33rd International Workshop on Statistical Genetic Methods for Human Complex Traits

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- David Evans (codirector)
- Nick Martin
- Dorret Boomsma
- Pak Sham
- Mike Neale
- Hermine Maes
- Sarah Medland
- Danielle Posthuma
- Meike Bartels
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- Matt Keller (cohost)
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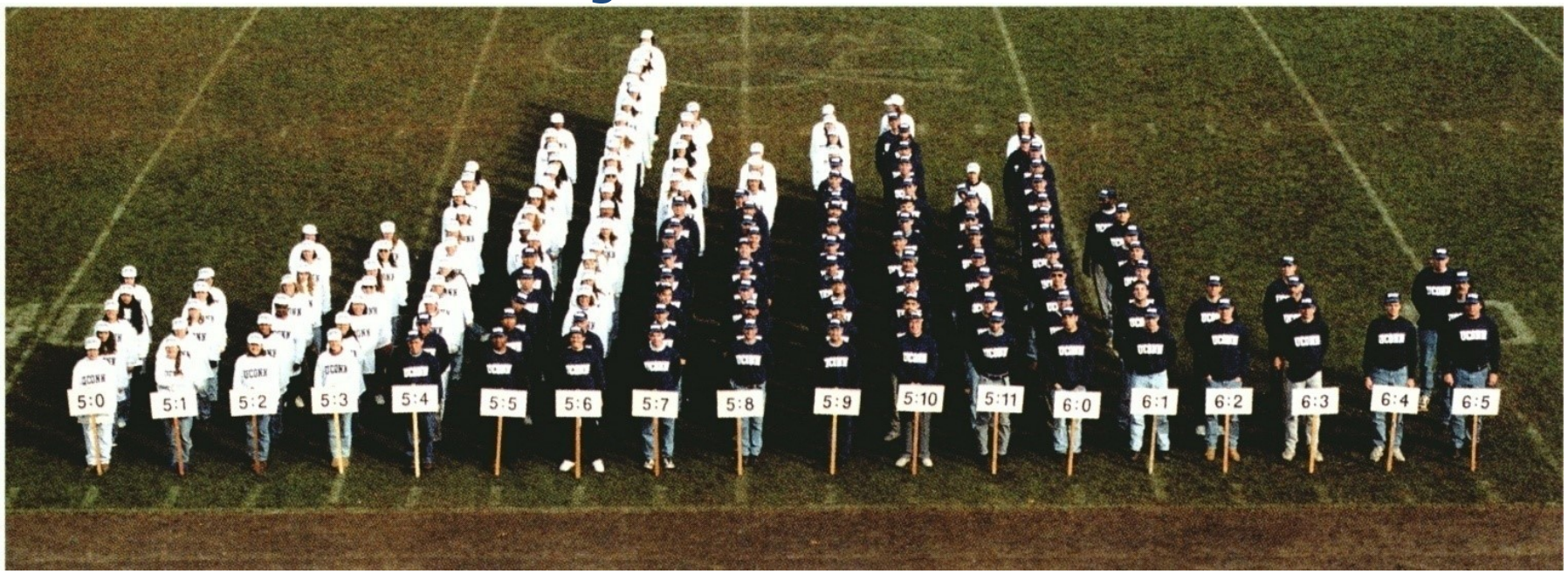
- Stacey Cherny
- Luke Evans
- Cotton Seed
- Tim Poterba
- Lucia Colodro Conde
- Katrina Grasby
- Kyoko Watanabe
- Aysu Okbay
- Loic Yengo
- Michael Simpson
- Joshua Pritikin

The genetics of complex traits:
historical context and current challenges

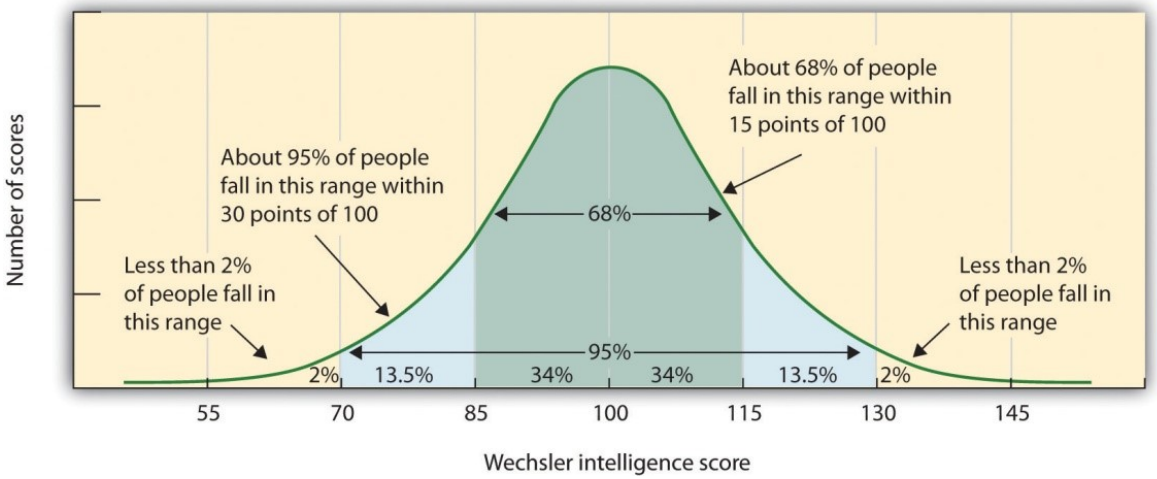
Nick Martin
Queensland Institute
of Medical Research
Brisbane

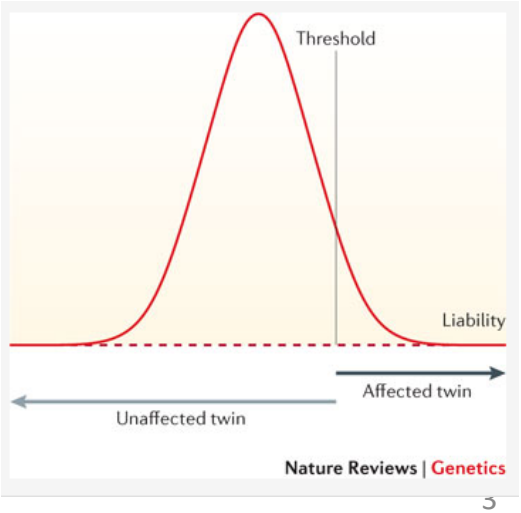
Boulder workshop
March 4, 2019

Human variation: Height



Human variation: IQ

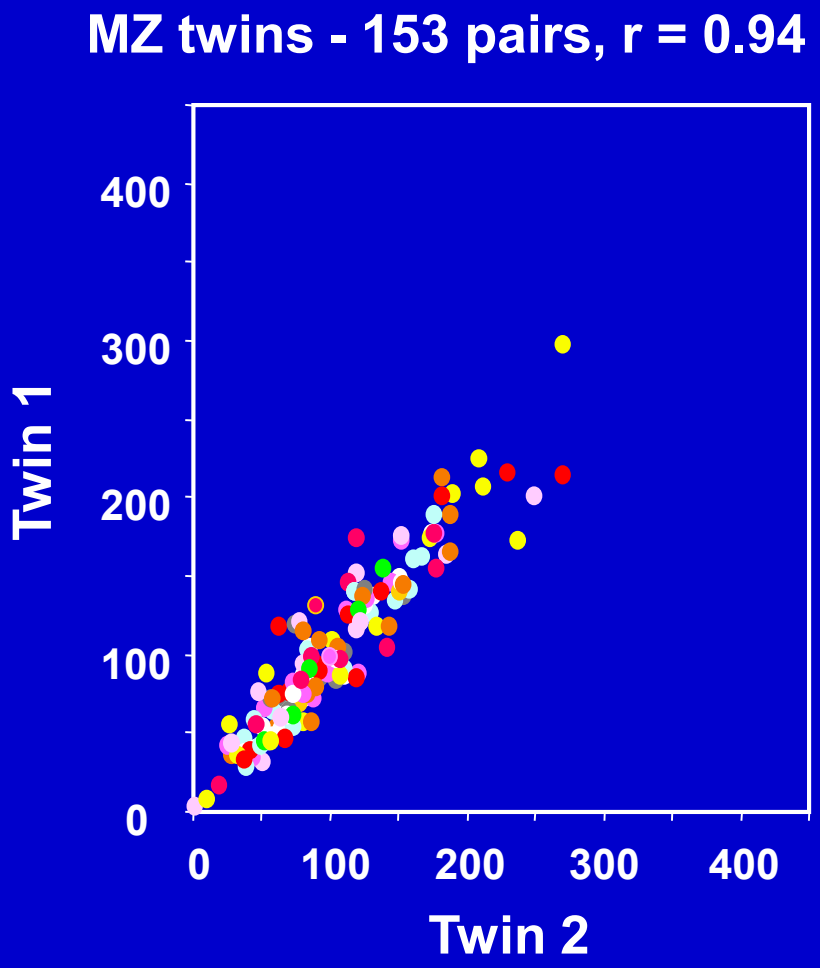


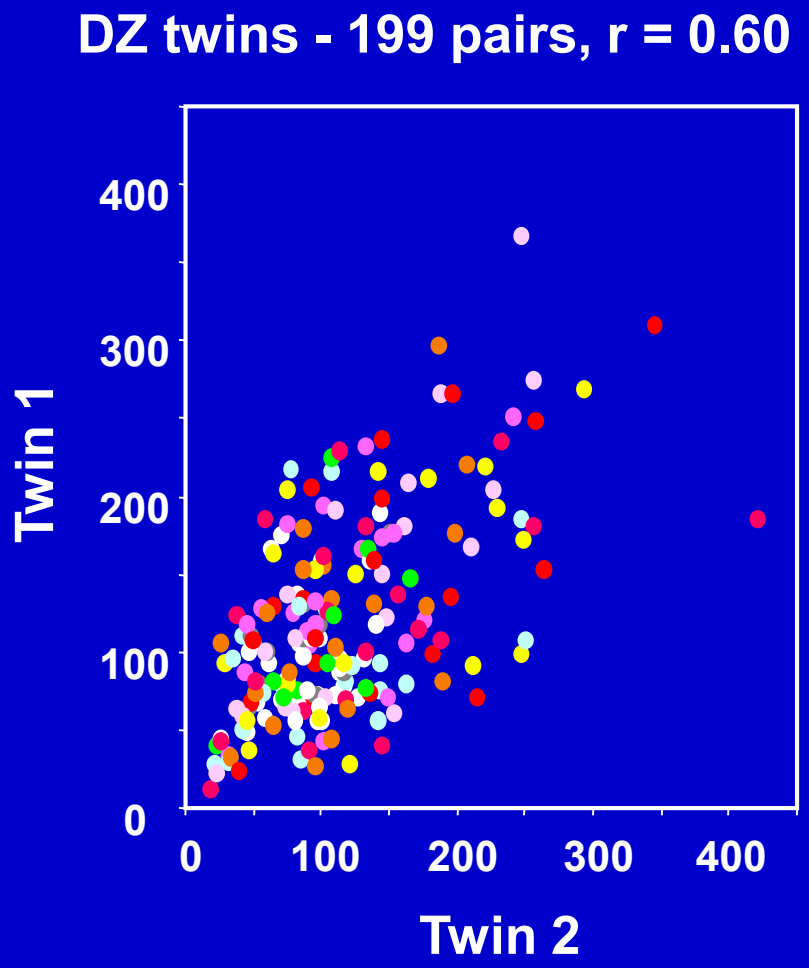


Genetic Epidemiology: Stages of Genetic Mapping

- Are there genes influencing this trait?
  - Genetic epidemiological (twin / family) studies OR heritability based on measured genetic variants
- Where are those genes?
  - Linkage analysis
- What are those genes?
  - Association analysis (meta-analysis / pathway)
- How do they work beyond the sequence?
  - Epigenetics, transcriptomics, proteomics
- What can we do with them ?
  - Translational medicine

Total mole count for MZ and DZ twins

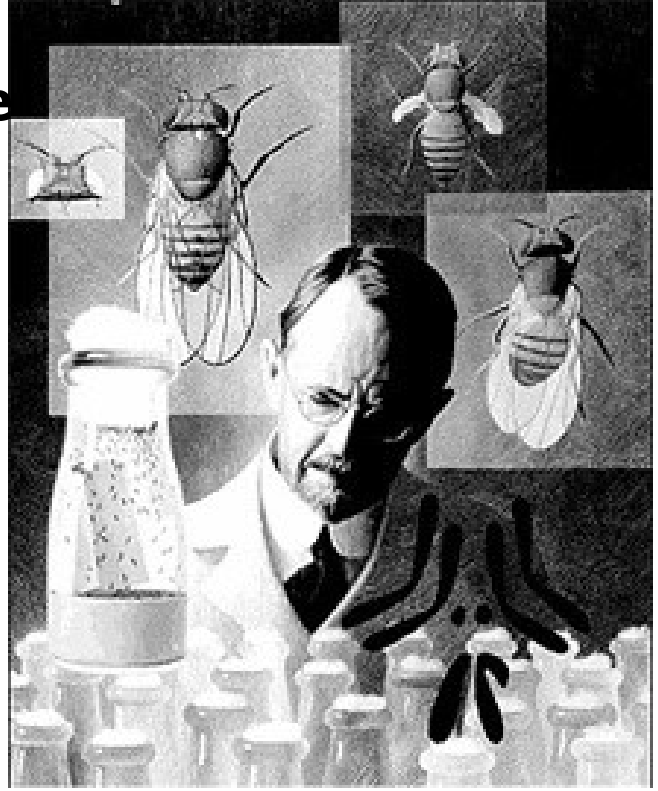




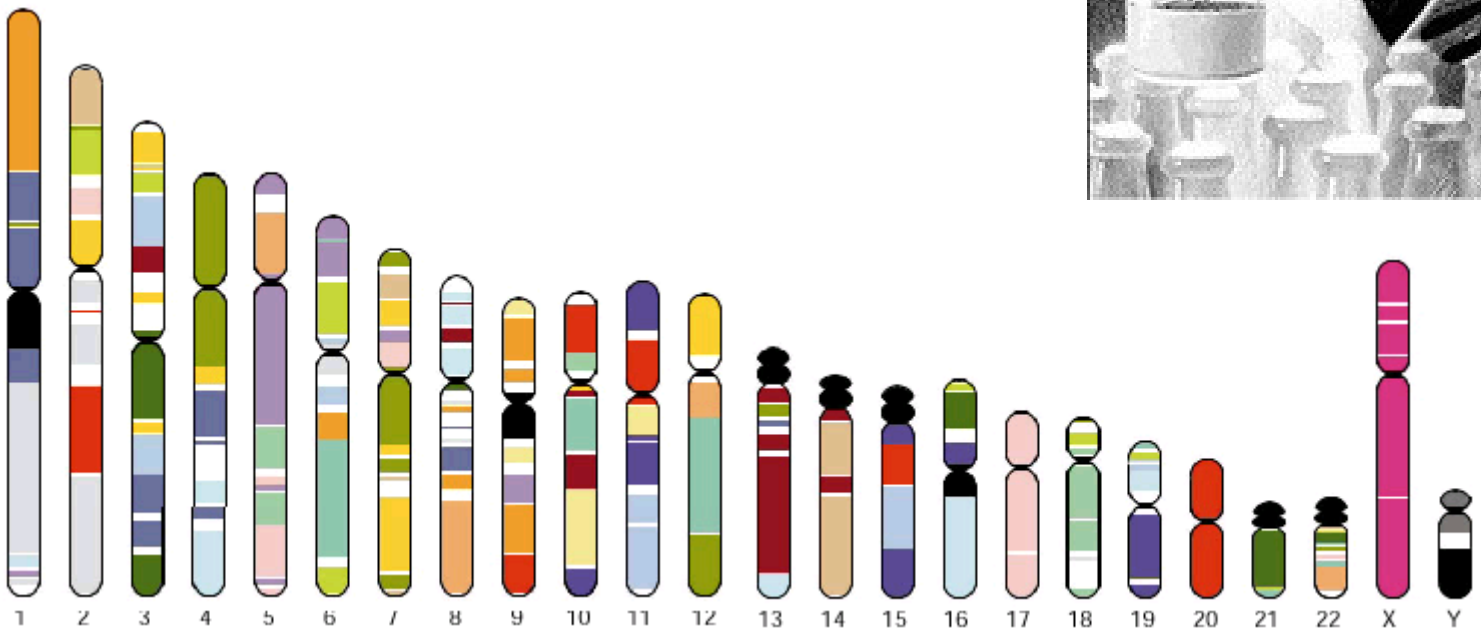
4 Stages of Genetic Mapping

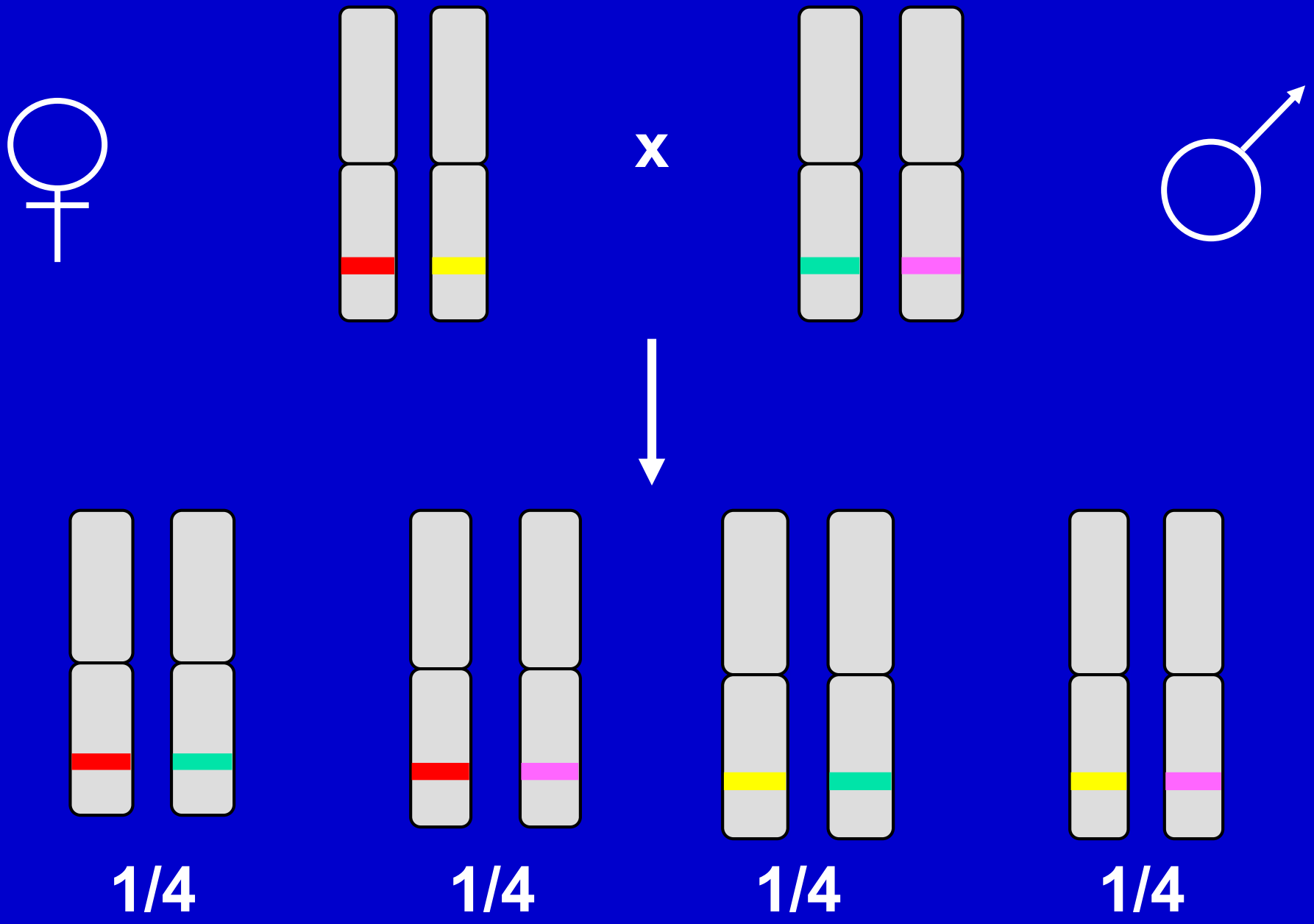
- Are there genes influencing this trait?
  - Genetic epidemiological studies
- Where are those genes?
  - Linkage analysis
- What are those genes?
  - Association analysis
- What can we do with them ?
  - Translational medicine

Thomas Hunt Morgan – discoverer of linkage

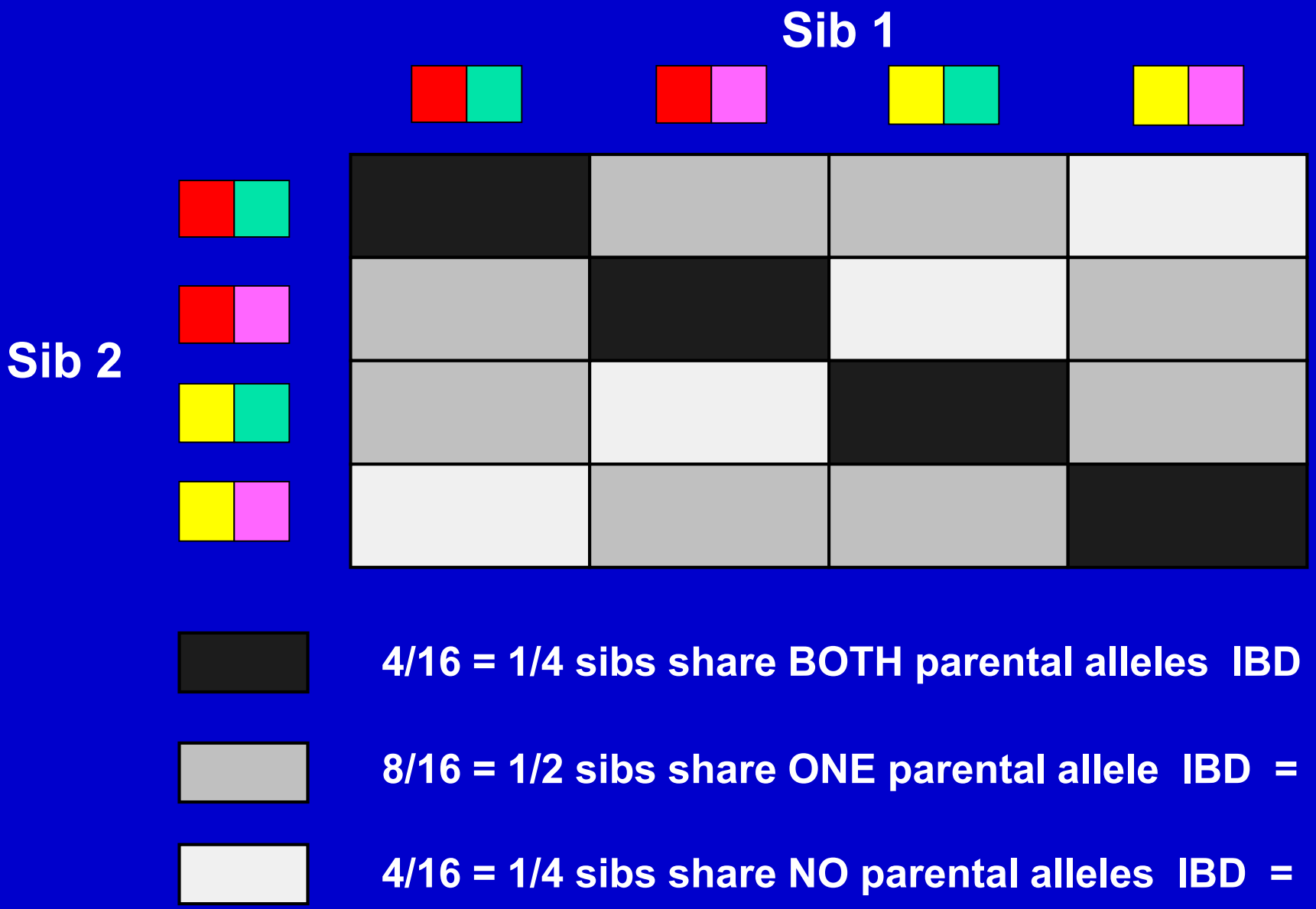


Linkage analysis

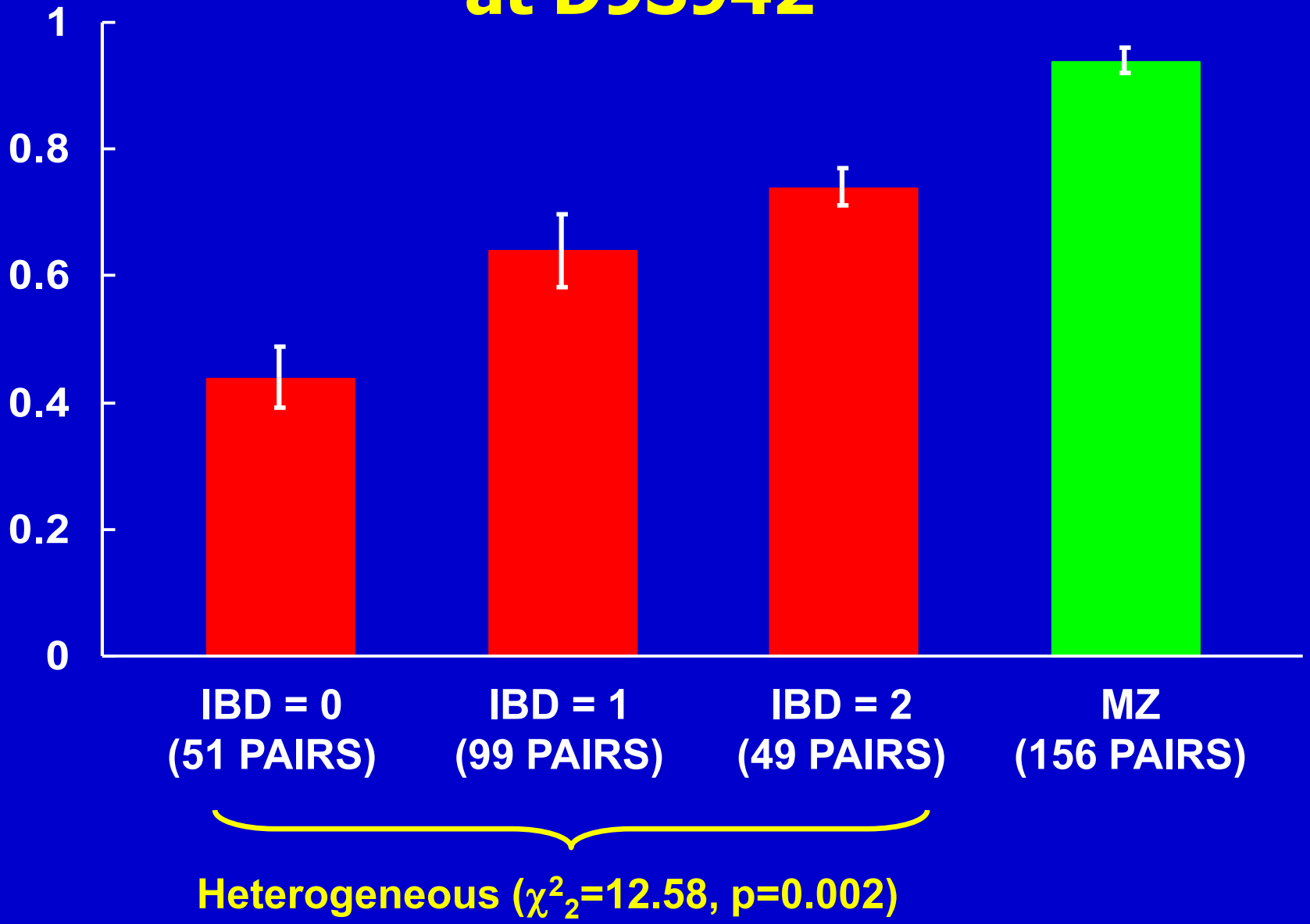



x
1/4
1/4
1/4
1/4

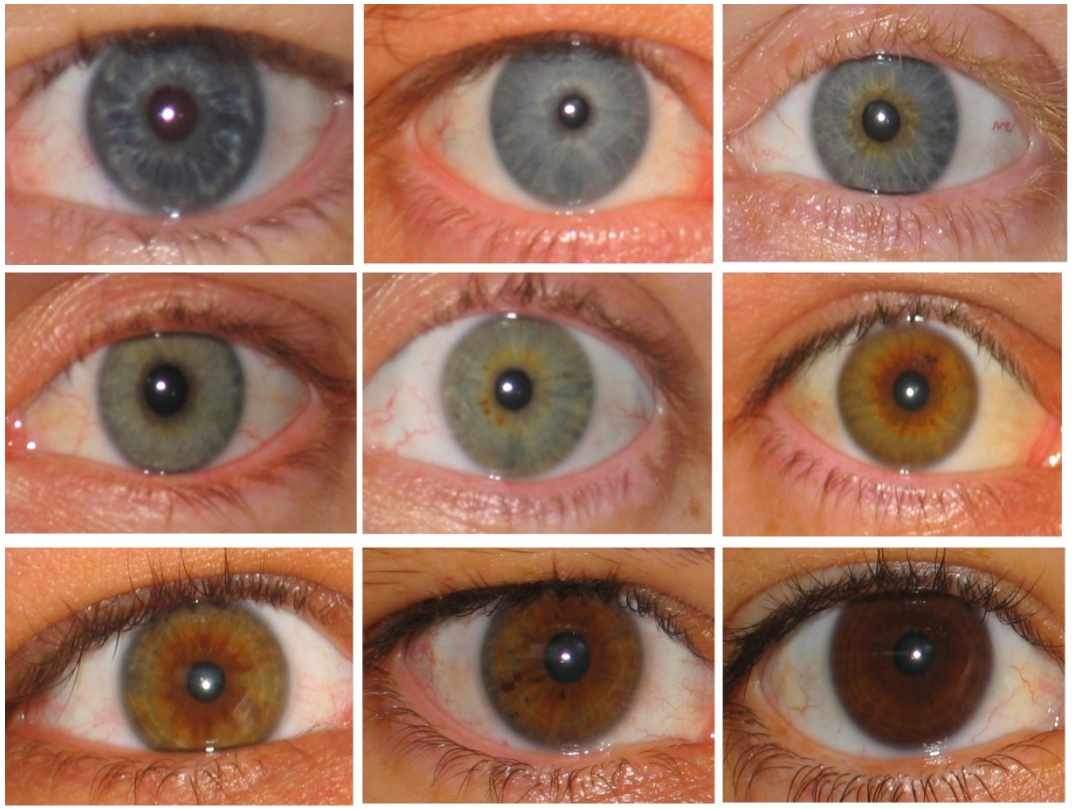
IDENTITY BY DESCENT

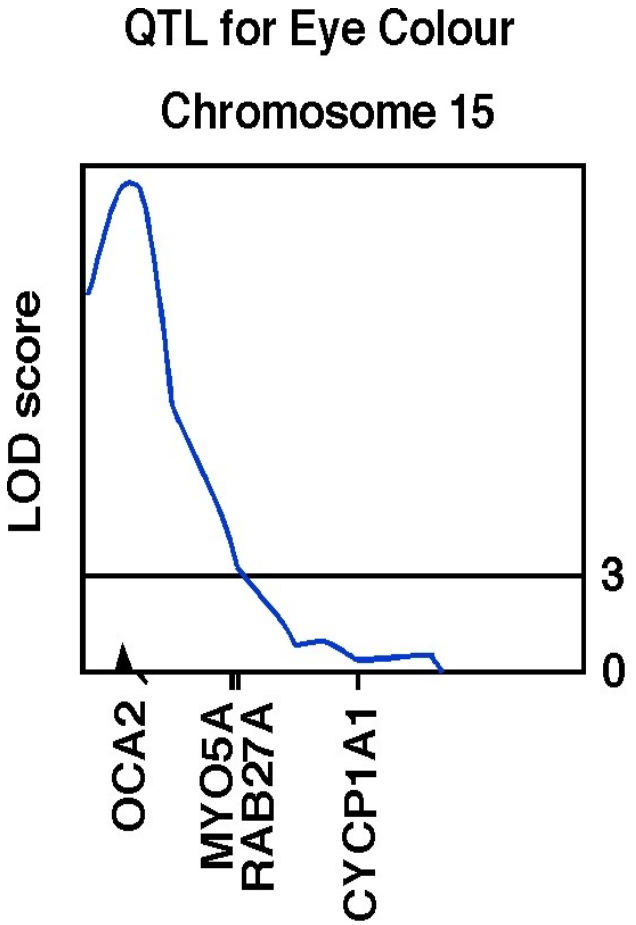


Total nevus count correlations by IBD class at D9S942



Human OCA2 and eye colour





Zhu et al., *Twin Research* 7:197-210 (2004)

- Linkage analysis is badly underpowered for complex traits with small gene effect sizes

- So we need a much more sensitive way to find the genes

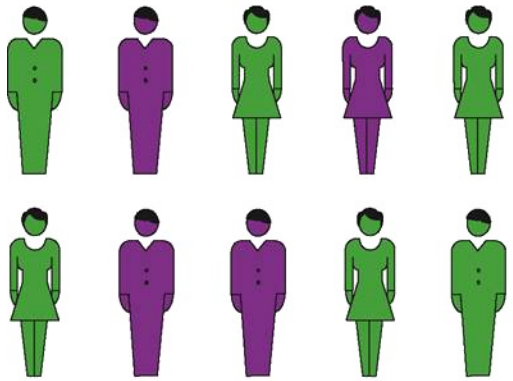
Complex disorders account for most health burden

- Examples
  - Ischaemic heart disease (30-50%, F-M)
  - Breast cancer (12%, F)
  - Colorectal cancer (5%)
  - Recurrent major depression (10%)
  - ADHD (5%)
  - Bipolar (2%)
  - Schizophrenia (1%)
  - Non-insulin dependent diabetes (5%)
  - Asthma (10%)
  - Essential hypertension (10-25%)
  - etc…..

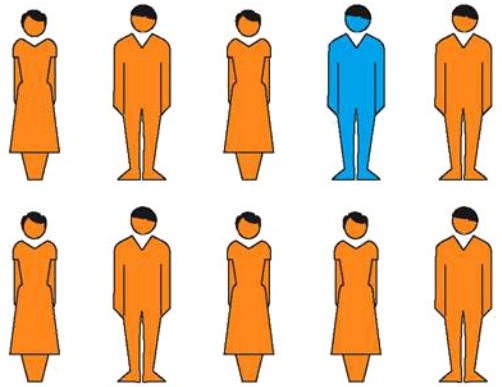
Basic principle of genetic association studies

Genetic Variant 1

Genetic Variant 2

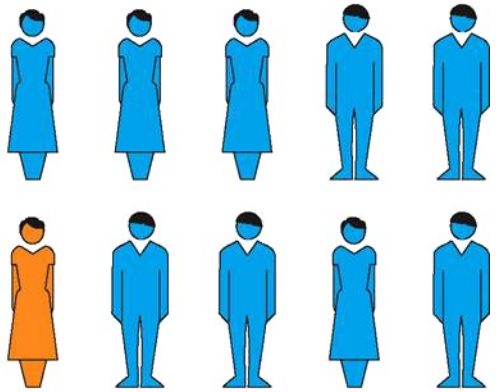


Affected



Affected

Unaffected

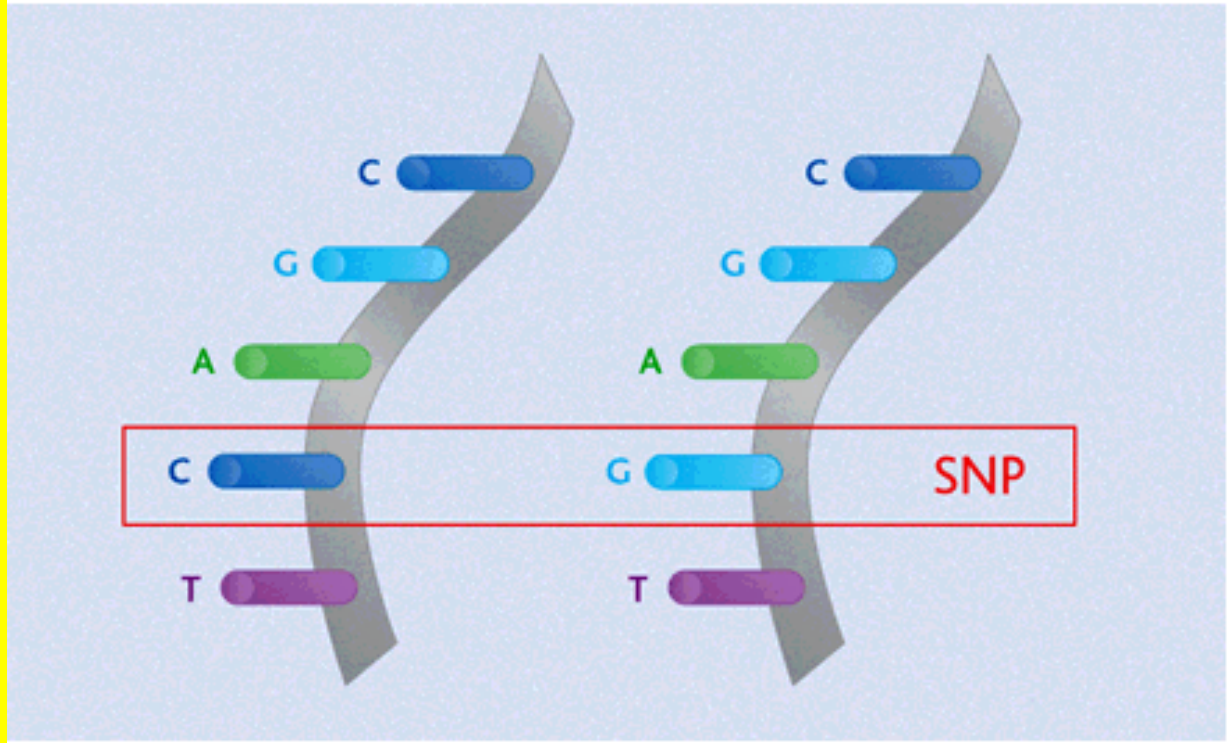


Unaffected

Association analysis

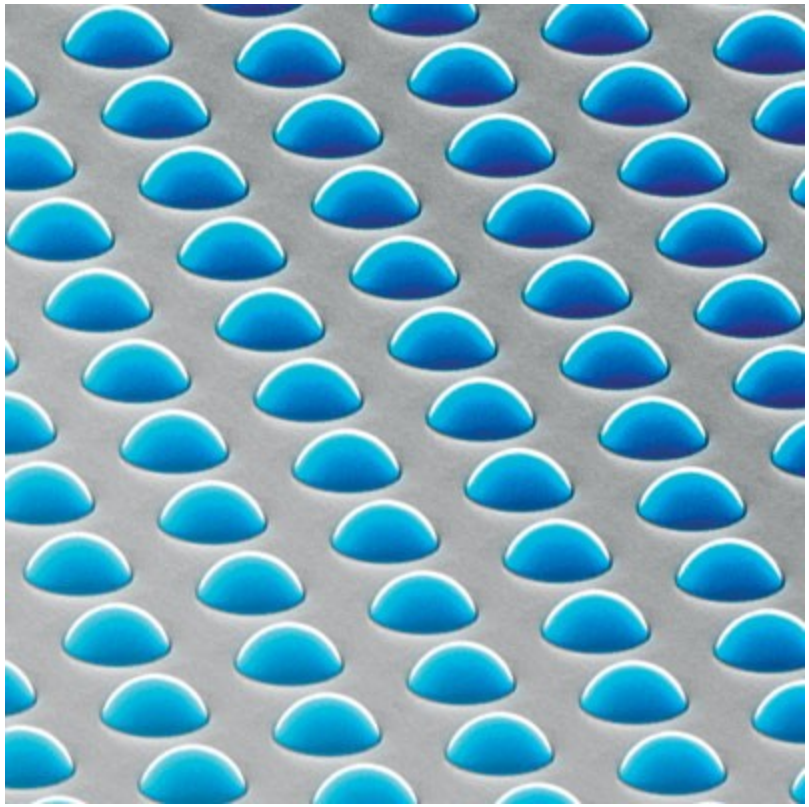
looks for correlation between specific alleles and phenotype (trait value, disease risk)

Single Nucleotide Polymorphisms (SNPs)

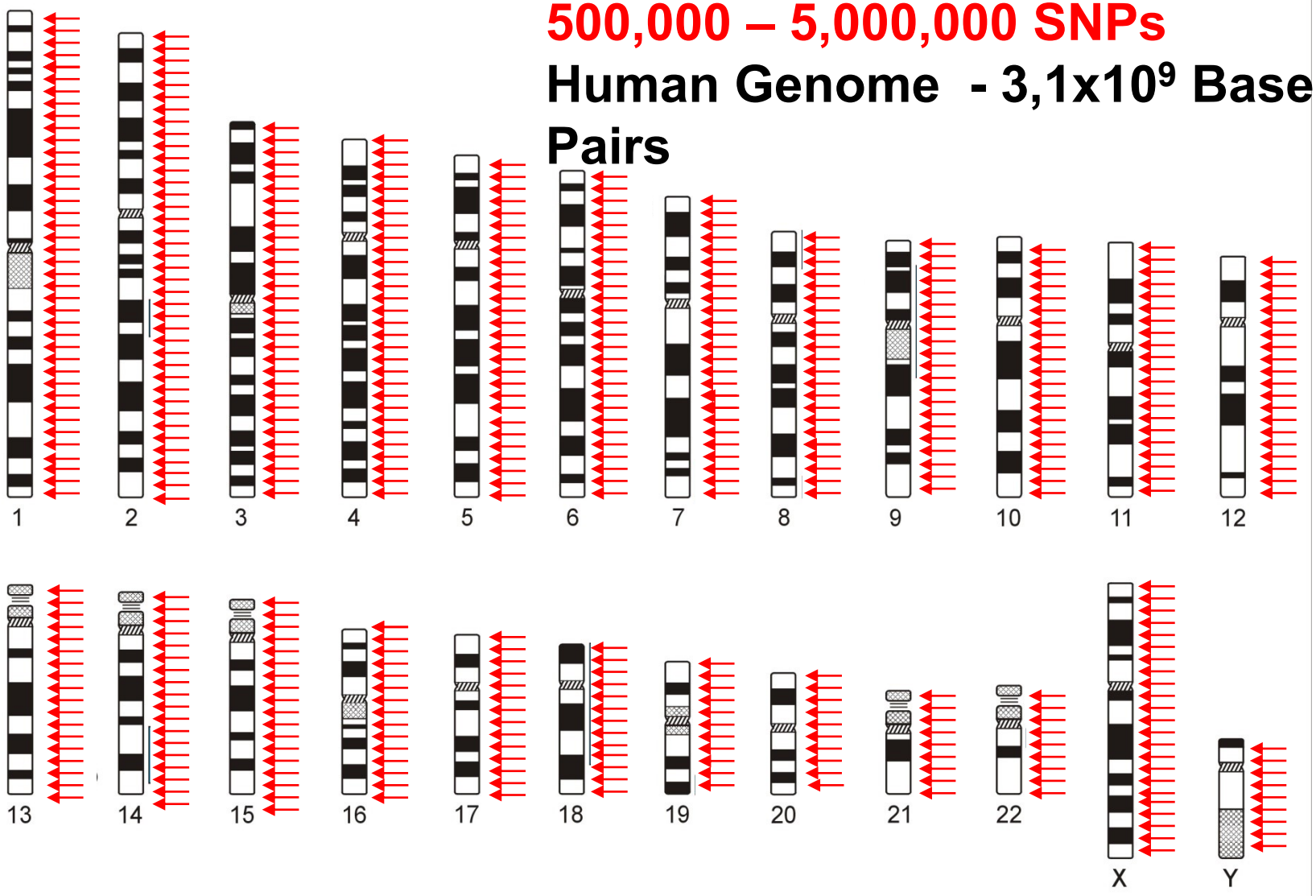


Complex disease marker? SNPs are single-base differences in DNA.

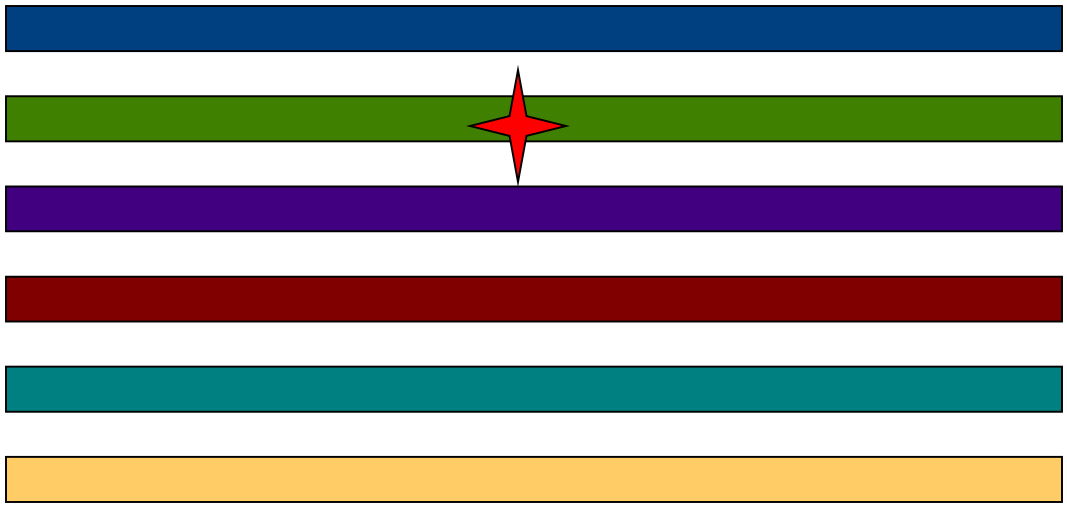
High density SNP arrays – up to 1 million SNPs



Genome-Wide Association Studies

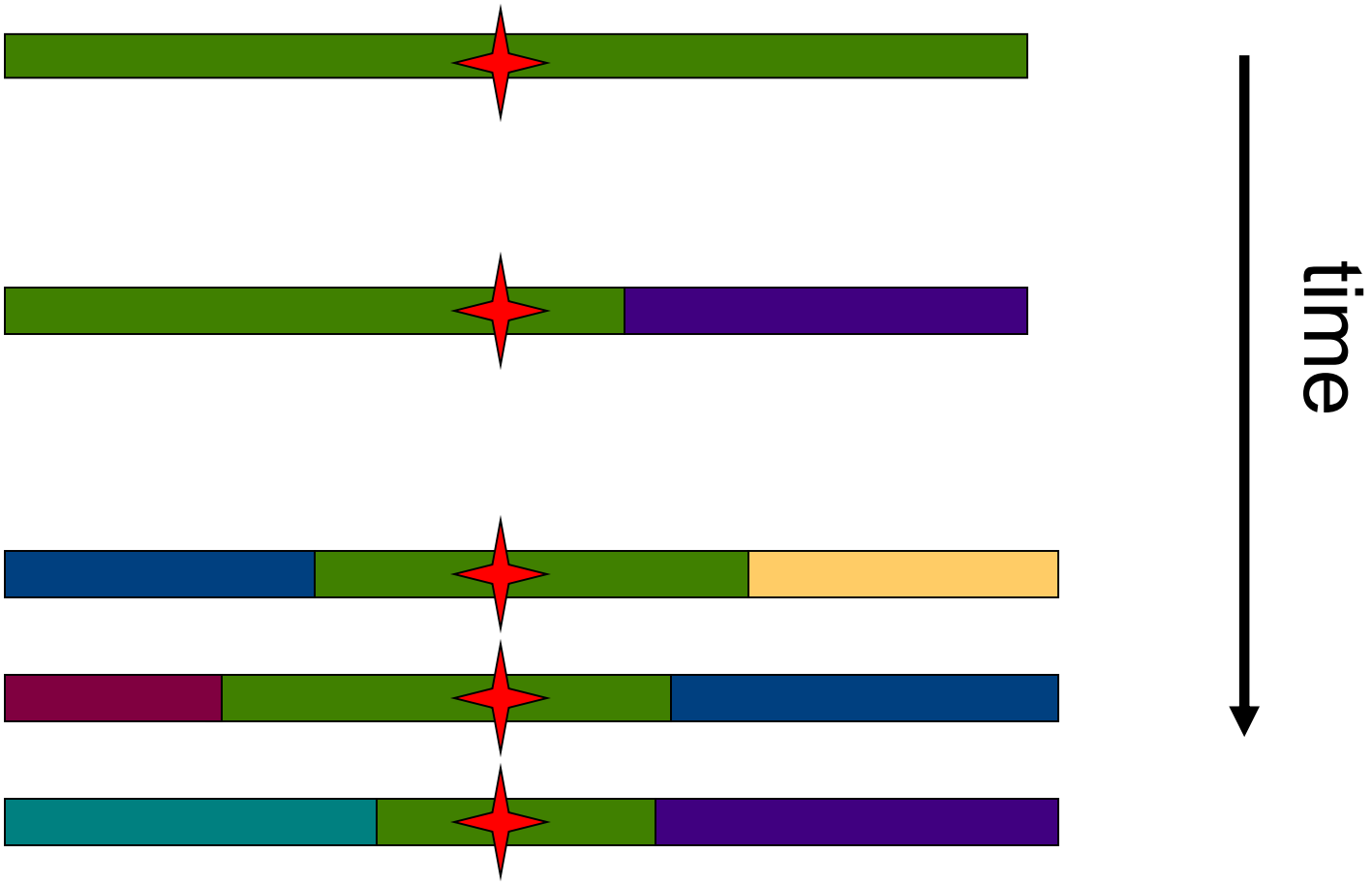


Linkage disequilibrium

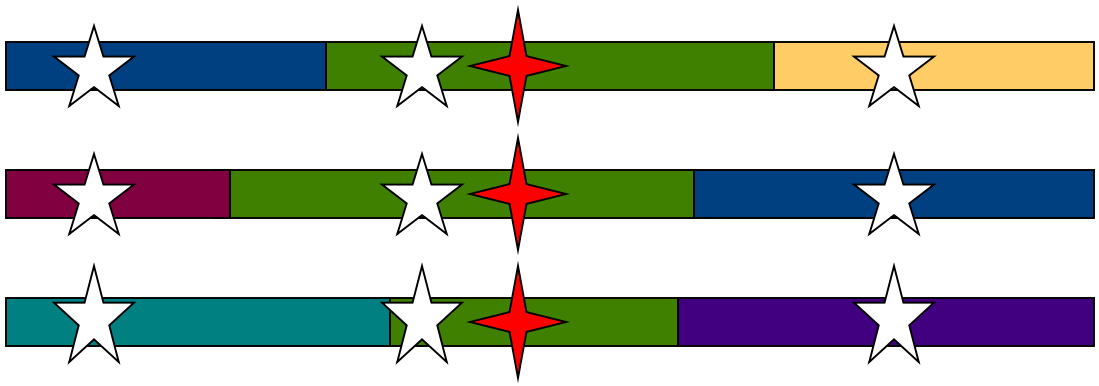


David Evans

Linkage disequilibrium

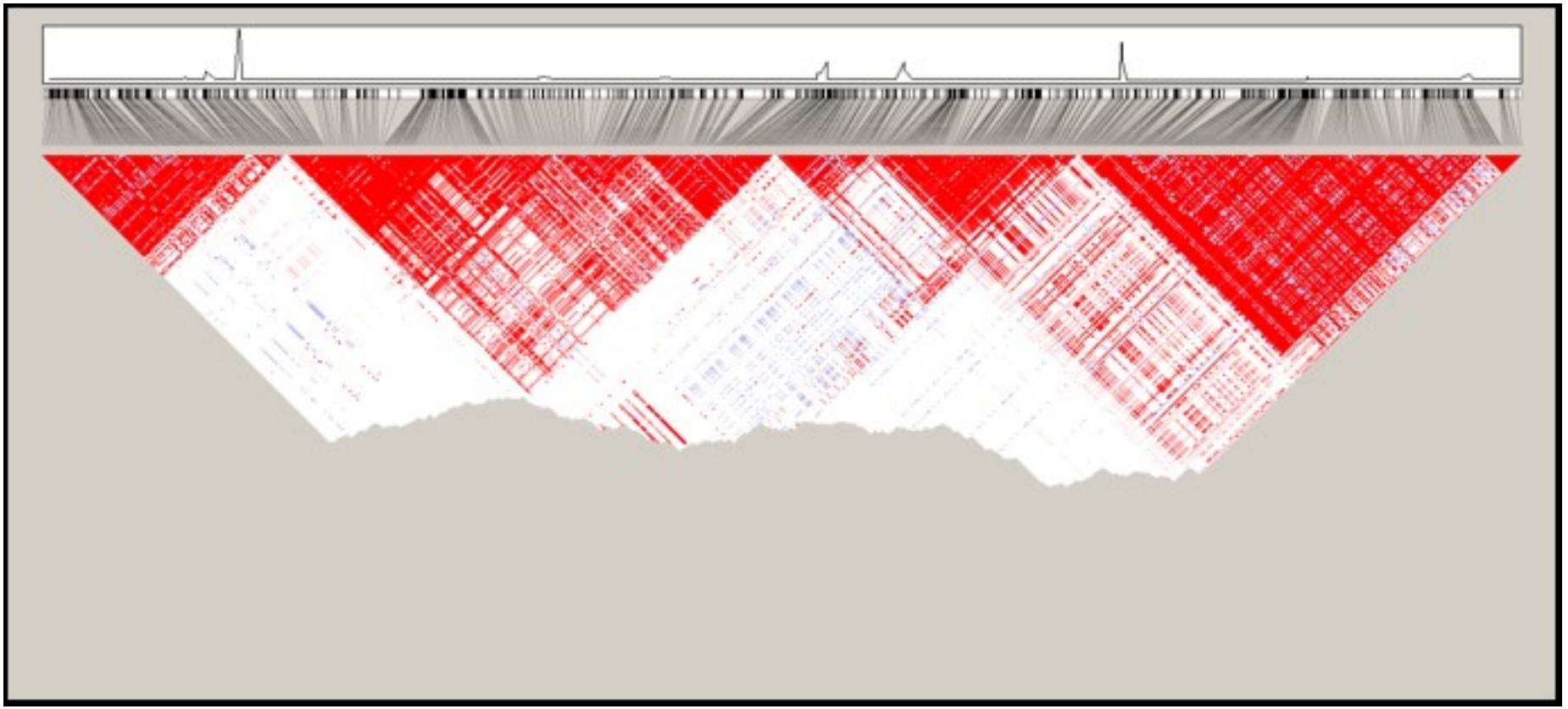


Indirect association



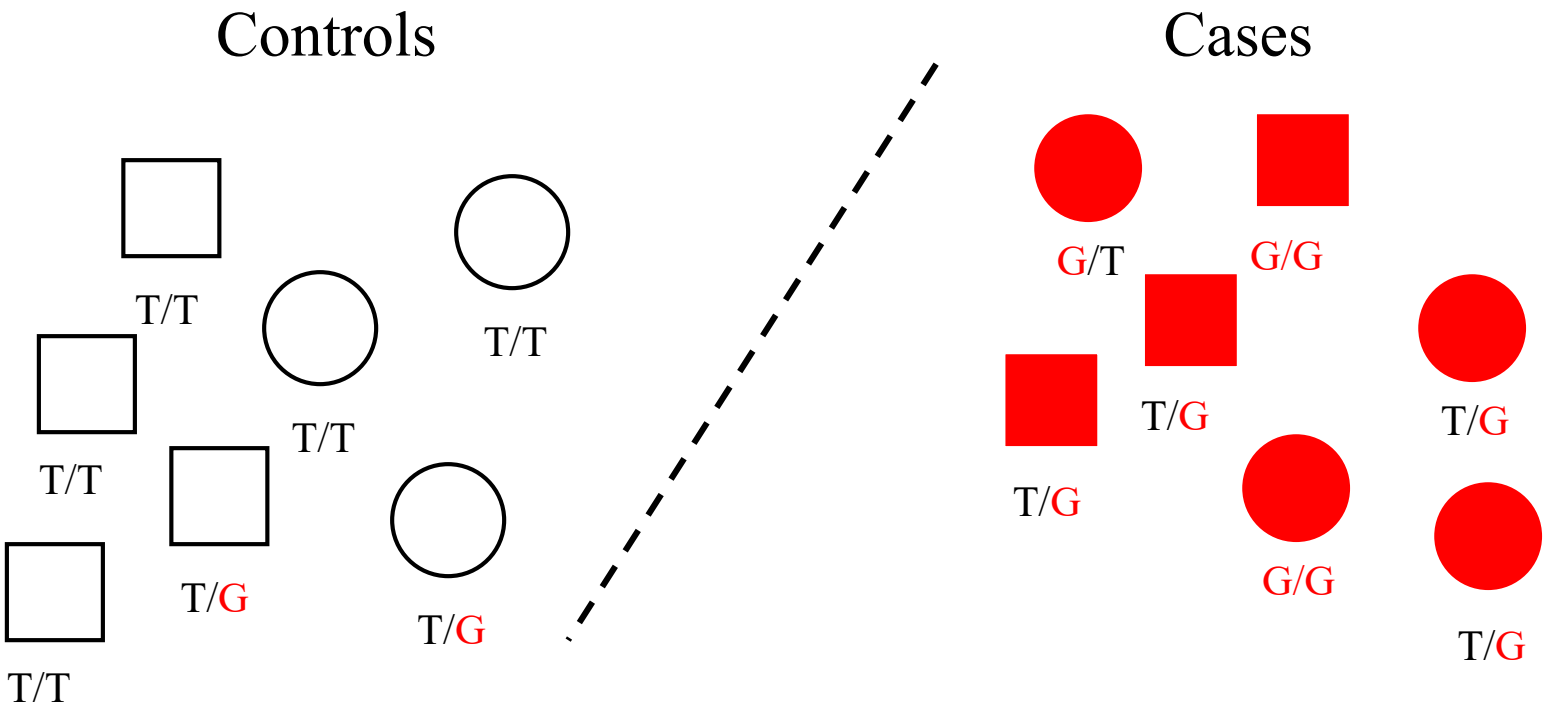
this SNP will be associated with disease

Linkage disequilibrium blocks



Jeff Barrett

Genetic Case Control Study



Allele G is ‘associated’ with disease

Allele-based tests (case-control)

- Each individual contributes two counts to 2x2 table.
- Test of association

$$X^2 = \sum_{i=0,1} \sum_{j=A,U} \frac{\left(n_{ij} - E\left[n_{ij}\right]\right)^2}{E\left[n_{ij}\right]}$$

where

$$E\left[n_{ij}\right] = \frac{n_{i\cdot} n_{\cdot j}}{n_{\cdot\cdot}}$$

	Cases	Controls	Total
G	n_{1A}	n_{1U}	$n_{1\cdot}$
T	n_{0A}	n_{0U}	$n_{0\cdot}$
Total	$n_{\cdot A}$	$n_{\cdot U}$	$n_{\cdot\cdot}$

- X^2 has χ^2 distribution with 1 degrees of freedom under null hypothesis.

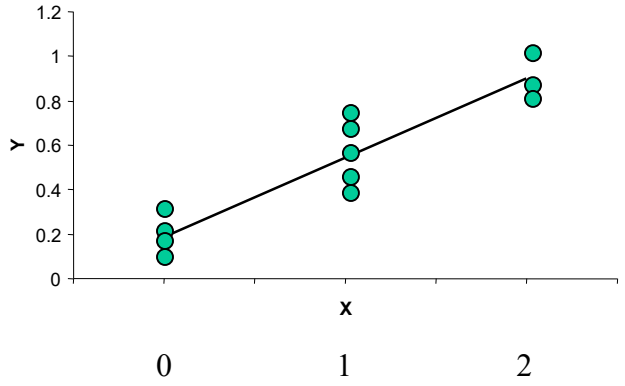
Simple Regression Model of Association (continuous trait)

$$Y_i = \alpha + \beta X_i + e_i$$

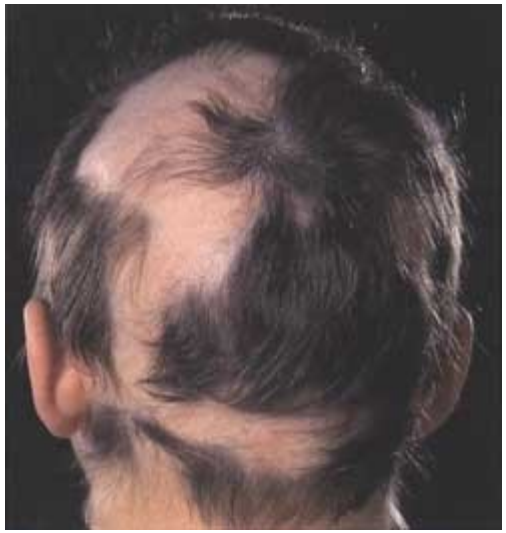
where

$Y_i =$ trait value for individual i

$X_i =$ number of 'A' alleles an individual has



Association test is whether $\beta > 0$



Genome-wide association study in alopecia areata implicates both innate and adaptive immunity

Lynn Petukhova[1], Madeleine Duvic[2], Maria Hordinsky[3], David Norris[4], Vera Price[5], Yutaka Shimomura[1], Hyunmi Kim[1], Pallavi Singh[1], Annette Lee[6], Wei V. Chen[7], Katja C. Meyer[8], Ralf Paus[8,9], Colin A. B. Jahoda[10], Christopher I. Amos[7], Peter K. Gregersen[6] & Angela M. Christiano[1,11]

NATURE | Vol 466 | 1 July 2010

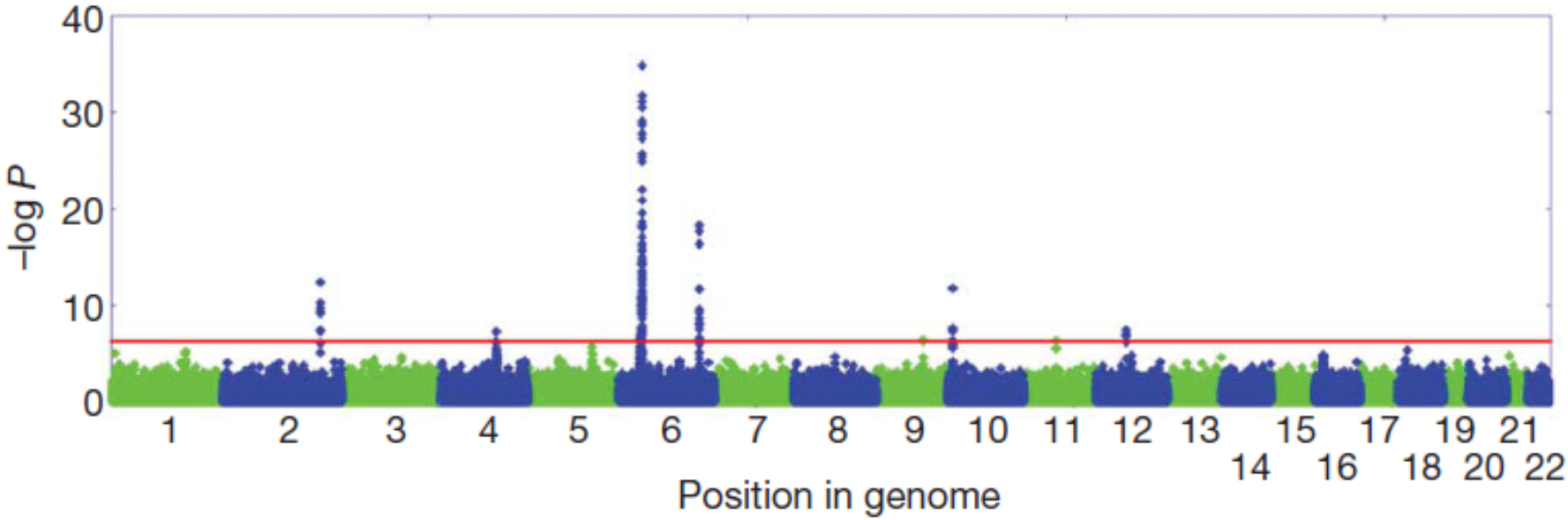
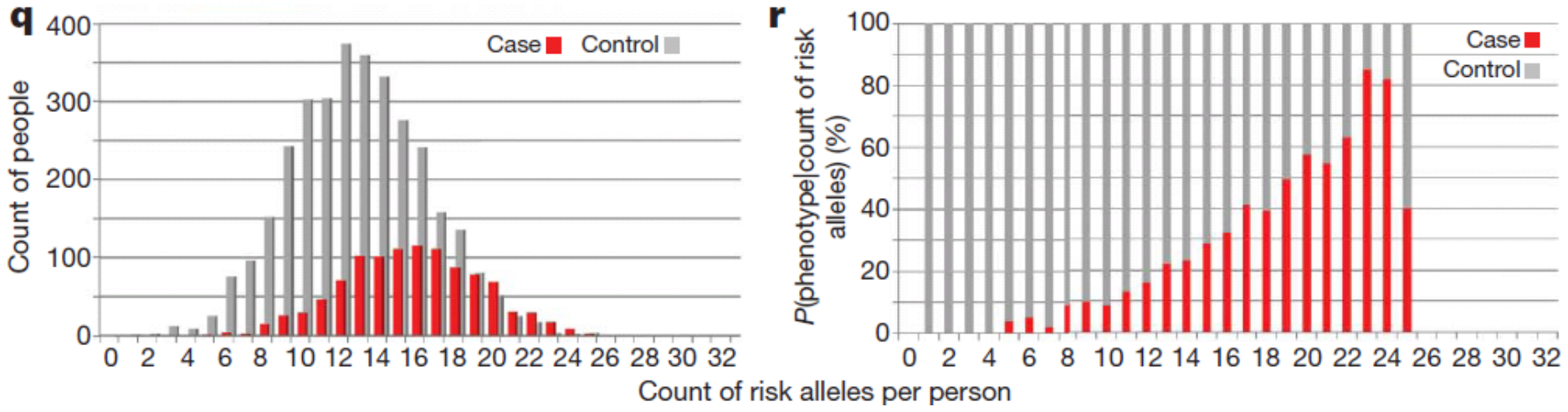


Table 1 | Genes with significant association to AA

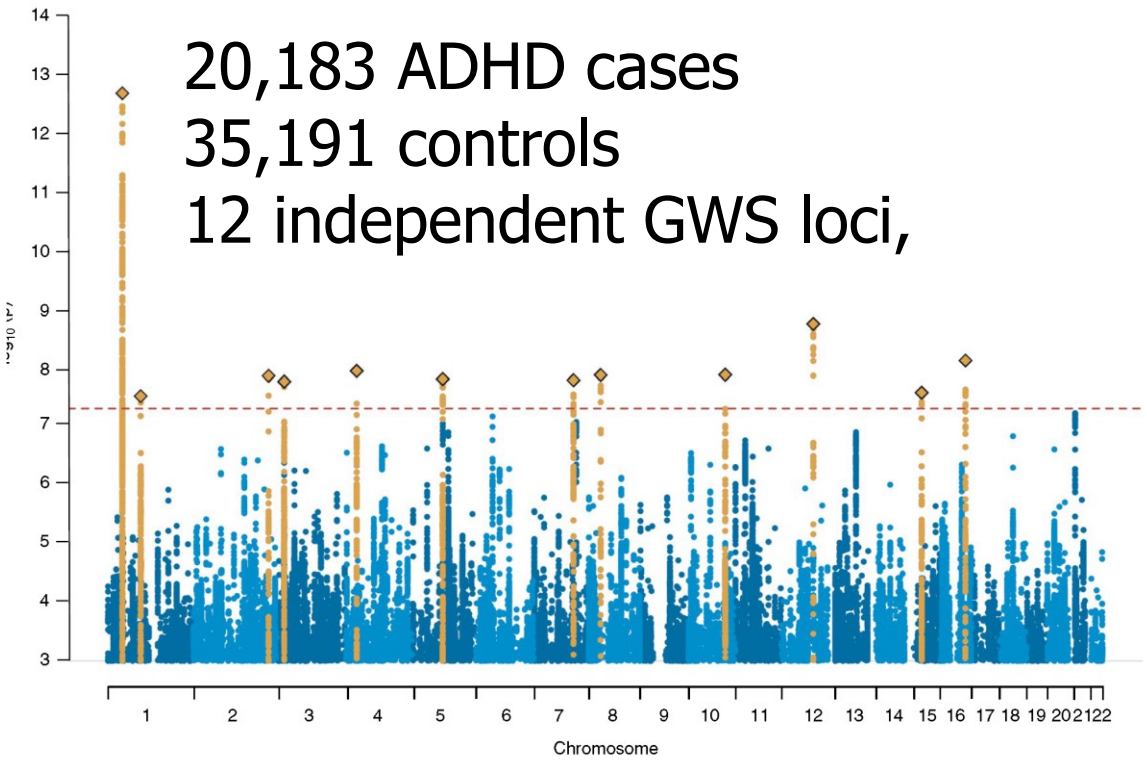
Region	Gene	Function	Strongest association (*P* value)	Maximum odds ratio	Involved in other autoimmune disease
2q33.2	*CTLA4*	Co-stimulatory family	3.55×10^{-13}	1.44	T1D, RA, CeD, MS, SLE, GD
	ICOS	Co-stimulatory family	4.33×10^{-8}	1.32	
4q27	*IL-21/IL-2*	T-, B- and NK-cell proliferation	4.27×10^{-8}	1.34	T1D, RA, CeD, PS
6q25.1	*ULBP6*	NKG2D activating ligand	4.49×10^{-19}	1.65	None
	ULBP3	NKG2D activating ligand	4.43×10^{-17}	1.52	None
9q31.1	*STX17*	Premature hair greying	3.60×10^{-7}	1.33	None
10p15.1	*IL-2RA*	T-cell proliferation	1.74×10^{-12}	1.41	T1D, MS, GD, GV
11q13	*PRDX5*	Antioxidant enzyme	4.14×10^{-7}	1.33	MS
12q13	*Eos (IKZF4)*	T_{reg} transcription factor	3.21×10^{-8}	1.34	T1D, SLE
	ERBB3	Epidermal growth factor receptor	1.27×10^{-7}	1.34	T1D, SLE
6p21.32	*MICA*	NKG2D activating ligand	1.19×10^{-7}	1.44	T1D, RA, CeD, UC, PS, SLE
(HLA)	*NOTCH4*	Haematopoietic differentiation	1.03×10^{-8}	1.61	T1D, RA, MS
	C6orf10	Unknown	1.45×10^{-16}	2.36	T1D, RA, PS, GV
	BTNL2	Co-stimulatory family	2.11×10^{-26}	2.70	T1D, RA, UC, CD, SLE, MS, GV
	HLA-DRA	Antigen presentation	2.93×10^{-31}	2.62	T1D, RA, CeD, MS, GV
	HLA-DQA1	Antigen presentation	3.60×10^{-17}	2.15	T1D, RA, CeD, MS, SLE, PS, CD, UC, GD
	HLA-DQA2	Antigen presentation	1.38×10^{-35}	5.43	T1D, RA
	HLA-DQB2	Antigen presentation	1.73×10^{-13}	1.60	RA

Each of the eight regions implicated in our study contains multiple significant SNPs, which are detailed in Supplementary Tables 1 and 2. Here we display candidate genes within the implicated regions, and include the *P* value of the most significant SNP, and the odds ratio for the SNP with the largest effect estimate. Diseases are listed for which a GWAS or previous candidate gene study identified the same region (http://www.genome.gov/gwastudies, http://www.cdc.gov/genomics/hugenet): Crohn's disease (CD), celiac disease (CeD), Graves disease (GD), generalized vitiligo (GV), multiple sclerosis (MS), psoriasis (PS), rheumatoid arthritis (RA), system lupus erythematosus (SLE), type I diabetes (T1D), and ulcerative colitis (UC).



Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder

Ditte Demontis , Raymond Walters …. Sarah Medland …. Benjamin Neale

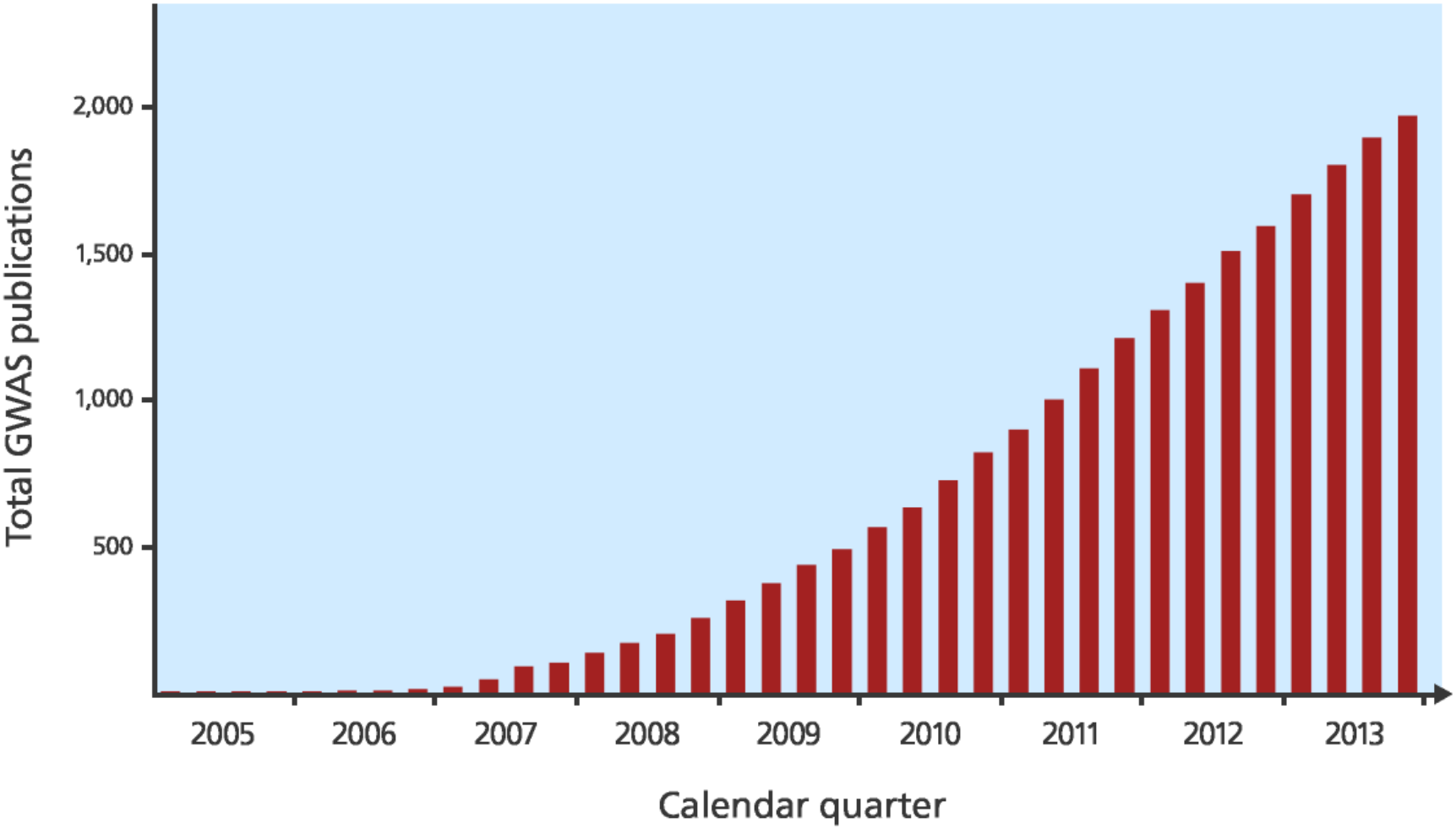


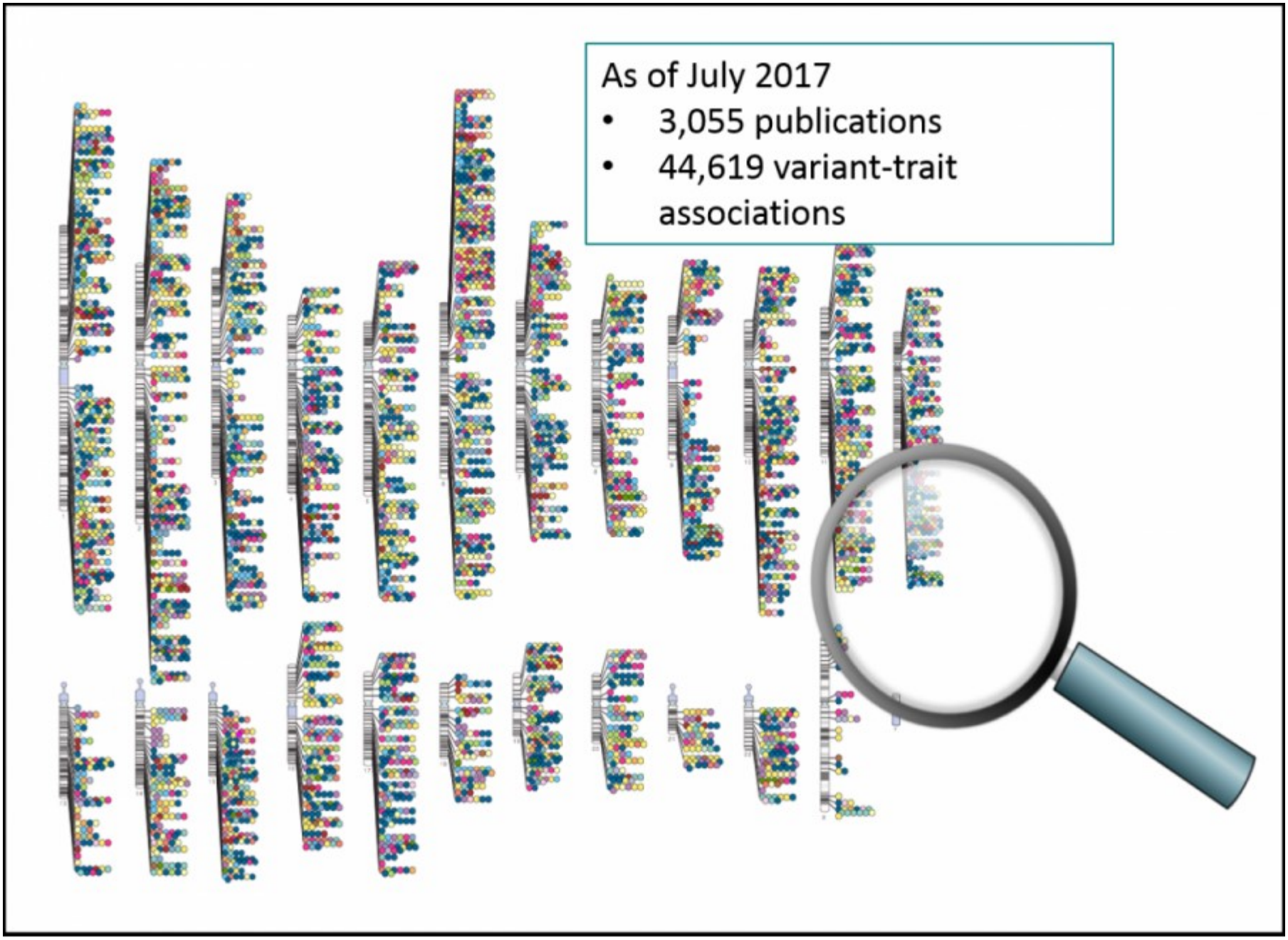
we developed a novel model to meta-analyze the GWAS of the continuous measure of ADHD with the clinical diagnosis in the ADHD GWAS. In brief, we perform a z-score based meta-analysis using a weighting scheme derived from the SNP heritability and effective sample size for each phenotype that fully accounts for the differences in measurement scale

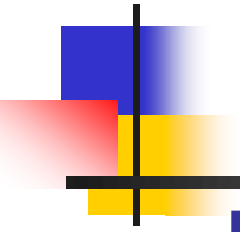
How to combine binary and continuous measures in GWAS

NATURE GENETICS | VOL 51 | JANUARY 2019 | 63–75

GWAS publications since 2005




As of July 2017
• 3,055 publications
• 44,619 variant-trait associations



Functional interpretation GWAS results

Find the right target gene

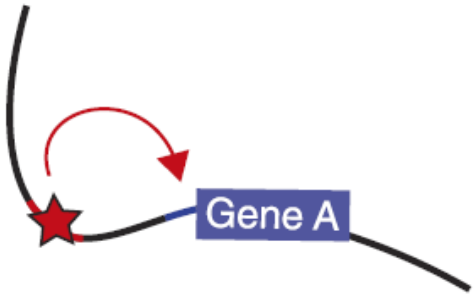
Knight *Genome Medicine* 2014, **6**:92
http://genomemedicine.com/content/6/10/92

Genome Medicine

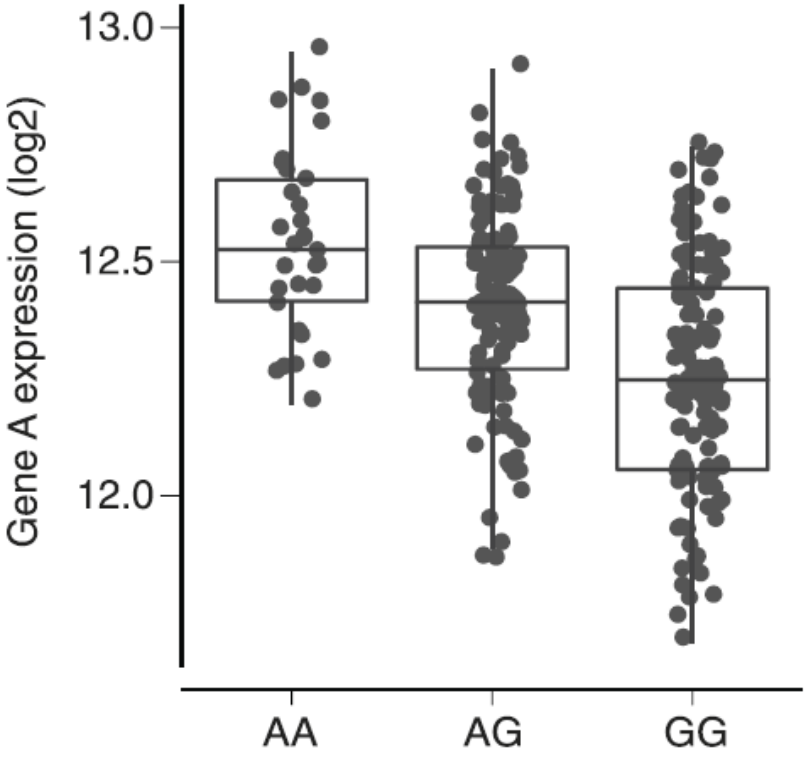
REVIEW

Approaches for establishing the function of regulatory genetic variants involved in disease

Julian Charles Knight



A local *cis*-acting variant ★ in a regulatory element – affects allele-specific transcription factor binding affinity and is associated with differential expression of gene A (see chart)



Knight *Genome Medicine* 2014, **6**:92
http://genomemedicine.com/content/6/10/92

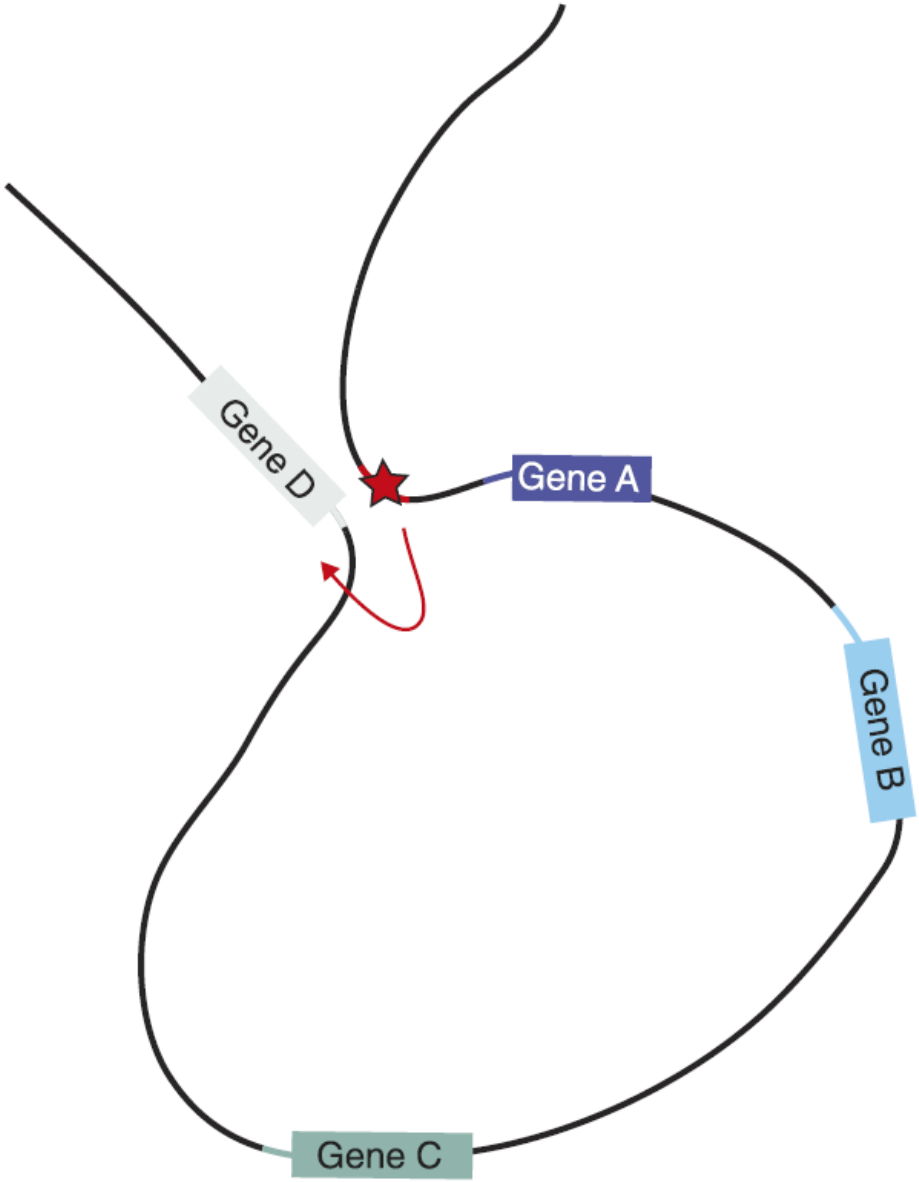
Genome Medicine

REVIEW

Approaches for establishing the function of regulatory genetic variants involved in disease

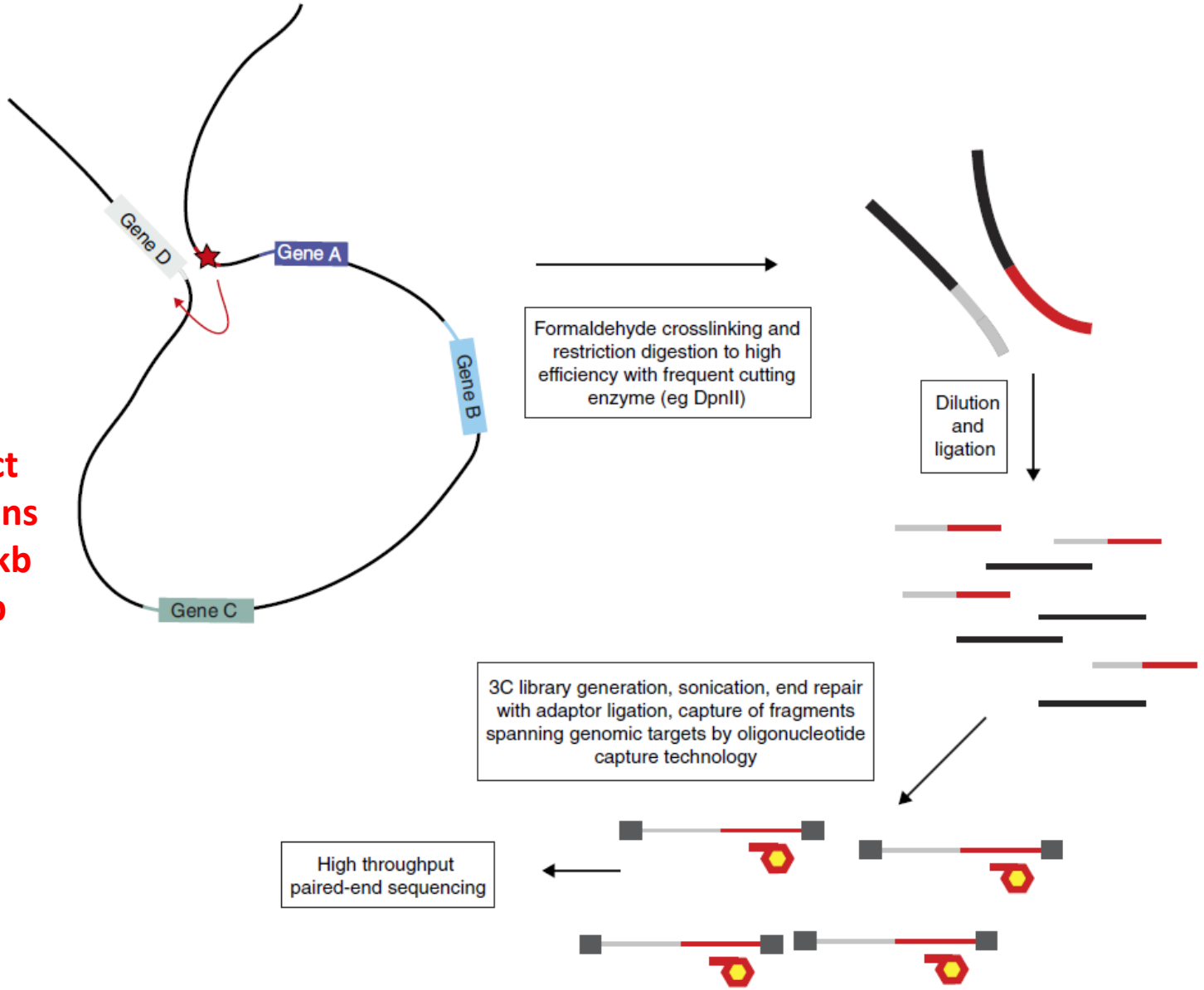
Julian Charles Knight

The same variant can modulate expression of **gene D** at a distance through DNA looping that brings the regulatory enhancer element close to the promoter of gene D on the same chromosome.



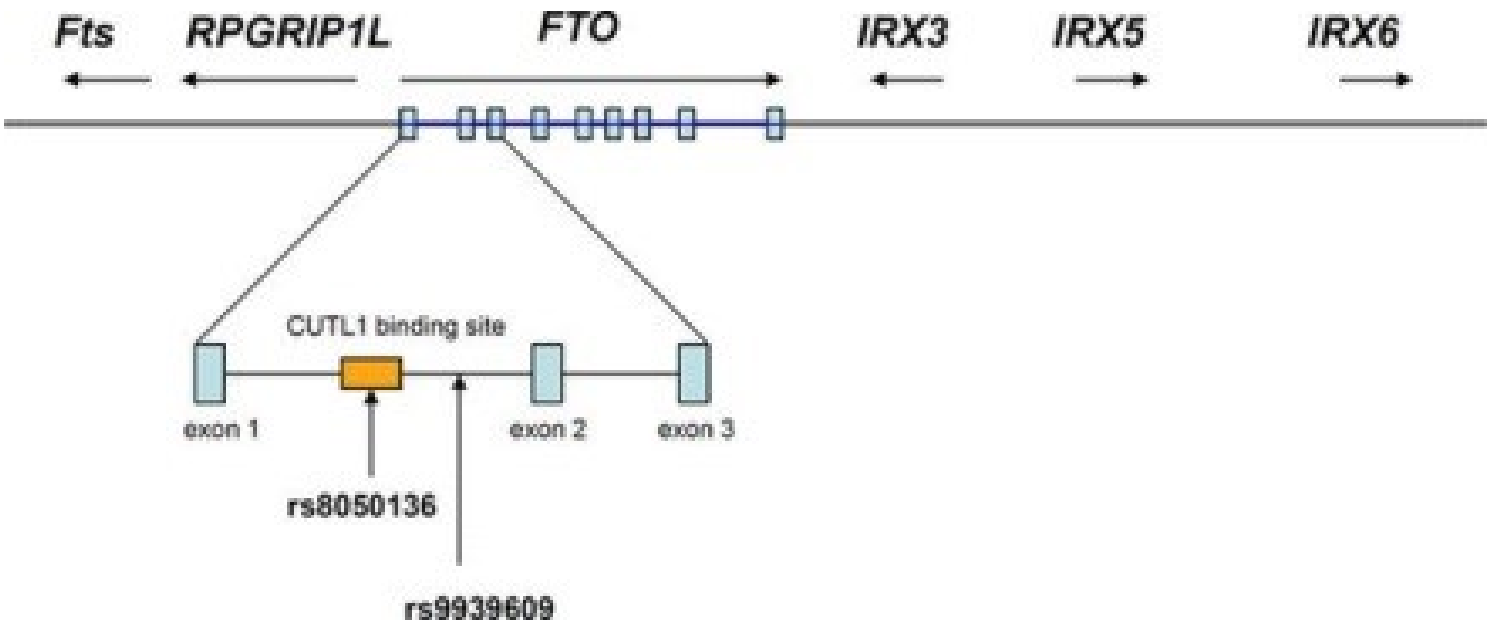
Chromatin conformation capture (3C) to find the target of a disease-associated SNP within an enhancer element

Can detect interactions from ~20kb to ~800kb

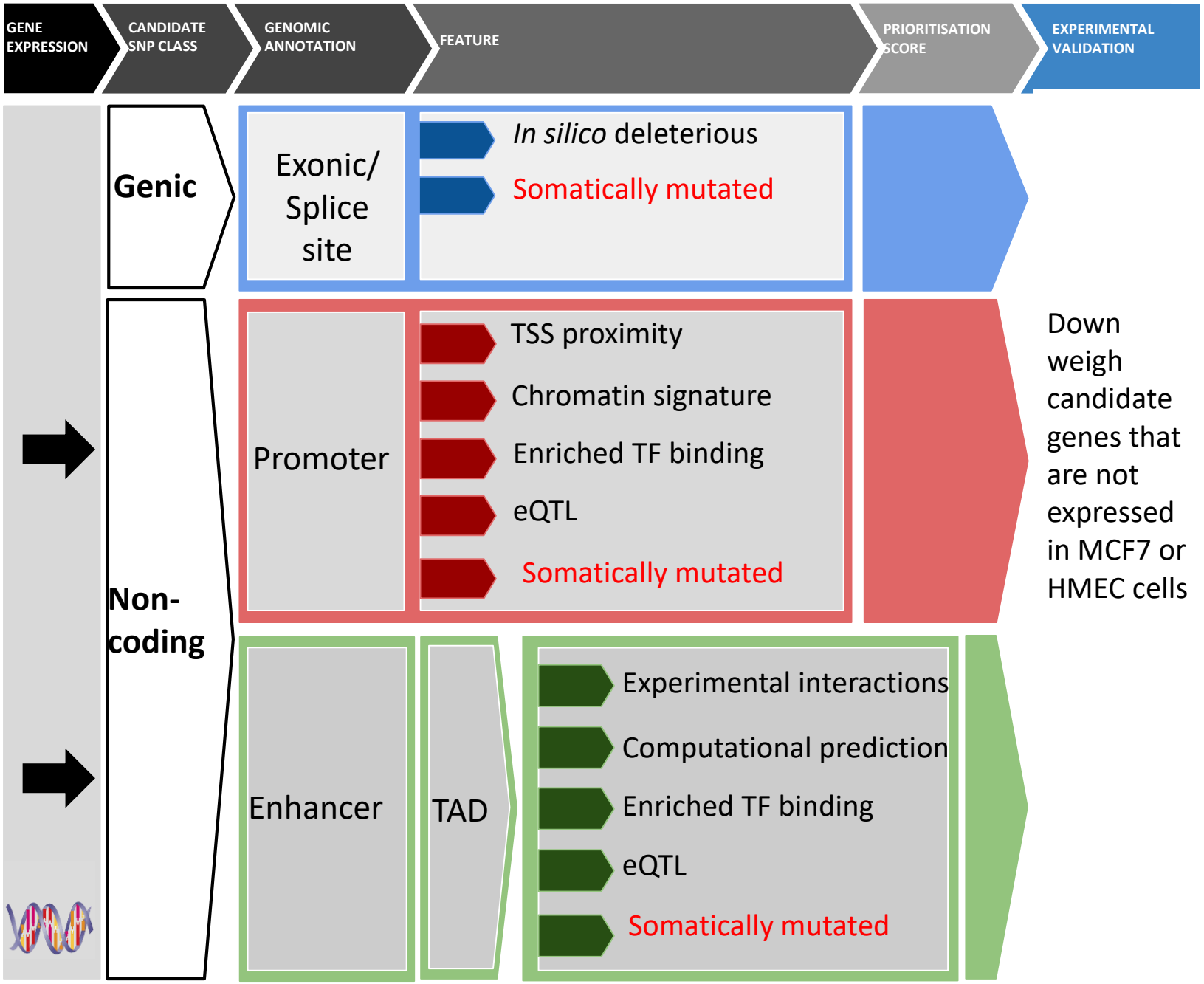


Obesity-associated variants within *FTO* form long-range functional connections with *IRX3*

Smemo et al 2014



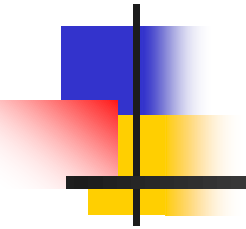
INQUISIT: Integrated eQTL and in silico prediction of gene targets



Weigh potential candidate SNPs by enriched chromatin features

Down weigh candidate genes that are not expressed in MCF7 or HMEC cells

Michailidou et al Nature 2017



Ways to increase power

Imputation

Imputation

```
a g a g t t g a g g g a a c c t g a g a a
t g a g a c g a g g g a a a t t g a g a c
t g c g a c g g t g a t t c t c c a g a c
a g c g a c g a t g g t a c t t g a t c a
t a a g t t a g t a a t t c c c g a g c a
t g c a a t g a g g g a a a t t g t t a a
a g a g a c g g g g g a a a t t c t g c c

  g       a     g   g       t     a     a
  g       c     t   a       t     t     c

  a       t     g   g       t     t     a
  g       c     g   g       c     a     a

  g       c     t   g       t     t     c
  g       c     g   g       c     a     a

  g       t     g   g       t     a     c
  a       t     t   a       c     a     a
```

Reference haplotypes via sequencing studies

eg. 1000 Genomes Project

Slide from Jonathan Marchini

Imputation

```
a g a g t t g a g g g a a c c t g a g a a
t g a g a c g a g g g a a a t t g a g a c
t g c g a c g g t g a t t c t c c a g a c
a g c g a c g a t g g t a c t t g a t c a
t a a g t t a g t a a t t c c c g a g c a
t g c a a t g a g g g a a a t t g t t a a
a g a g a c g g g g g a a a t t c t g c c

? g ? ? ? a ? ? g ? g ? ? ? t ? ? a ? ? a
? g ? ? ? c ? ? t ? a ? ? ? t ? ? t ? ? c

? a ? ? ? t ? ? g ? g ? ? ? t ? ? t ? ? a
? g ? ? ? c ? ? g ? g ? ? ? c ? ? a ? ? a

? g ? ? ? c ? ? t ? g ? ? ? t ? ? t ? ? c
? g ? ? ? c ? ? g ? g ? ? ? c ? ? a ? ? a

? g ? ? ? t ? ? g ? g ? ? ? t ? ? a ? ? c
? a ? ? ? t ? ? t ? a ? ? ? c ? ? a ? ? a
```

Reference haplotypes via sequencing studies

eg. 1000 Genomes Project

Slide from Jonathan Marchini

Imputation

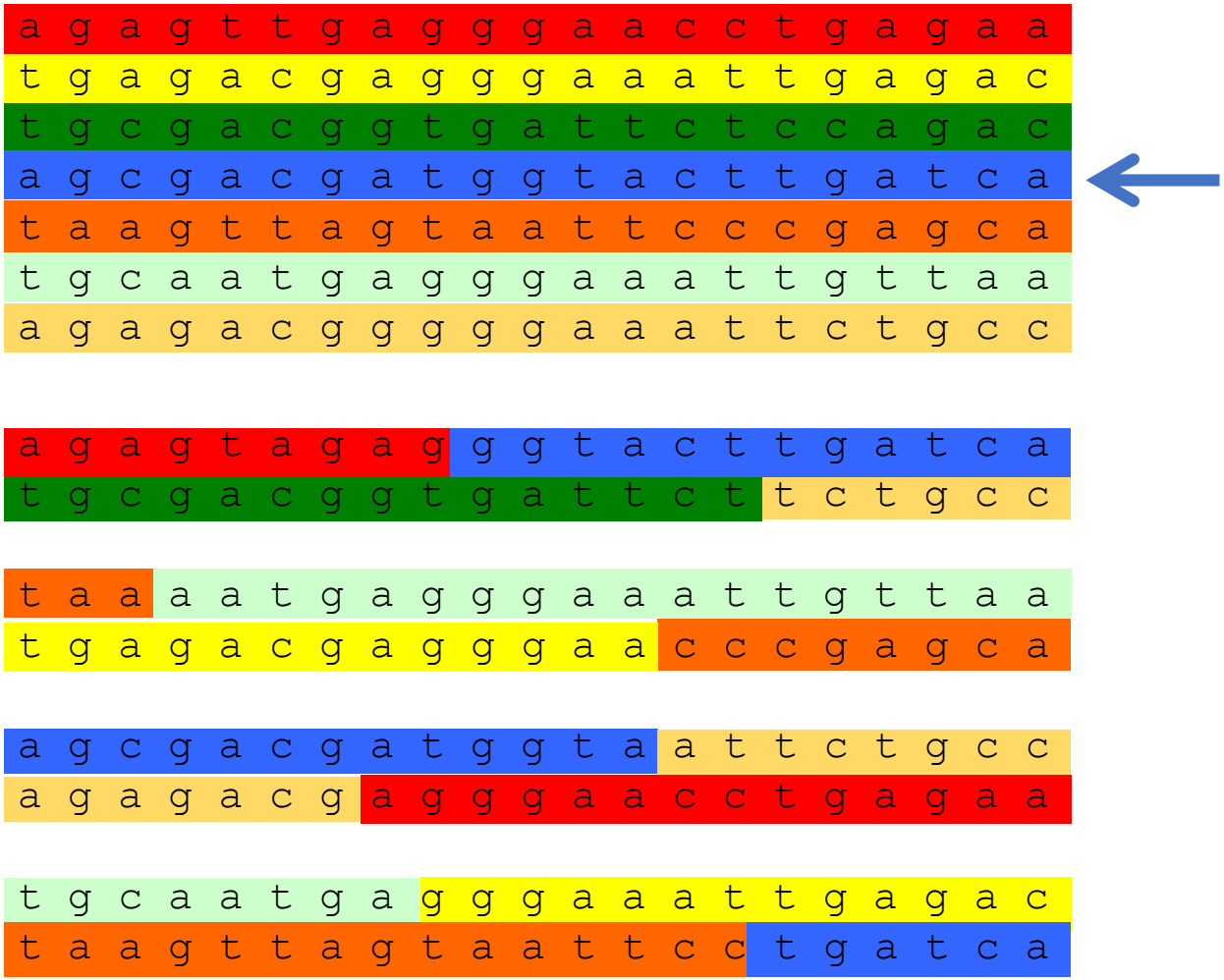
Reference haplotypes via sequencing studies

eg. 1000 Genomes Project

Imputation of unobserved alleles via matching of shared haplotypes

Slide from Jonathan Marchini

Imputation



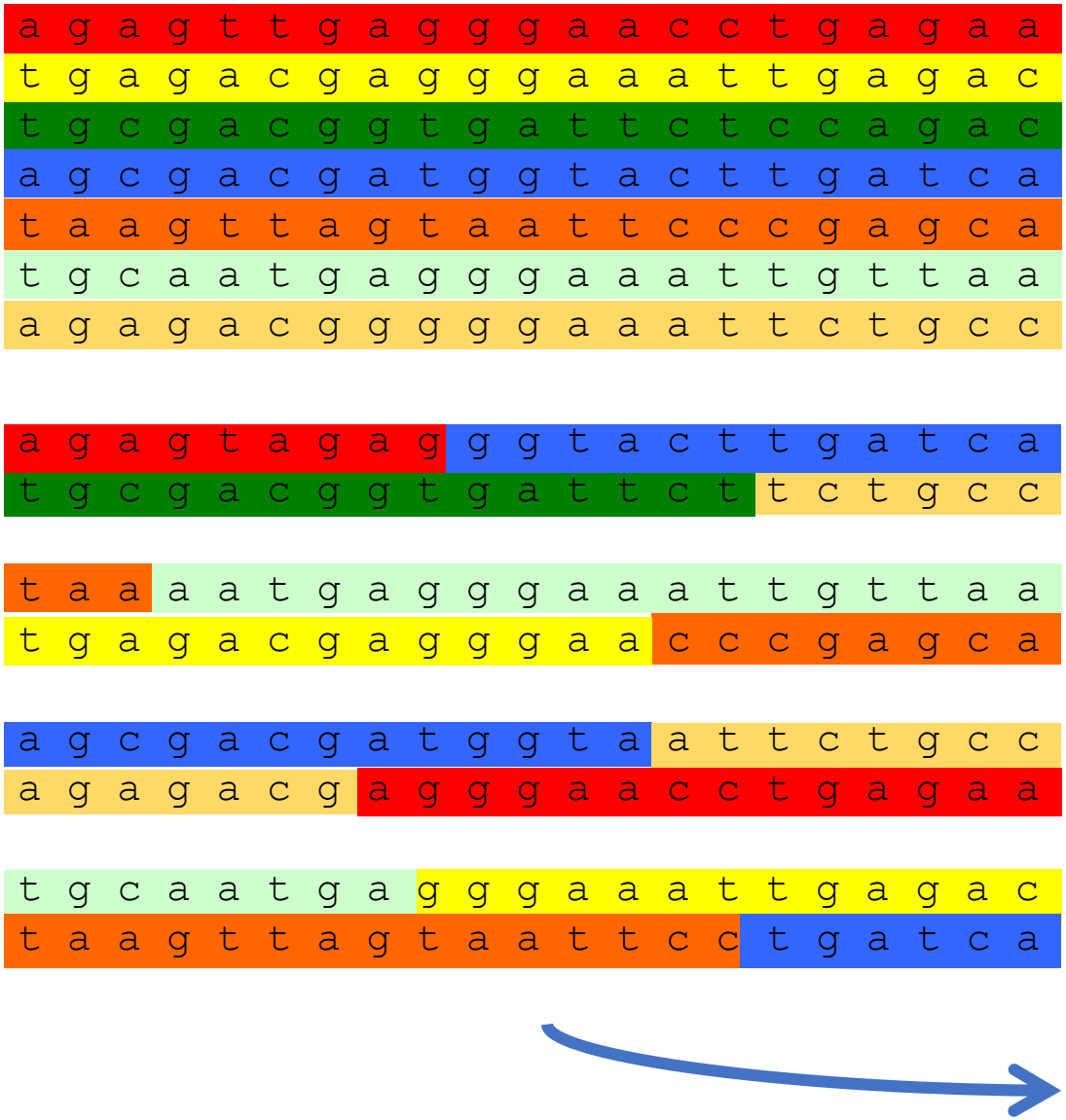
Reference haplotypes via sequencing studies

eg. 1000 Genomes Project

Imputation of unobserved alleles via matching of shared haplotypes

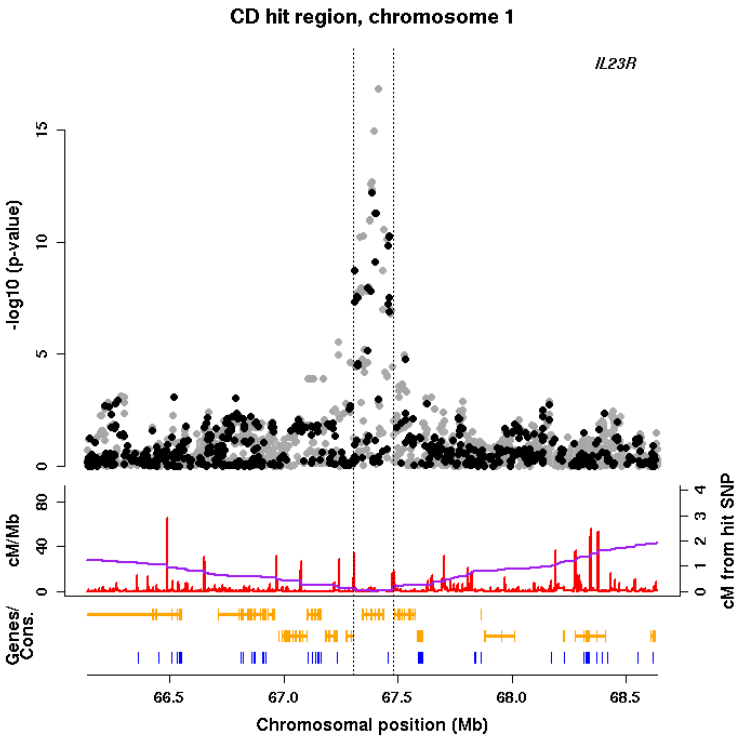
Slide from Jonathan Marchini

Imputation



GWAS of imputed genotypes

- Increased power
- Better resolution
- Facilitates meta-analysis



Slide from Jonathan Marchini

Reference Panels

Our server offers imputation from the following reference panels:

TOPMed (TOPMed Freeze5 on GRCh38, in preperation)

The TOPmed panel consists of currently 125,568 haplotypes.

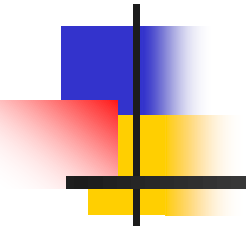
Number of Samples	62784
Sites (chr1-22)	463,000,000
Chromosomes	1-22, X
Website:	https://www.nhlbiwgs.org/

HRC (Version r1.1 2016)

The HRC panel consists of 64,940 haplotypes of predominantly European ancestry.

Number of Samples	
Sites (chr1-22)	39,635,008
Chromosomes	1-22, X
Website:	http://www.haplotype-reference-consortium.org; HRC r1.1 Release Note

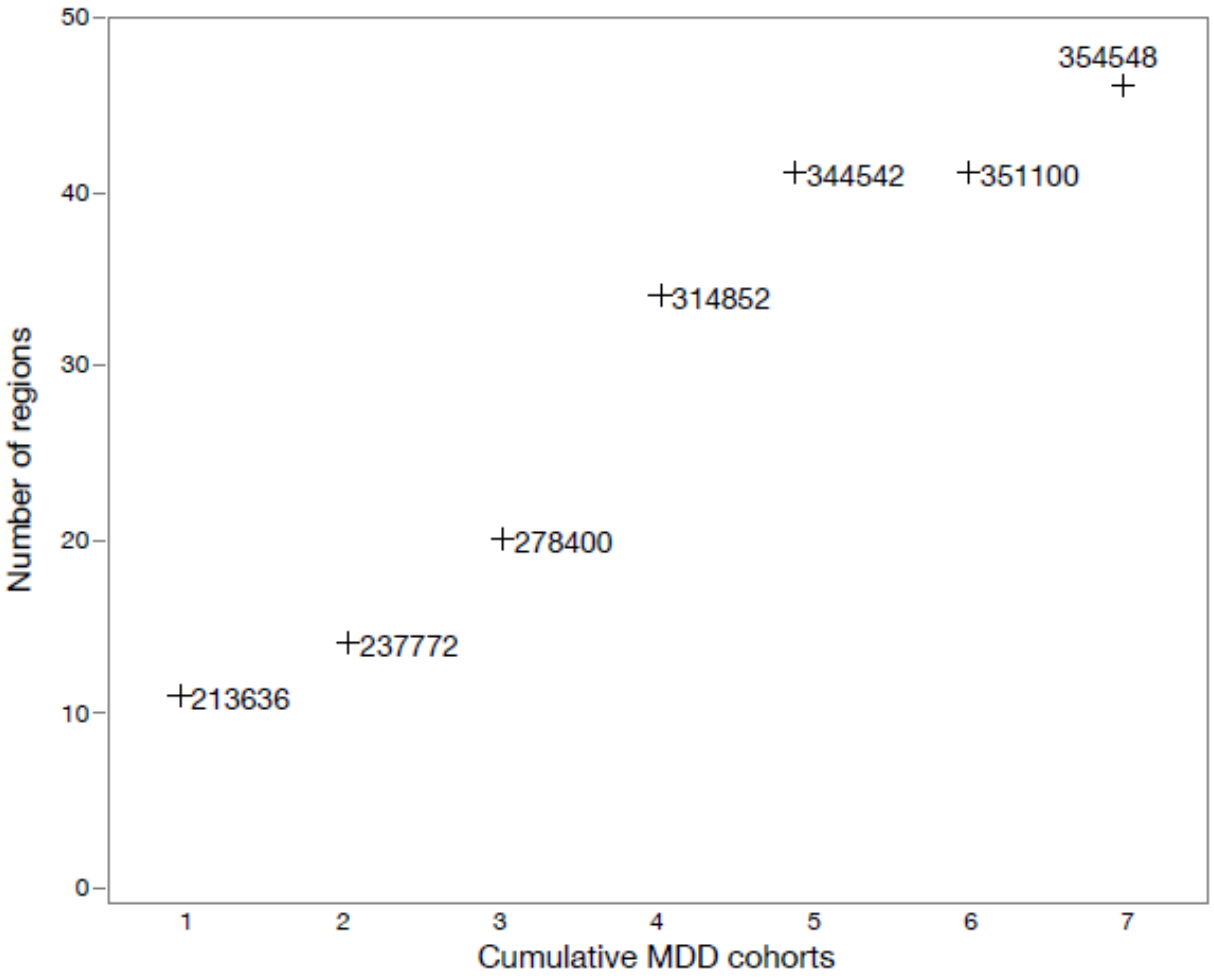
https://imputationserver.readthedocs.io/en/latest/reference-panels/



Ways to increase power

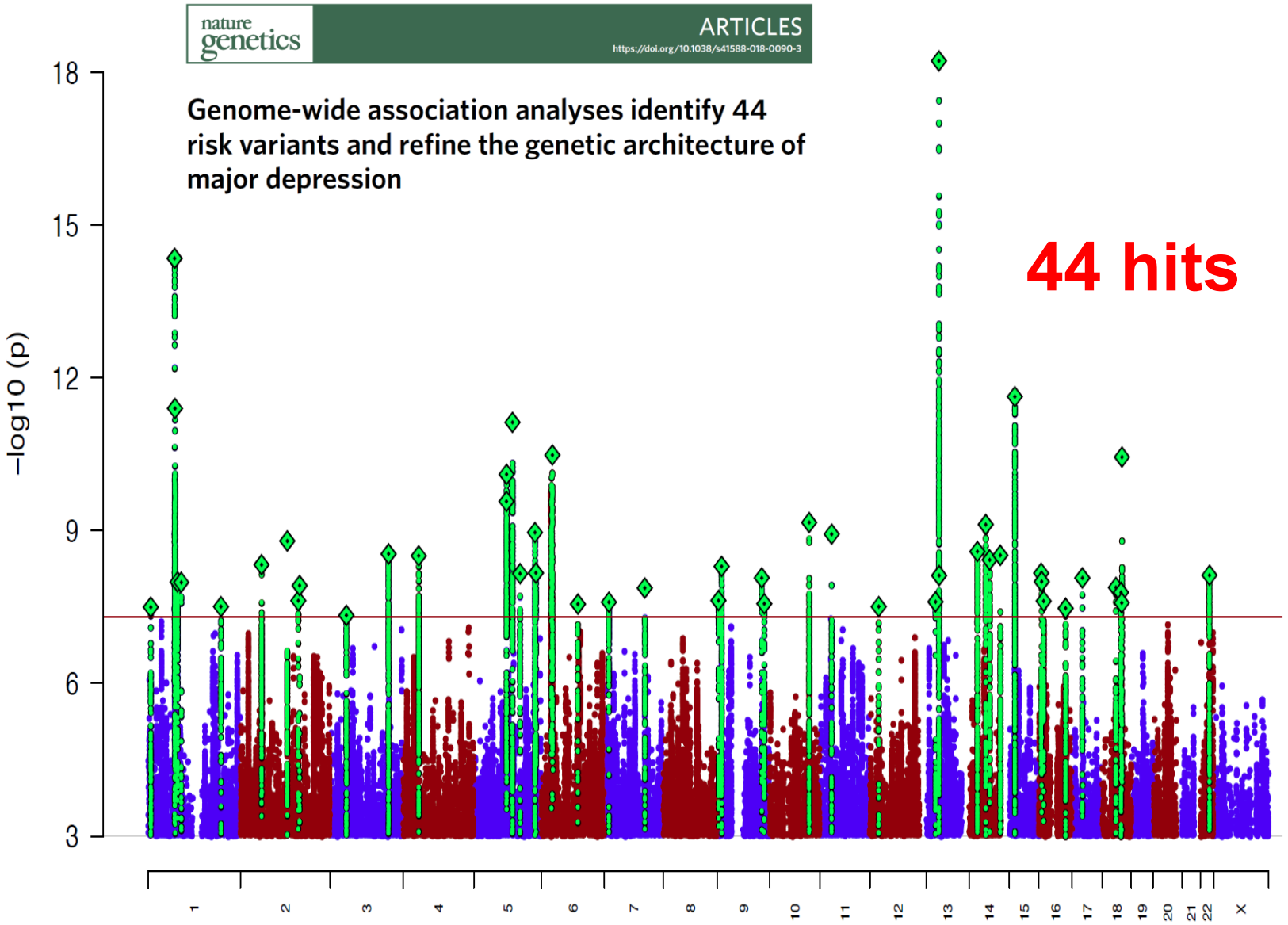
Increase sample size

Larger samples lead to more SNP discovery



Results of GWA meta-analysis of seven cohorts for MDD. (a) Relation between adding cohorts and number of genome-wide significant genomic regions. Beginning with the largest cohort (1), added the next largest cohort (2) until all cohorts were included (7). The number next to each point shows the total effective sample size.

Depression : 135K MDD Cases and 345K Controls

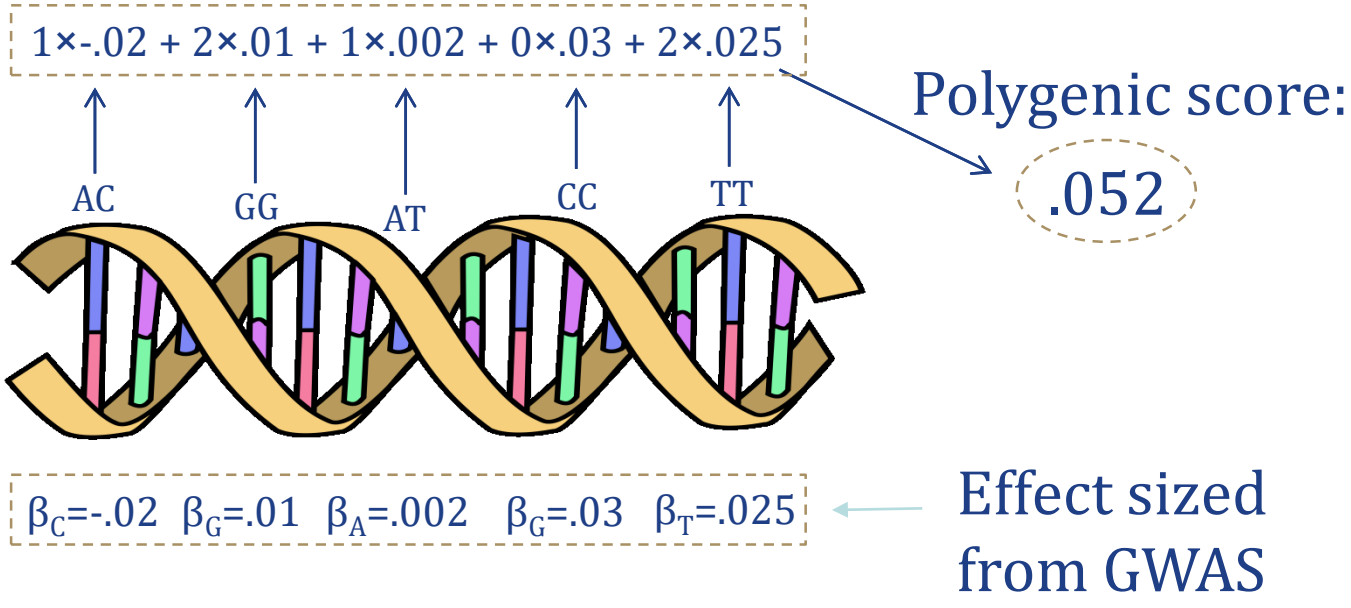


Nat Genet. 2018 May;50(5):635-637.

Led by Naomi Wray

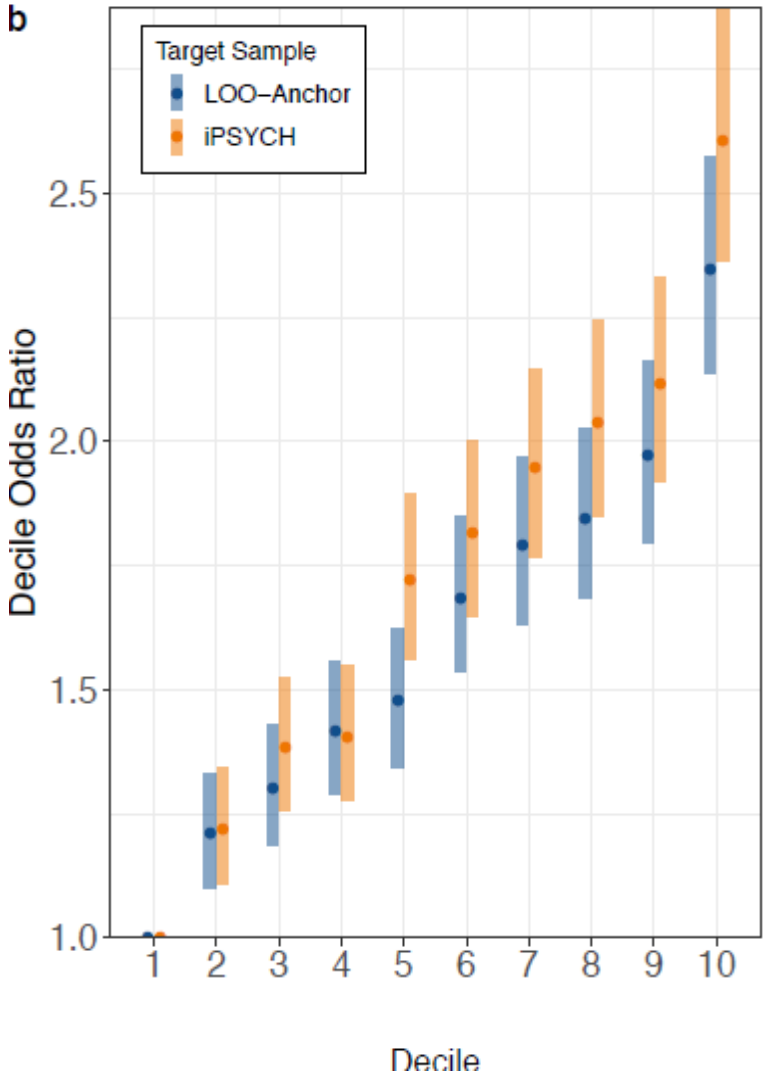
Polygenic Risk Scores

Polygenic Risk Scores capture (part of) someone's genetic "risk" by summing all risk alleles weighted by the effect sizes estimated in a Genome-Wide Association Study (GWAS)



Wray, Visscher, Goddard, 2007 – Oz!

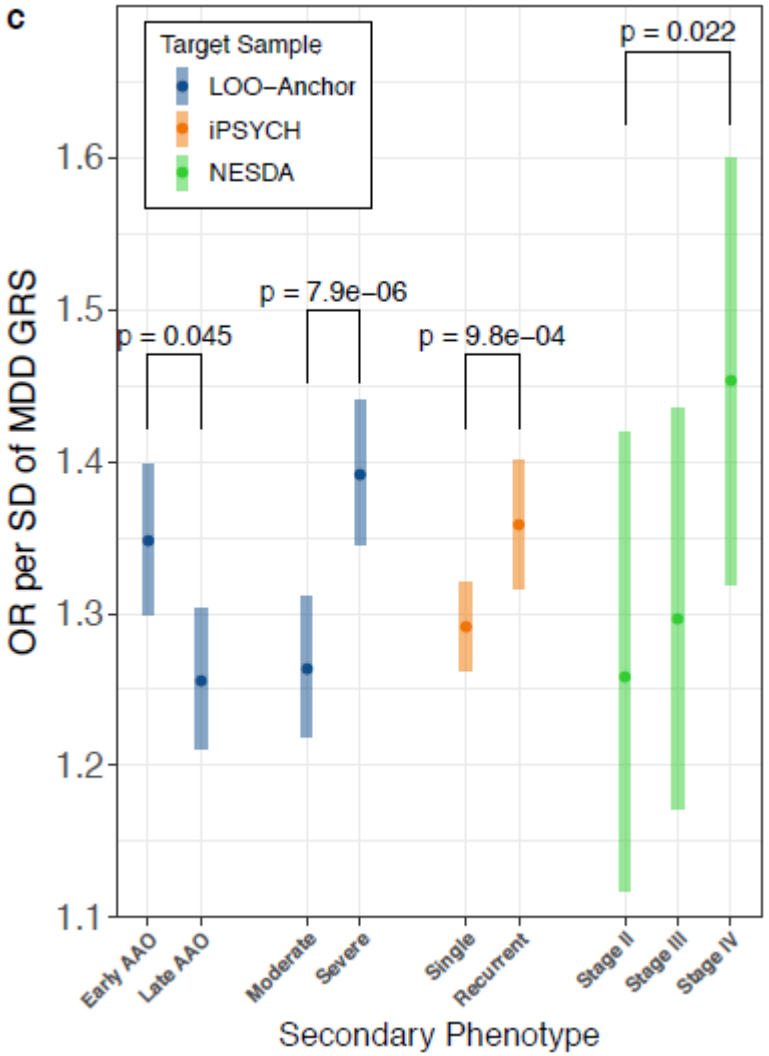
MDD Polygenic Risk Score predicts risk in independent samples



Odd ratios of MDD per PRS decile relative to the first decile for iPSYCH and anchor cohorts.

Interdecile risk ~2.5

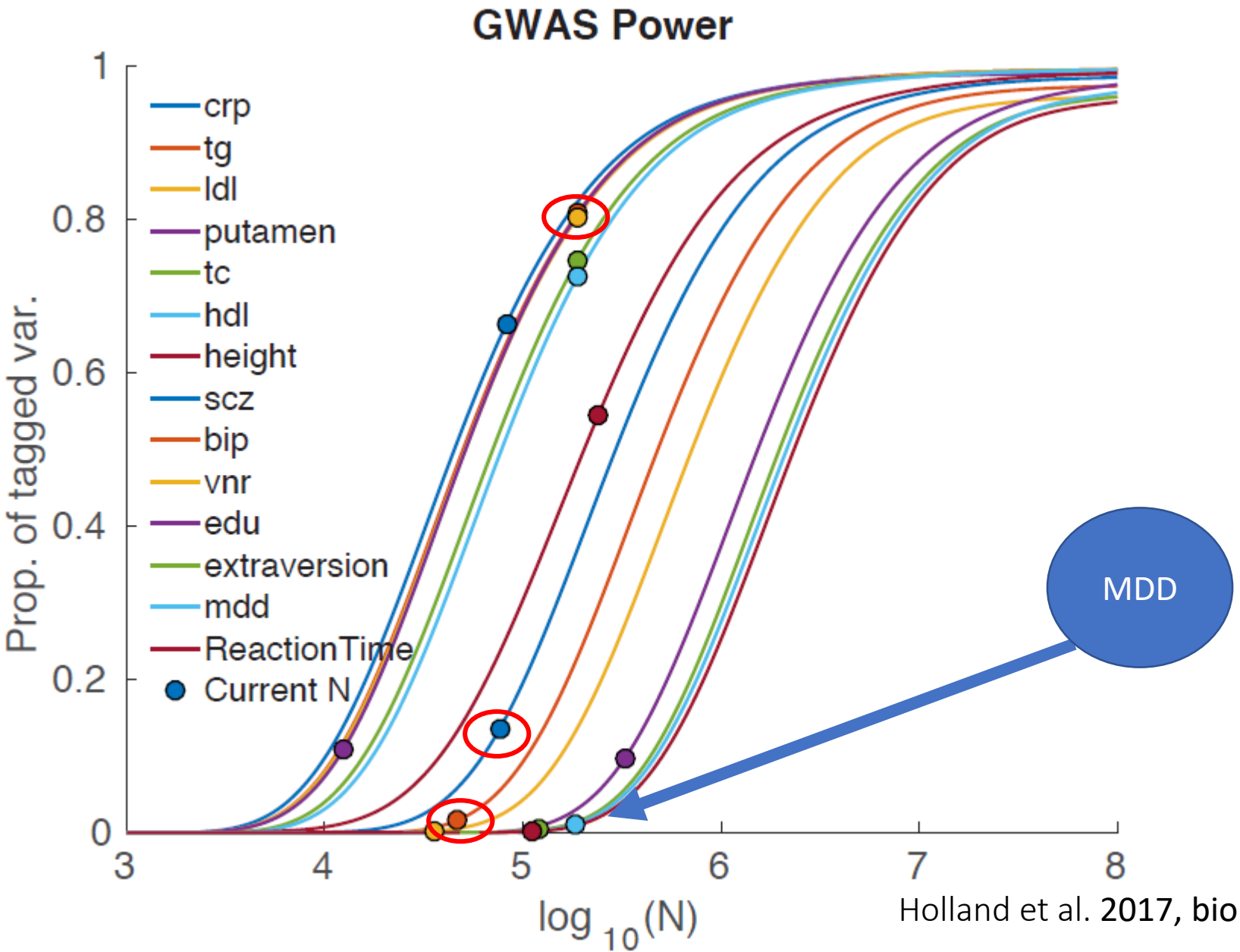
MDD Polygenic Risk Score predicts age at onset, recurrence, and severity in independent samples



MDD PRS (from out-of-sample discovery sets) were significantly higher in MDD cases with:

- *earlier age at onset; more severe MDD symptoms (based on number of criteria endorsed)*
- *recurrent MDD compared to single episode*
- *chronic/unremitting MDD ("Stage IV" compared to "Stage II", first-episode MDD)*

Error bars represent 95% CI



Holland et al. **2017, biorXiv**

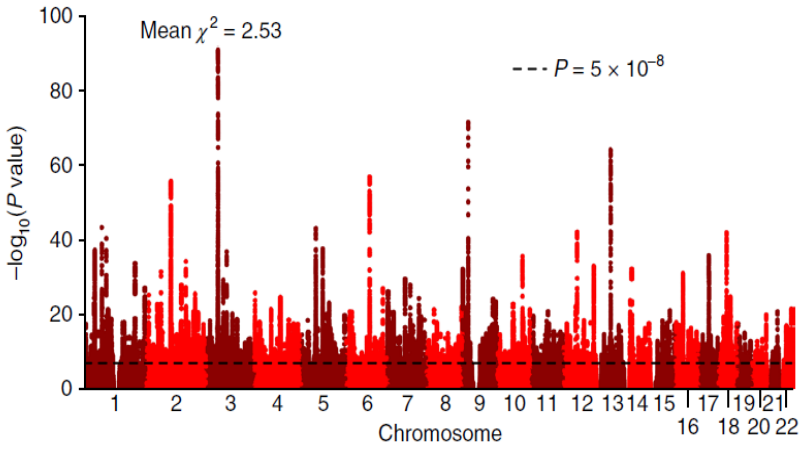
nature genetics

ARTICLES

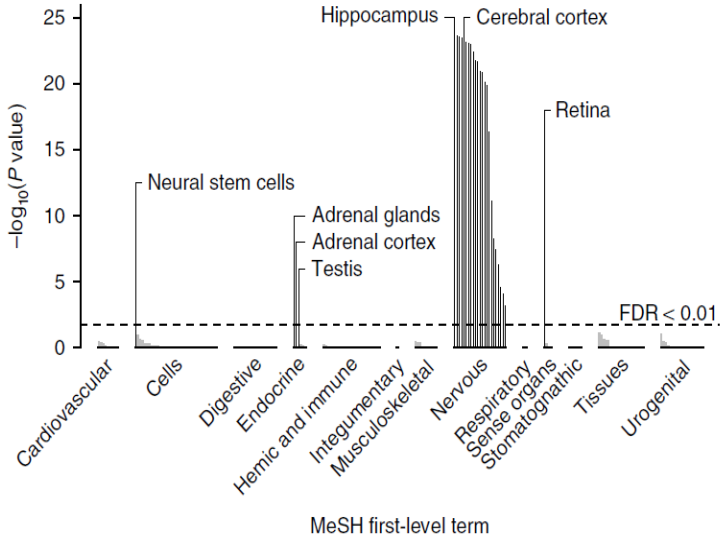
https://doi.org/10.1038/s41588-018-0147-3

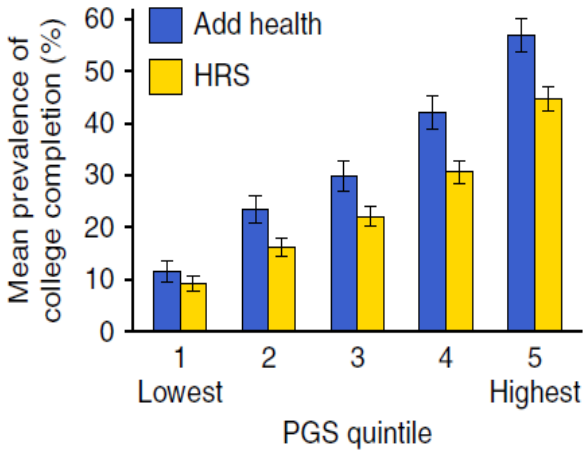
Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals

James J. Lee[1,58], Robbee Wedow[2,3,4,58], Aysu Okbay[5,6,58]*, Edward Kong[7], Omeed Maghzian[7],



- **1,271 independent GWS SNPs**
- **implicate genes involved in brain-development processes and neuron-to-neuron communication**
- **polygenic scores explain 11–13% of the variance in educational attainment and 7–10% of the variance in cognitive performance.**





Nat Genet. 2018 Aug;50(8):1112-1121

GWAS of 126,559 Individuals Identifies Genetic Variants Associated with Educational Attainment

All authors with their affiliations appear at the end of this paper.

A genome-wide association study (GWAS) of educational attainment was conducted in a discovery sample of 101,069 individuals and a replication sample of 25,490. Three independent single-nucleotide polymorphisms (SNPs) are genome-wide significant (rs9320913, rs11584700, rs4851266), and all three replicate. Estimated effects sizes are small (coefficient of determination $R^2 \approx 0.02\%$), approximately 1 month of schooling per allele. A linear polygenic score from all measured SNPs accounts for ≈2% of the variance in both educational attainment and cognitive function. Genes in the region of the loci have previously been

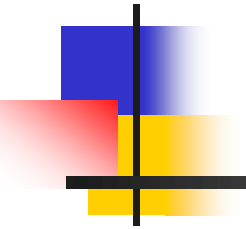
The value of DZ twins for within-pair association tests for ruling out population stratification

Within-family regression results of the polygenic scores on *College* and *EduYears* in the QIMR and Swedish Twin Registry cohorts using SNPs selected from the meta-analysis excluding the QIMR and STR cohorts.

		Prediction in QIMR + STR			
Phenotype (PGS)		$p_{SNPs} < 5\times10^{-8}$	$p_{SNPs} < 5\times10^{-5}$	$p_{SNPs} < 5\times10^{-3}$	All SNPs
EduYears (*College*)	R^2 (%)	0.017	0.003	0.220	0.310
	P	0.455	0.739	0.006	0.001
EduYears (*EduYears*)	R^2 (%)	0.002	0.001	0.110	0.190
	P	0.791	0.846	0.065	0.011

Analyses for QIMR are based on 572 full-sib pairs from independent 572 families. Analyses for STR are based on 2,774 DZ twins from 2,774 independent families.

Science. 2013 Jun 21;340:1467-71



Ways to increase power

Refine the phenotype

Human Reproduction, Vol.25, No.6 pp. 1569–1580, 2010
Advanced Access publication on April 8, 2010 doi:10.1093/humrep/deq084

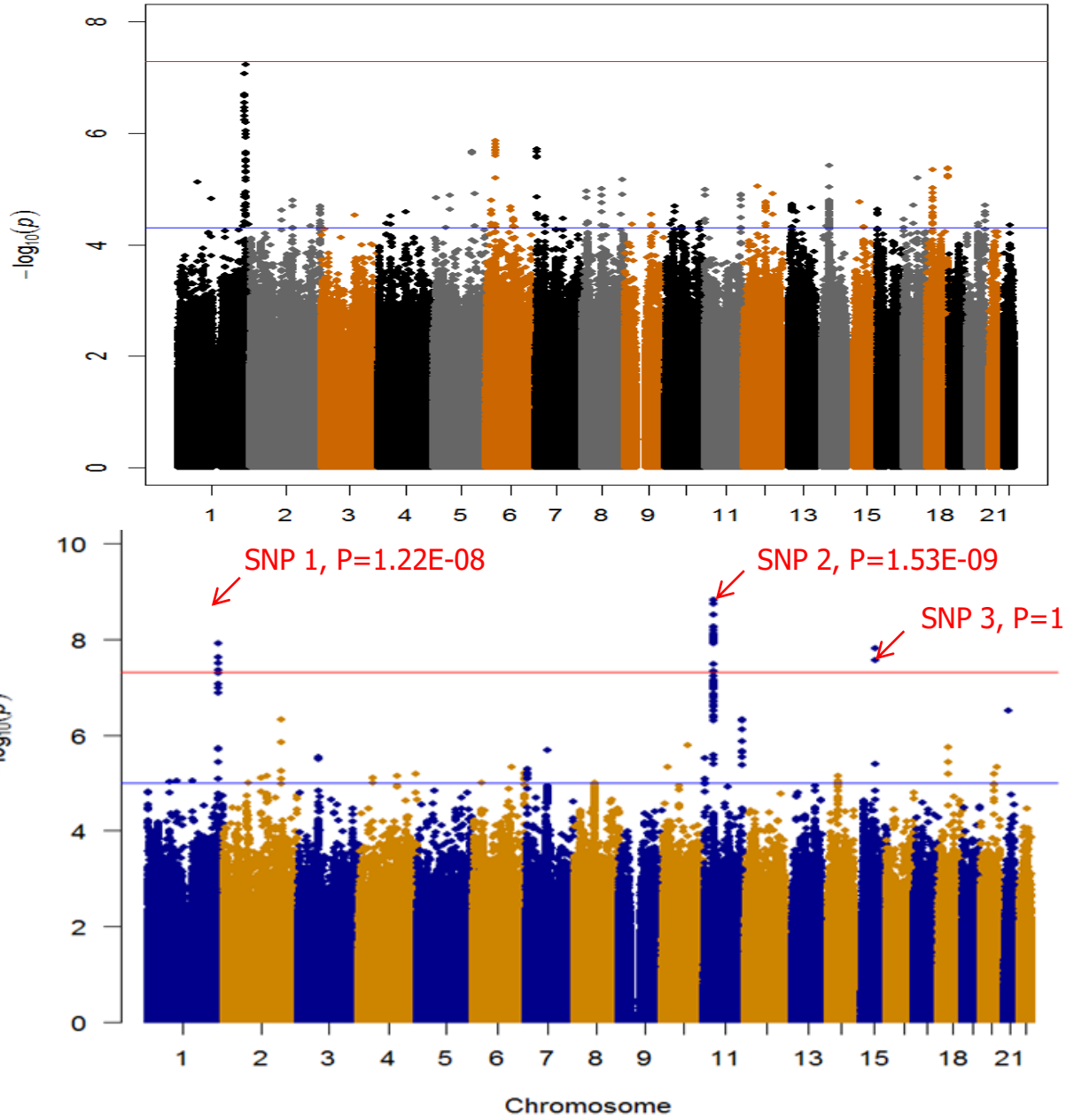
human reproduction

ORIGINAL ARTICLE *Reproductive genetics*

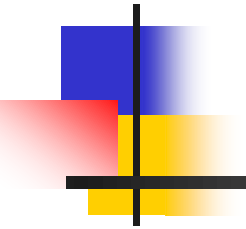
A genome wide linkage scan for dizygotic twinning in 525 families of mothers of dizygotic twins

Jodie N. Painter[1,*], Gonneke Willemsen[2], Dale Nyholt[1], Chantal Hoekstra[2], David L. Duffy[1], Anjali K. Henders[1], Leanne Wallace[1], Sue Healey[1], Lisa A. Cannon-Albright[3], Mark Skolnick[3], Nicholas G. Martin[1], Dorret I. Boomsma[2,†], and Grant W. Montgomery[1,†]

The importance of accurate phenotyping: GWAS for Being a Mother of DZ Twins - Before and after removing mothers who had used assisted reproductive technology



Hamdi Mbarek

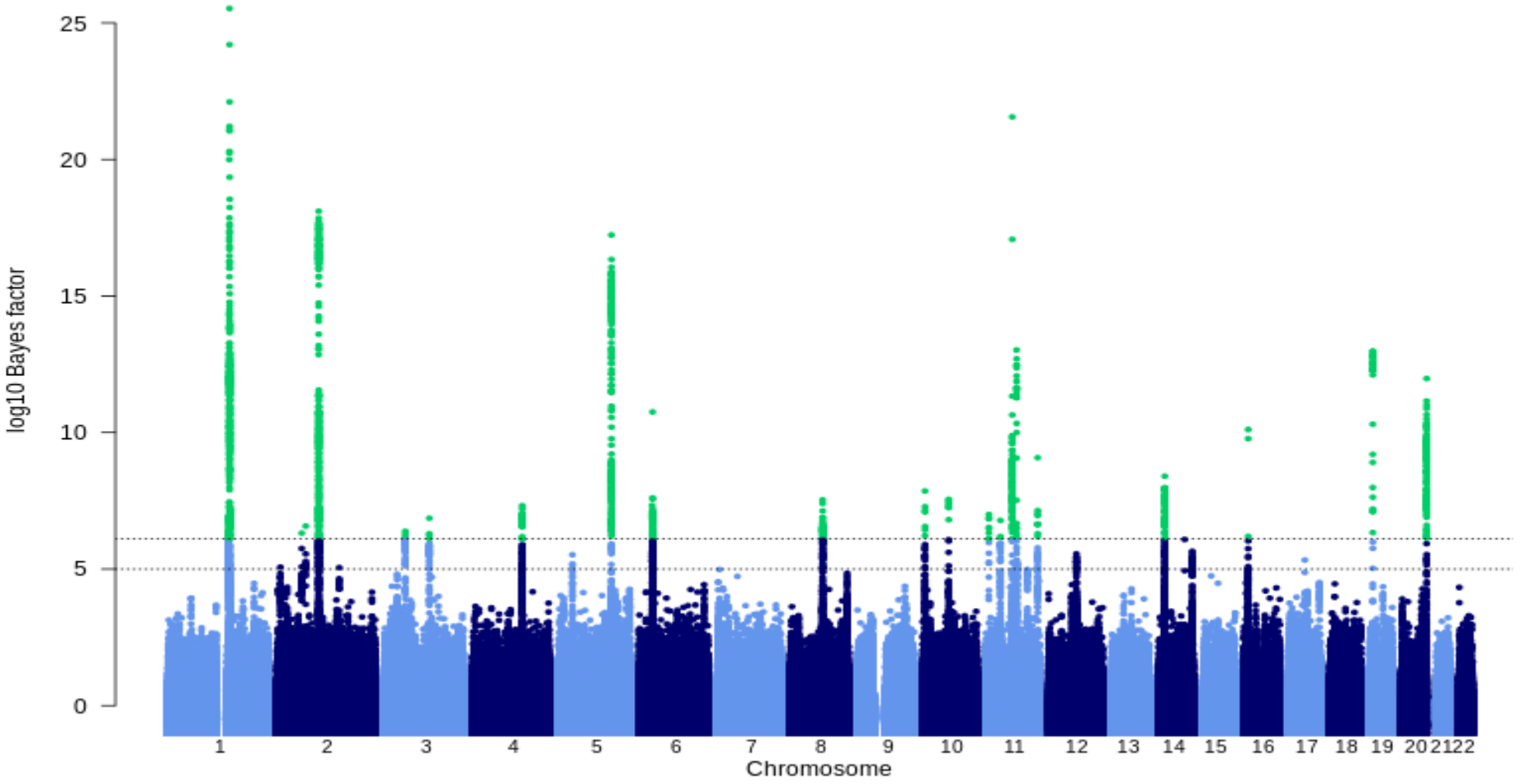


Ways to increase power

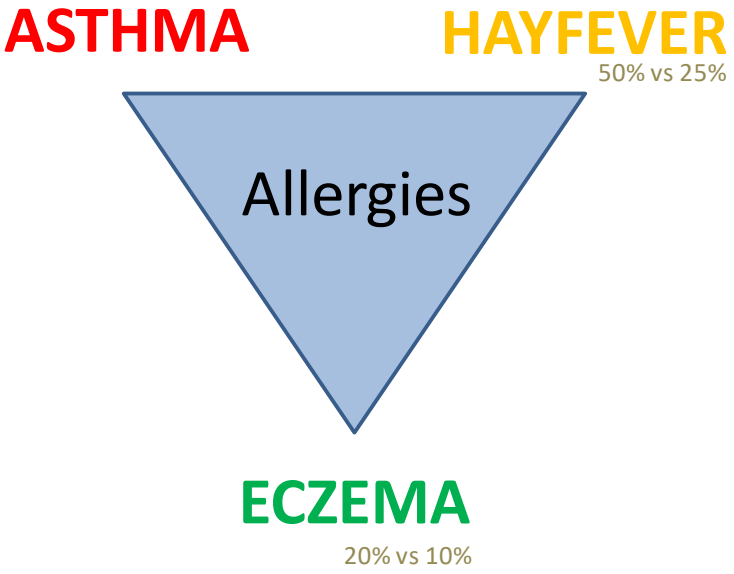
Combine related phenotypes

We define genome-wide significance as .05/1 million effective tests = 5×10^{-8}

GWAS for eczema (21k cases, 98k controls, 27 hits)

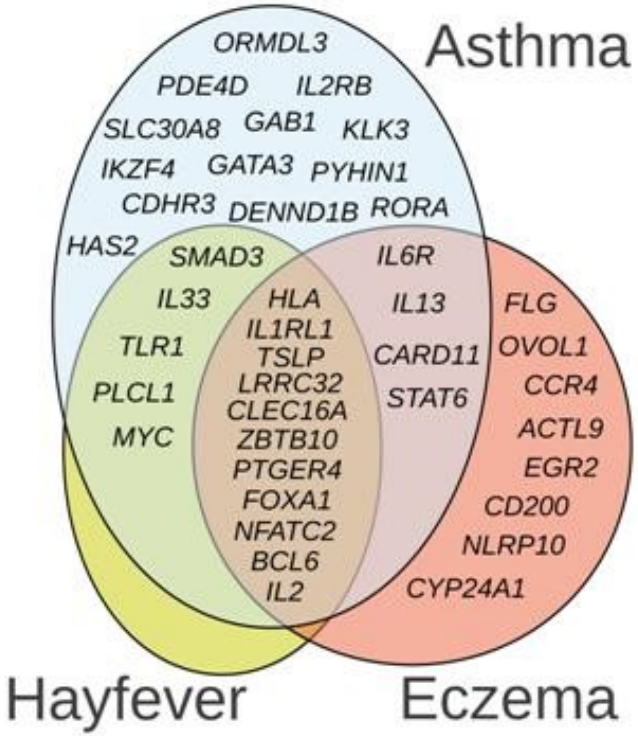


Lavinia Paternoster



Risk factors overlap

(Thomsen 2006; van Beijsterveldt 2007)



ENVIRONMENTAL risk factors:

20% to 70% shared

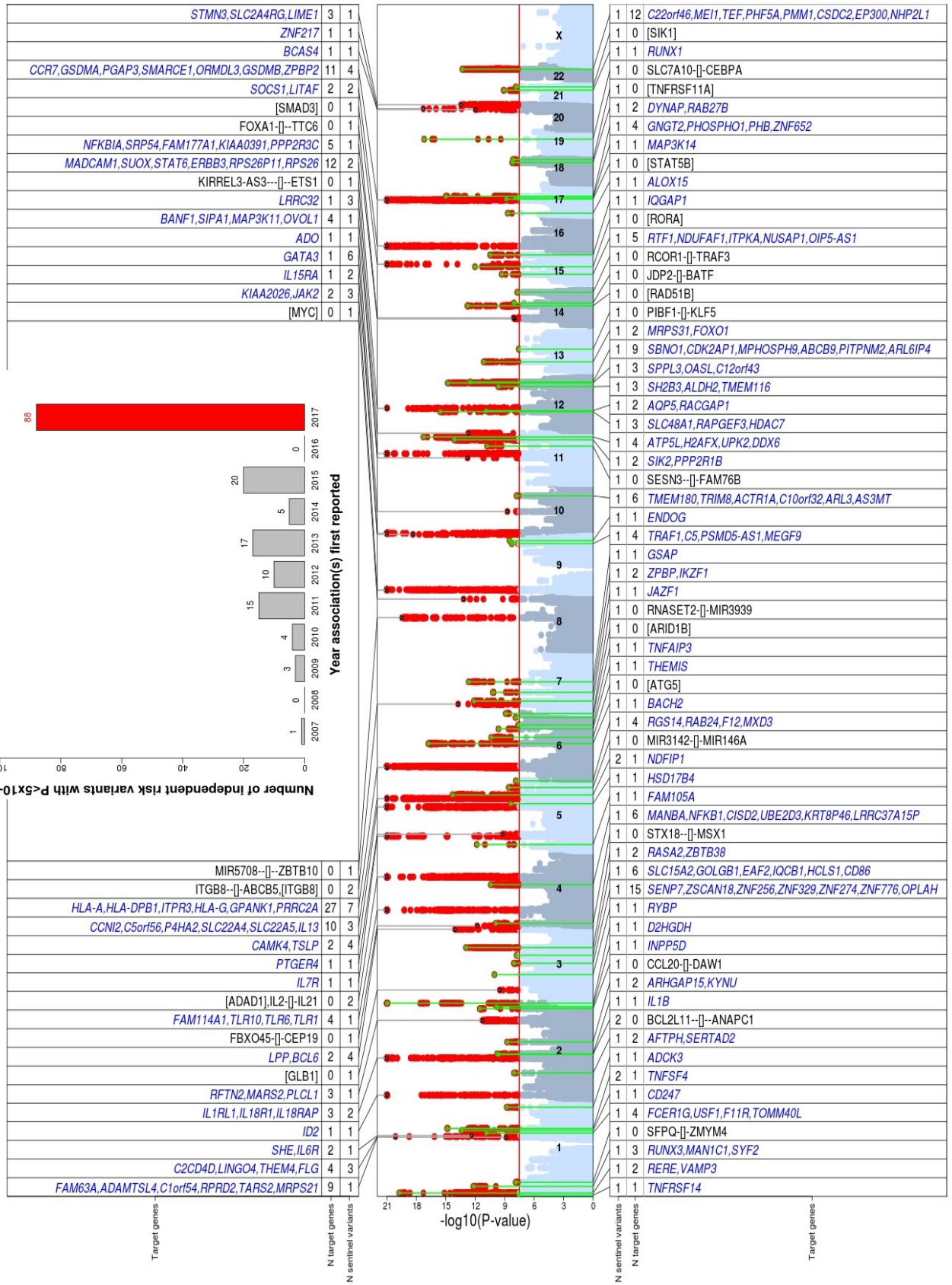
COMMON TRIGGERS

GENETIC risk factors:

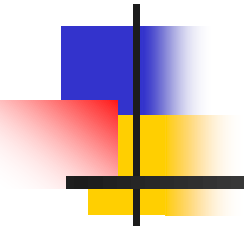
40% to 60% shared

COMMON MOLECULAR MECHANISMS

Manuel Ferreira



Manuel Ferreira



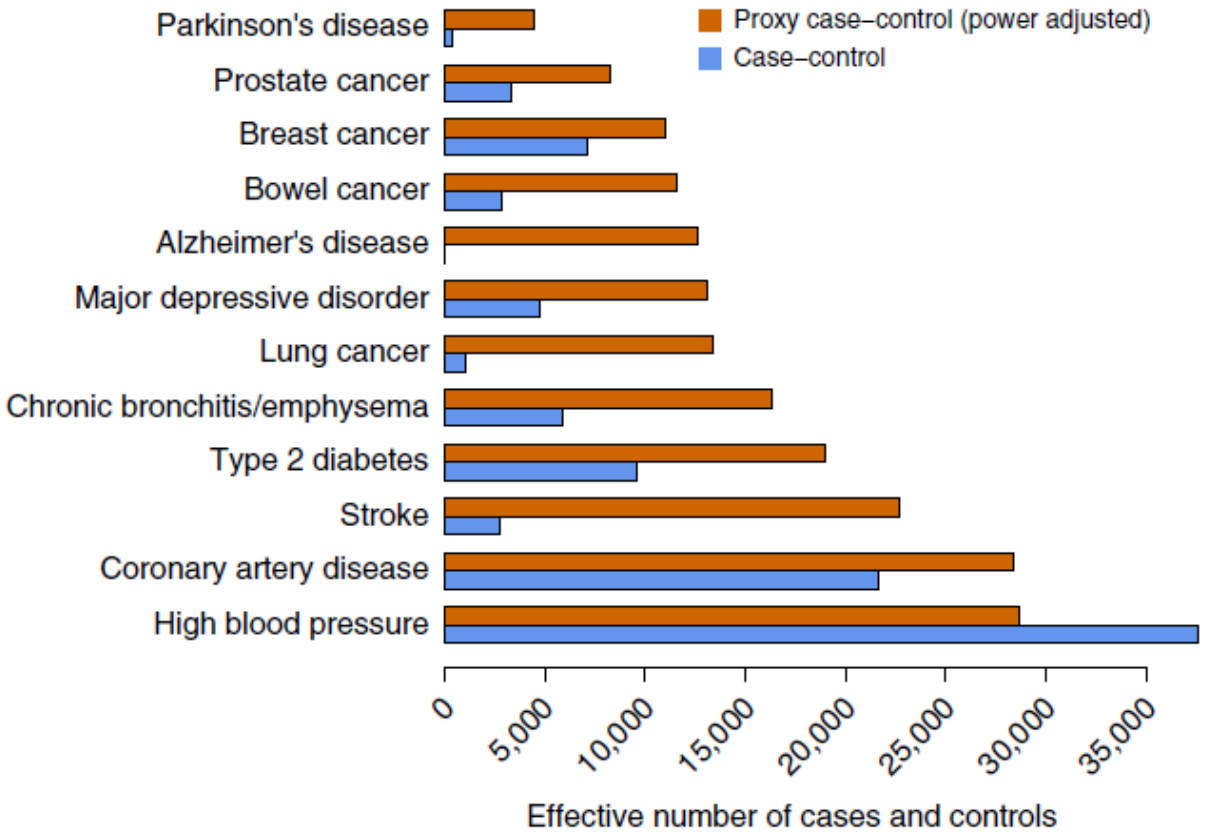
Ways to increase power

Use ungenotyped relatives as proxy cases (GWAX)

Case–control association mapping by proxy using family history of disease • (GWAX)

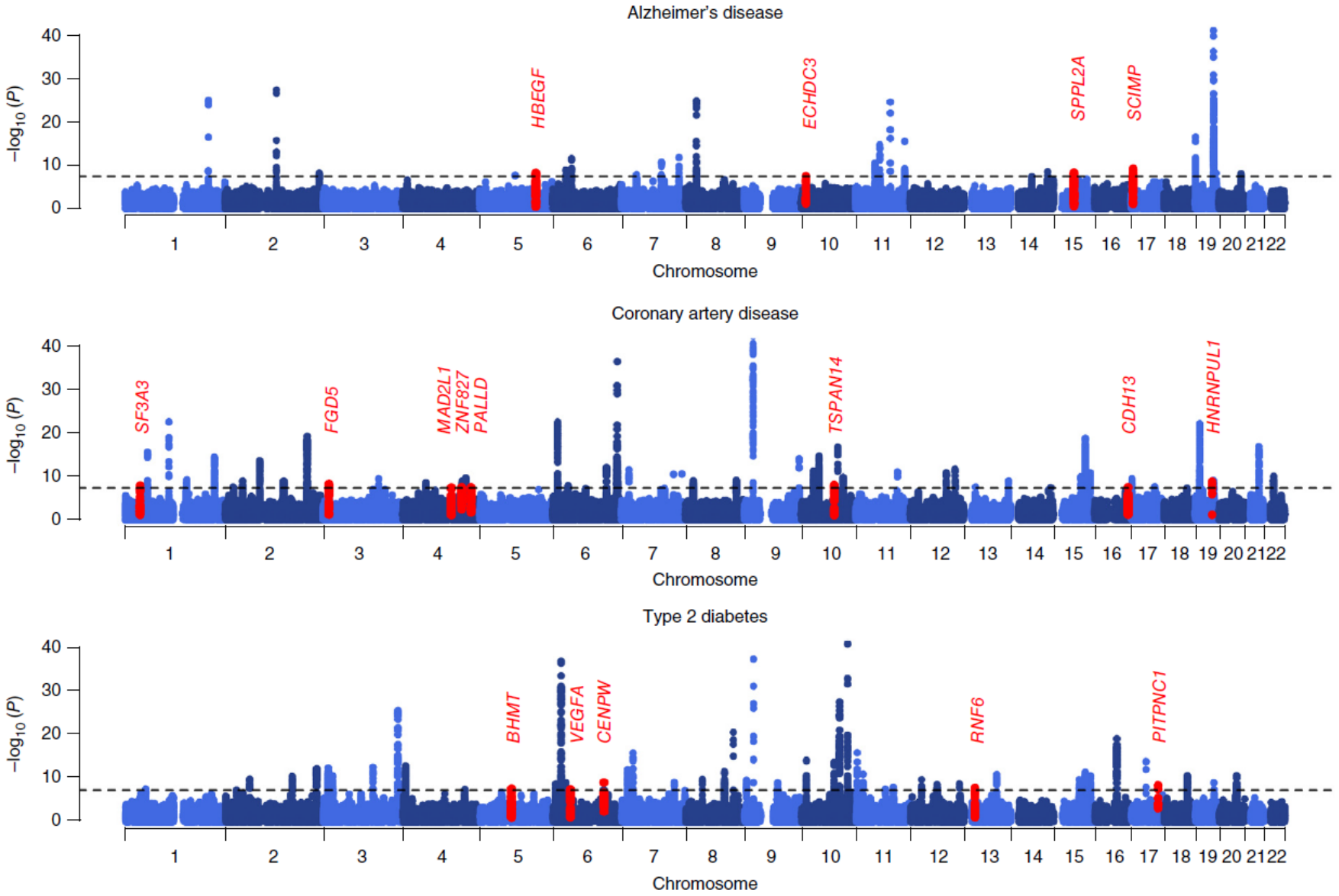
Jimmy Z Liu[1], Yaniv Erlich[1,2] & Joseph K Pickrell[1,3]

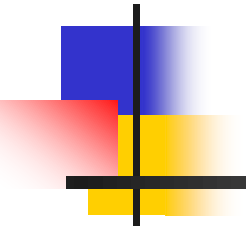
For late-onset or rapidly lethal diseases it may be more practical to identify family members of cases.



NATURE GENETICS VOLUME 49 | NUMBER 3 | MARCH 2017

Meta-analysis results for GWAX + case-control studies
New hits are shown in red

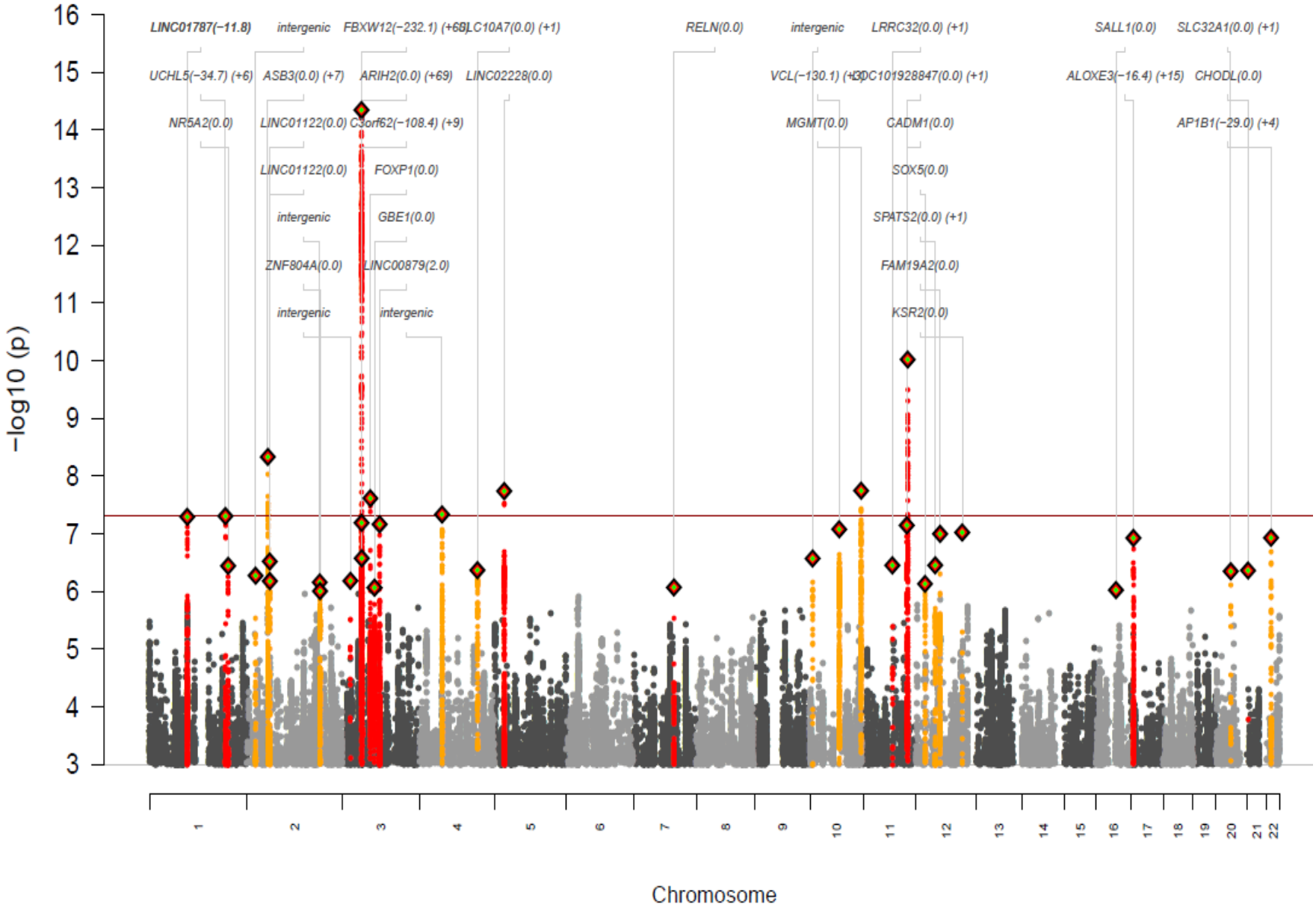




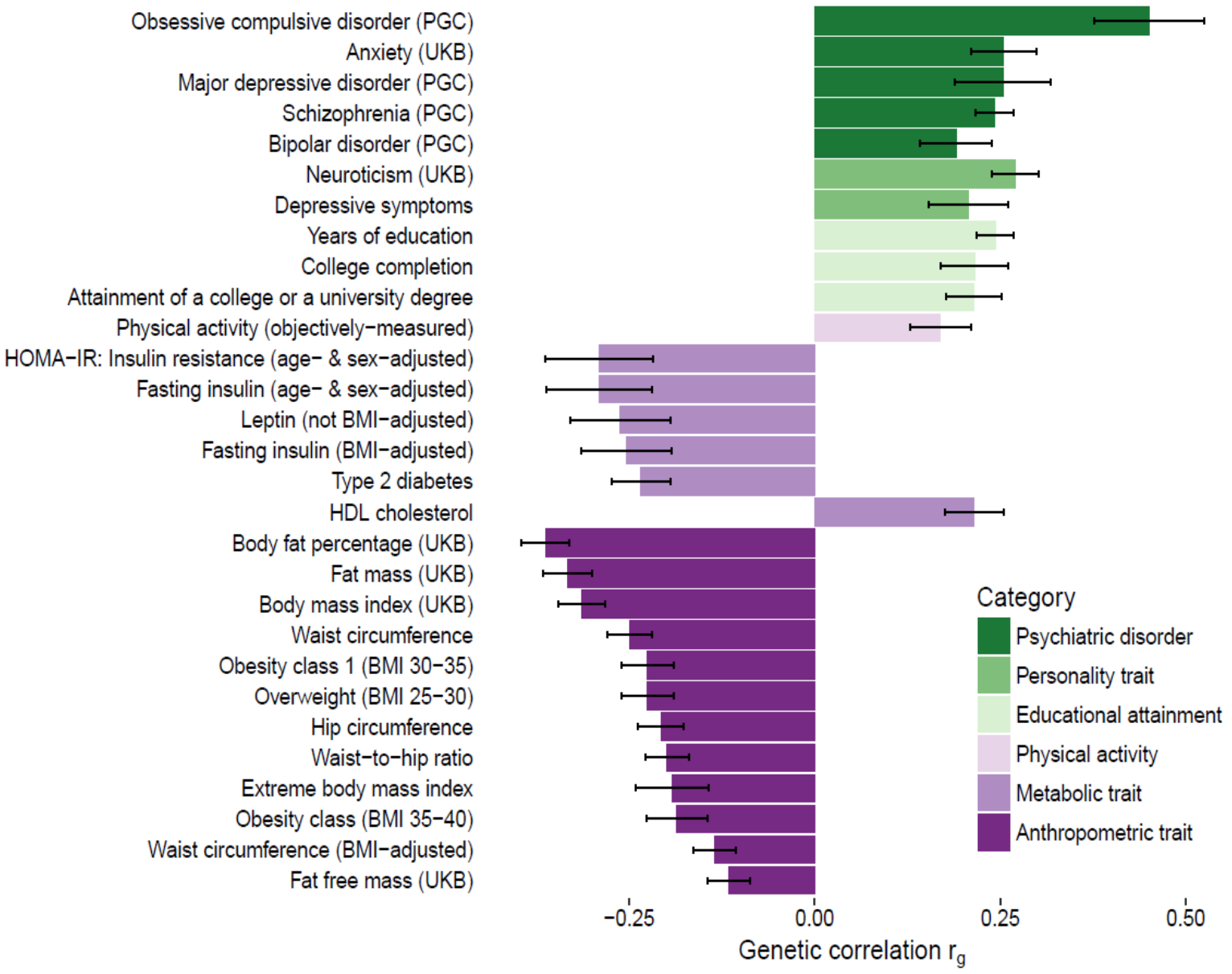
Applications of GWAS

- Investigate genetic correlation
- The genetics of nurture
- Direction of causation

GWAS meta-analysis of anorexia nervosa (16,991 cases and 56,059 cor

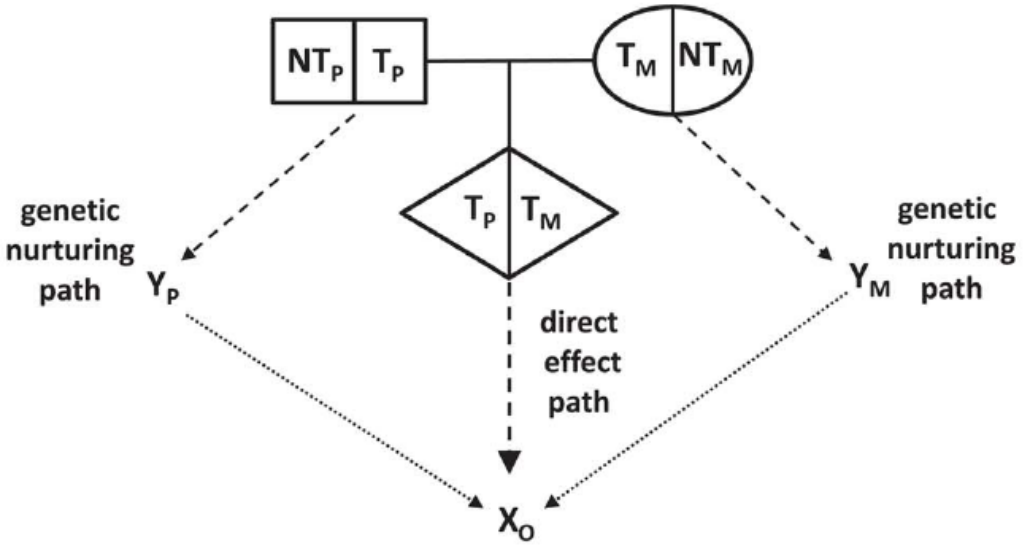


Significant genetic correlations (SNP-Rg) and 95% confidence intervals (error bars) between anorexia nervosa and traits, as estimated by LD score regression



The nature of nurture: Effects of parental genotypes

Augustine Kong …….Kari Stefansson



Nontransmitted alleles can affect a child through their impacts on the parents and other relatives, a phenomenon we call "genetic nurture." Using results from a meta-analysis of educational attainment, we find that the polygenic score computed for the nontransmitted alleles of 21,637 probands with at least one parent genotyped has an estimated effect on the educational attainment of the proband that is 29.9% ($P = 1.6 \times 10^{-14}$) of that of the transmitted polygenic score.

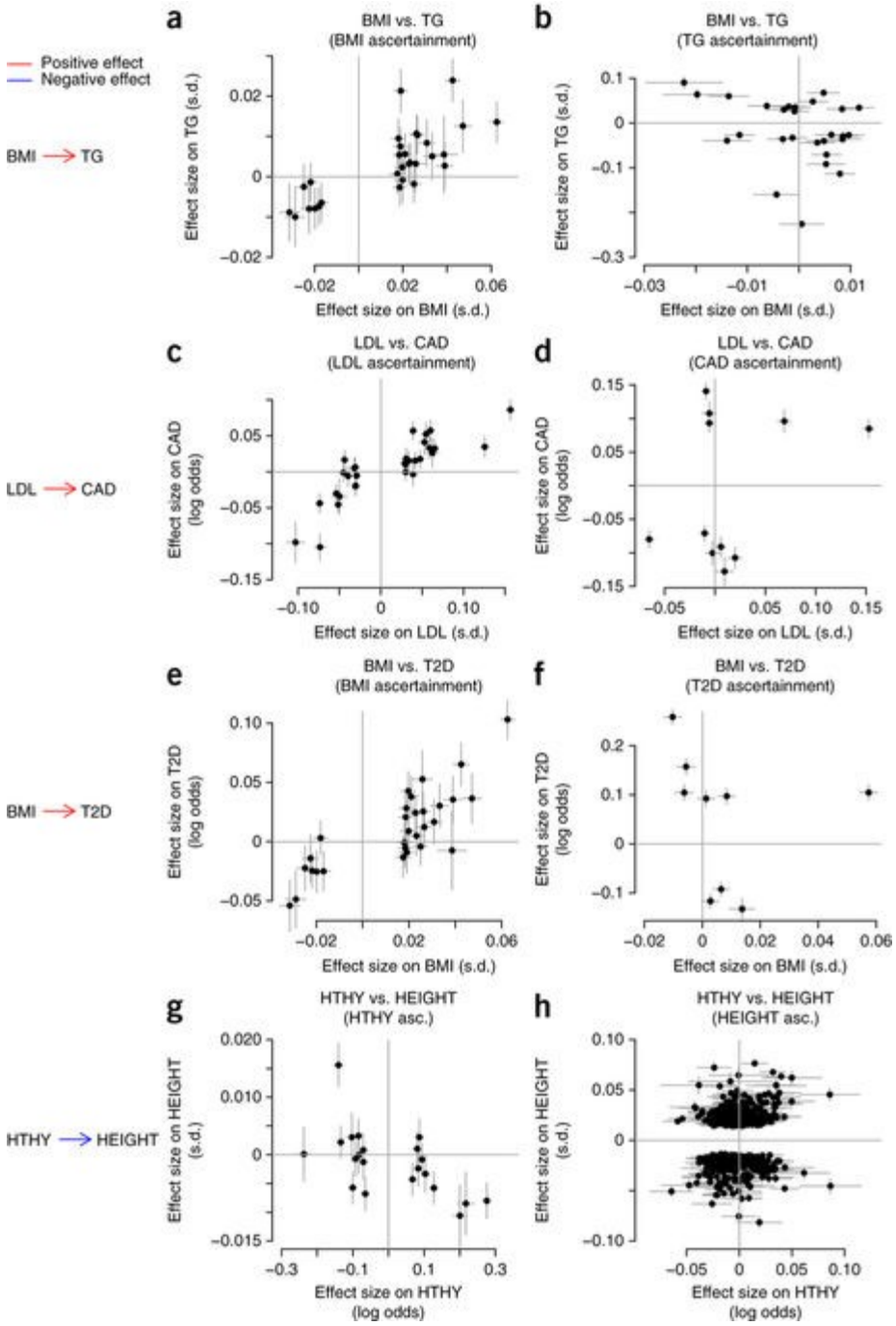
Kong *et al.*, *Science* **359**, 424–428 (2018) 26 January 2018

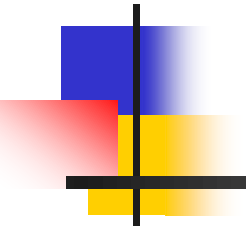
Detection and interpretation of shared genetic influences on 42 human traits

Joseph K Pickrell, Tomaz Berisa, Jimmy Z Liu, Laure Ségurel, Joyce Y Tung & David A Hinds.

Nature Genetics 48; 709–717, 2016

Powerful GWAS for traits A and B can help determine direction of causation





Pushing power to the limit

Search for rare variants

Rare and low-frequency coding variants alter human adult height

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

Height is a highly heritable, classic polygenic trait with approximately 700 common associated variants identified through genome-wide association studies so far. Here, we report 83 height-associated coding variants with lower minor-allele frequencies (in the range of 0.1–4.8%) and effects of up to 2 centimetres per allele (such as those in *IHH*, *STC2*, *AR* and *CRISPLD2*), greater than ten times the average effect of common variants. In functional follow-up studies, rare height-increasing alleles of *STC2* (giving an increase of 1–2 centimetres per allele) compromised proteolytic inhibition of PAPP-A and increased cleavage of IGFBP-4 *in vitro*, resulting in higher bioavailability of insulin-like growth factors. These 83 height-associated variants overlap genes that are mutated in monogenic growth disorders and highlight new biological candidates (such as *ADAMTS3*, *IL11RA* and *NOX4*) and pathways (such as proteoglycan and glycosaminoglycan synthesis) involved in growth. Our results demonstrate that sufficiently large sample sizes can uncover rare and low-frequency variants of moderate-to-large effect associated with polygenic human phenotypes, and that these variants implicate relevant genes and pathways.

- used an ExomeChip11 to test the association between 241,453 variants (of which 83% are coding variants with a MAF ≤ 5%) and adult height variation in **711,428** individuals (discovery and validation sample sizes were 458,927 and 252,501, respectively)

- The ExomeChip is a genotyping array designed to query in very large sample sizes coding variants identified by whole-exome DNA sequencing of approximately 12,000 participants

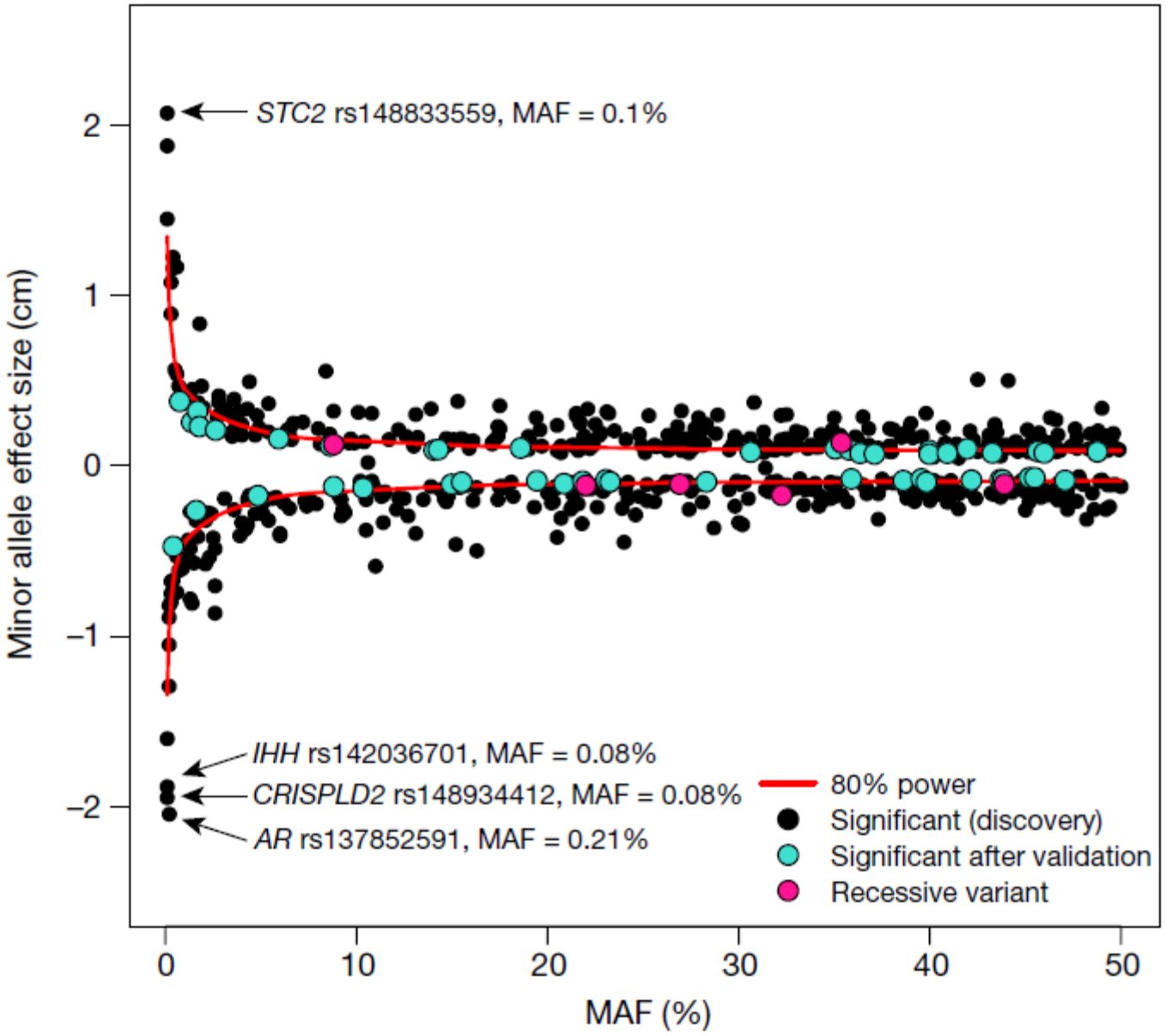


Figure 1 | Variants with a larger effect size on height variation tend to be rarer. An inverse relationship between the effect size (from the combined

NEWS & VIEWS

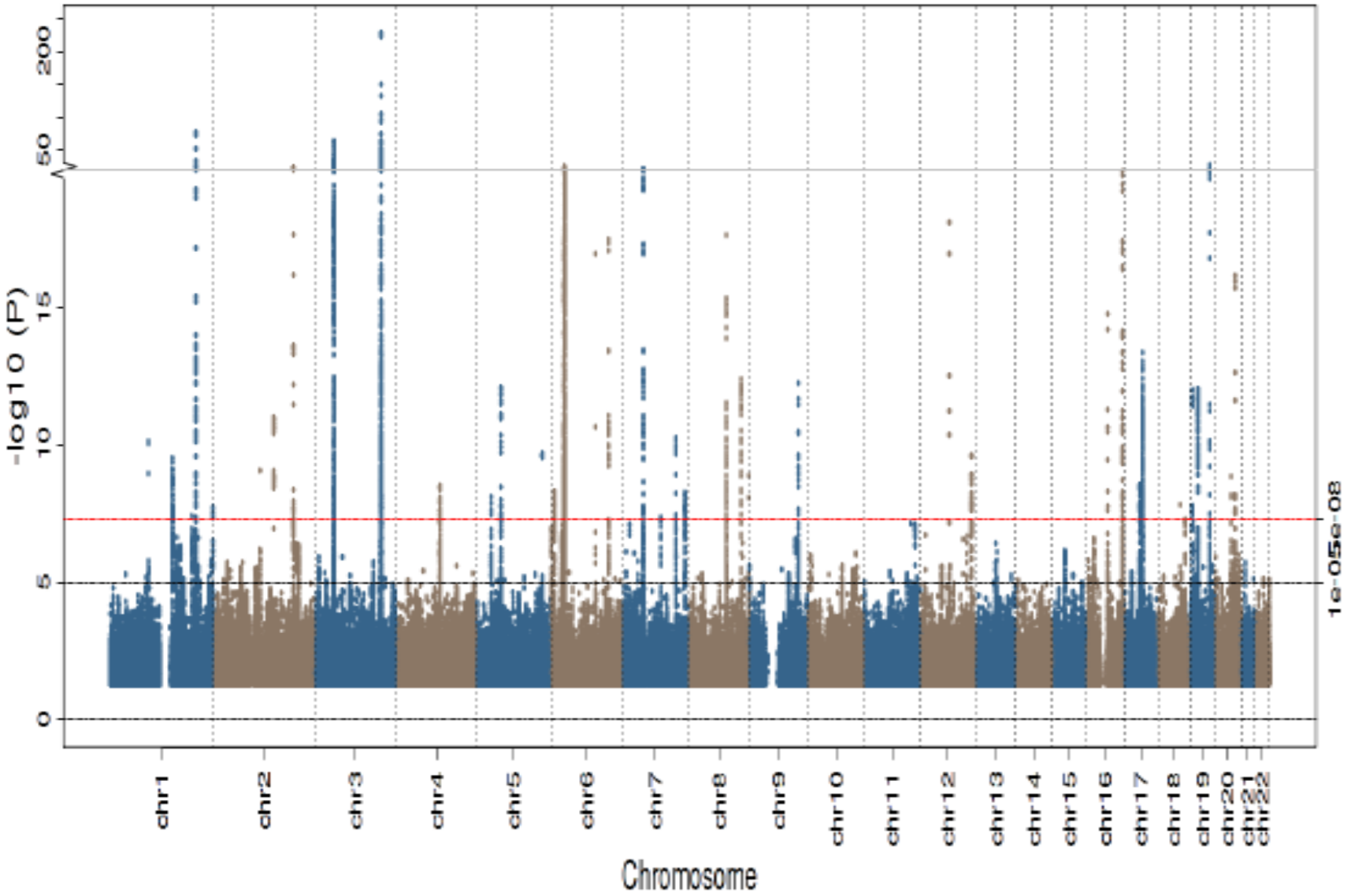
HUMAN GENOMICS

Biobank for the masses

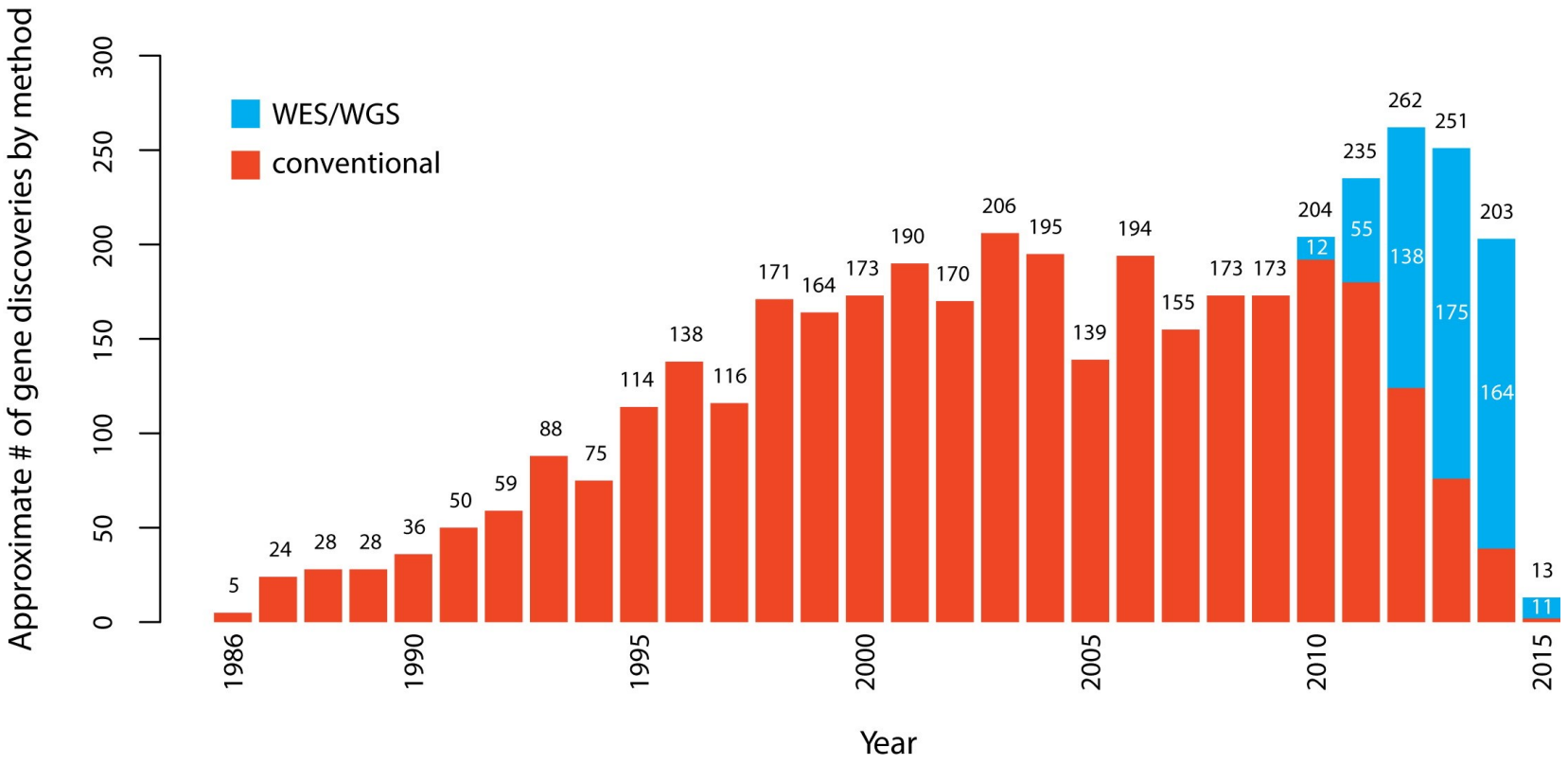
UK Biobank contains a wealth of data on genetics, health and more from 500,000 participants.

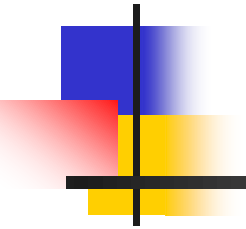
NATURE | VOL 562 | 11 OCTOBER 2018

Mouth ulcers in UK BioBank n > 461k, 97 variants



Mendelian gene discovery

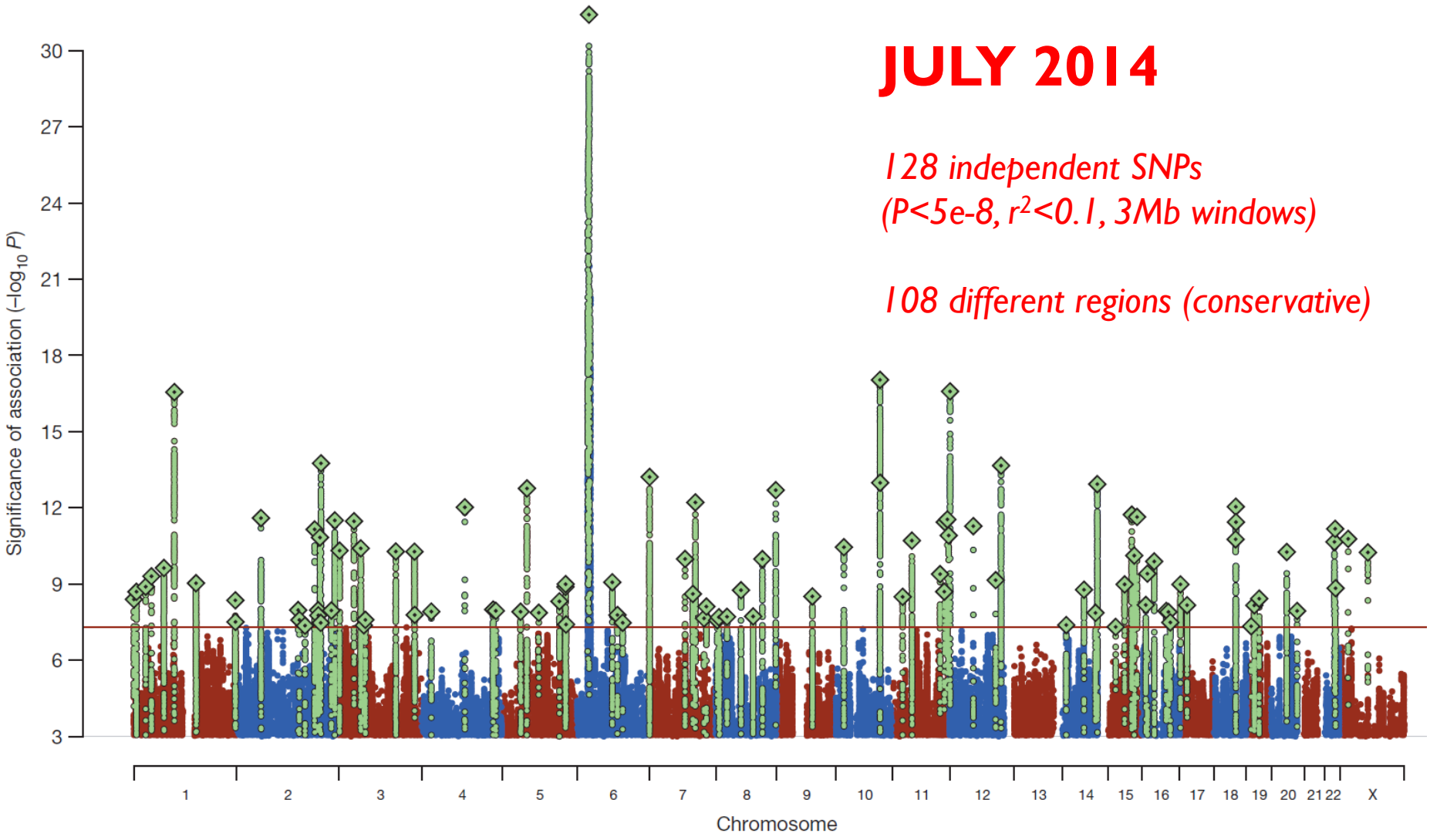




Translation of GWAS results

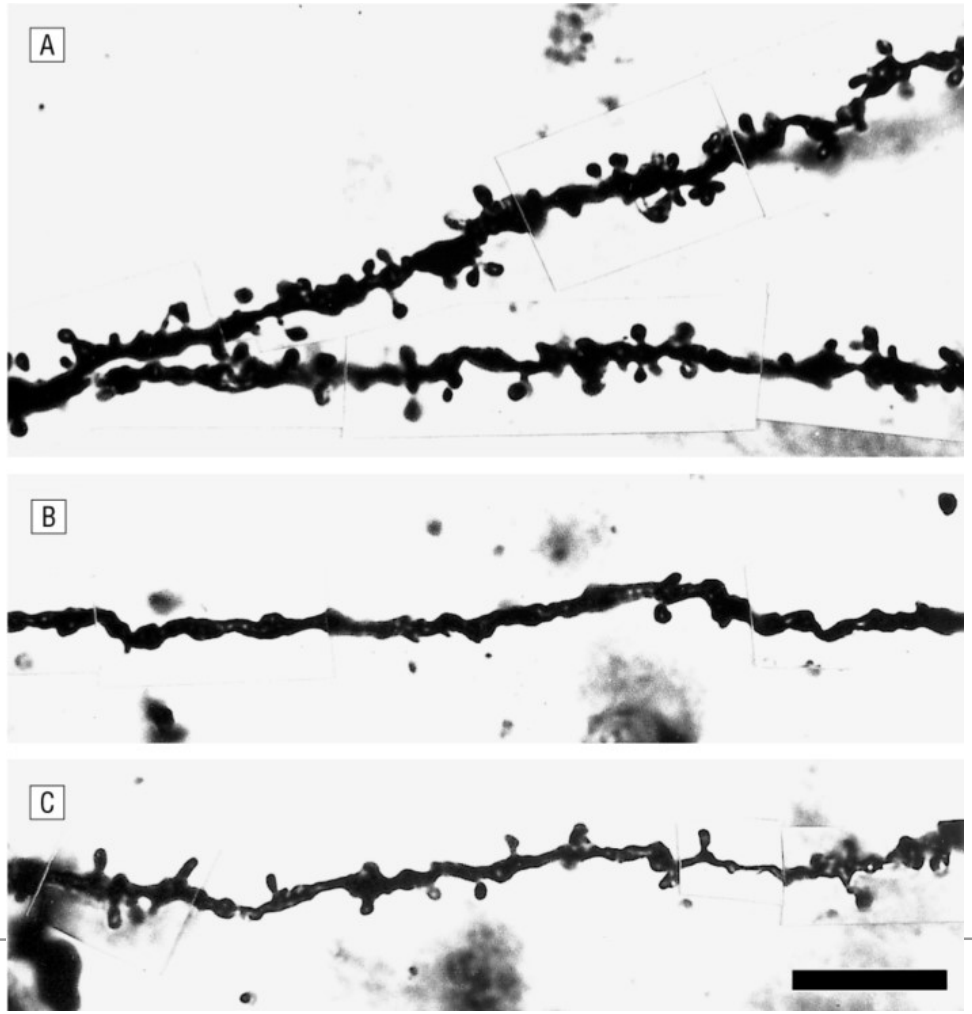
Find the causal variant that is actionable

Schizophrenia: meta-analysis of 49 case control samples (34,241 cases and 45,604 controls)



From: **Decreased Dendritic Spine Density on Prefrontal Cortical Pyramidal Neurons in Schizophrenia**

Arch Gen Psychiatry. 2000;57(1):65-73. doi:10.1001/archpsyc.57.1.65



Basilar dendrites and spines on dorsolateral prefrontal cortex layer 3 pyramidal neurons from normal control subject (A) and 2 subjects with schizophrenia (B and C). The calibration bar equals 10 μm.

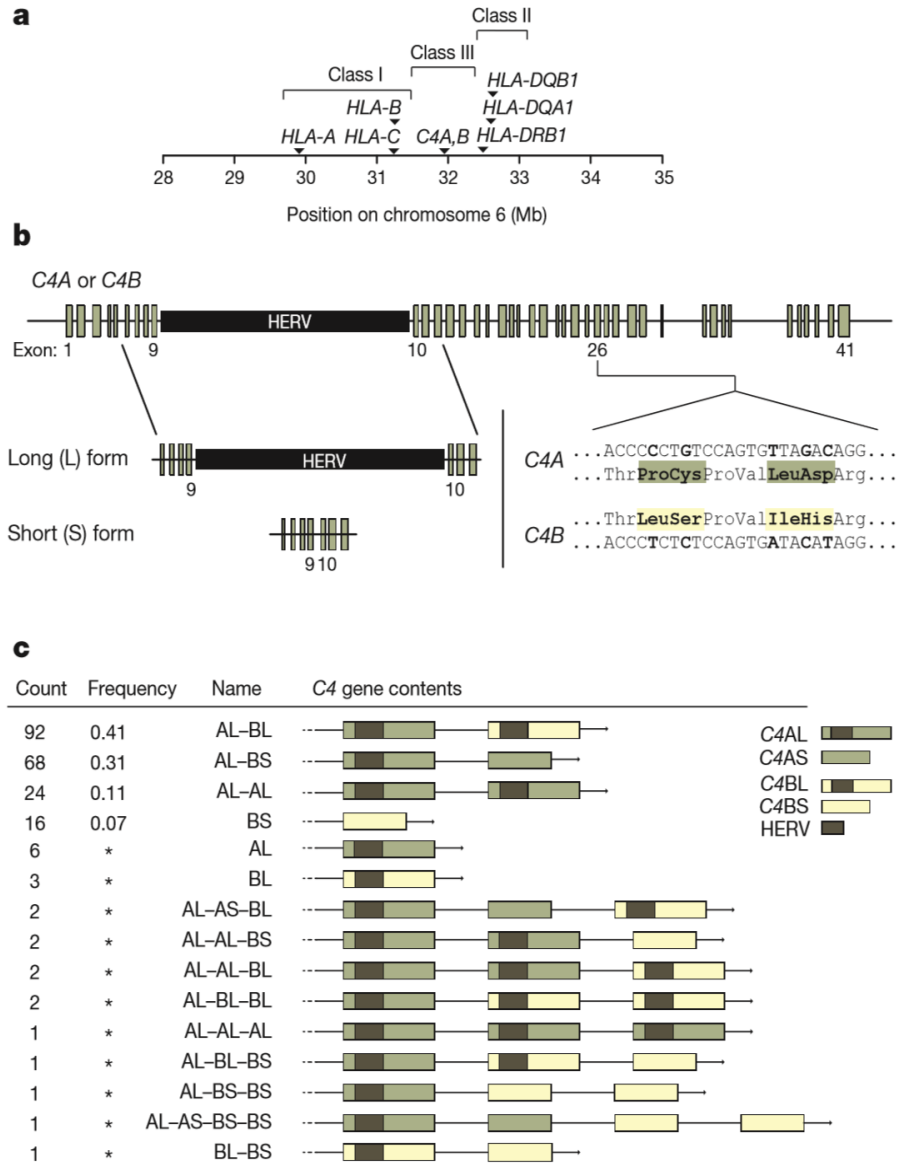


Figure 1 | Structural variation of the complement component 4 (*C4*) gene. a, Location of the *C4* genes within the major histocompatibility complex (MHC) locus on human chromosome 6. **b**, Human *C4* exists

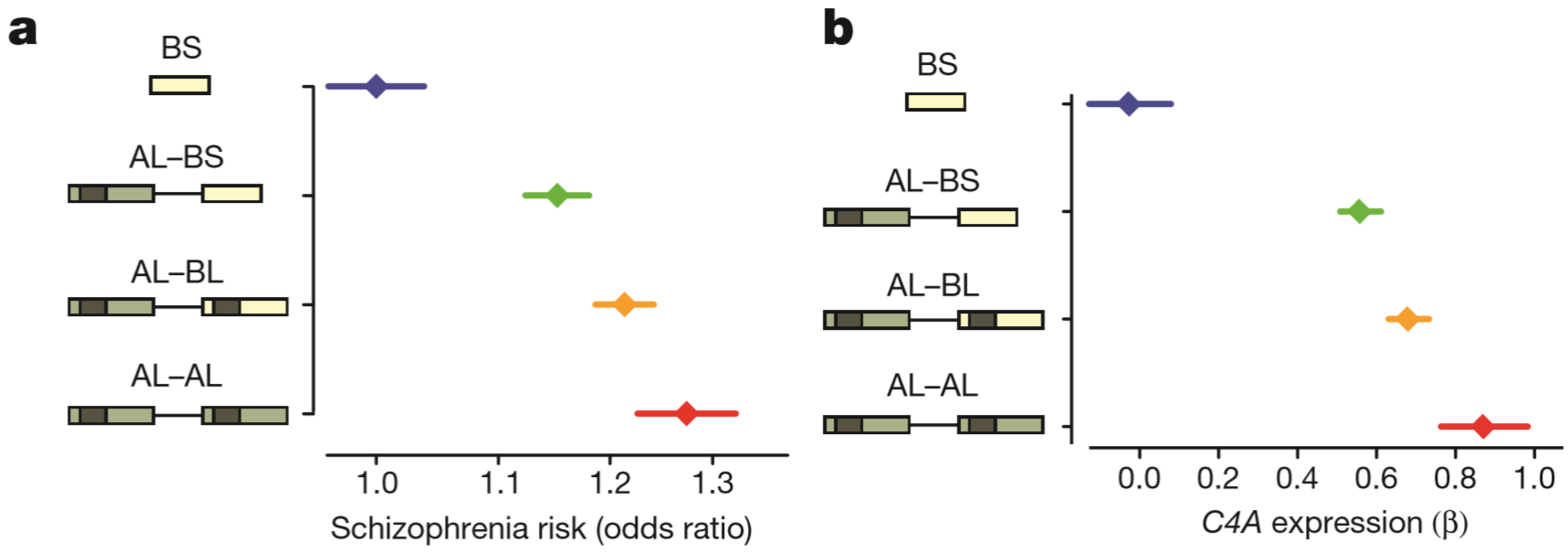
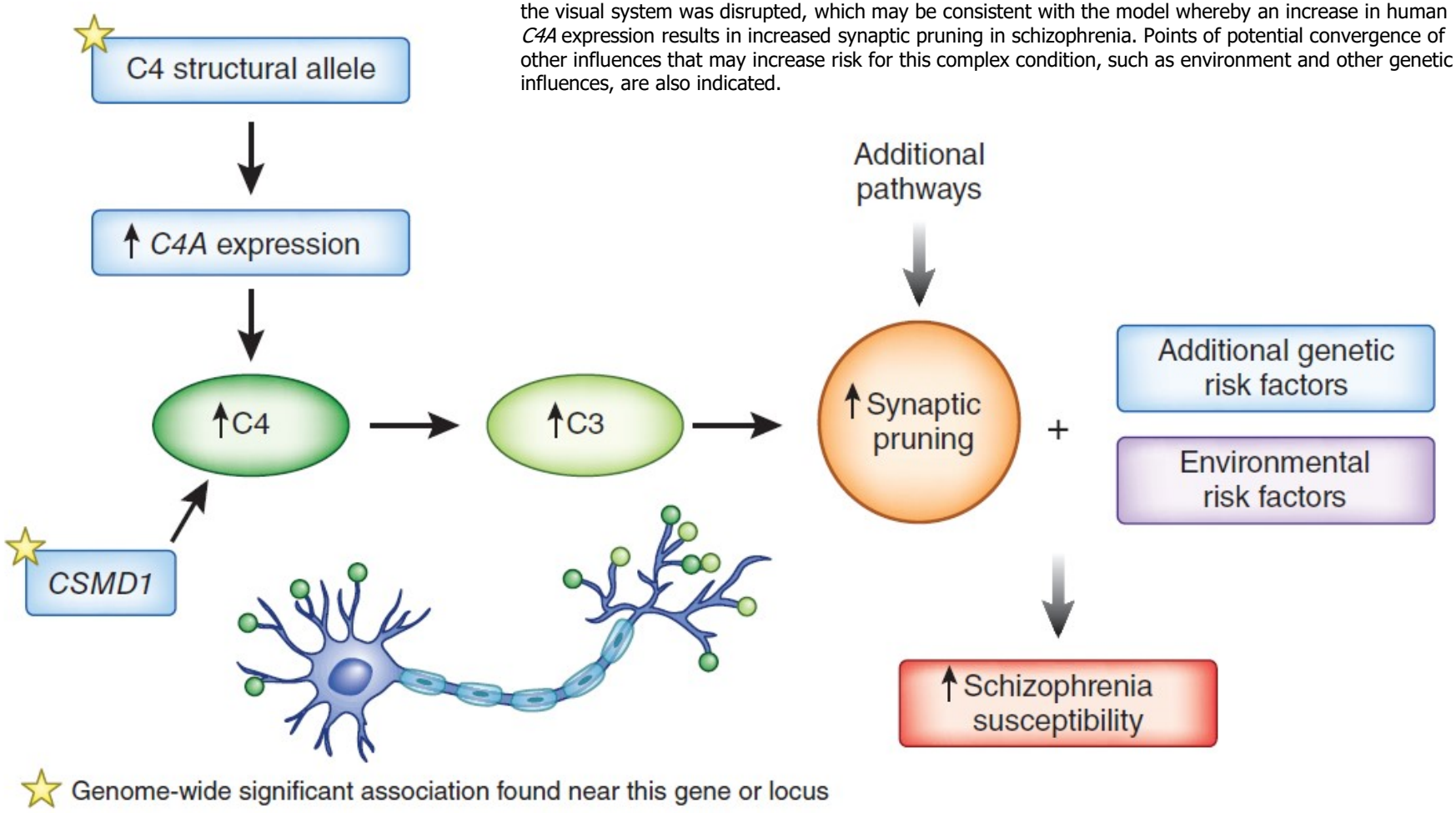


Figure 5 | *C4* structures, *C4A* expression, and schizophrenia risk. a, Schizophrenia risk associated with four common structural forms of *C4* in analysis of 28,799 schizophrenia cases and 35,986 controls. **b**, Brain *C4A* RNA expression levels associated with four common structural forms of *C4*. β was calculated from fitting *C4A* RNA expression (in

Schizophrenia genetics complements its mechanistic understanding

Elizabeth K Ruzzo & Daniel H Geschwind

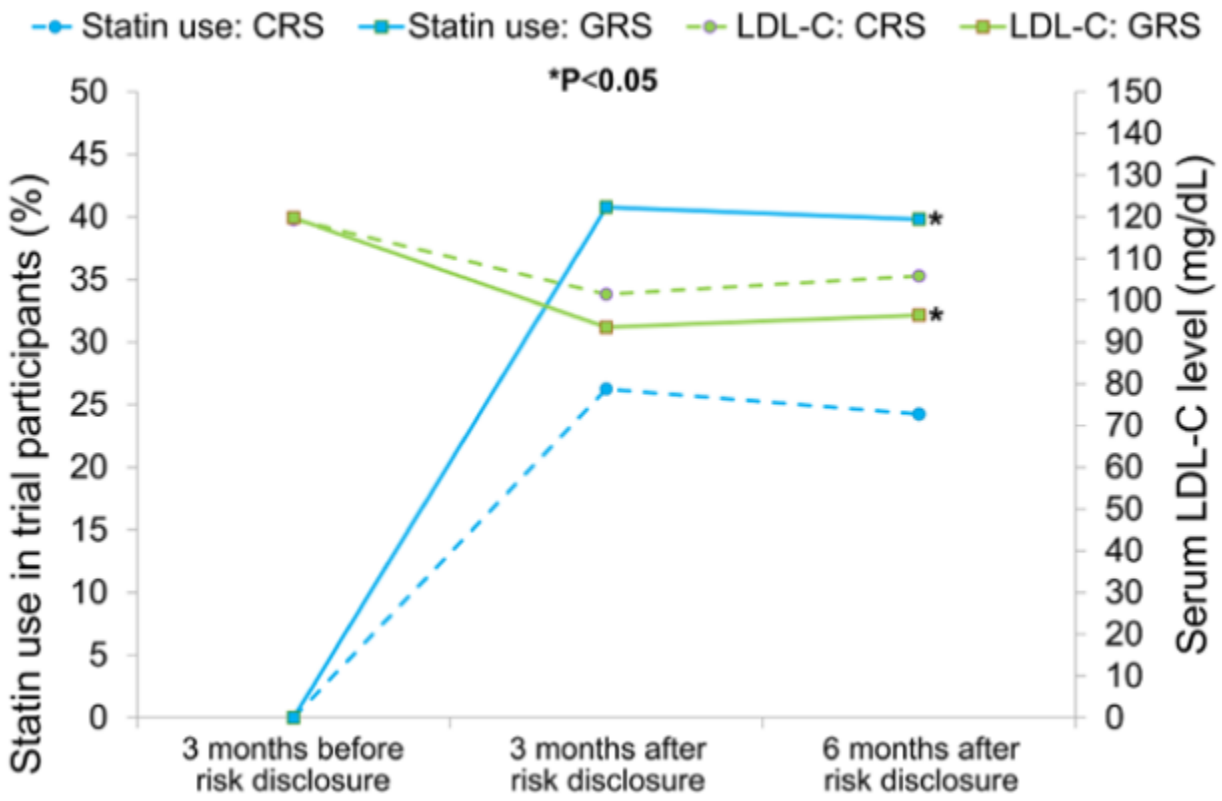
Schematic of the findings and model of Sekar *et al.*4. Careful refinement of the schizophrenia GWAS locus in the MHC revealed that structural alleles of the C4 locus increase schizophrenia risk. These structural alleles increase *C4A* RNA levels in human brain, which predict a subsequent increase in C3, increasing synaptic pruning. A mouse knockout of C4 demonstrated that C3 levels decreased and synaptic pruning in the visual system was disrupted, which may be consistent with the model whereby an increase in human *C4A* expression results in increased synaptic pruning in schizophrenia. Points of potential convergence of other influences that may increase risk for this complex condition, such as environment and other genetic influences, are also indicated.



Effect of Disclosing Genetic Risk for Coronary Heart Disease on Information Seeking and Sharing

The MI-GENES Study (Myocardial Infarction Genes)

Sherry-Ann N. Brown, MD, PhD; Hayan Jouni, MD; Tariq S. Marroush, MD; Iftikhar J. Kullo, MD



Statin use significantly higher in patients given genetic risk score than conventional risk score

Circ Cardiovasc Genet. 2017;10:e001613.

nature genetics
Published online 14/8/18
LETTERS
https://doi.org/10.1038/s41588-018-0183-z

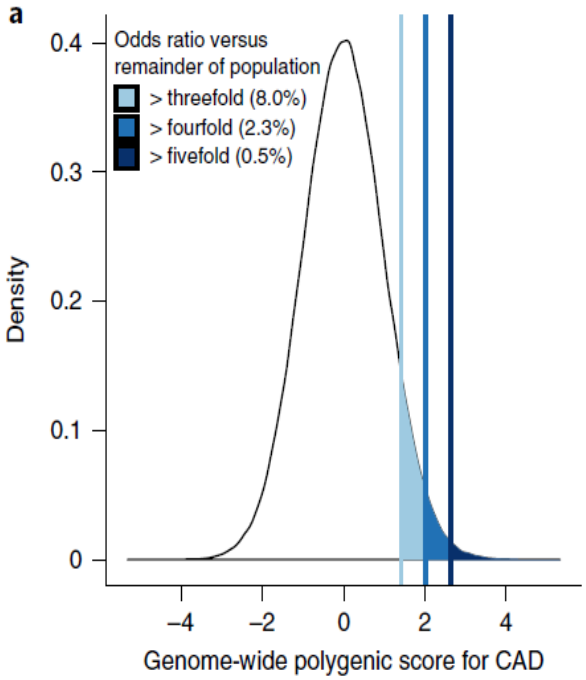
Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

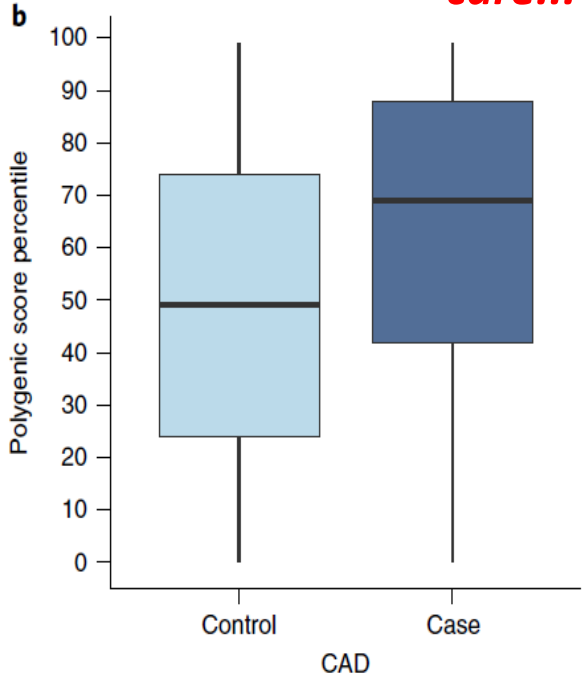
Amit V. Khera[1,2,3,4,5], Mark Chaffin[4,5], Krishna G. Aragam[1,2,3,4], Mary E. Haas[4], Carolina Roselli[4], Seung Hoan Choi[4], Pradeep Natarajan[2,3,4], Eric S. Lander[4], Steven A. Lubitz[2,3,4], Patrick T. Ellinor[2,3,4] and Sekar Kathiresan[1,2,3,4*]

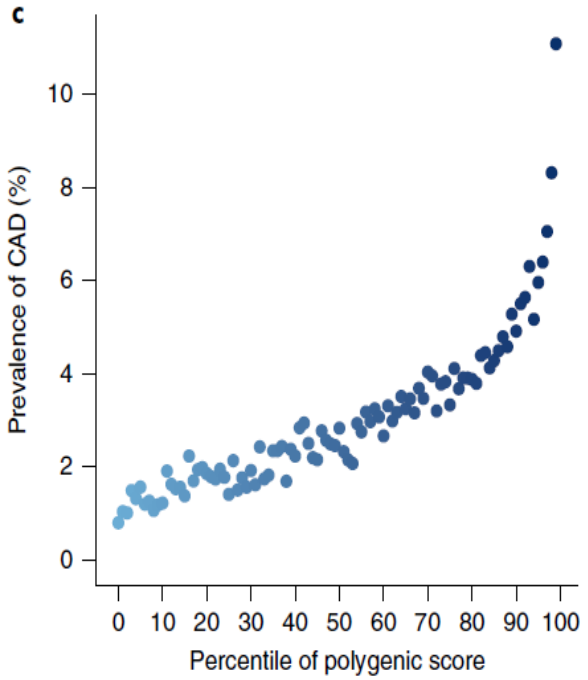
% Population at >3fold increased risk

- CAD 8.0%,
- atrial fibrillation 6.1%
- type 2 diabetes 3.5%
- IBD 3.2%
- breast cancer 1.5%

"We propose that it is time to contemplate the inclusion of polygenic risk prediction in clinical care... "



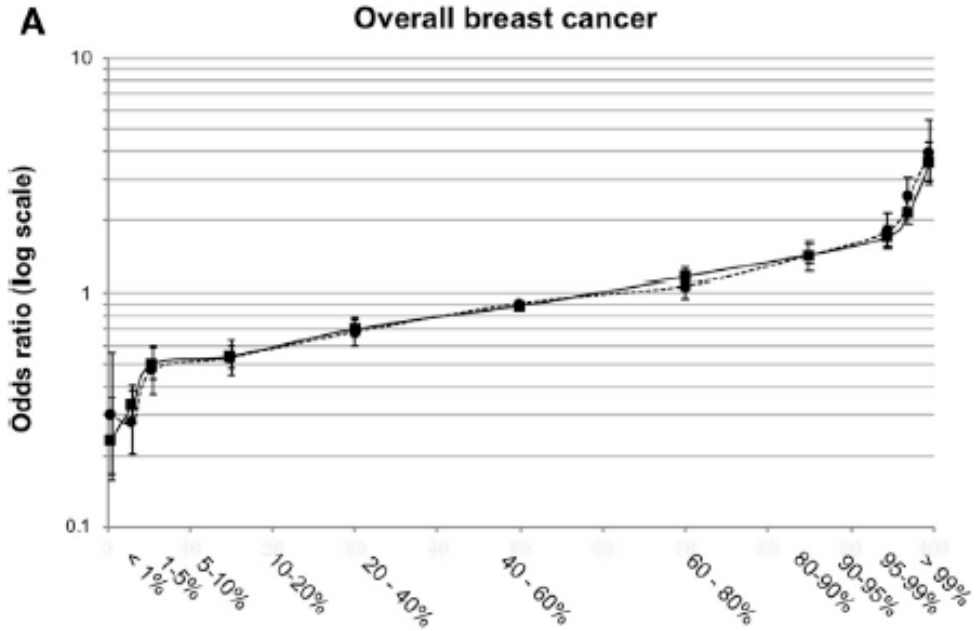




Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes

Nasim Mavaddat,[1,*] Kyriaki Michailidou,[1,2] Joe Dennis,[1] Michael Lush,[1] Laura Fachal,[3] Andrew Lee,[1]

Compared with women in the middle quintile, those in the highest 1% of risk had 4.37- and 2.78-fold risks, and those in the lowest 1% of risk had 0.16- and 0.27-fold risks, of developing ER-positive and ER-negative disease, respectively. This PRS is a powerful and reliable predictor of breast cancer risk that may improve breast cancer prevention programs.



American Journal of Human Genetics 104, 21–34, January 3, 2019

NATURE GENETICS ADVANCE ONLINE PUBLICATION

The support of human genetic evidence for approved drug indications

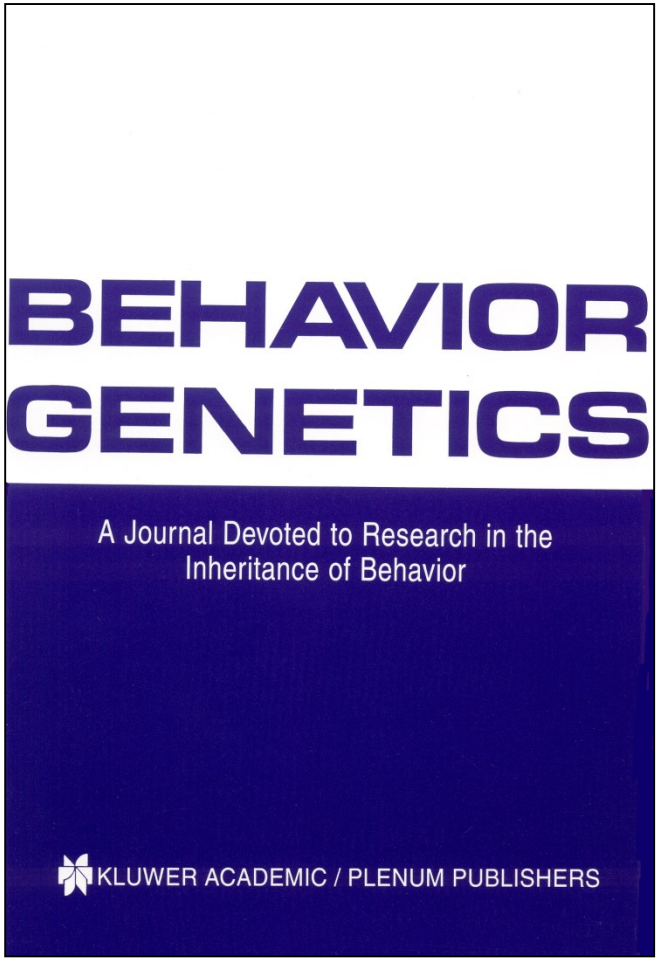
Matthew R Nelson[1], Hannah Tipney[2], Jeffery L Painter[1], Judong Shen[1], Paola Nicoletti[3], Yufeng Shen[3,4], Aris Floratos[3,4], Pak Chung Sham[5,6], Mulin Jun Li[6,7], Junwen Wang[6,7], Lon R Cardon[8], John C Whittaker[2] & Philippe Sanseau[2]

Table 1 The relative value of genetic support for the probability that a target-indication pair progresses along the drug development pipeline, based on historical drug trial information

	p(progress|genetic support)/(progress|no genetic support)		
Progression	GWASdb and OMIM	GWASdb	OMIM
Phase I to phase II	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Phase II to phase III	1.5 (1.3–1.7)	1.4 (1.2–1.7)	1.6 (1.3–1.9)
Phase III to approval	1.1 (1.0–1.2)	1.0 (0.8–1.2)	1.1 (0.9–1.3)
Phase I to phase III	1.8 (1.5–2.1)	1.8 (1.4–2.1)	1.9 (1.5–2.3)
Phase I to approval	2.0 (1.6–2.4)	1.8 (1.3–2.3)	2.2 (1.6–2.8)

"We estimate that selecting genetically supported targets could double the success rate in clinical development. Therefore, using the growing wealth of human genetic data to select the best targets and indications should have a measurable impact on the successful development of new drugs."

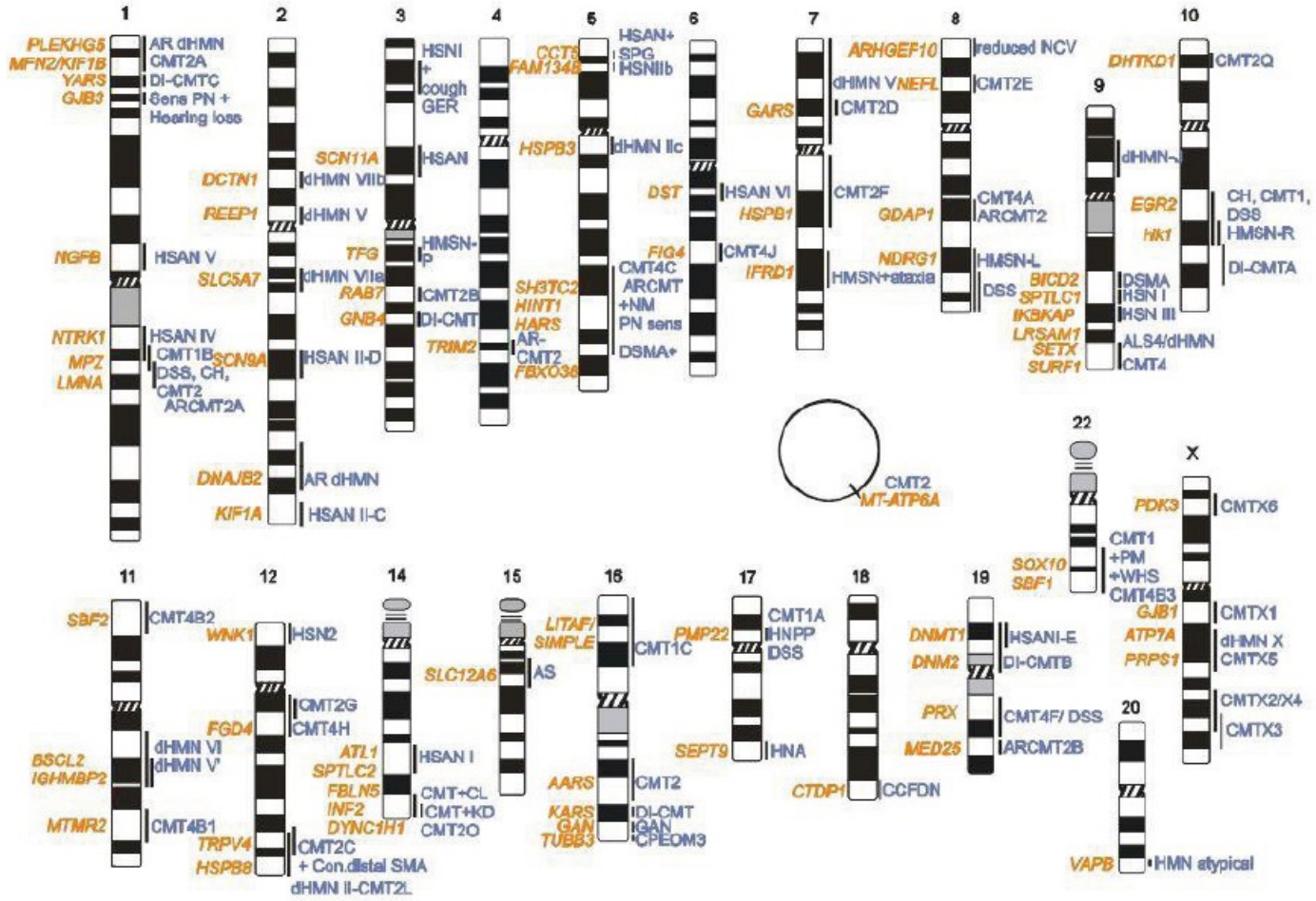
We also run two journals (1)



- Editor: John Hewitt
- Editorial assistant Christina Hewitt
- Publisher: Kluwer /Plenum
- Fully online
- http://www.bga.org

- Editor: Nick Martin
- Publisher: Cambridge University Press
- Fully online
- Fast turnaround
- **First submission free to workshop participants!!!!!☺**

Charcot-Marie-Tooth disease: > 1000 Mendelian mutations identified in 85+ genes



Timmerman …….Zuchner Hum. Genet 2014