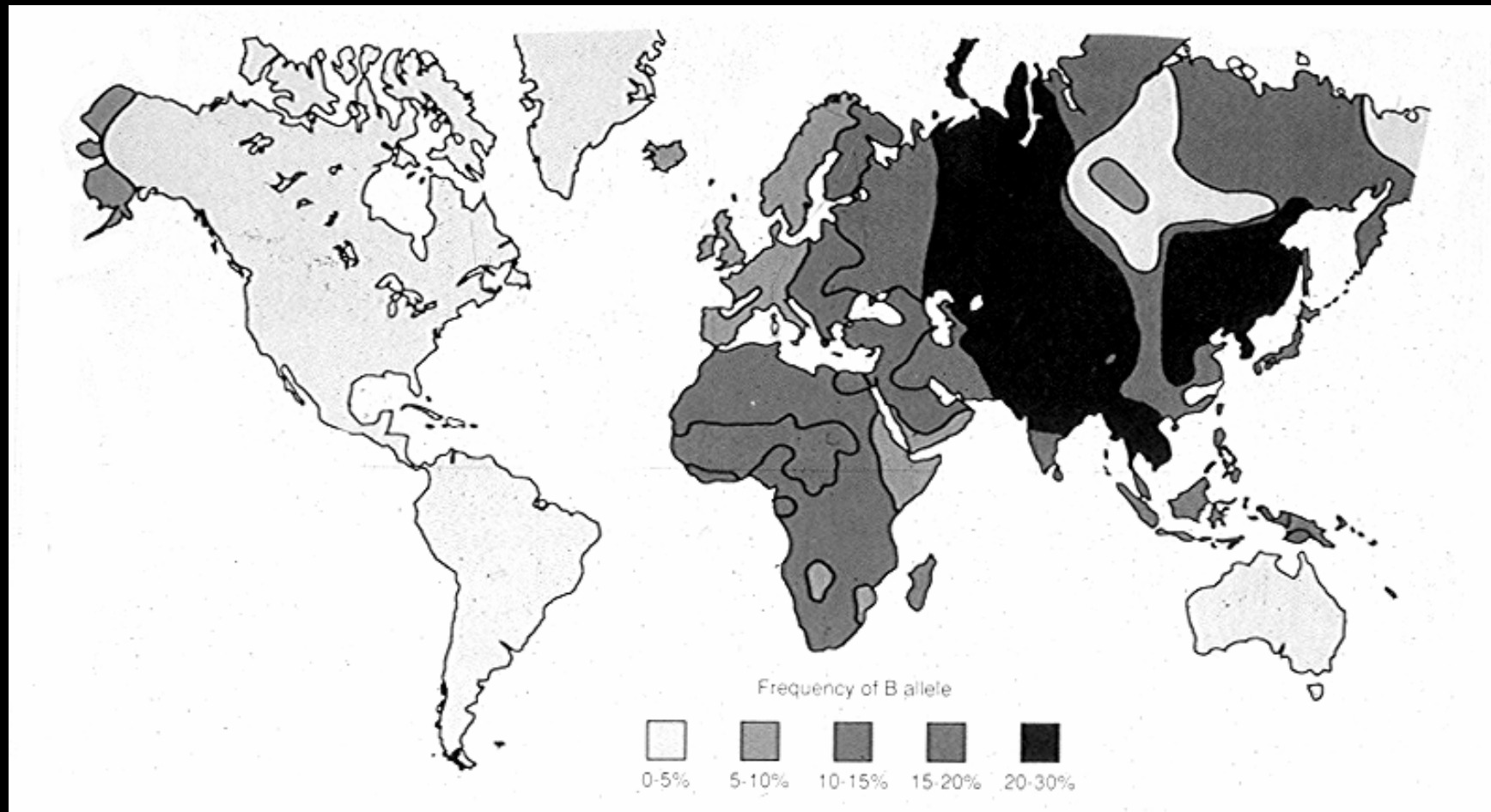
It is to be noted that the results of the investigation of the distribution of the blood groups in patients suffering from malignant disease are given in the following table. It is to be noted that the results of the investigation of the distribution of the blood groups in patients suffering from malignant disease are given in the following table.

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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

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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 numbers have so far been obtained are peptic ulceration and carcinoma of the colon-rectum, breast, and bronchus. They are all associated in the gastric cancer case with group A, and in the breast cancer case with group O. In relation to the other two diseases there has been no clear association with any particular blood group. A detailed comparison of our data indicates that the cancer of the colon-rectum and breast cancer are statistically independent of blood group, whereas the cancer of the stomach is significantly associated with group A.

Materials and Methods

The material was collected from 11 hospitals in England. All the data were collected during the years 1948-51. In the first hospital selected, St. Mark's, London, data have been collected for all the blood groups, from 1948 to 1951, inclusive. In the other hospitals, data have been collected for the various blood groups, from 1948 to 1951, inclusive. In the other hospitals, data have been collected for the various blood groups, from 1948 to 1951, inclusive.

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One of all patients suffering from peptic ulceration. Similarly, the majority of the carcinoma cases were those surgically treated.

The same system of collection was used throughout the survey. A member of the team (J.A.B.) visited each hospital and extracted the data directly from the patients' case notes. In all, more than 1,000 case records were correlated, and of these, 2,000 were available for analysis. The patients were divided into blood groups. In the first instance, a further check was made on the records to ensure that the patients had been correctly classified. The patients were then divided into two main groups: those with peptic ulceration and those with carcinoma. The patients were then divided into two main groups: those with peptic ulceration and those with carcinoma.

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Results of the survey

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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

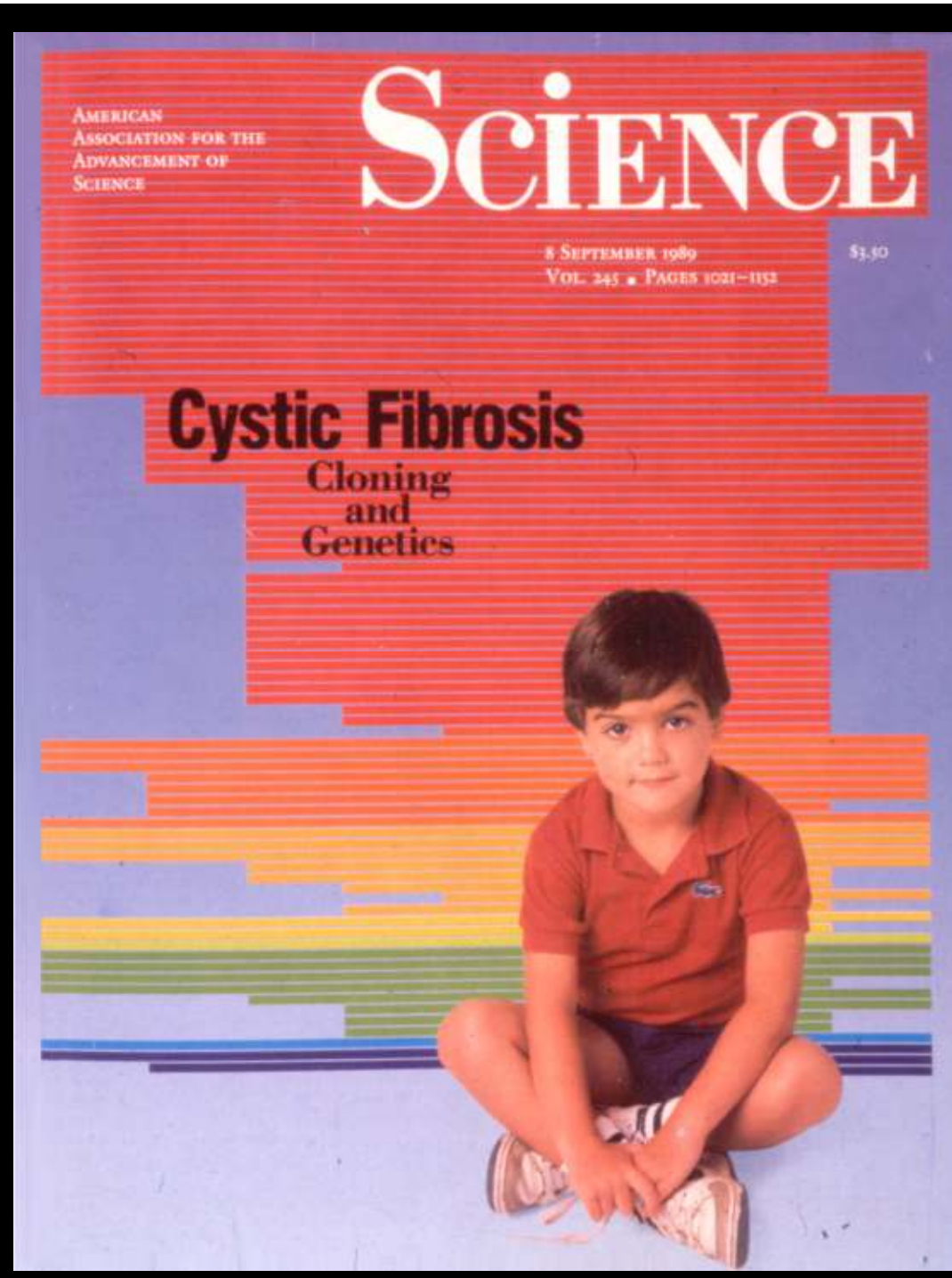
- Case-control studies, comparing the frequencies of common gene variants can identify susceptibility and protective alleles
- Some have multiple identified genes (*)

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	$\Delta 32$
Colorectal cancer	APC	3920A
NIDDM	PPAR γ	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**

**$\Delta F508$ ~ 70% of all
mutants**

**$\Delta F508$ modifies
the pancreatic
sufficiency
phenotype**

The NEW ENGLAND JOURNAL of MEDICINE

ISSN 0028-2718

OCTOBER 6, 2005

VOL 353 NO 16

Genetic Modifiers of Lung Disease in Cystic Fibrosis

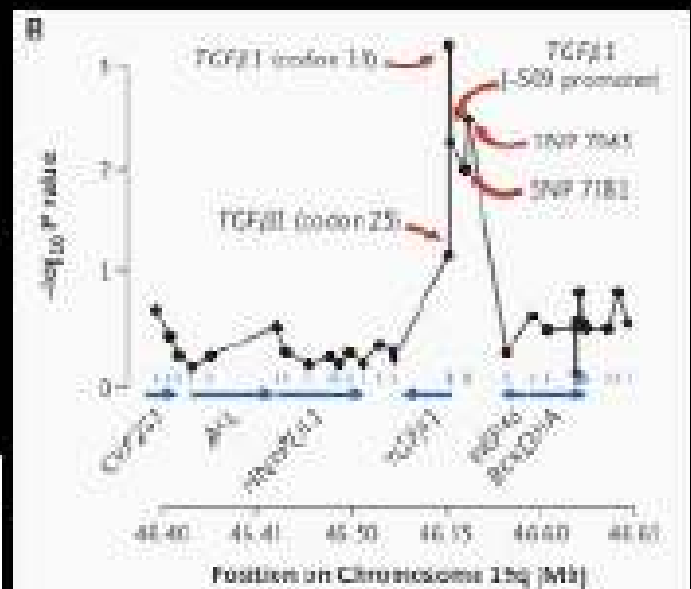
Michael L. Drummer, Ph.D., Michael W. Konstant, M.D., Mark D. Schluchter, Ph.D., Alison Handley, R.N., Rhonda Price, B.S., Fei Bai, Ph.D., Malinor Zariwala, Ph.D., David Fong, Ph.D., Ailing Xu, M.D., John M. Dunn, M.S., Rebecca J. Durrant, M.S., Susan Durfee, Ph.D., Andrew J. Sandford, Ph.D., Mary Carey, Ph.D., Julian Zelenak, Ph.D., Peter Davis, 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 *TGFβ1* 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)**