CC, MD, Nader PERROUD

Genetic and psychiatry : can genes help psychiatrists choose the right treatment?

1. Department of Mental Health and Psychiatry, Service of Psychiatric Specialties, University Hospitals of Geneva, Geneva, Switzerland.

2. Department of Psychiatry, University of Geneva, Geneva, Switzerland.

Why genes in psychiatry?

The example of pharmacogenetics and response to treatment in depression

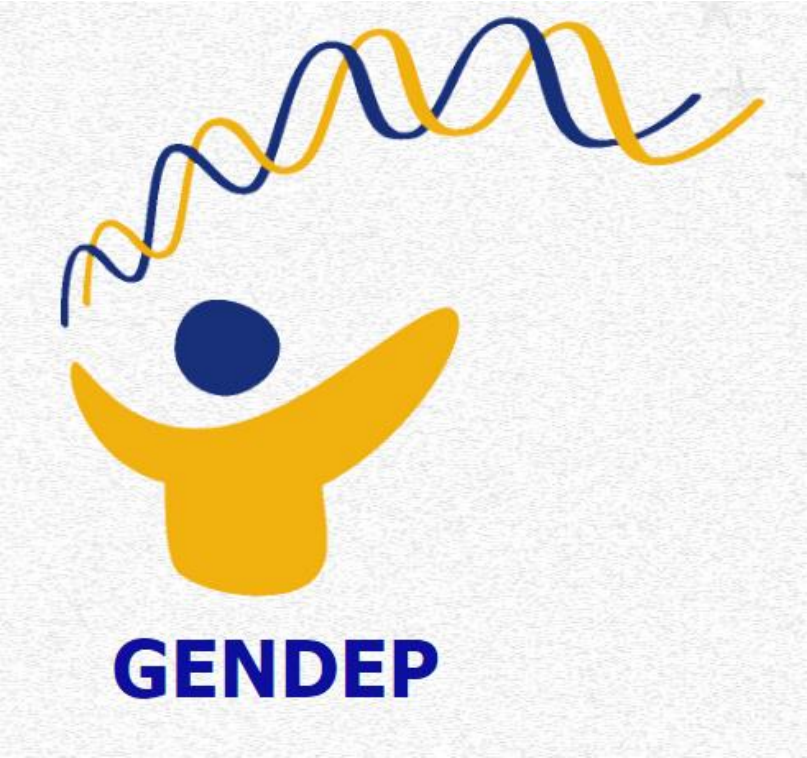
Why Pharmacogenetics?

- A clinician presented with a case of depression has to make a choice among more than 20 available antidepressant drugs
- Efficacy of … average, the response …
- Less than … remission of symptoms wit…
- Pharmacogenetics explores the potential of genetic measurements to inform the individualized choice of treatment.

Personalized Medicine

Hôpitaux Universitaires Genève

Université de Genève
Faculté de Médecine

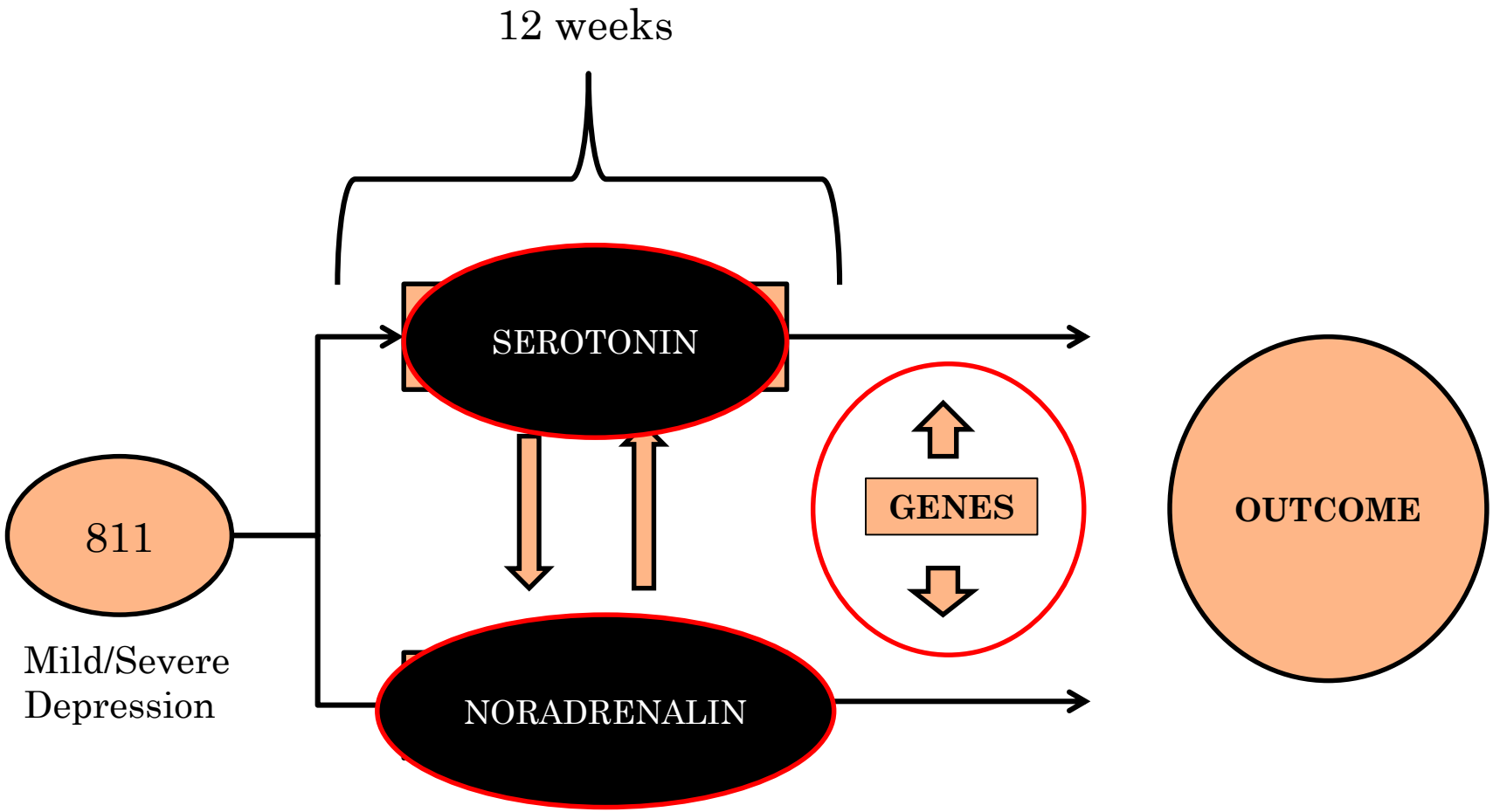


The Genome-based Therapeutic Drugs for Depression

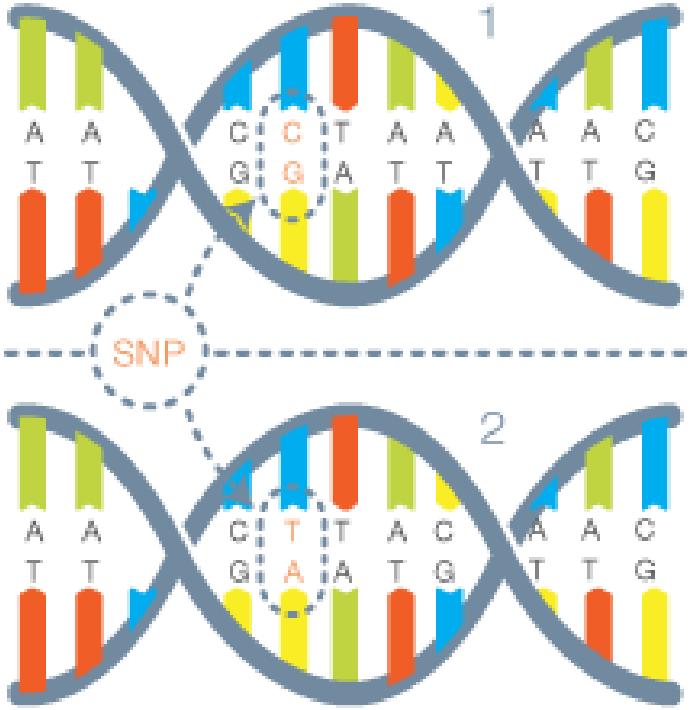
- Institute of Psychiatry
- University of Wales College of Medicine
- London School of Economics and Political Science
- Trinity College
- Free University of Brussels
- Central Institute for Mental Health
- University of Bonn
- Karolinska Institute
- University of Milan
- IRCCS-FBF
- University of Aarhus
- Institute of Public Health
- University of Medical Sciences
- University of Zagreb
- Proteome Sciences plc
- GlaxoSmithKline Research and Development Ltd
- GlaxoSmithKline SpA
- GABO mbH & Co. KG
- Roche Diagnostics

HUG Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

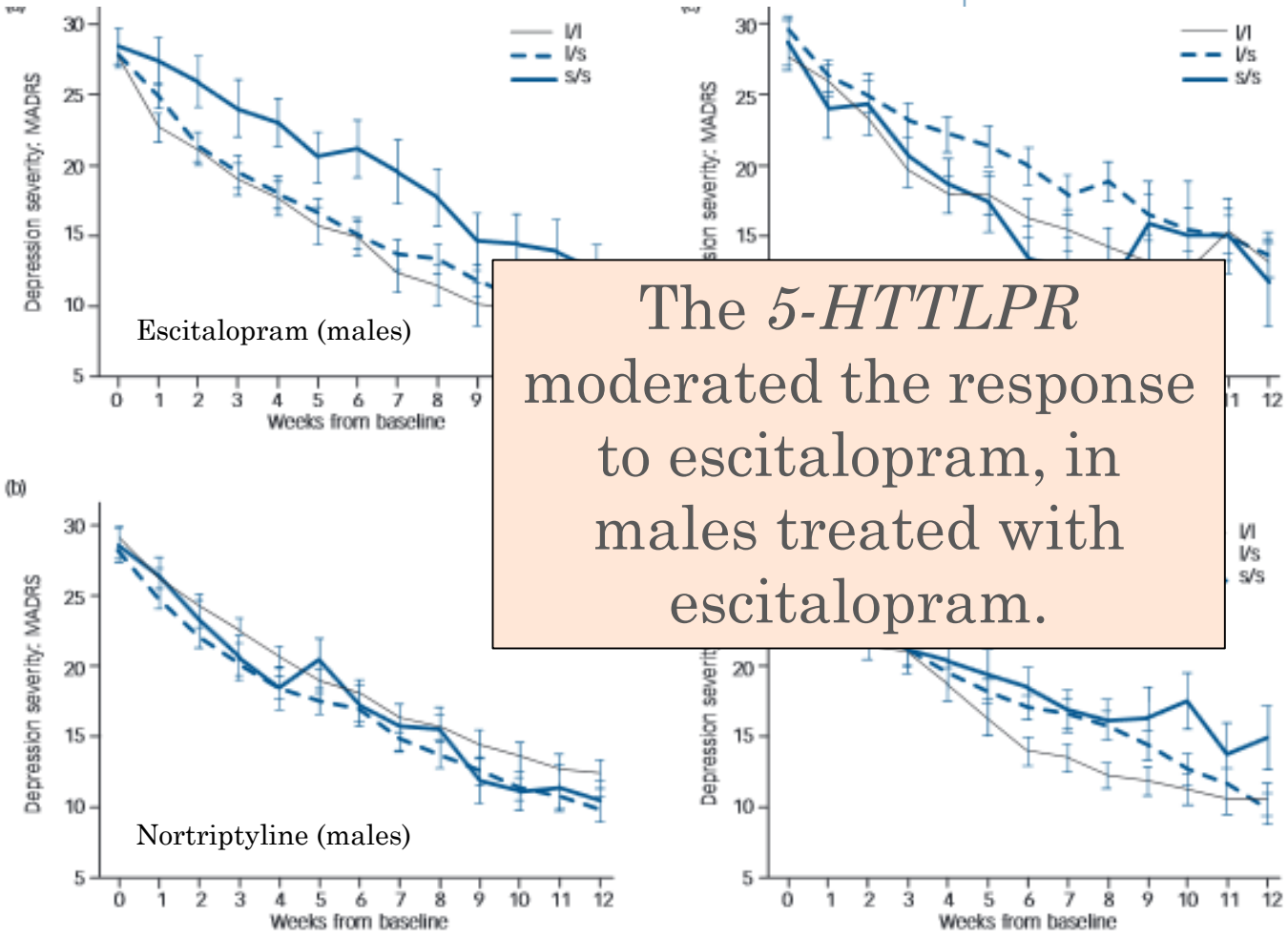

12 weeks
SEROTONIN
811
Mild/Severe
Depression
GENES
OUTCOME
NORADRENALIN

CANDIDATE GENES



Moderation of antidepressant response by the serotonin transporter gene

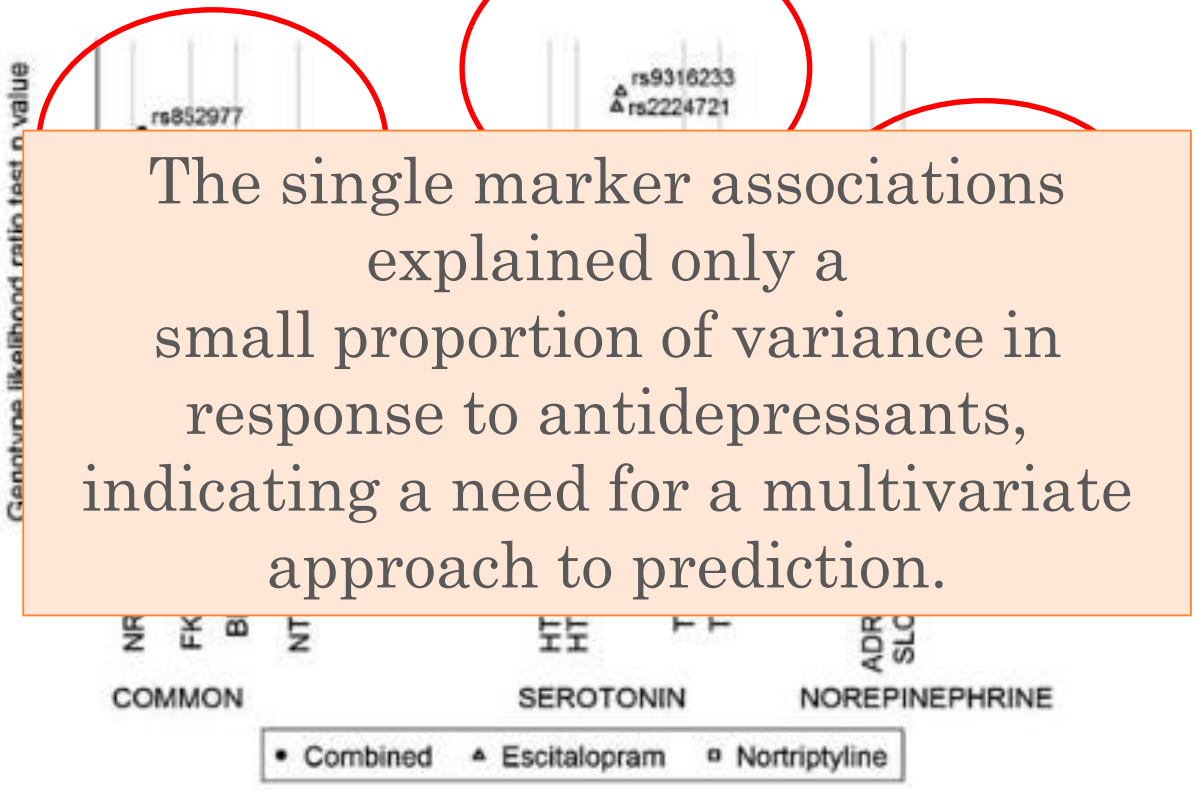
Patricia Huezo-Diaz,* Rudolf Uher,* Rebecca Smith, Marcella Rietschel, Neven Henigsberg, Andrej Marušič, Ole Mors, Wolfgang Maier, Joanna Hauser, Daniel Souery, Anna Placentino, Astrid Zobel, Erik Roj Larsen, Piotr M. Czerski, Bhanu Gupta, Farzana Hoda, Nader Perroud, Anne Farmer, Ian Craig, Katherine J. Aitchison and Peter McGuffin



The *5-HTTLPR* moderated the response to escitalopram, in males treated with escitalopram.

BJPsych The British Journal of Psychiatry (2009) 195, 30–38. doi: 10.1192/bjp.bp.108.062521

Ge ssants
in

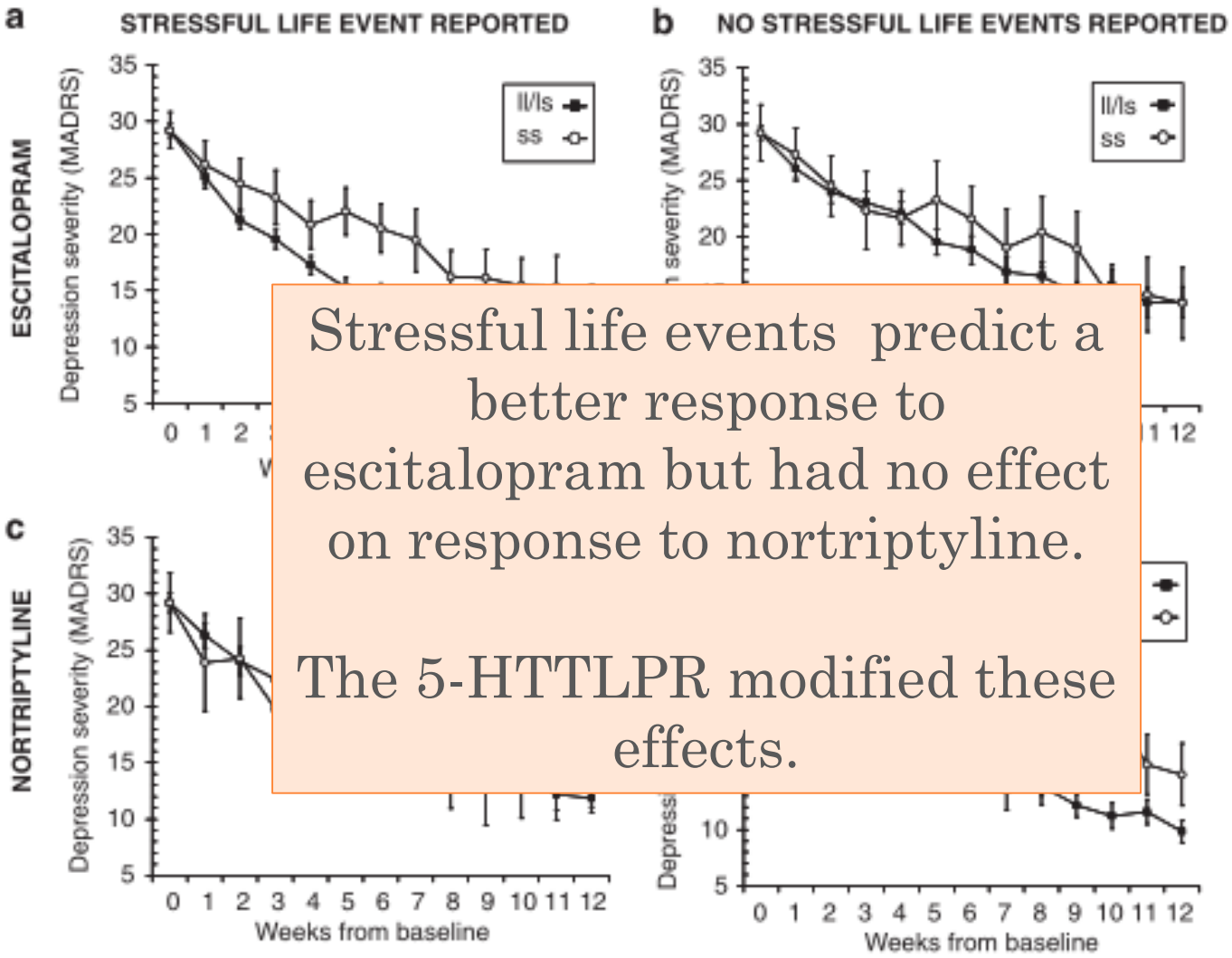


The single marker associations explained only a small proportion of variance in response to antidepressants, indicating a need for a multivariate approach to prediction.

Rudolf U
Nader P
Marcella
Hauser[4],
Neven K
Placenti
Thomas
Zobel[5],
Daniel Souery[6], Caterina Giovannini[7],
Joanna M Gray[1], Cathryn M Lewis[1],
Anne Farmer[1], Katherine J Aitchison[1],
Peter McGuffin[1] and Ian Craig[1]

pression study
key proteins in
signaling in
norepinephr-
gle nucleotide
adult patients
n (a serotonin
reuptake inhibitor) of nortriptyline (a norepinephrine reuptake inhibitor) for 12 weeks in an open-label part-randomized multicenter study. The effect of genetic variants on change in depressive symptoms was evaluated using mixed linear models. Several variants in a serotonin receptor gene (*HTR2A*)

Gene-environment interaction



pressants in

entino A, Larsen

Stressful life events predict a better response to escitalopram but had no effect on response to nortriptyline.

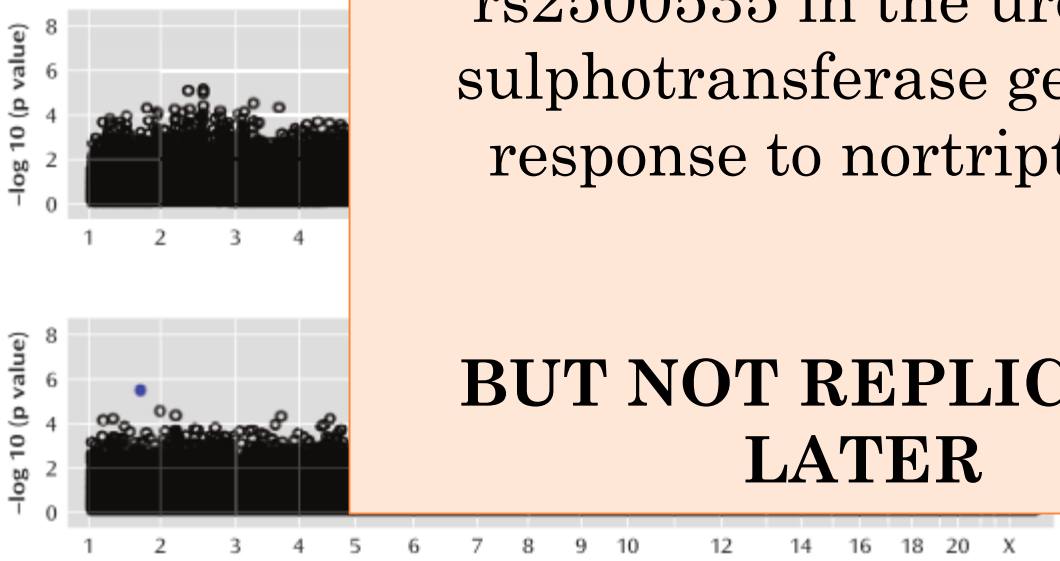
The 5-HTTLPR modified these effects.

GWAS

Article

Genome-Wide Pharmacogenetics of Antidepressant Response in the GENDEP Project

Rudolf Uher, M.D., Ph.D., M.R.C.Psych.; Nader Perroud, M.D.; Mandy Y.M. Ng, Ph.D.; Joanna Hauser, Ph.D.; Neven Henigsberg, M
Marcella Rietschel, M.D.; Da
Jerman, B.Sc.; Erik Roj Larse
Cohen-Woods, Ph.D.; Katrin
Barnes, Ph.D.; Mark Lathrop
Katherine J. Aitchison, M.D.,



Drug-specific analyses revealed a genome-wide significant association between marker rs2500535 in the uronyl 2-sulphotransferase gene and response to nortriptyline.

BUT NOT REPLICATED LATER

GWAS: INCREASING POWER

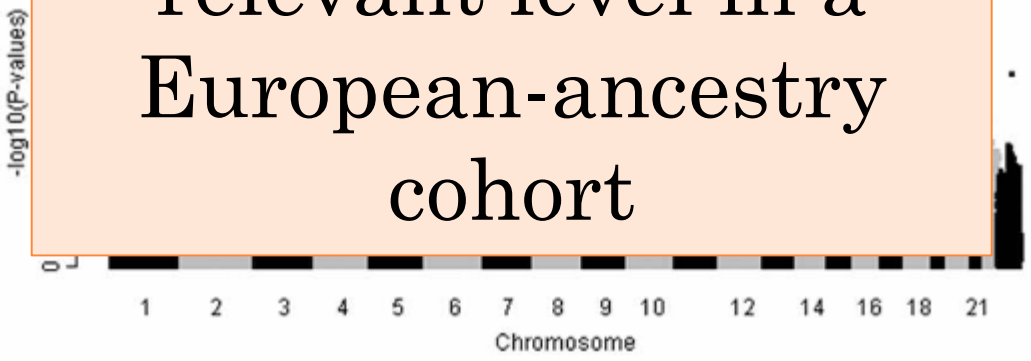
OPEN ACCESS Freely available online

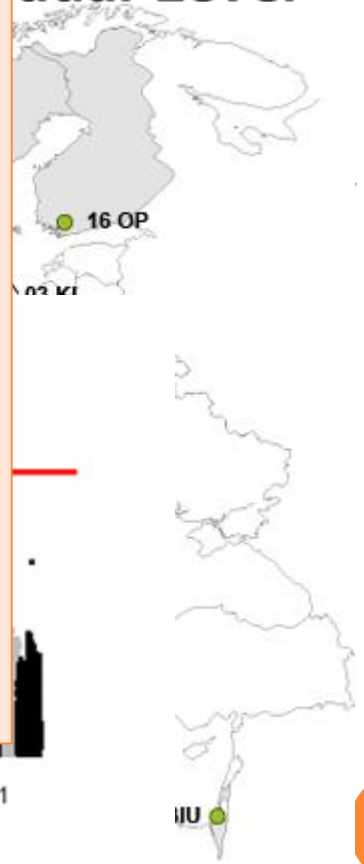
PLOS | MEDICINE

Genetic Predictors of Response to Serotonergic and Noradren… …pressive Disorder: …dual-Level Data and…

Katherine E. Tan…
David Evans[6], St…
Wolfgang Maier[1]
Marcella Rietsch…
Jens R. We…
Bryan Ster…

No single common genetic variant was associated with antidepressant response at a clinically relevant level in a European-ancestry cohort





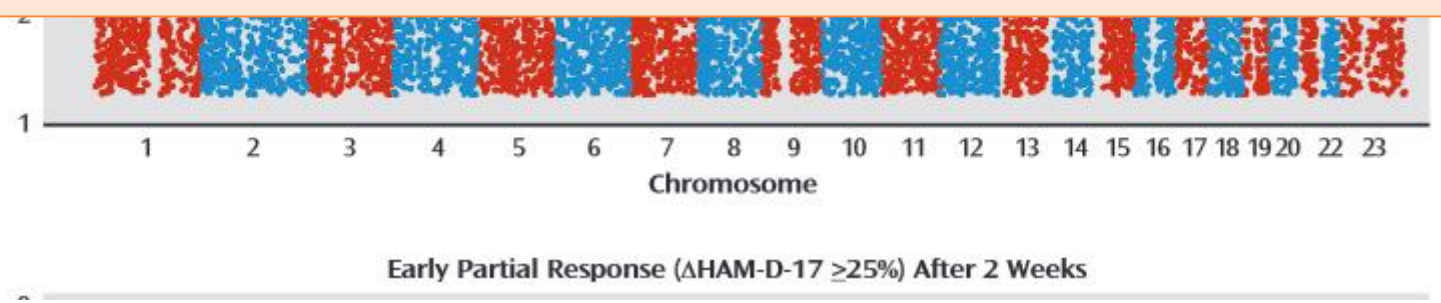
The N…
acader…
assem…
Europ…
major depressive disorder

GWAS: INCREASING POWER META-ANALYSIS

New Research

Despite increased statistical power no reliable predictors of antidepressant treatment outcome were found.

Modest evidence that common genetic variation contributes to individual differences in antidepressant response.



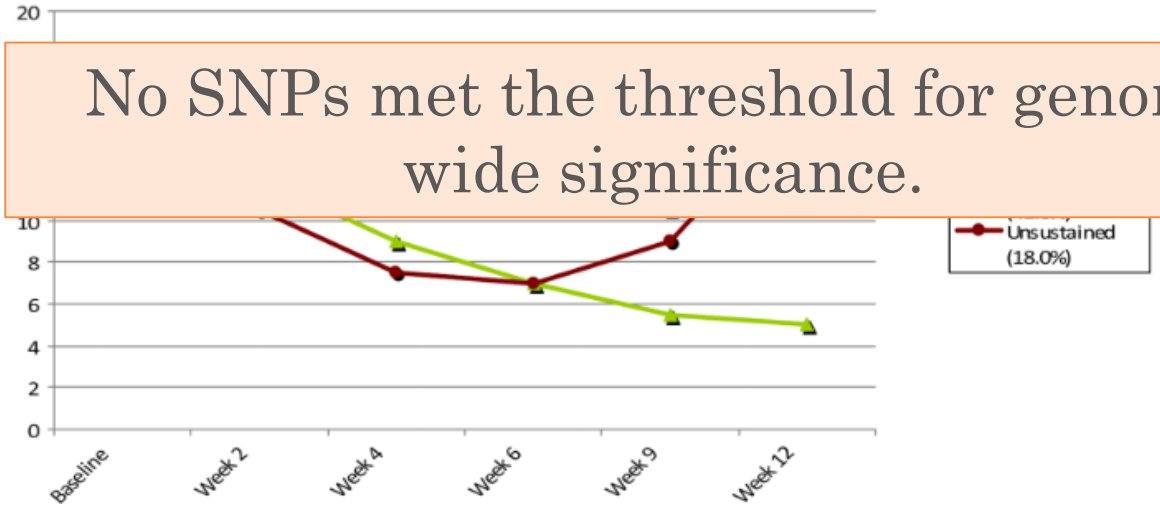
Early Partial Response (ΔHAM-D-17 ≥25%) After 2 Weeks

Using pattern of response: increasing power by better define phenotype

A Genome-wide Association Study of a Sustained Pattern of Antidepressant Response

Aimee M. Hunter, Ph.D.[1], Andrew F. Leuchter, M.D.[1], Robert Power, MSc[2], Bengt Muthén, Ph.D.[3], Patrick J. McGrath, M.D.[4], Cathryn M. Lewis, Ph.D.[2], Ian A. Cook, M.D.[1], Holly A. Garriock, Ph.D.[5,6], Peter McGuffin, MB, Ph.D.[2], Rudolf Uher, Ph.D.[2,7], and **Steven P. Hamilton, M.D., Ph.D.[5]**

[1] Department of Psychiatry and Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles



No SNPs met the threshold for genome-wide significance.

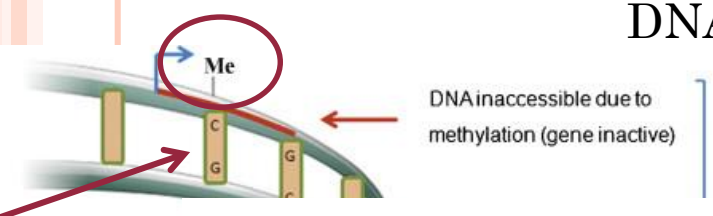
Figure 1.
Estimated mean QIDS-C scores (y-axis) across 12 weeks of citalopram treatment (x-axis) for four classes of subjects in STAR*D[2].

The absence of pharmacogenetic associations with clinically meaningful effect suggests that common genetic variation is not ready to inform personalization of treatment for depression.

Perspectives: epigenetics

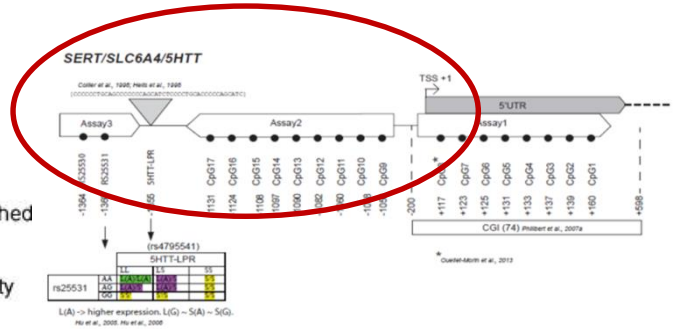
Epigenetics

«Any potentially inheritable change that might alter the expression of a gene without any direct modification of the nucleotide sequence in the DNA»



DNA inaccessible due to methylation (gene inactive)

CpG sites

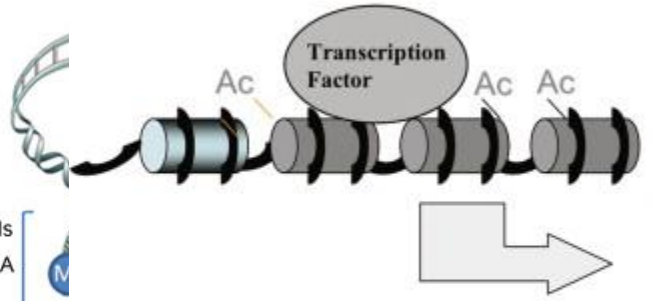


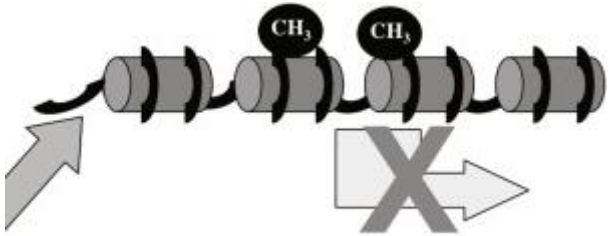
1

/l groups attached

CpG islands

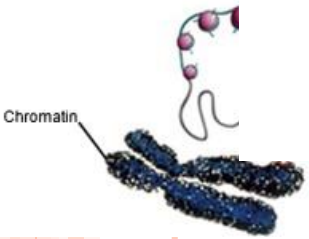
ate gene activity





2

Groups attached to histone tails determine the activity of the DNA wrapped around them



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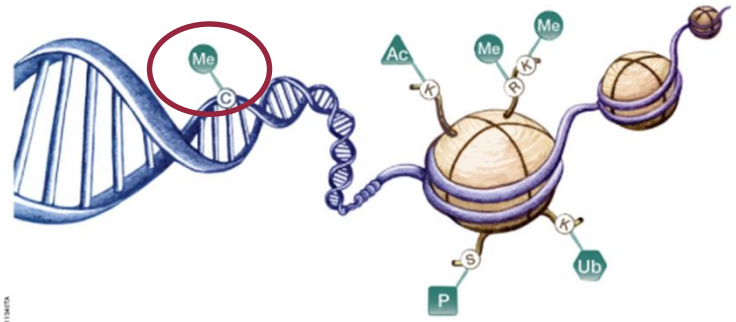
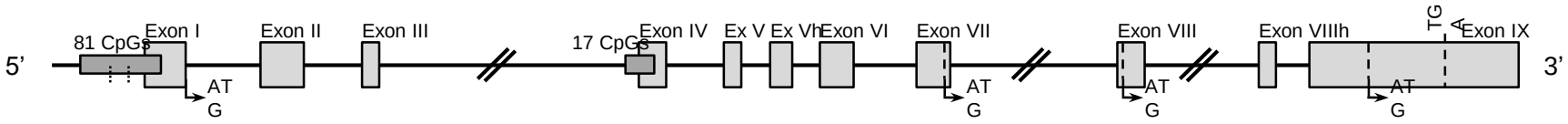
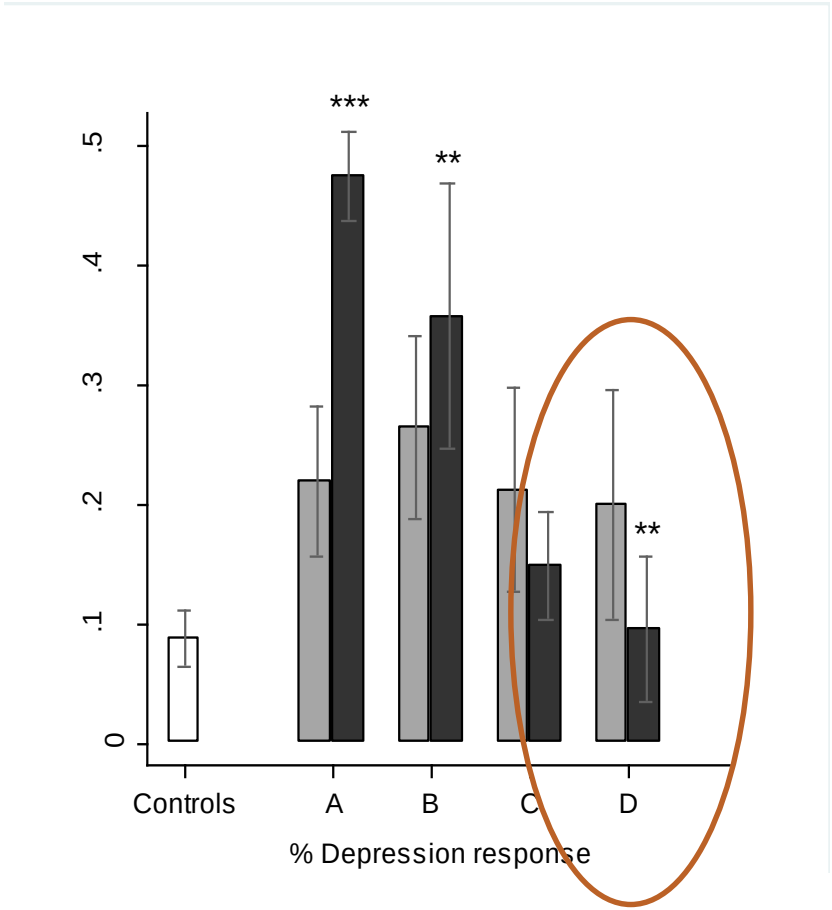


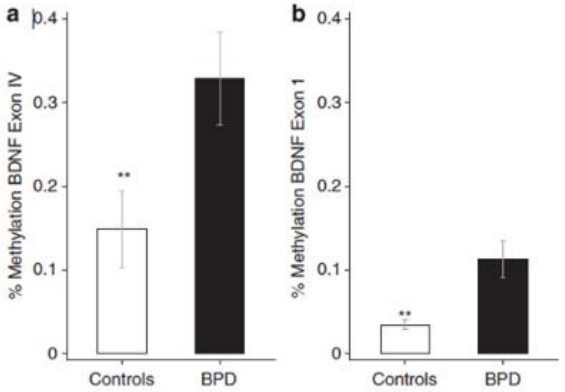
McGowan and Szyf 2010

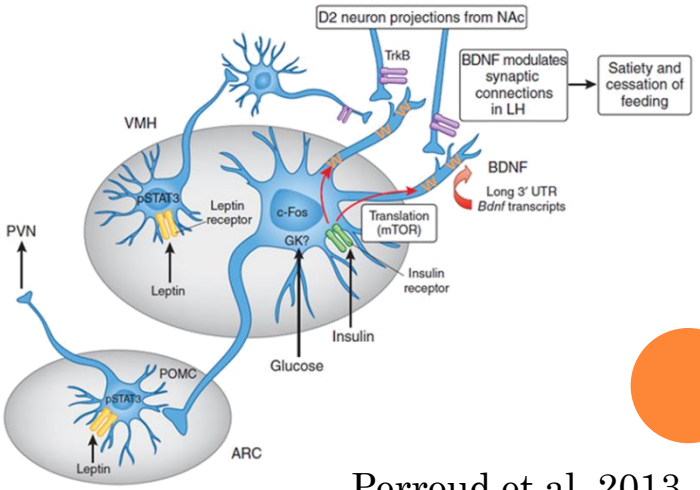
The Neurotrophic system: *BDNF*



The effect of I-DBT







Perroud et al. 2013

Perspectives: BIG BIG numbers

Psychiatric GWAS Consortium (PGC) and Polygenic risk scores (PRS)

PRS

Polygenic risk scores (PRS) capture in a single variable the additive effect of SNP alleles across the genome

PRS are constructed from multiple SNPs with lower evidence of association, with the assumption that genetic markers that do not meet the genome-wide significance threshold might have good predictive power when they are considered collectively.

Dudbridge, 2013

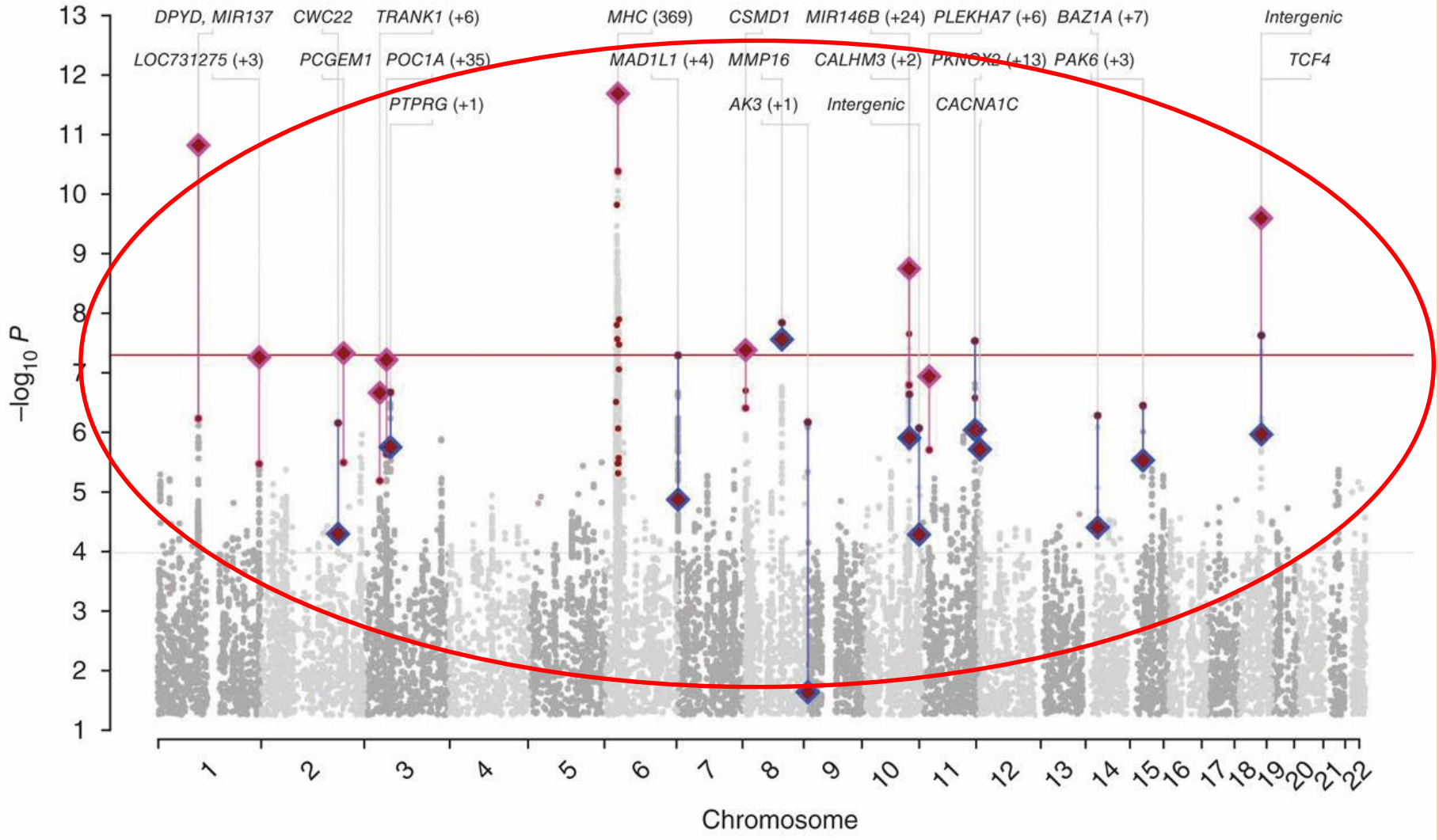
Published in final edited form as:
Nat Genet. ; 43(10): 969–976. doi:10.1038/ng.940.

Genome-wide association study identifies five new schizophrenia loci

The Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium[1]

Abstract

We examined the role of common genetic variation in schizophrenia in a genome-wide association study of substantial size: a stage 1 discovery sample of 21,856 individuals of European ancestry and a stage 2 replication sample of 29,839 independent subjects. The combined stage 1 and 2 analysis yielded genome-wide significant associations with schizophrenia for seven loci, five of which are new (1p21.3, 2q32.3, 8p23.2, 8q21.3 and 10q24.32-q24.33) and two of which have been previously implicated (6p21.32-p22.1 and 18q21.2). The strongest new finding ($P = 1.6 \times 10^{-11}$) was with rs1625579 within an intron of a putative primary transcript for *MIR137* (microRNA 137), a known regulator of neuronal development. Four other schizophrenia loci achieving genome-wide significance contain predicted targets of *MIR137*, suggesting *MIR137*-mediated dysregulation as a previously unknown etiologic mechanism in schizophrenia. In a joint analysis with a bipolar disorder sample (16,374 affected individuals and 14,044 controls), three loci reached genome-wide significance: *CACNA1C* (rs4765905, $P = 7.0 \times 10^{-9}$), *ANK3* (rs10994359, $P = 2.5 \times 10^{-8}$) and the *ITIH3-ITIH4* region (rs2239547, $P = 7.8 \times 10^{-9}$).


DPYD, MIR137
LOC731275 (+3)
CWC22
PCGEM1
TRANK1 (+6)
POC1A (+35)
PTPRG (+1)
MHC (369)
MAD1L1 (+4)
CSMD1
MMP16
AK3 (+1)
MIR146B (+24)
CALHM3 (+2)
Intergenic
PLEKHA7 (+6)
PKNOX2 (+13)
CACNA1C
BAZ1A (+7)
PAK6 (+3)
Intergenic
TCF4
−log10 P
Chromosome

Published in final edited form as:
Lancet. 2013 April 20; 381(9875): 1371–1379. doi:10.1016/S0140-6736(12)62129-1.

Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis

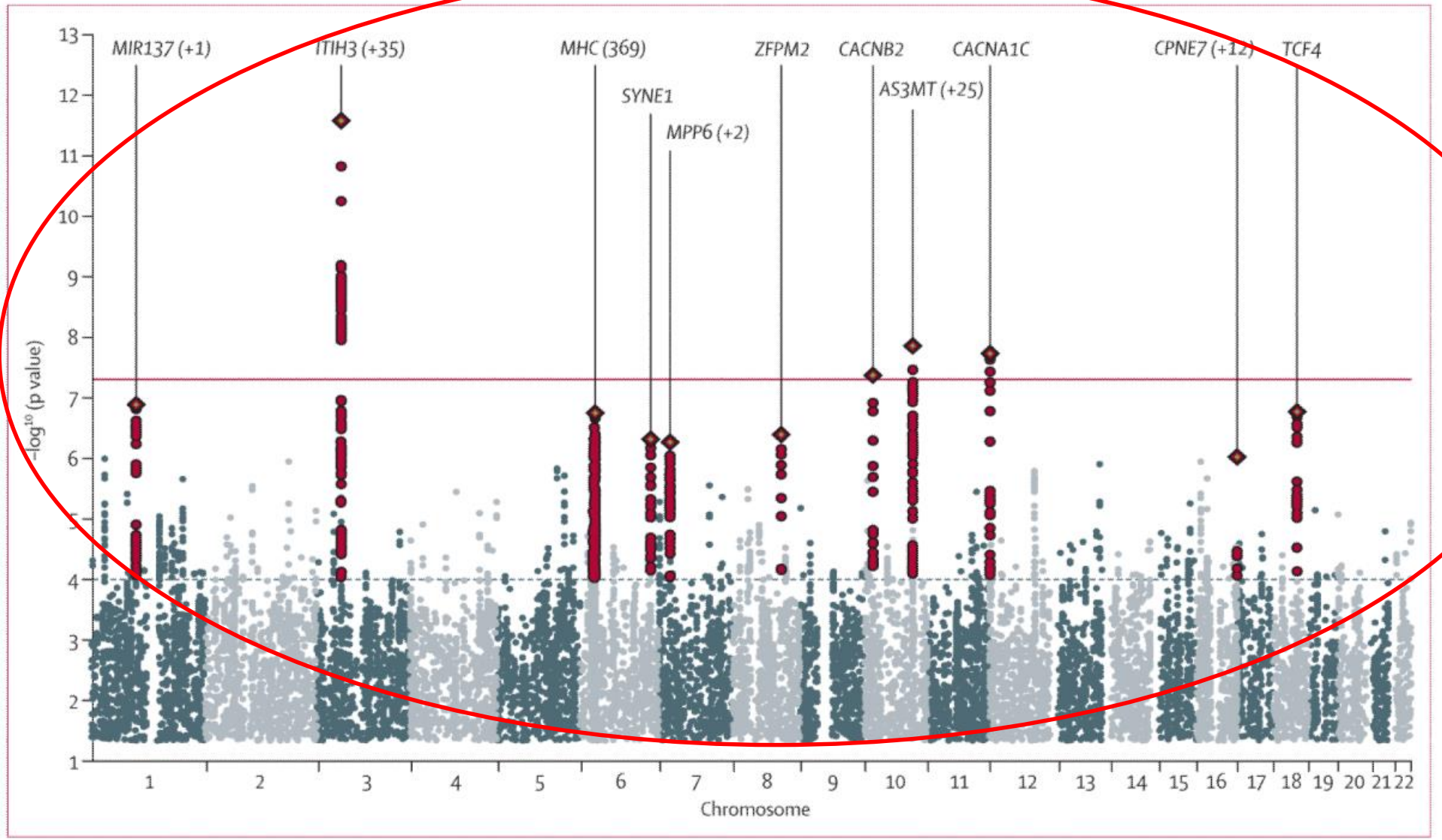
Cross-Disorder Group of the Psychiatric Genomics Consortium*

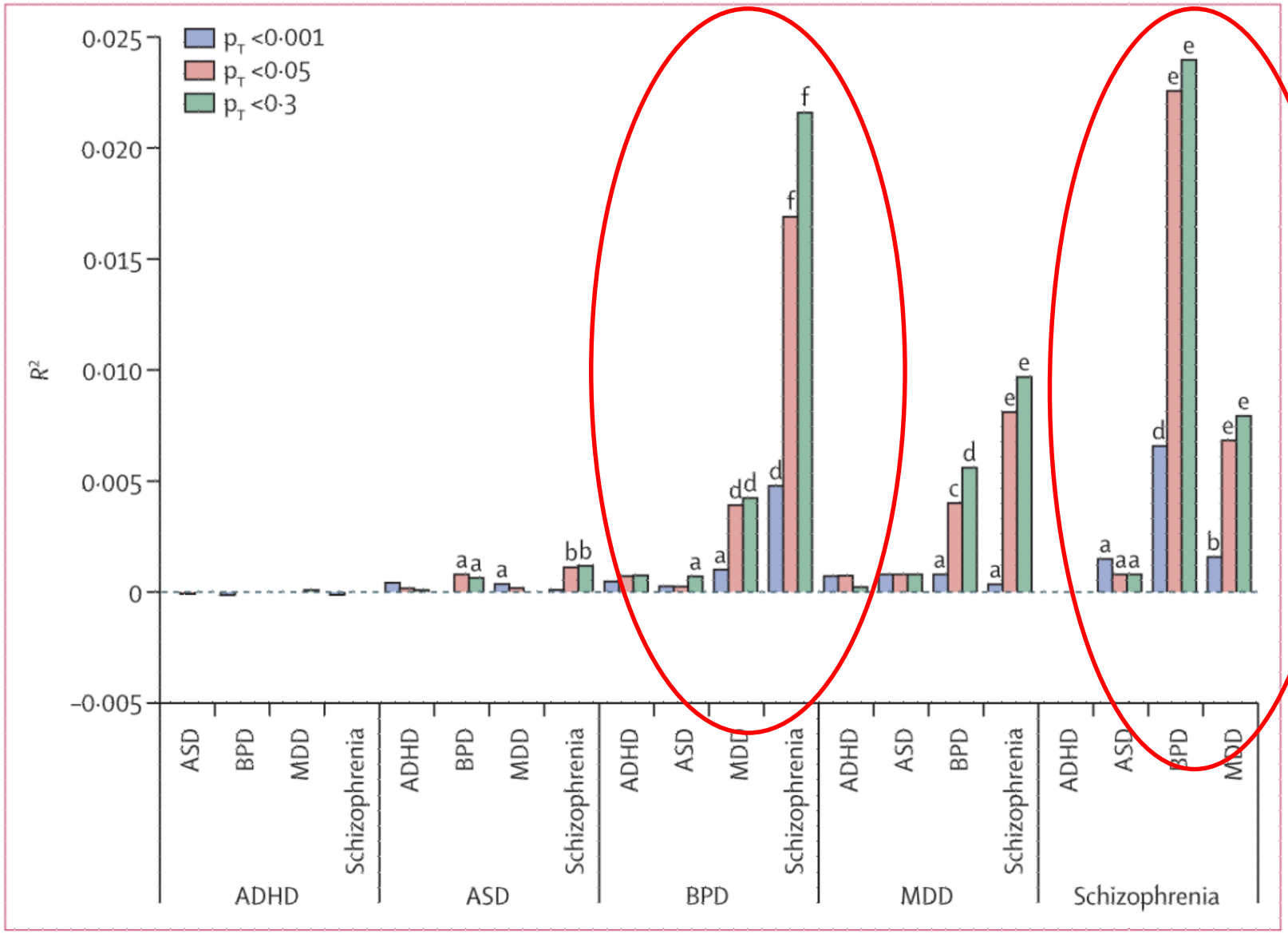
Summary

Background—Findings from family and twin studies suggest that genetic contributions to psychiatric disorders do not in all cases map to present diagnostic categories. We aimed to identify specific variants underlying genetic effects shared between the five disorders in the Psychiatric Genomics Consortium: autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia.

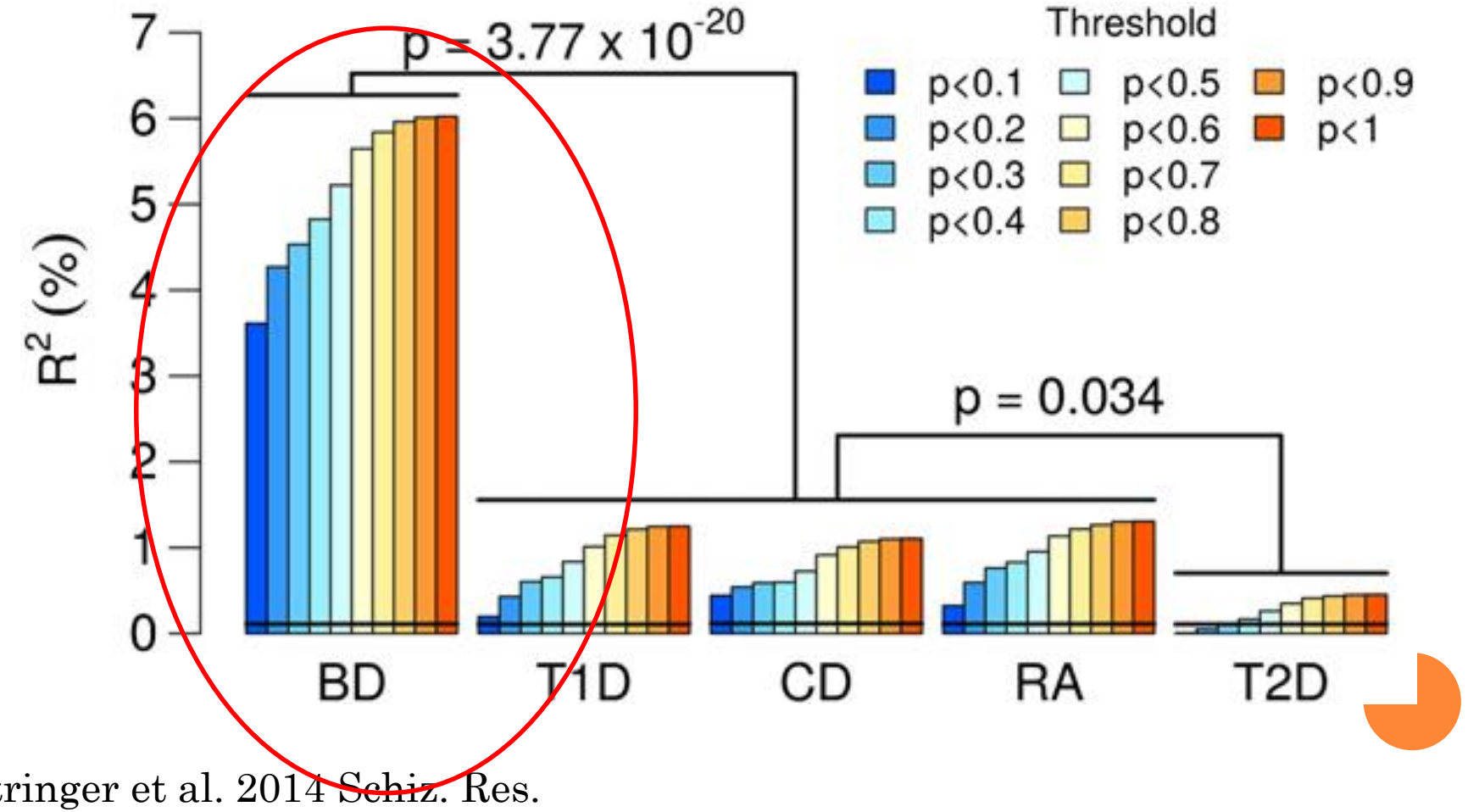
Methods—We analysed genome-wide single-nucleotide polymorphism (SNP) data for the five disorders in 33 332 cases and 27 888 controls of European ancestory. To characterise allelic effects on each disorder, we applied a multinomial logistic regression procedure with model selection to identify the best-fitting model of relations between genotype and phenotype. We examined cross-disorder effects of genome-wide significant loci previously identified for bipolar disorder and schizophrenia, and used polygenic risk-score analysis to examine such effects from a broader set of common variants. We undertook pathway analyses to establish the biological associations underlying genetic overlap for the five disorders. We used enrichment analysis of expression quantitative trait loci (eQTL) data to assess whether SNPs with cross-disorder association were enriched for regulatory SNPs in post-mortem brain-tissue samples.

Findings—SNPs at four loci surpassed the cutoff for genome-wide significance ($p<5\times10^{-8}$) in the primary analysis: regions on chromosomes 3p21 and 10q24, and SNPs within two L-type voltage-gated calcium channel subunits, *CACNA1C* and *CACNB2*. Model selection analysis supported effects of these loci for several disorders. Loci previously associated with bipolar


MIR137 (+1)
ITIH3 (+35)
MHC (369)
SYNE1
MPP6 (+2)
ZFPM2
CACNB2
AS3MT (+25)
CACNA1C
CPNE7 (+12)
TCF4
−log10 (p value)
Chromosome

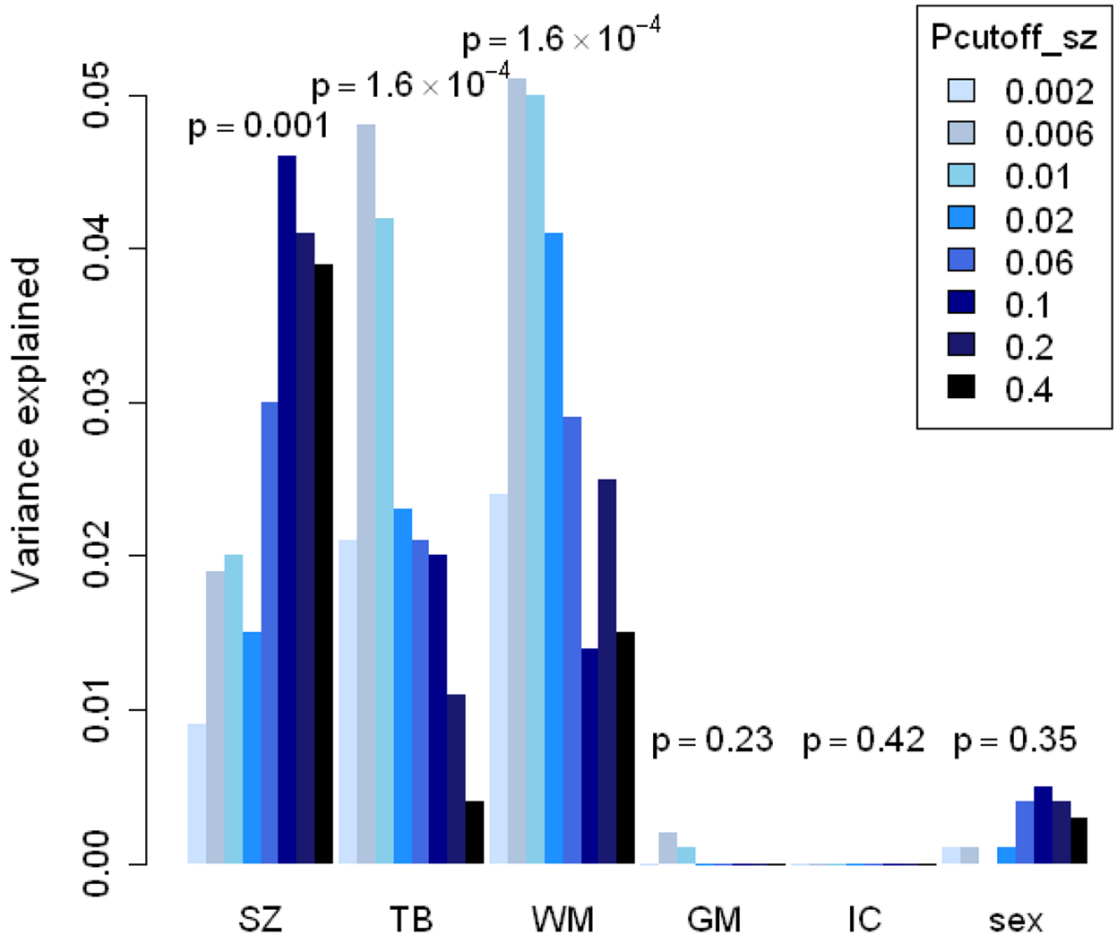

p_T <0·001
p_T <0·05
p_T <0·3
R^2
0·025
0·020
0·015
0·010
0·005
0
−0·005
ASD
BPD
MDD
Schizophrenia
ADHD
ASD
BPD
MDD
Schizophrenia

Predicting bipolar disorder (BD), type-1 diabetes (T1D), Crohn's disease (CD), rheumatoid arthritis (RA), and type-2 diabetes (T2D) from a polygenic score for schizophrania from the results from the PGC.



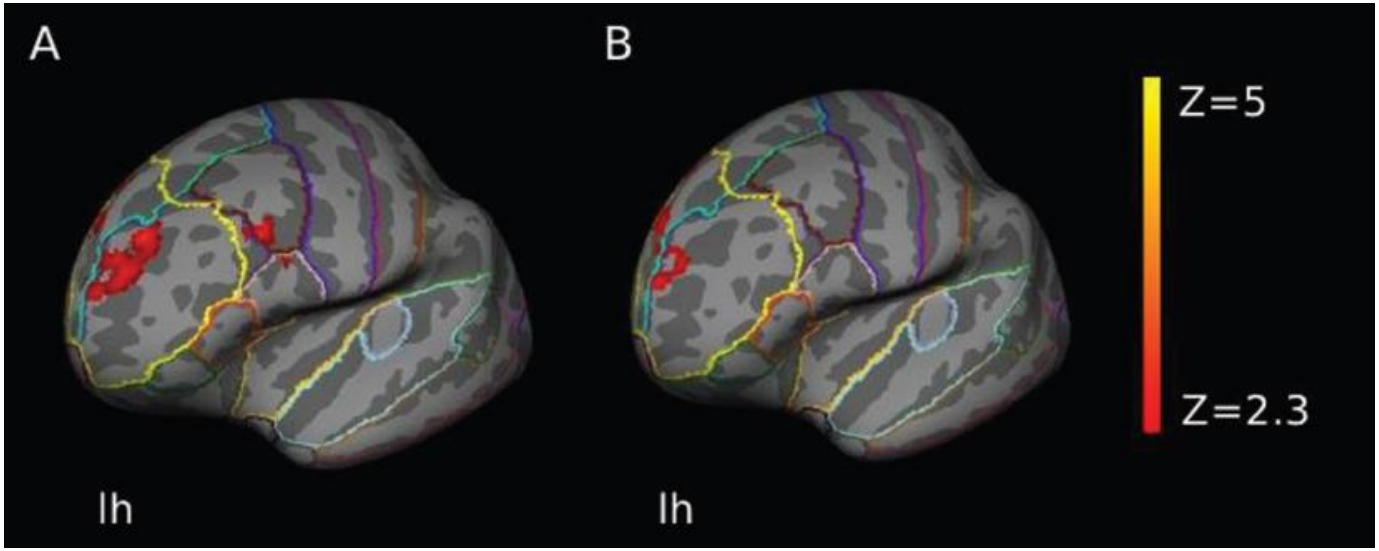
Stringer et al. 2014 Schiz. Res.

Using the PGS to predict total brain volume and disease status



van Scheltinga et al 2013

Using the results from PGRS to predict neural inefficiency in the left dorsolateral prefrontal cortex



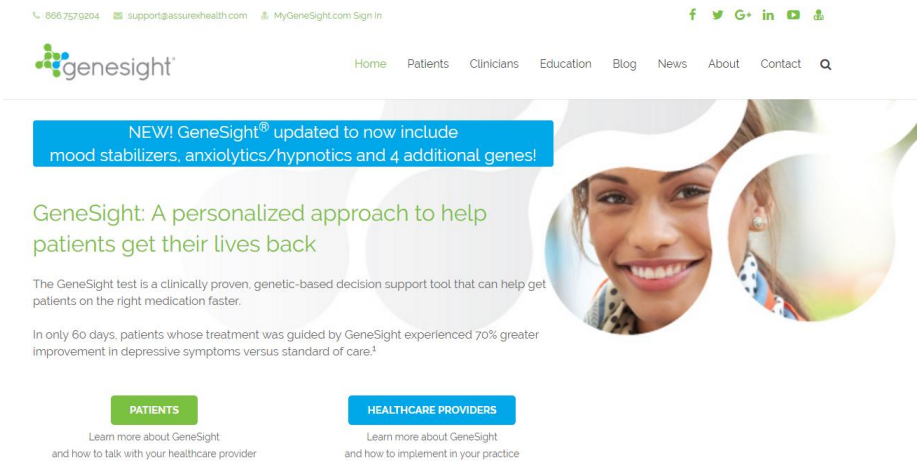
Walton et al 2014

Commercial pharmacogenetic tests?

Hall-Flavin et al. 2013; Winner et al. 2015; Altar et al 2015

COMMERCIAL PHARMACOGENETIC TESTS?

- Based on algorithm that is not public and not tested by independent researchers



- 50 alleles in :
  SLC6A4, HTR2A, CYP2D6, CYP2C19, CYP2C9, CYP1A2

- Three categories of patients
  - The 'red' group ('use with caution and frequent monitoring')
  - The yellow ('use with caution')
  - The green group ('use as directed')

- Report that provides prescribing options for 99% of all FDA-approved antidepressant

- Improve response and remission rates and reduce total medication cost of $1035.60 over 1 year

Hall-Flavin et al. 2013; Winner et al. 2015; Altar et al 2015

Conclusions

Lancet. 2016 Mar 12;387(10023):1085-93. doi: 10.1016/S0140-6736(16)00143-4. Epub 2016 Jan 22.

Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study.

Hou L, Heilbronner U, Degenhardt F, Adli M, Akiyama K, Akula N, Ardau R, Arias B, Backlund L, Banzato CE, Benabarre A, Bengesser S, Bhattacharjee AK, Biernacka JM, Birner A, Brichant-Petitjean C, Bui ET, Cervantes P, Chen GB, Chen HC, Chillotti C, Cichon S, Clark SR, Colom F, Cousins DA, Cruceanu C, Czerski PM, Dantas CR, Dayer A, Étain B, Falkai P, Forstner AJ, Frisén L, Fullerton JM, Gard S, Garnham JS, Goes FS, Grof P, Gruber O, Hashimoto R, Hauser J, Herms S, Hoffmann P, Hofmann A, Jamain S, Jiménez E, Kahn JP, Kassem L, Kittel-Schneider S, Kliwicki S, König B, Kusumi I, Lackner N, Laje G, Landén M, Lavebratt C, Leboyer M, Leckband SG, Jaramillo CA, MacQueen G, Manchia M, Martinsson L, Mattheisen M, McCarthy MJ, McElroy SL, Mitjans M, Mondimore FM, Monteleone P, Nievergelt CM, Nöthen MM, Ösby U, Ozaki N, Perlis RH, Pfennig A, Reich-Erkelenz D, Rouleau GA, Schofield PR, Schubert KO, Schweizer BW, Seemüller F, Severino G, Shekhtman T, Shilling PD, Shimoda K, Simhandl C, Slaney CM, Smoller JW, Squassina A, Stamm T, Stopkova P, Tighe SK, Tortorella A, Turecki G, Volkert J, Witt S, Wright A, Young LT, Zandi PP, Potash JB, DePaulo JR, Bauer M, Reininghaus EZ, Novák T, Aubry JM, Maj M, Baune BT, Mitchell PB, Vieta E, Frye MA, Rybakowski JK, Kuo PH, Kato T, Grigoroiu-Serbanescu M, Reif A, Del Zompo M, Bellivier F, Schalling M, Wray NR, Kelsoe JR, Alda M, Rietschel M, McMahon FJ, Schulze TG.

Abstract

BACKGROUND: Lithium is a first-line treatment in bipolar disorder, but individual response is variable. Previous studies have suggested that lithium response is a heritable trait. However, no genetic markers of treatment response have been reproducibly identified.

METHODS: Here, we report the results of a genome-wide association study of lithium response in 2563 patients collected by 22 participating sites from the International Consortium on Lithium Genetics (ConLiGen). Data from common single nucleotide polymorphisms (SNPs) were tested for association with categorical and continuous ratings of lithium response. Lithium response was

THANK-YOU FOR YOUR ATTENTION