Will a genetic test help us select treatment for individuals with depression?

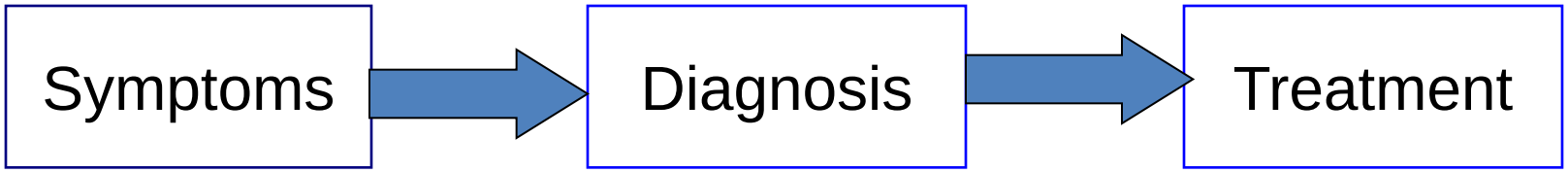
Rudolf Uher

Dalhousie University, Halifax, NS, Canada

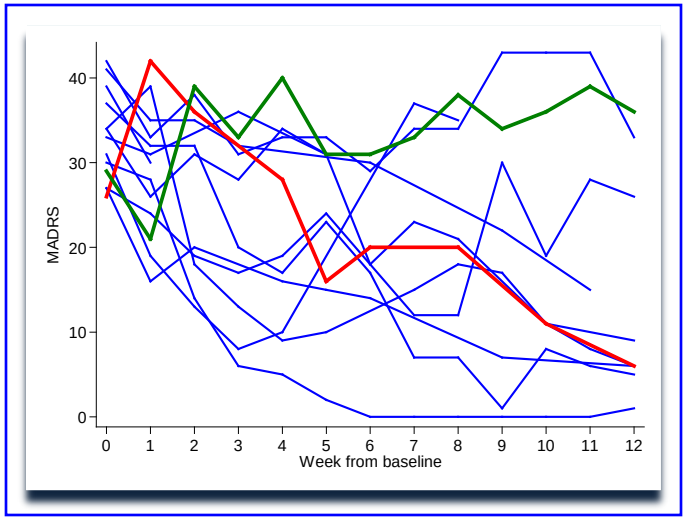
uher@dal.ca

THE NEED TO PREDICT

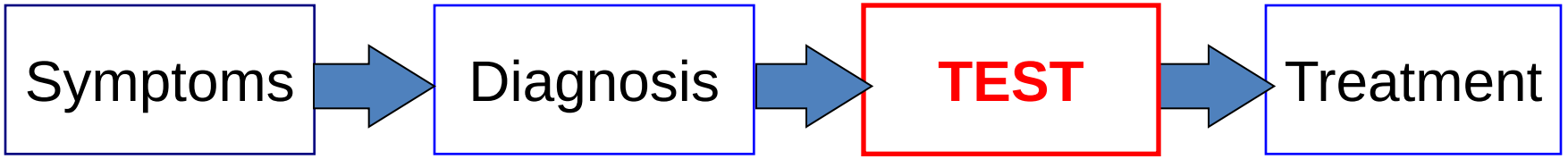
Current Status: evidence based psychiatry



Problem: individual heterogeneity in treatment effects



Solution: personalized psychiatry?



What kind of test?

Predicting treatment response

- Environmental exposure history (E)
- Subtypes of depression
- Symptomatic predictors
- Genetic variation (G)
- Epigenetics
- Transcriptomics
- Combination of G and E

Why a genetic test?

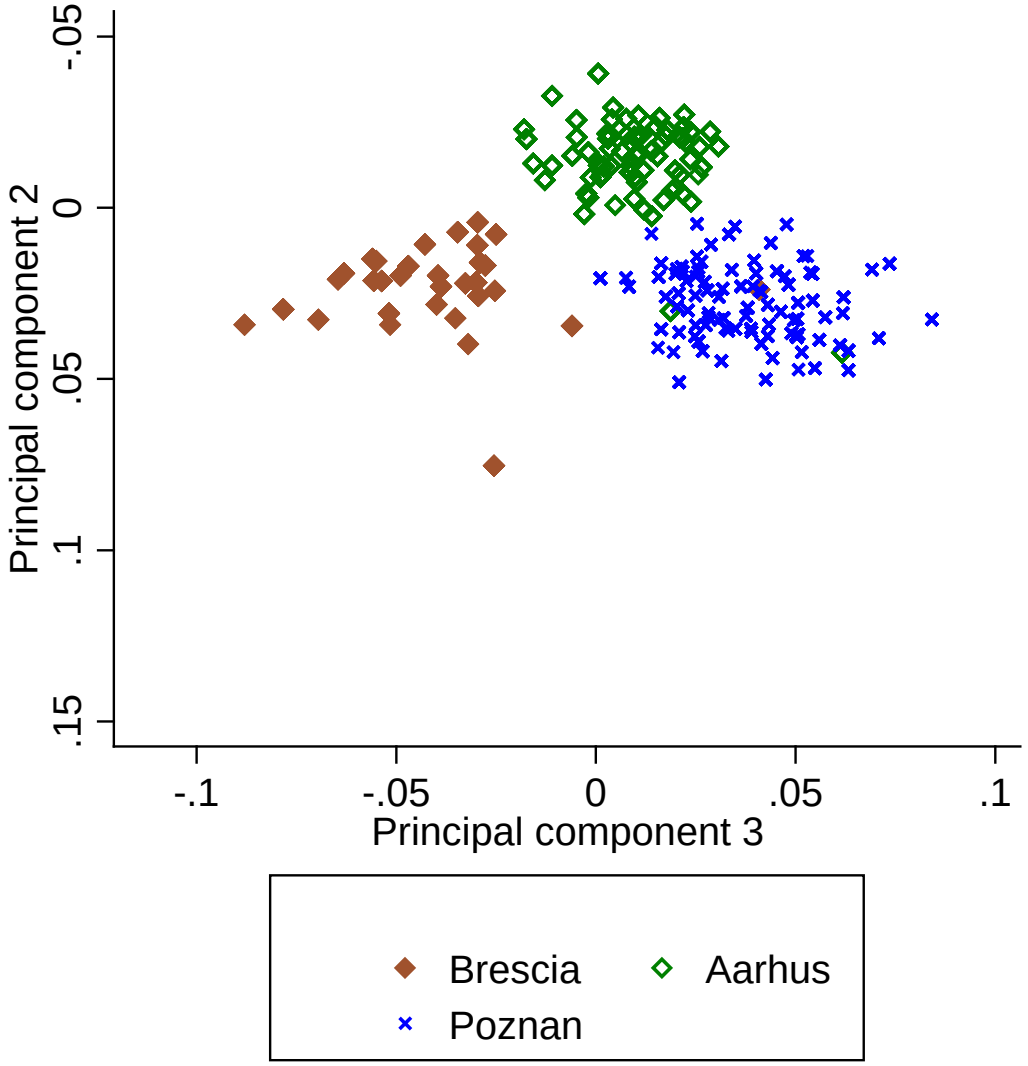
For

- Minimally invasive
- Accessible
- Accurate
- Objective
- Single test good for life

Against

- Only captures personally stable information

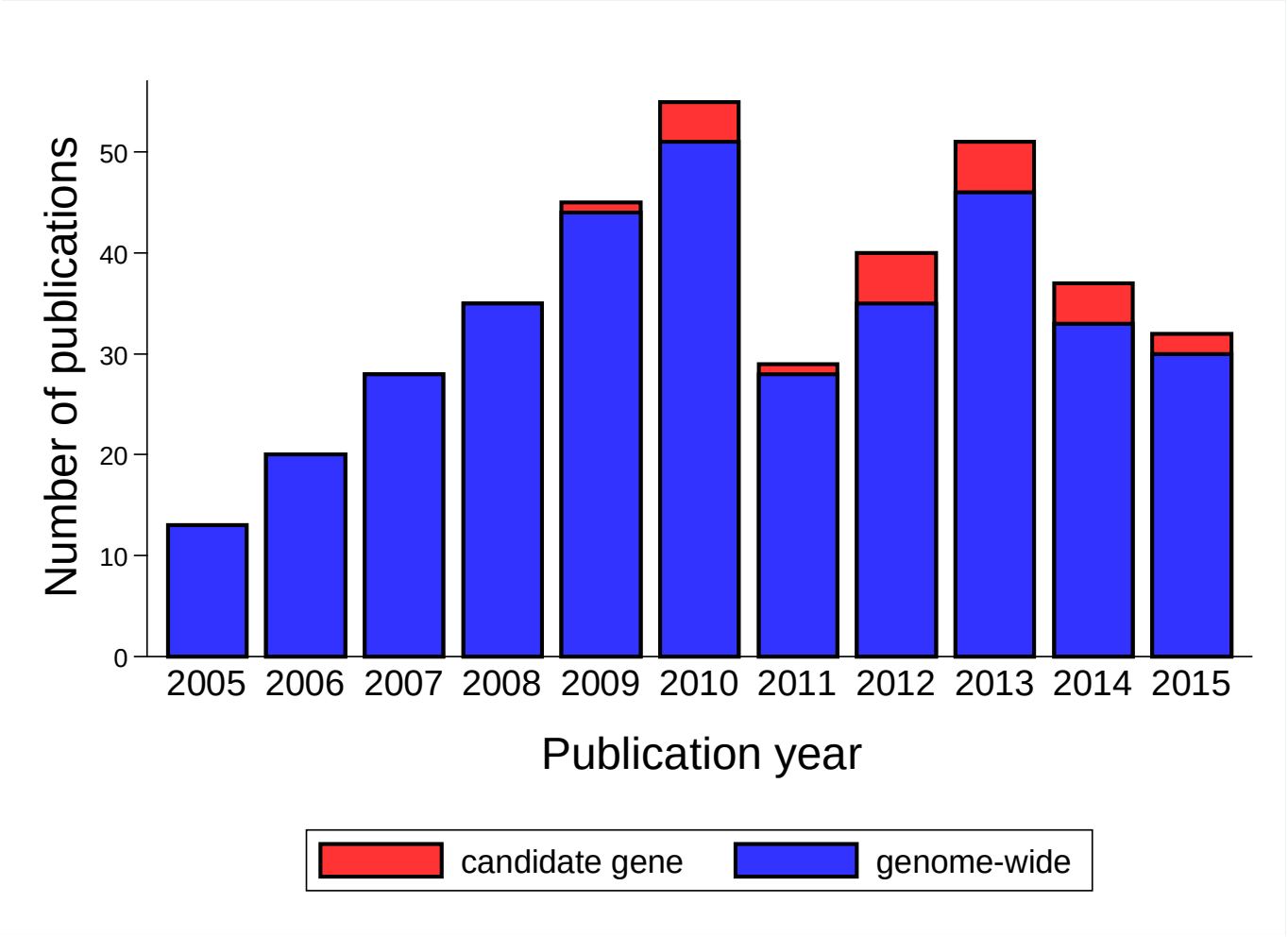
Geography genetics



PHARMACOGENETICS

PHARMACOGENETICS – THERAPYGENETICS

A decade of antidepressant pharmacogenetics



Pharmacogenetics in **GENDEP**

Uher et al 2009 British J. Psychiatry, 194: 252-259

HYPOTHESIS

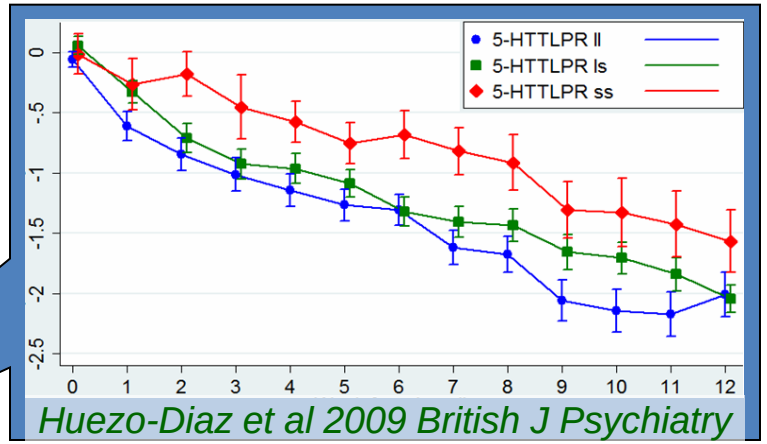
DISCOVERY

POWER

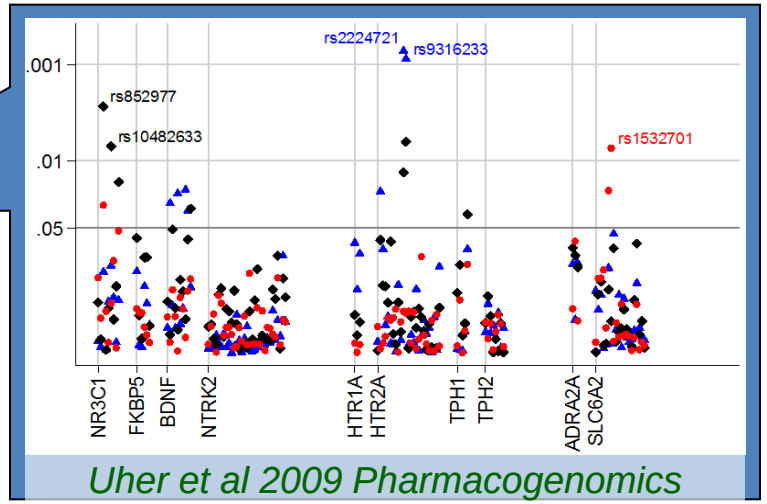
5-HTTLPR

116 SNP in10 candidate genes with specific hypotheses

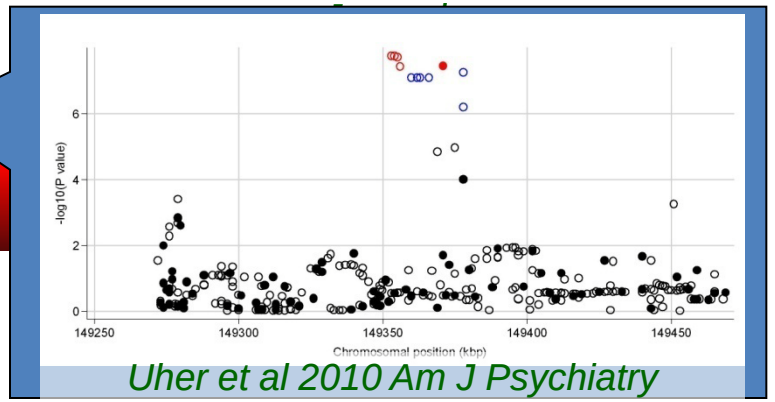
550,000 SNP tagging most common variants in human genome



Huezo-Diaz et al 2009 British J Psychiatry



Uher et al 2009 Pharmacogenomics



Uher et al 2010 Am J Psychiatry

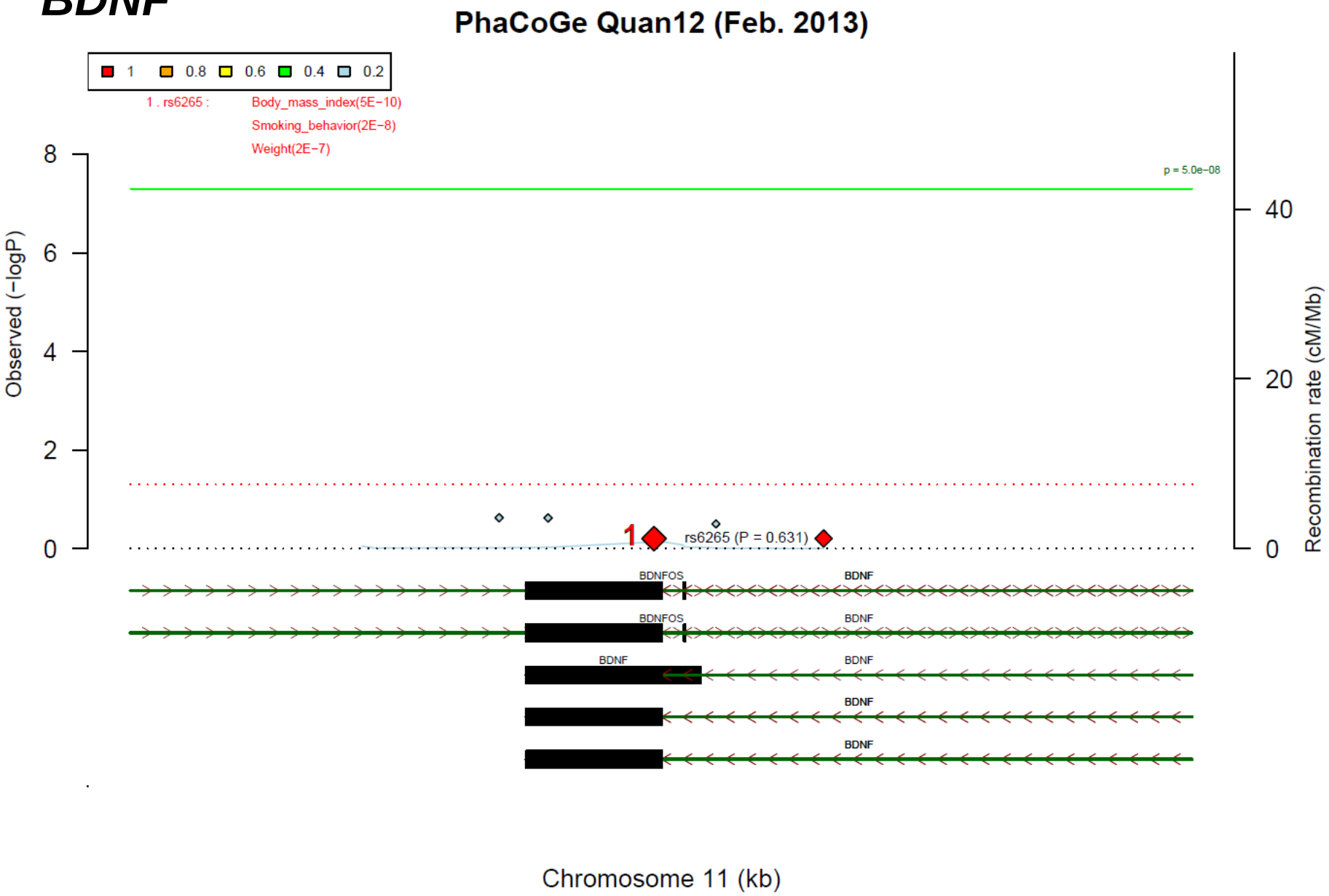
CANDIDATE GENES

Do candidate gene associations with antidepressant response replicate?

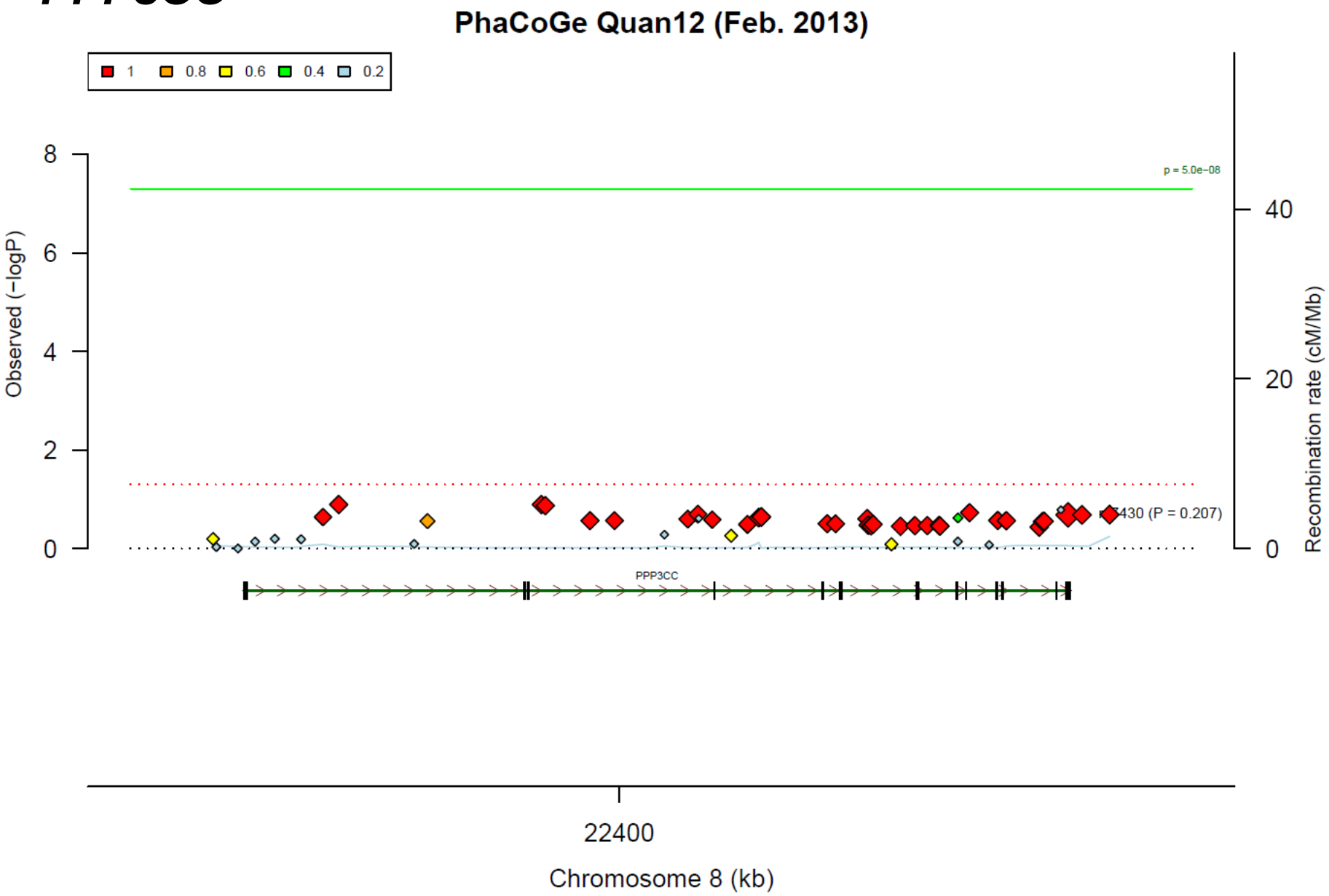
			Previously reported			GENDEP-MARS-STAR*D meta-analysis	
Gene	Variant	Reference	n	OR	p	n	p
TPH1	rs1800532	Kato 2010	754	2.37	0.0001	2256	0.544
BDNF	rs6265	Kato 2010	490	1.63	0.02	2256	0.631
COMT	rs2075507	Kocabas 2010	367	1.90	0.005	2256	0.273
PPP3CC	rs7430	Fabbri 2014	1861	4.35	0.0002	2256	0.207
FKBP5	rs1360780	Binder 2004	294	14.96	0.0005	2256	0.353
ABCB1	rs22032582	Niitsu 2013	2112	1.33	0.03	2256	0.243

*GENDEP, MARS & STAR*D Investigators 2013 Am J Psychiatry 170:207-217*
http://www.broadinstitute.org/mpg/ricopili/ (dataset: PhaCoGe Quan12)

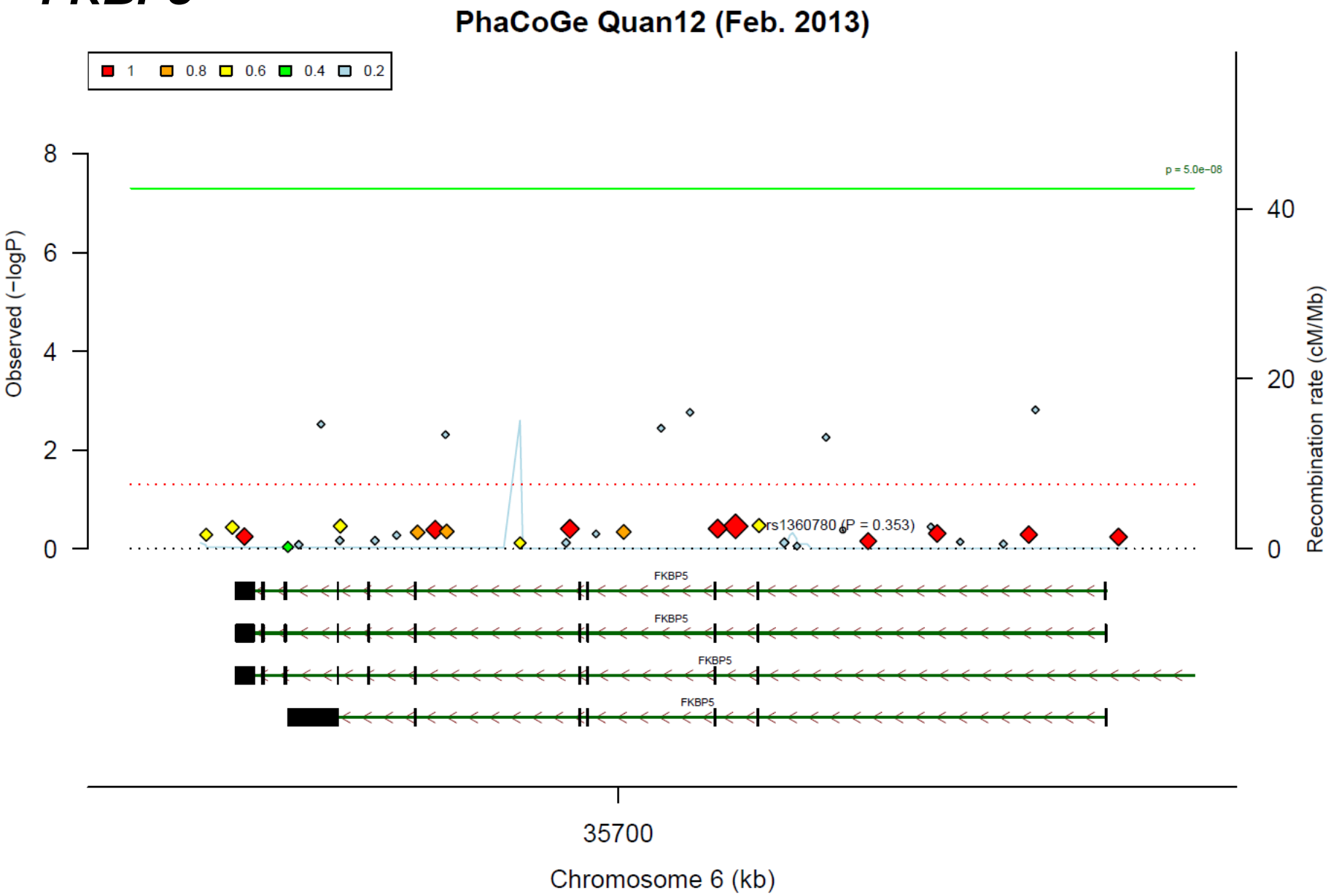
BDNF


PhaCoGe Quan12 (Feb. 2013)
1
0.8
0.6
0.4
0.2
1 . rs6265 :
Body_mass_index(5E−10)
Smoking_behavior(2E−8)
Weight(2E−7)
p = 5.0e−08
Observed (−logP)
Recombination rate (cM/Mb)
rs6265 (P = 0.631)
BDNFOS
BDNF
Chromosome 11 (kb)

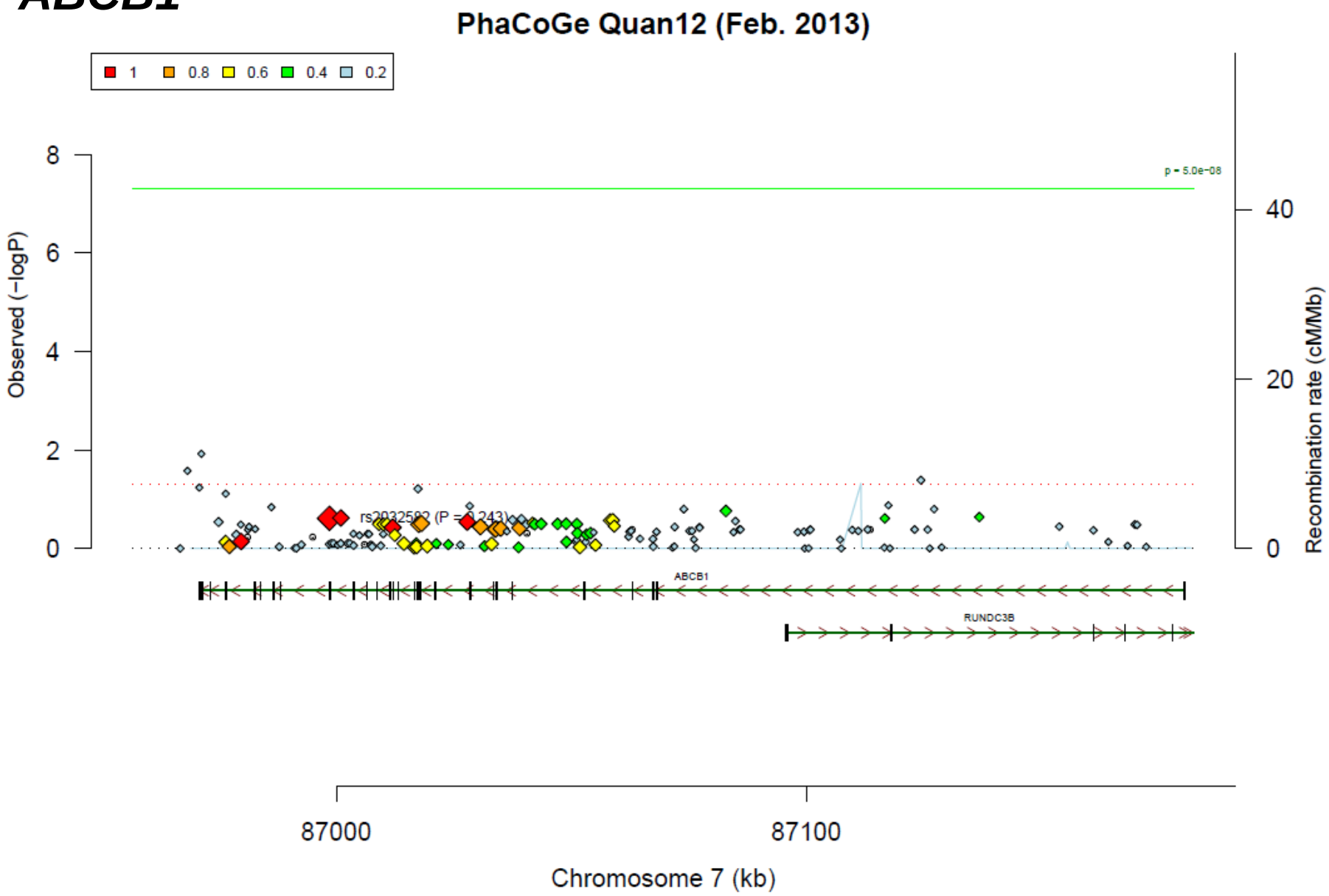
PPP3CC


PhaCoGe Quan12 (Feb. 2013)
1
0.8
0.6
0.4
0.2
Observed (−logP)
8
6
4
2
0
p = 5.0e−08
40
20
0
Recombination rate (cM/Mb)
5430 (P = 0.207)
PPP3CC
22400
Chromosome 8 (kb)

FKBP5


PhaCoGe Quan12 (Feb. 2013)
1
0.8
0.6
0.4
0.2
Observed (−logP)
8
6
4
2
0
p = 5.0e−08
40
20
0
Recombination rate (cM/Mb)
rs1360780 (P = 0.353)
FKBP5
FKBP5
FKBP5
FKBP5
35700
Chromosome 6 (kb)

ABCB1


PhaCoGe Quan12 (Feb. 2013)
1
0.8
0.6
0.4
0.2
Observed (−logP)
8
6
4
2
0
p = 5.0e−08
40
20
0
Recombination rate (cM/Mb)
ABCB1
RUNDC3B
87000
87100
Chromosome 7 (kb)

Do pharmacokinetic candidate genes (cytochromes) predict response?

OPEN ACCESS Freely available online

PLoS one

Pharmacokinetic Genes Do Not Influence Response or Tolerance to Citalopram in the STAR*D Sample

Eric J. Peters[1¤], Susan L. Slager[2], Jeffrey B. Kraft[1], Greg D. Jenkins[2], Megan S. Reinalda[2], Patrick J. McGrath[3], Steven P. Hamilton[1*]

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J Psychopharmacol. 2014 Feb;28(2):133-41. doi: 10.1177/0269881113512041. Epub 2013 Nov 20.

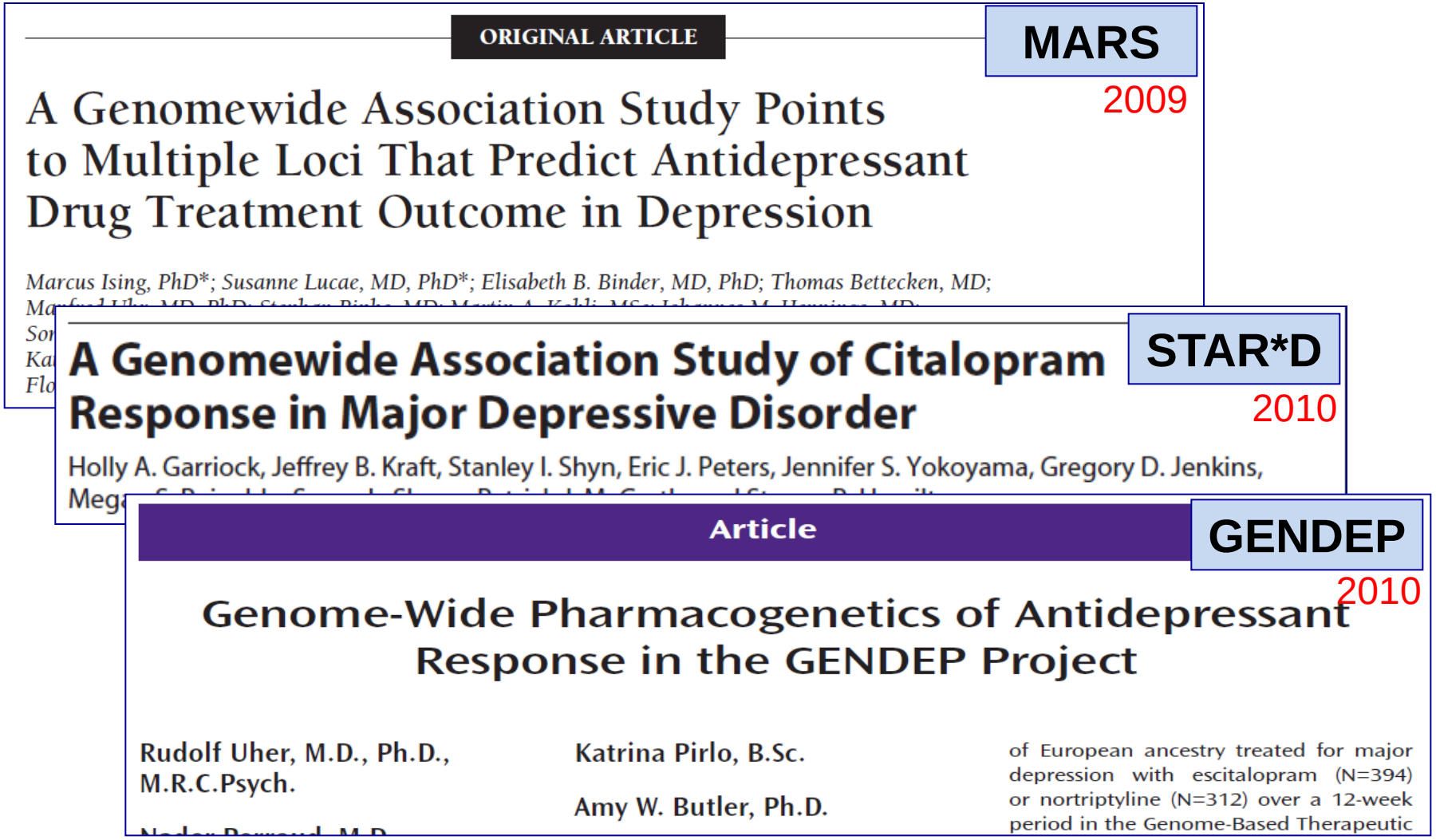
Genetic differences in cytochrome P450 enzymes and antidepressant treatment response.

Hodgson K[1], Tansey K, Dernovsek MZ, Hauser J, Henigsberg N, Maier W, Mors O, Placentino A, Rietschel M, Souery D, Smith R, Craig IW, Farmer AE, Aitchison KJ, Belsy S, Davis OS, Uher R, McGuffin P.

- CYP2C19 was significantly associated with escitalopram serum concentrations and desmethylescitalopram:escitalopram ratio
- CYP2D6 genotype was significantly associated with nortriptyline and 10-hydroxynortriptyline serum concentrations and 10-hydroxynortriptyline:nortriptyline ratio.
- no significant association was found between either CYP450 genotype and treatment response.

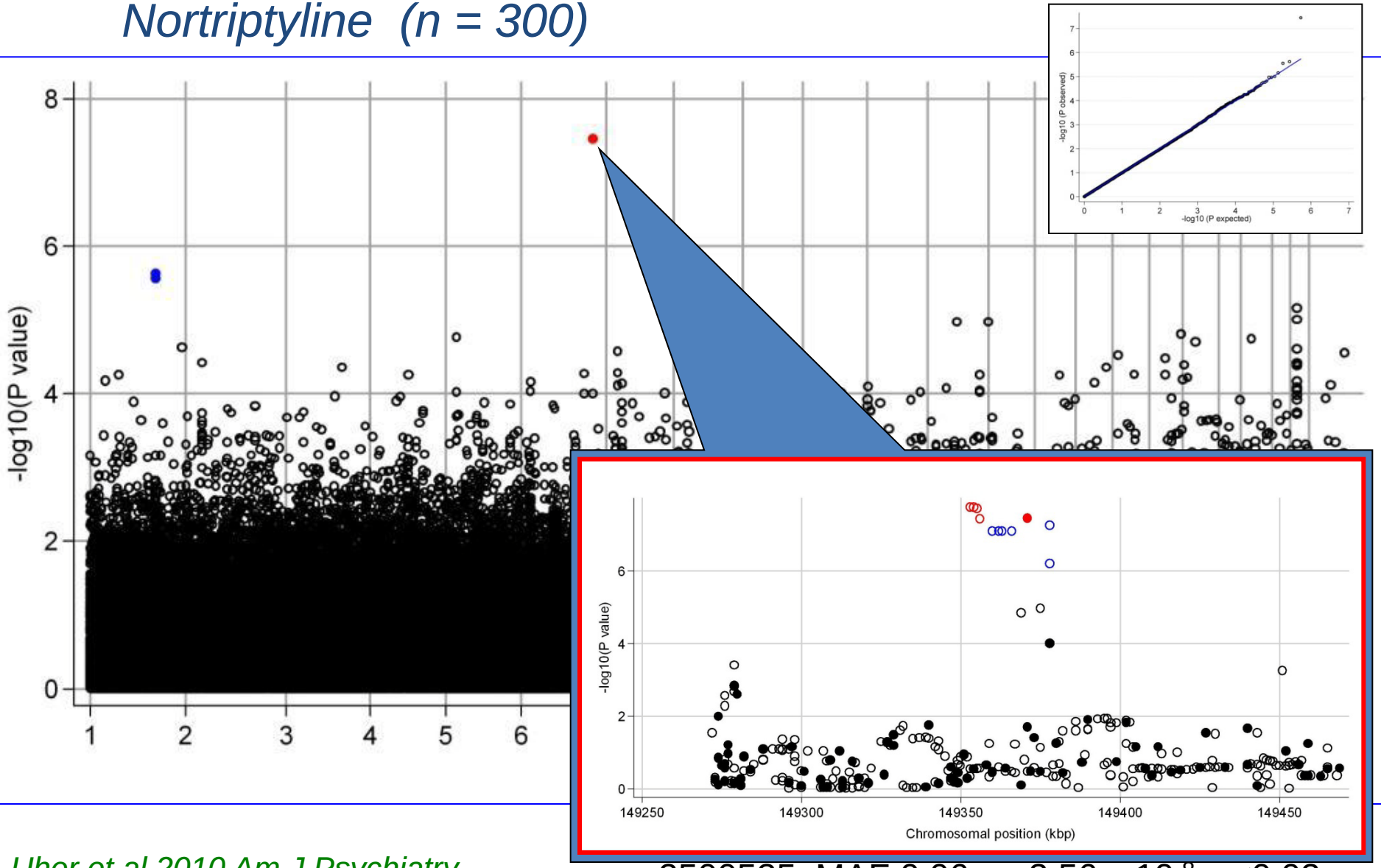
SEARCHING THE GENOME

Genome-wide studies



Genotype & Response to Treatment: Genome-wide (GENDEP)

Nortriptyline (n = 300)



Uher et al 2010 Am J Psychiatry

rs2500535, MAF 0.06, $p=3.56 \times 10^{-8}$, $q<0.02$

GENDEP (n=706)

- Chromosome 1 and 10 regions containing structural variants
- NORTRIPTYLINE: uronyl-sulfotransferase gene
- ESCITALOPRAM: interleukine 11 and 6 genes

Uher et al (2010) American Journal of Psychiatry, 167:555-564.

STAR*D (n=1491)

- CITALOPRAM: ubiquitine-protein ligase gene (*UBE3C)*
- CITALOPRAM: bone morphogenic protein 7 (*BMP7)* gene
- CITALOPRAM: RAR-related orphan receptor alpha gene (*RORA)*

Garriock et al (2010) Biological Psychiatry, 2, 133-138

MARS (n=339)

- Gene score predicted response in an independent sample

Ising et al (2009) Archives of General Psychiatry, 66, 966-975.

How large a sample is needed to detect a clinically significant prediction *?*

Sample size needed to detect an effect at genome-wide significance level ($p<0.00000005$)

		Tagging (R^2)				
		1	0.9	0.8	0.7	0.6
Variance explained	0.063	**606**	**752**	**958**	**1257**	**1718**
	0.032	**1231**	**1525**	**1935**	**2534**	**3456**
	0.021	**1857**	**2297**	**2913**	**3810**	**5193**

Power analyses

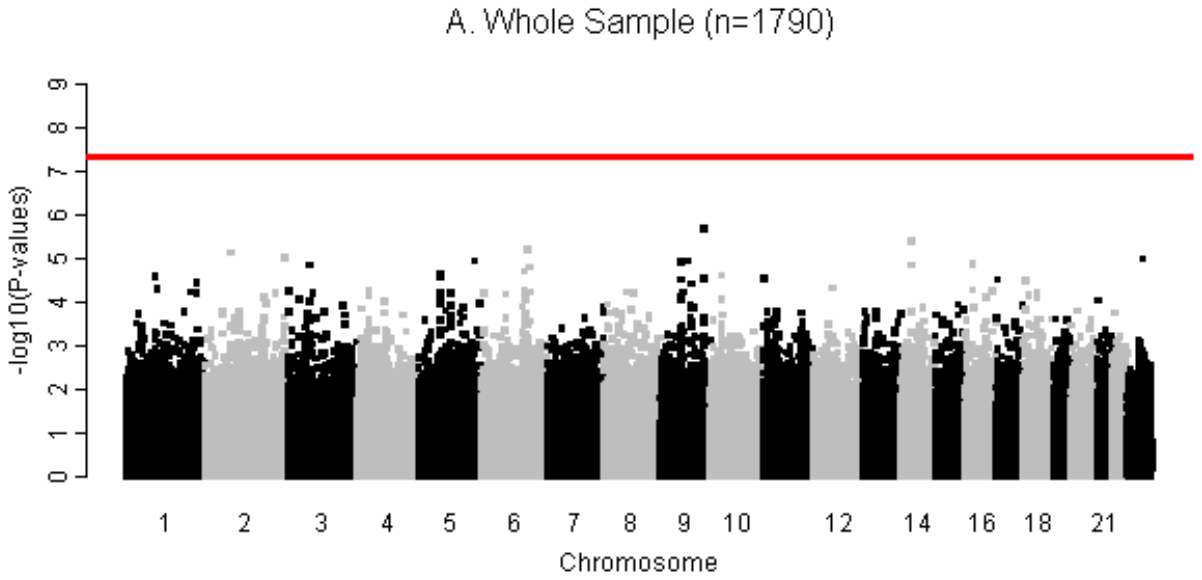
- To detect an effect explaining 6.33% outcome variance at tagging $R^2 = 0.8$ as genome-wide sig. ($p<0.00000005$)

	Sample	Variance explained	
	n	6.33%	3.16%
Any antidepressant	1790	**1.00**	0.73
SRI antidepressant	1222	**0.95**	0.33
NRI antidepressant	568	0.27	0.02
Differential response	949	**1.00**	0.15
SRI meta-analysis	2329	**1.00**	**0.93**

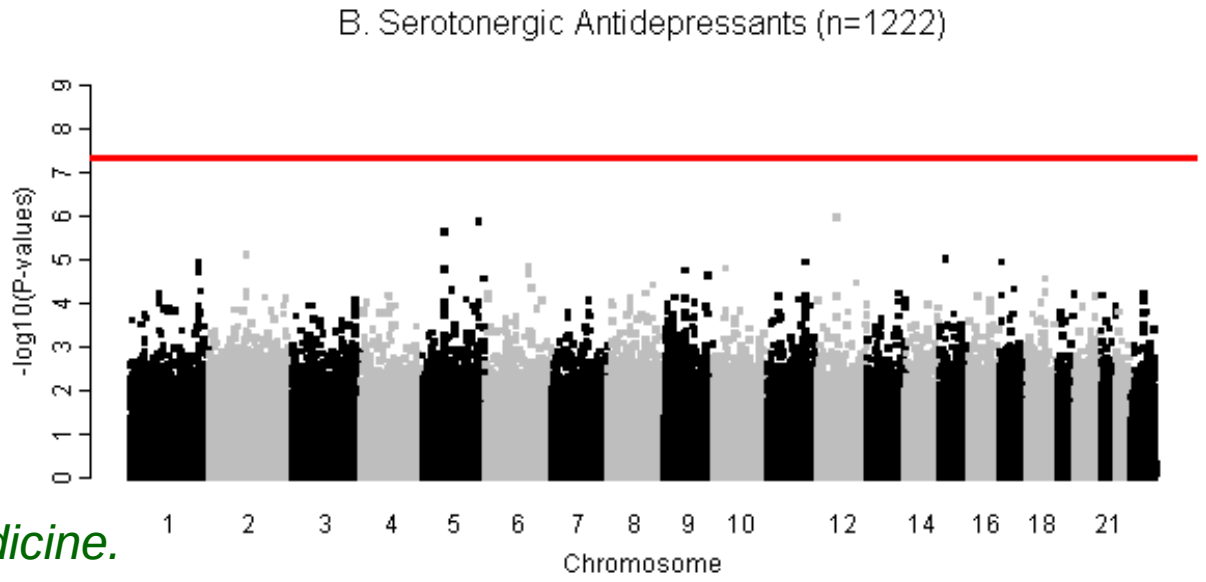
Tansey et al 2013, PLoS Medicine.

Genotype & Treatment Response: Genome-wide (NEWMEDS)

- No significant association in spite of adequate power to detect clinically significant effects.



- No significant association in spite of adequate power to detect clinically significant effects.



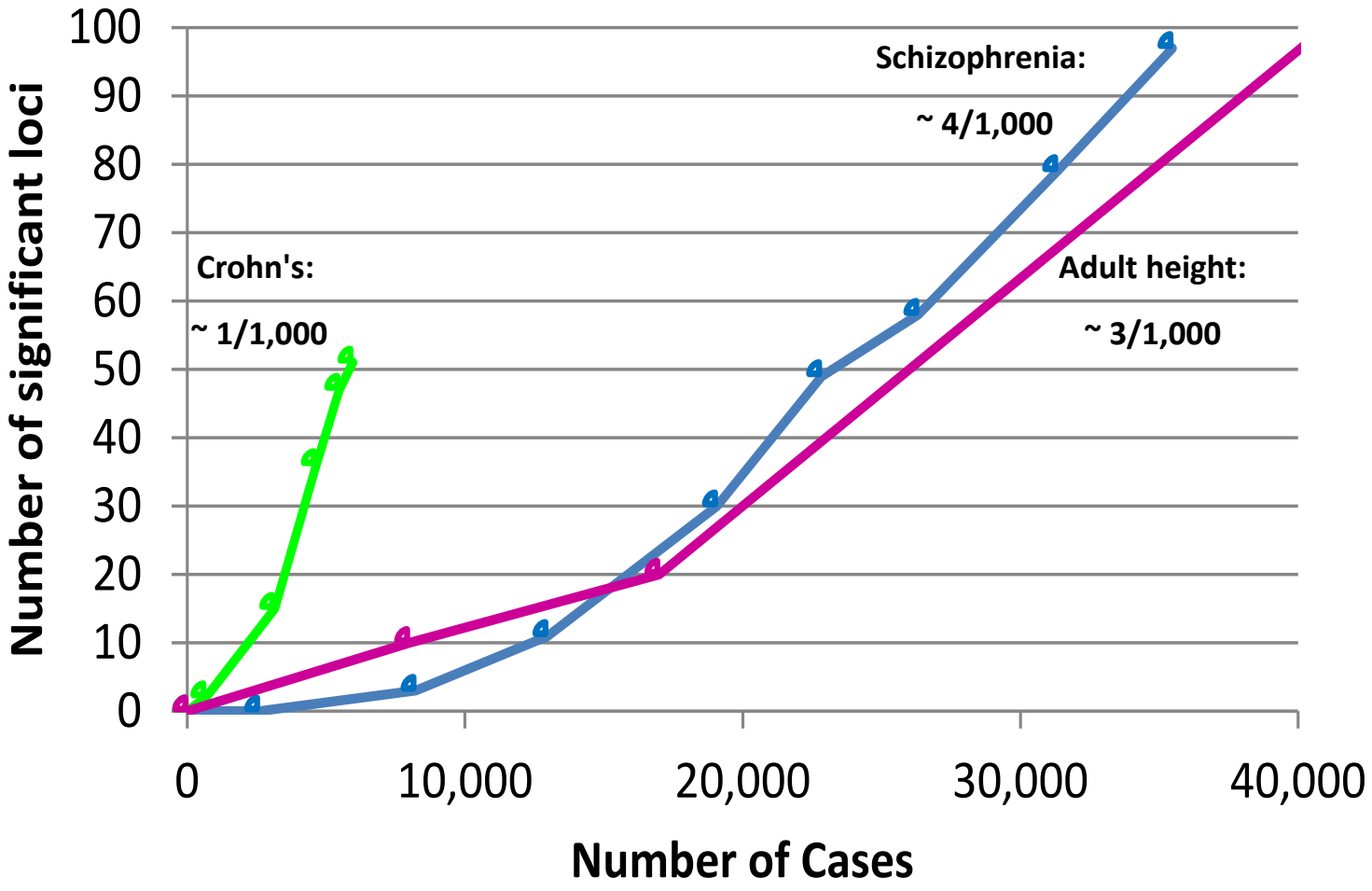
Tansey et al 2013, PLoS Medicine.

WHAT NEXT?

What next in depression pharmaco/therapygenetics?

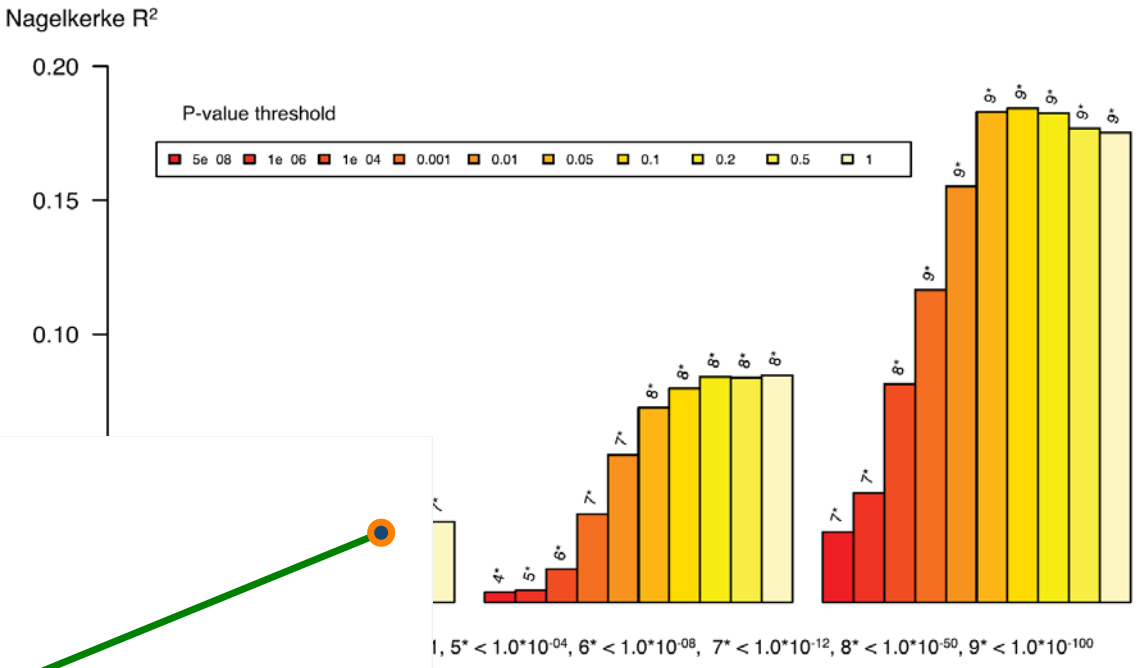
1. Larger samples
2. Combining predictors
3. Other treatments
4. Other phenotypes

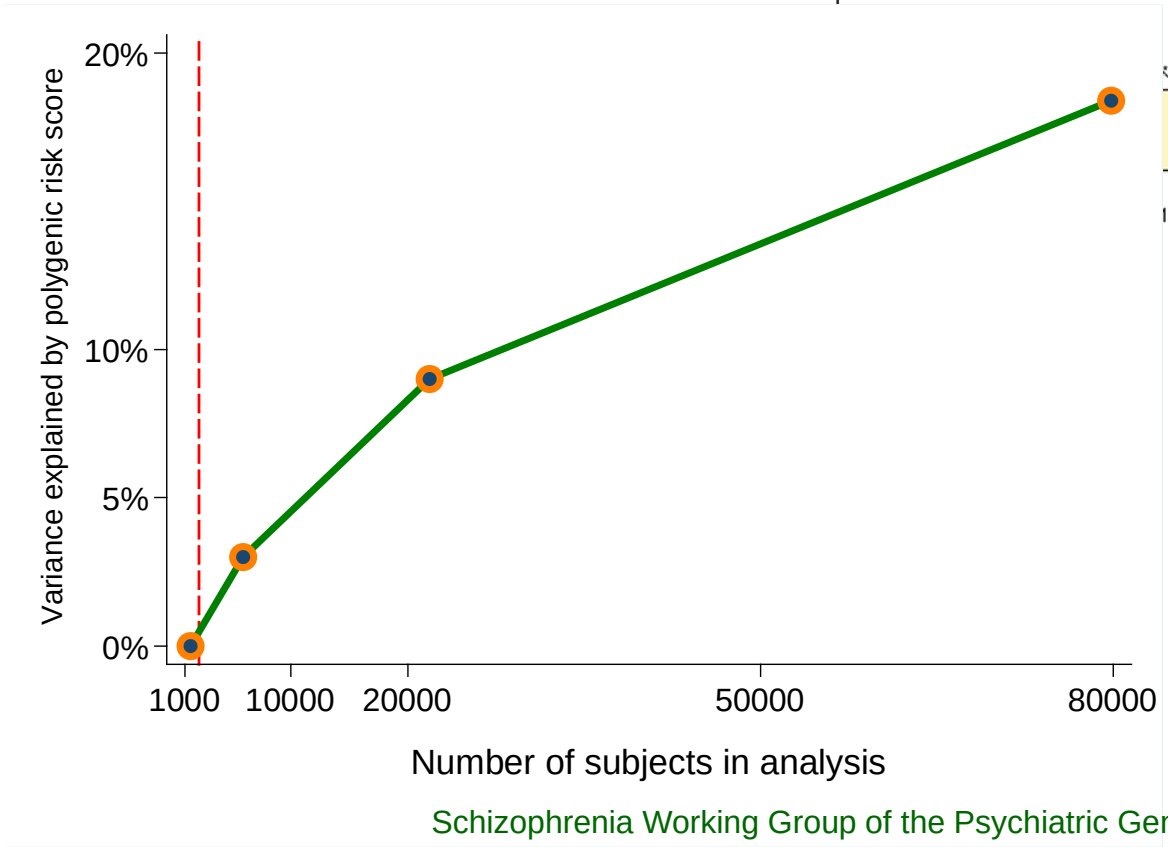
Directions: Larger samples greater power



Levinson et al Biological Psychiatry 2014 76, 510-512DOI: (10.1016/j.biopsych.2014.07.029)
Copyright © 2014 Society of Biological Psychiatry.

Schizophrenia GWAS





Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Nature, 511: 421-427.

Proportion of variance in antidepressant response explained by common genetic variation ?

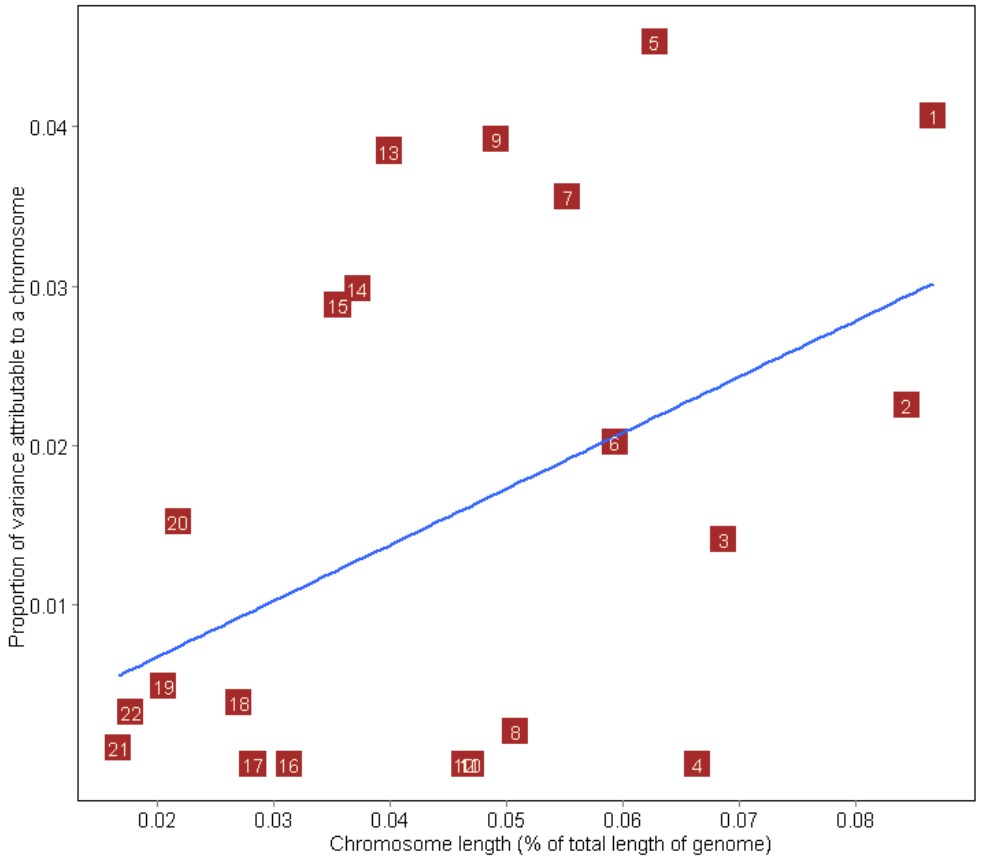
n = 1790 (NEWMEDS) + 1009 (STAR*D) **= 2799**

Genome-wide Complex Trait Analysis (GCTA)

$h^2_{SNP} =$

42%

(SE = 0.18, p = 0.009)



Tansey et al 2013 Biological Psychiatry 73: 679-682.

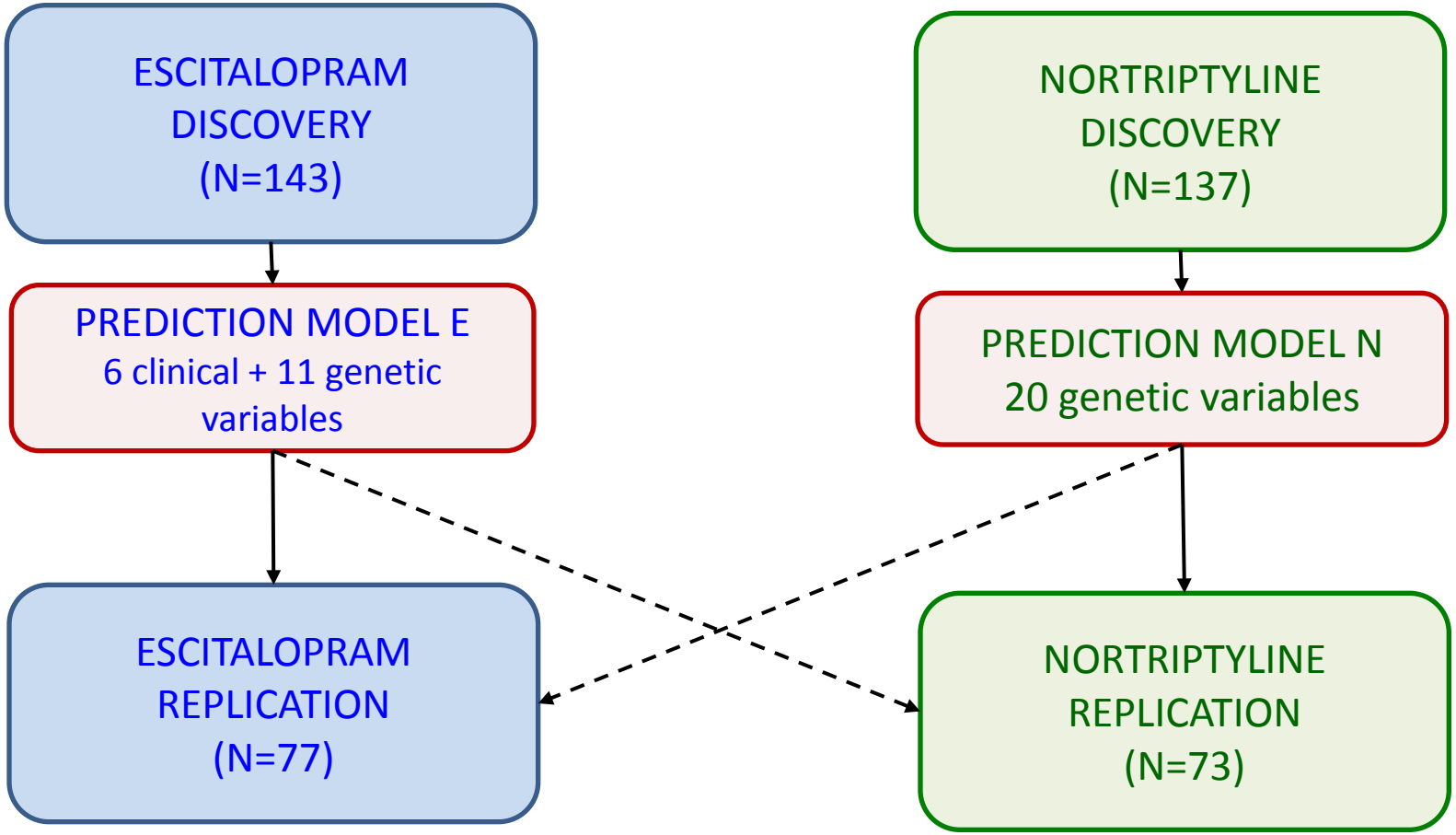
COMBINING PREDICTORS

Combining clinical and genetic predictors

- 430 adults with depression who were randomly allocated to escitalopram (n=220) or nortriptyline (n=210) and received 4-12 weeks of treatment
- 139 clinical and demographic predictors (severity, symptom dimensions, life events, …) + 524,871 common genetic variants (single nucleotide polymorhisms)
- Non-overlapping discovery (n=280) and replication (150) samples
- Correlation-adjusted T-scores (CAT) variable selection in discovery sample
- Elastic net logistic models to predict remission (MADRS≤ 10)

Iniesta et al 2016, under review

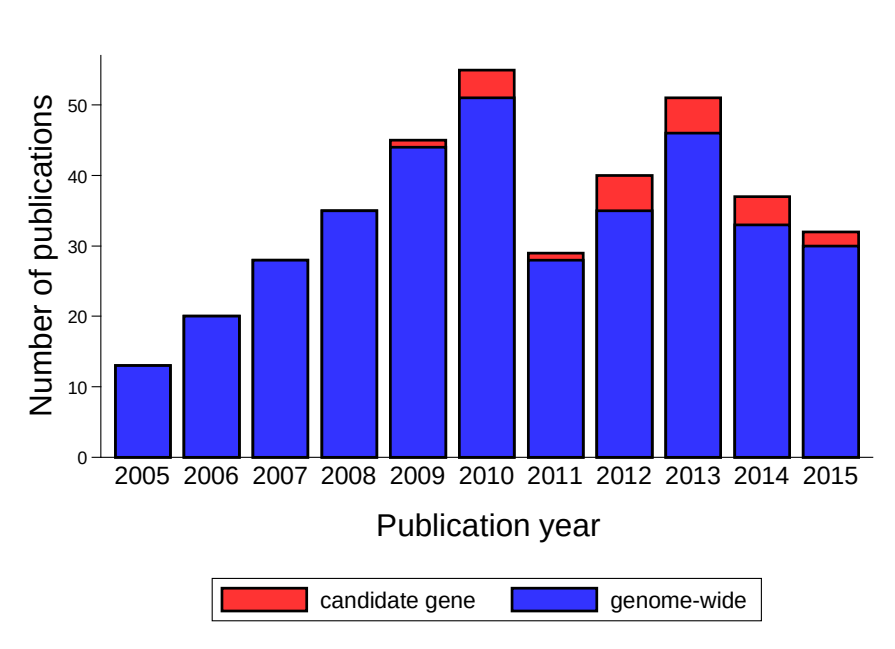
Combining clinical and genetic predictors



Iniesta et al 2016, under review

OTHER TREATMENTS

A decade of pharmaco/therapy-genetics



Published genetic studies

treatment	number of studies
SSRI	233
SNRI	44
TCA	7
MAOI	0
mirtazapine	20
bupropione	1
agomelatine	1
CBT	0

COMBINING PREDICTORS

Which treatments ?

- Mono- amine oxidase inhibitors
- Lithium augmentation
- Repetitive transcranial magnetic stimulation
- PharmacoRx post ECT
- Psychotherapy

Overview

- Genetic test has potential for uptake
- Presently no meaningful genetic treatment selection
- Directions:
- Much larger samples (10,000^{+} per treatment) needed
- Combination of clinical + genetic variables may efficiently predict