LD Score: theory

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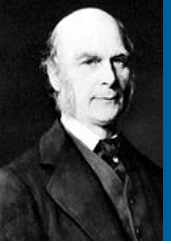


Francis Galton
Twin and family studies

RATE OF REGRESSION IN HEREDITARY STATURE.
Fig. (a.)

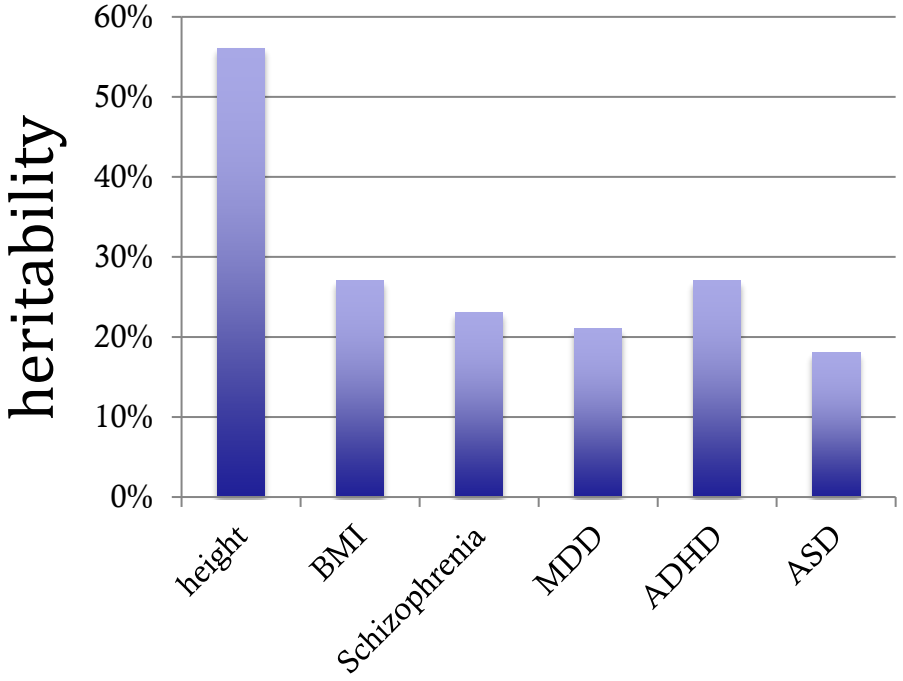
- Relatives are more similar

Meta-analysis of the heritability of human traits based on fifty years of twin studies

Tinca J C Polderman[1,10], Beben Benyamin[2,10], Christiaan A de Leeuw[1,3], Patrick F Sullivan[4–6], Arjen van Bochoven[7], Peter M Visscher[2,8,11] & Danielle Posthuma[1,9,11]

Average estimate of heritability 49%
69% of twin studies support a purely additive genetic model

GREML/GCTA



- Use estimated genetic similarity

REPORT

GCTA: A Tool for Genome-wide Complex Trait Analysis

Jian Yang,[1,*] S. Hong Lee,[1] Michael E. Goddard,[2,3] and Peter M. Visscher[1]

ANALYSIS

nature genetics

Common SNPs explain a large proportion of the heritability for human height

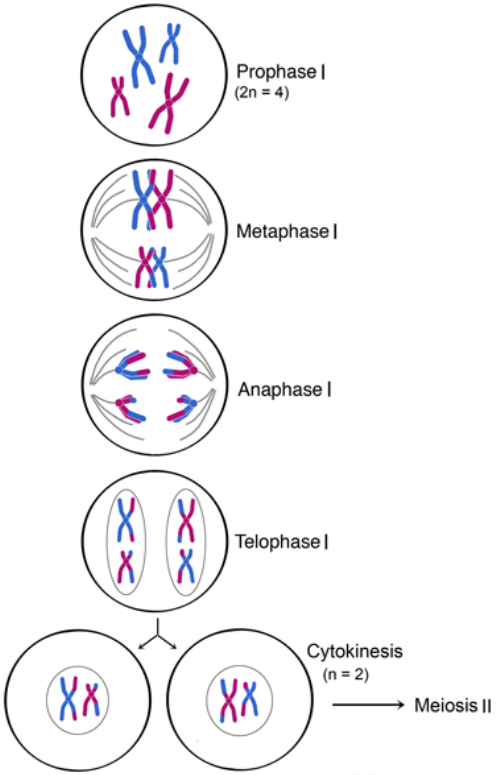
Jian Yang[1], Beben Benyamin[1], Brian P McEvoy[1], Scott Gordon[1], Anjali K Henders[1], Dale R Nyholt[1], Pamela A Madden[2], Andrew C Heath[2], Nicholas G Martin[1], Grant W Montgomery[1], Michael E Goddard[3] & Peter M Visscher[1]

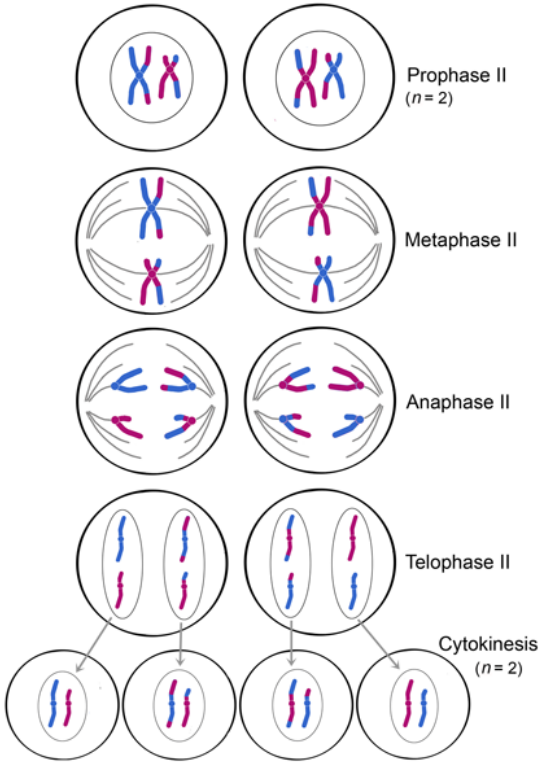
ARTICLE

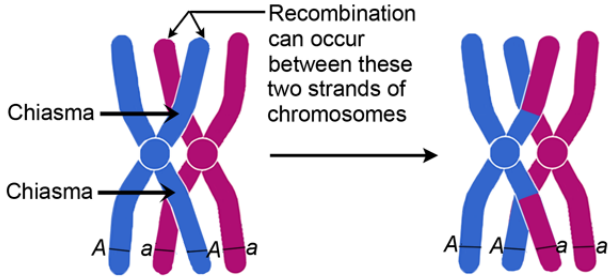
Estimating Missing Heritability for Disease from Genome-wide Association Studies

Sang Hong Lee,[1] Naomi R. Wray,[1] Michael E. Goddard,[2,3] and Peter M. Visscher[1,*]

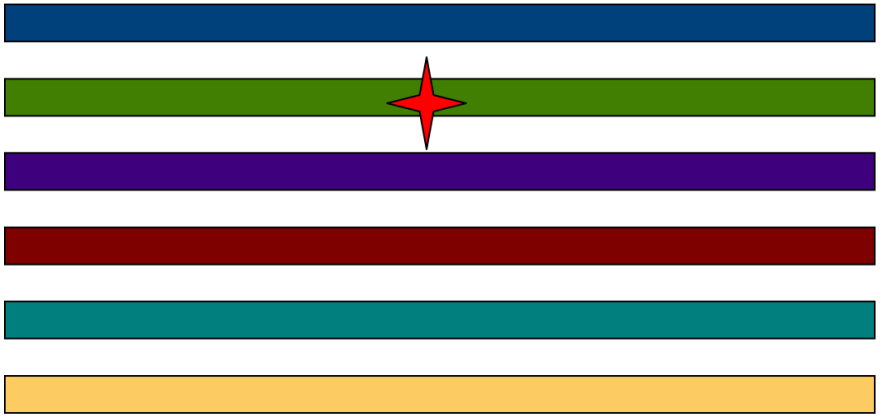
What happens to our genomes when making sperm and egg cells?



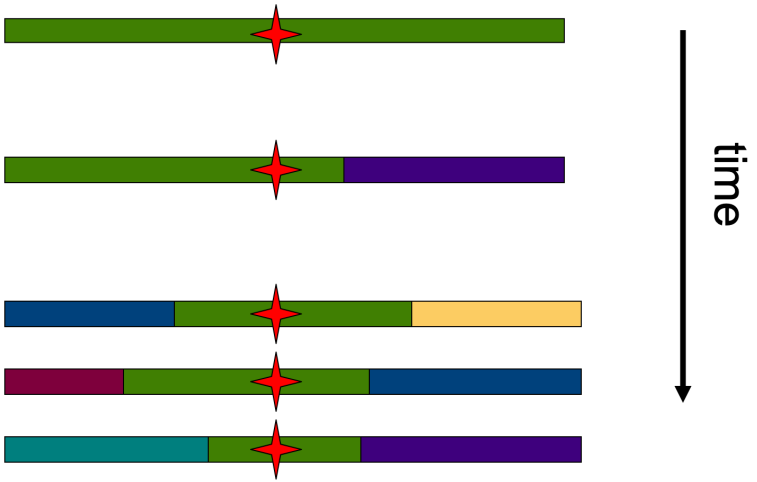




What happens when a new mutation arises?



Recombination mixes up the haplotype structure



Estimators of LD

A/a B/b

Two SNPs A and B
Genotypes: AA, Aa, aa
BB, Bb, bb

$$D_{AB} = p_{AB} - p_A p_B$$

$$D' = \frac{D}{D_{\max}}$$

where

$$D_{\max} = \begin{cases} \max\{-p_A p_B,\ -(1-p_A)(1-p_B)\} & \text{when } D < 0 \\ \min\{p_A(1-p_B),\ (1-p_A)p_B\} & \text{when } D > 0 \end{cases}$$

$$r^2 = \frac{D^2}{p_A(1-p_A)p_B(1-p_B)}.$$

nature › nature reviews genetics › review articles › article

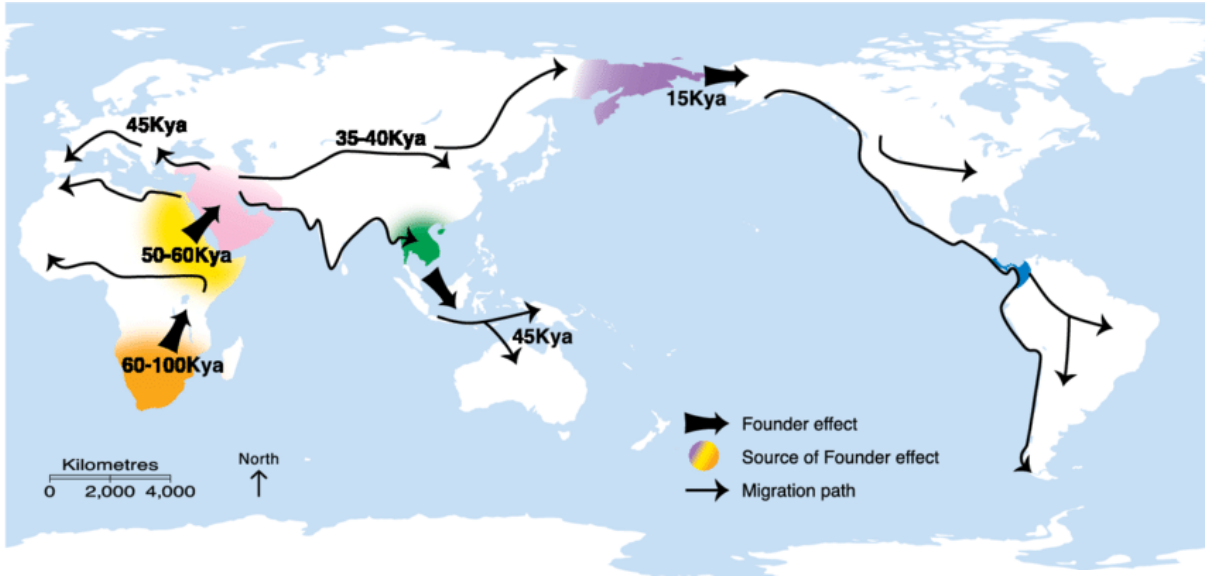
Review Article | Published: June 2008

Linkage disequilibrium – understanding the evolutionary past and mapping the medical future

Montgomery Slatkin

Nature Reviews Genetics **9**, 477–485 (2008) | Cite this article

Genetic ancestry



Henn et al. (2012)

PERSPECTIVE | BIOLOGICAL SCIENCES |

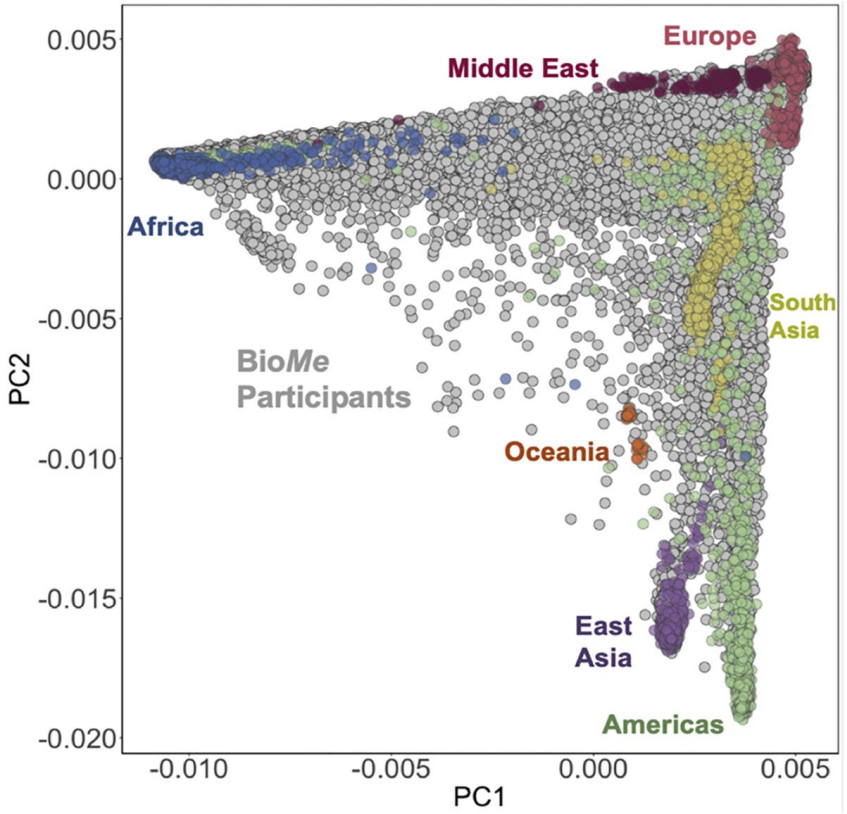
The great human expansion

Brenna M. Henn, L. L. Cavalli-Sforza, and Marcus W. Feldman Authors Info & Affiliations

Edited by C. Owen Lovejoy, Kent State University, Kent, OH, and approved September 25, 2012 (received for review July 19, 2012)

October 17, 2012 | 109 (44) 17758-17764 | https://doi.org/10.1073/pnas.1212380109

Principal component analysis on genetic data estimates structure



POLICY FORUM | GENETICS AND SOCIETY

Getting genetic ancestry right for science and society

We must embrace a multidimensional, continuous view of ancestry and move away from continental ancestry categories

ANNA C. F. LEWIS , SANTIAGO J. MOLINA, PAUL S. APPELBAUM, BEGE DAUDA, ANNA DI RIENZO, AGUSTIN FUENTES, STEPHANIE M. FULLERTON, NANIBAA' A. GARRISON, NAYANIKA GHOSH, [...], AND DANIELLE S. ALLEN +10 authors Authors Info & Affiliations

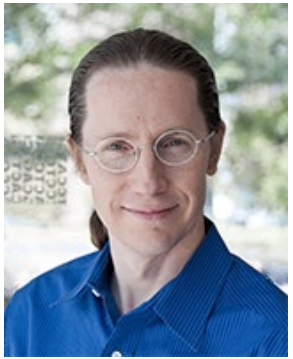
LD Score regression

With thanks

Brendan Bulik-Sullivan

Hilary Finucane

Po-Ru Loh



Mark Daly

Alkes Price

How does LD shape association?

LD Score regression distinguishes confounding from polygenicity in genome-wide association studies

Brendan K Bulik-Sullivan, Po-Ru Loh, Hilary K Finucane, Stephan Ripke, Jian Yang, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Nick Patterson, Mark J Daly, Alkes L Price & Benjamin M Neale

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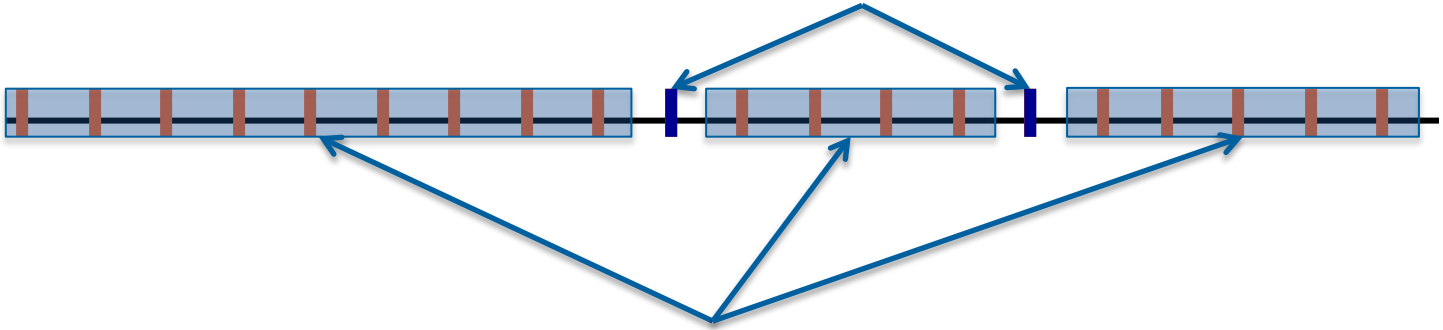
Lonely SNPs [no LD]



LD blocks

How does LD shape association?

- Lonely SNPs [no LD]
- LD blocks
- * Causal variants

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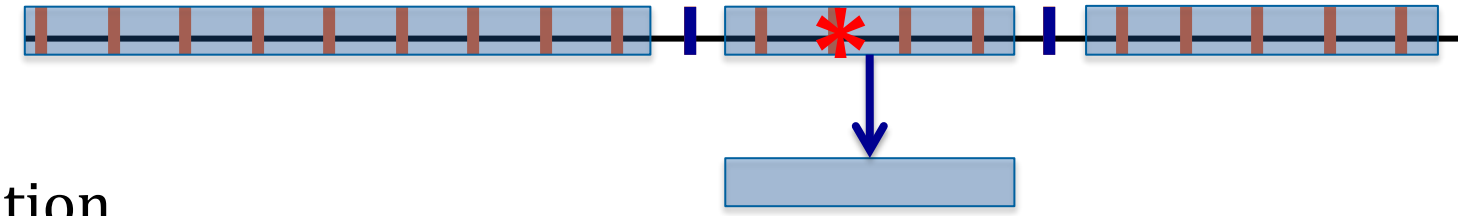

Association

All markers correlated with a causal variant show association

How does LD shape association?

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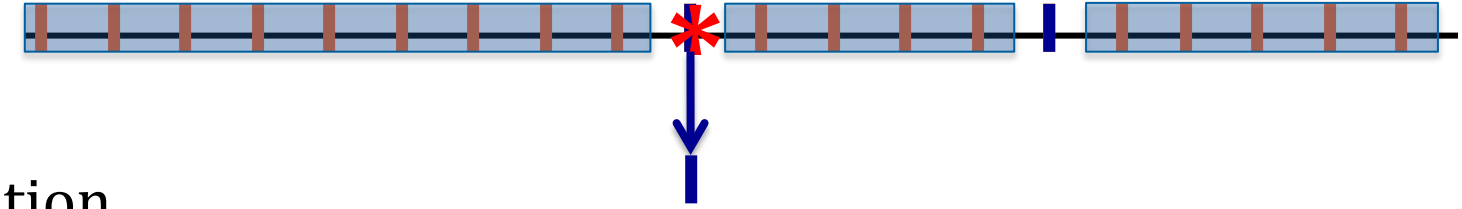

Association

Lonely SNPs only show association if they are causal

What happens under polygenicity?

- Lonely SNPs [no LD]
- LD blocks
- * Causal variants

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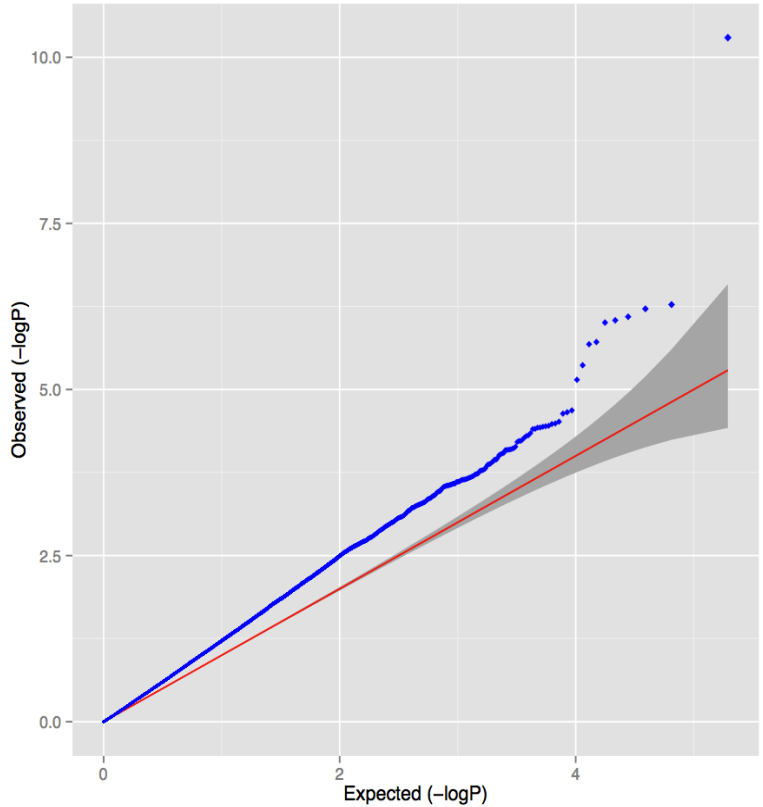
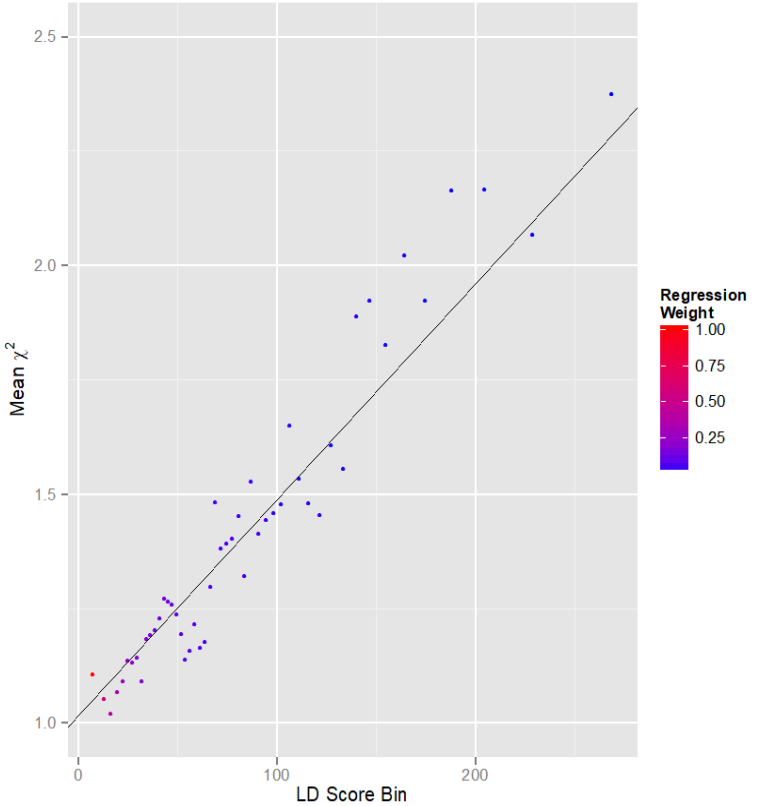
Assuming a uniform prior, we see SNPs with more LD friends showing more association

The more you tag, the more likely you are to tag a causal variant

Simulated polygenic architecture

Lambda = 1.30 LD score intercept = 1.02





What happens under stratification?

- Lonely SNPs [no LD]
- LD blocks
- * Causal variants

LD Score regression distinguishes confounding from polygenicity in genome-wide association studies

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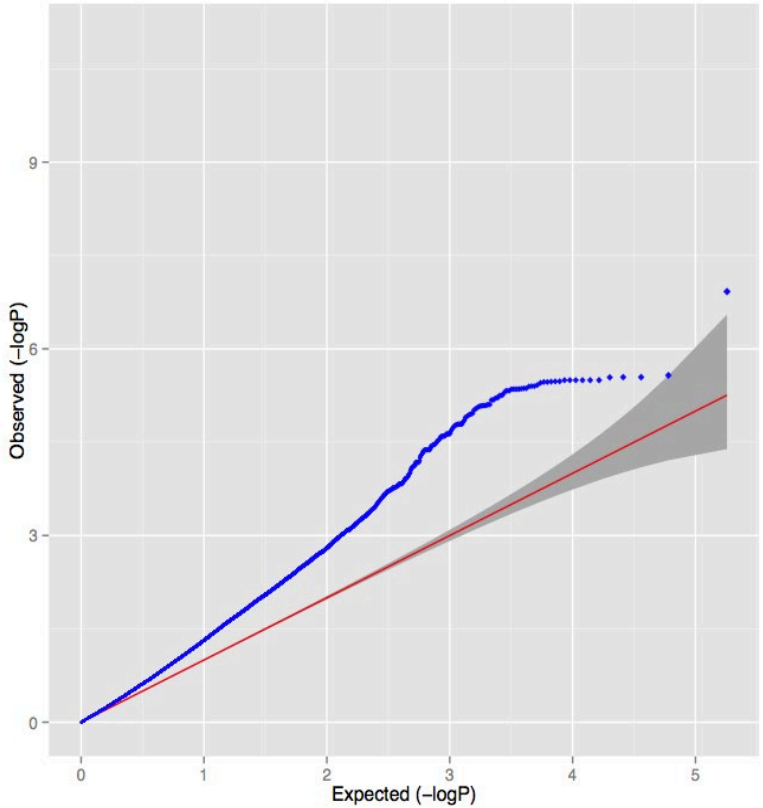
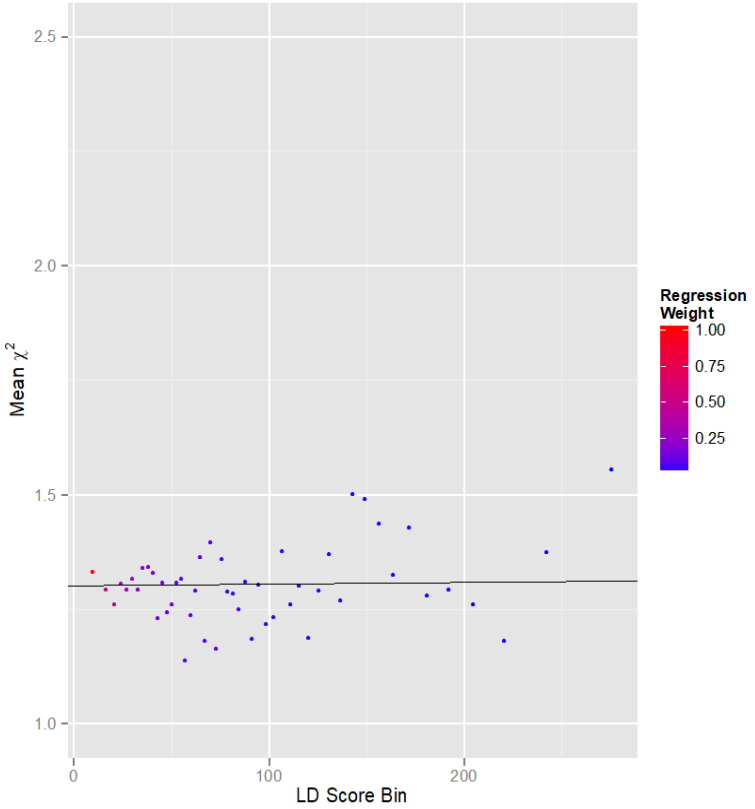
Under pure drift we expect LD to have no relationship to differences in allele frequencies between populations

UK controls versus Sweden controls

Lambda = 1.30 LD score intercept = 1.32





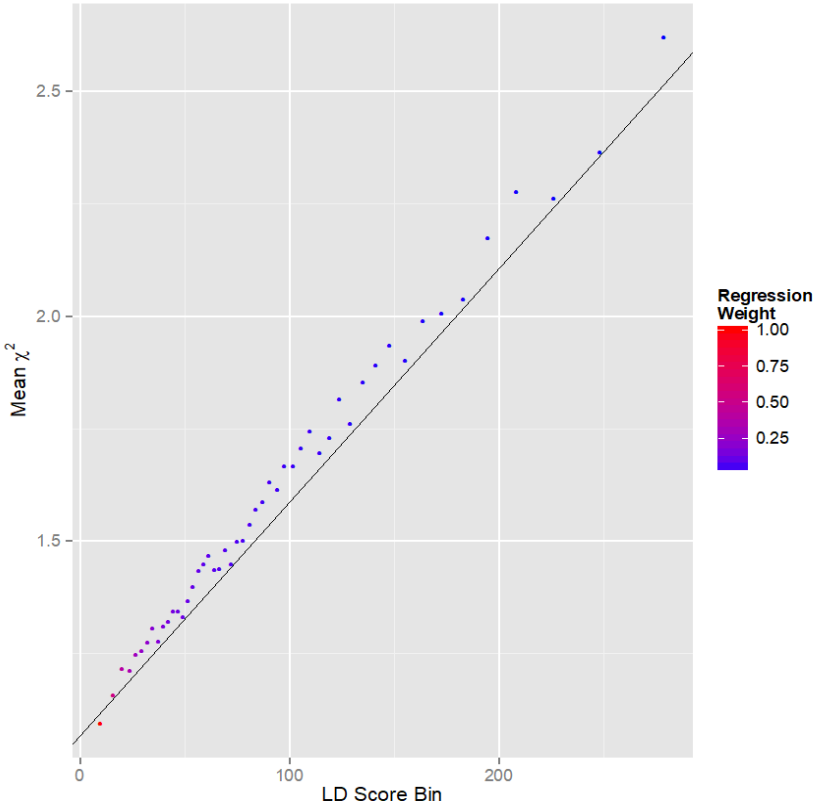
PGC Schizophrenia

Lambda = 1.48

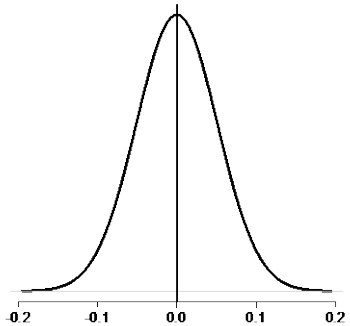
Intercept = 1.06

Slope p-value < 10^{-300}

Overwhelming majority of inflation is consistent with polygenic architecture



LD Score regression



Draw polygenic effects from
N (0, n/m^2), var =

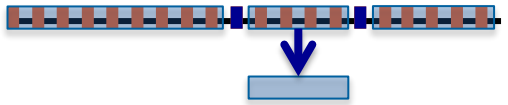
What is the E[χ^2] for variant *j*?

$$E[\chi_j^2] = 1 + Na + \frac{h_g^2 N}{M} l_j$$ New estimator of heritability

where N=sample size, M=# of SNPs, a=inflation due to confounding, h^2g is heritability (total obs.) and l_j is the *LD Score*

Bulik-Sullivan et al. Nature Genetics 2015
Yang et al. EJHG 2011

$$l_j = \sum_{k \neq j} r_{jk}^2$$



What isn’t in LD score?

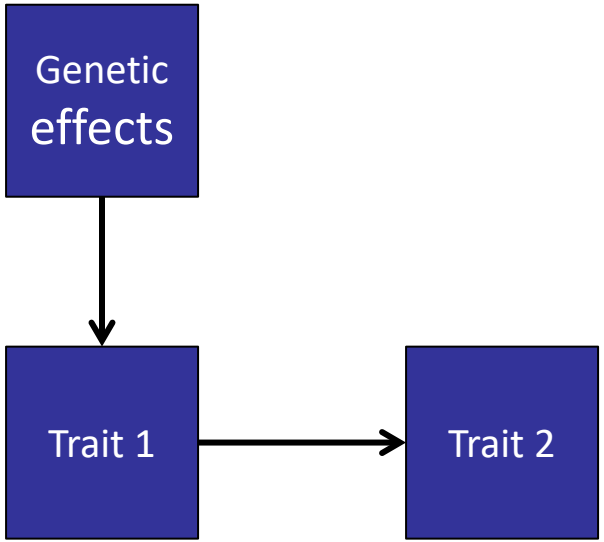
- Genetic variation that is not tagged well by common variation
- Heterogeneity of traits

Genetic Correlation Method in:

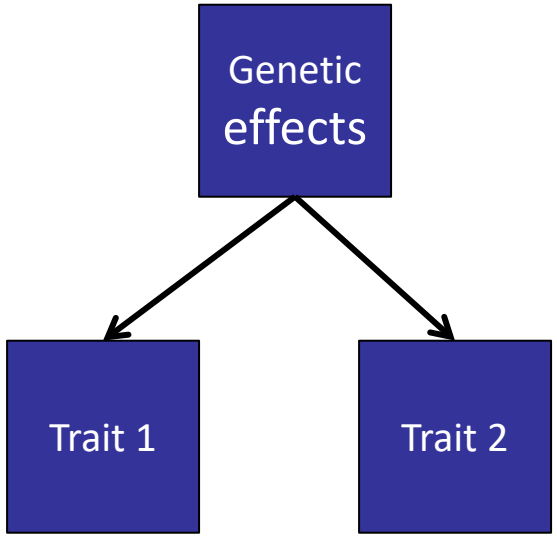
nature genetics

An atlas of genetic correlations across human diseases and traits

Potential sources of genetic correlation



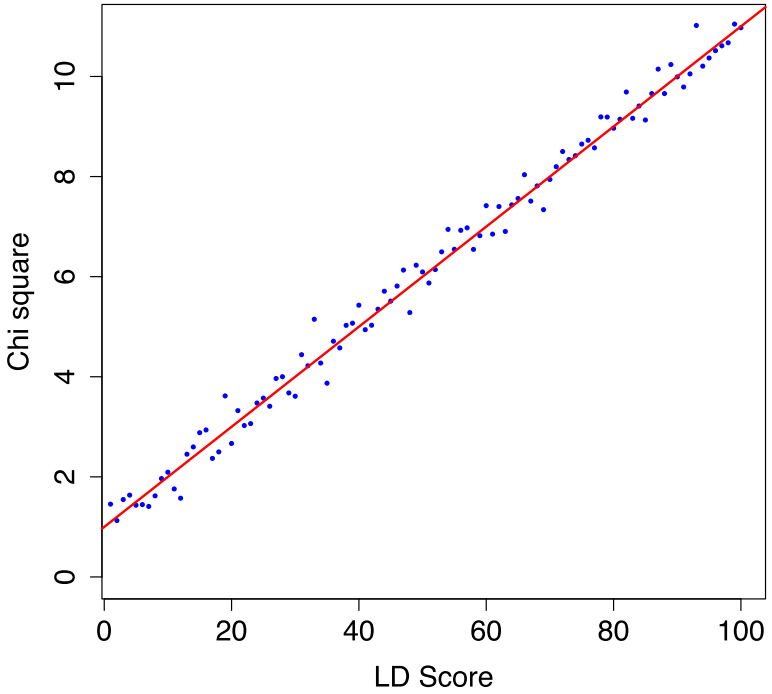
Trait 1 exerts causal effect on Trait 2



Genetic effects influence Trait 1 and Trait 2

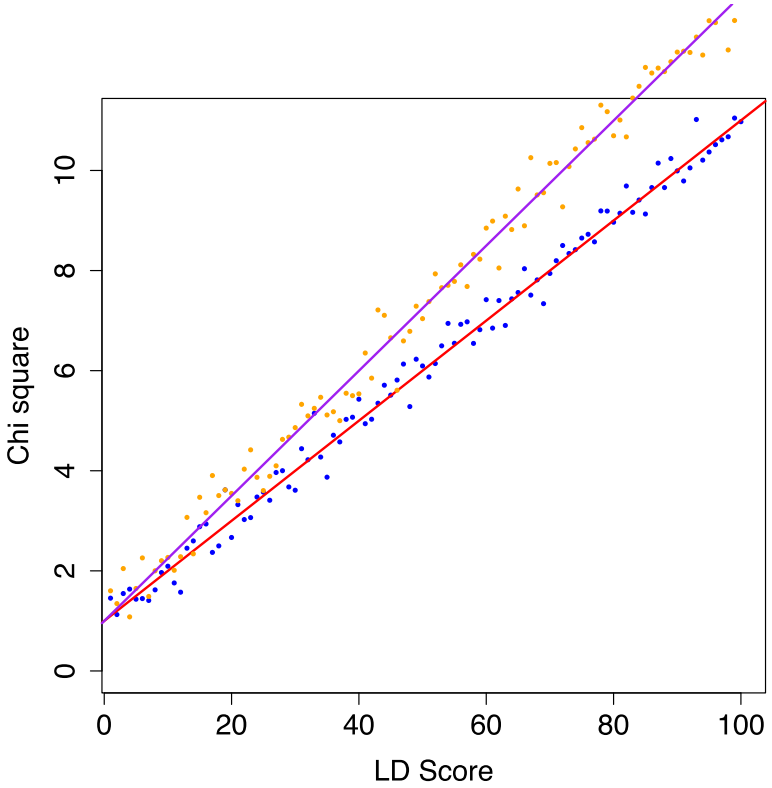
LD Score regression
Genetic correlation

Trait 1



Slope estimates heritability

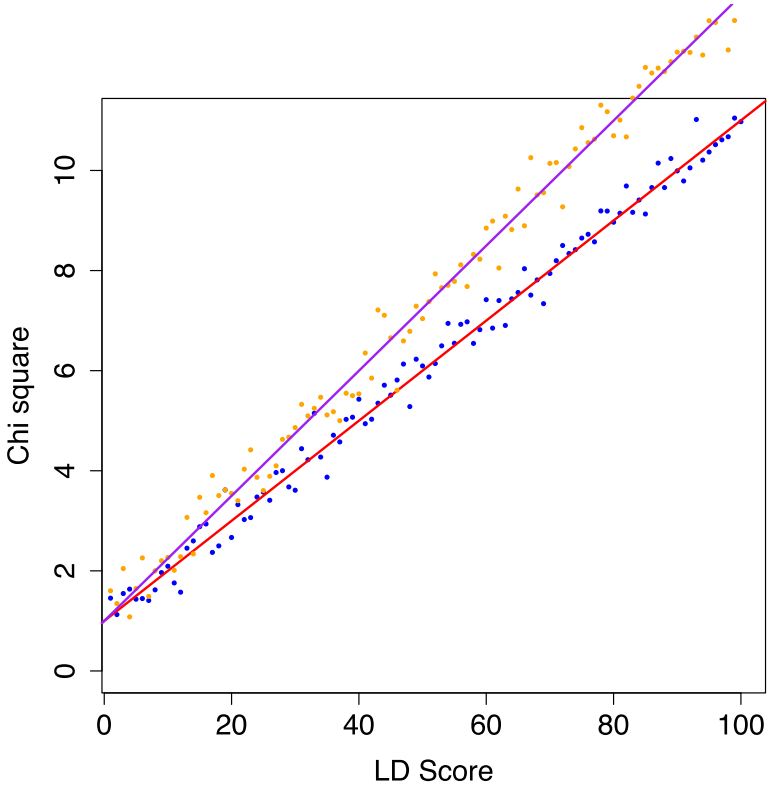
LD Score regression
Genetic correlation



Trait 1
Trait 2

We can a second trait and obtain two heritability estimates

LD Score regression
Genetic correlation

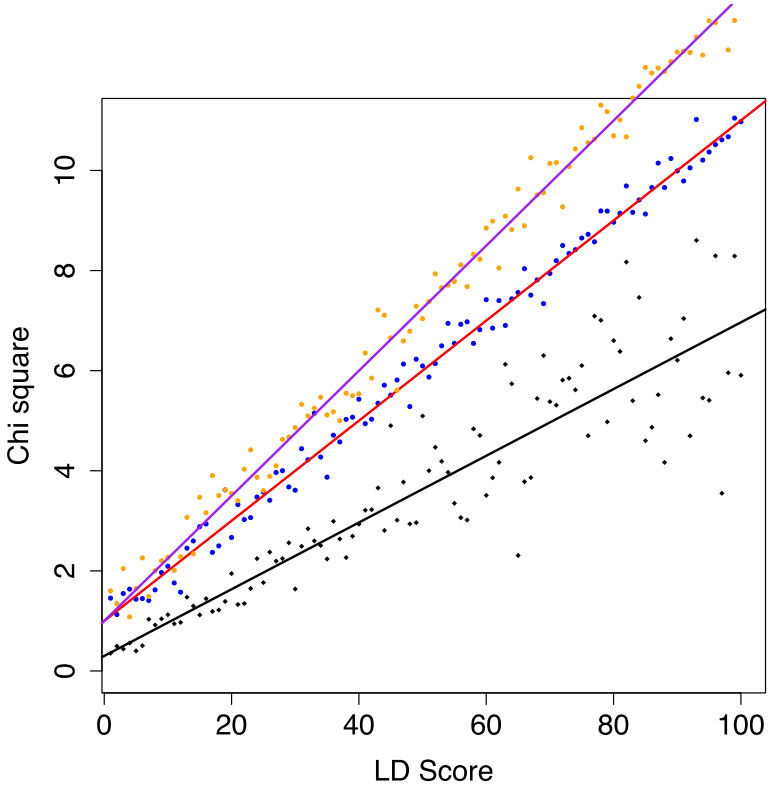


Trait 1
Trait 2

$Z^*Z = \chi^2$

So we can estimate genetic covariance from the product of the Z-scores

LD Score regression
Genetic correlation



Trait 1

Trait 2

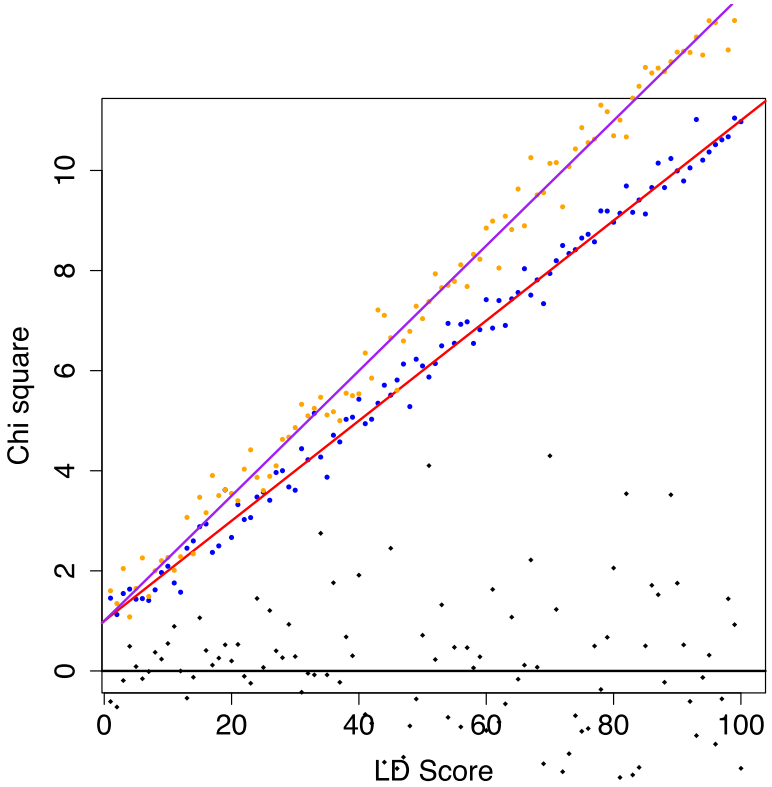
R_G

$Z^*Z = \chi^2$

So we can estimate genetic covariance from the product of the Z-scores for the two traits

$R_G = 0.5$

LD Score regression
Genetic correlation



Trait 1

Trait 2

R_G

Here $R_G = 0$

This approach is robust to sample overlap as all variants are equally inflated