LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN
CAMPUS GROSSHADERN
INSTITUTE FOR STROKE AND DEMENTIA RESEARCH

1000 Genomes imputation update

Rainer Malik

For the ISGC analysis group

ISGC Workshop, Salt Lake City,, 2014

Funded by:
Solorz-Zak Research Foundation

Overview

- Studies included - update
- Analysis strategy
- Results - update
- Trans-ethnic meta-analysis
- European replication

First…..

New vice-chair will be elected soon

Discovery phase is finished

(data still confidential)

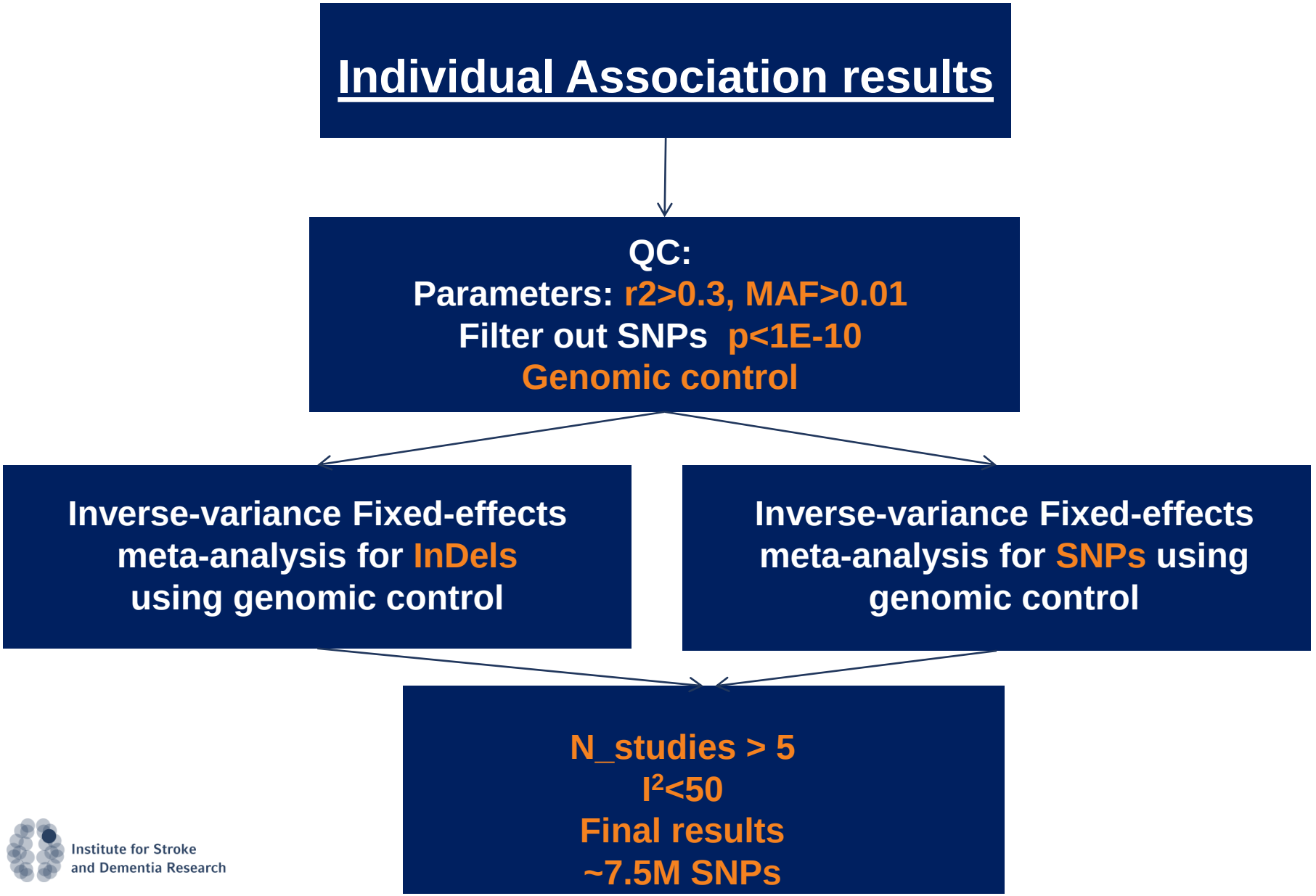
Studies included

Study	N cases (IS)	N controls	TOAST
ASGC	1,162	1,244	Y
BRAINS	371	2,640	Y
GASROS_affy	485	3,030	Y
GASROS_illumina	296	377	Y
GEOS	448	498	Y
HPS	588	571	N
ISGS-SWISS	1,014	1,370	Y
MILANO	366	407	Y
VISP	1,723	1,047	N
WHI	306	2,170	Y
WTCCC2-D	1,174	797	Y
WTCCC2-UK	2,374	5,175	Y
TOTAL	**10,307**	**19,326**	

Subtype information

Study	N cases (LAS)	N_cases (CE)	N_cases (SVD)	N controls
ASGC	421	240	310	1,244
BRAINS	40	78	29	2,640
GASROS_affy	102	198	59	3030
GASROS_illu	68	106	24	377
GEOS	37	90	54	498
ISGS-SWISS	217	235	187	1,370
MILANO	73	64	25	407
WHI	31	42	81	2,170
WTCCC2-D	330	346	106	797
WTCCC2-UK	498	460	474	5,175
TOTAL	**1,817**	**1,859**	**1,349**	**17,708**

Analysis strategy



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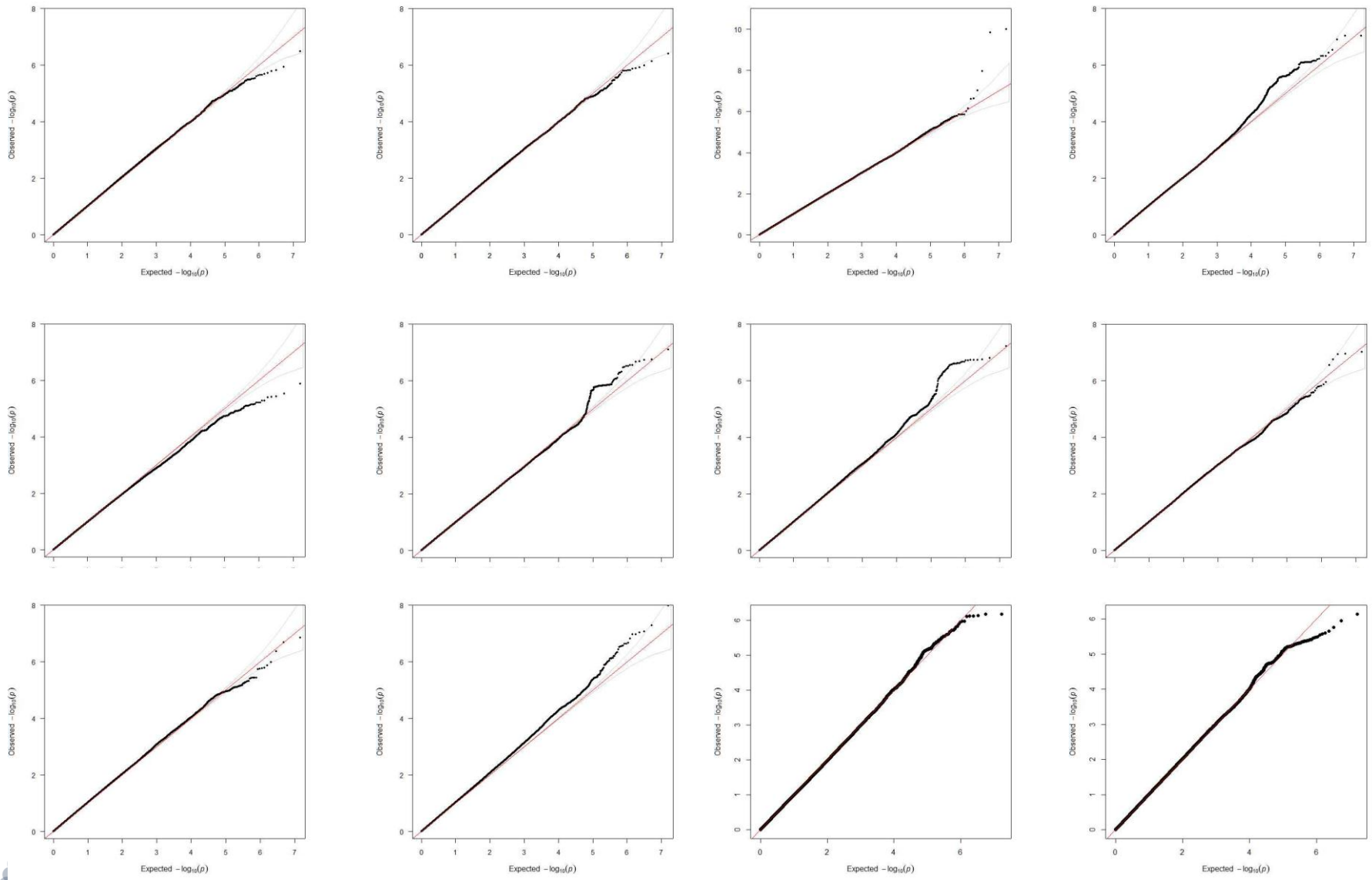
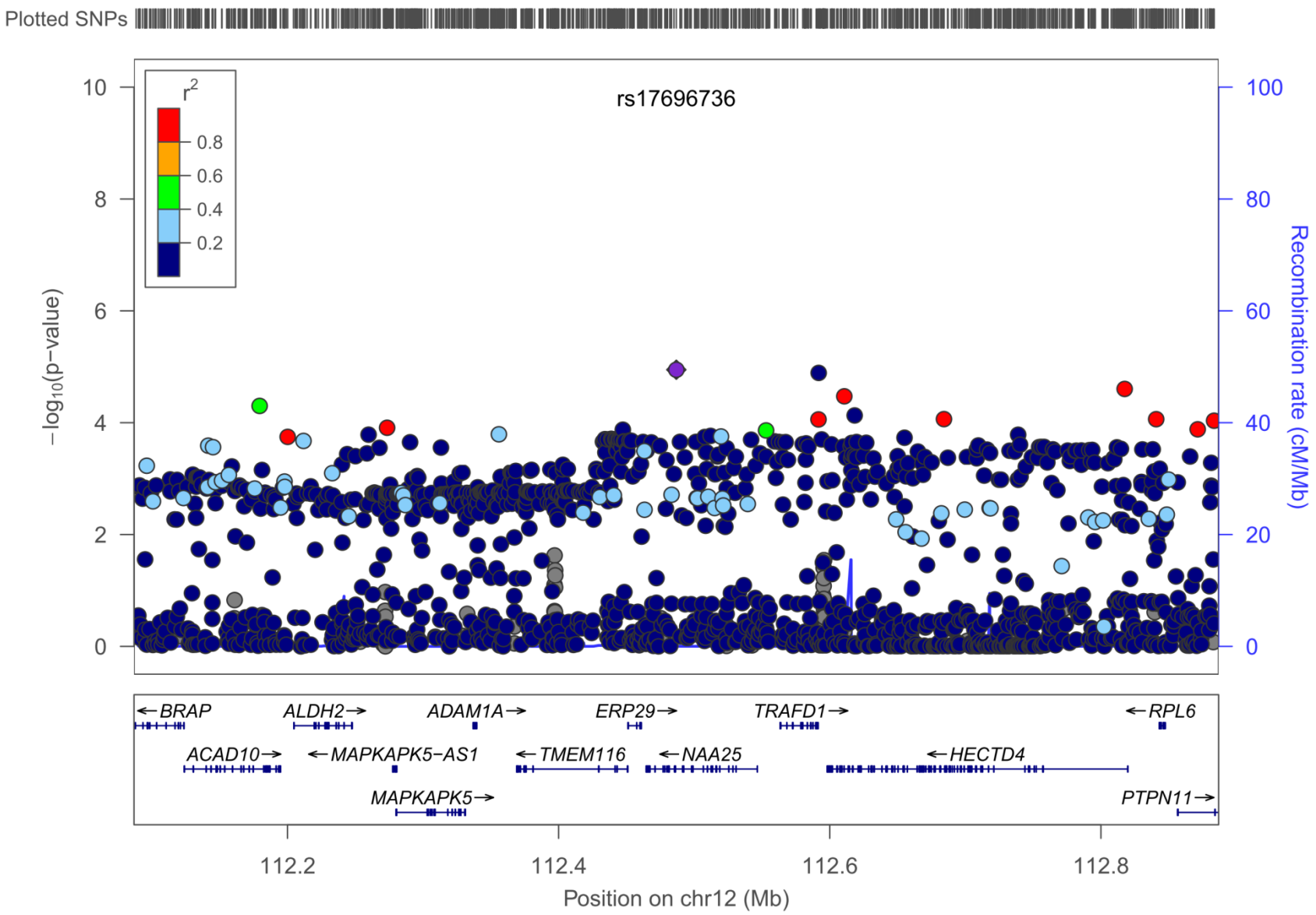
QC results – individual studies (IS)



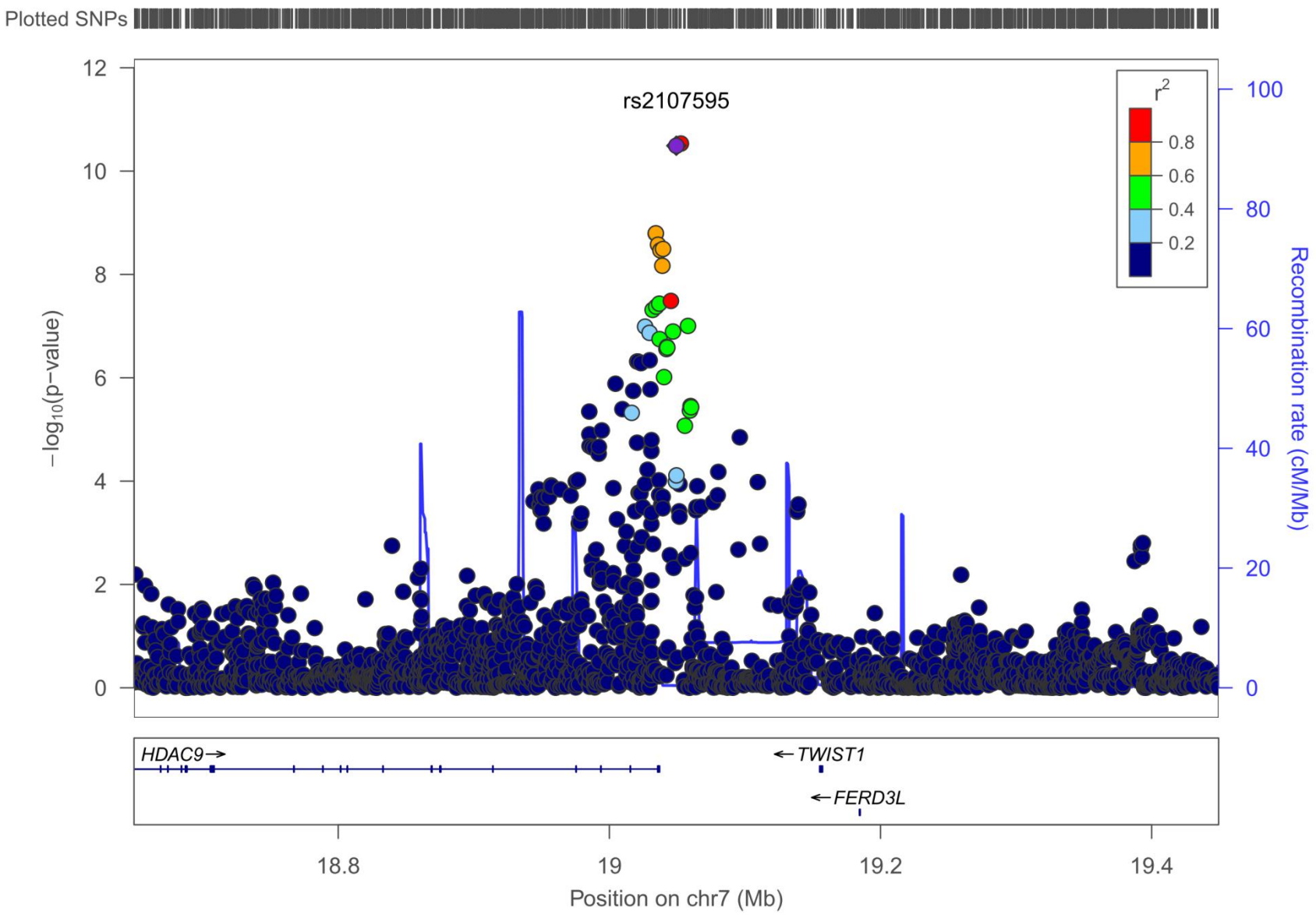
Known loci – IS (chr12), p=1.13E-5, MAF=0.45, OR=1.09 [1.05-1.13]



and Dementia Research

Previous lead SNP in known locius is shown as purple diamond

HDAC9 – LAS, p=2.99E-11, MAF=0.16, OR=1.39 [1.26-1.53]



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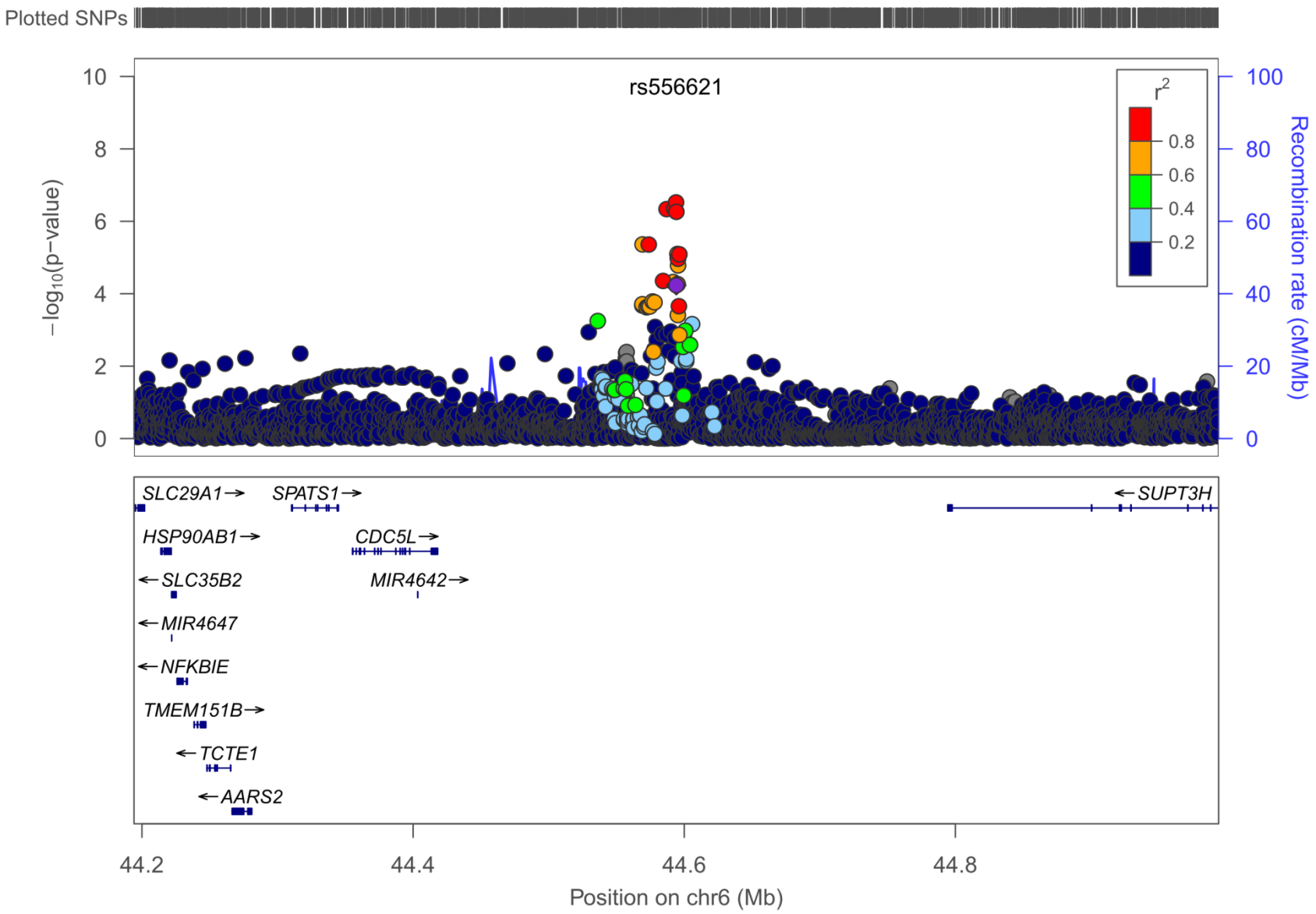
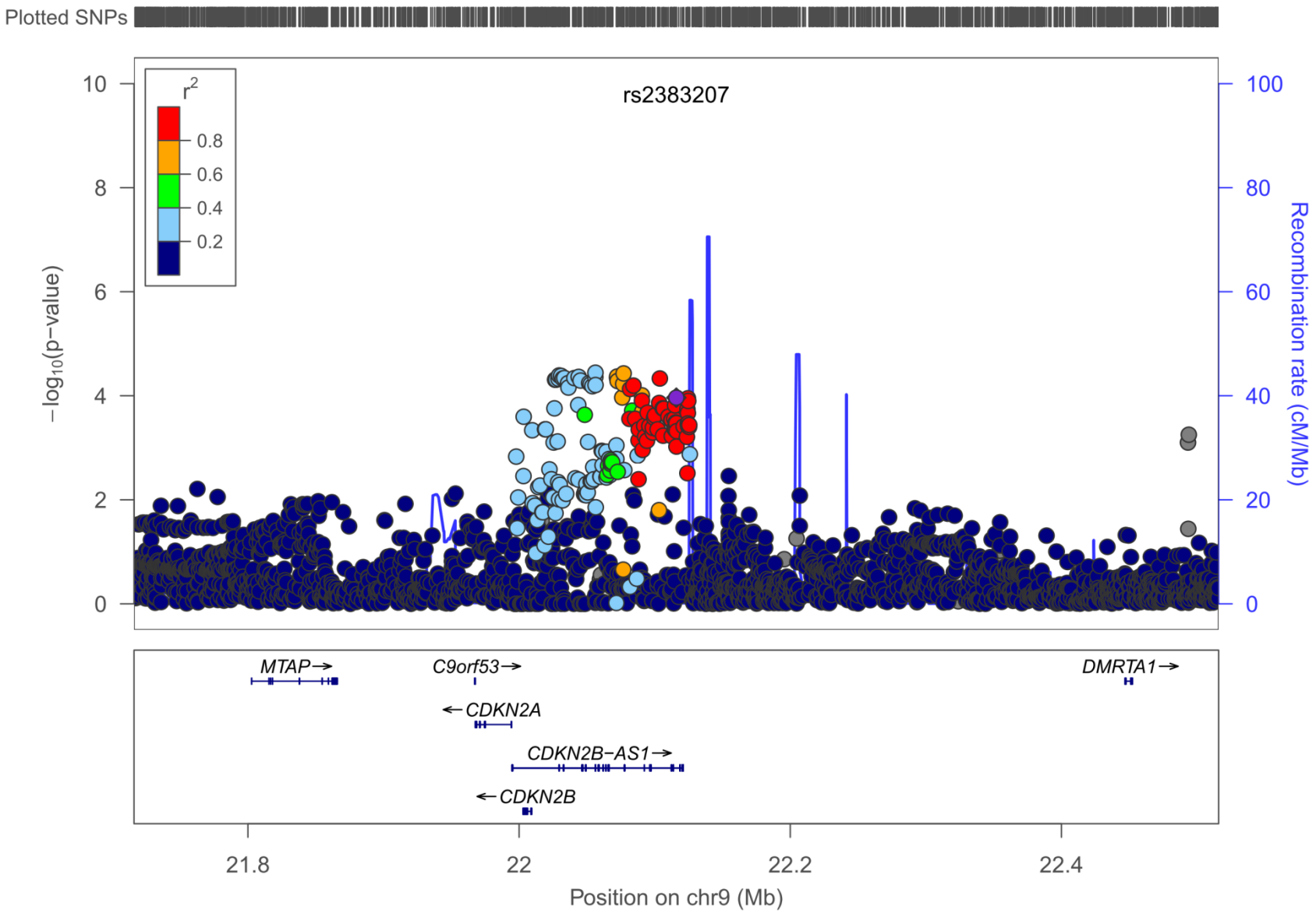
Chr6p21 – LAS, p=3.00E-7, MAF=0.33, OR=1.23 [1.14-1.33]



9p21 – LAS, p=3.6E-5, MAF=0.45, OR=0.85 [0.78-0.92]



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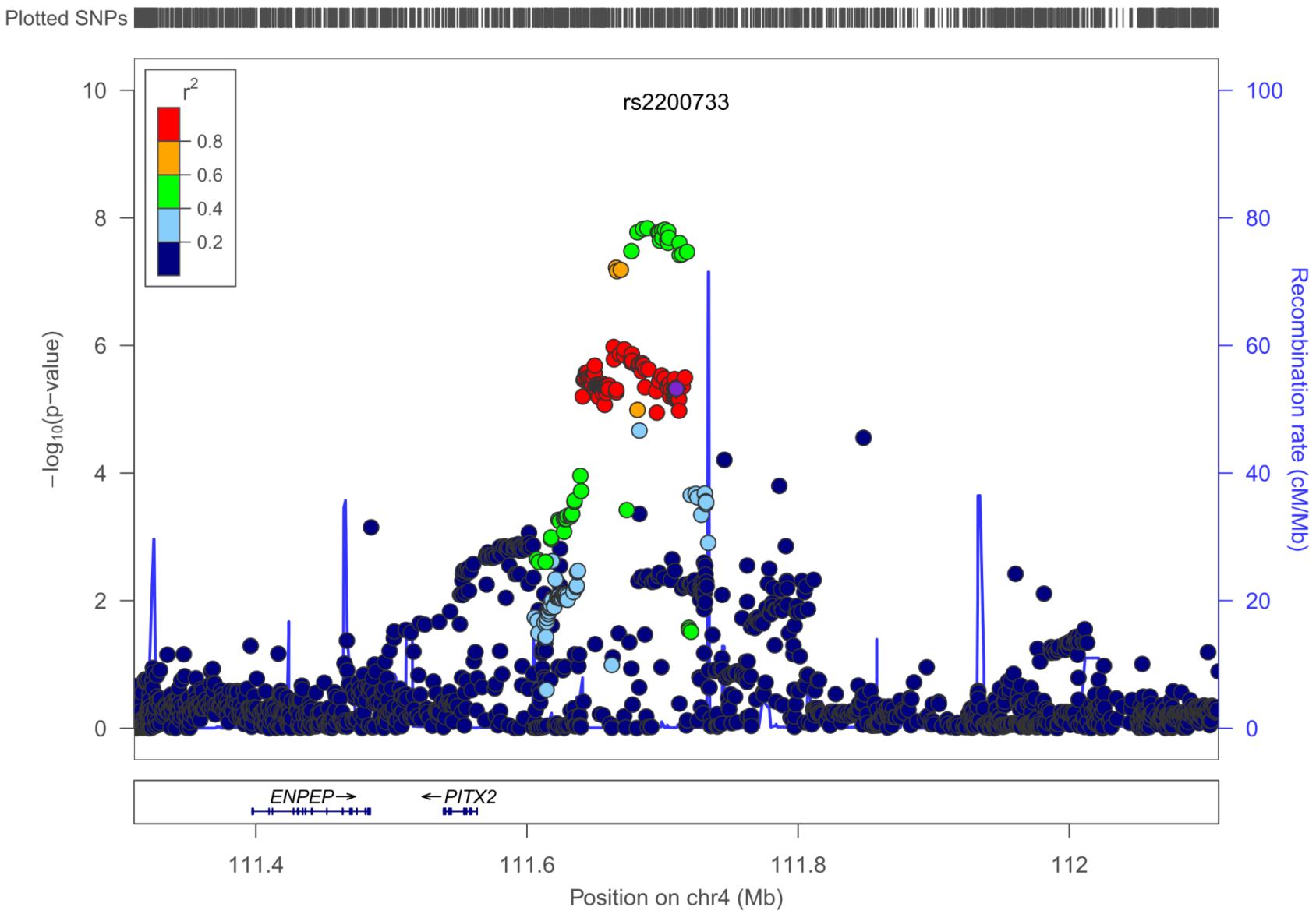
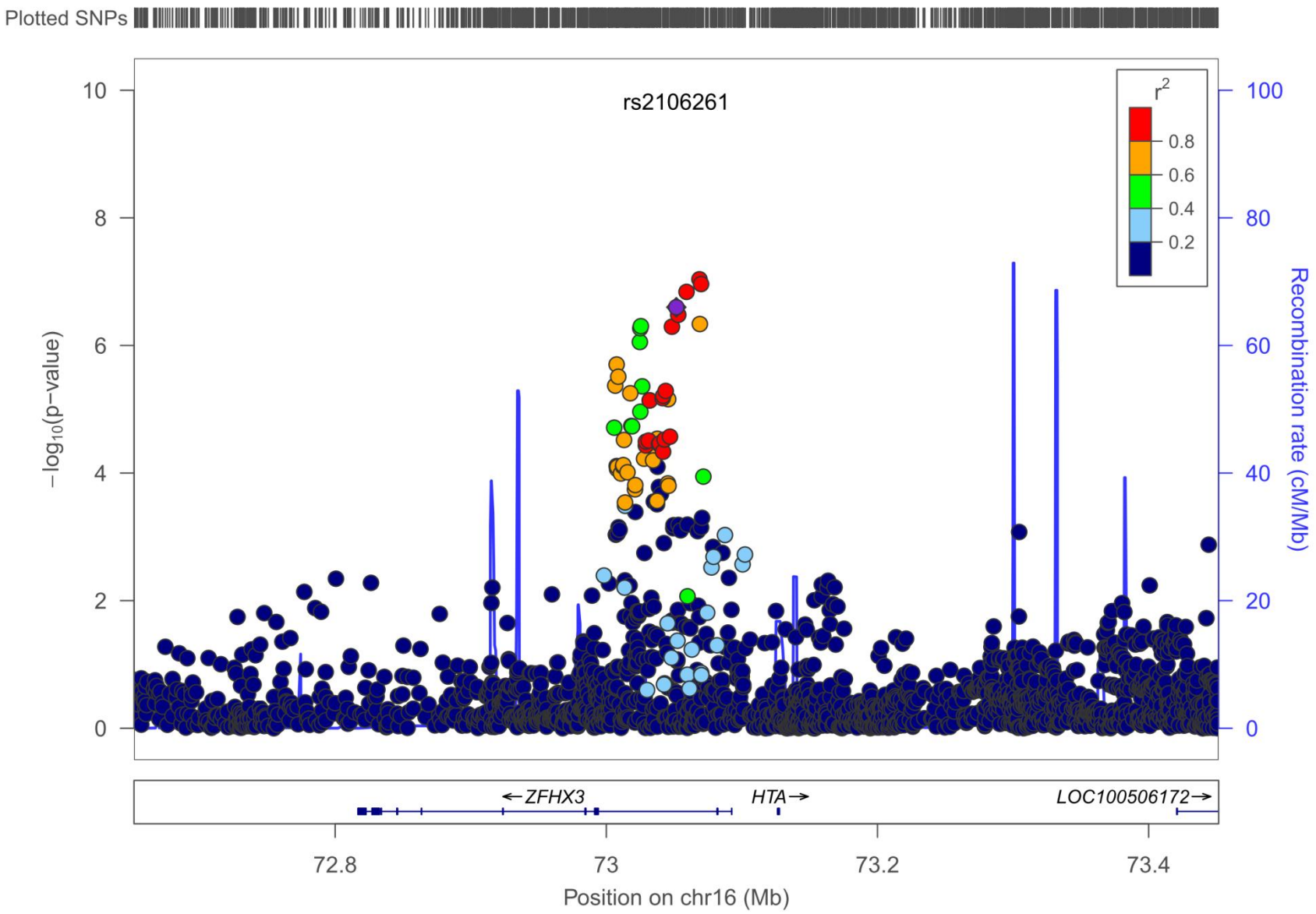
PITX2 – CE, p=1.61E-8, MAF=0.21, OR=1.30 [1.18-1.42]



and Dementia Research

Previous lead SNP in known loci is shown as purple diamond

ZFHX3 – CE, p=1.27E-7, MAF=0.17, OR=1.29 [1.18-1.42]



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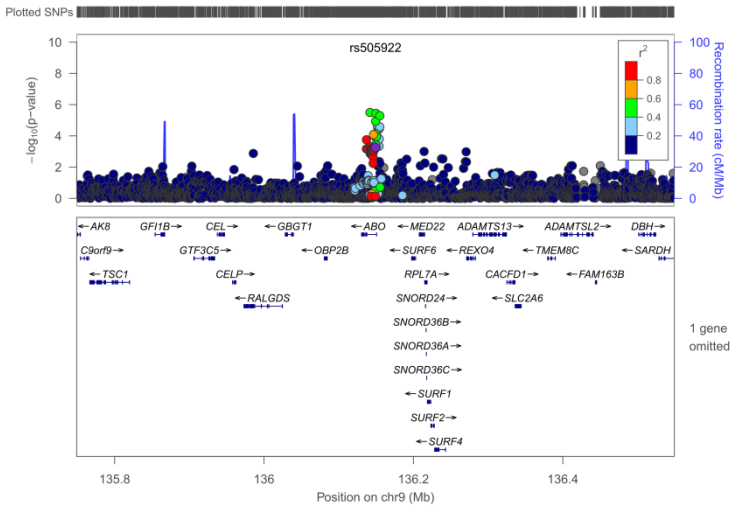
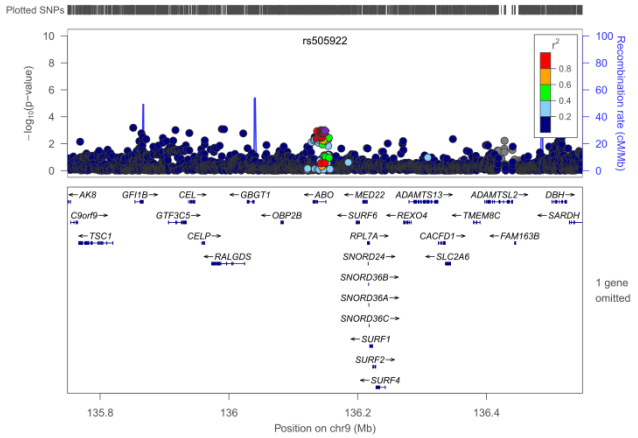
ABO – IS/LAS/CE, p=3.15E-6 / 6.26E-4 / 3.14E-6

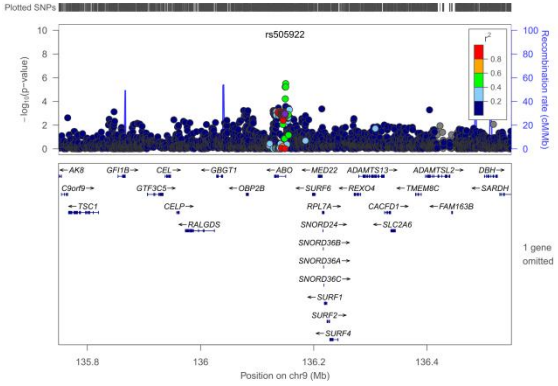
IS



LAS



CE



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New loci

Replicating all findings with a p-value < 5E-6 with support of multiple SNPs (peak)

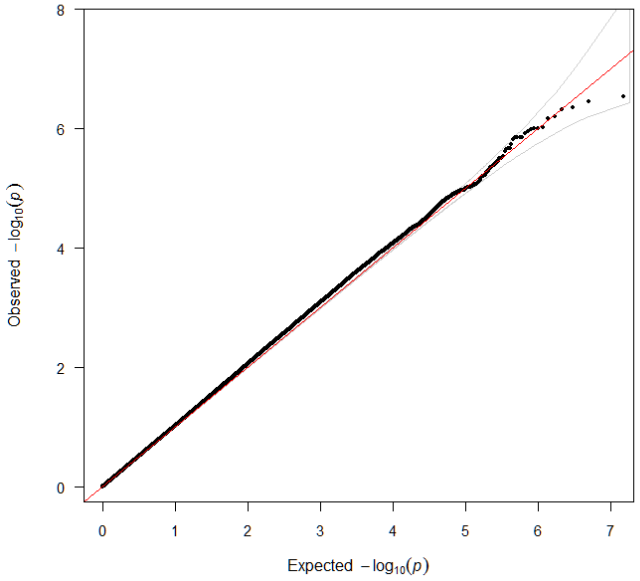
Loci with support of >2 SNPs, sometimes singleton was added

Mean imputation accuracy > 0.8

Low heterogeneity (I^2<50%)

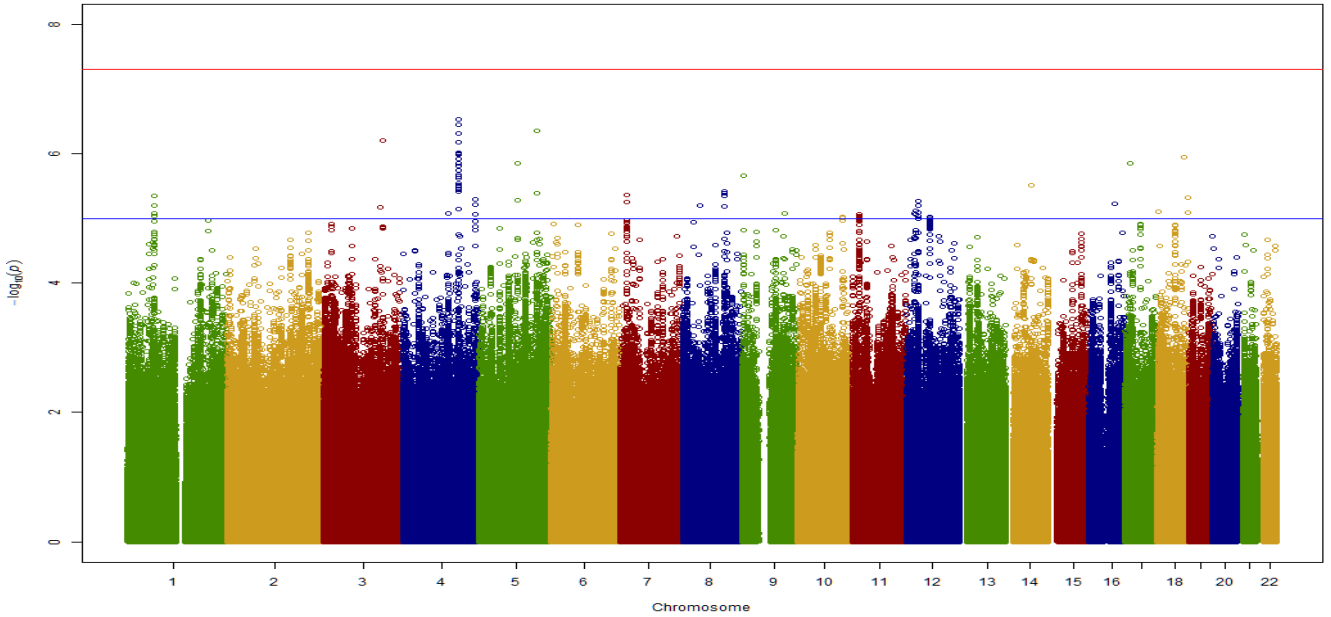
Present in >60% of studies

IS



Filtered data!

λ(GC_filtered)=1.003
λ(GC_unfiltered)=1.002



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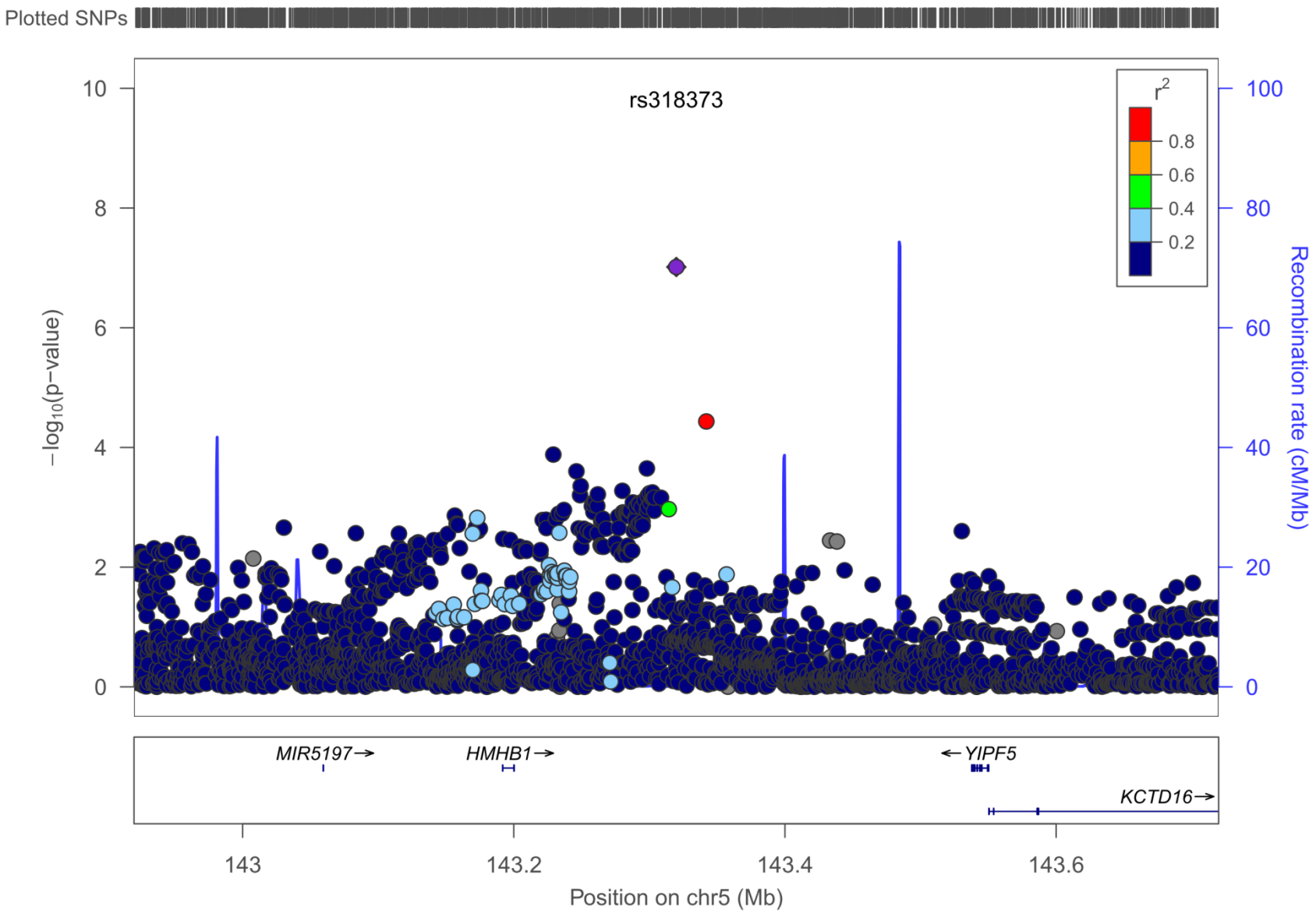
Note: λ1000 is used

HMHB1-YIPF5, p=9.67E-8, MAF=0.49, OR=1.11 [1.07-1.16]



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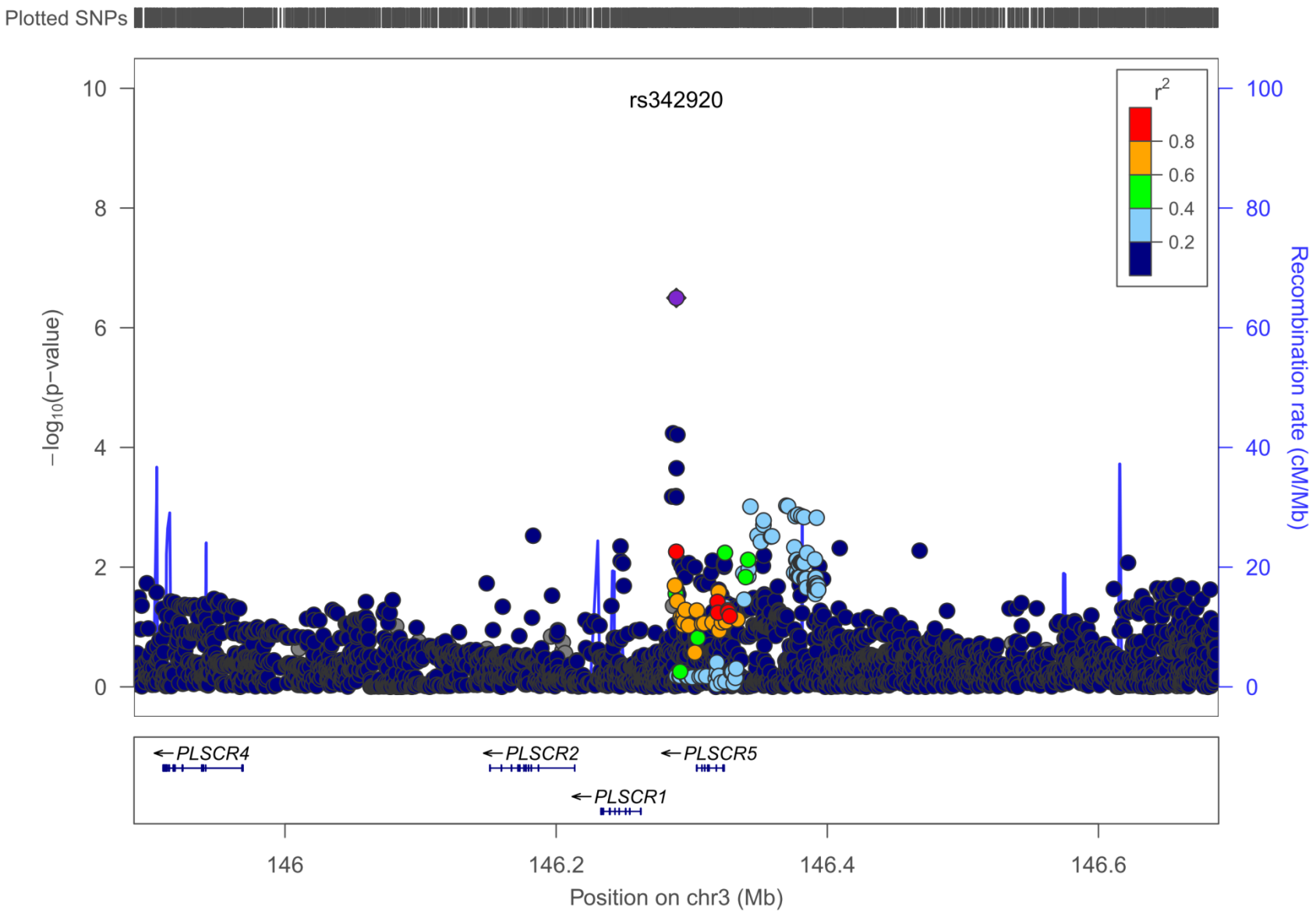
PLSCR5, p=3.18E-7, MAF=0.38, OR=1.11 [1.07-1.15]



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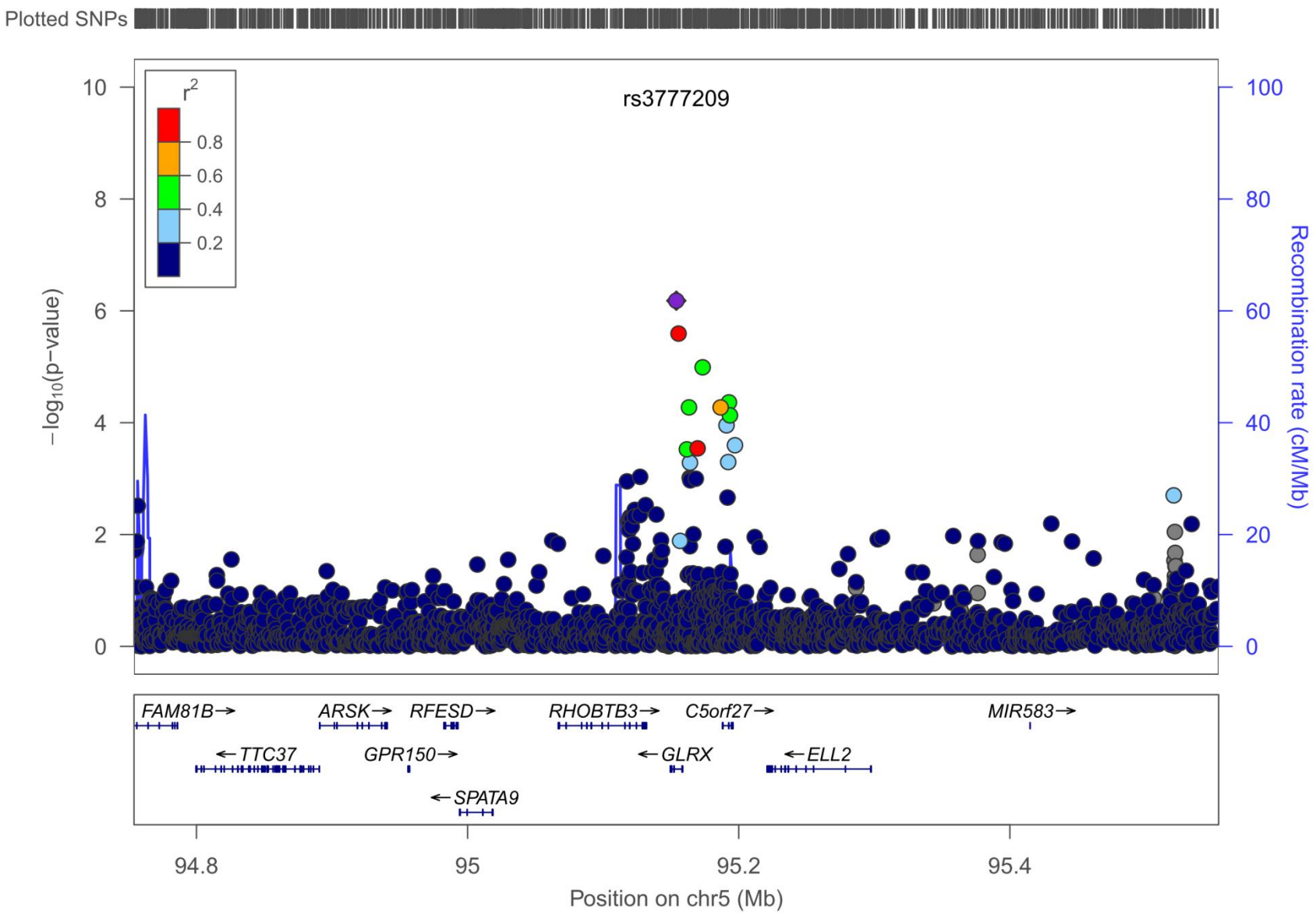
GLRX, p=6.59E-7, MAF=0.06, OR=1.23 [1.14-1.34]



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Lead SNP in promoter region

Arteriosclerosis, Thrombosis, and Vascular Biology

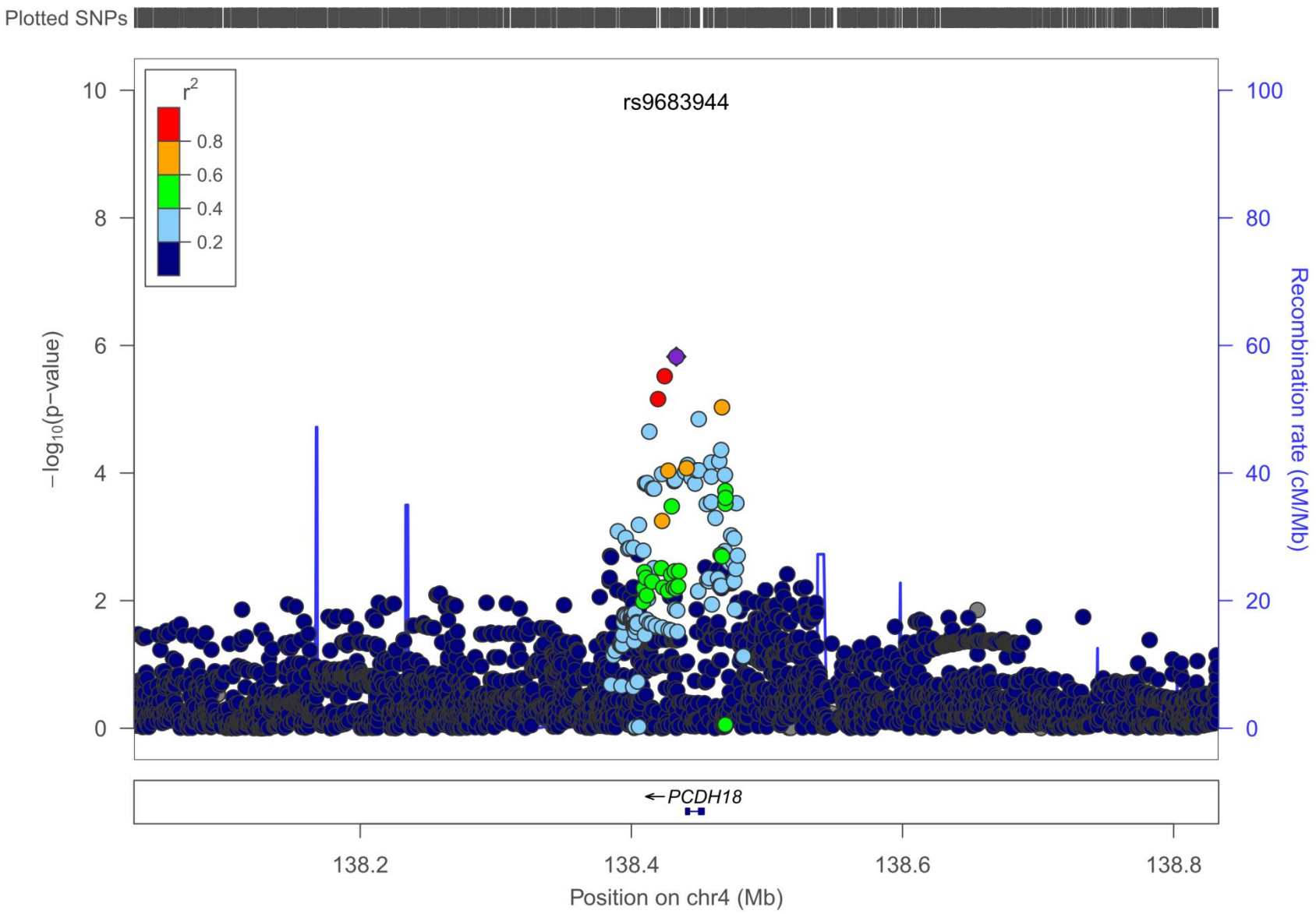
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

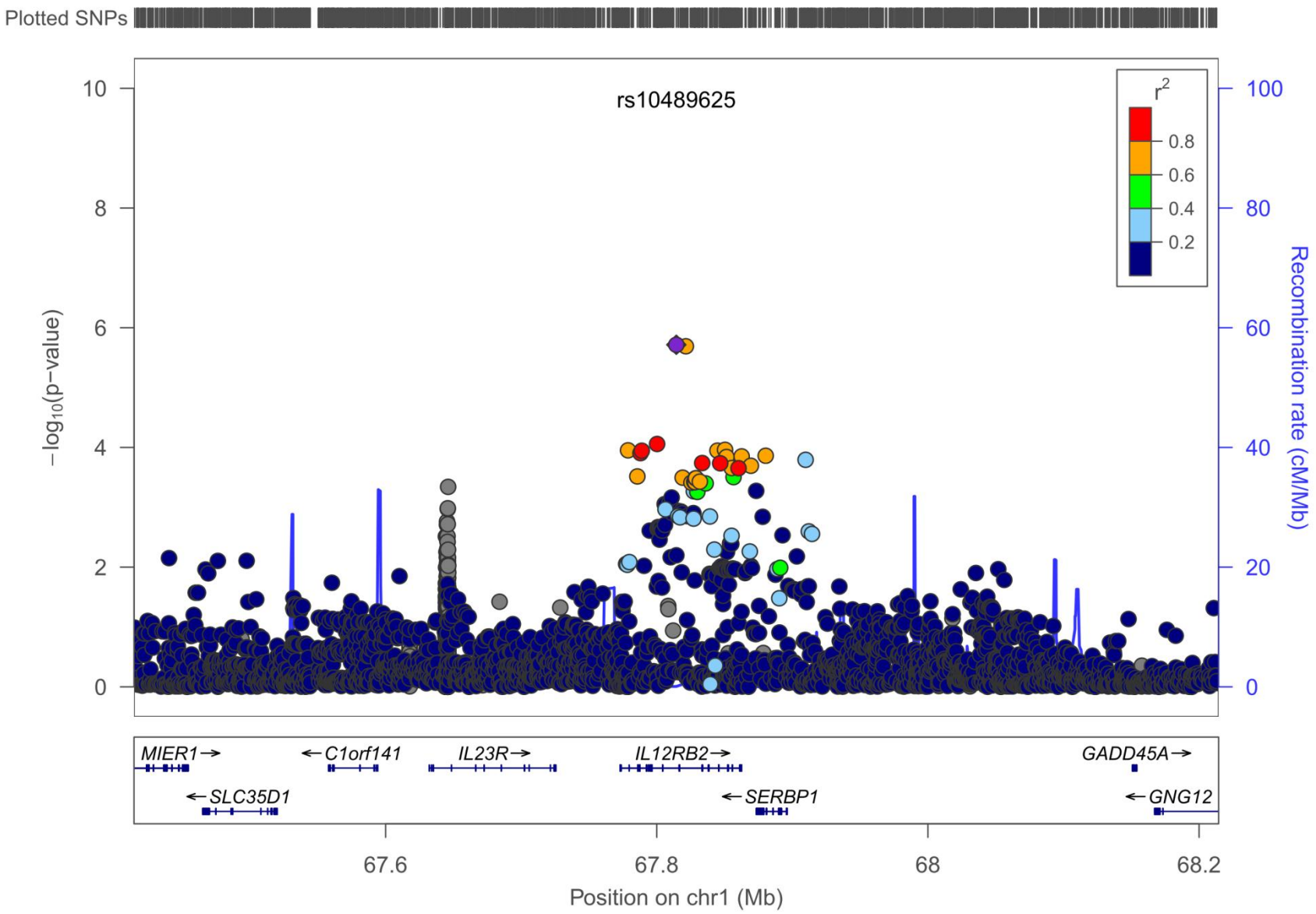
Glutaredoxin Mediates Akt and eNOS Activation by Flow in a Glutathione Reductase-Dependent Manner

Jing Wang, Shi Pan and Bradford C. Berk

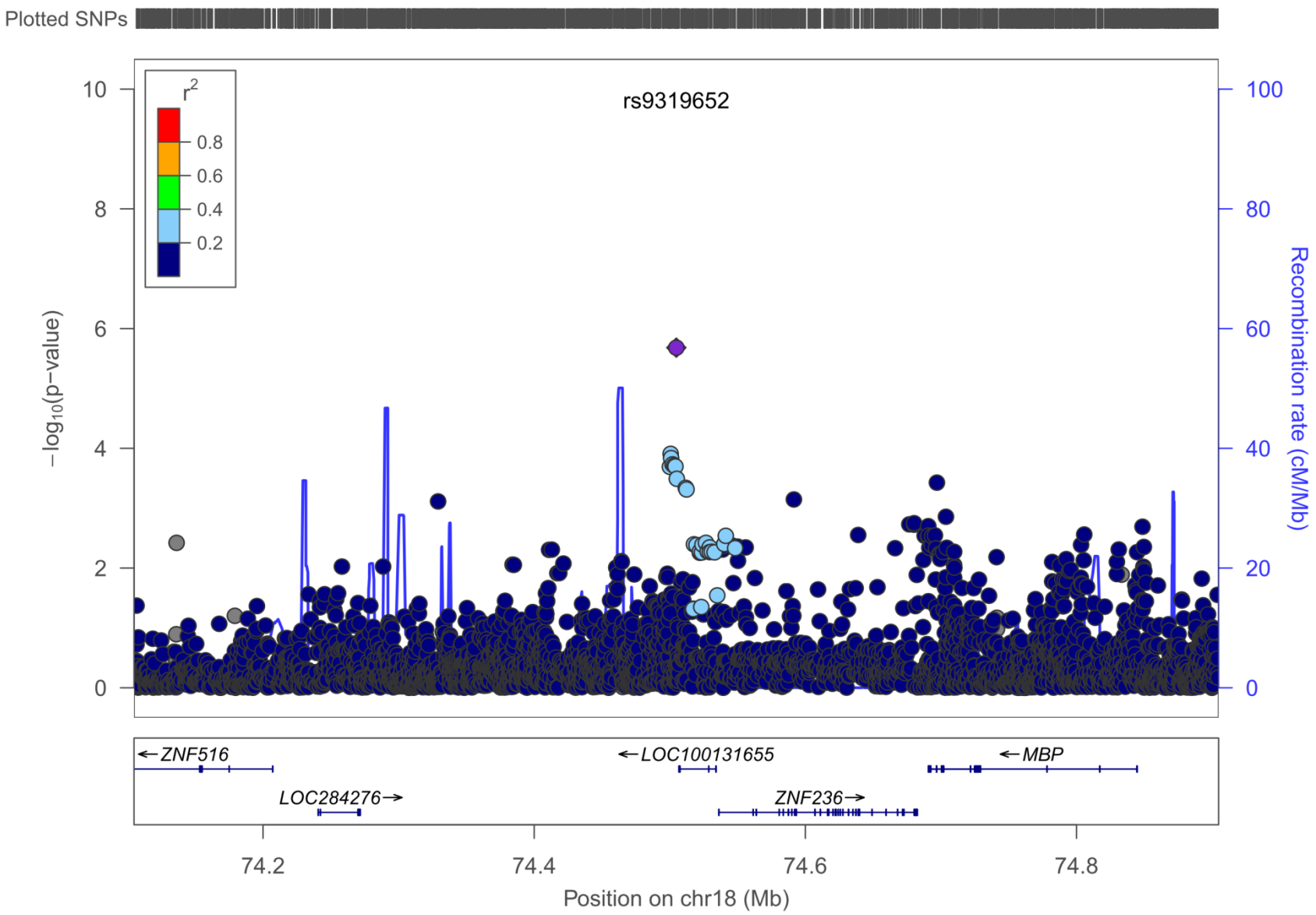
PCDH18, p=1.5E-6, MAF=0.21, OR=1.13 [1.08-1.19]



IL12RB2, p=1.93E-6, MAF=0.05, OR=0.80 [0.73-0.88]



ZNF236, p=2.08E-6, MAF=0.23, OR=0.87 [0.82-0.92]



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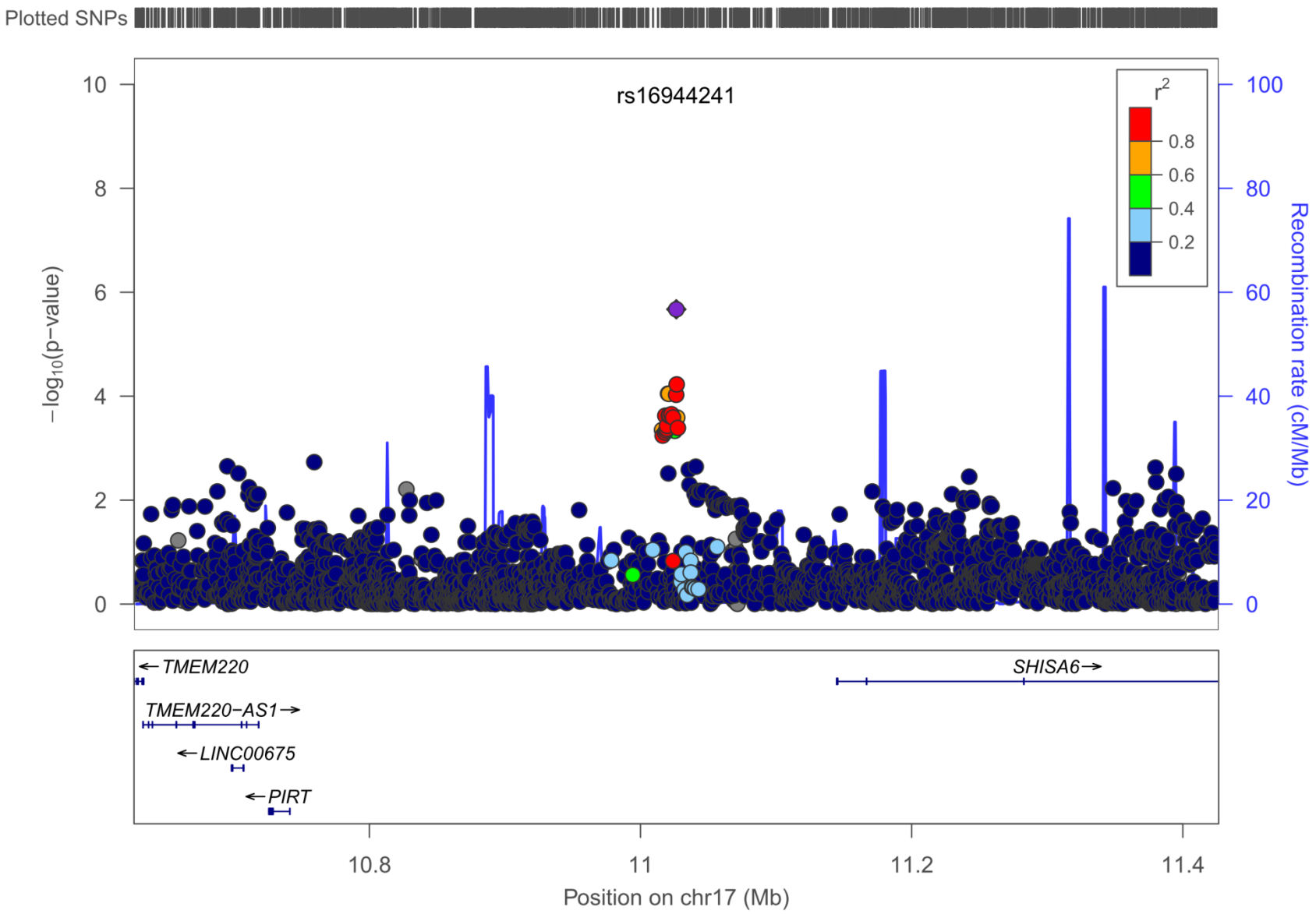
SHISA6, p=2.13E-6, MAF=0.02, OR=1.40 [1.22-1.62]



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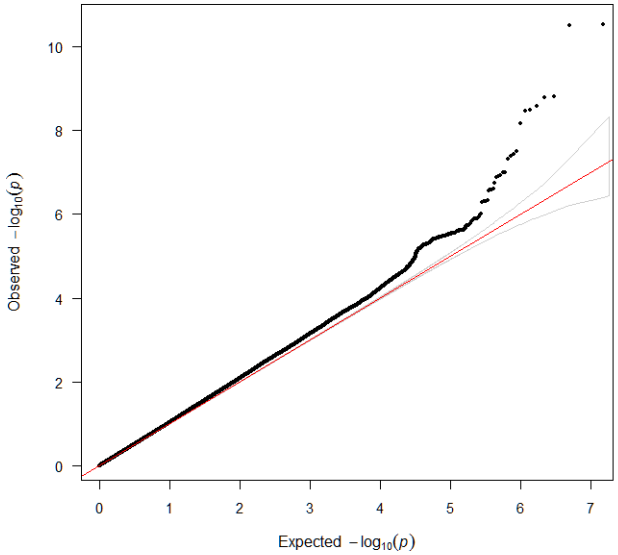
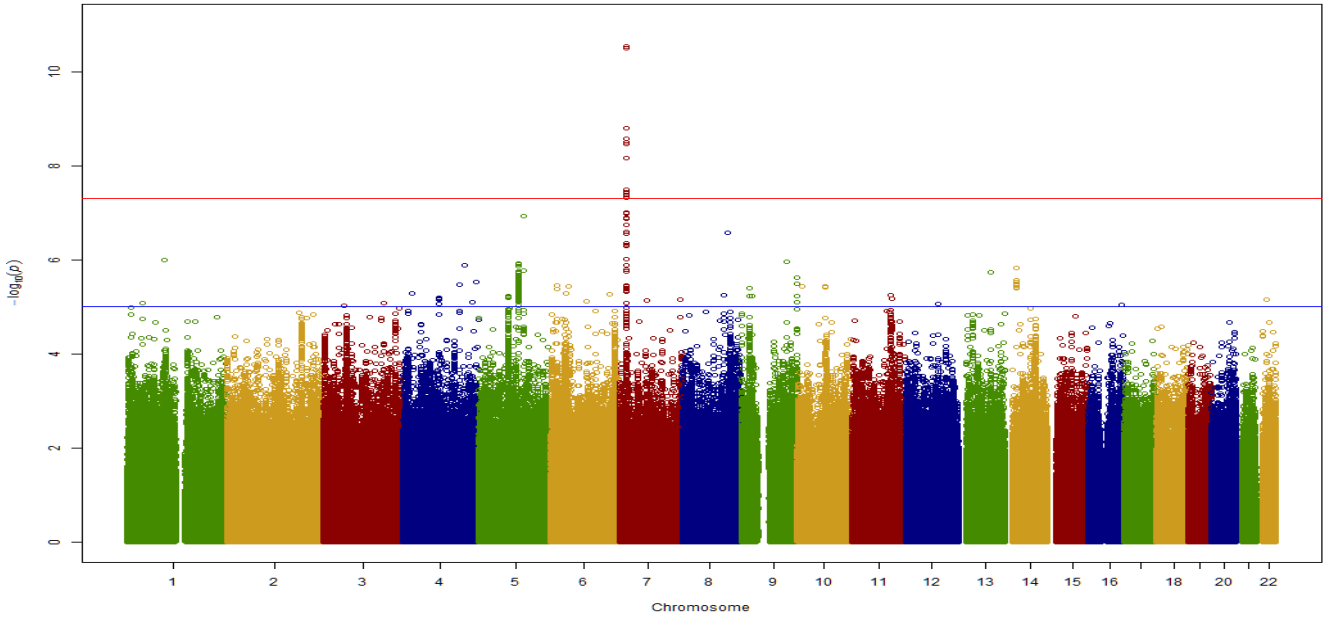
LAS



Filtered data!

λ(GC_filtered)=1.015
λ(GC_unfiltered)=1.012



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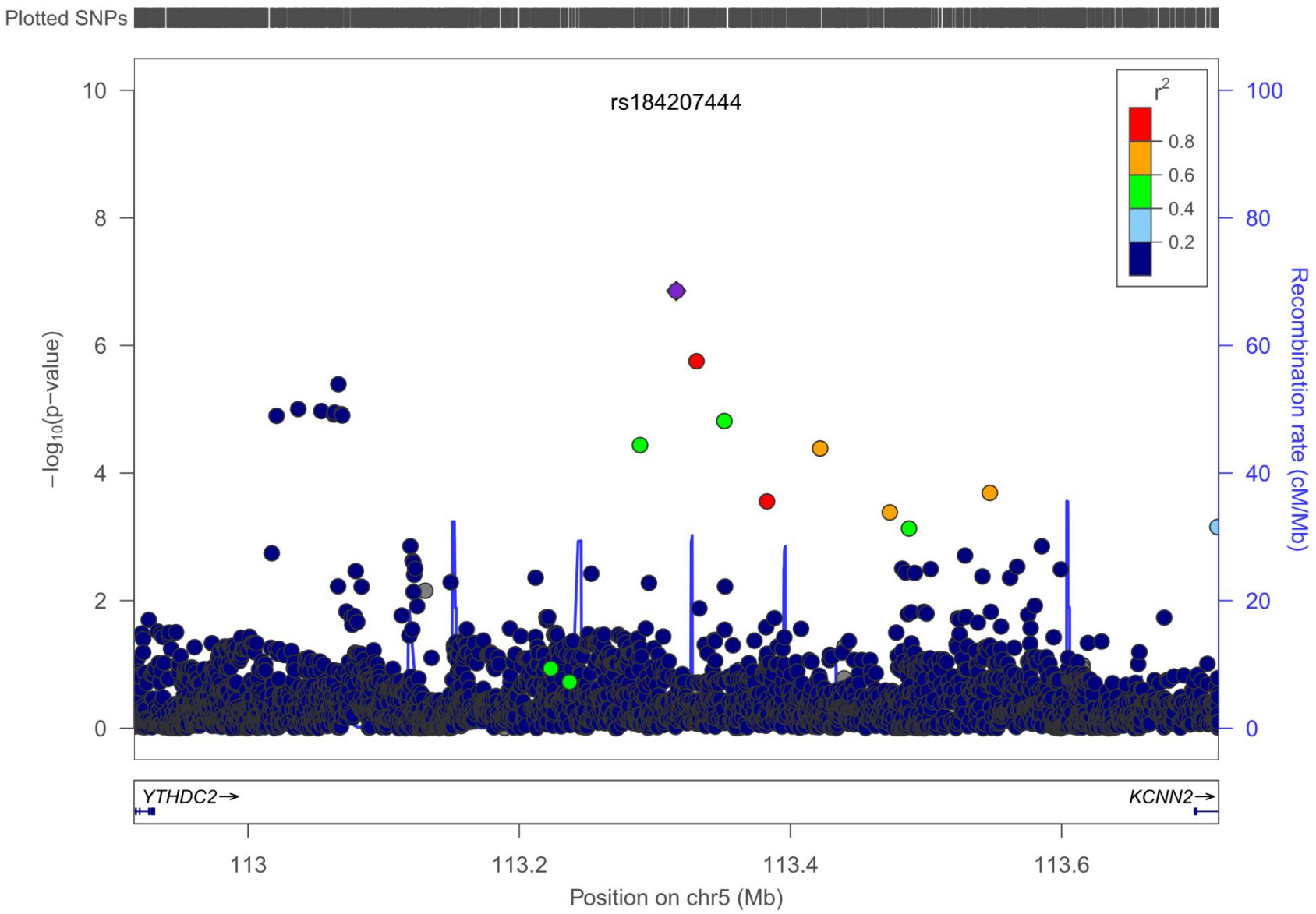
Note: λ1000 is used

KCNN2, p=1.4E-7, MAF=0.21, OR=1.13 [1.08-1.19]



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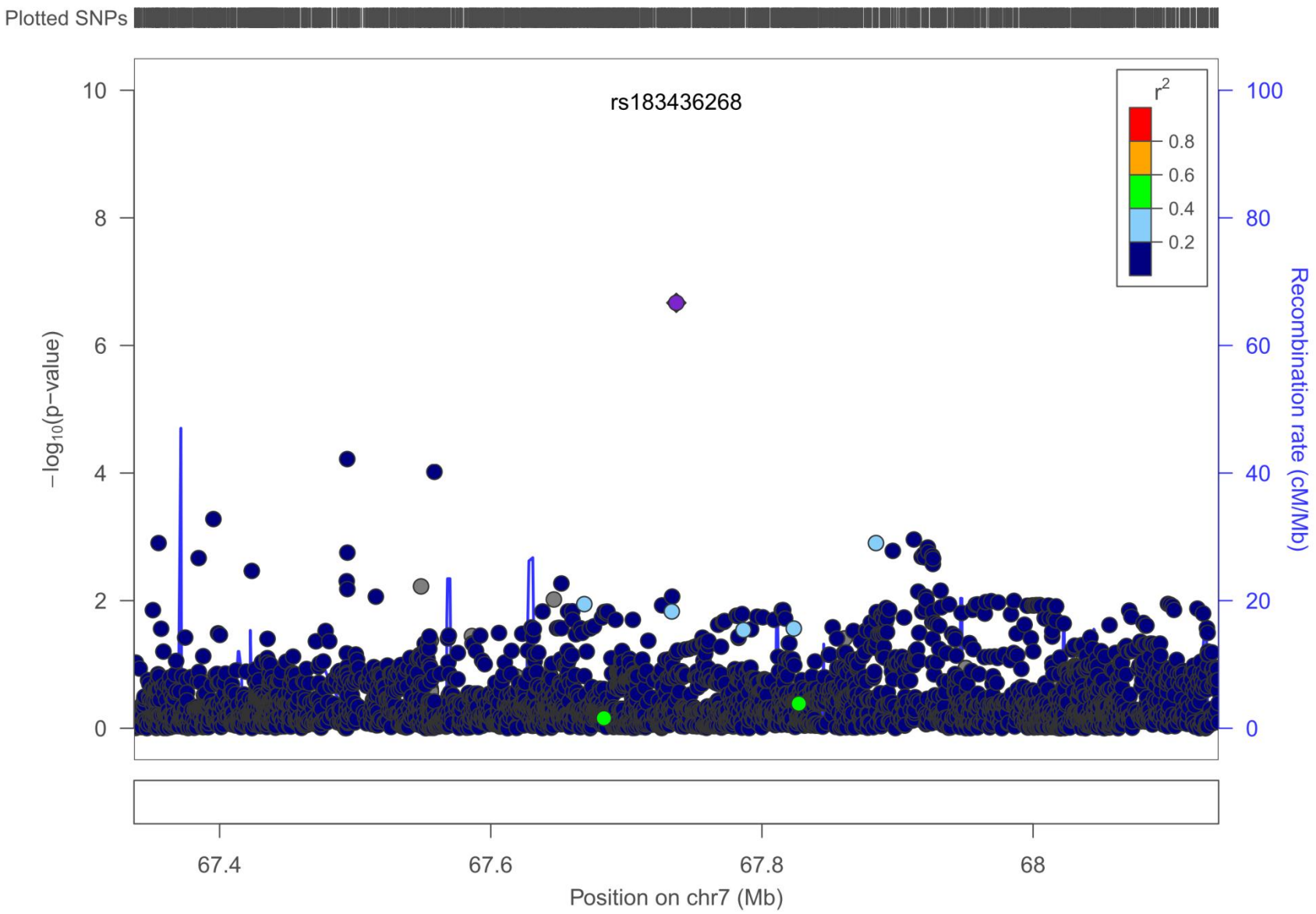
Intergenic, p=2.15E-7, MAF=0.01, OR=2.44 [1.75-3.41]



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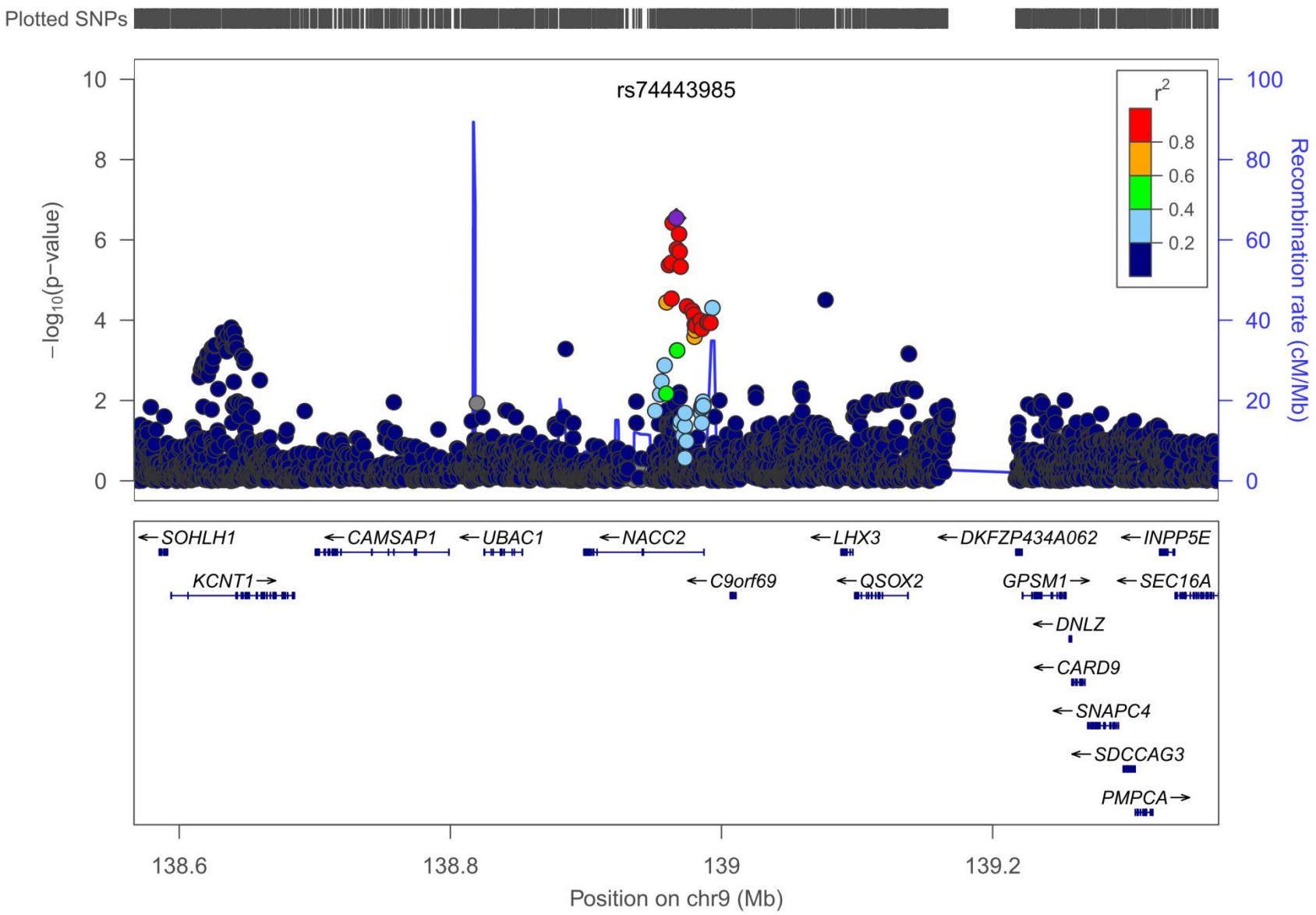
NACC2, p=2.86E-7, MAF=0.03, OR=2.23 [1.68-3.21]



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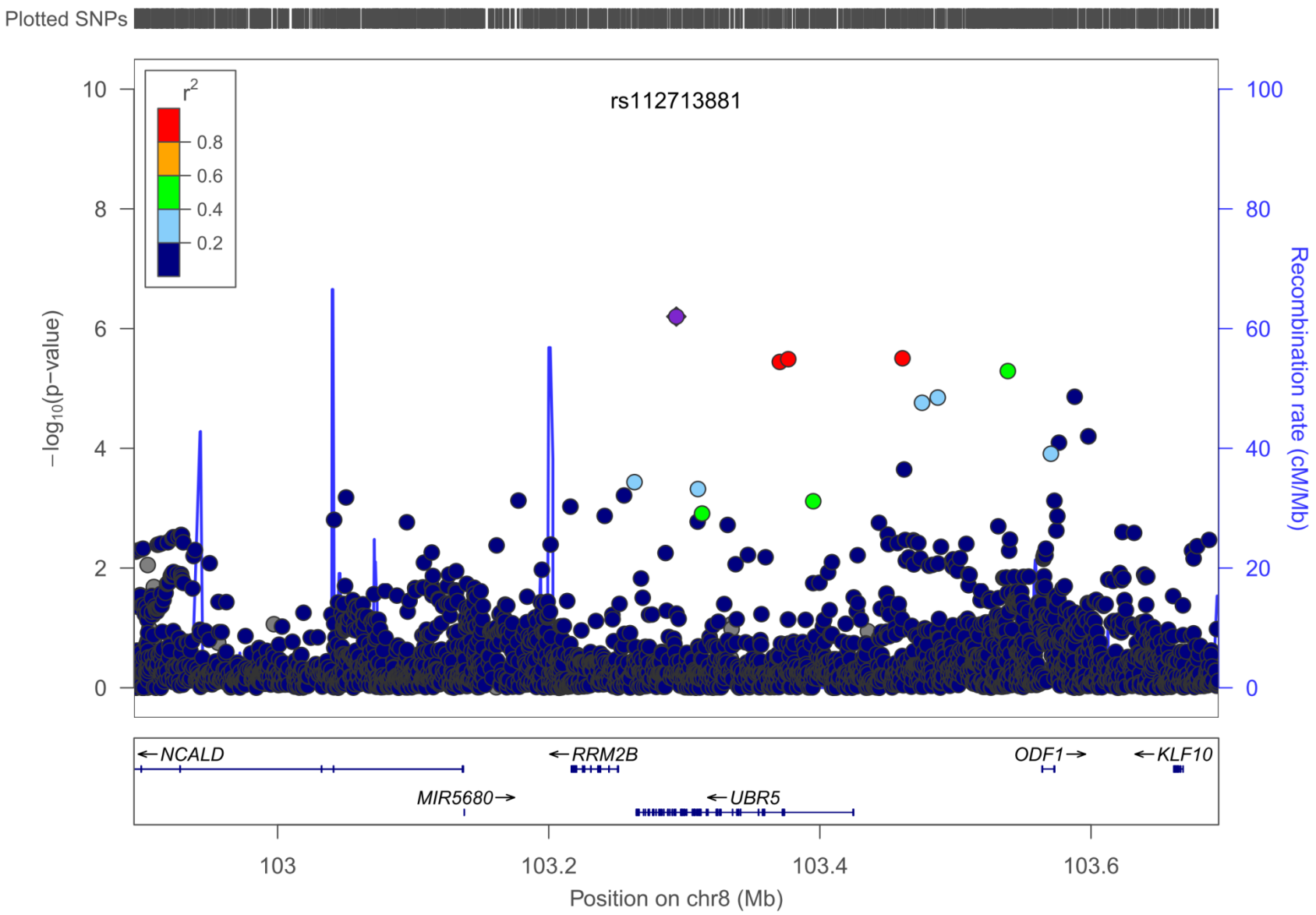
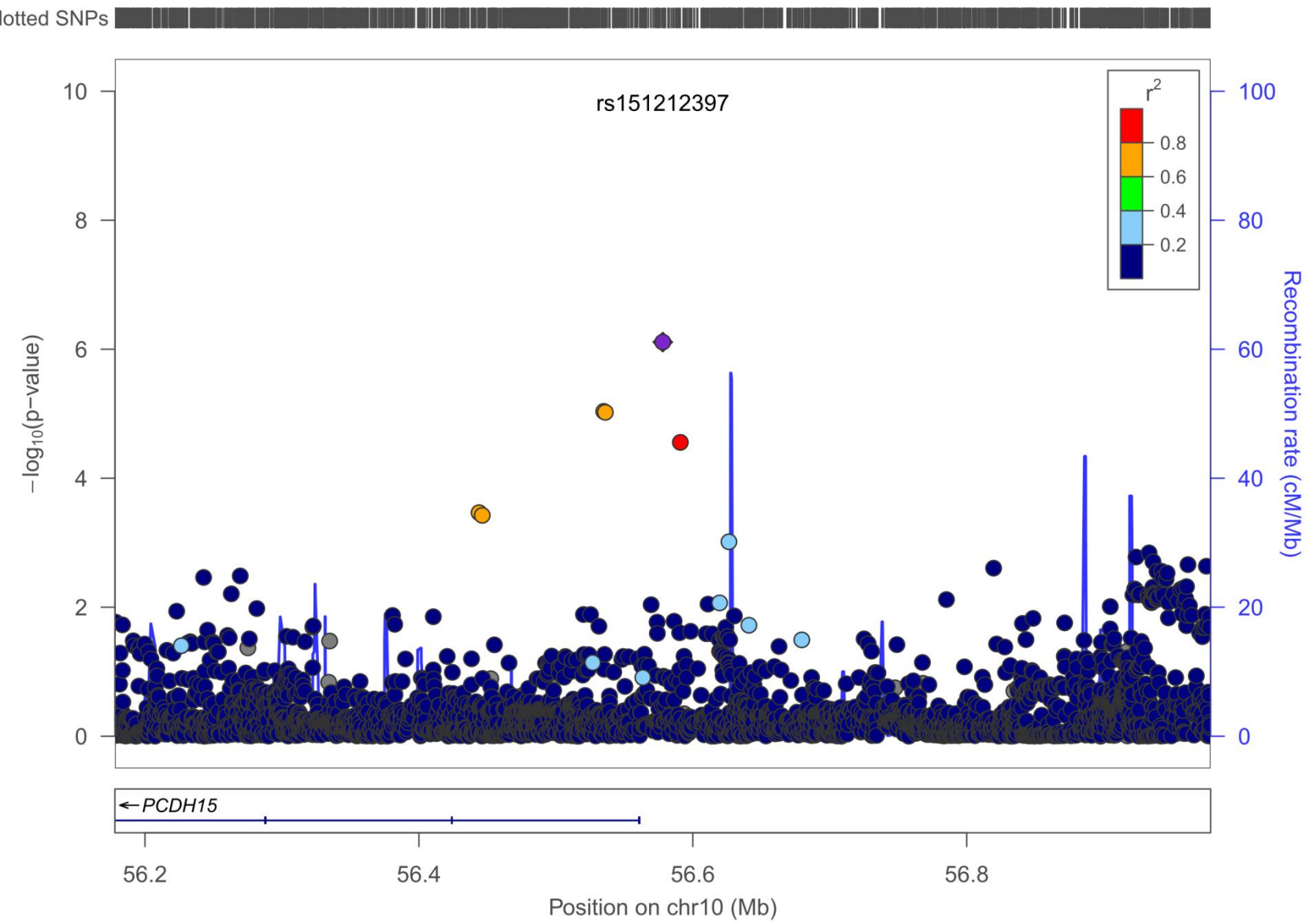
UBR5, p=6.30E-7, MAF=0.05, OR=1.64 [1.35-1.99]



PCDH15, p=7.75E-7, MAF=0.01, OR=2.32 [1.66-3.23]



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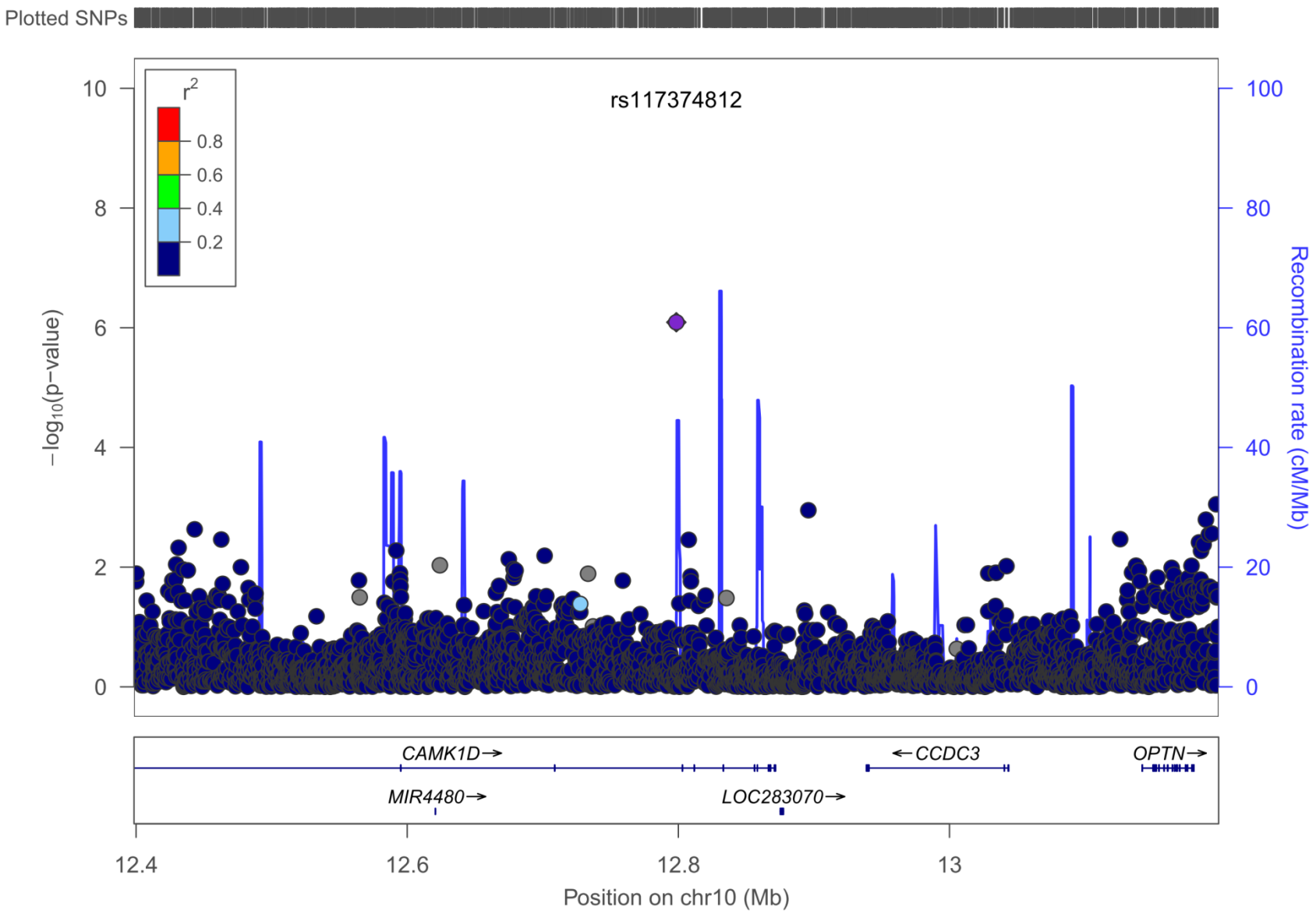
CAMK1D, p=8.11E-7, MAF=0.03, OR=1.82 [1.43-2.30]



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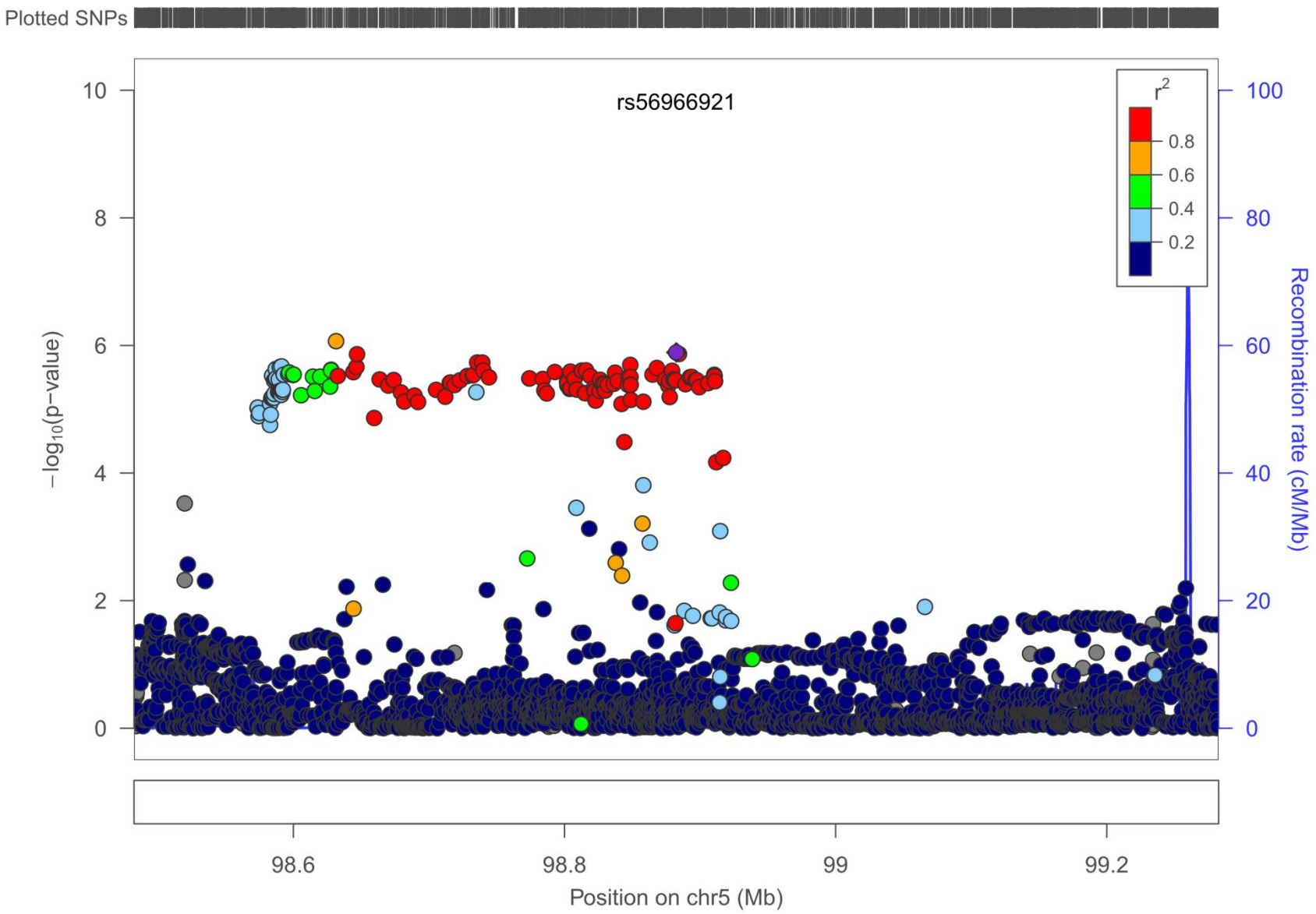
Intergenic, p=8.56E-7, MAF=0.02, OR=2.05 [1.54-2.75]



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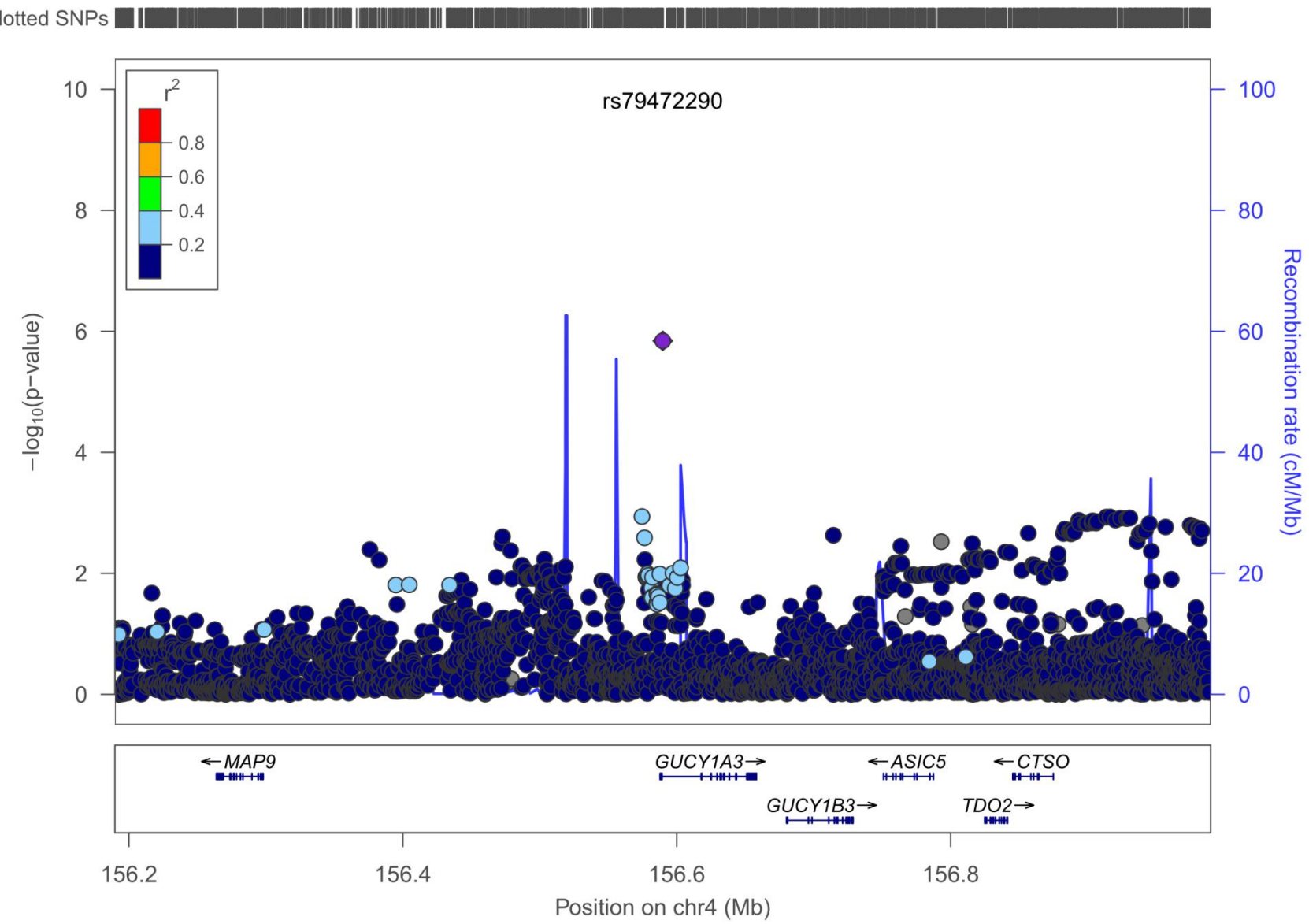
GUCY1A3, p=1.44E-6, MAF=0.01, OR=2.24 [1.61-3.11]



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Lead SNP in promoter region

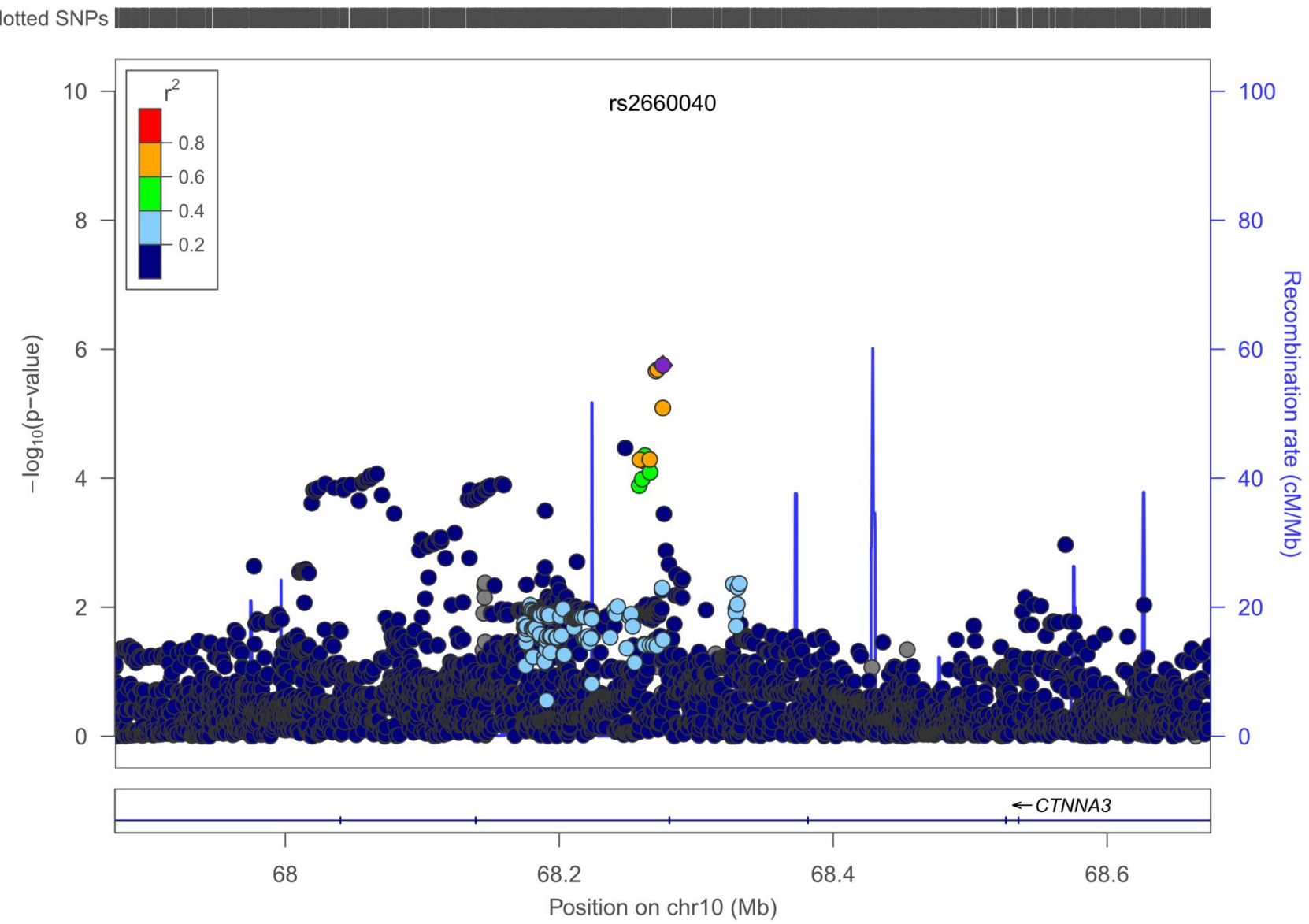
LETTER

doi:10.1038/nature12722

Dysfunctional nitric oxide signalling increases risk of myocardial infarction

Jeanette Erdmann[1,2]*, Klaus Stark[3,4]*, Ulrike B. Esslinger[3,5]*, Philipp Moritz Rumpf[6,7]*, Doris Koesling[8], Cor de Wit[2,9], Frank J. Kaiser[2,10], Diana Braunholz[10], Anja Medack[1], Marcus Fischer[3], Martina E. Zimmermann[3], Stephanie Tennstedt[1], Elisabeth Graf[11,12], Sebastian Eck[11,12], Zouhair Aherrahrou[1,2], Janja Nahrstaedt[1], Christina Willenborg[1,2], Petra Bruse[1], Ingrid Brænne[1], Markus M. Nöthen[13,14], Per Hofmann[13,15], Peter S. Braund[16,17], Evanthia Mergia[8], Wibke Reinhard[6,7], Christof Burgdorf[6], Stefan Schreiber[18], Anthony J. Balmforth[19], Alistair S. Hall[20], Lars Bertram[21], Elisabeth Steinhagen-Thiessen[22], Shu-Chen Li[23,24], Winfried März[25,26,27], Muredach Reilly[28], Sekar Kathiresan[29,30,31], Ruth McPherson[32], Ulrich Walter[33,34], CARDIoGRAM†, Jurg Ott[35,36], Nilesh J. Samani[16,17], Tim M. Strom[11,12], Thomas Meitinger[6,11,12], Christian Hengstenberg[6,7] & Heribert Schunkert[6,7]

CTNNA3, p=1.77E-6, MAF=0.30, OR=1.22 [1.13-1.33]



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CTNNA3

catenin (cadherin-associated protein), alpha 3

key protein of the adherens junctional complex in epithelial cells playing a crucial role in cellular adherence

Alzheimer risk gene

Has LRRTM3 nested inside -> see SVD!!

co-localizes with plakophilin 2; mutations of which lead to cardiac muscle malfunction

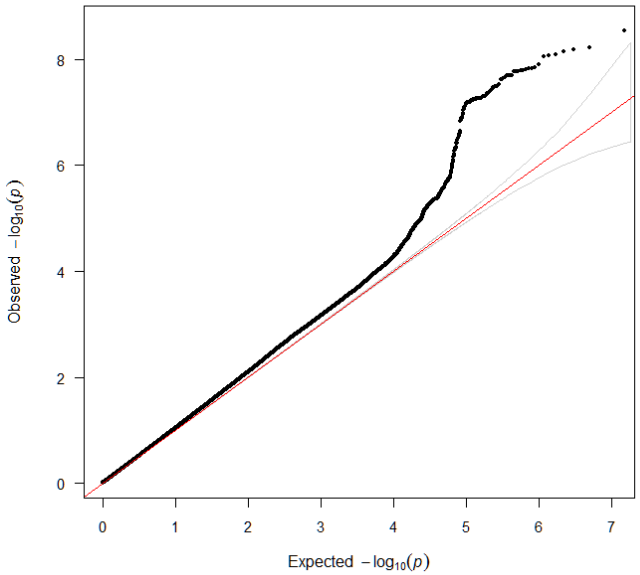
LETTER TO JMG

Interaction between the α-T catenin gene (VR22) and APOE in Alzheimer's disease

E R Martin, P G Bronson, Y-J Li, N Wall, R-H Chung, D E Schmechel, G Small, P-T Xu, J Bartlett, N Schnetz-Boutaud, J L Haines, J R Gilbert, M A Pericak-Vance

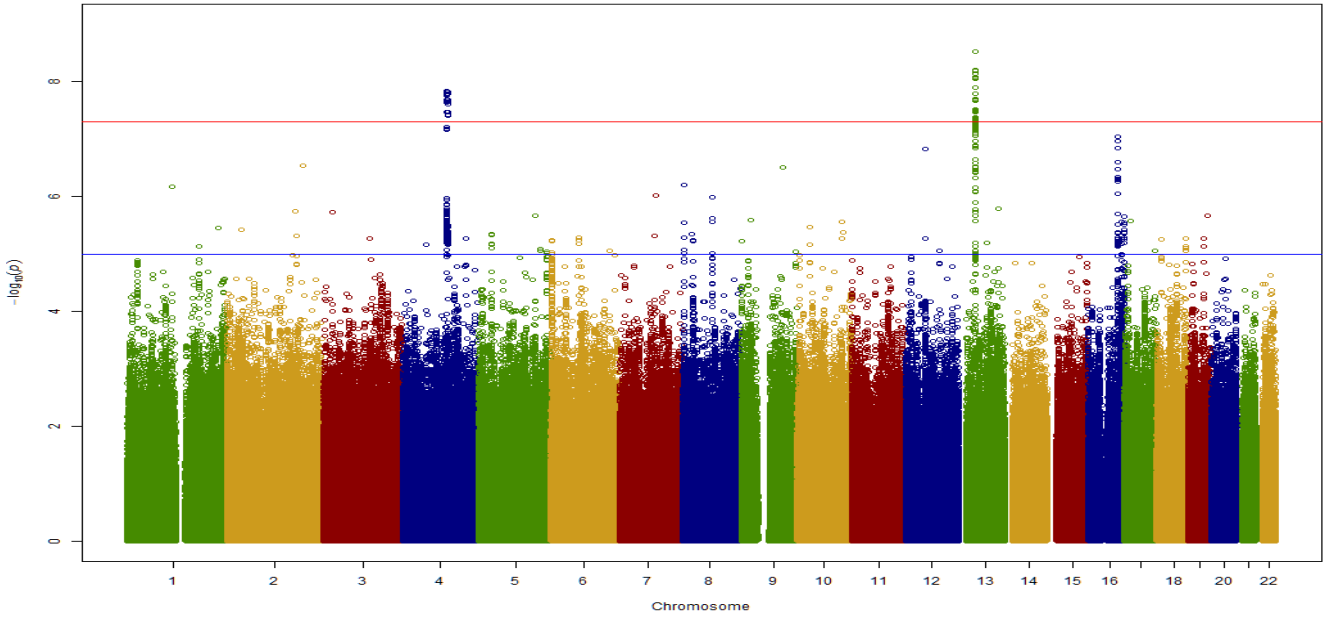
J Med Genet 2005;**42**:787–792. doi: 10.1136/jmg.2004.029553

CE



Filtered data!

λ(GC_filtered)=1.017
λ(GC_unfiltered)=1.013



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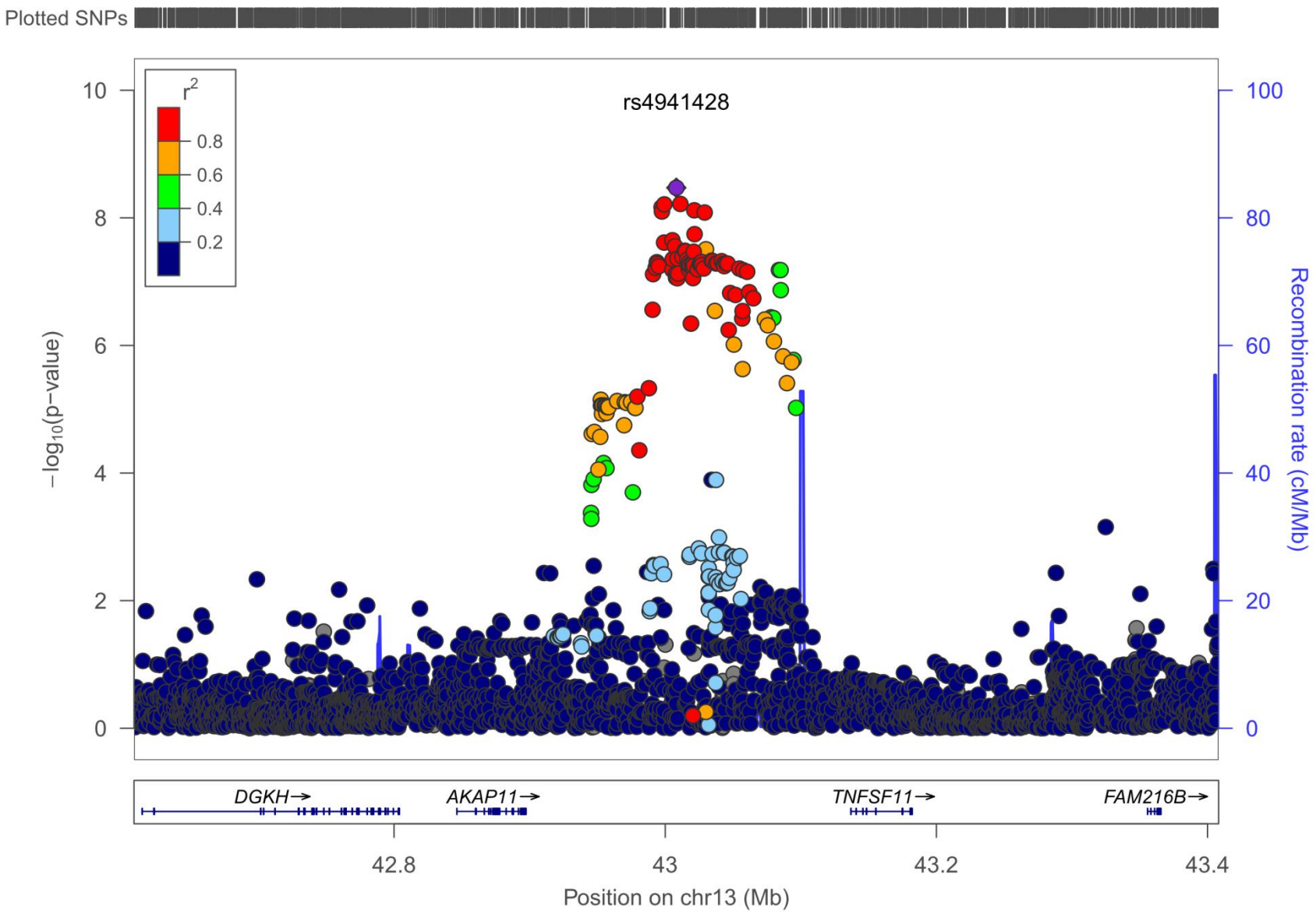
Note: λ1000 is used

TNFSF11-AKAP11, p=3.37E-9, MAF=0.25, OR=1.28 [1.18-1.39]



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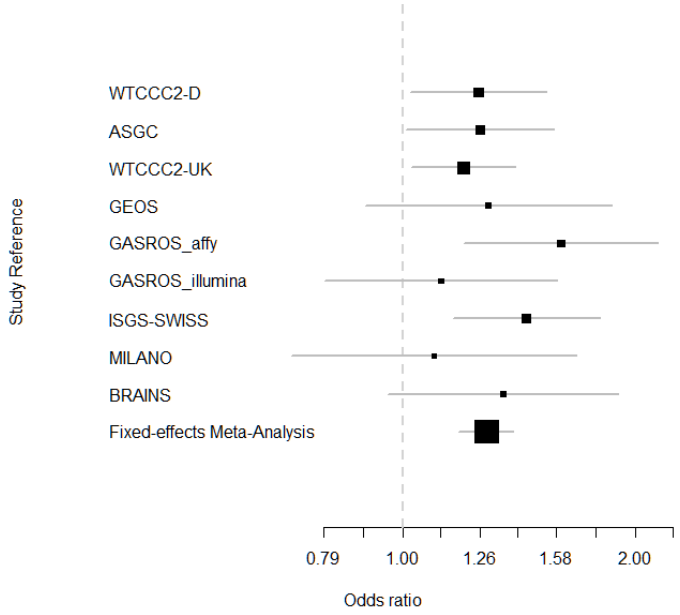
TNFSF11

tumor necrosis factor (ligand) superfamily, member 11
Formerly known as: RANKL

Important player in the RANK/RANKL/OPG pathway of osteogenesis

One of main risk loci for osteoporosis

Top SNP is eQTL for TNFSF11



OR=1.28 [1.18-1.39]
I^2=0.0%
P_{het}=0.7185

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TNFSF11

Not seen in AF so far (contact AF consortium)

Mechanism?

CARDIOLOGY

Letter to the Editor/Reply

Cardiology 2013;125:174–175
DOI: 10.1159/000351441

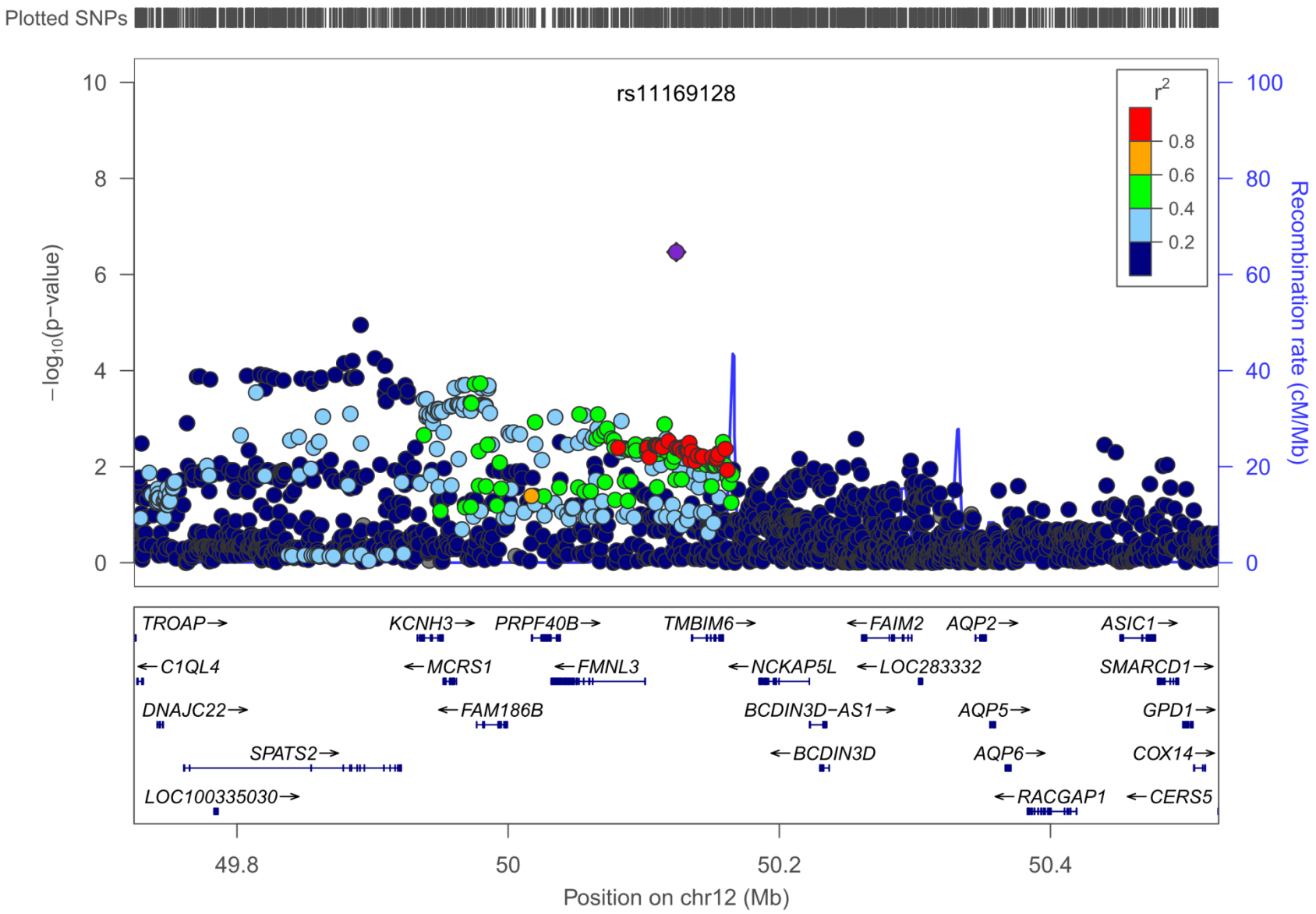
Received: April 11, 2013
Accepted: April 11, 2013
Published online: June 7, 2013

OPG/RANK/RANKL Axis in Atrial Fibrillation

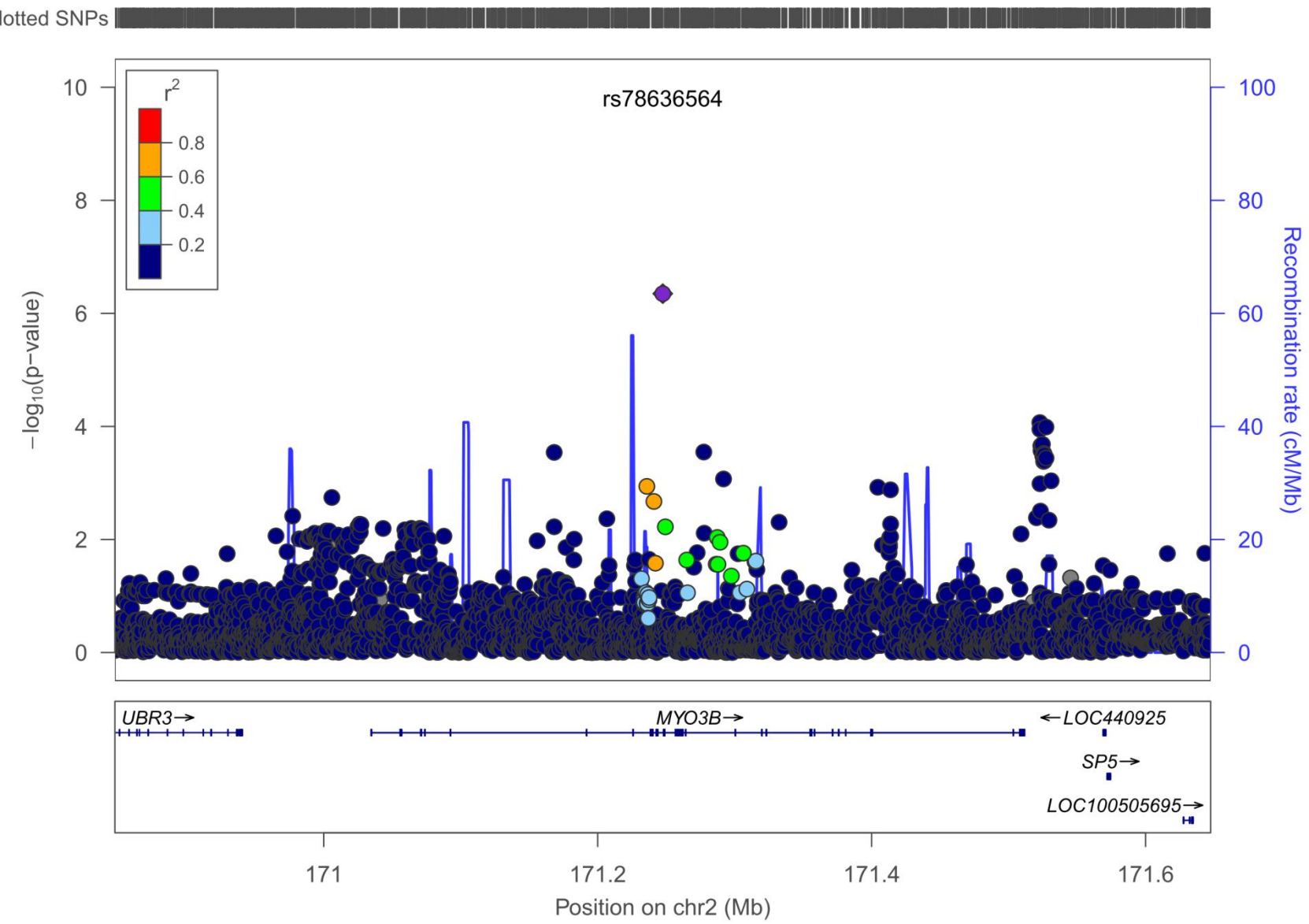
Lei Xi[a] Hailong Cao[b] Yijiang Chen[a]

[a]Department of Thoracic and Cardiovascular Surgery, The First Affiliated Hospital of Nanjing Medical University, and [b]Department of Thoracic and Cardiovascular Surgery, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China

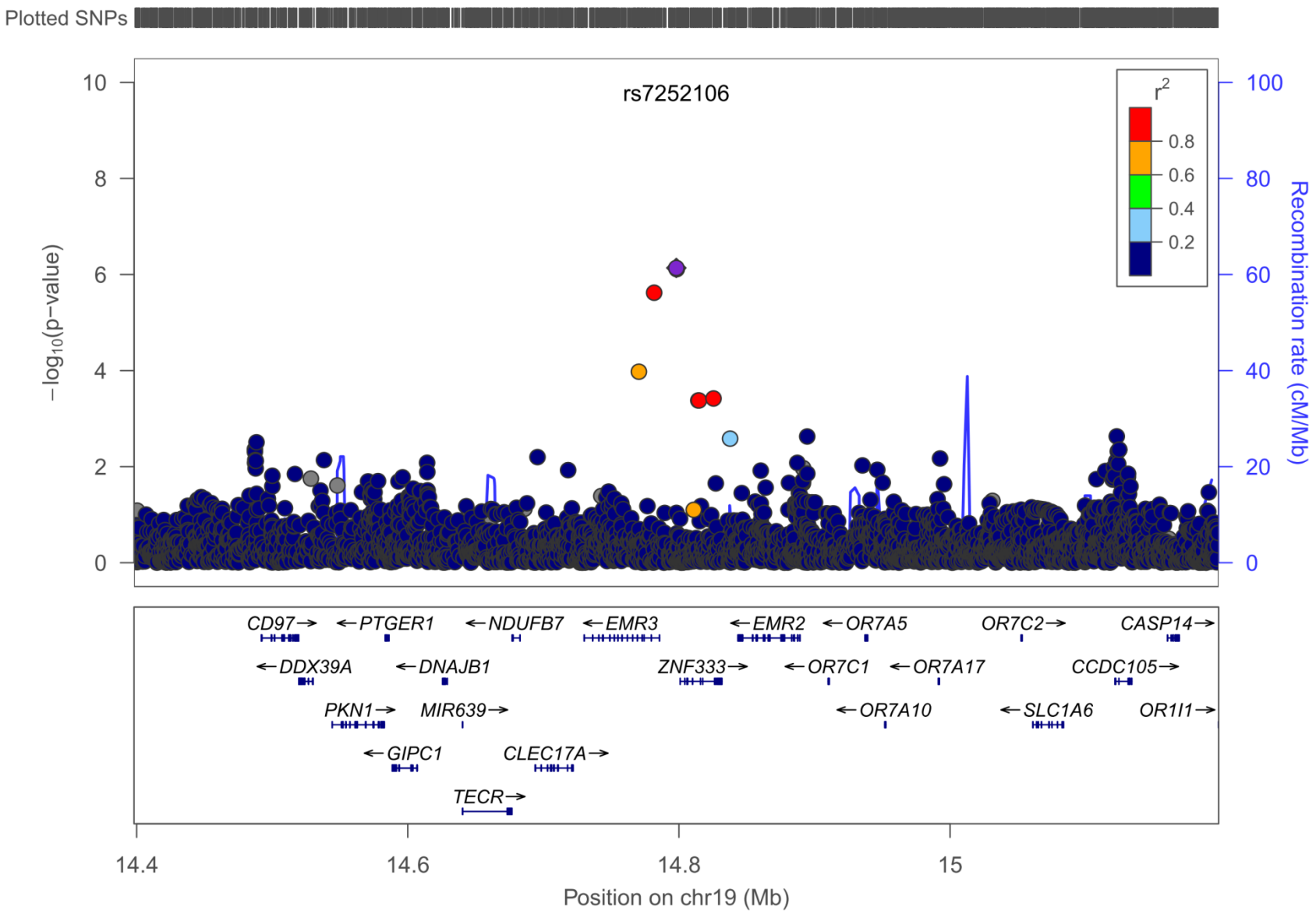
TMBIM6-FMNL3, p=3.4E-7, MAF=0.02, OR=1.70 [1.38-2.08]



MYO3B, p=4.48E-7, MAF=0.08, OR=1.47 [1.26-1.70]



EMR2-EMR3, p=7.29E-7, MAF=0.01, OR=2.56 [1.77-3.72]



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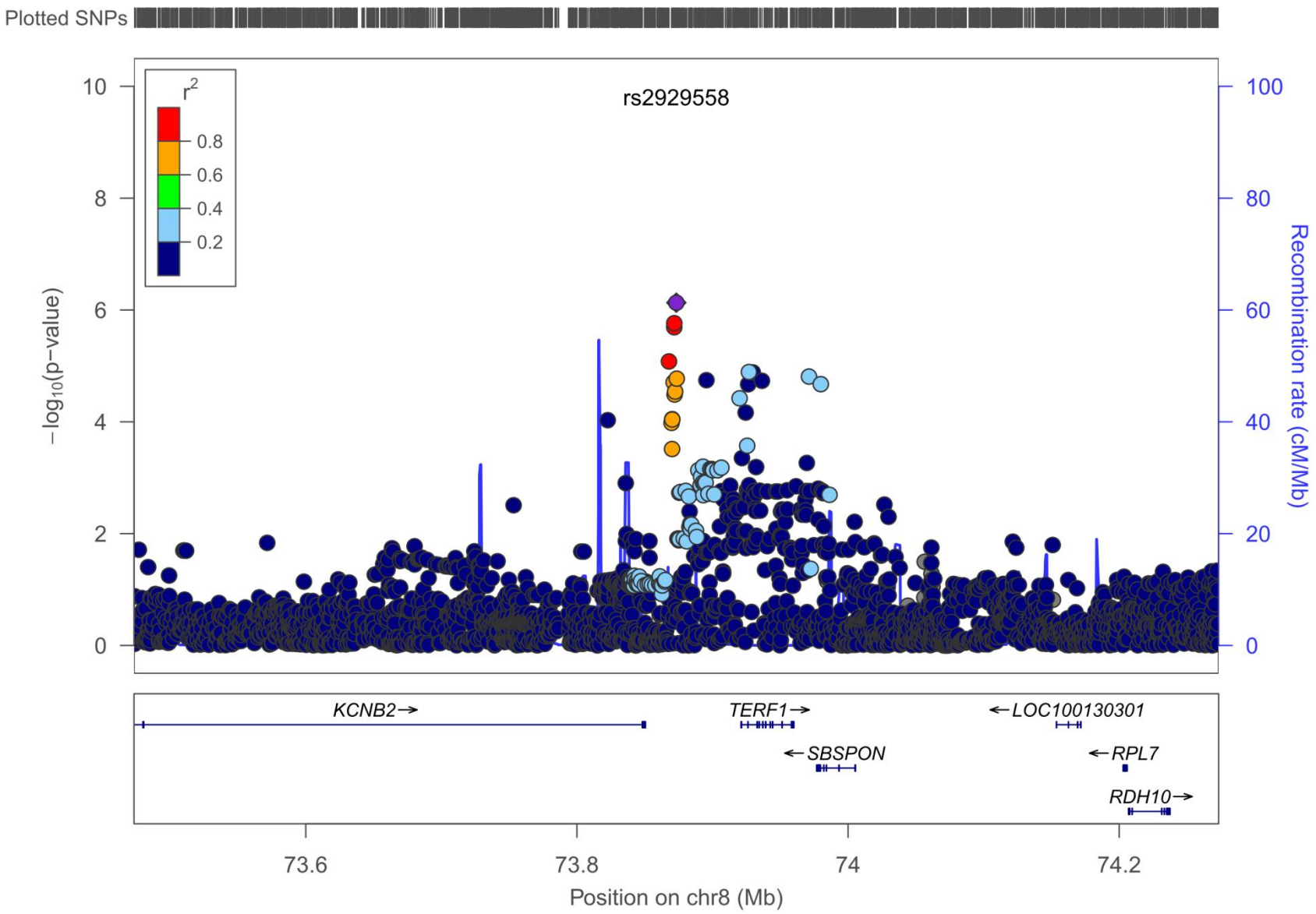
TERF1, p=7.40E-7, MAF=0.33, OR=1.22 [1.13-1.32]



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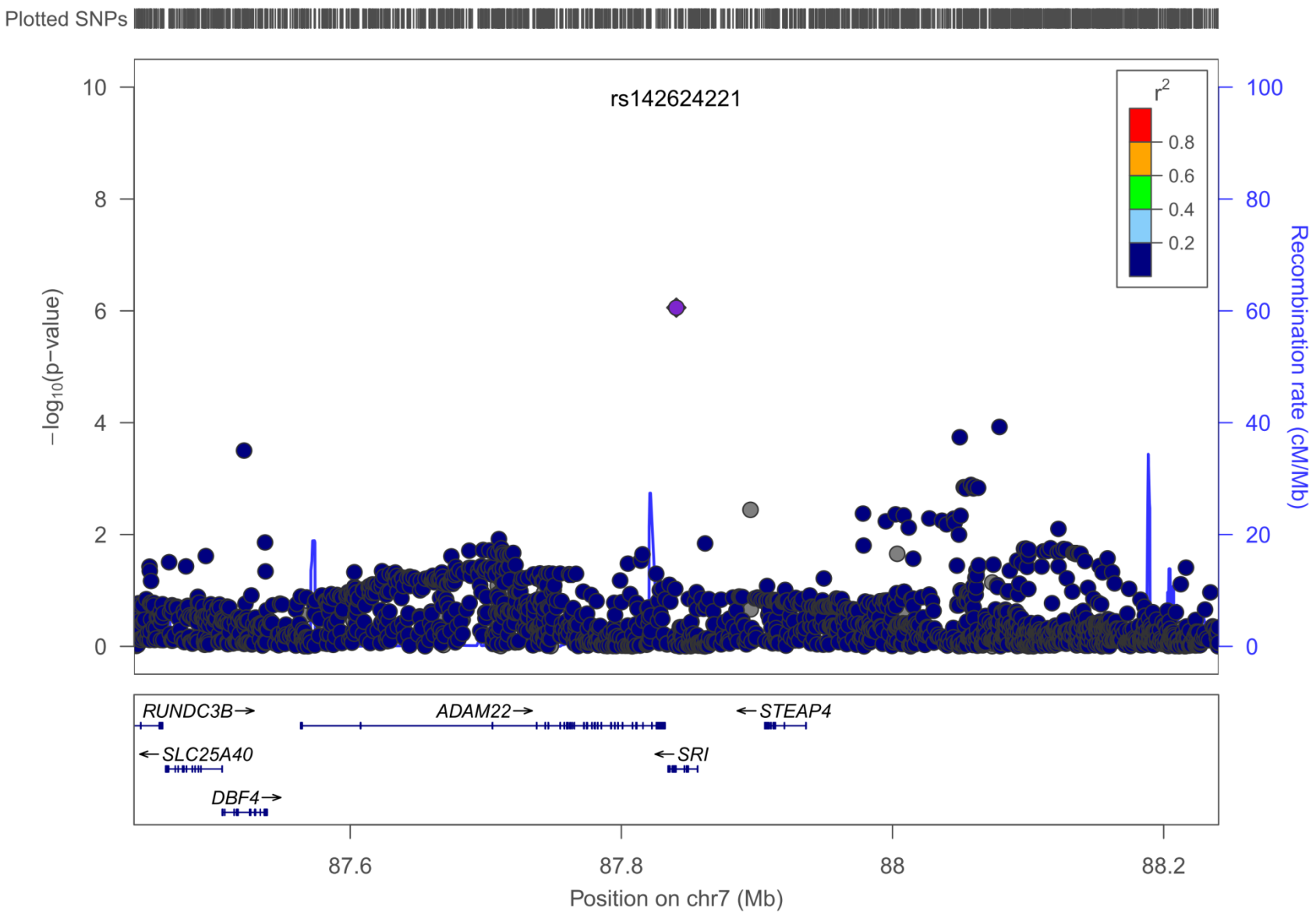
LETTERS

nature genetics

Identification of seven loci affecting mean telomere length and their association with disease

SRI, p=8.77E-7, MAF=0.01, OR=2.90 [1.90-4.43]



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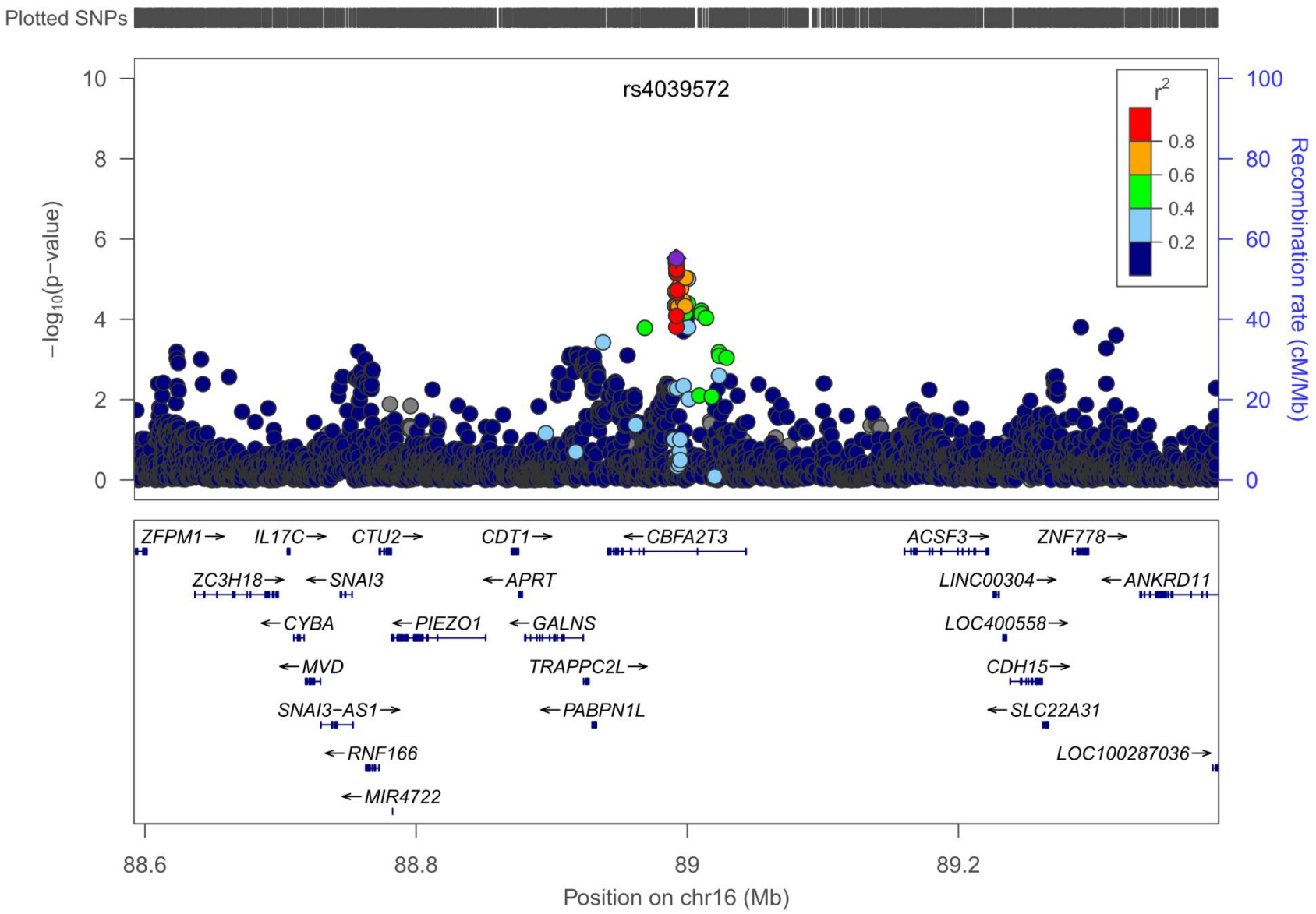
CBFA2T3, p=3.04E-6, MAF=0.04, OR=1.65 [1.34-2.04]



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CBFA2T3

Core-Binding Factor, Runt Domain, Alpha Subunit 2

myeloid translocation gene family which interact with DNA-bound transcription factors and recruit a range of corepressors to facilitate transcriptional repression

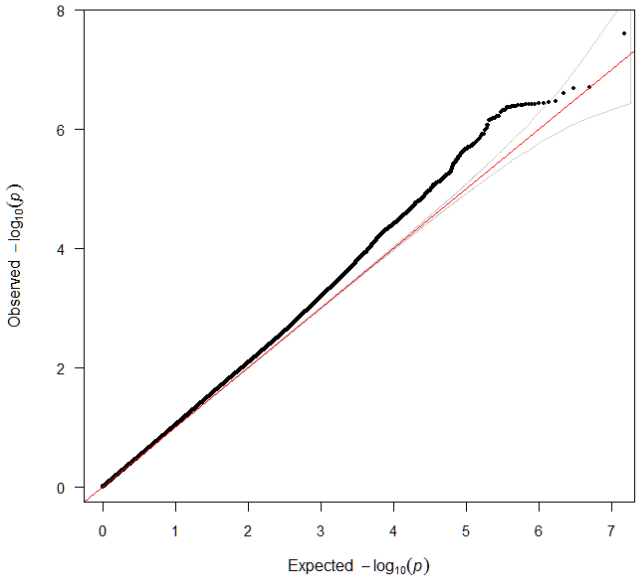
is a component of a protein complex containing master regulators of hematopoiesis

Regulates the proliferation and the differentiation of erythroid progenitors by repressing the expression of TAL1 target genes.

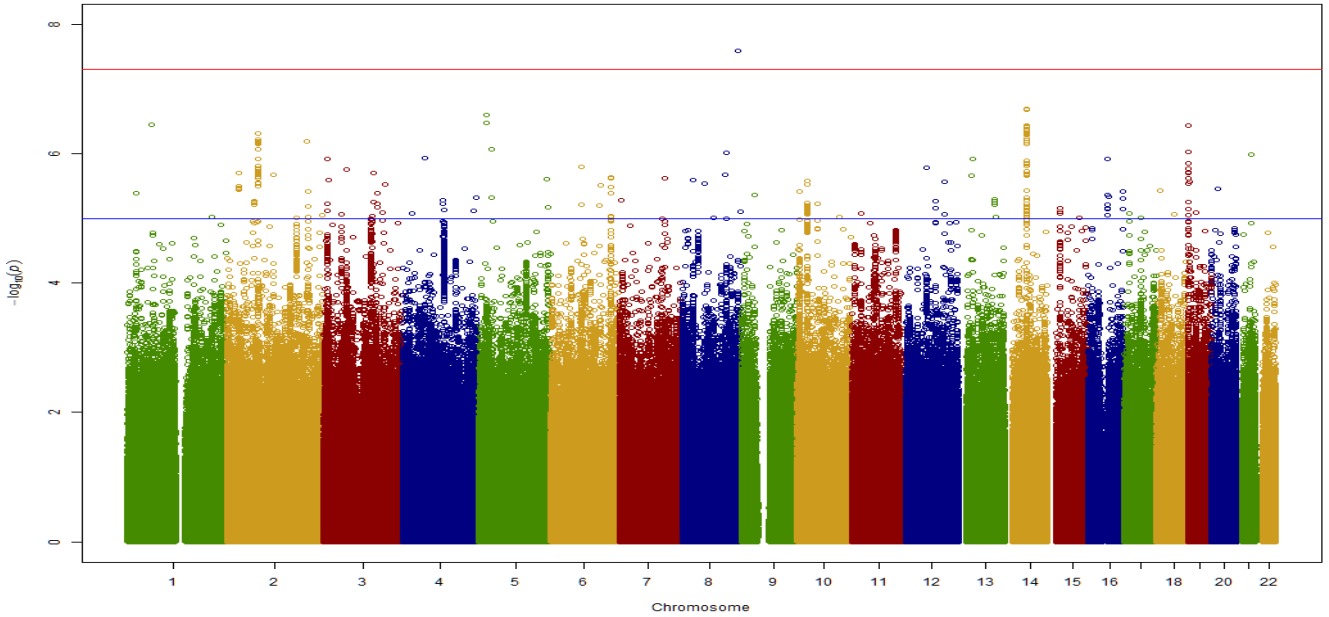
Plays a role in granulocyte differentiation

SVD

λ(GC_filtered)=1.023
λ(GC_unfiltered)=1.021



Filtered data!



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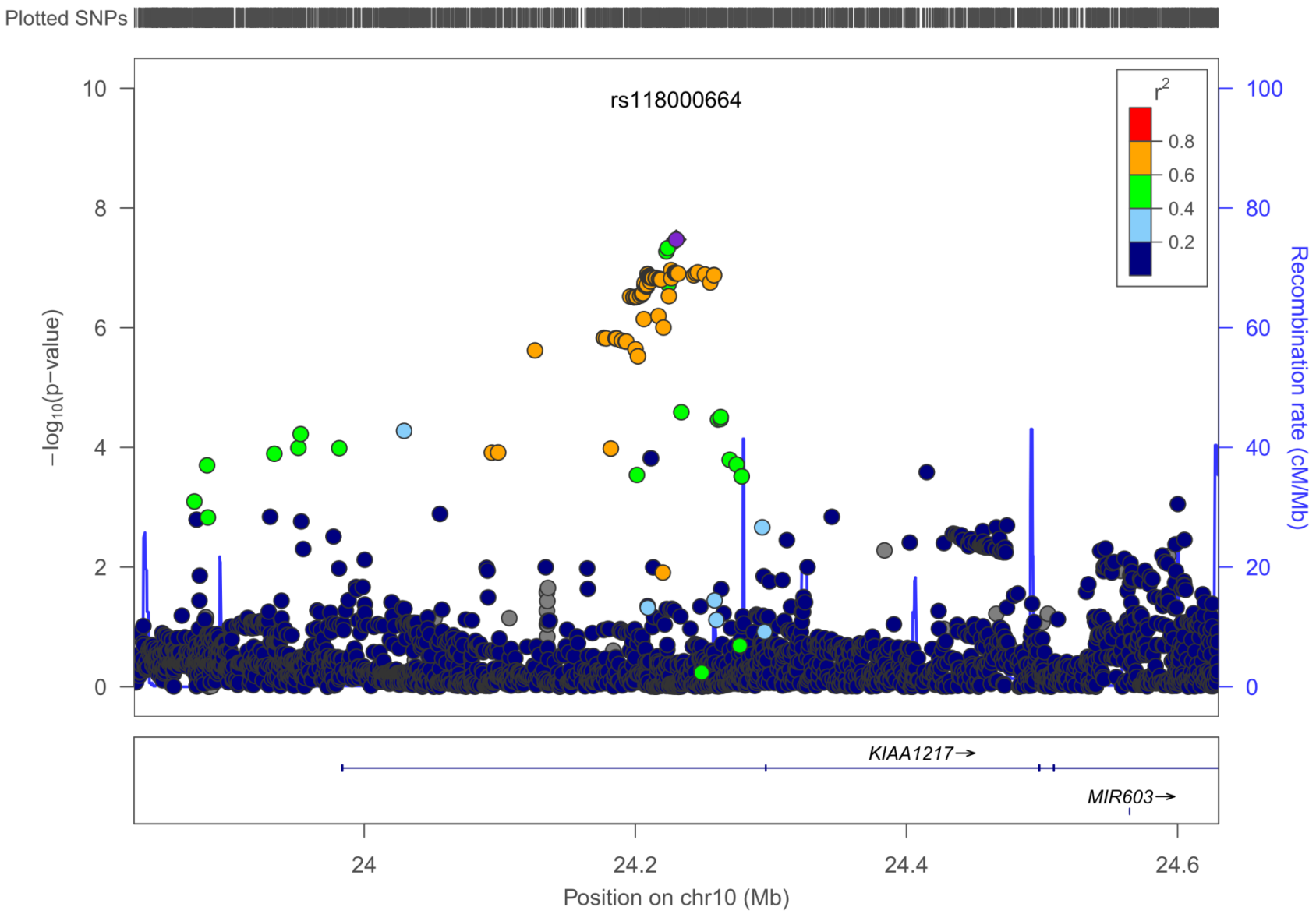
Note: λ1000 is used

KIAA1217, p=3.36E-8, MAF=0.01, OR=3.09 [2.07-4.61]



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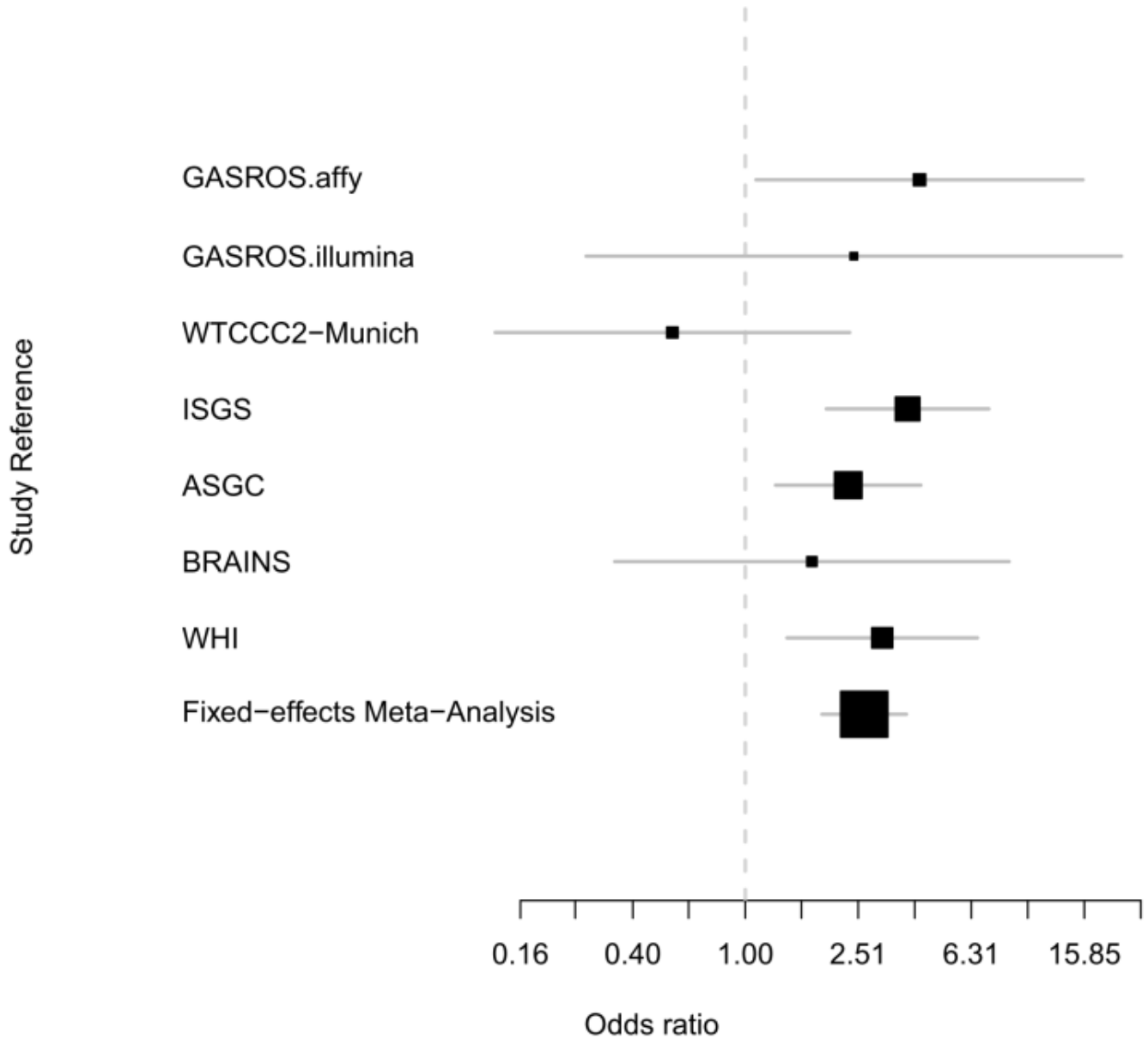
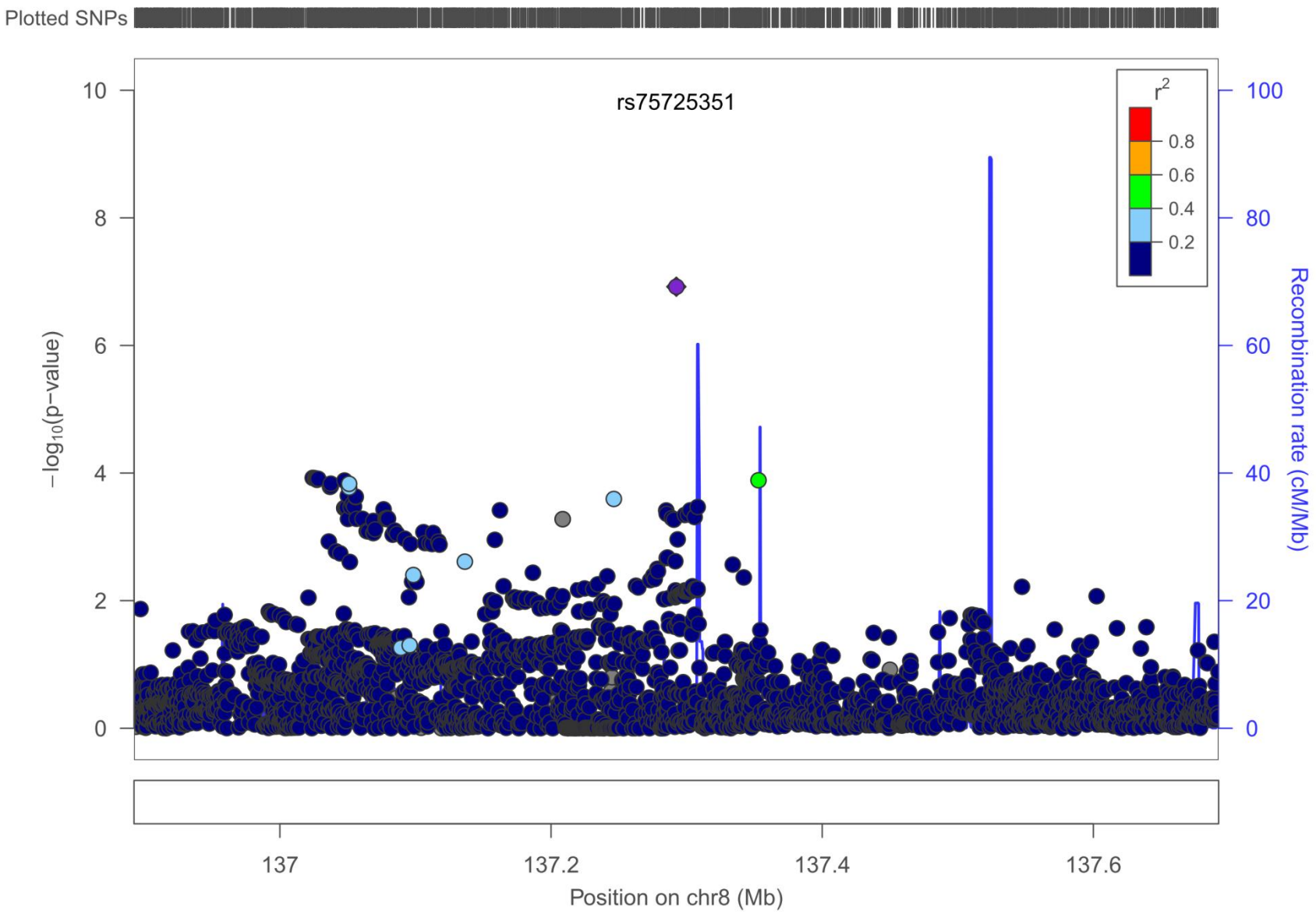


Intergenic, p=1.2E-7, MAF=0.07, OR=1.67 [1.38-2.02]



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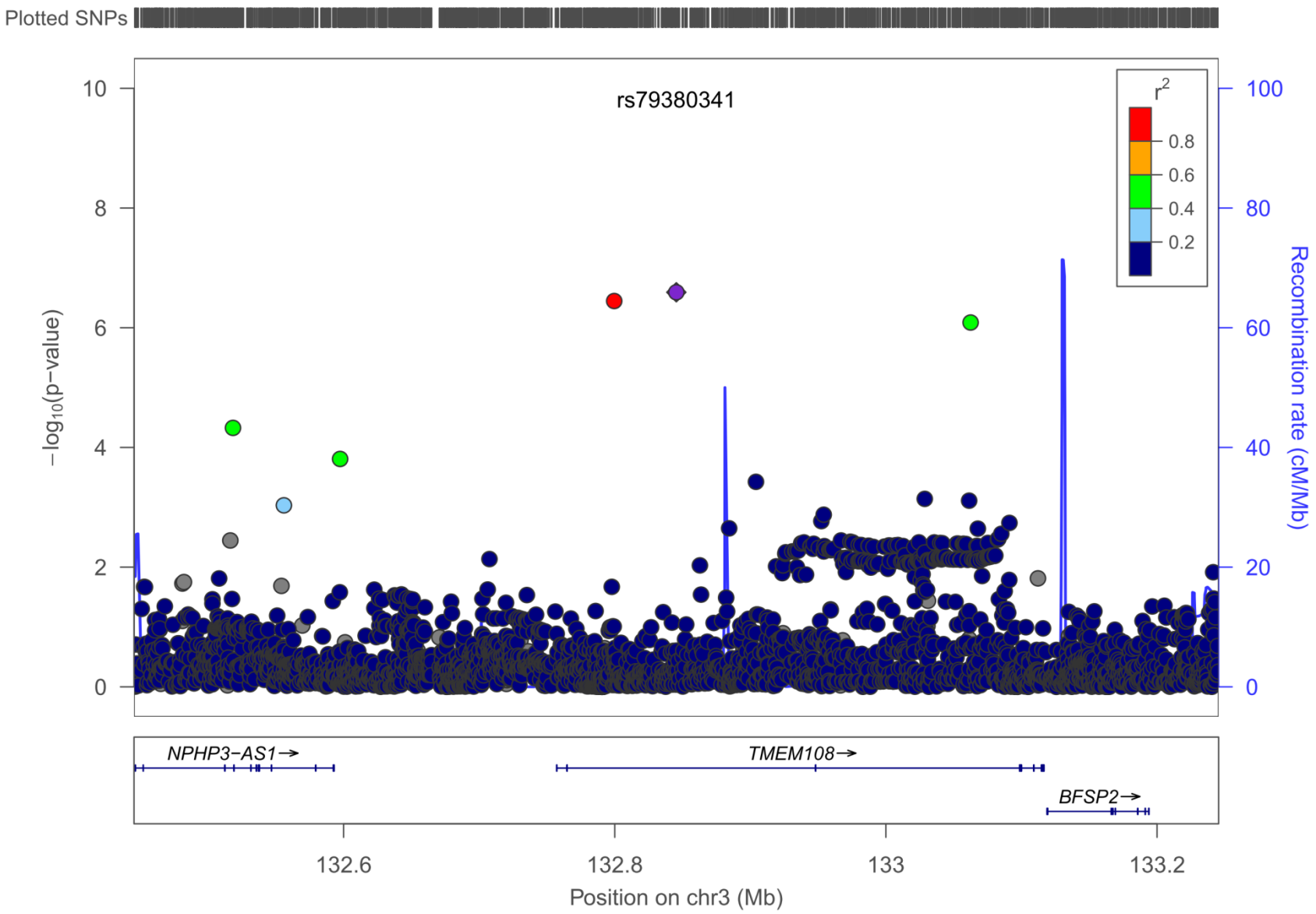
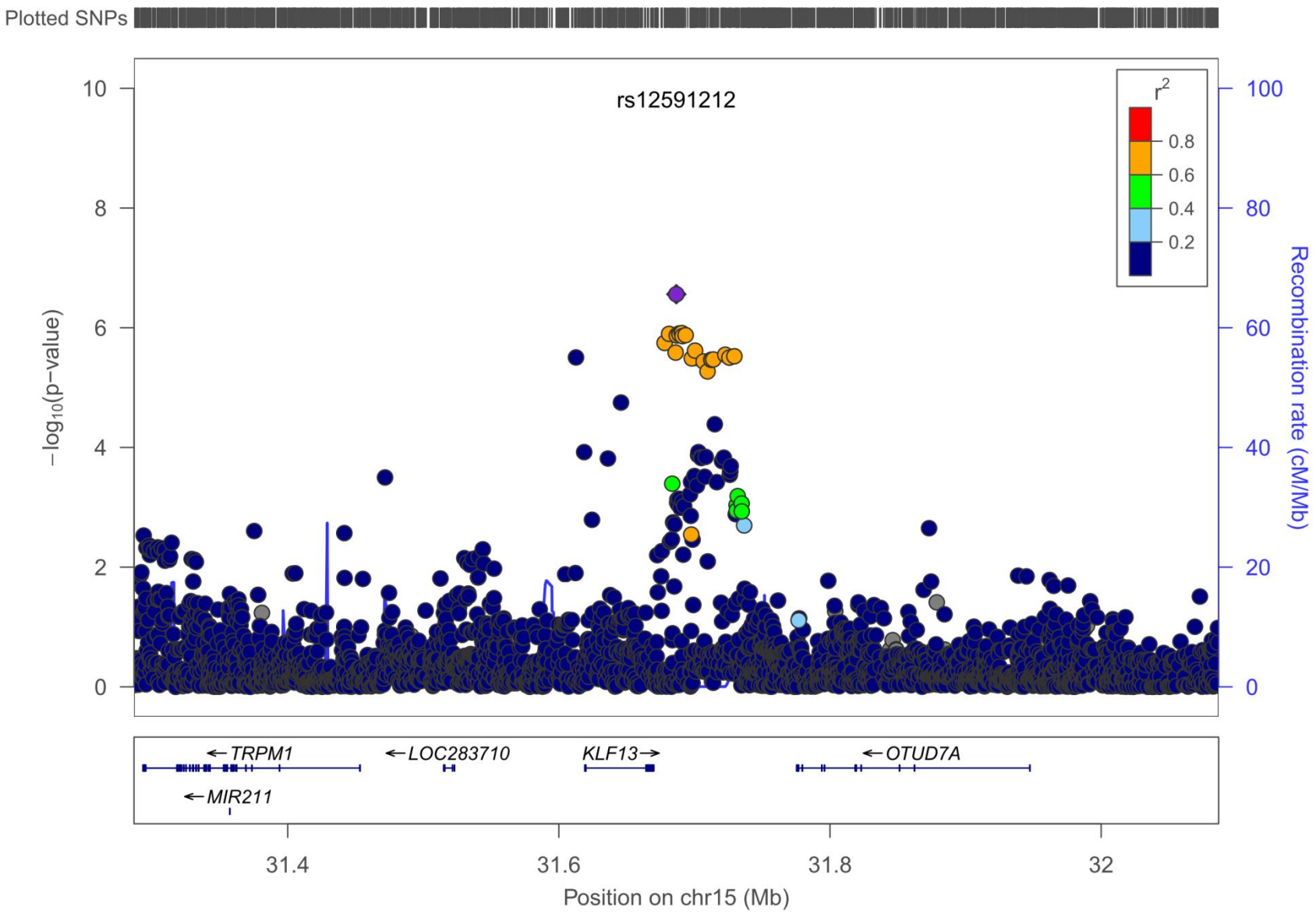
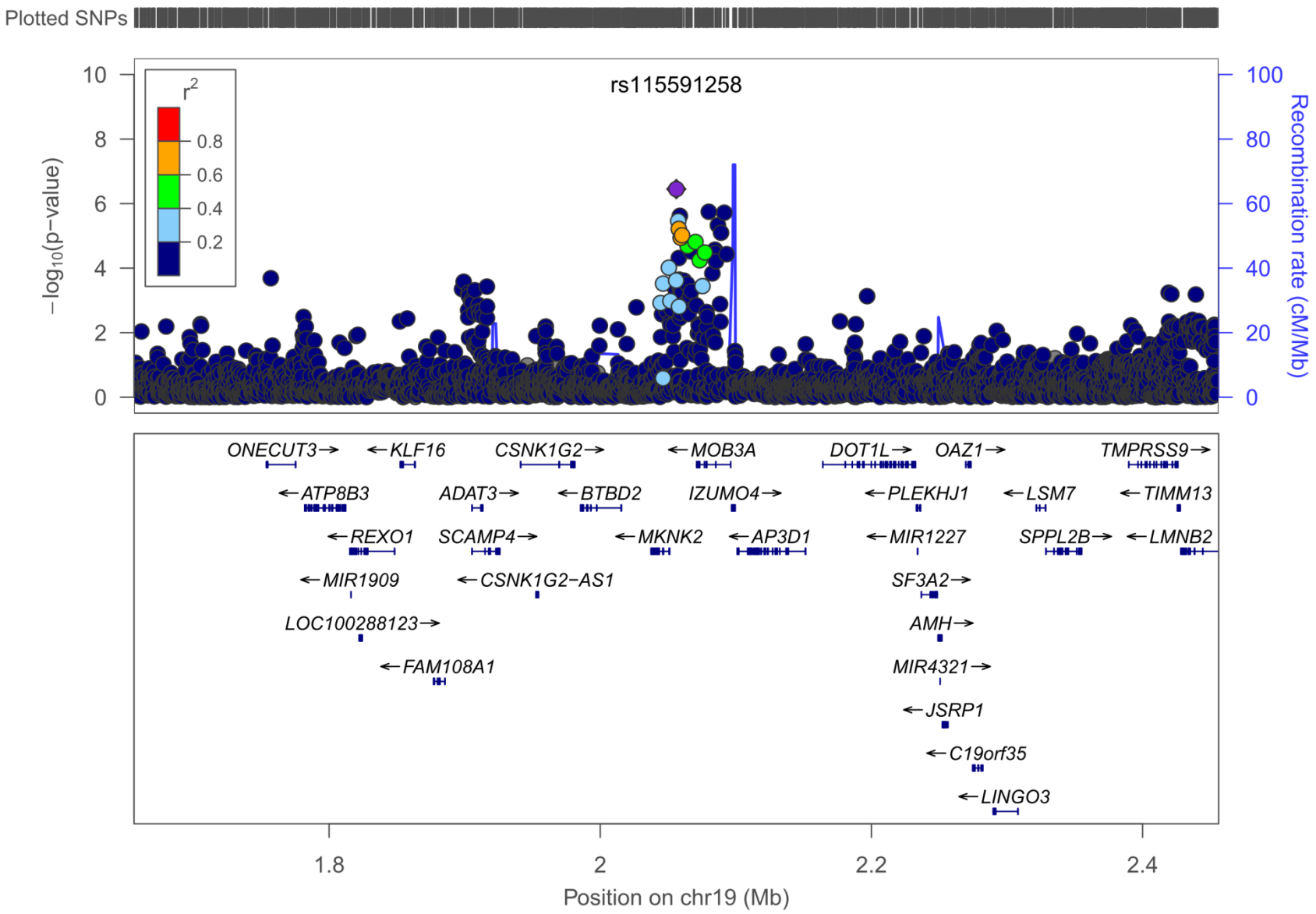
TMEM108, p=2.56E-7, MAF=0.02, OR=2.37 [1.71-3.29]



KLF13, p=2.75E-7, MAF=0.11, OR=1.43 [1.25-1.64]



MOB3A, p=3.55E-7, MAF=0.06, OR=1.69 [1.38-2.07]



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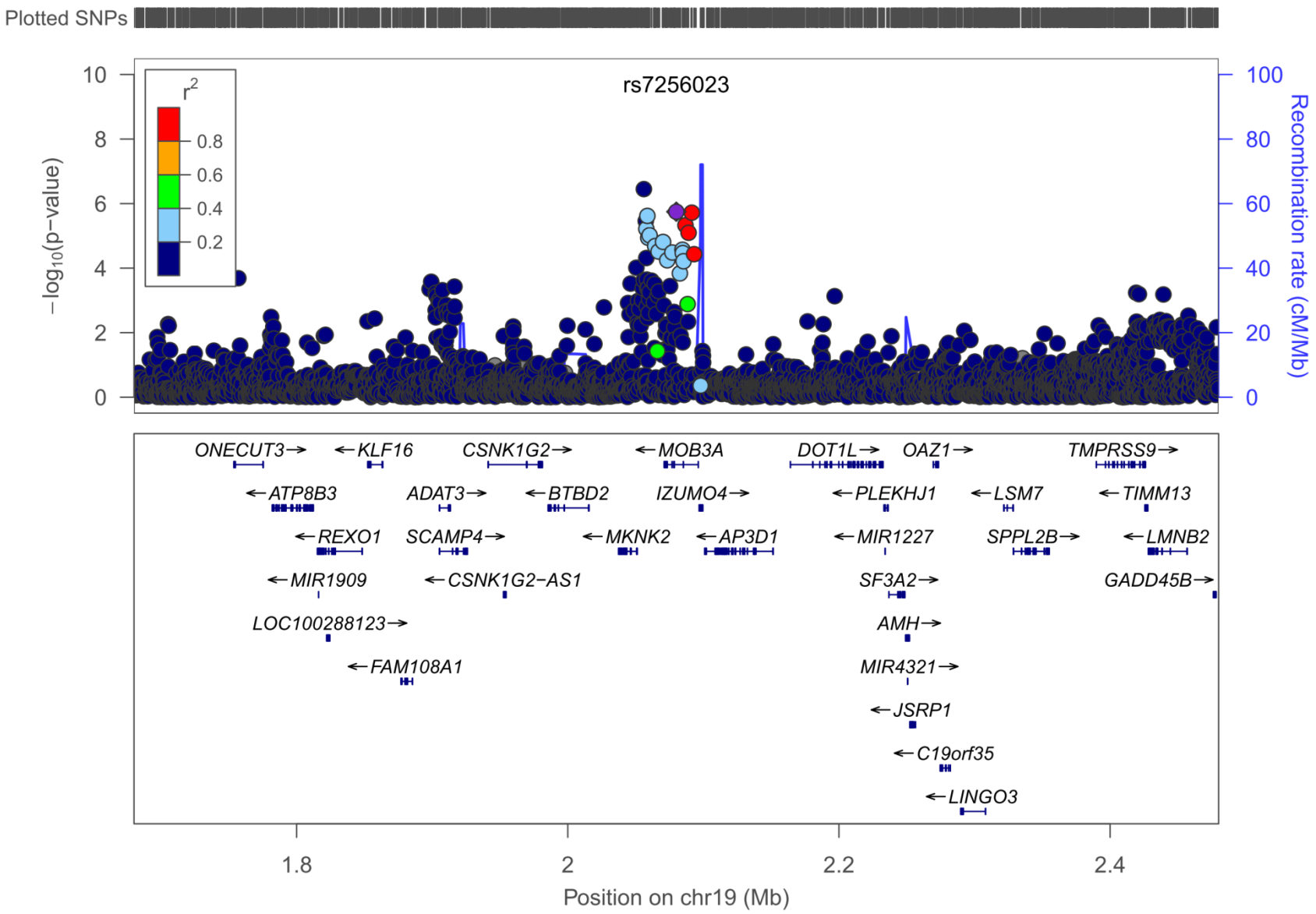
MOB3A, alternative, p=3.55E-7, MAF=0.08, OR=1.44 [1.24-1.67]



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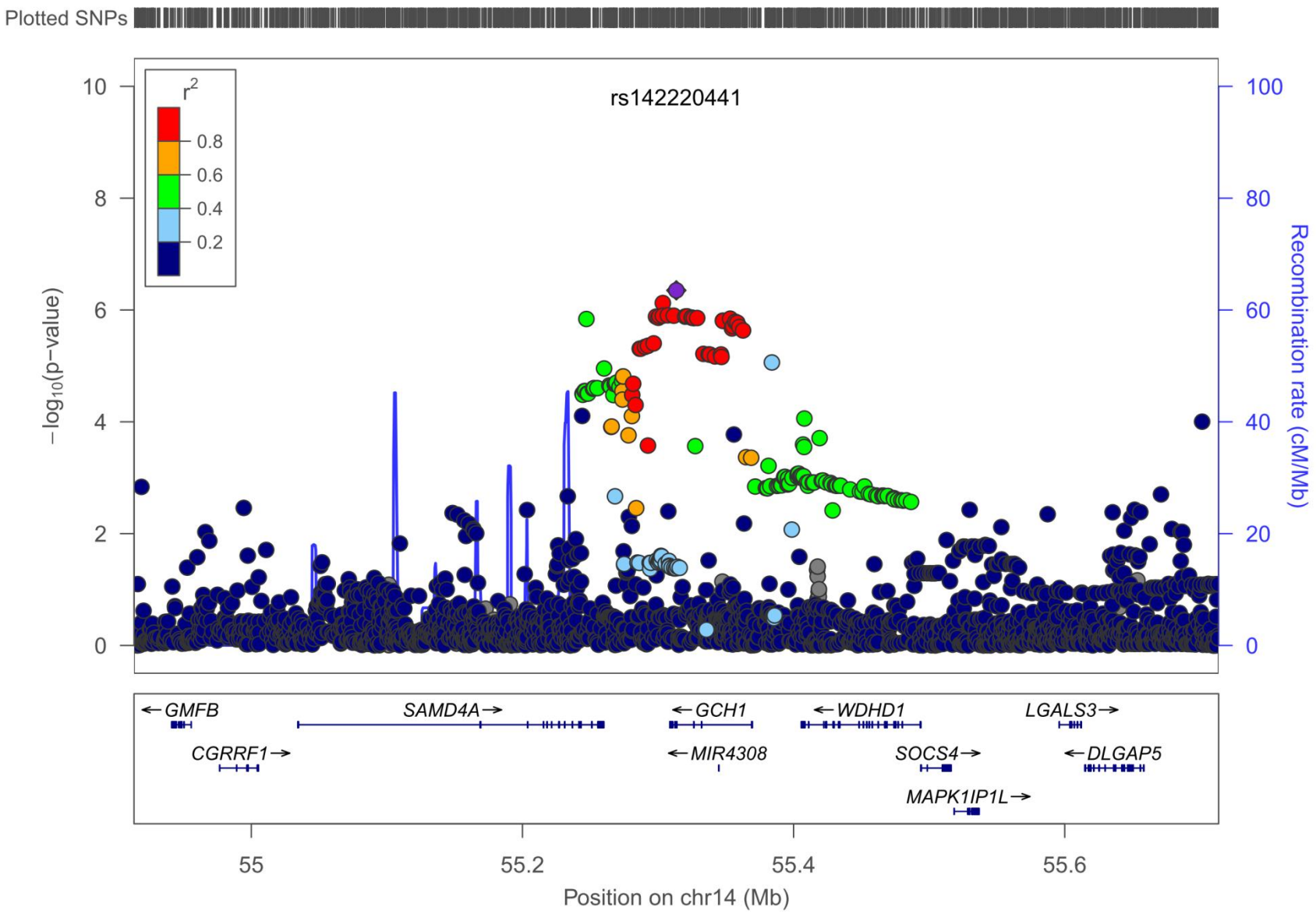
GCH1, p=4.45E-7, MAF=0.02, OR=2.19 [1.61-2.98]



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GCH1

GTP cyclohydrolase 1

The encoded protein is the first and rate-limiting enzyme in tetrahydrobiopterin (BH4) biosynthesis

BH4 is an essential cofactor required by aromatic amino acid hydroxylases as well as nitric oxide synthases

Positively regulates nitric oxide synthesis in umbilical vein endothelial cells (HUVECs)

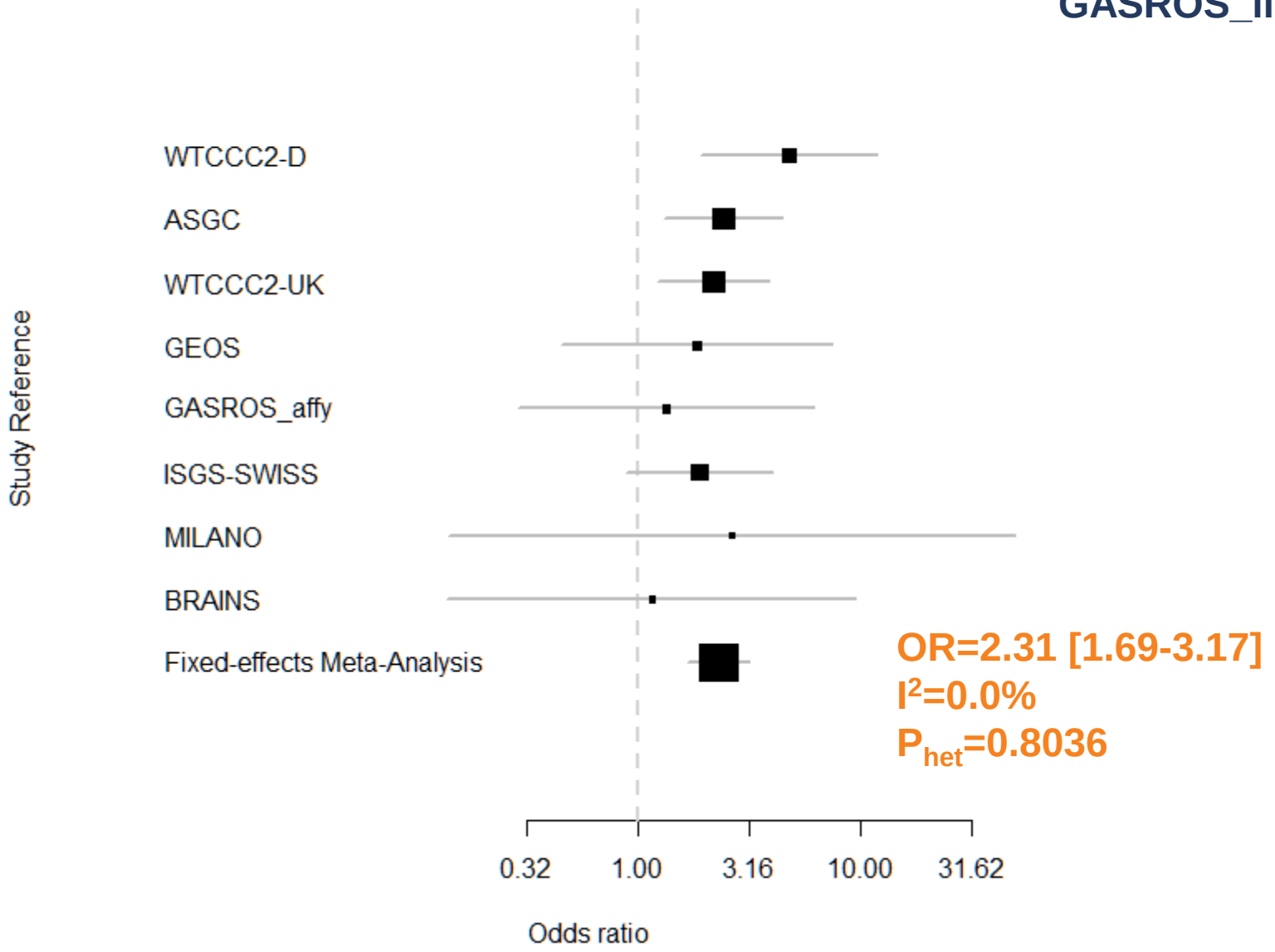
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Induction of Vascular GTP-Cyclohydrolase I and Endogenous Tetrahydrobiopterin Synthesis Protect Against Inflammation-Induced Endothelial Dysfunction in Human Atherosclerosis

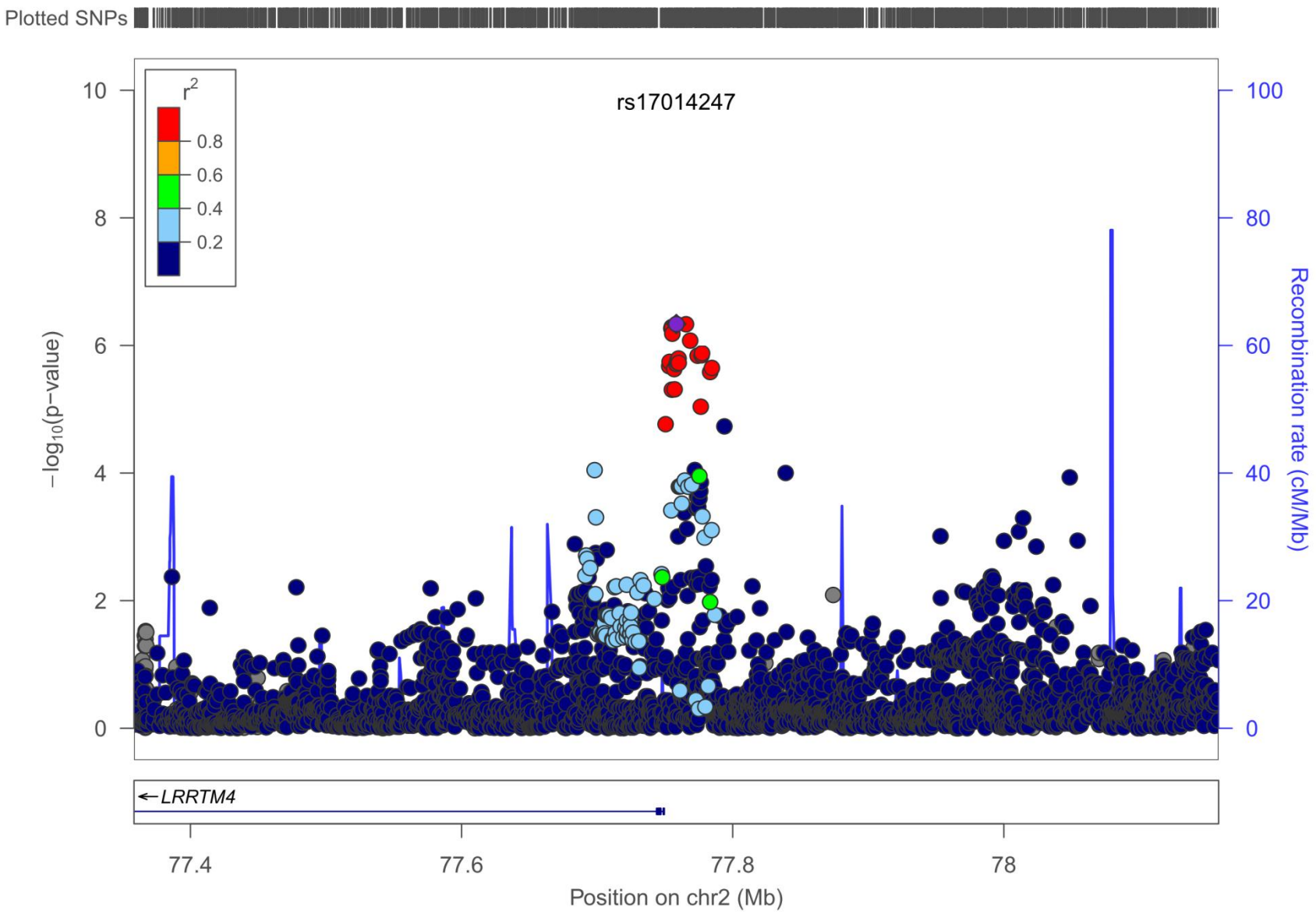
Charalambos Antoniades, Colin Cunnington, Alexis Antonopoulos, Matt Neville, Marios Margaritis, Michael Demosthenous, Jennifer Bendall, Ashley Hale, Ruha Cerrato, Dimitris Tousoulis, Constantinos Bakogiannis, Kyriakoula Marinou, Marina Toutouza, Charalambos Vlachopoulos, Paul Leeson, Christodoulos Stefanadis, Fredrik Karpe and Keith M. Channon

No data on GASROS_illumina



OR=2.31 [1.69-3.17]
I^2=0.0%
P_{het}=0.8036

LRRTM4, p=4.61E-7, MAF=0.30, OR=1.25 [1.15-1.37]



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LRRTM4

leucine rich repeat transmembrane neuronal 4

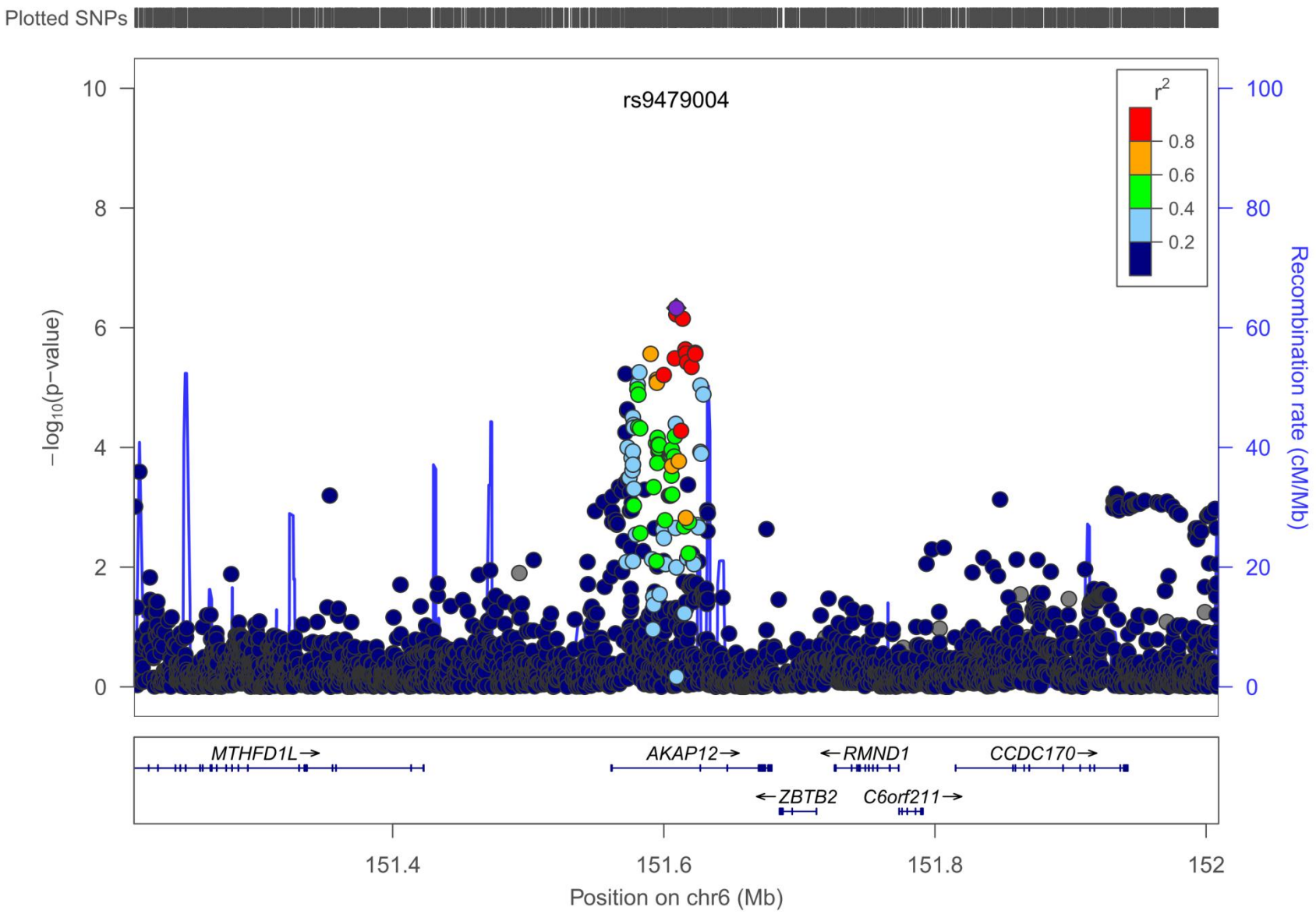
May play a role in the development and maintenance of the vertebrate nervous system.

Exhibits strong synaptogenic activity, restricted to excitatory presynaptic differentiation

Binding partners: heparan sulfate proteoglycans (HSPG) e.g. perlecan, syndecan, agrin, collagen XVIII

Role in aneurysms, AD, is pro-angiogenic and protective after stroke

AKAP12, p=4.68E-7, MAF=0.40, OR=1.24 [1.14-1.35]



AKAP12

A-kinase anchor protein 12 (Gravin)

Interactor of PDE4D and EGFR

Regulates vascular integrity

Angiogenesis supressor

European Replication

Wet-lab Replication

Genotyping center	No. cases	No. controls	TOAST
Munich	4,296	2,373	Y
Boston	435	1,021	Y

In-silico replication

Study	No. cases	No. controls	TOAST
CADISP	555	9,259	Y
GoDARTS	737	8,424	Y

Total: 6,023 cases / 21,077 controls

Wet lab replication

Group	No cases	No controls
M. Dichgans	544	0
D. Woo	254	1,021
S. Oliveira	370	370
J. Rosand	181	0
K. Berger	2,345	1,053
A. Slowik	300	300
A. Lindgren	500	250
V. Thijs	140	400

Trans-ethnic meta-analysis – South Asian Samples

RACE1: 1,218 IS cases / 1,158 controls (200 LAS, 229 CE, 192 SVD)
RACE2: 1,167 IS cases / 4,035 controls (155 LAS, 193 CE, 122 SVD)

Including subtypes, eQTL etc….

METASOFT (Han&Eskin, Am. J. Hum. Genet, 2011, Han&Eskin, Plos Genet, 2012)

New „random effects model“ optimized to detect associations under heterogeneity.

Assumption: if heterogeneity is too high –> random effects model

Downstream Analyses

- •eQTL analysis
- • ANNOVAR to check SNP function through the UCSC browser
- •ENCODE: Haploreg and Regulome DB
- •GWAS catalog: overlapping traits
- •GWAS-based Pathway Analysis tool (Tune Pers)
- •GRAIL
- •DAPPLE: protein-protein interaction
- •MAGENTA : pathway analysis
- •Cell specificity based on DNA hypersensitivity

- Further analyse InDels – no genome-wide loci so far

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DZNE Deutsches Zentrum für Neurodegenerative Erkrankungen in der Helmholtz-Gemeinschaft

Bundesministerium für Bildung und Forschung
neuron
DFG Deutsche Forschungsgemeinschaft
Fondation Leducq