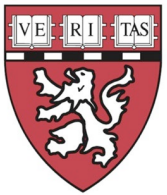
LD Score: theory

Benjamin Neale, Ph.D.
Analytic and Translational Genetics Unit, MGH
Stanley Center for Psychiatric Research & Program in Medical and Population Genetics, Broad Institute



BGA 2025 – Atlanta!

55th Annual Meeting of the Behavior Genetics Association

25 - 28 June 2025

Atlanta, Georgia, USA

About the 2025 BGA Meeting

Get ready for BGA in ATLanta! We are looking forward to seeing you and learning about your science. The 55th annualGet ready for BGA in ATLanta! We are looking forward to seeing you and learning about your science. The annual BGA meeting will be held on the Emory University Campus. The 2025 meeting will bring together renowned researchers in the field of behavior genetics, including plenary sessions by local researchers. The theme of this year's meeting is "Harnessing broader perspectives of phenotypic and genotypic risk and liability". The meeting will include both formal presentations by faculty and trainees and multiple networking opporutnities. Please join the conversation about the meeting on social media (INCLUDE LINK HERE)

Local Hosts

Rohan HC Palmer **and** Irwin Waldman

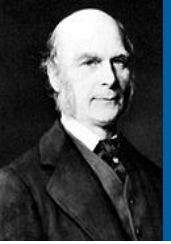
Program Chair

Benjamin Neale

Important Dates (Event)

- **55th Annual Meeting, Atlanta, GA, USA, 25-28 June 2025**
- **Welcome Reception, Evening of 25 June, Location TBD**
- **Closing Reception, Evening of 28 June, Location TBD**

Here is the abstract submission



Francis Galton
Twin and family studies

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

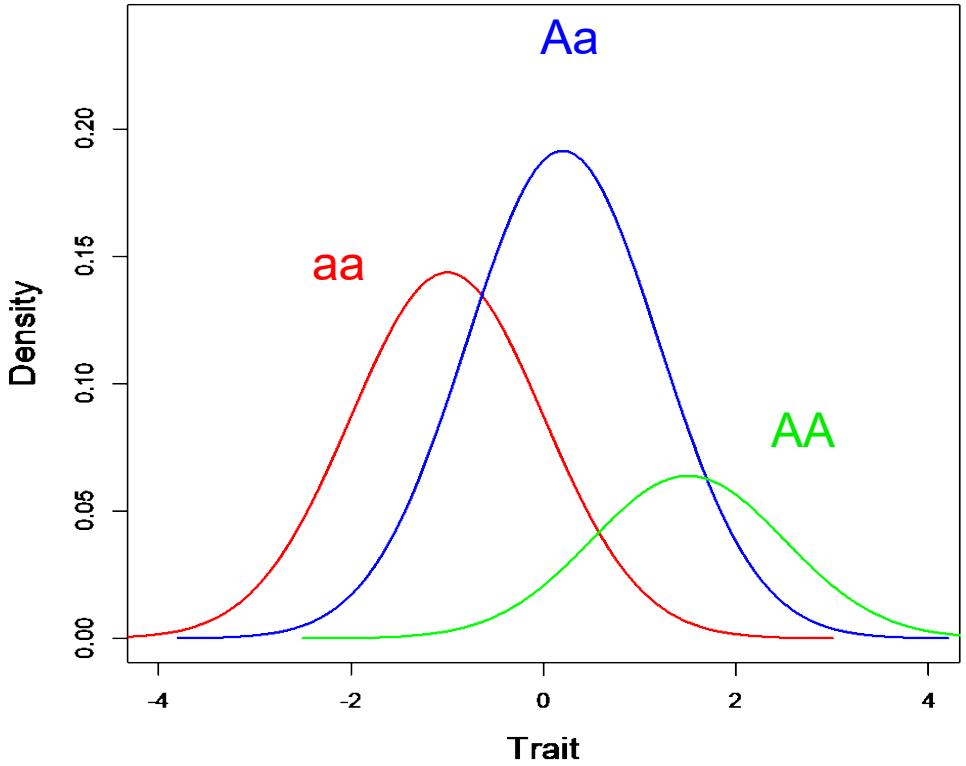
- Relatives are more similar

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

Source of variation



How much mean and variance?

1. Defining the Mean (*X*)

e.g. cholesterol levels in the population

$$\mu = \sum_i x_i f(x_i)$$

Genotypes	***AA***	***A a***	***aa***
Effect, x	***a***	***d***	***-a***
Frequencies, *f*(x)	p^2	***2pq***	q^2

Mean (X)= $a(p^2) + d(2pq) - a(q^2) = a(p-q) + 2pqd$

How much mean and variance?

2. Contribution of the QTL to the Variance *(X)*

$$Var = \sum_i (x_i - \mu)^2 f(x_i)$$

Genotypes	**AA**	**A a**	**aa**
Effect, x	**a**	**d**	**-a**
Frequencies, *f*(x)	p^2	$2pq$	q^2

$$Var\ (X) = (a-m)^2p^2 + (d-m)^2 2pq + (-a-m)^2q^2$$

$$= V_{QTL}$$

Heritability of *X* at this locus = V_{QTL} / V_{Total}

How much mean and variance?

$$Var\,(X) = (a-m)^2p^2 + (d-m)^2 2pq + (-a-m)^2q^2$$

$$= \underline{2pq[a+(q-p)d]^2} + \underline{(2pqd)^2}$$

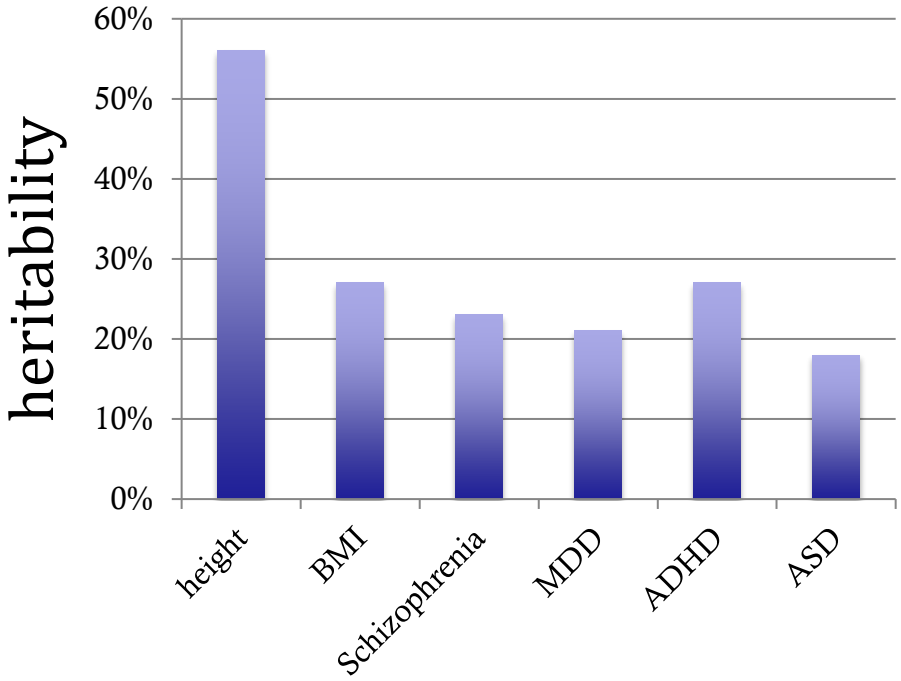
$$= V_{A_{QTL}} + V_{D_{QTL}}$$

Additive effects: the main effects of individual alleles

Dominance effects: represent the deviation from additive effects

$m = a(p-q) + 2pqd$

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

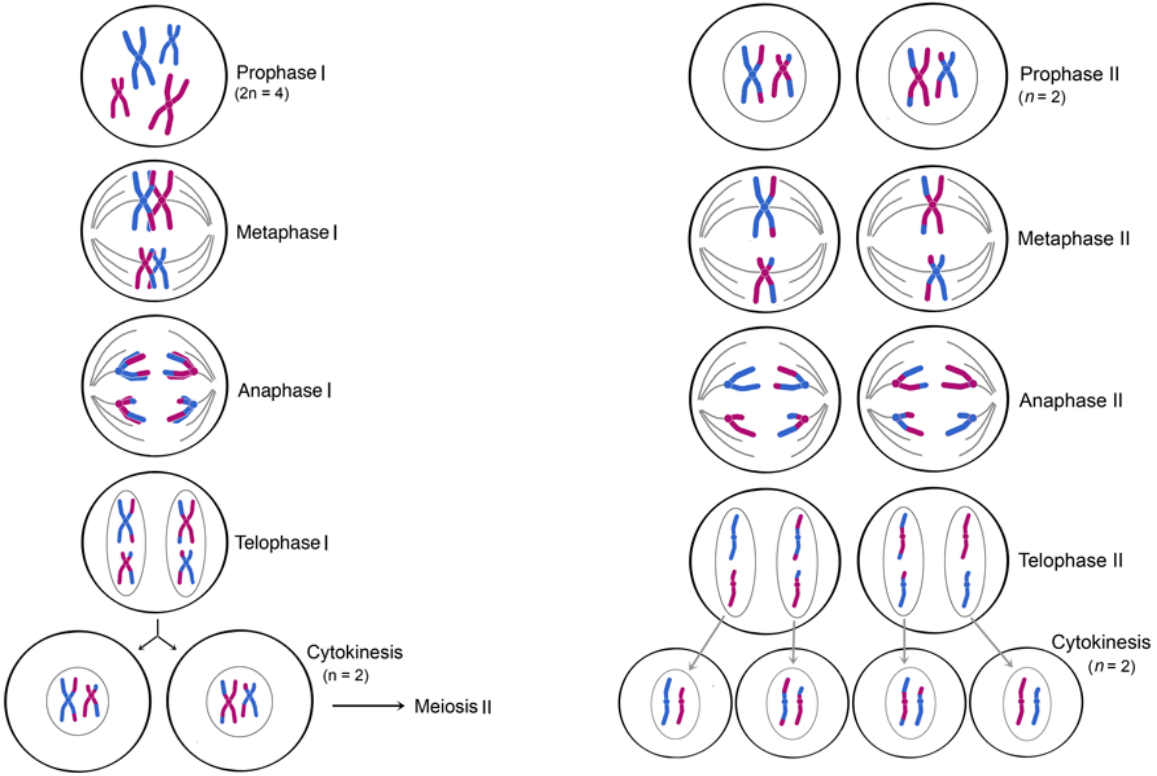
Jian Yang[1], Beben Benyamin[1], Brian P McEvoy[1], Scott Gordon[1], Anjali K Henders[1], Dale R Nyholt[1], Pamela A Madden[2], Andrew C Heath[2], Nicholas G Martin[1], Grant W Montgomery[1], Michael E Goddard[3] & Peter M Visscher[1]

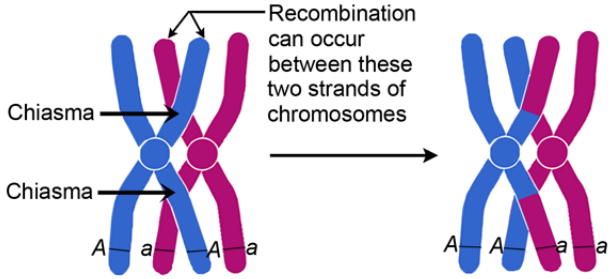
ARTICLE

Estimating Missing Heritability for Disease from Genome-wide Association Studies

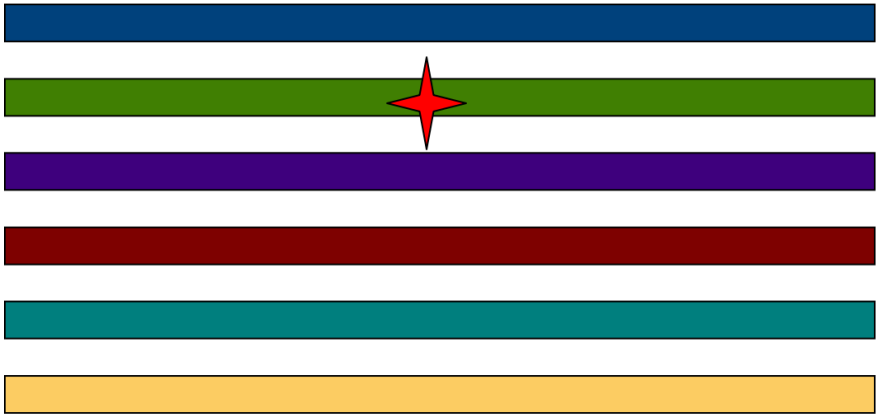
Sang Hong Lee,[1] Naomi R. Wray,[1] Michael E. Goddard,[2,3] and Peter M. Visscher[1,*]

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

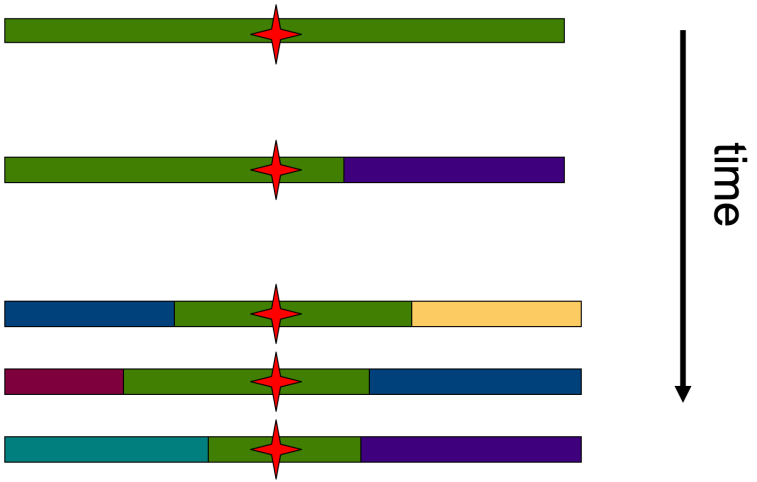




What happens when a new mutation arises?



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

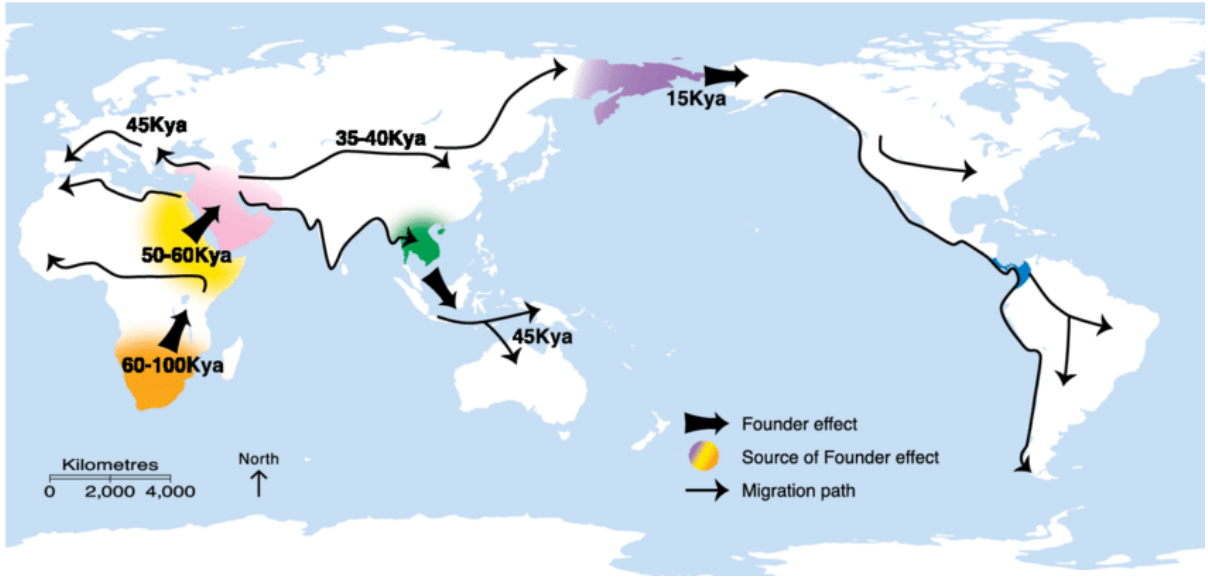
Review Article | Published: June 2008

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 |

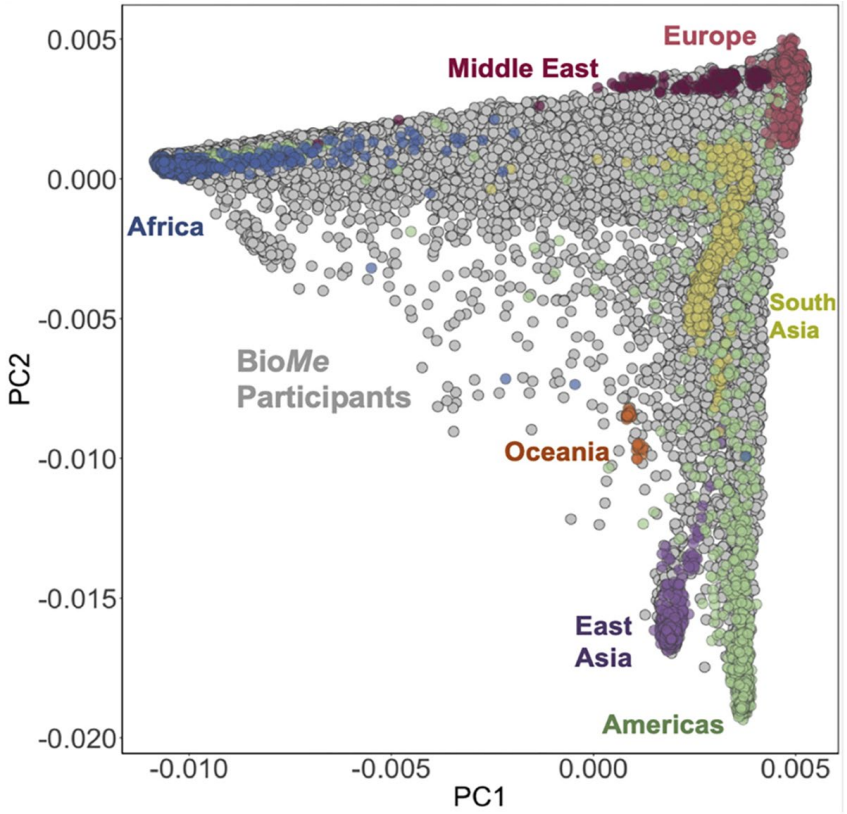
The great human expansion

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

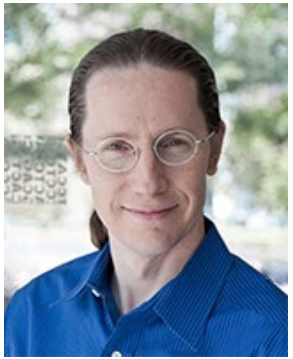
LD Score regression

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

Affiliations | Contributions | Corresponding author

Nature Genetics **47**, 291–295 (2015) | doi:10.1038/ng.3211
Received 07 March 2014 | Accepted 07 January 2015 | Published online 02 February 2015

How does LD shape association?

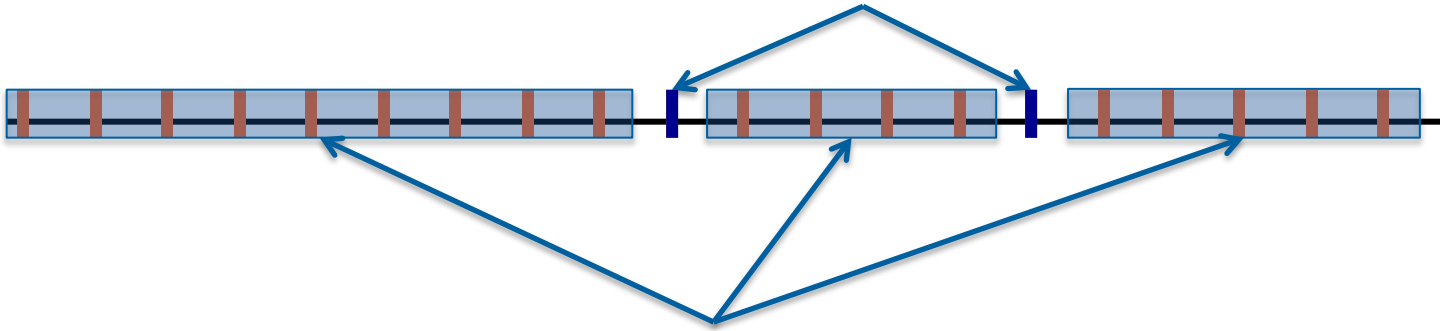
LD Score regression distinguishes confounding from polygenicity in genome-wide association studies

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

Affiliations | Contributions | Corresponding author

Nature Genetics **47**, 291–295 (2015) | doi:10.1038/ng.3211
Received 07 March 2014 | Accepted 07 January 2015 | Published online 02 February 2015

Lonely SNPs [no LD]



LD blocks

How does LD shape association?

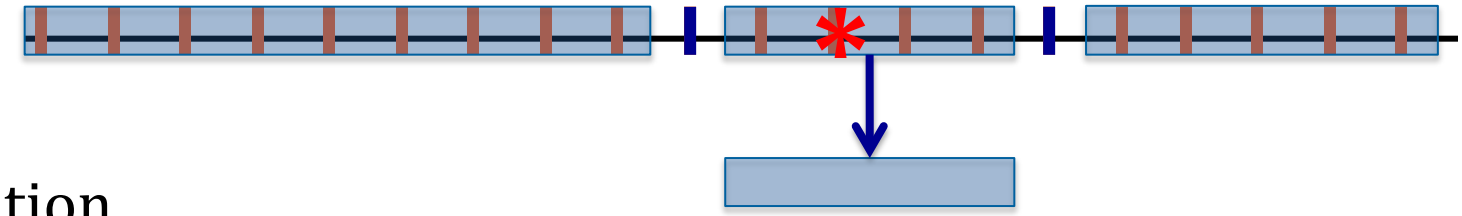
- Lonely SNPs [no LD]
- LD blocks
- * Causal variants

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

Affiliations | Contributions | Corresponding author

Nature Genetics **47**, 291–295 (2015) | doi:10.1038/ng.3211
Received 07 March 2014 | Accepted 07 January 2015 | Published online 02 February 2015



Association

All markers correlated with a causal variant show association

How does LD shape association?

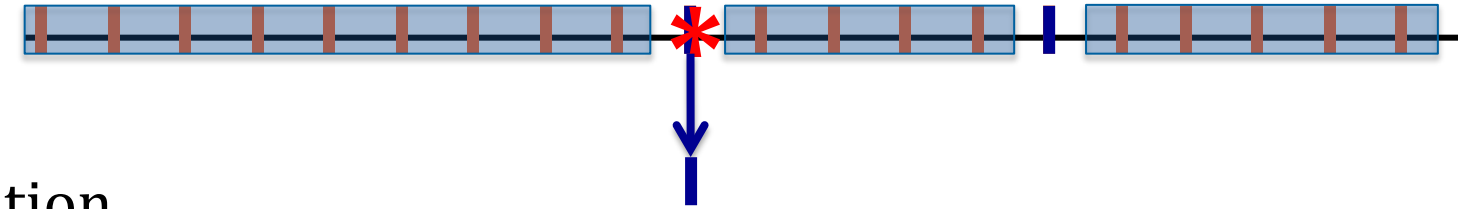
- Lonely SNPs [no LD]
- LD blocks
- * Causal variants

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

Affiliations | Contributions | Corresponding author

Nature Genetics **47**, 291–295 (2015) | doi:10.1038/ng.3211
Received 07 March 2014 | Accepted 07 January 2015 | Published online 02 February 2015



Association

Lonely SNPs only show association if they are causal

What happens under polygenicity?

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

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

Affiliations | Contributions | Corresponding author

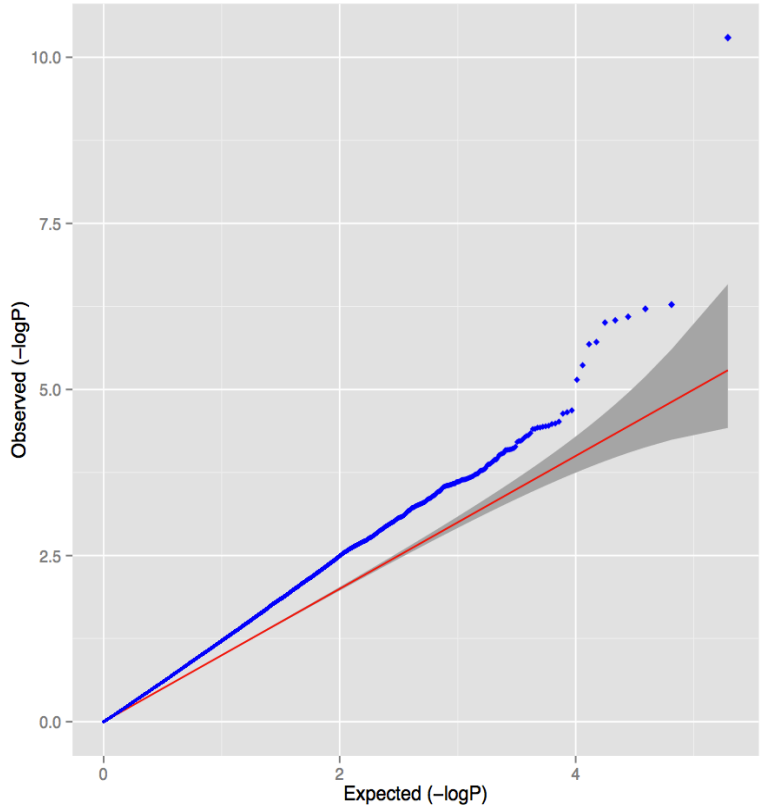
Nature Genetics **47**, 291–295 (2015) | doi:10.1038/ng.3211
Received 07 March 2014 | Accepted 07 January 2015 | Published online 02 February 2015

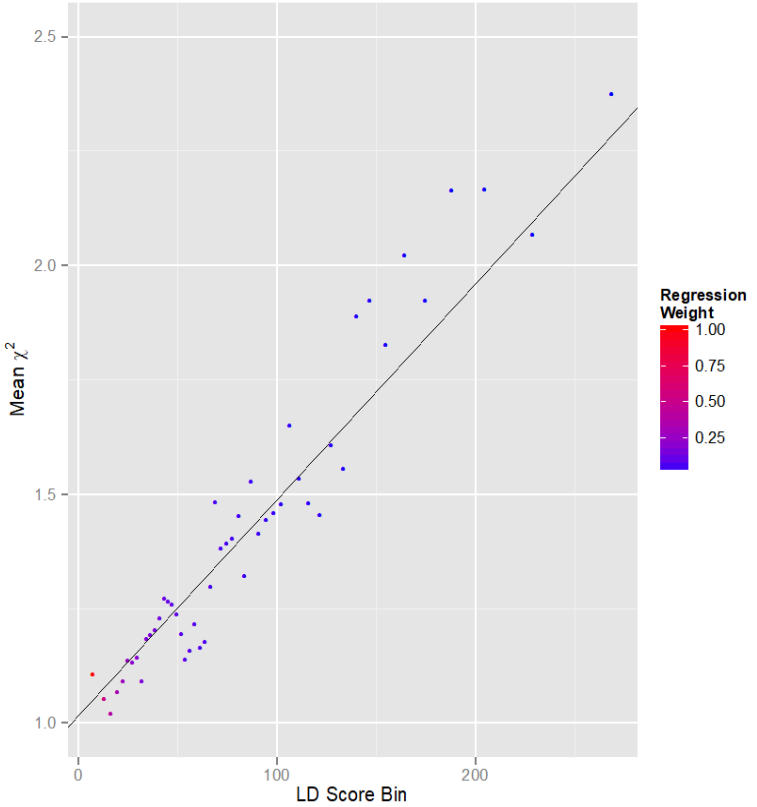
Assuming a uniform prior, we see SNPs with more LD friends showing more association

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

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

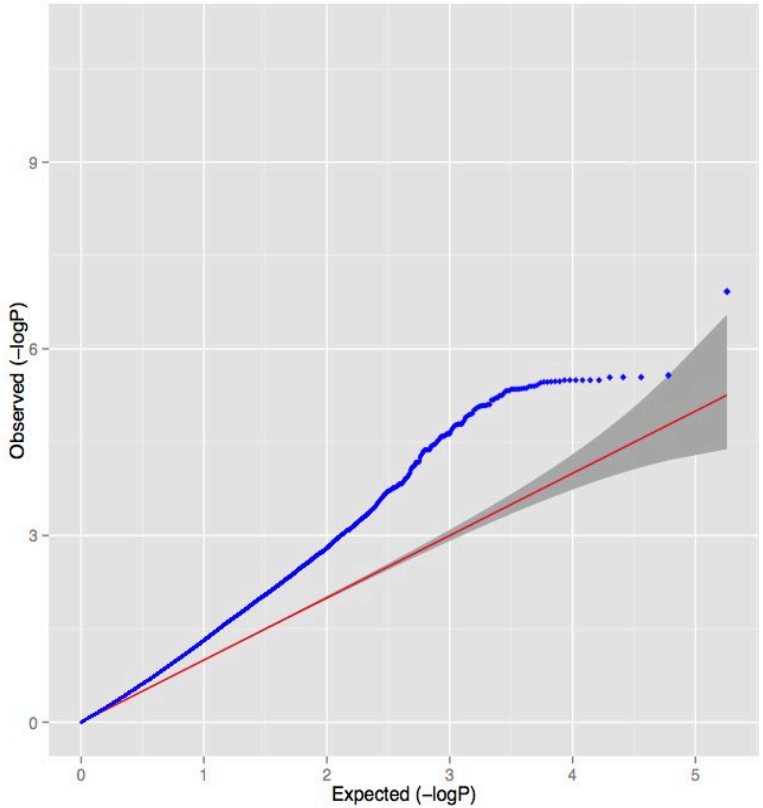
Affiliations | Contributions | Corresponding author

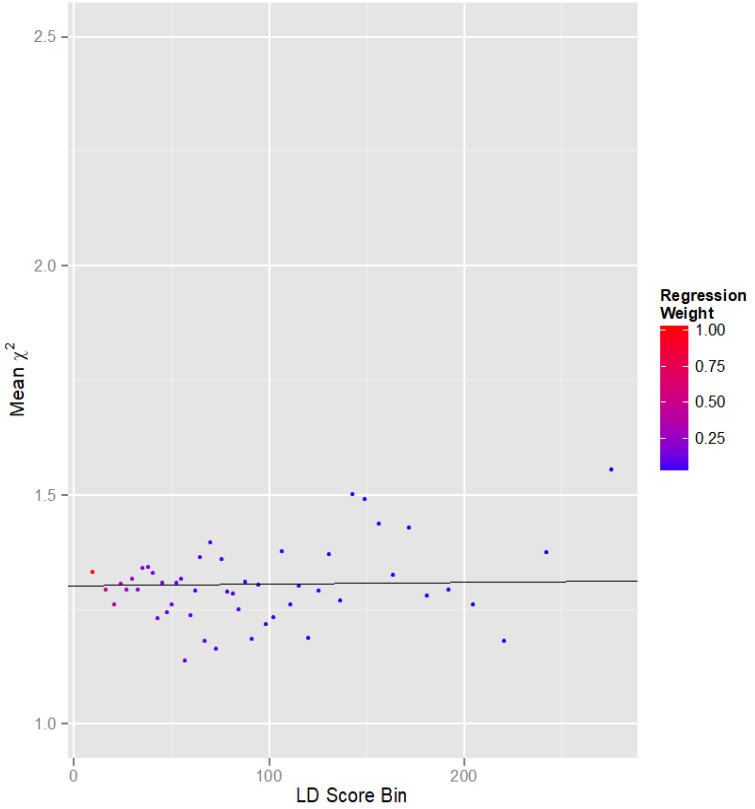
Nature Genetics **47**, 291–295 (2015) | doi:10.1038/ng.3211
Received 07 March 2014 | Accepted 07 January 2015 | Published online 02 February 2015

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





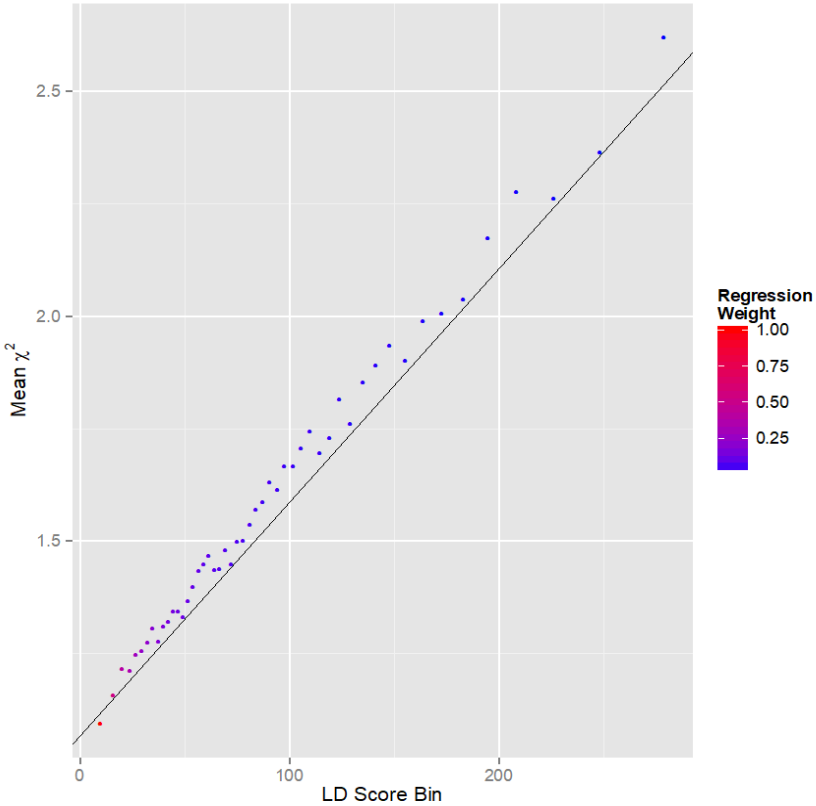
PGC Schizophrenia

Lambda = 1.48

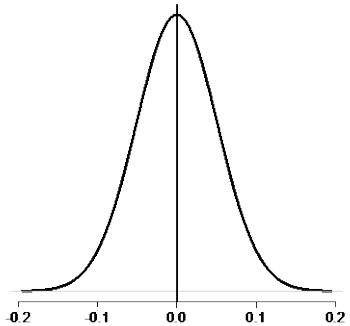
Intercept = 1.06

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 =

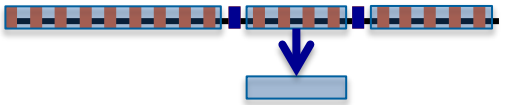
What is the E[χ^2] for variant *j*?

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

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*

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



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

What isn’t in LD score?

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

Thank you!

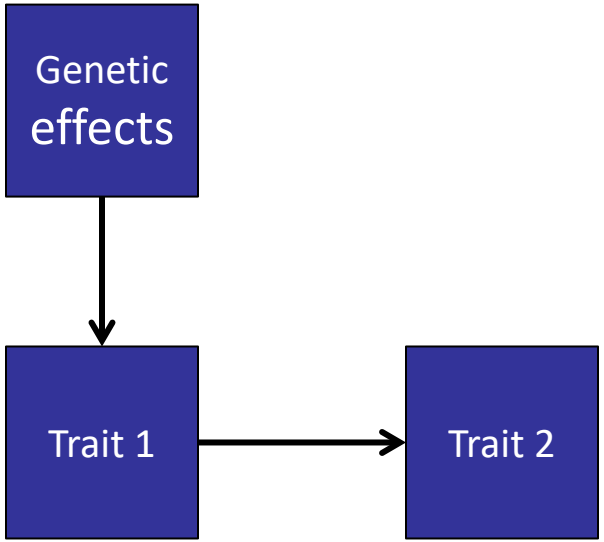
BROAD INSTITUTE

Genetic Correlation Method in:

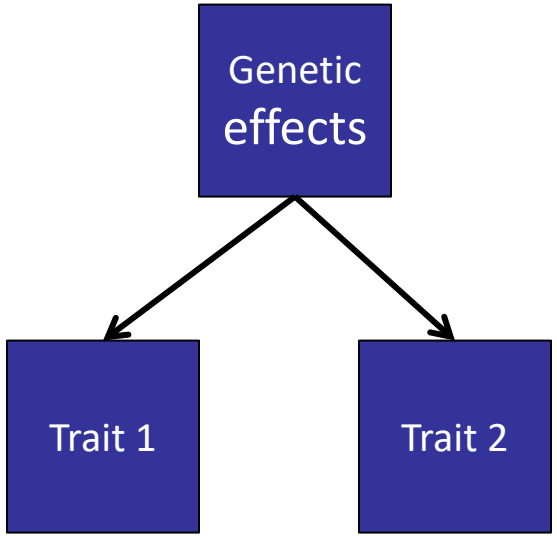
nature genetics

An atlas of genetic correlations across human diseases and traits

Potential sources of genetic correlation



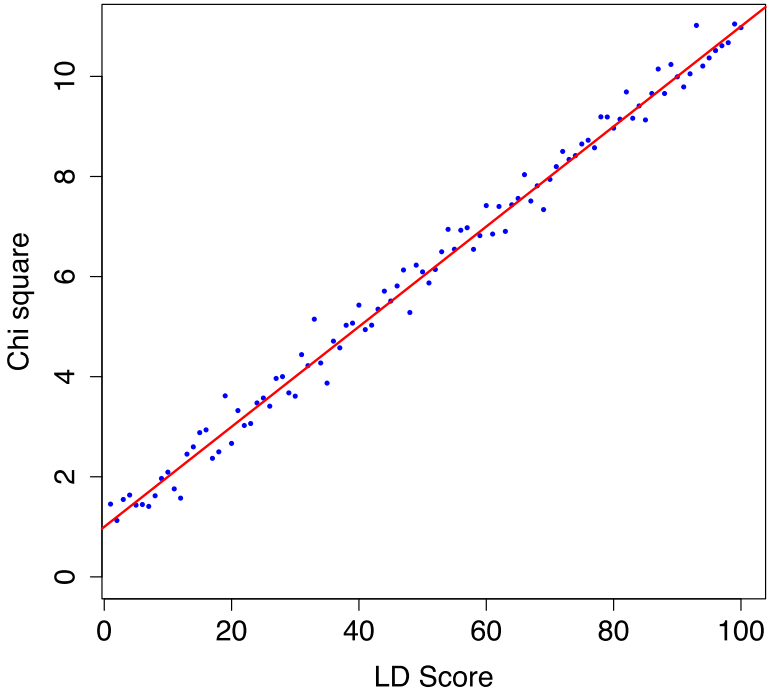
Trait 1 exerts causal effect on Trait 2



Genetic effects influence Trait 1 and Trait 2

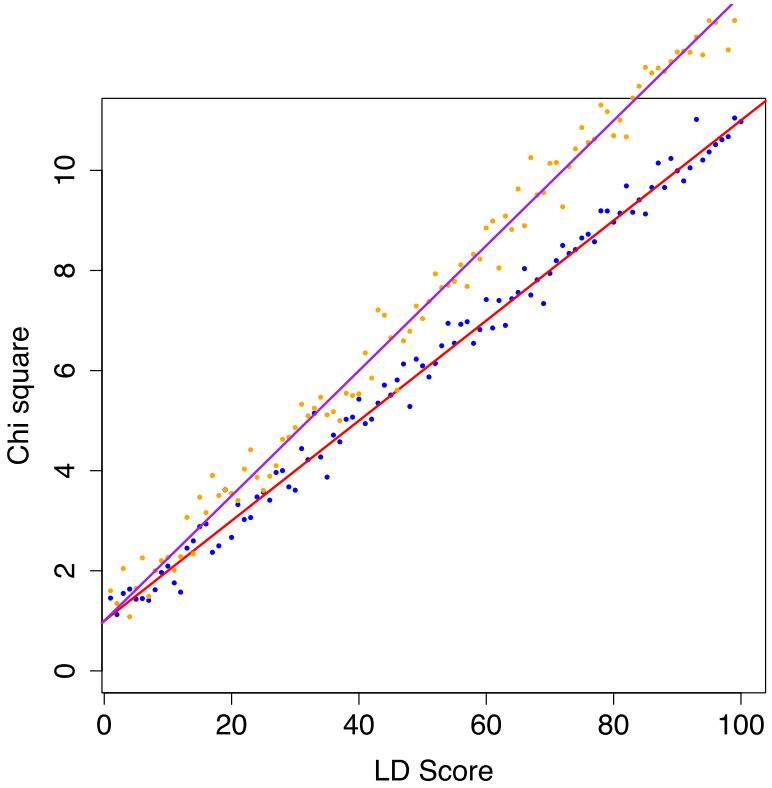
LD Score regression
Genetic correlation

Trait 1



Slope estimates heritability

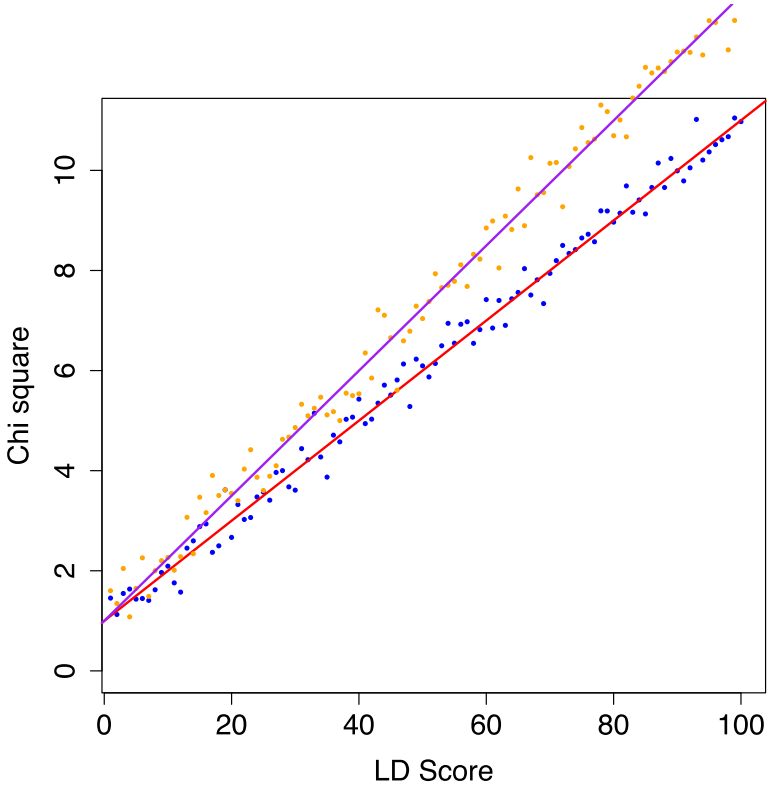
LD Score regression
Genetic correlation



Trait 1
Trait 2

We can a second trait and obtain two heritability estimates

LD Score regression
Genetic correlation

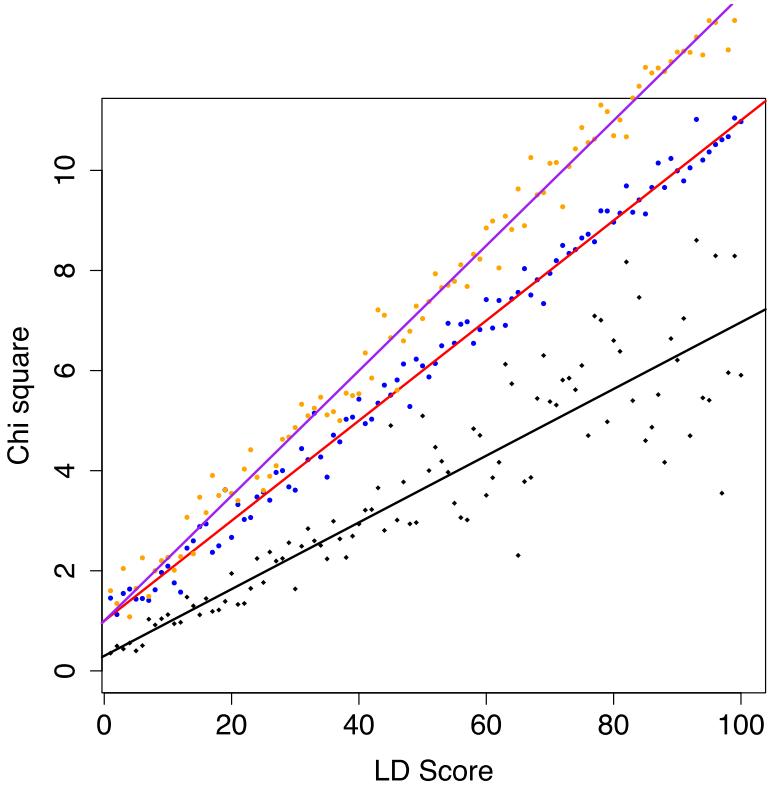


Trait 1
Trait 2

$Z^*Z = \chi^2$

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

LD Score regression
Genetic correlation



Trait 1

Trait 2

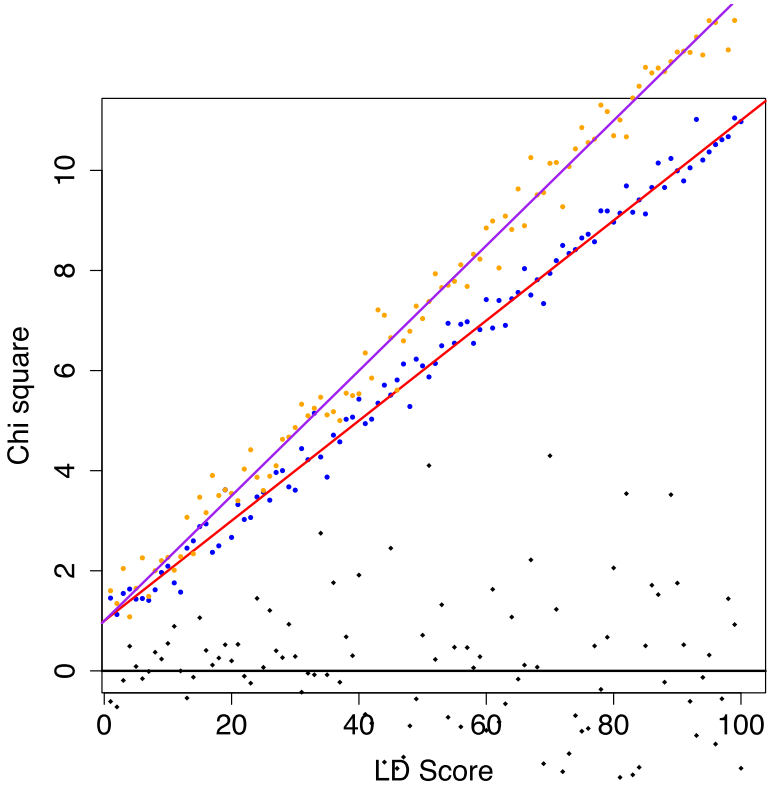
R_G

$Z^*Z = \chi^2$

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