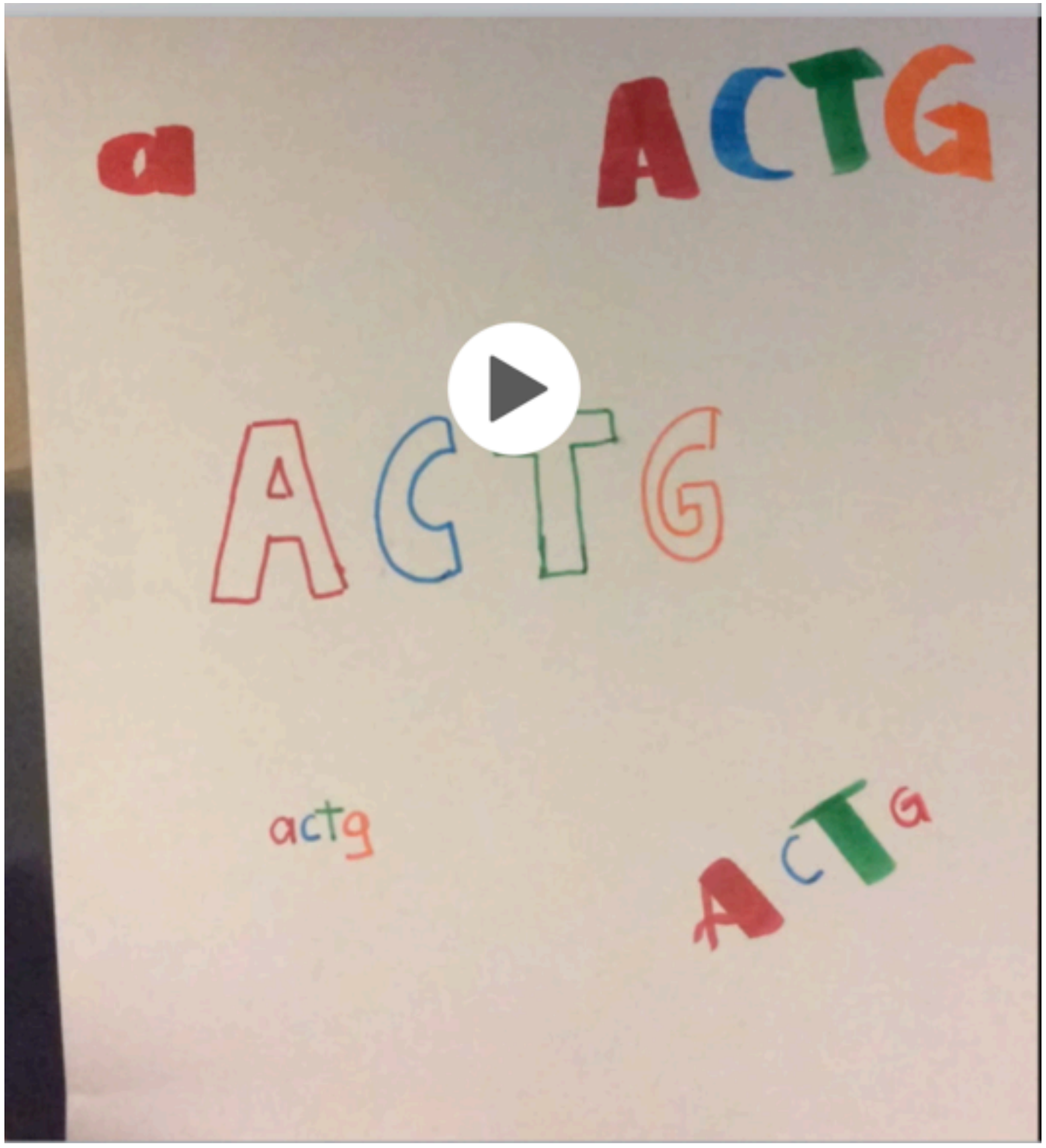
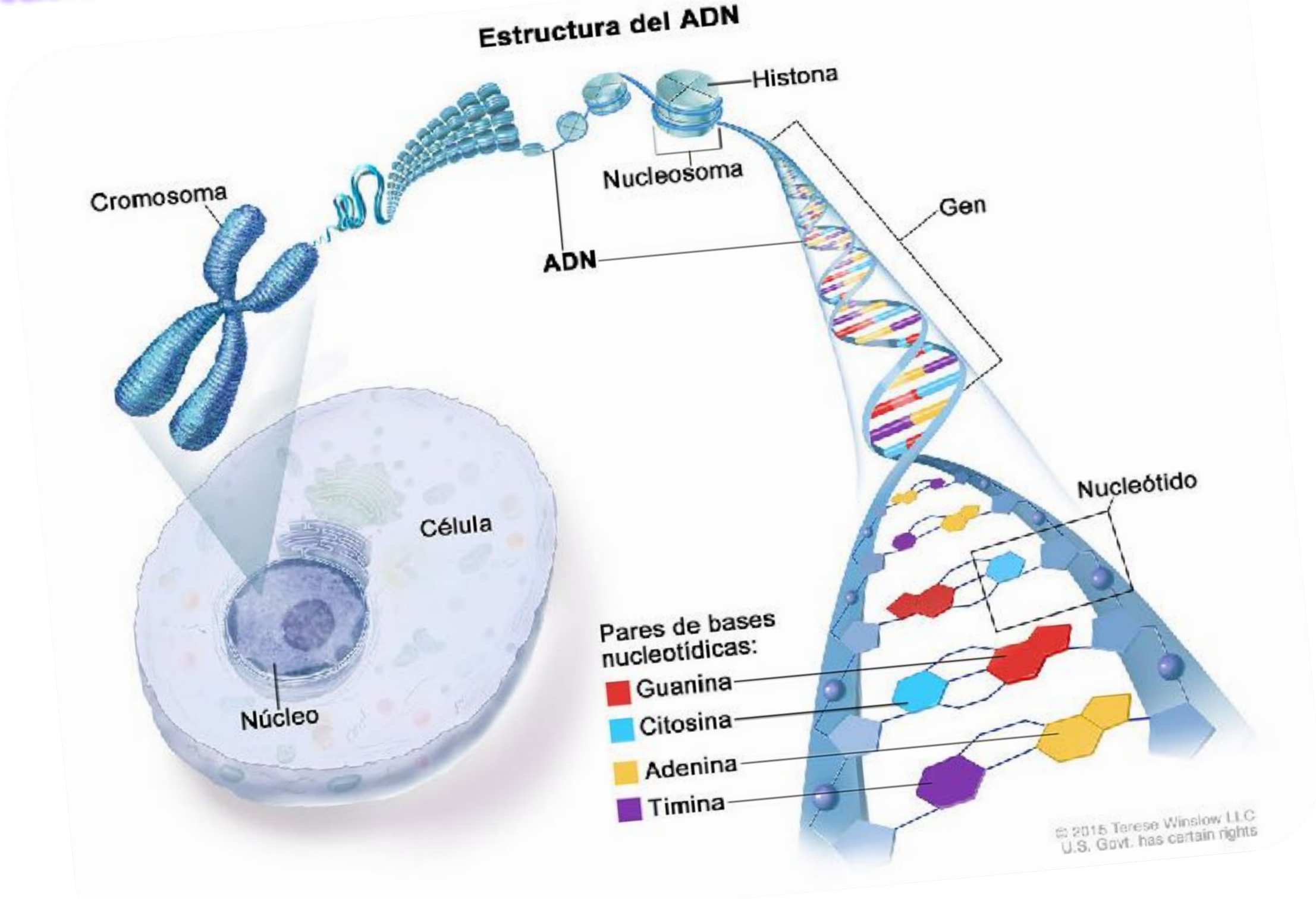
¿De qué hablamos cuando hablamos de Genómica y Economía?

Marcelo Kauffman
Programa de Medicina de Precisión y Genómica Clínica
Universidad Austral
Consultorio de Neurogenetica
Hospital JM Ramos Mejia

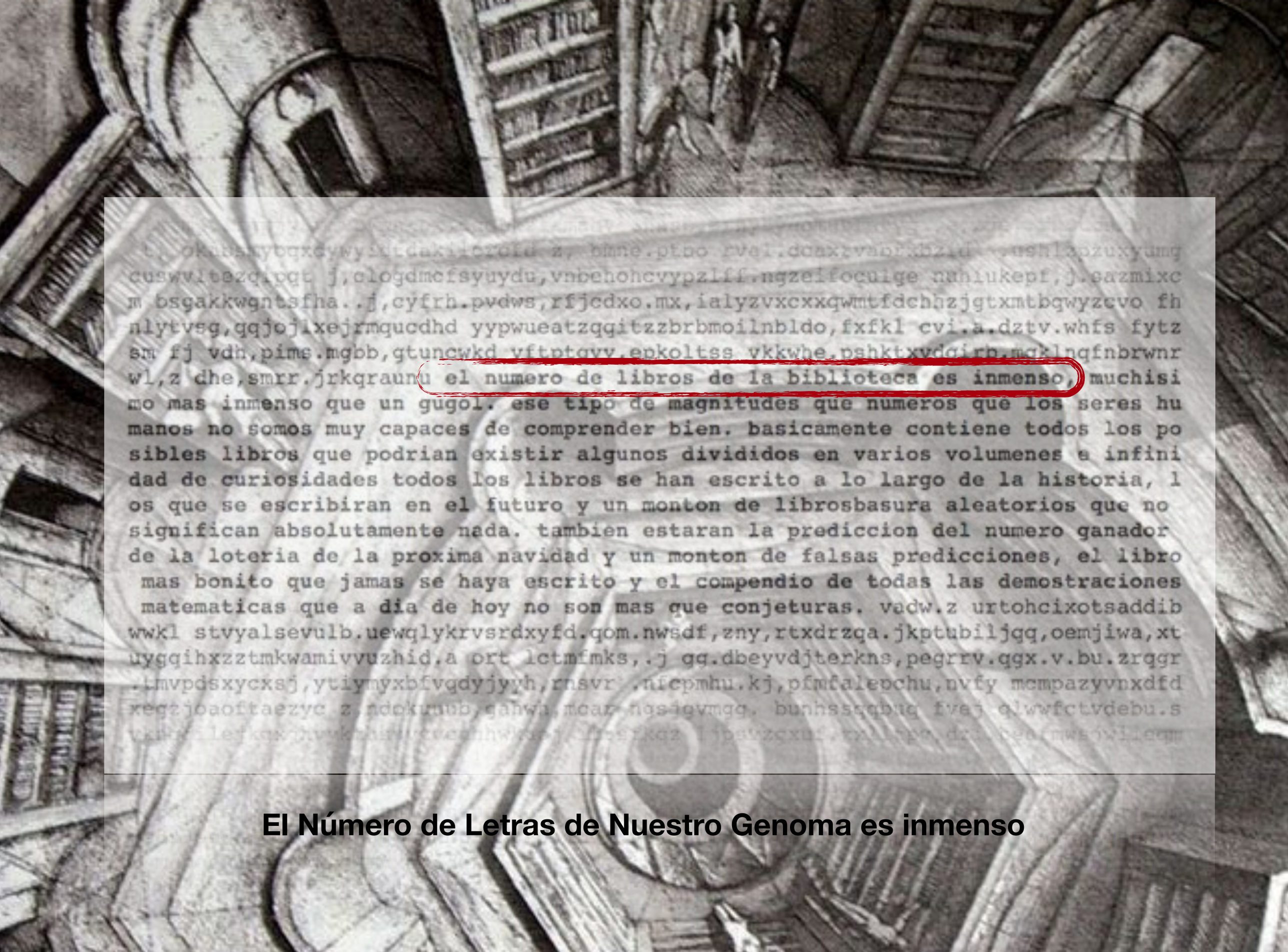
Nuestro Genoma es una Sucesión de 4 Letras: ACTG



MATERIAL GENÉTICO

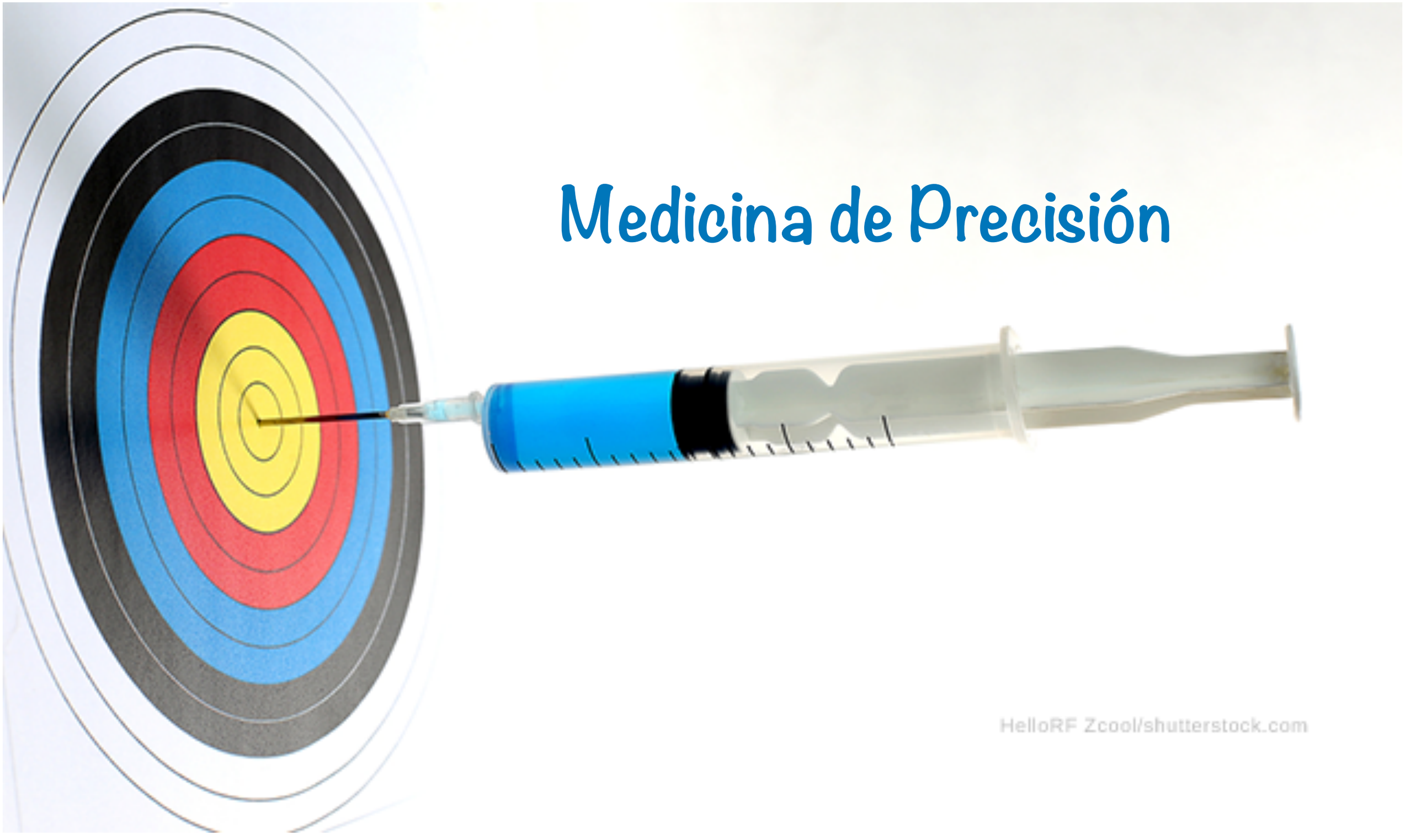


El universo (que otros llaman la Biblioteca) se compone de un número indefinido, y tal vez infinito, de galerías hexagonales, con vastos pozos de ventilación en el medio, cercados por barandas bajísimas. Desde cualquier hexágono, se ven los pisos inferiores y superiores: interminablemente. La distribución de las galerías es invariable. Veinte anaqueles, a cinco largos anaqueles por lado, cubren todos los lados menos dos; su altura, que es la de los pisos, excede apenas la de un bibliotecario normal. Una de las caras libres da a un angosto zaguán, que desemboca en otra galería, idéntica a la primera y a todas. A izquierda y a derecha del zaguán hay dos gabinetes minúsculos. Uno permite dormir de pie; otro, satisfacer



El Número de Letras de Nuestro Genoma es inmenso

Medicina de Precisión



HelloRF Zcool/shutterstock.com

Estudios de asocaición

Estudios caso-control

Población

Controles sanos

Pacientes (Sujetos de Interes) ~~Enfermos~~

Buscan relacionar un marcador genético particular con una enfermedad con herencia compleja, a través de una población, más que dentro de familias..
¿Cómo?

Se buscan los allelos (variantes) más frecuentes en una población de pacientes no relacionados, en comparación con una población similar de controles sanos

EN GWAS

examinando la mayor cantidad posible de genes.
Luego se realiza un mapeo fino de los sectores asociados a los SNPs validados, en busca de sitios de significativa asociación con el fenotipo estudiado

What is heritability?

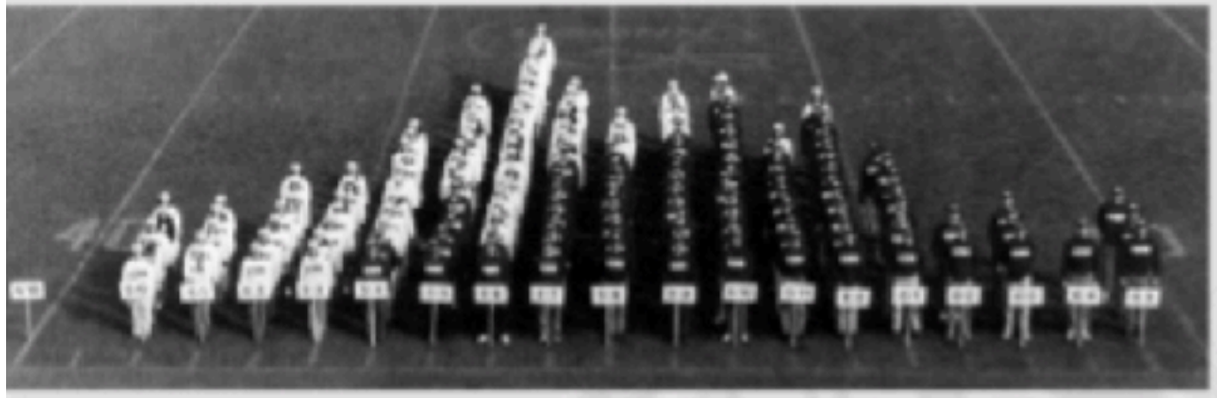
Heritability is an estimation of the proportion of observed trait variance, attributable to genetic influences.

Trait variance (Vp)

↓

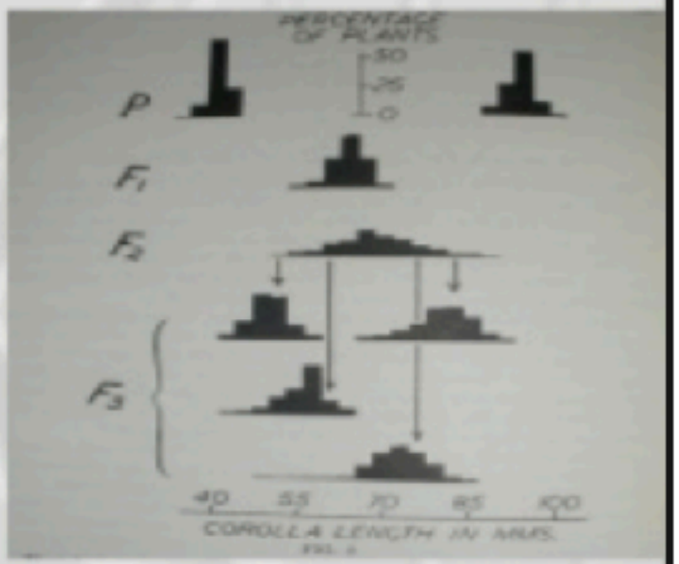
Vp = Variance due to genetics (V_g) +
variance due to non genetics (V_E)

1900-1925: the Dawn of Polygenicity



Biometricians recognize many traits are highly heritable but do not apparently adhere to Mendel's laws…violently opposed by Mendelians

Key experiments in plants, flies demonstrate that large phenotypic differences can arise from the sum of many contributors



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.)

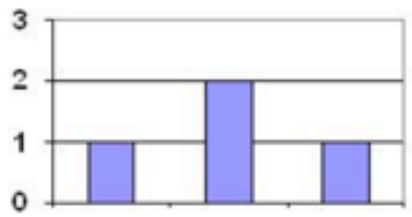
CONTENTS

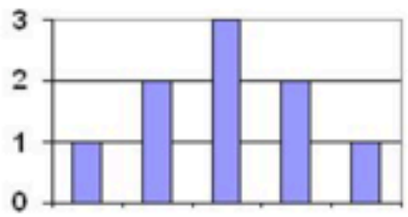
Fisher synthesizes model wherein large number of small 'Mendelian' factors can explain high heritability of continuous traits

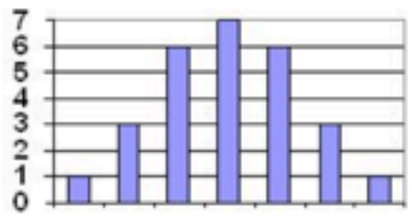
R.A. Fisher, 1918

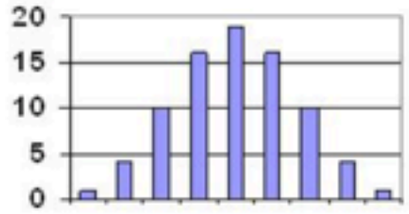
The explanation of quantitative inheritance in Mendelian terms

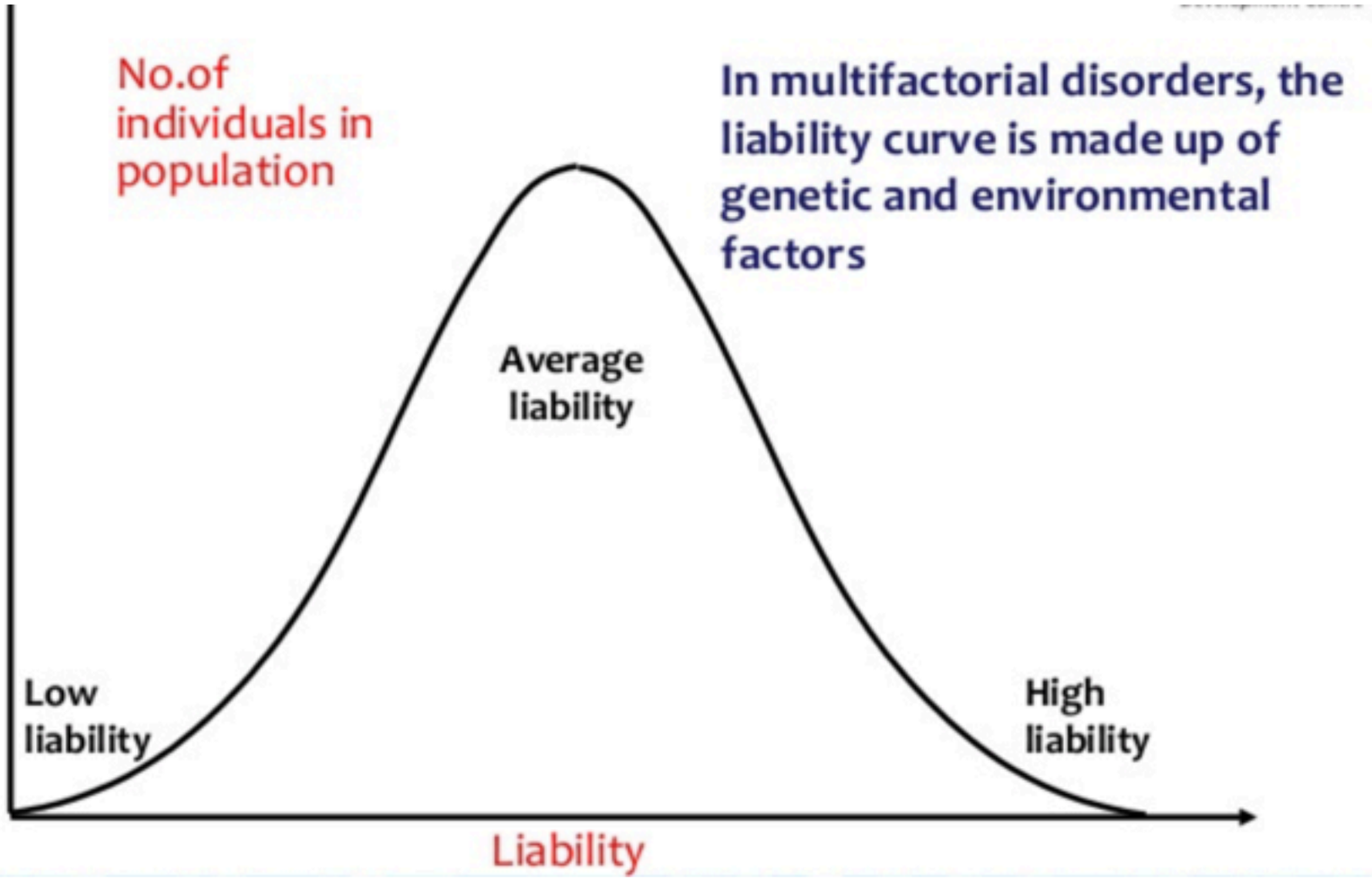
1 Gene	2 Genes	3 Genes	4 Genes
→ 3 Genotypes	→ 9 Genotypes	→ 27 Genotypes	→ 81 Genotypes
→ 3 Phenotypes	→ 5 Phenotypes	→ 7 Phenotypes	→ 9 Phenotypes










No.of individuals in population
In multifactorial disorders, the liability curve is made up of genetic and environmental factors
Average liability
Low liability
High liability
Liability

ORIGINAL ARTICLE

The False-positive to False-negative Ratio in Epidemiologic Studies

John P. A. Ioannidis,[a] *Robert Tarone,*[b] *and Joseph K. McLaughlin*[b]

Abstract: The ratio of false-positive to false-negative findings (FP:FN ratio) is an informative metric that warrants further evaluation. The FP:FN ratio varies greatly across different epidemiologic areas. In genetic epidemiology, it has varied from very high values (possibly even >100:1) for associations reported in candidate-gene studies to very low values (1:100 or lower) for associations with genome-wide significance. The substantial reduction over time in the FP:FN ratio in human genome epidemiology has corresponded to the routine adoption of stringent inferential criteria and comprehensive, agnostic reporting of all analyses. Most traditional fields of epidemiologic research more closely follow the practices of past candidate gene epidemiology, and thus have high FP:FN ratios

investigation. Finally, we discuss the interpretation and im plications of FP:FN ratios.

CONCEPTUALIZING THE FP:FN RATIO

For any tested association, in a binary framework, th resulting inference could be categorized as a true negativ false positive, false negative, or true positive. The categor zation can be applied to single studies as well as to collecti results derived from many data sets (meta-analyses). A though it may not be optimal to categorize results in dichotomous fashion, such an approach is common in th


I want more samples!...More more!
2000 is not enough
5000, 10000, 20000...they are not enough!
Do you hear me!!! I want more!
GENOMICS
CORE
GWASmania!
www.biocomicals.com

Genome-wide analysis of risk-taking behaviour and cross-disorder genetic correlations in 116 255 individuals from the UK Biobank cohort.

Rona J. Strawbridge PhD[1,2*+], Joey Ward MSc[1*] Breda Cullen DClinPsy [1], Elizabeth M. Tunbridge DPhil[3,4], Sarah Hartz MD[5], Laura Bierut MD[5], Amy Horton PhD[5,6], Mark E. S. Bailey PhD[7], Nicholas Graham MBChB[1], Amy Ferguson BSc[1], Donald M. Lyall PhD[1], Daniel Mackay PhD[1], Laura M. Pidgeon PhD[1], Jonathan Cavanagh MD[1], Jill P. Pell MD[1], Michael O'Donovan PhD[8], Valentina Escott-Price PhD[8], Paul J. Harrison FRCPsych[3,4], Daniel J. Smith MD[1].

[1]Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK. [2]Department of Medicine

Why It Is Hard to Find Genes Associated With Social Science Traits: Theoretical and Empirical Considerations

Christopher F. Chabris, PhD, James J. Lee, PhD, Daniel J. Benjamin, PhD, Jonathan P. Beauchamp, PhD, Edward L. Glaeser, PhD, Gregoire Borst, PhD, Steven Pinker, PhD, and David I. Laibson, PhD

LETTER

doi:10.1038/nature17671

Genome-wide association study identifies 74 loci associated with educational attainment

A list of authors and their affiliations appears in the online version of the paper.

Educational attainment is strongly influenced by social and other environmental factors, but genetic factors are estimated to account for at least 20% of the variation across individuals[1]. Here we report the results of a genome-wide association study (GWAS) for educational attainment that extends our earlier discovery sample[1,2] of 101,069 individuals to 293,723 individuals, and a replication study in an independent sample of 111,349 individuals from the UK Biobank. We identify 74 genome-wide significant loci associated with the number of years of schooling completed. Single-

Our meta-analysis identified 74 approximately independent genome-wide significant loci. For each locus, we define the 'lead SNP' as the SNP in the genomic region that has the smallest *P* value (Supplementary Information section 1.6.1). Figure 1 shows a Manhattan plot with the lead SNPs highlighted. This includes the three SNPs that reached genome-wide significance in the discovery stage of our previous GWAS meta-analysis of educational attainment[1]. The quantile–quantile (Q–Q) plot of the meta-analysis (Extended Data Fig. 1) exhibits inflation ($\lambda_{GC} = 1.28$), as expected under polygenicity[3].

Selection against variants in the genome associated with educational attainment

Augustine Kong[a,b,1], Michael L. Frigge[a], Gudmar Thorleifsson[a], Hreinn Stefansson[a], Alexander I. Young[c], Florian Zink[a], Gudrun A. Jonsdottir[a], Aysu Okbay[d,e], Patrick Sulem[a], Gisli Masson[a], Daniel F. Gudbjartsson[a,b], Agnar Helgason[a,f], Gyda Bjornsdottir[a], Unnur Thorsteinsdottir[a,g], and Kari Stefansson[a,g,1]

[a]deCODE genetics/Amgen Inc., Reykjavik 101, Iceland; [b]School of Engineering and Natural Sciences, University of Iceland, Reykjavik 101, Iceland; [c]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, United Kingdom; [d]Department of Applied Economics, Erasmus School of Applied Economics, Erasmus University Rotterdam, 3062 PA Rotterdam, The Netherlands; [e]Institute for Behavior and Biology, Erasmus University Rotterdam, 3062 PA Rotterdam, The Netherlands; [f]Department of Anthropology, University of Iceland, Reykjavik 101, Iceland; and [g]Faculty of Medicine, University of Iceland, Reykjavik 101, Iceland

Edited by Andrew G. Clark, Cornell University, Ithaca, NY, and approved December 5, 2016 (received for review July 22, 2016)

Epidemiological and genetic association studies show that genet- 62 cohorts were used to determine the weightings for $\mathrm{POLY}_{\mathrm{EDU}}$.

Leading Edge
Perspective

Cell

An Expanded View of Complex Traits: From Polygenic to Omnigenic

Evan A. Boyle,[1,*] Yang I. Li,[1,*] and Jonathan K. Pritchard[1,2,3,*]
[1]Department of Genetics
[2]Department of Biology
[3]Howard Hughes Medical Institute
Stanford University, Stanford, CA 94305, USA
*Correspondence: eaboyle@stanford.edu (E.A.B.), yangili@stanford.edu (Y.I.L.), pritch@stanford.edu (J.K.P.)
http://dx.doi.org/10.1016/j.cell.2017.05.038

A central goal of genetics is to understand the links between genetic variation and disease. Intuitively, one might expect disease-causing variants to cluster into key pathways that drive disease etiology. But for complex traits, association signals tend to be spread across most of the genome—including near many genes without an obvious connection to disease. We propose that gene regulatory networks are sufficiently interconnected such that all genes expressed in disease-relevant cells are liable to affect the functions of core disease-related genes and that most heritability can be explained by effects on genes outside core pathways. We refer to this hypothesis as an "omnigenic" model.

ble de libros. Yo me atrevo a insinuar esta
ma: La Biblioteca es ilimitada y periódica. Si
anara en cualquier dirección, comprobaría al
os mismos volúmenes se repitan en el mismo de
n orden: el Orden). Mi soledad se alegra con esa

Jorge Luis Borges

¡GRACIAS!

marcelokauffman@marcelokauffman.info