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SUPPLEMENTARY INFORMATION

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Genetic architecture of subcortical brain structures in 38,851 individuals

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[206]Department of Developmental Disability Neuropsychiatry, School of Psychiatry, UNSW Medicine, Sydney, New South Wales, Australia. [207]Biomedical Research Unit for Dementia, King's College London, London, UK. [208]Department of Neuroimaging, Institute of Psychiatry, King's College London, London, UK. [209]Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Stockholm, Sweden. [210]Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA. [211]Section of Computational Biomedicine, Department of Medicine, Boston University School of Medicine, Boston, MA, USA. [212]Department of Radiology, Mayo Clinic, Rochester, MN, USA. [213]School of Medical Sciences, UNSW, Sydney, New South Wales, Australia. [214]Department of Biomedicine, University of Basel, Basel, Switzerland. [215]Cécile and Oskar Vogt Institute for Brain Research, Heinrich Heine University Düsseldorf, Düsseldorf, Germany. [216]Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, USA. [217]Laboratory of Neuro Imaging, USC Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA. [218]Radiation Sciences, Umeå University, Umeå, Sweden. [219]Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. [220]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands. [221]Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [222]Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [223]Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [224]Imaging Physics, Faculty of Applied Sciences, Delft University of Technology, Delft, the Netherlands. [225]Institut Pasteur, Paris, France. [226]Department of

Neurology, CHU de Bordeaux, Bordeaux, France. [227]Department of Neurology, University of Washington, Seattle, WA, USA. [228]Department of Neurology, Erasmus MC, Rotterdam, the Netherlands. [229]Cognitive Neuroscience Center, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands. [230]Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, Toronto, Ontario, Canada. [231]Department of Psychology, University of Toronto, Toronto, Ontario, Canada. [232]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada. [233]Clinic for Cognitive Neurology, University Clinic Leipzig, Leipzig, Germany. [234]HMNC Brain Health, Munich, Germany. [235]Department of Neurology, Hopital Erasme, Universite Libre de Bruxelles, Brussels, Belgium. [236]Department of Psychology, Georgia State University, Atlanta, GA, USA. [237]Department of Medical Genetics, Oslo University Hospital, Oslo, Norway. [238]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany. [239]Institute of Translational Medicine, University of Liverpool, Liverpool, UK. [240]Institute of Clinical Medicine—Neurology, University of Eastern Finland, Kuopio, Finland. [241]Neurocentre Neurology, Kuopio University Hospital, Kuopio, Finland. [242]Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany. [243]German Center for Cardiovascular Research (partner site Greifswald), Greifswald, Germany. [244]Department of Neuroinformatics, Araya, Tokyo, Japan. [245]Institute of Cognitive Neuroscience, University College London, London, UK. [246]School of Psychology, University of Sussex, Brighton, UK. [247]Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden. [248]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [249]Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands. [250]Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, the Netherlands. [251]GROW School for Oncology and Developmental Biology, Maastricht, the Netherlands. [252]Centre for Advanced Imaging, University of Queensland, Brisbane, Queensland, Australia. [253]Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany. [254]Department of Psychiatry, Erasmus Medical Center, Rotterdam, the Netherlands. [255]Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, New South Wales, Australia. [256]Department of Psychology, VU University Amsterdam, Amsterdam, the Netherlands. [257]Center for Imaging of Neurodegenerative Disease, San Francisco VA Medical Center, University of California, San Francisco, San Francisco, CA, USA. [258]Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, USA. [259]Leiden Academic Centre for Drug Research, Leiden University, Leiden, the Netherlands. [260]Human Genetics Center, University of Texas Health Science Center at Houston, Houston, TX, USA. [261]UK Dementia Research Institute, University of Edinburgh, Edinburgh, UK. [262]Department of Neurology, Center for Neuroscience, University of California, Davis, Sacramento, CA, USA. [263]Department of Neuroscience, Baylor College of Medicine, Houston, TX, USA. [264]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA. [265]Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, TX, USA. [266]These authors contributed equally: Claudia L. Satizabal, Hieab H. H. Adams, Derrek P. Hibar, Charles C. White. [267]These authors jointly supervised this work: Sarah E. Medland, Joshua M. Shulman, Paul M. Thompson, Sudha Seshadri, M. Arfan Ikram. *e-mail: satizabal@uthscsa.edu; m.a.ikram@erasmusmc.nl

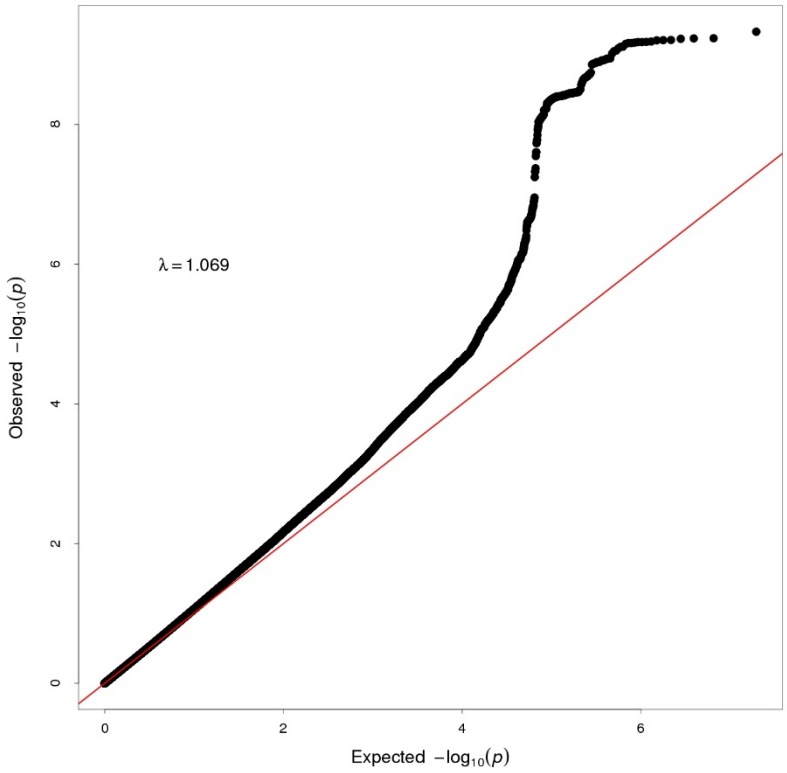
Genetic Architecture of Subcortical Brain Structures in 38,851 Individuals

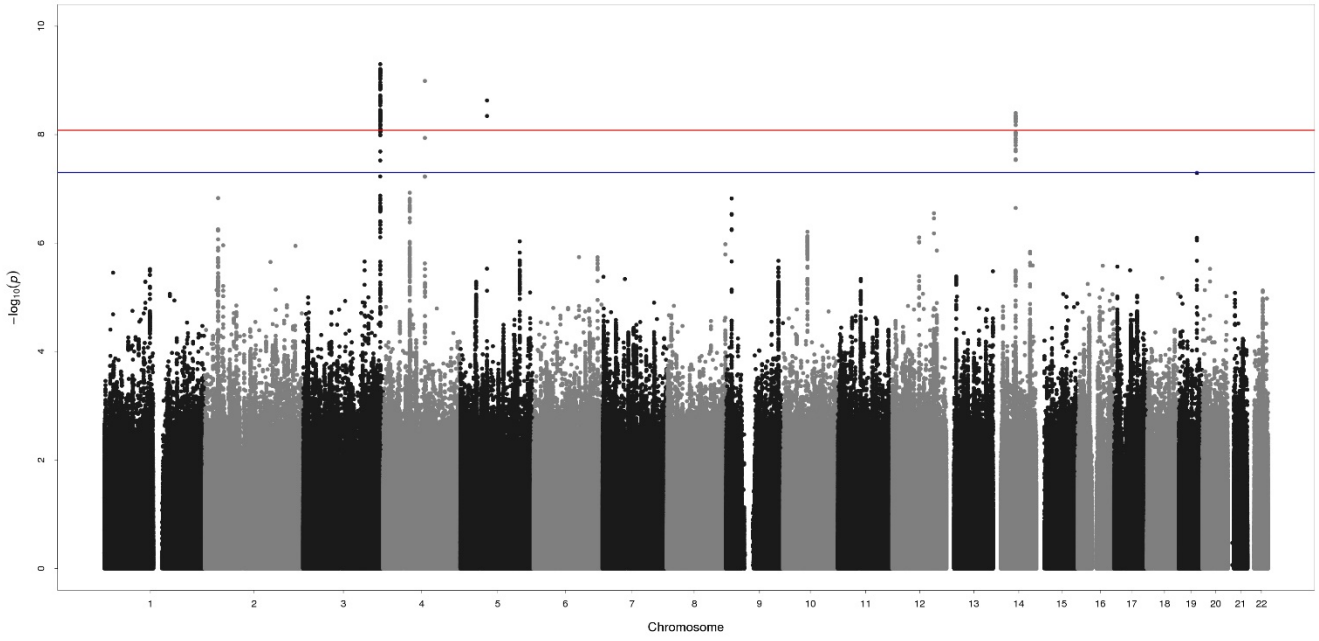
Supplementary note

SUPPLEMENTARY FIGURES

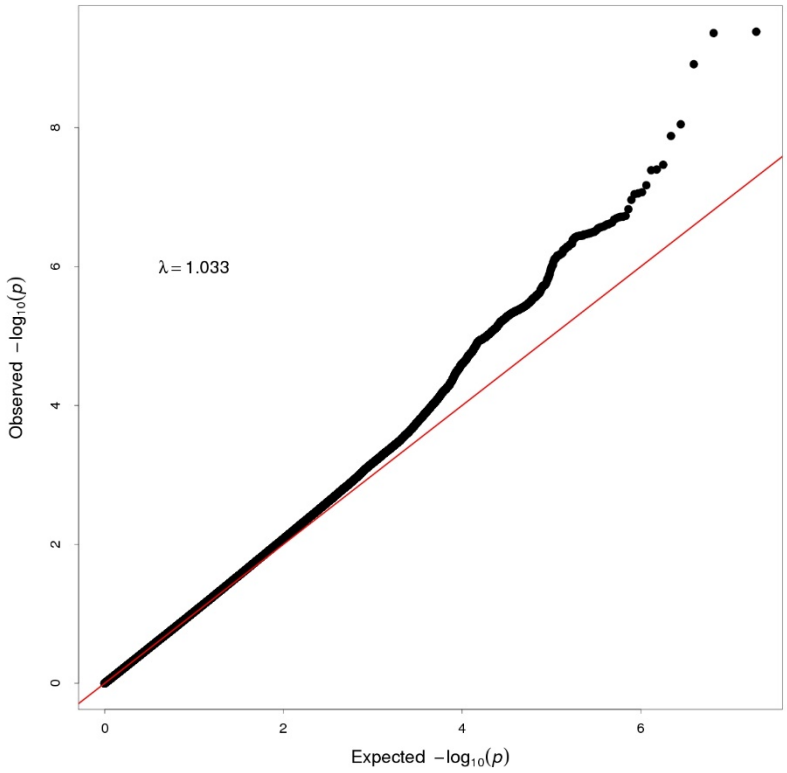
Supplementary Figure 1. **Quantile-quantile (QQ) and Manhattan plots in the European sample**. In QQ-plots, the red line represents the expected null distribution and Lambda inflation factors (λ) are provided inside each plot. In Manhattan plots, each point represents a single genetic variant plotted according to its genomic position (x-axis) and its −log10(P) for two-tailed associations with subcortical structures (y-axis). Linear regression models were adjusted for sex, age, age^2, total intracranial volume (CHARGE) or total brain volume (UKBB), and population stratification. The blue horizontal line represents a classic GWAS significance threshold of $P < 5 \times 10^{-8}$ and the red horizontal line represents genome-wide significance of $P < 8.3 \times 10^{-9}$ as defined for this study after additional Bonferroni correction for six independent traits ($P < 5 \times 10^{-8}/6$).

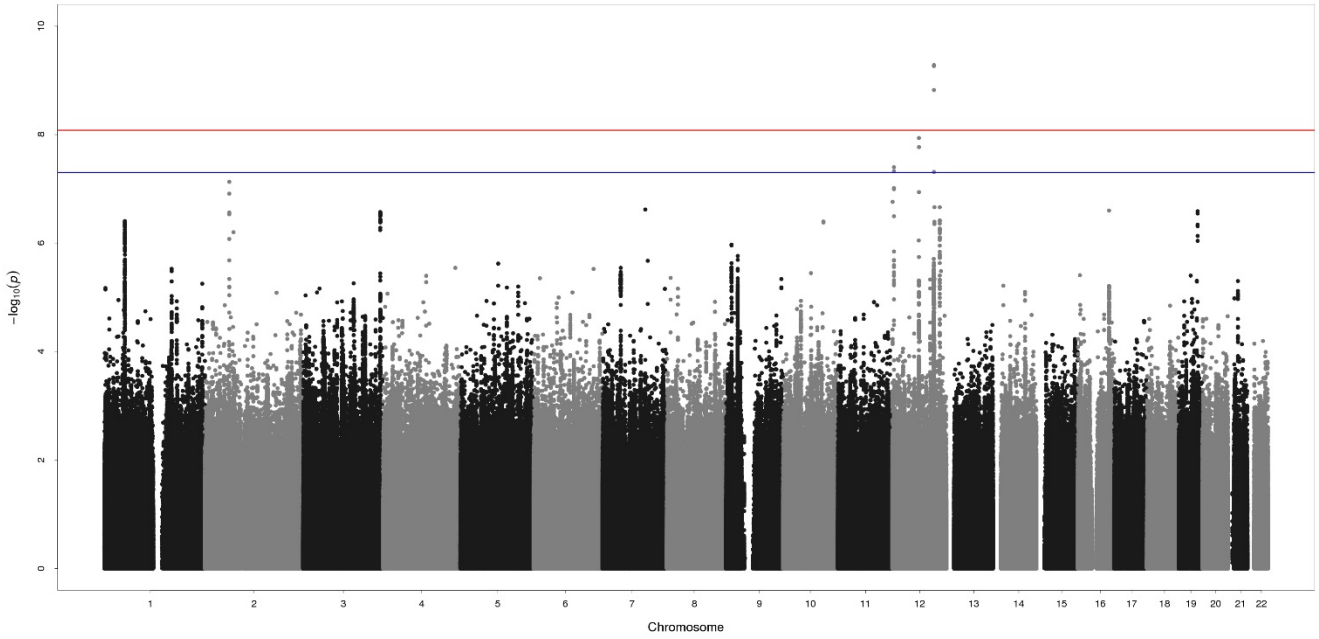
1. Nucleus accumbens **(n=32,562)**



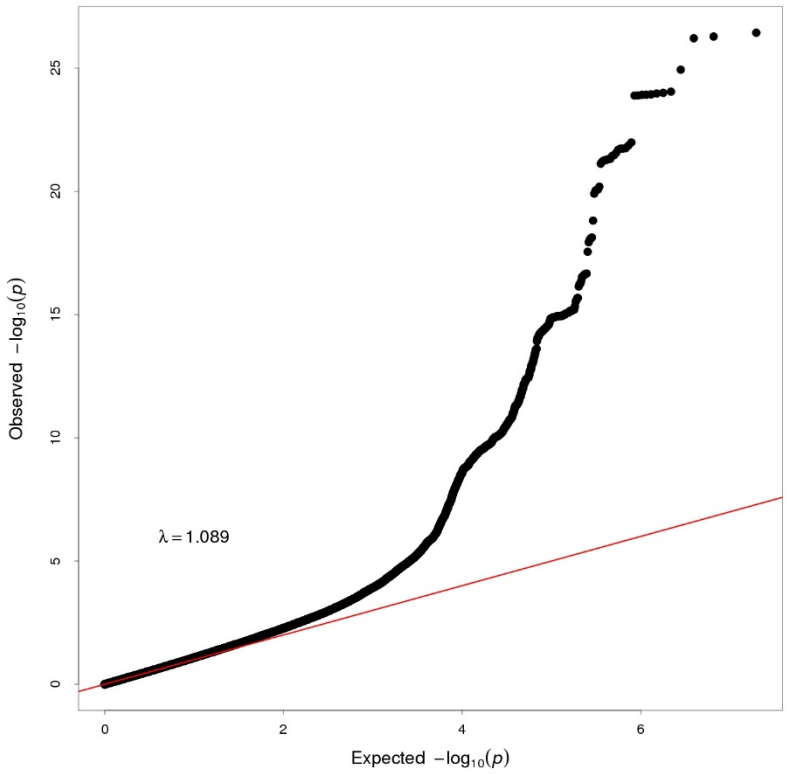


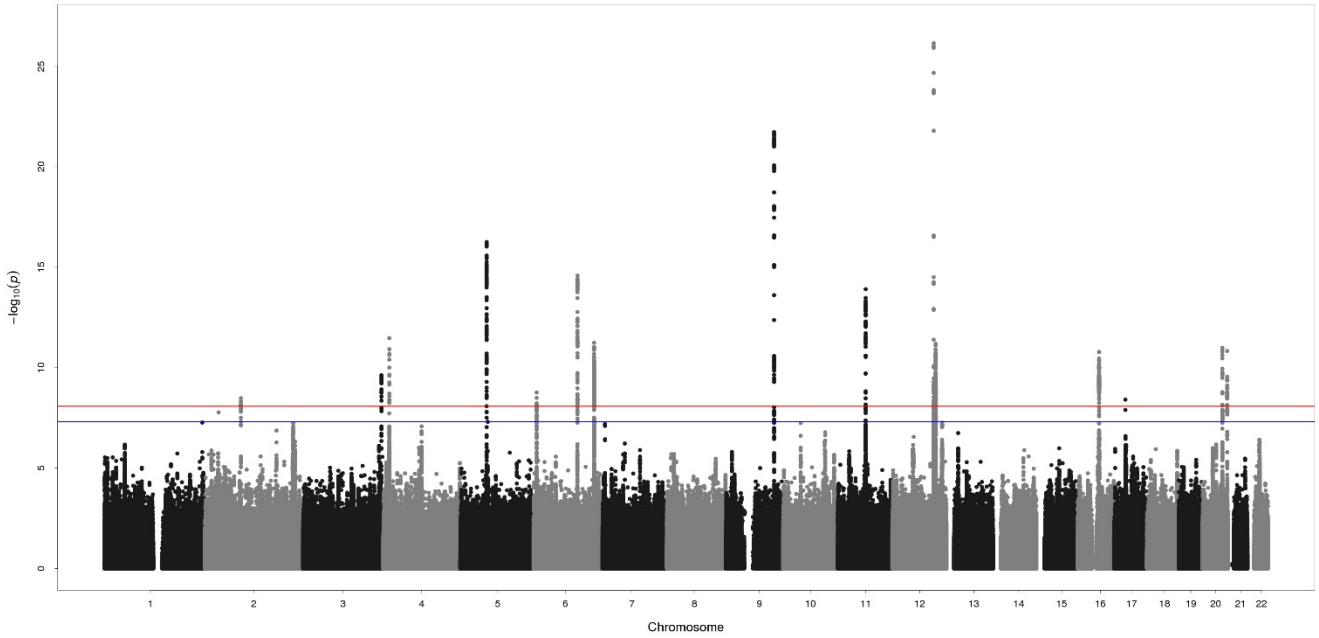
2. Amygdala **(n=34,431)**



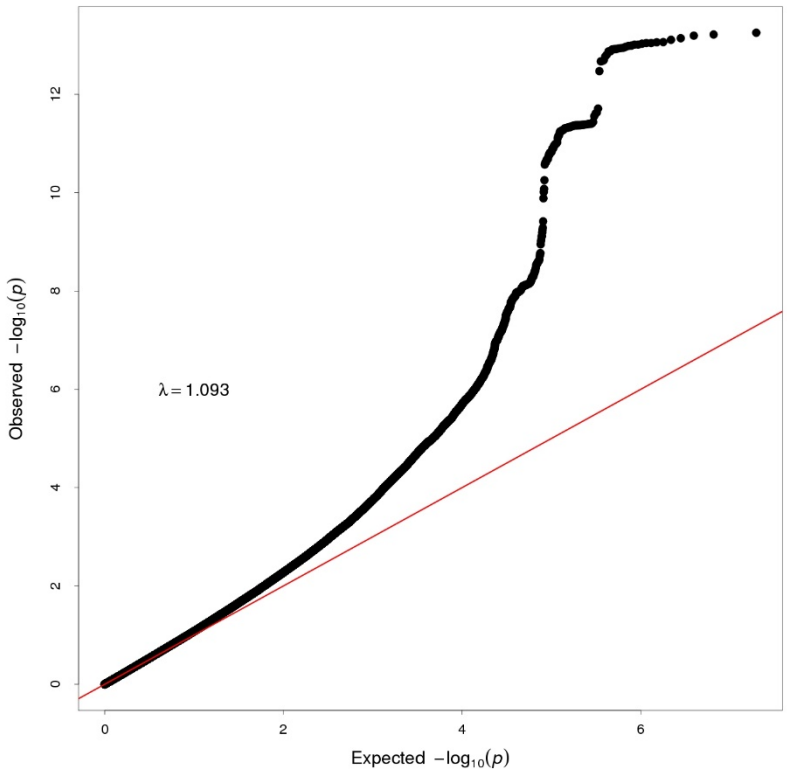


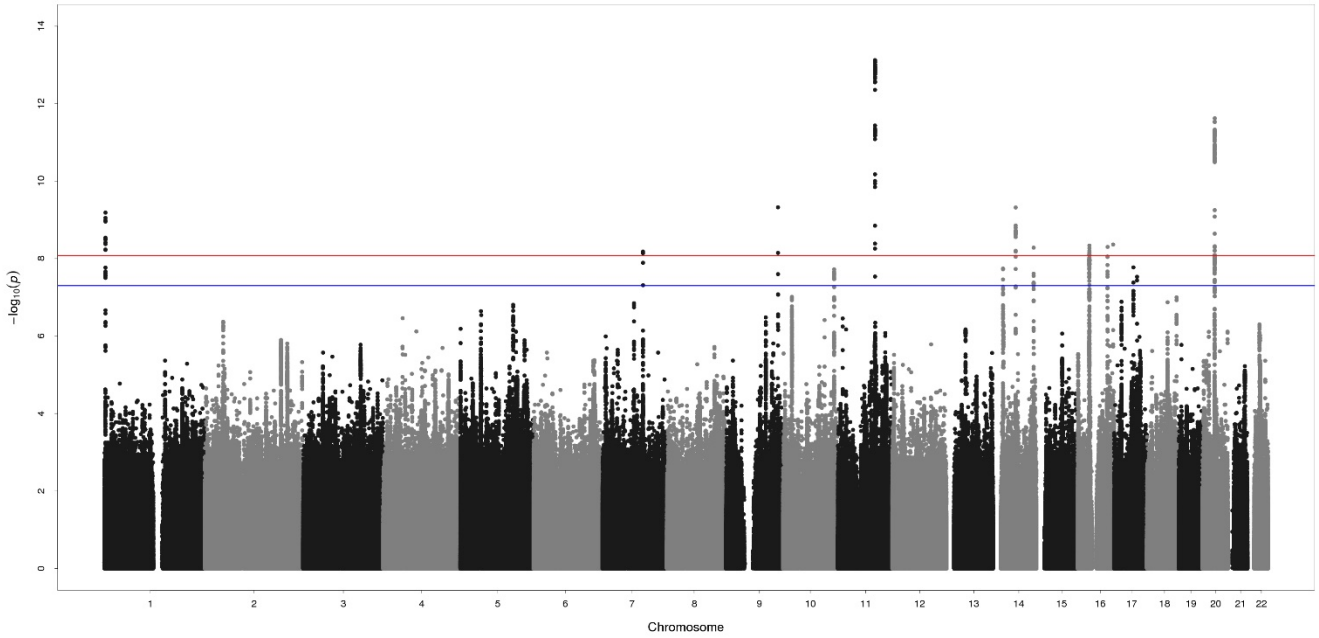
3. Brainstem **(n=28,809)**



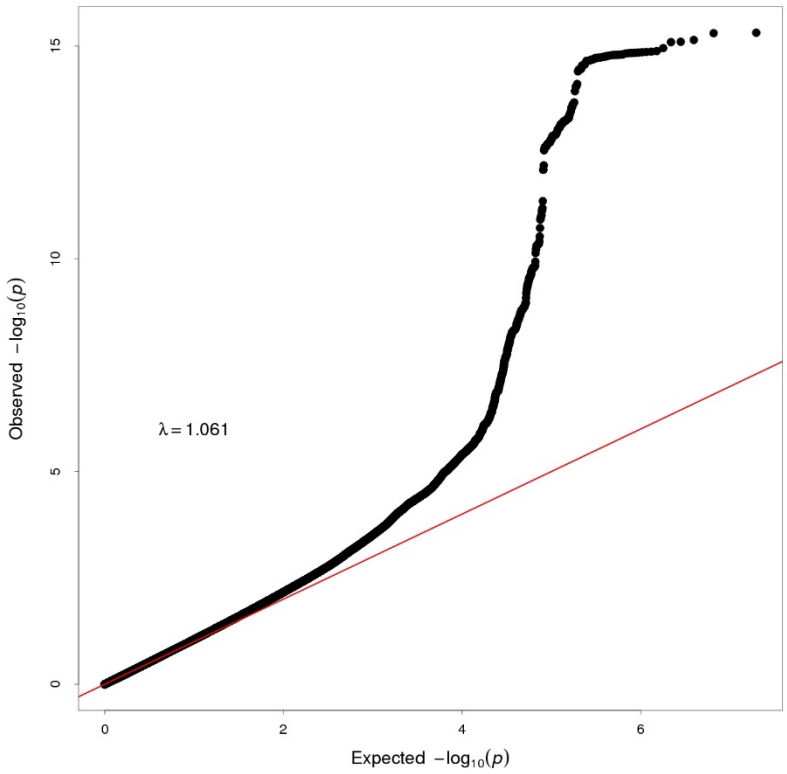


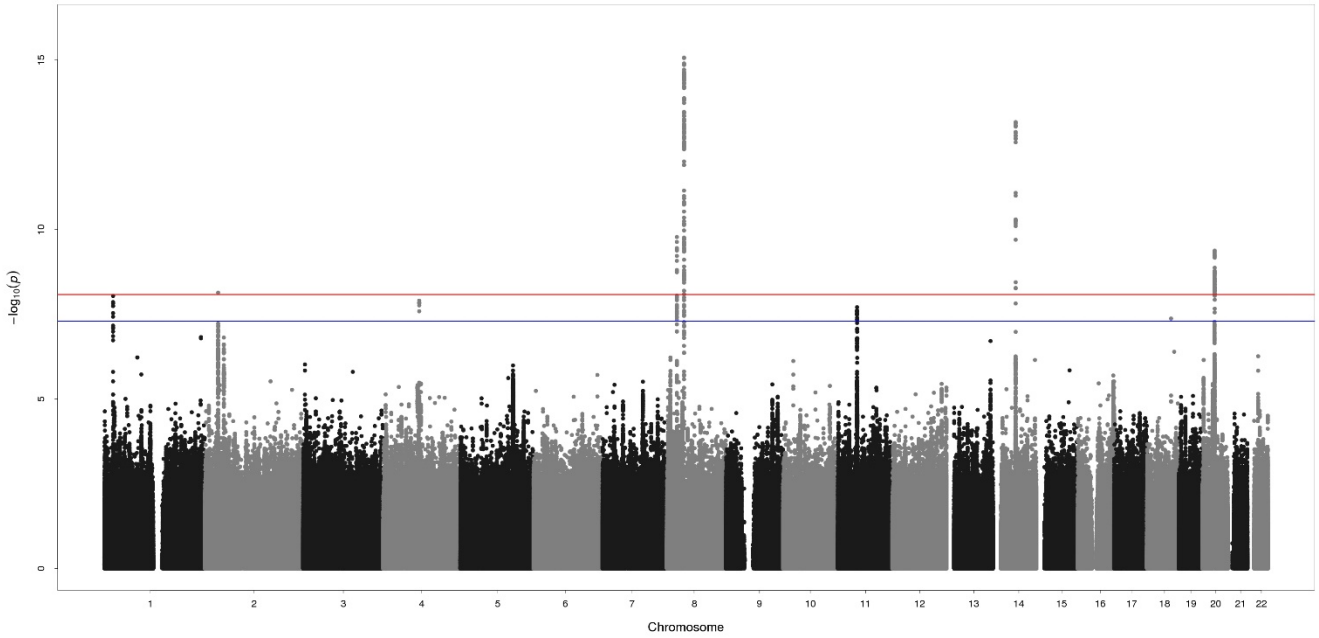
4. Caudate nucleus **(n=37,741)**



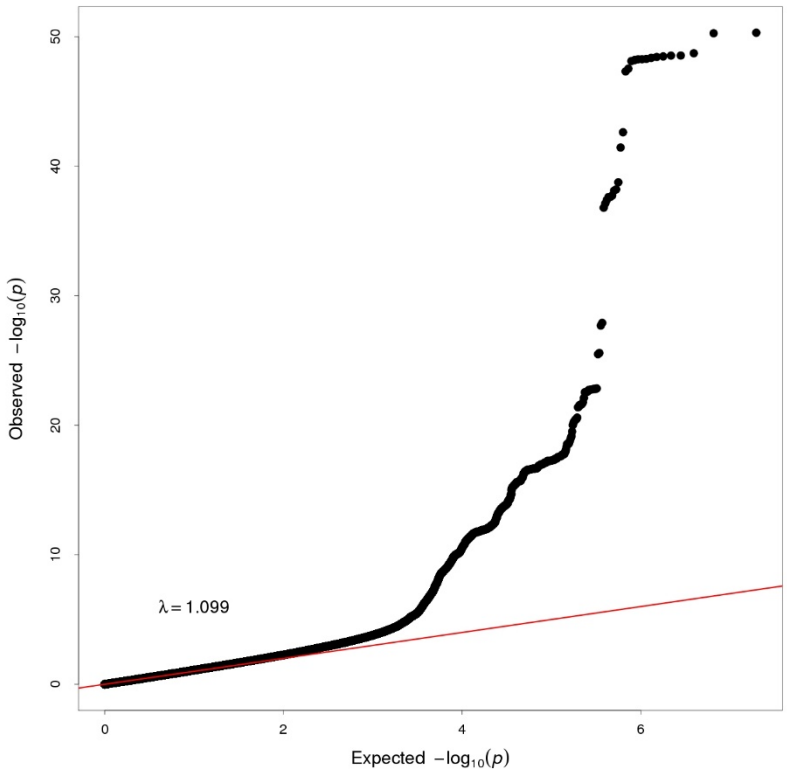


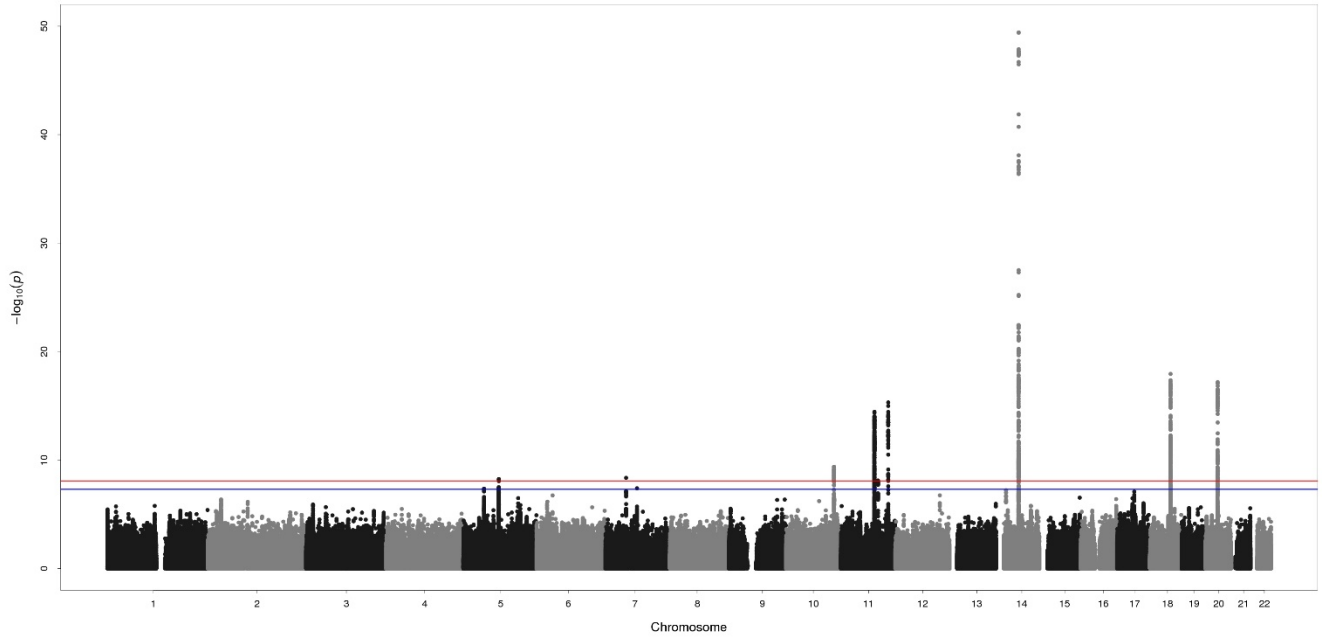
5. Globus pallidus **(n=34,413)**



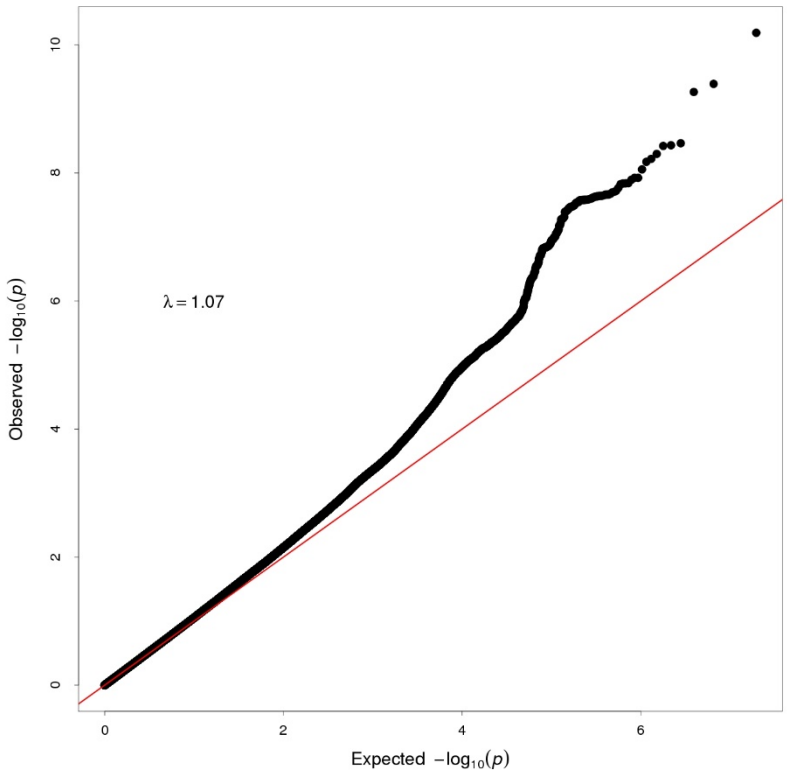


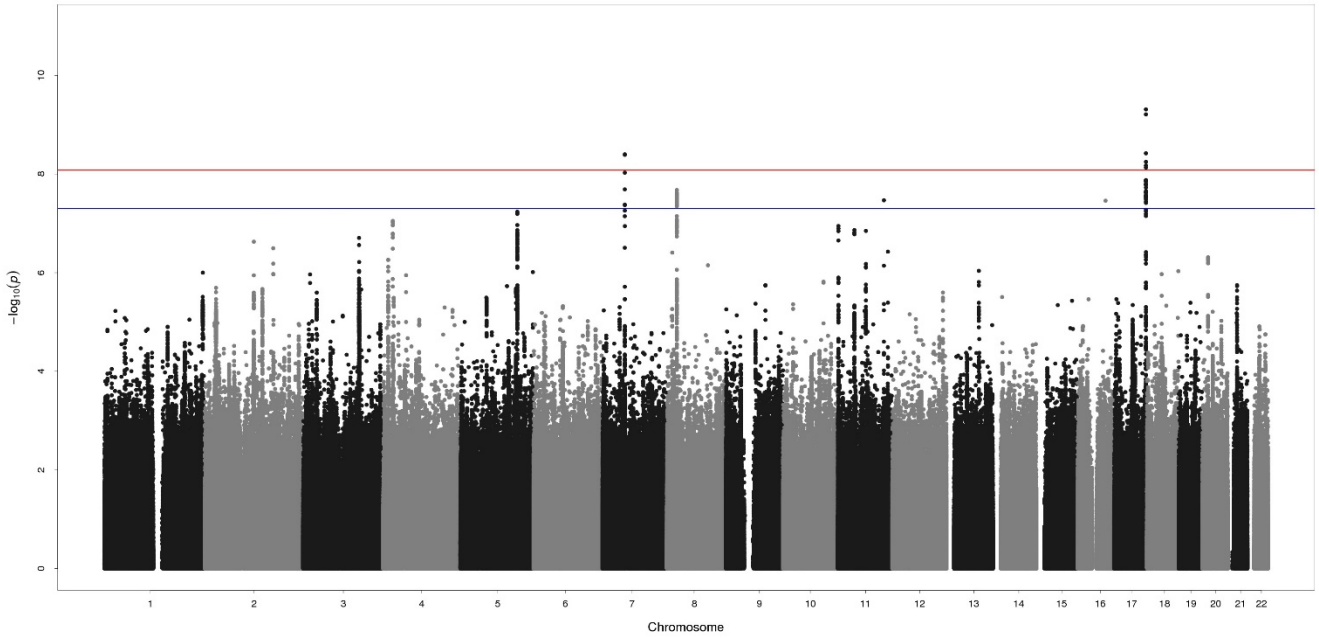
6. Putamen **(n=37,571)**





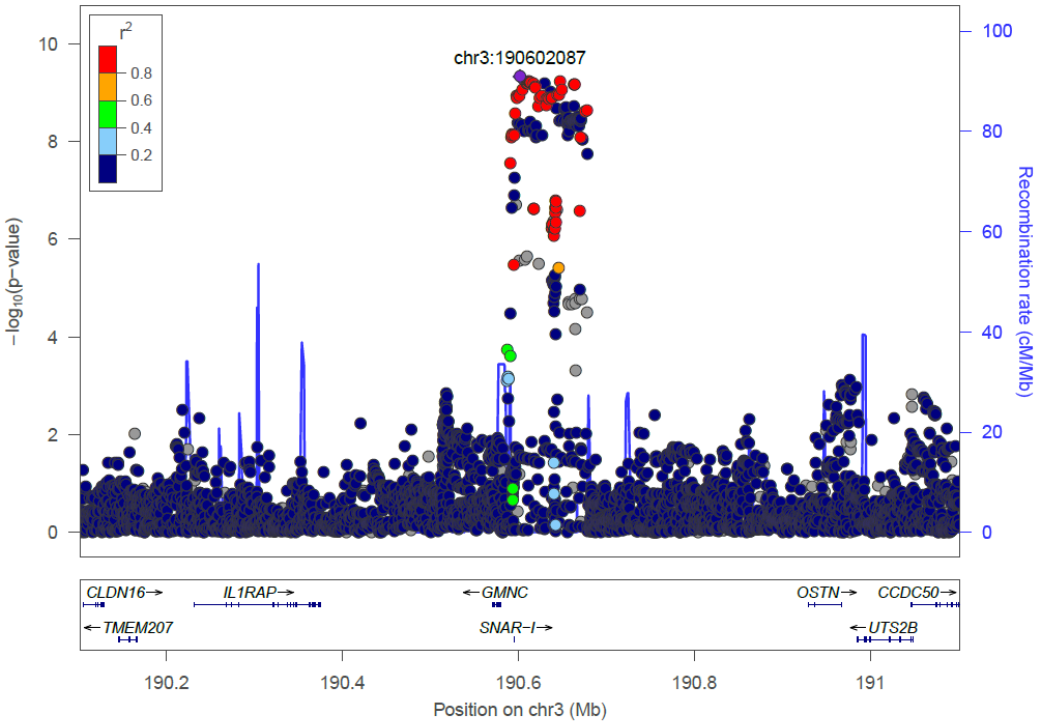
7. Thalamus **(n=34,464)**



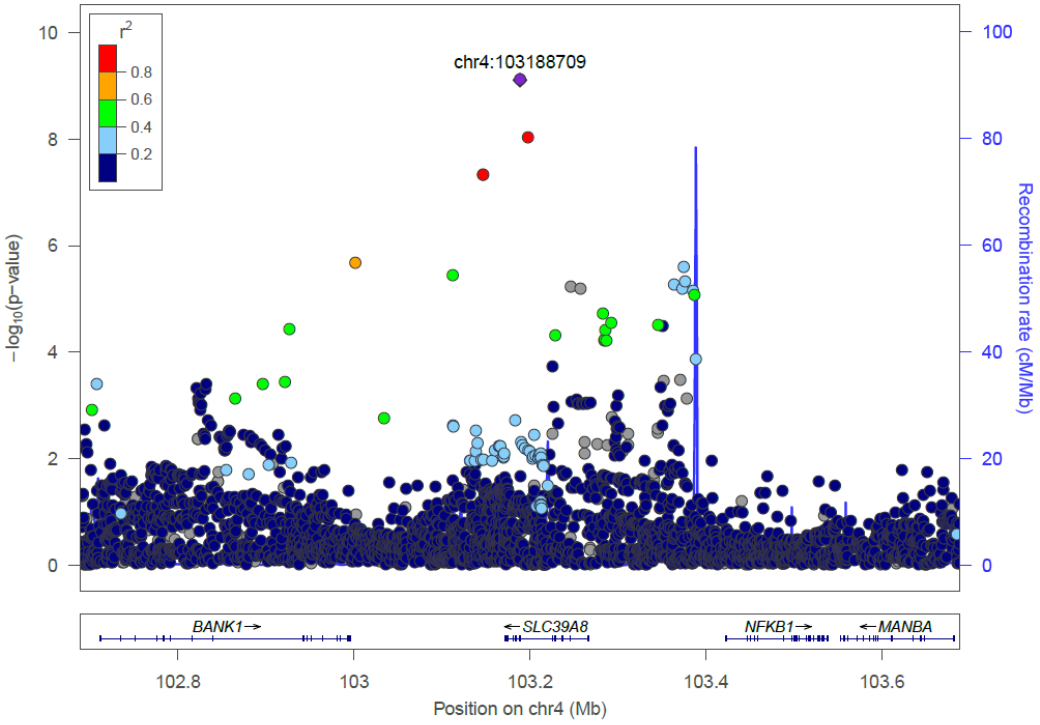


Supplementary Figure 2. **Regional association plots for variants influencing the volume of subcortical brain structures.** Plots were generated with Locus Zoom for the European sample (nucleus accumbens = 32,562; amygdala = 34,431; brainstem =28,809; caudate = 37,741; pallidum = 34,413; putamen = 37,571; thalamus = 34,464). Linear regression models were adjusted for sex, age, age^2, total intracranial volume (CHARGE) or total brain volume (UKBB), and population stratification.

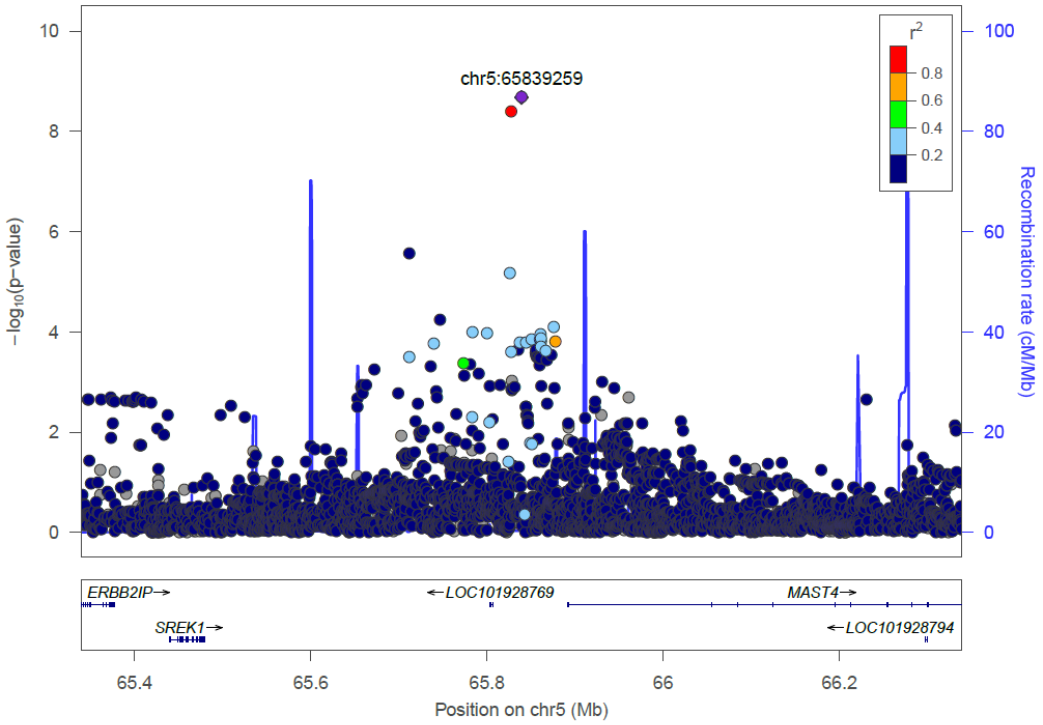
1. Nucleus accumbens (rs9818981)



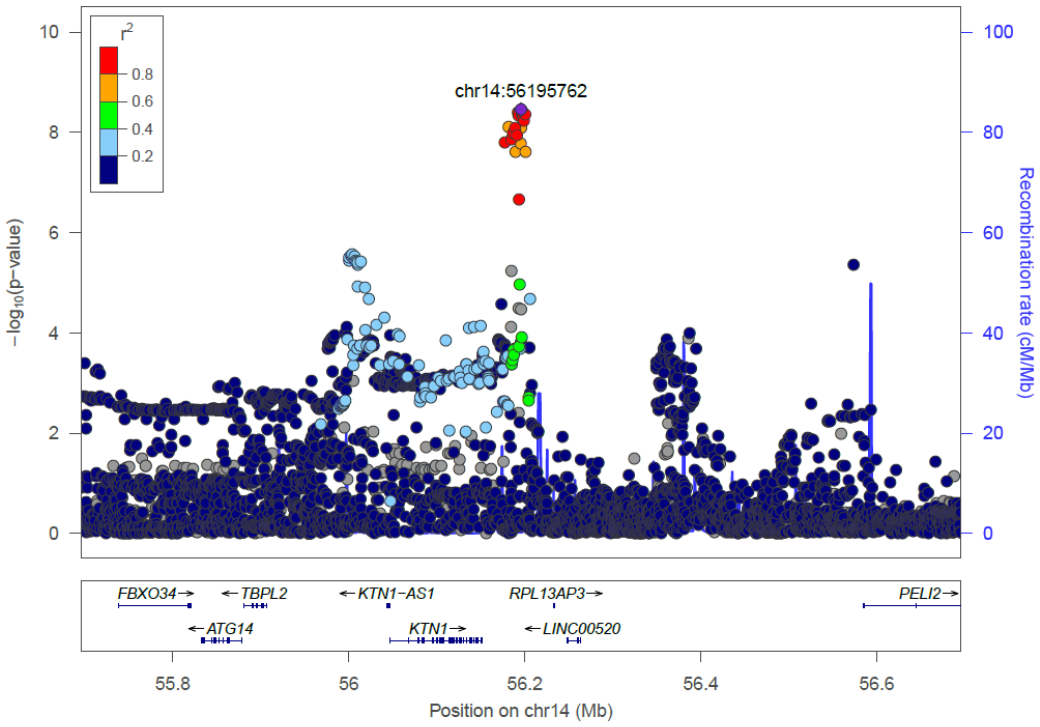
2. Nucleus accumbens (rs13107325)



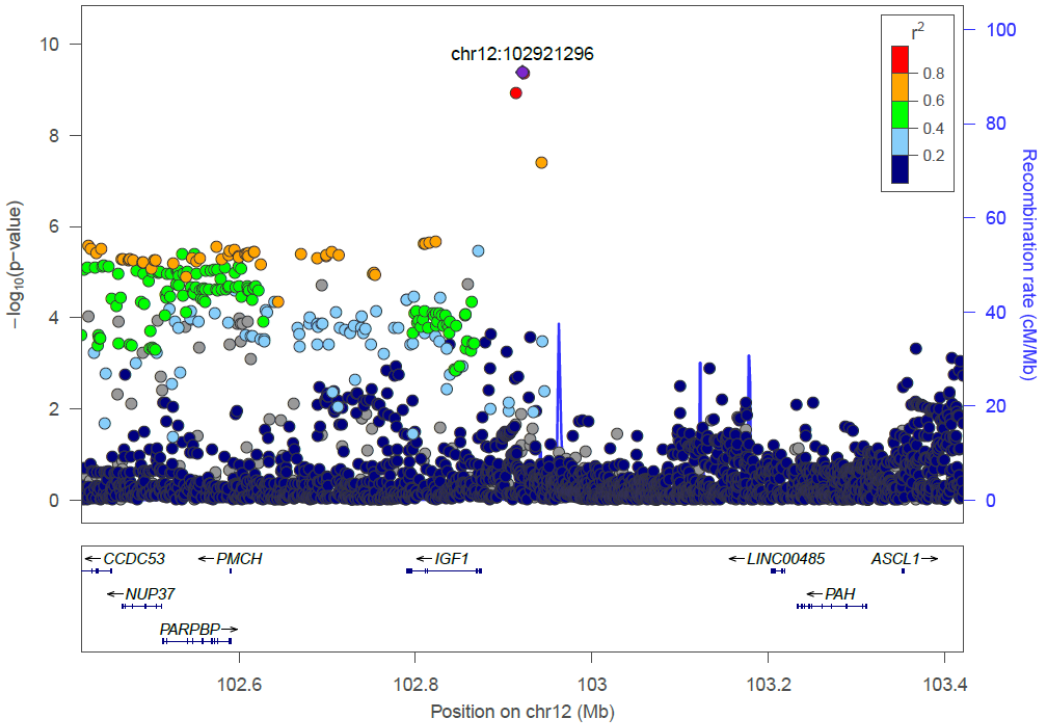
3. Nucleus accumbens (rs11747514)



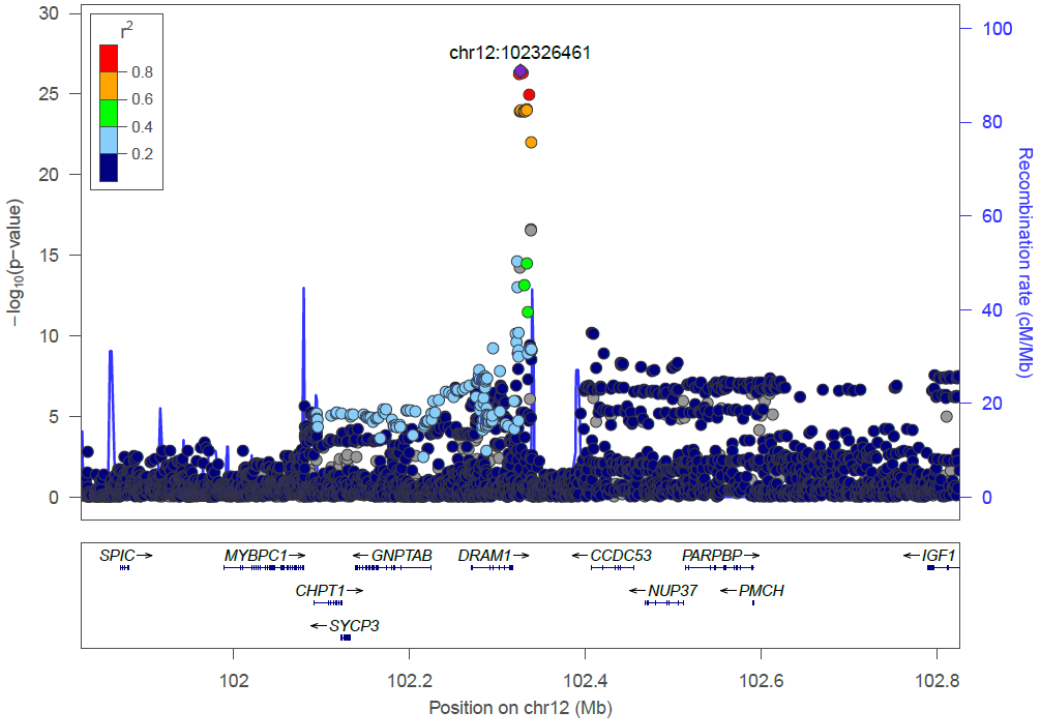
4. Nucleus accumbens (rs868202)



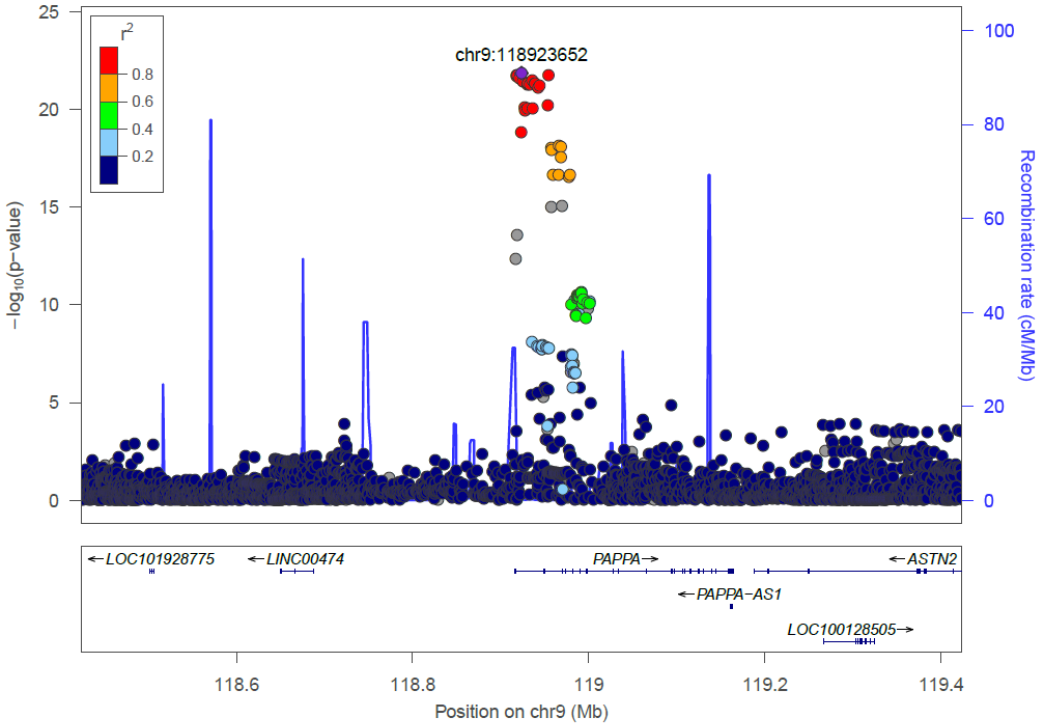
5. Amygdala (rs11111293)



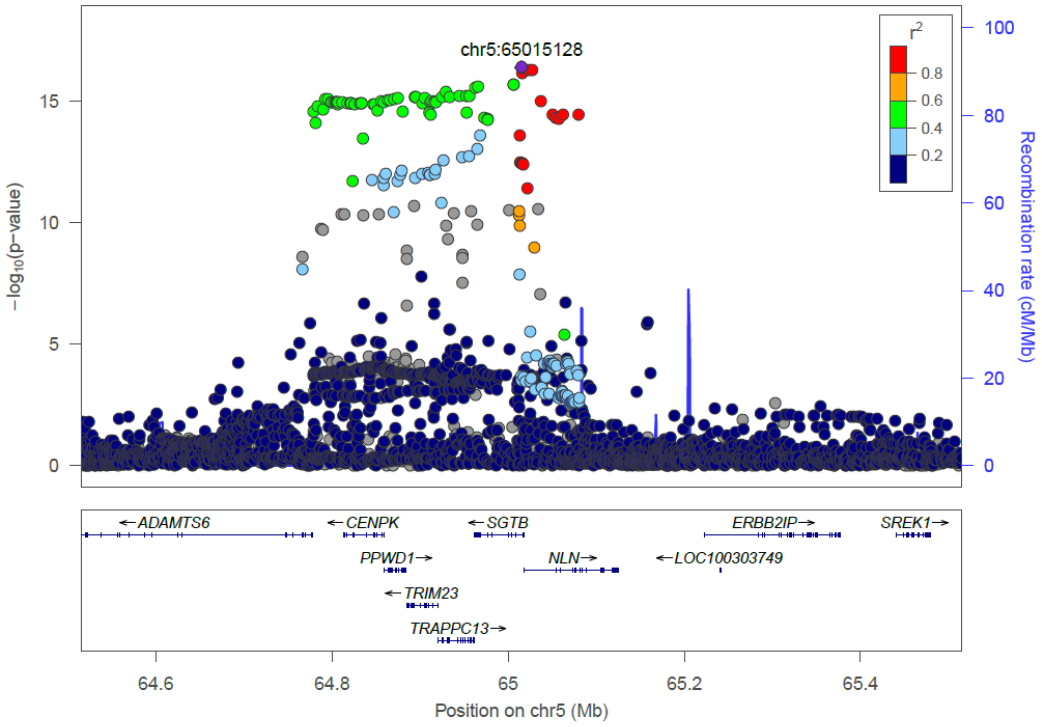
6. Brainstem (rs11111090)



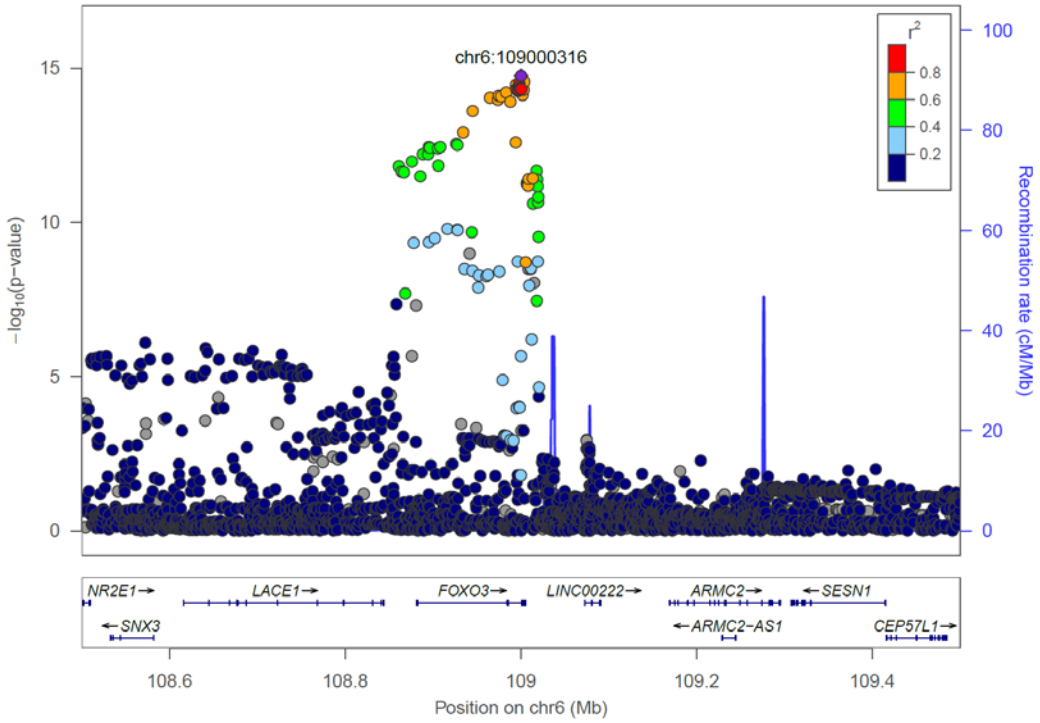
7. Brainstem (rs10217651)



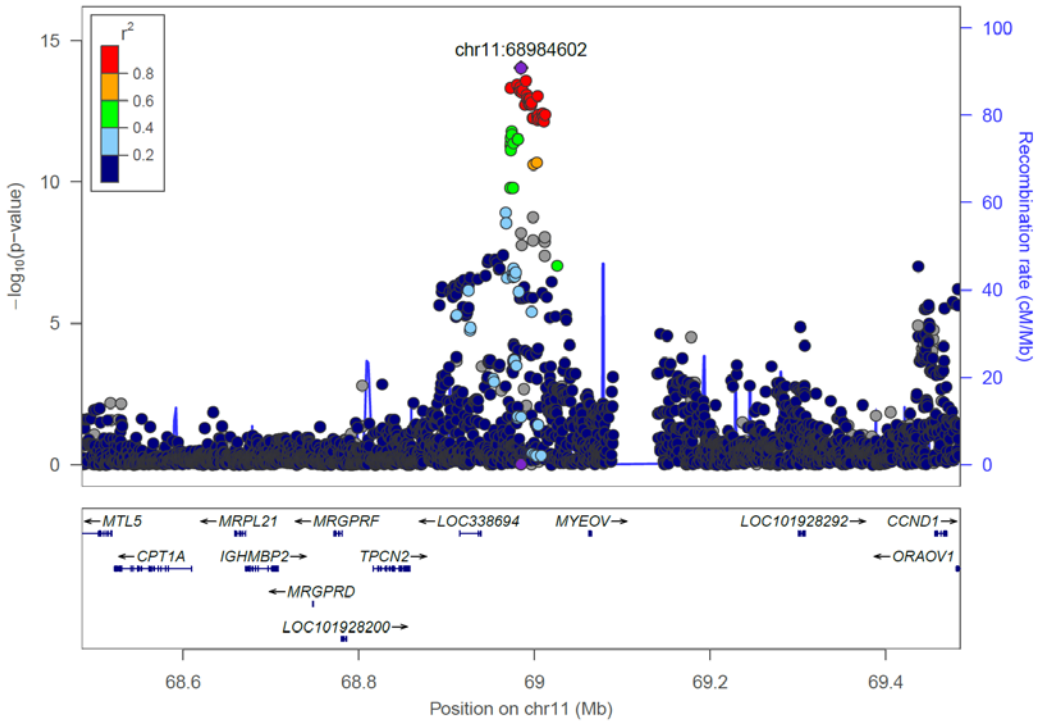
8. Brainstem (rs869640)



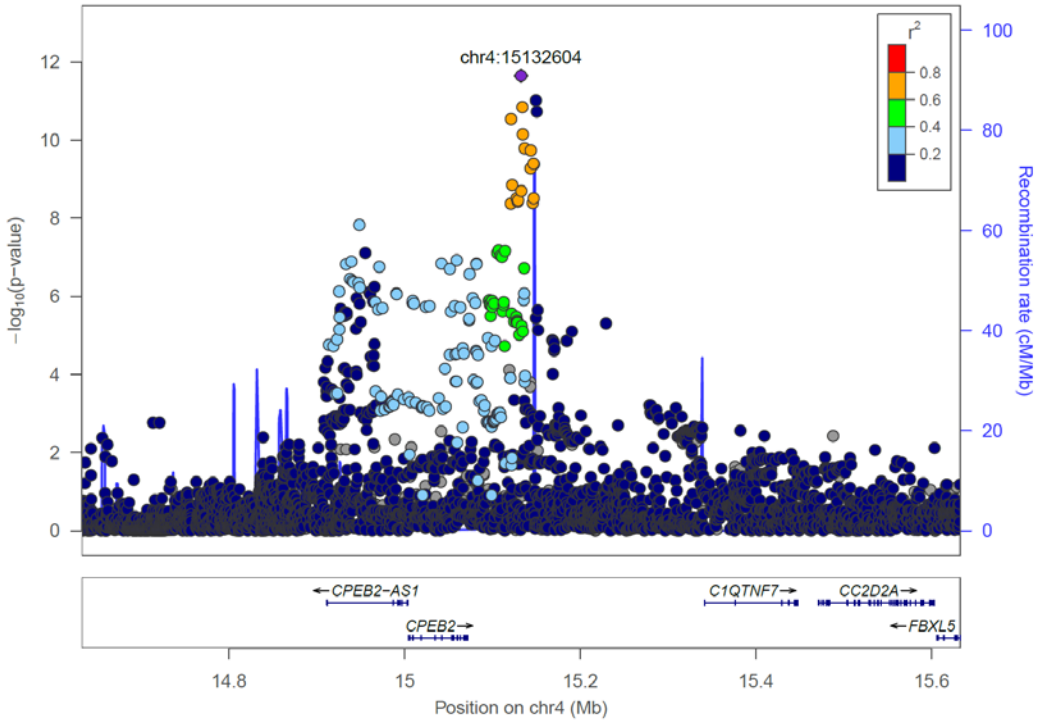
9. Brainstem (rs9398173)



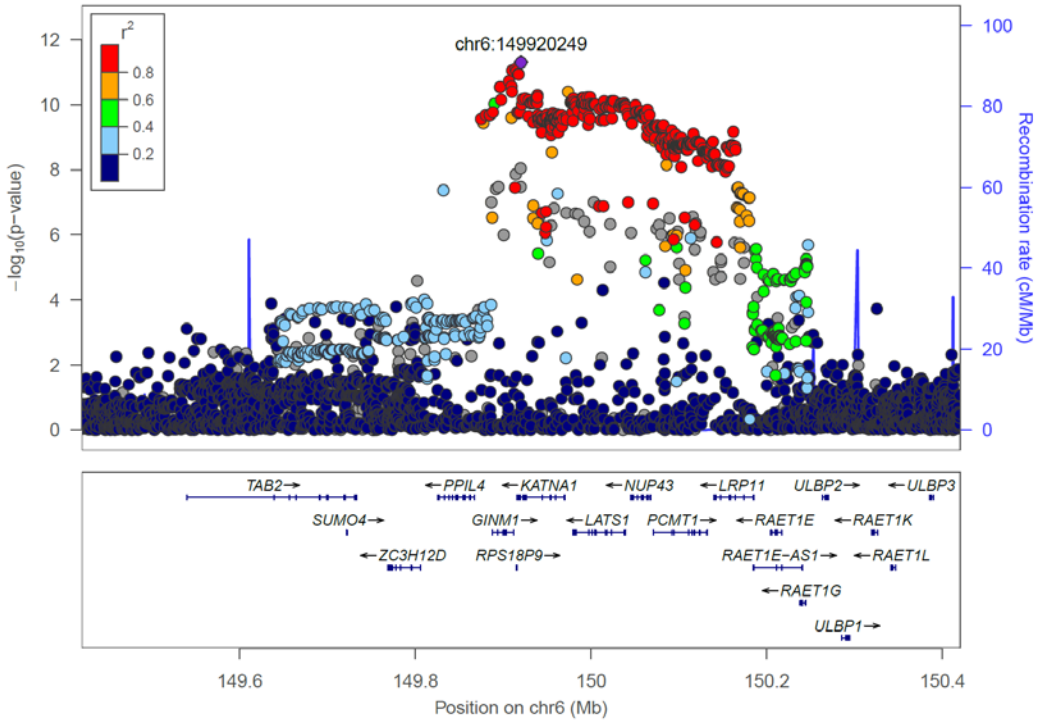
10. Brainstem (rs10792032)



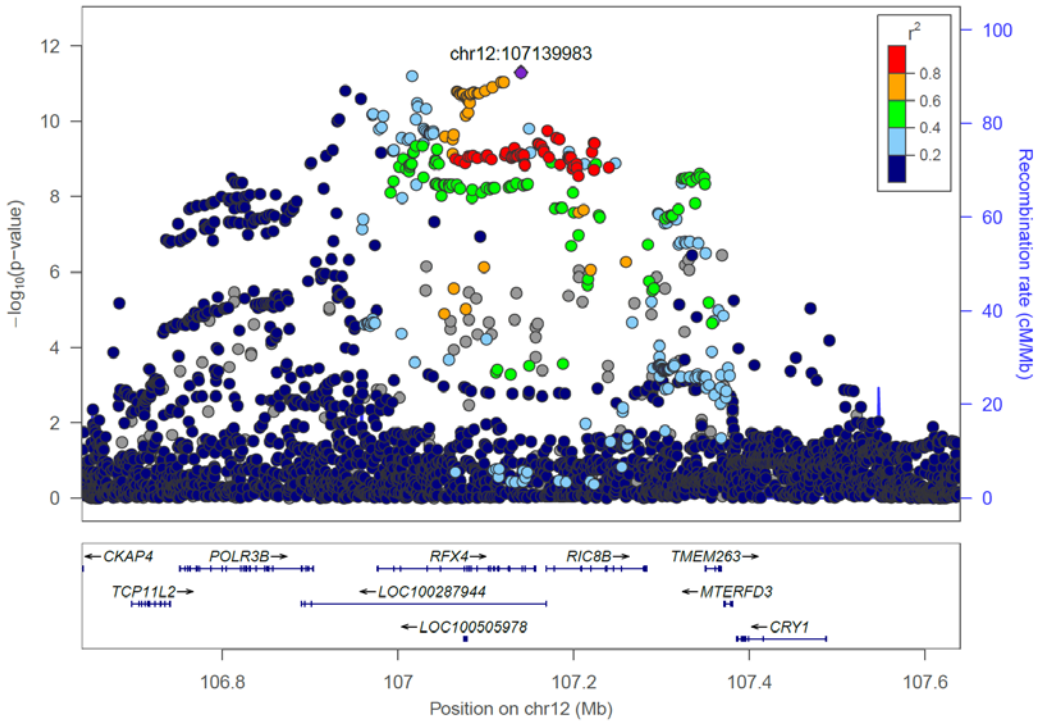
11. Brainstem (rs4396983)



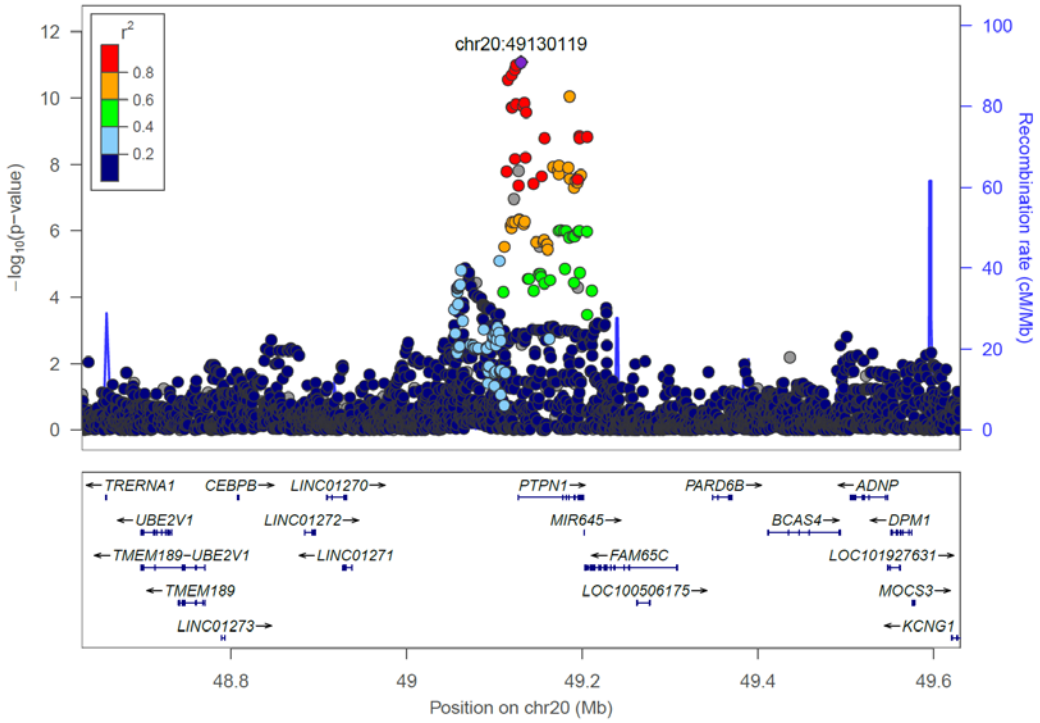
12. Brainstem (rs9322194)



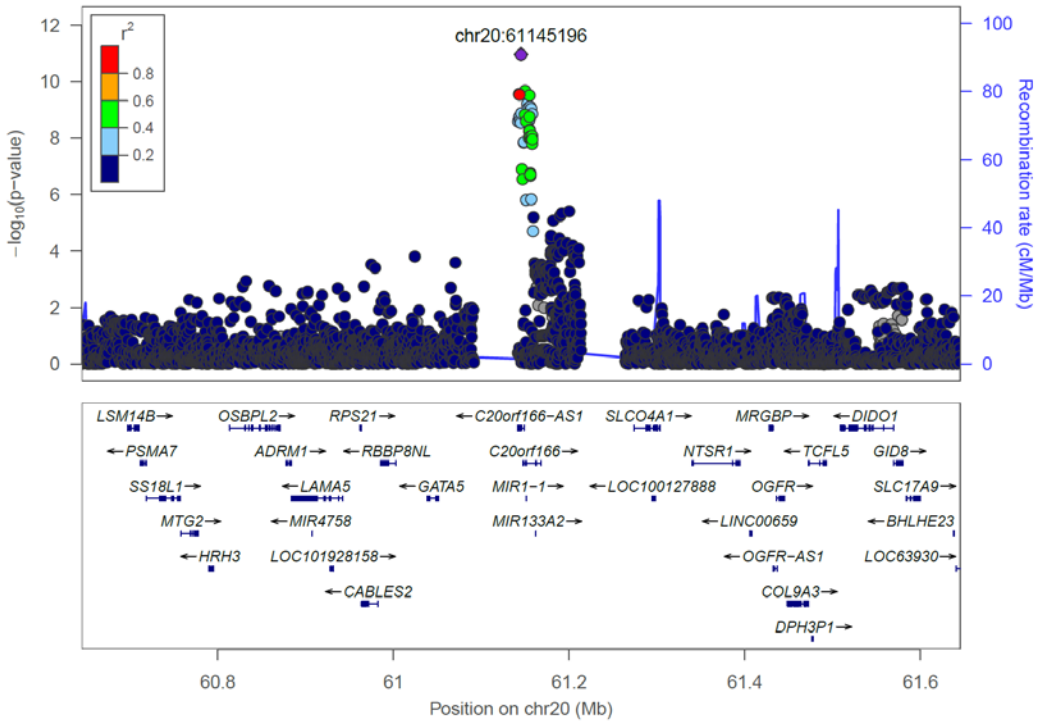
13. Brainstem (rs7972561)



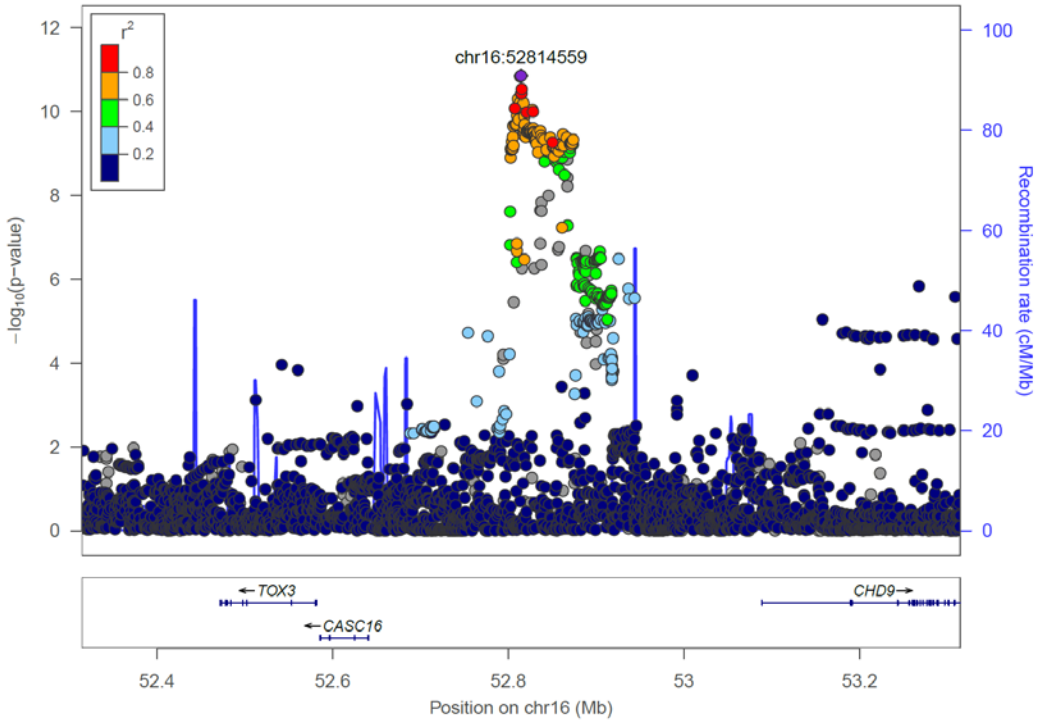
14. Brainstem (rs2206656)



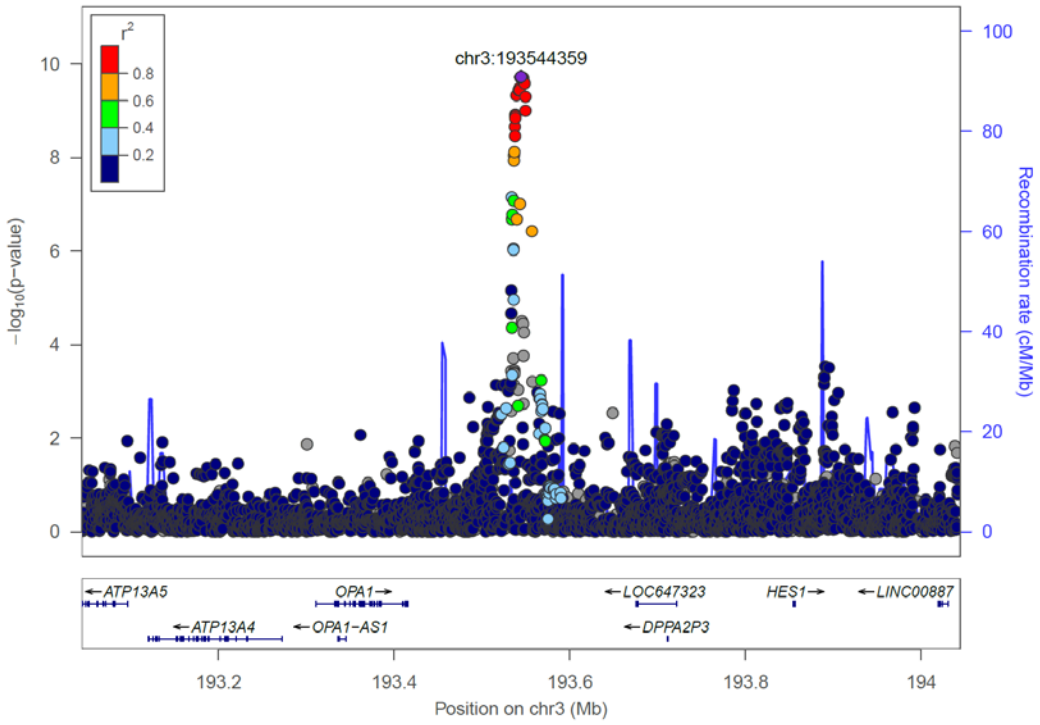
15. Brainstem (rs12479469)



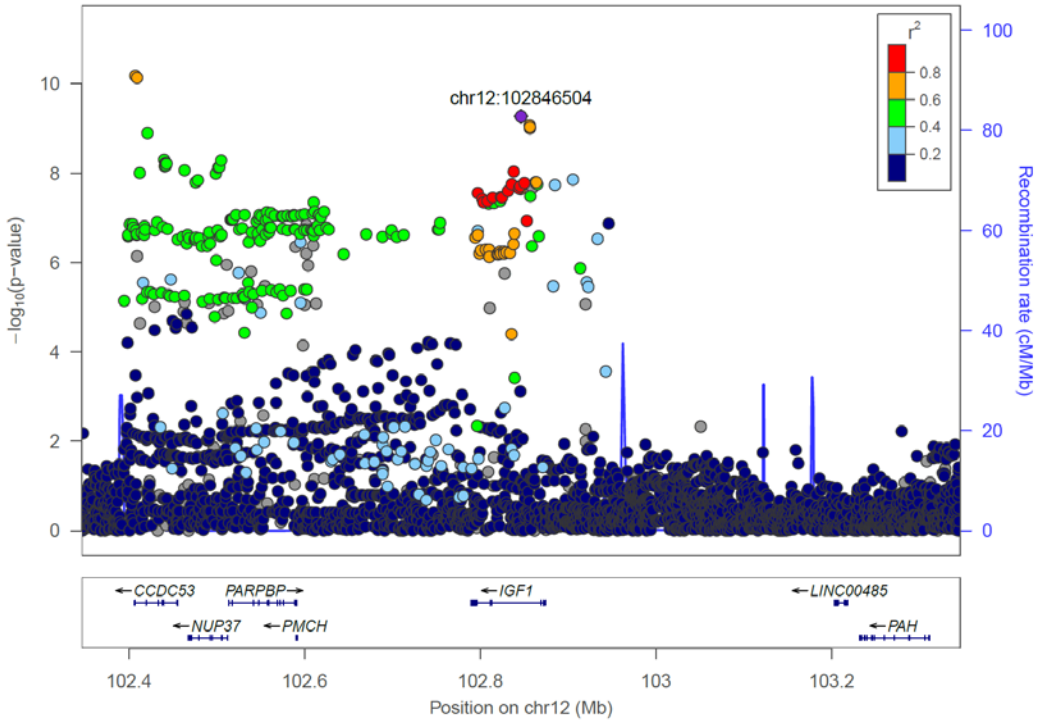
16. Brainstem (rs4784256)



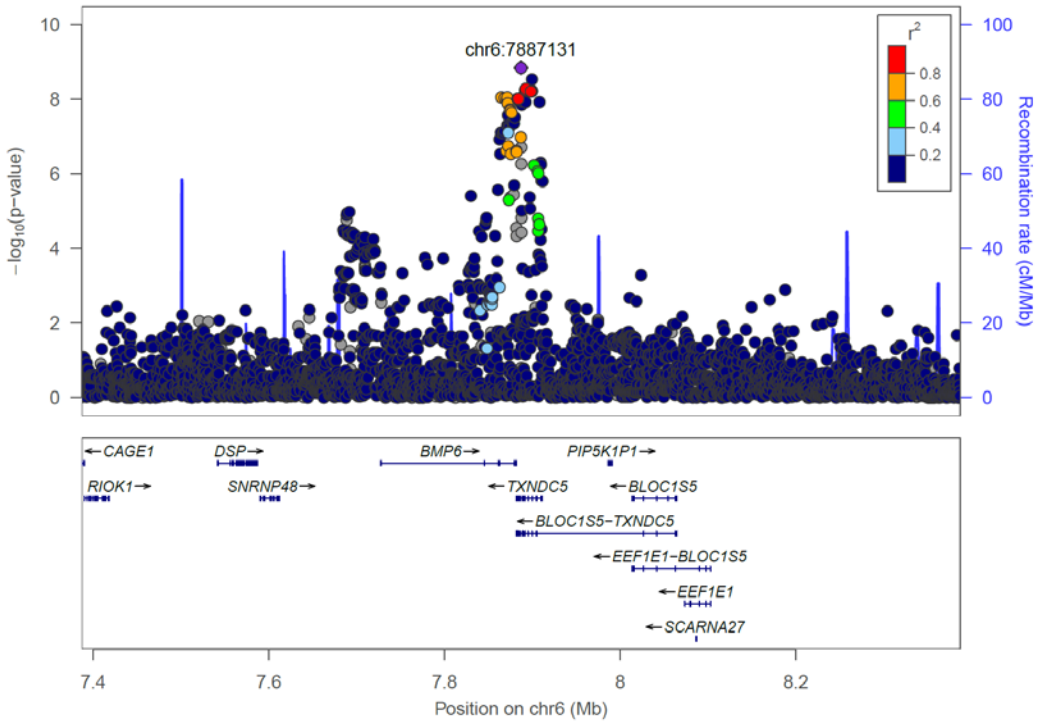
17. Brainstem (rs555925)



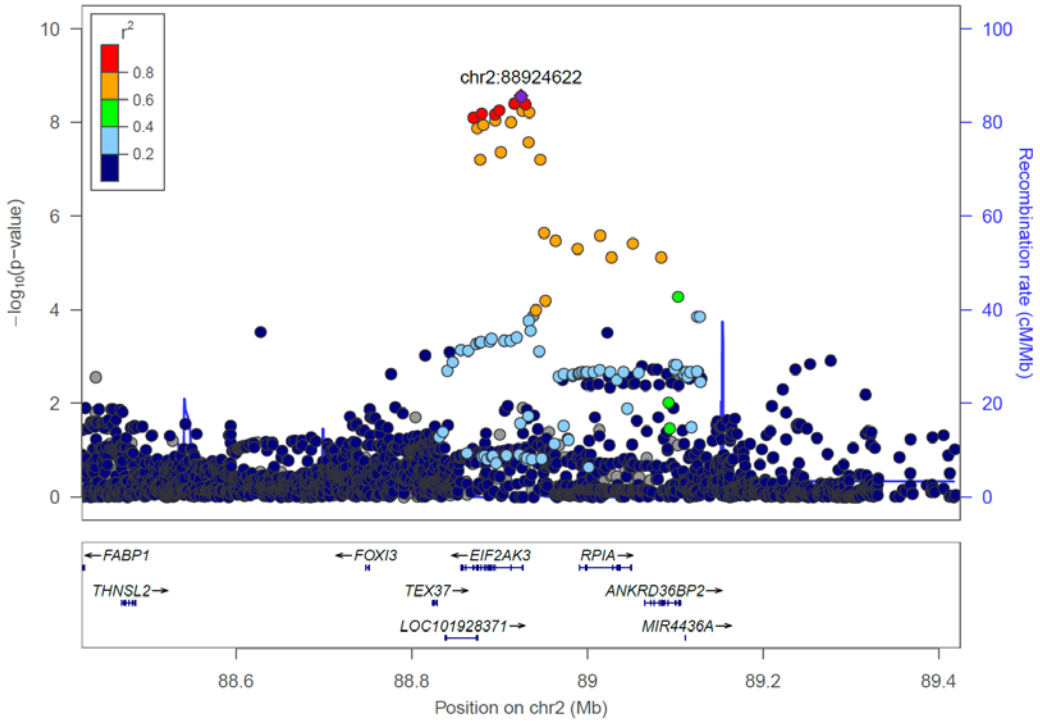
18. Brainstem (rs12313279)



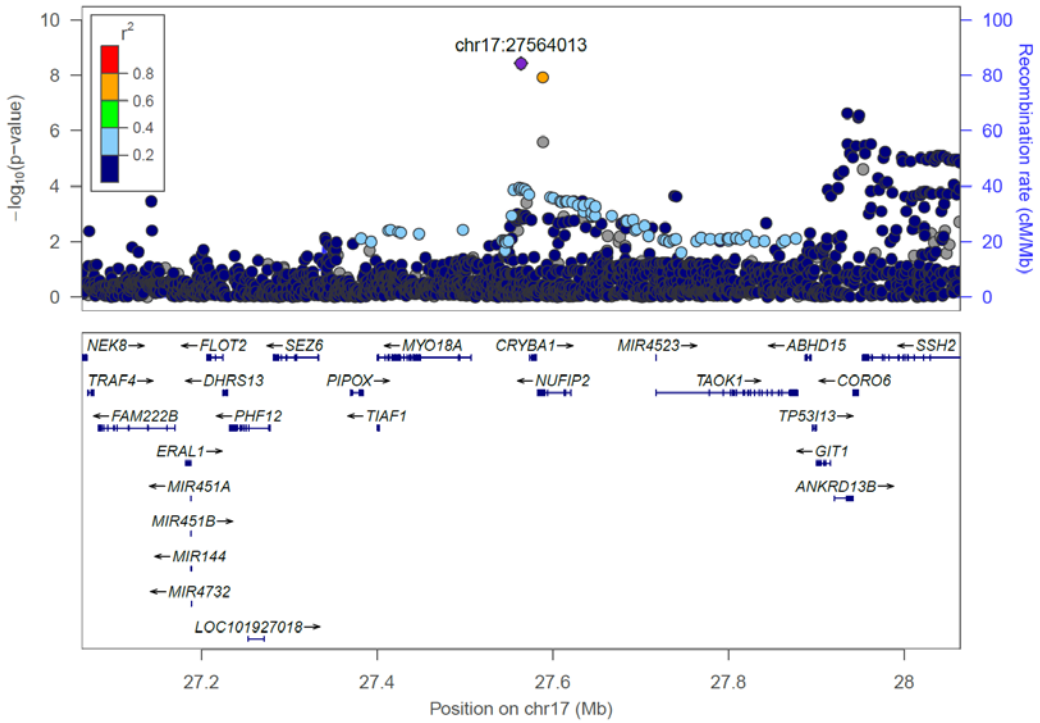
19. Brainstem (rs9505301)



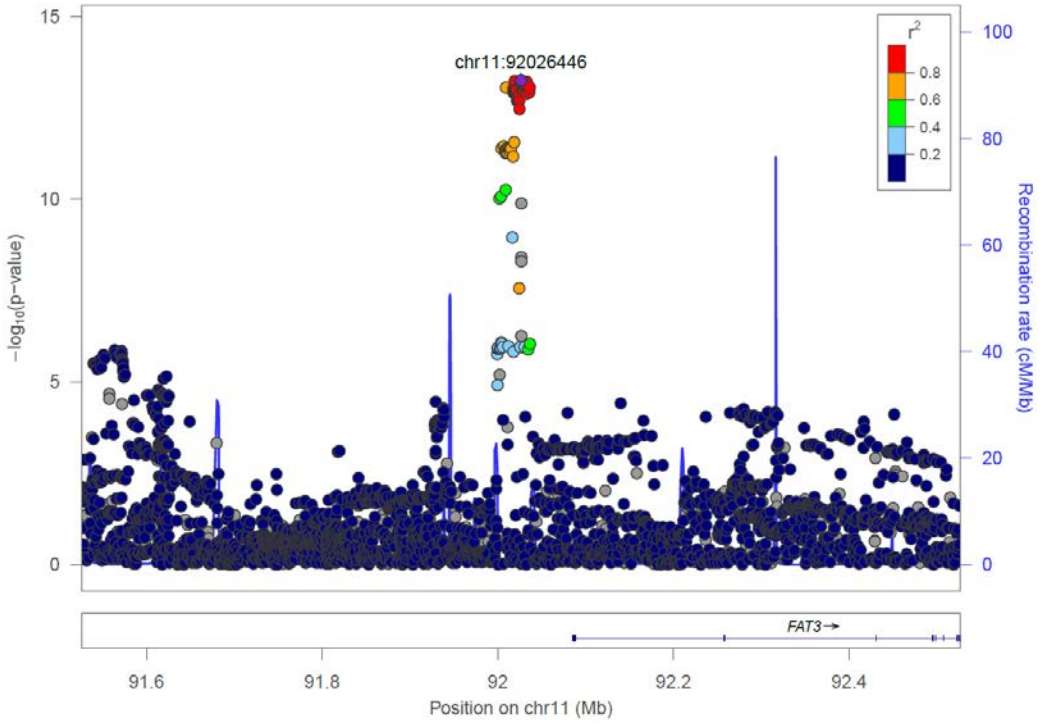
20. Brainstem (rs11684404)



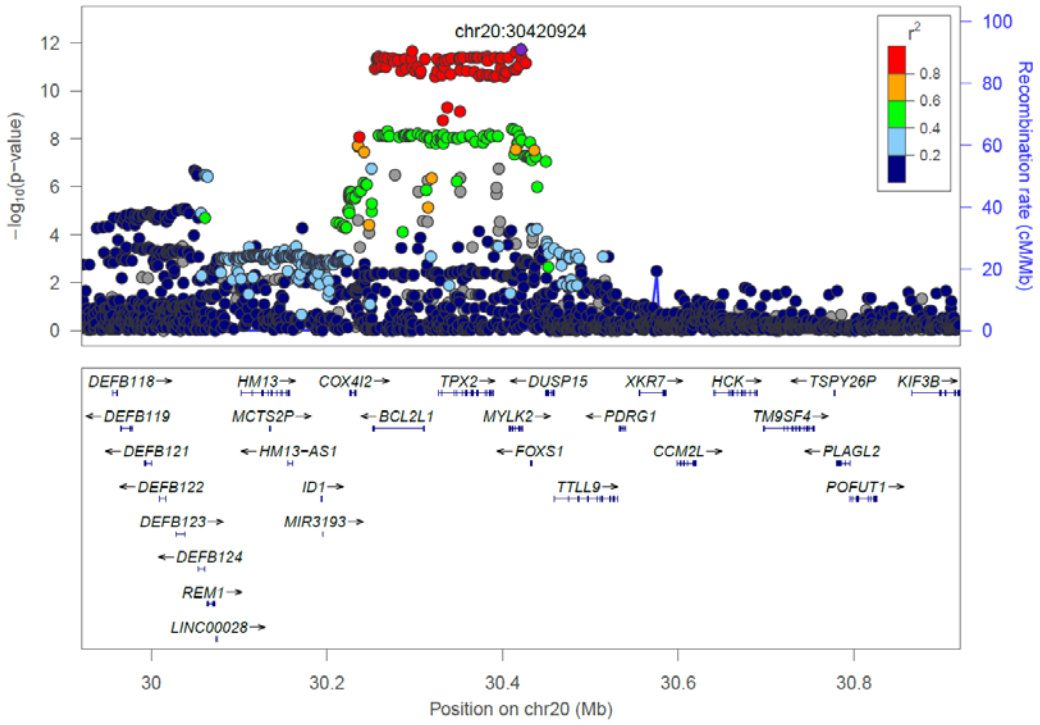
21. Brainstem (rs112178027)



22. Caudate nucleus (rs3133370)



23. Caudate nucleus (rs6060983)



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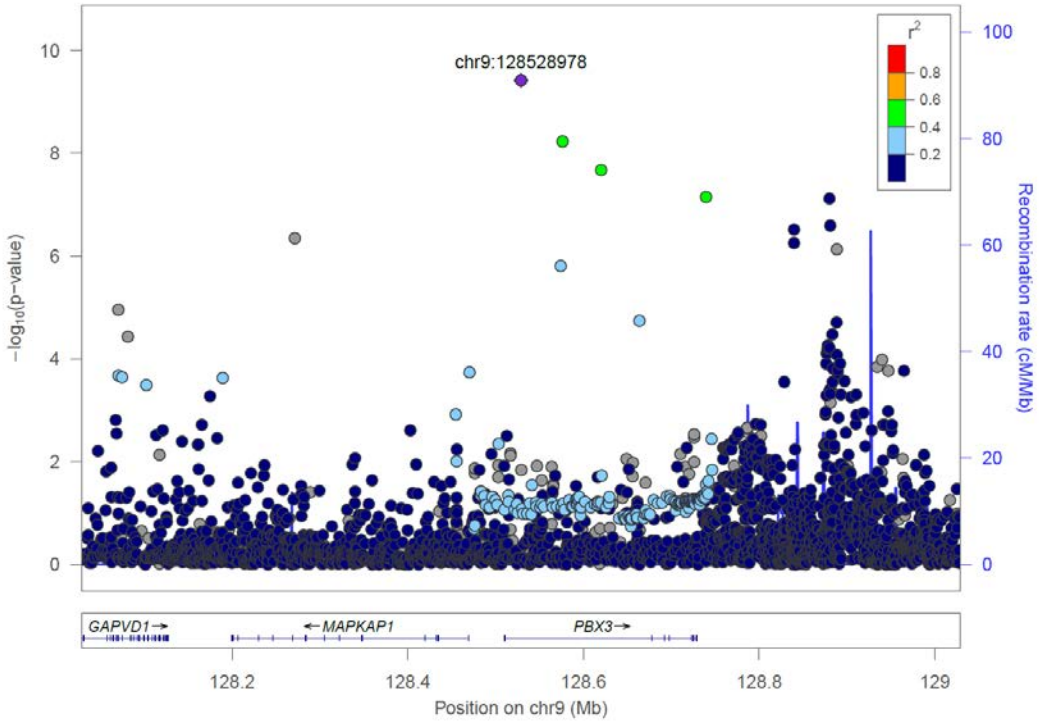
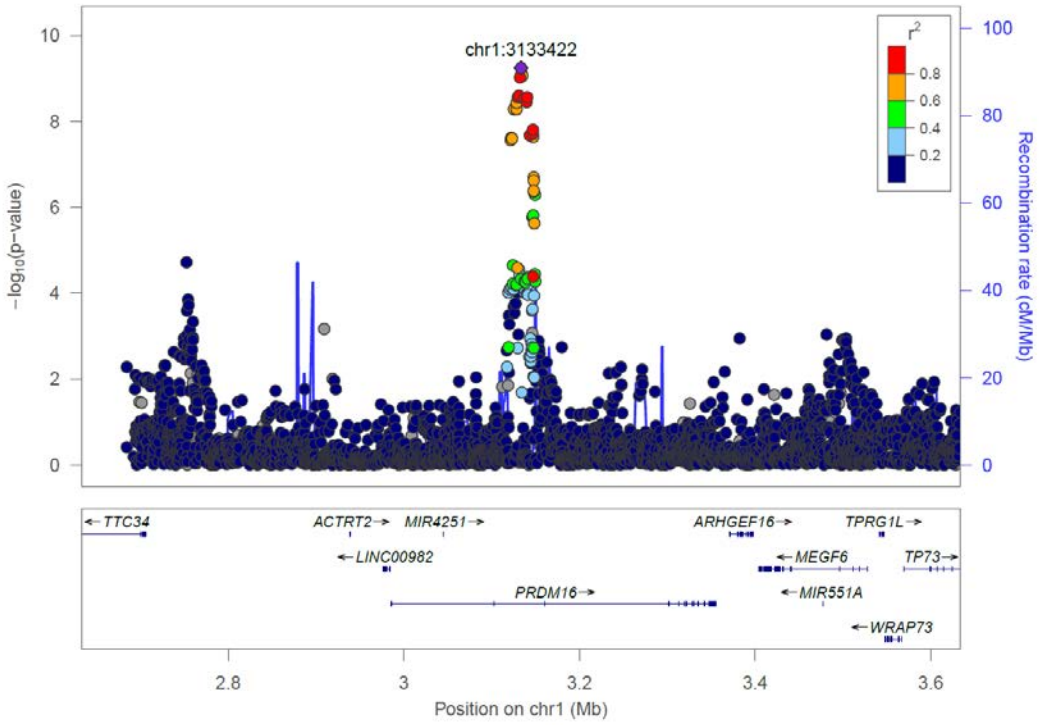
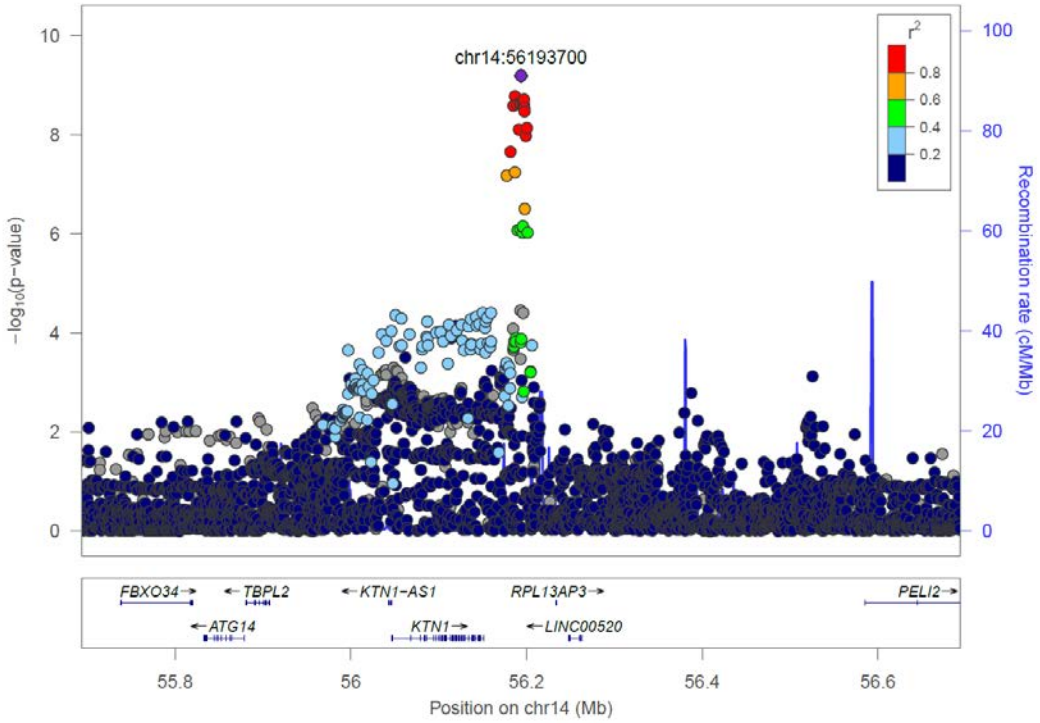


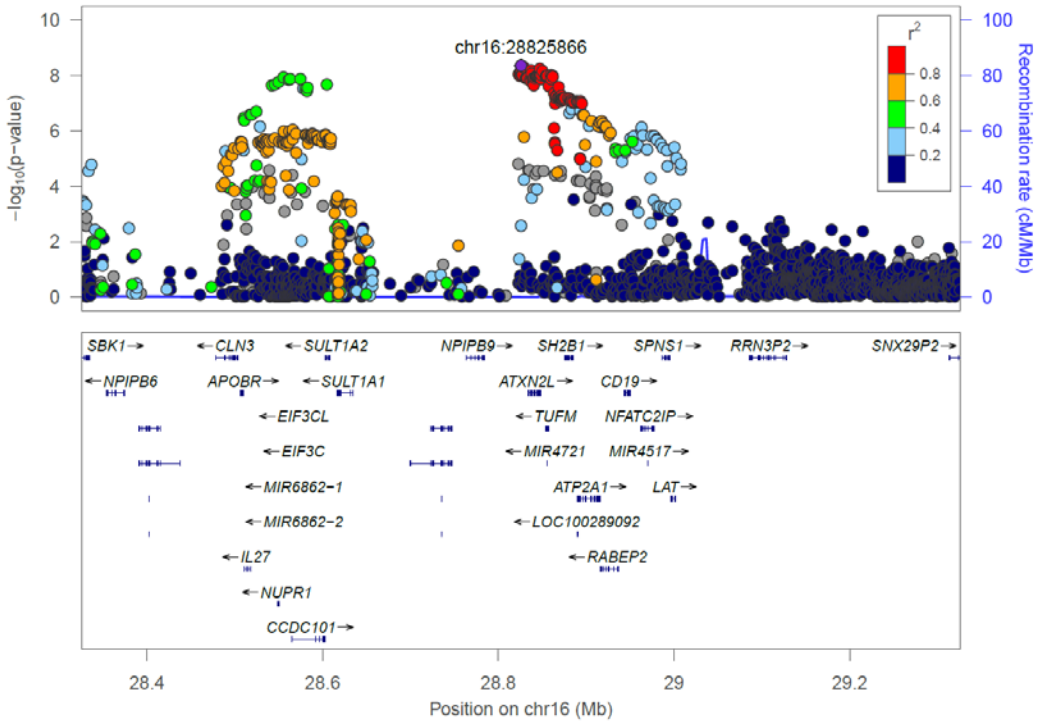
25. Caudate nucleus (rs2817145)



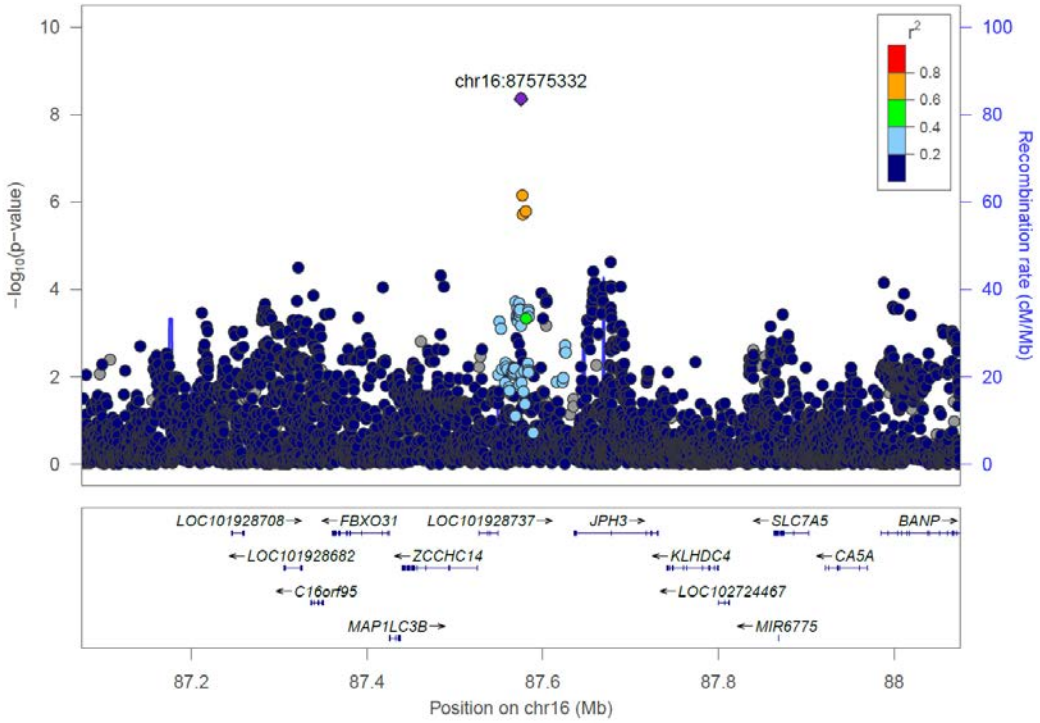
26. Caudate nucleus (rs148470213)



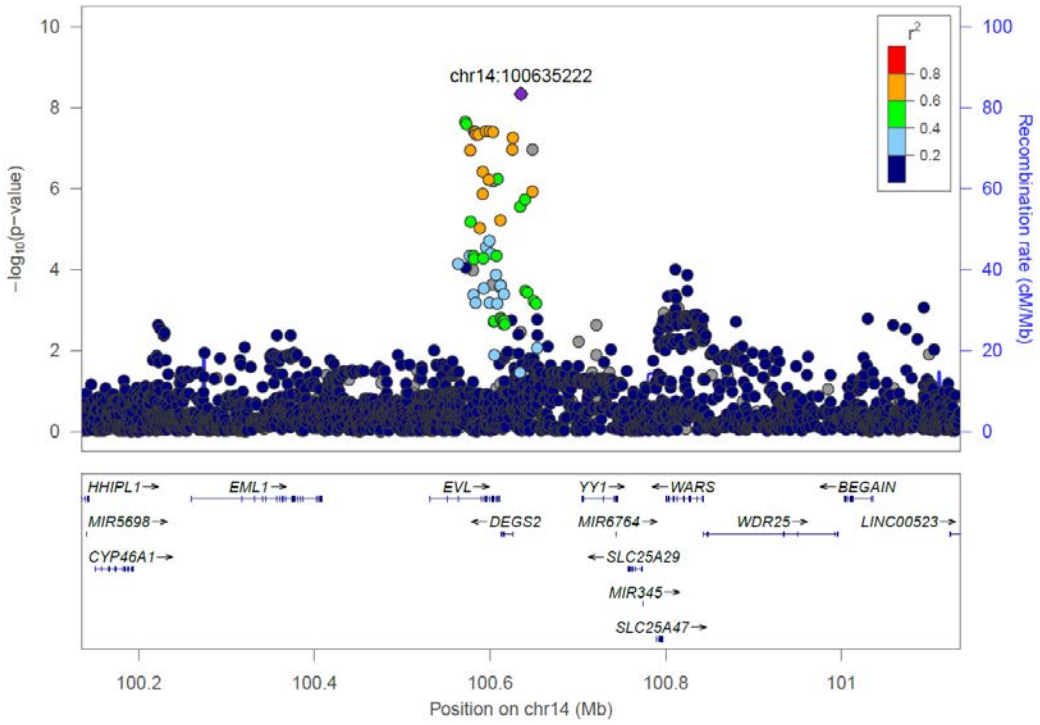
27. Caudate nucleus (rs1987471)



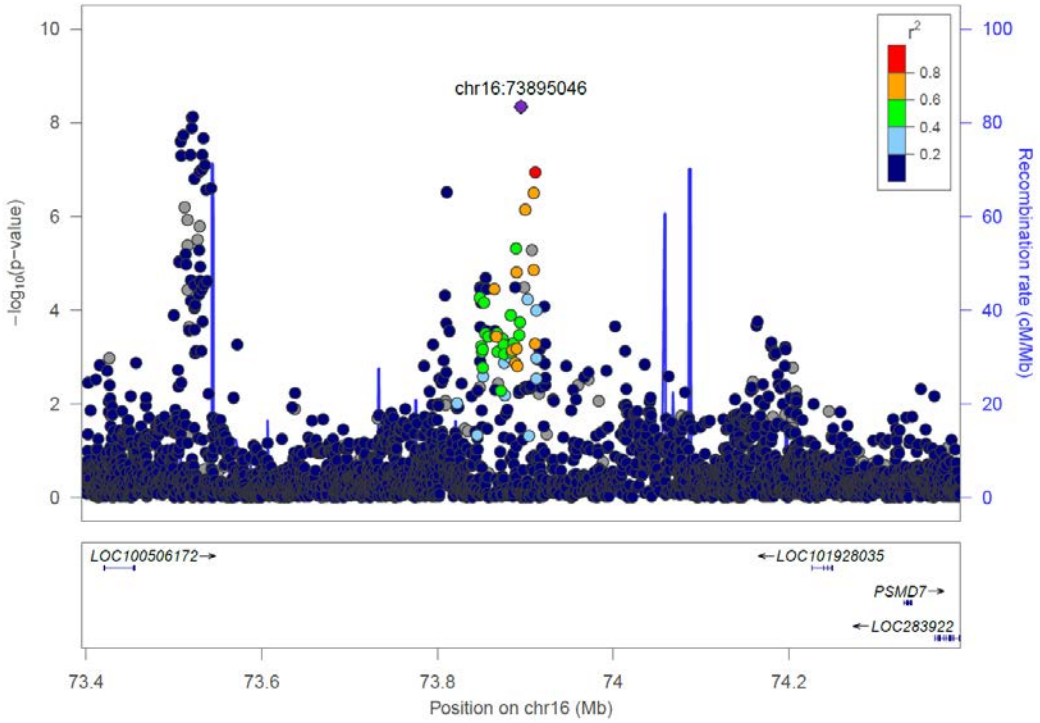
28. Caudate nucleus (rs12445022)



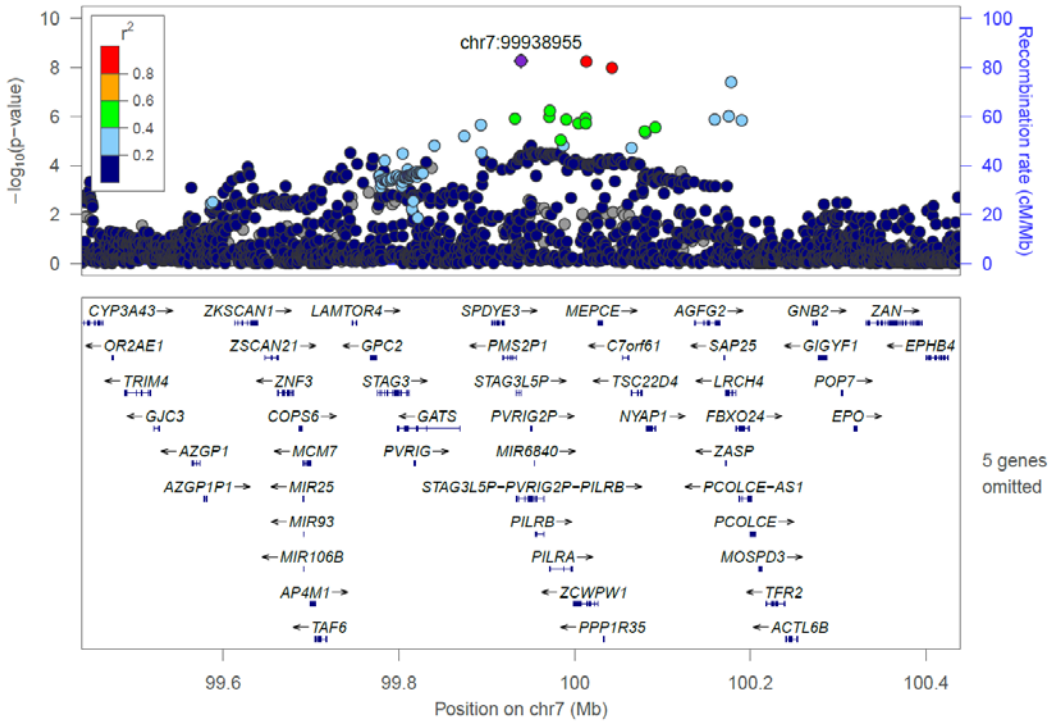
29. Caudate nucleus (rs55989340)



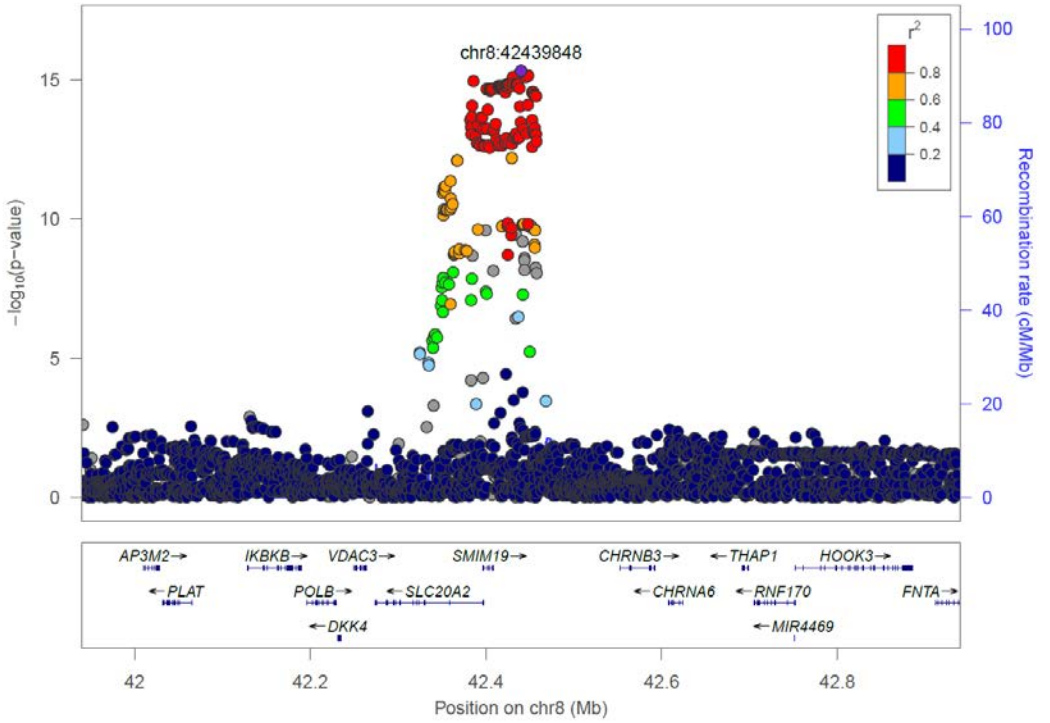
30. Caudate nucleus (rs4888010)



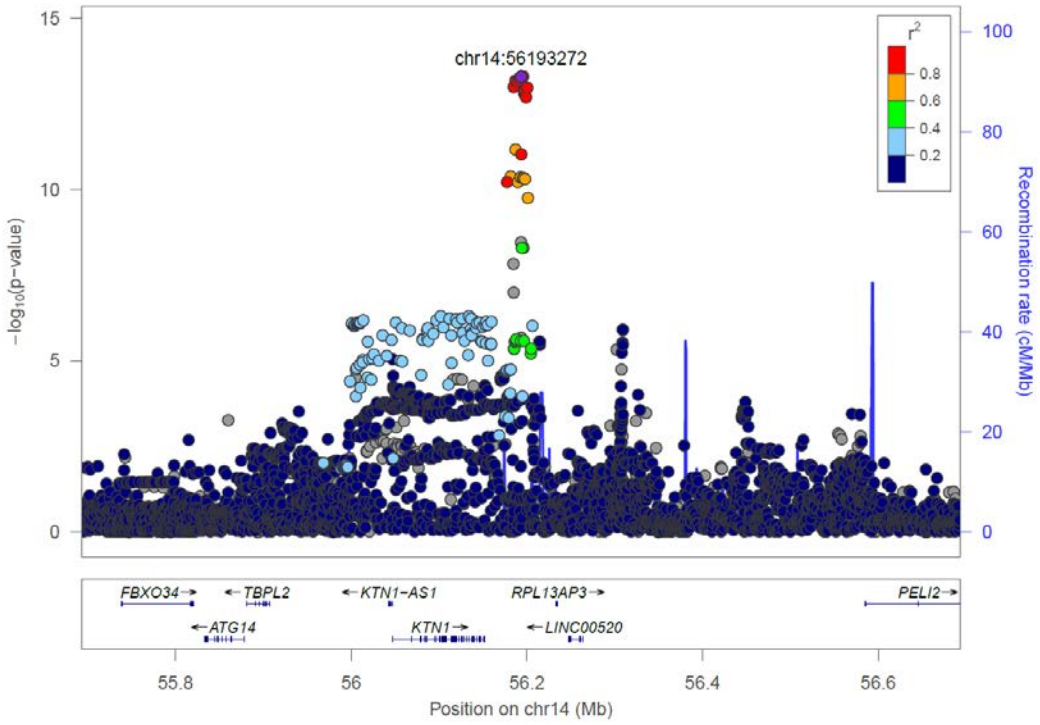
31. Caudate nucleus (rs35305377)



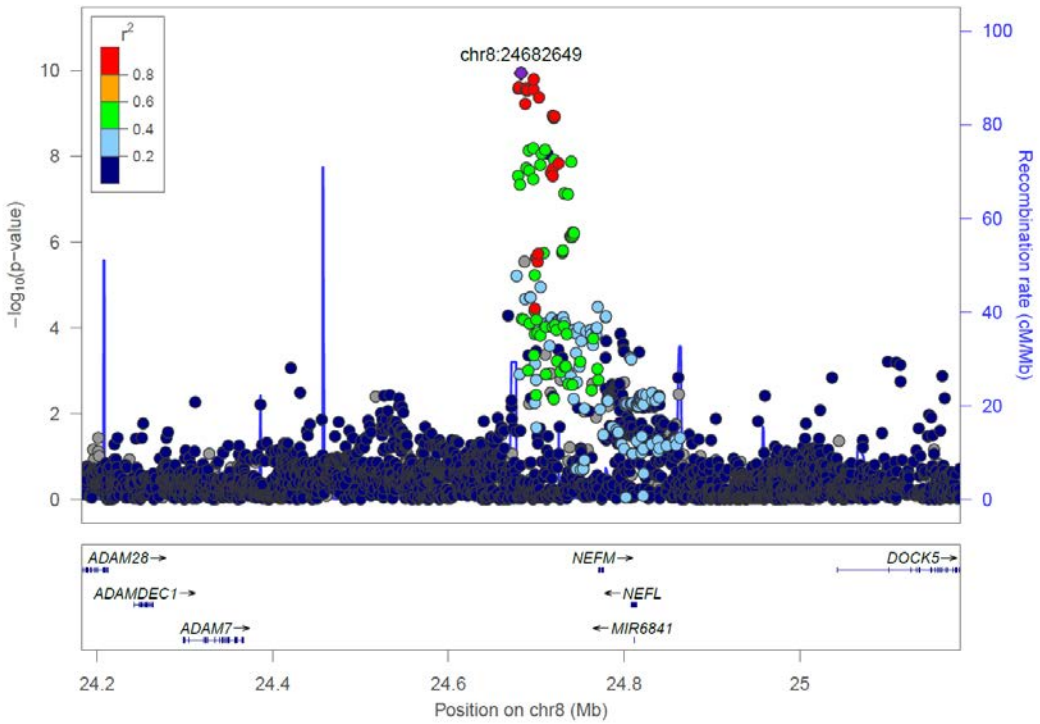
32. Globus pallidus (rs2923447)



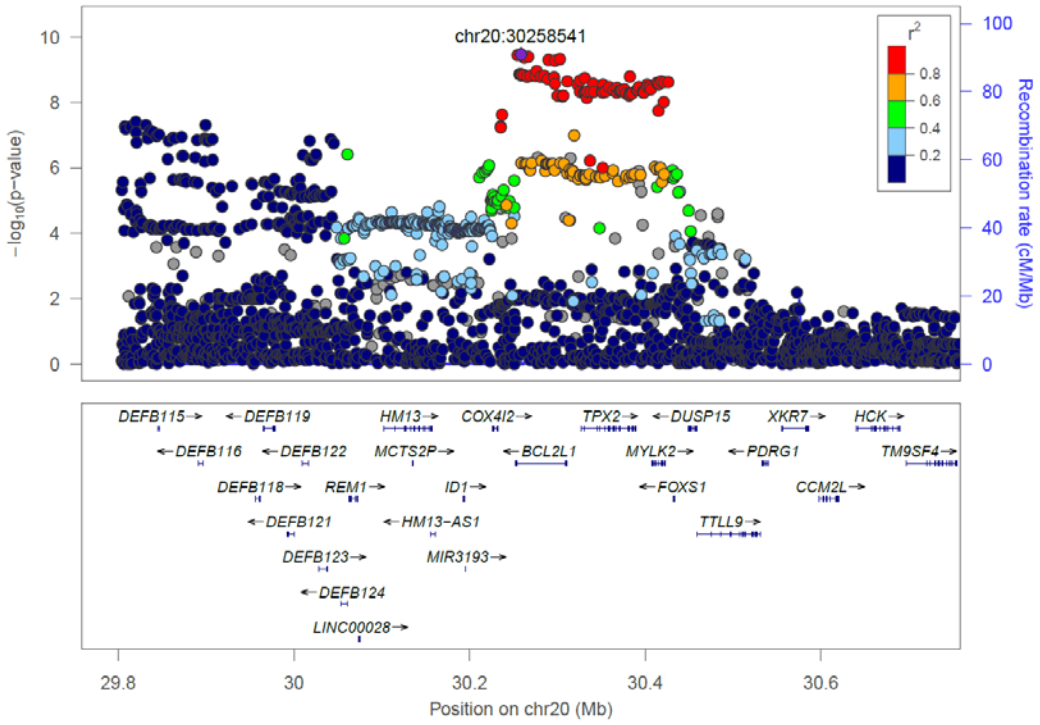
33. Globus pallidus (rs10129414)



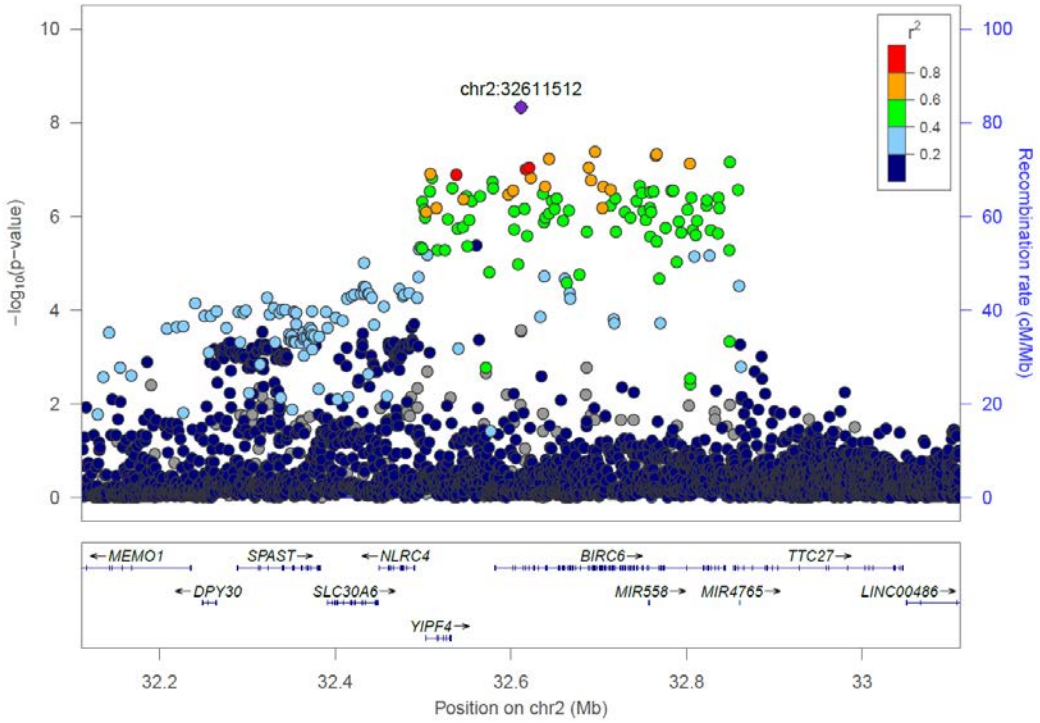
34. Globus pallidus (rs196807)



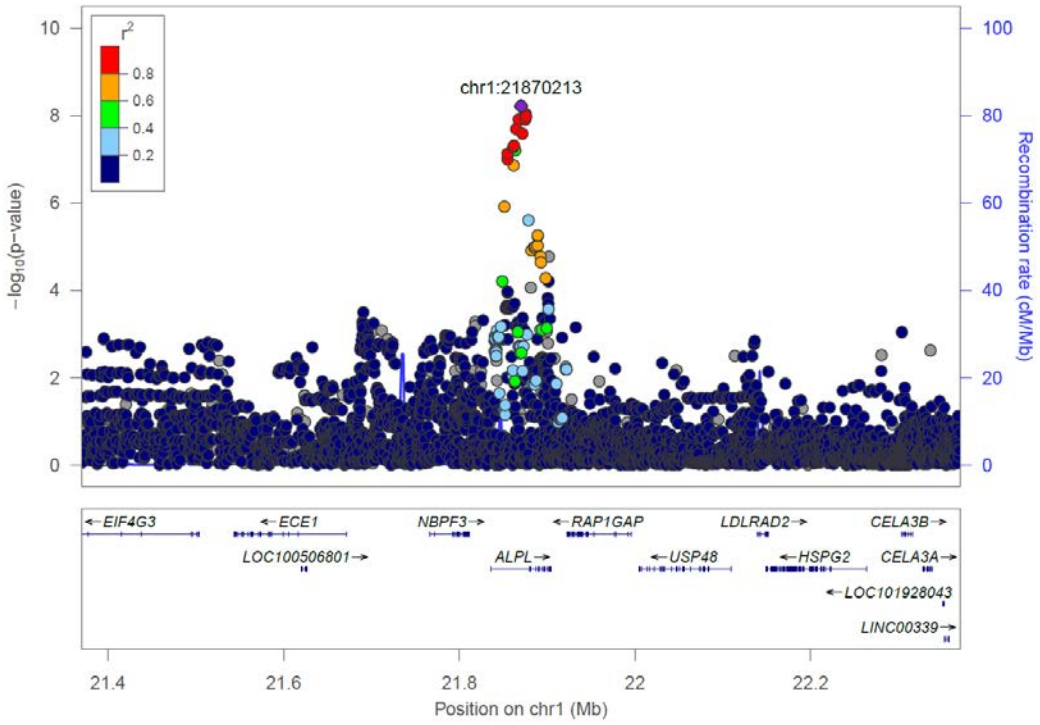
35. Globus pallidus (rs10439607)



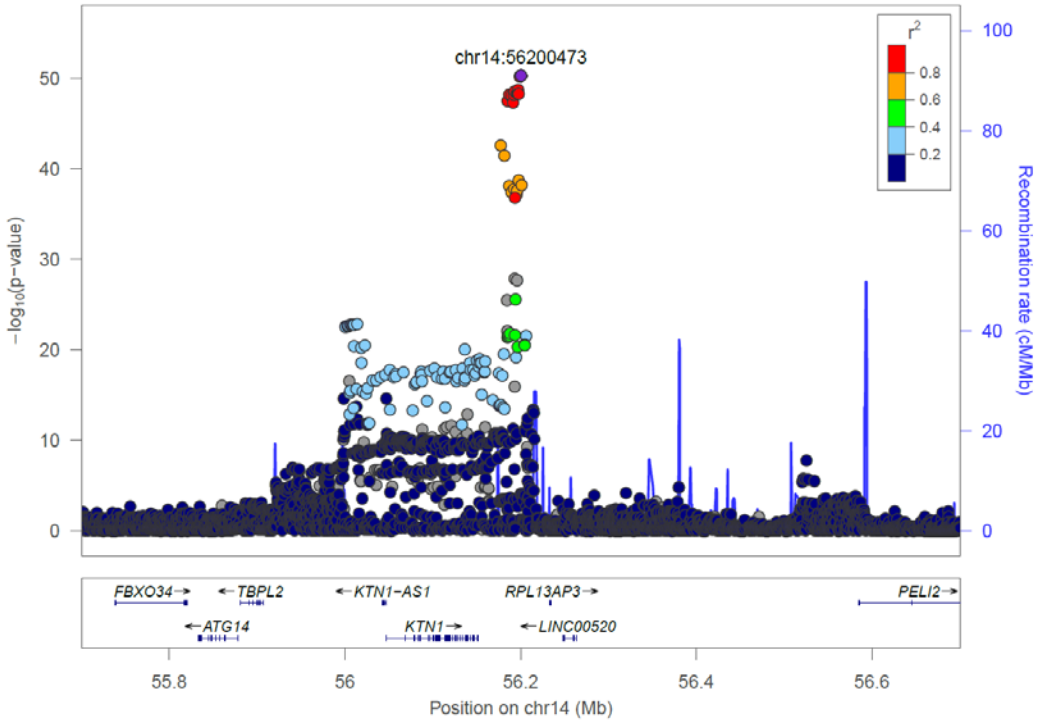
36. Globus pallidus (rs4952211)



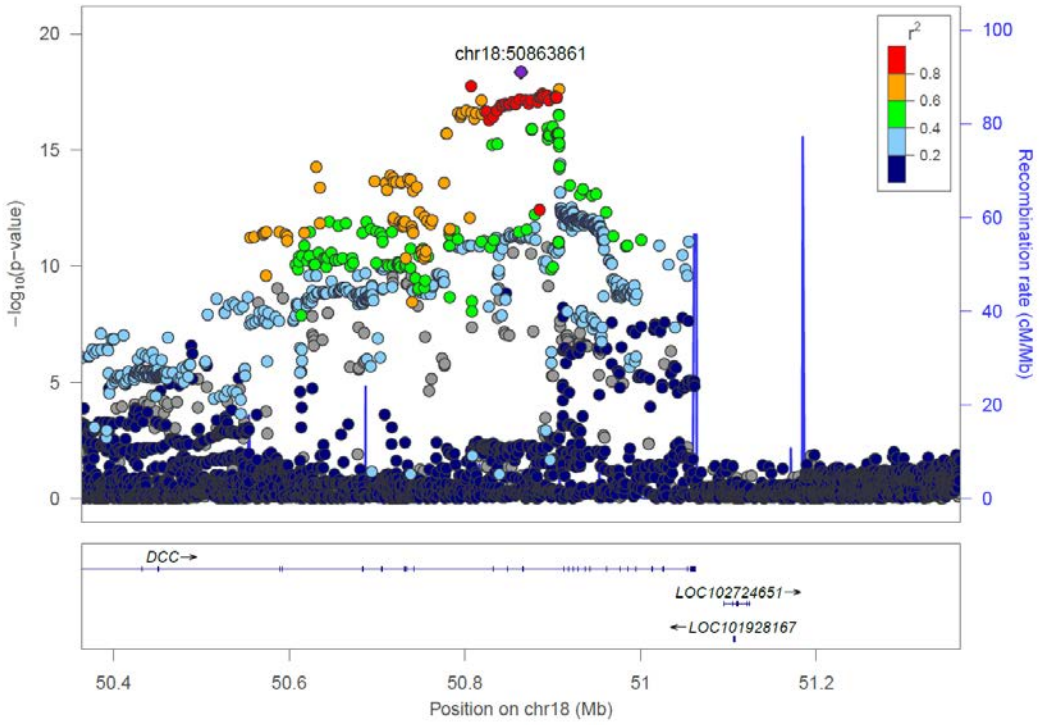
37. Globus pallidus (rs12567402)



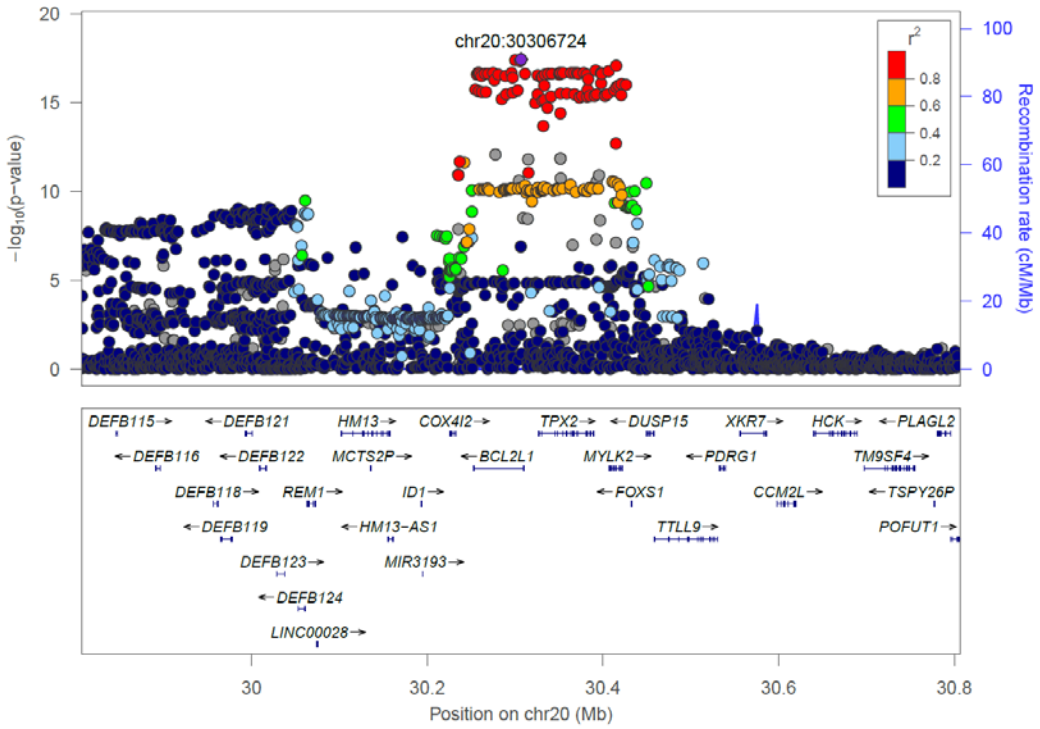
38. Putamen (rs945270)



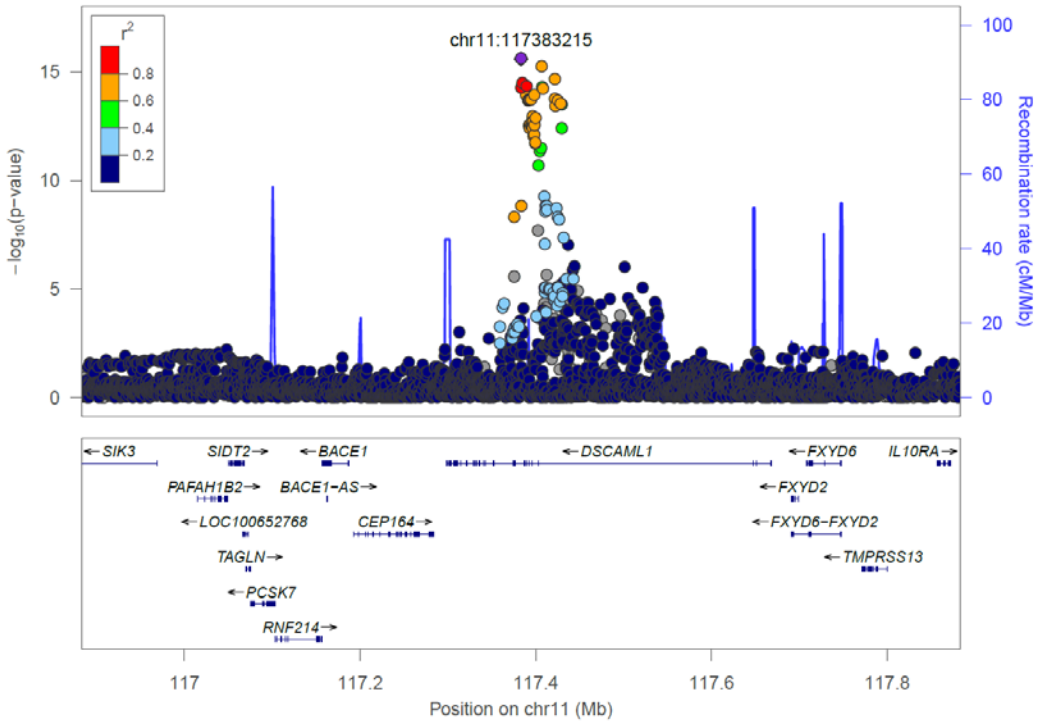
39. Putamen (rs62098013)



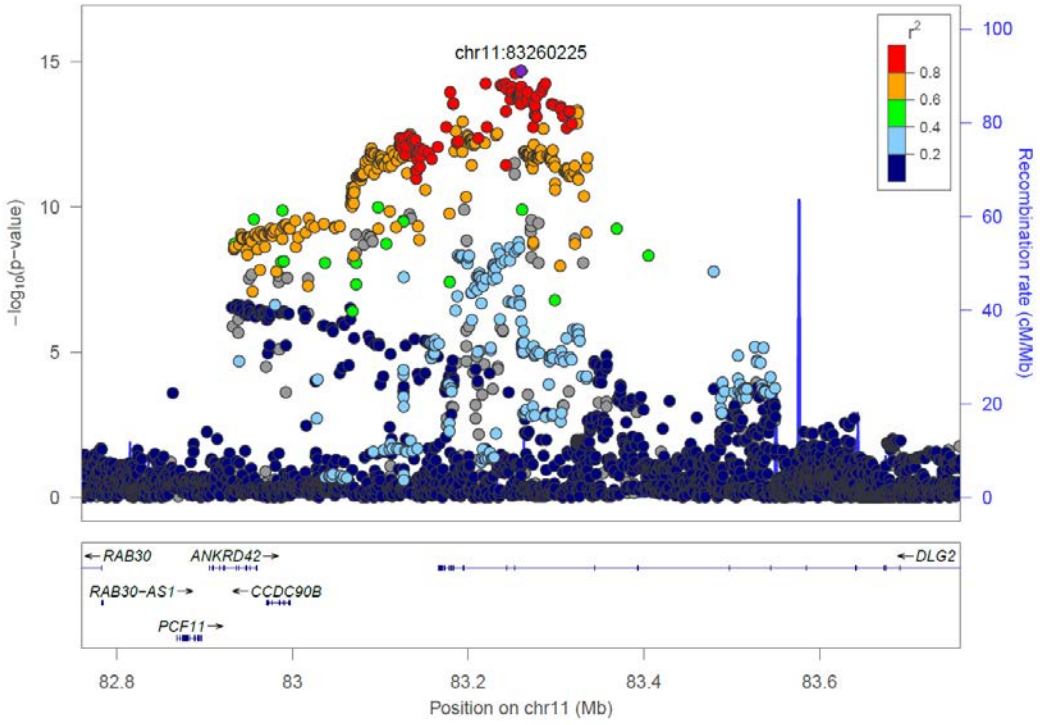
40. Putamen (rs6087771)



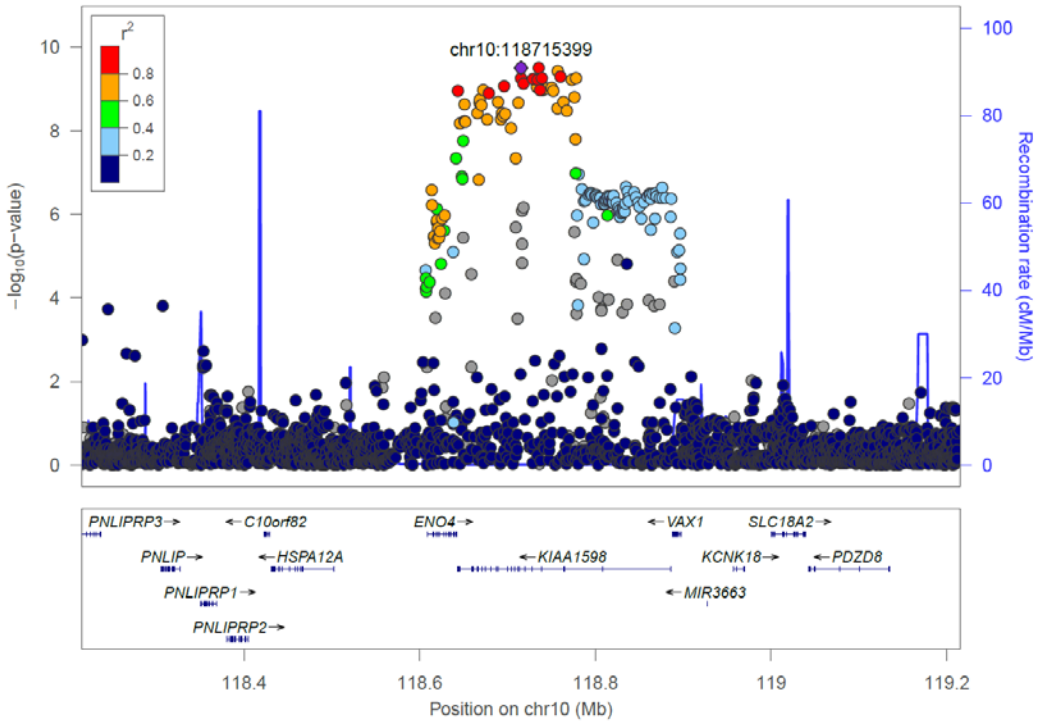
41. Putamen (rs35200015)



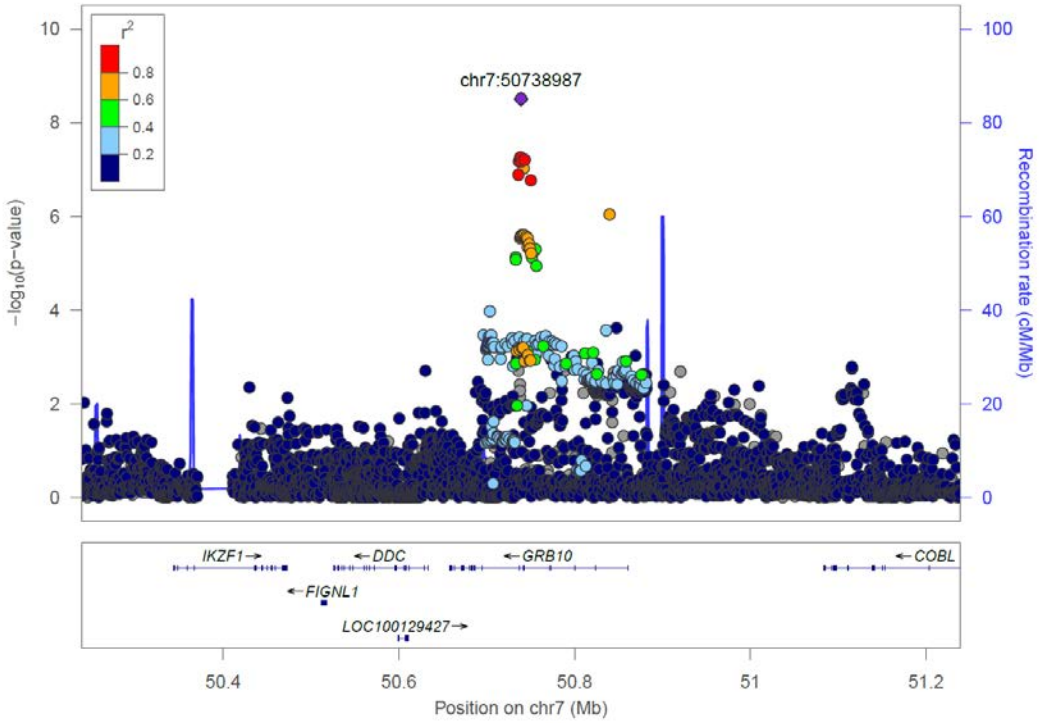
42. Putamen (rs1432054)



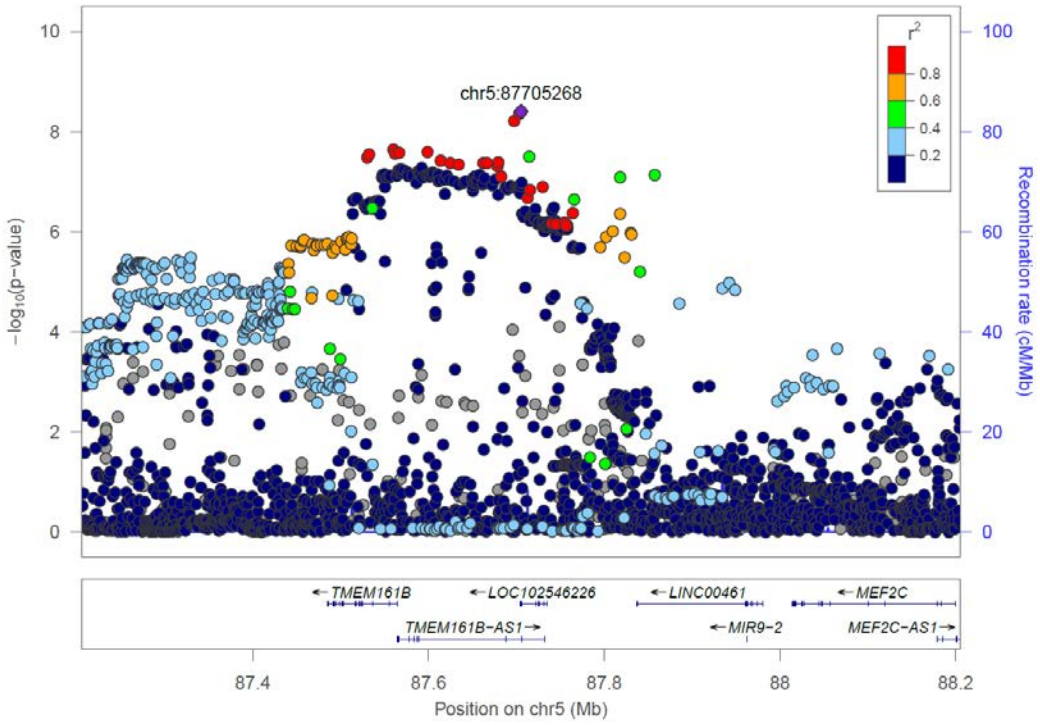
43. Putamen (rs7902527)



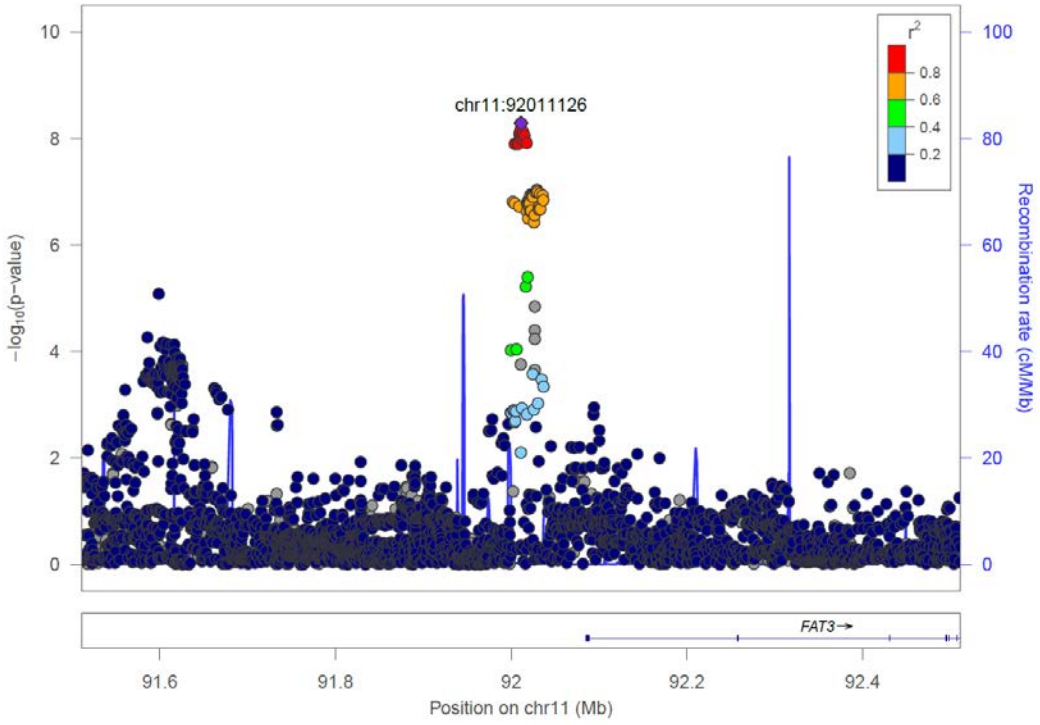
44. Putamen (rs2244479)



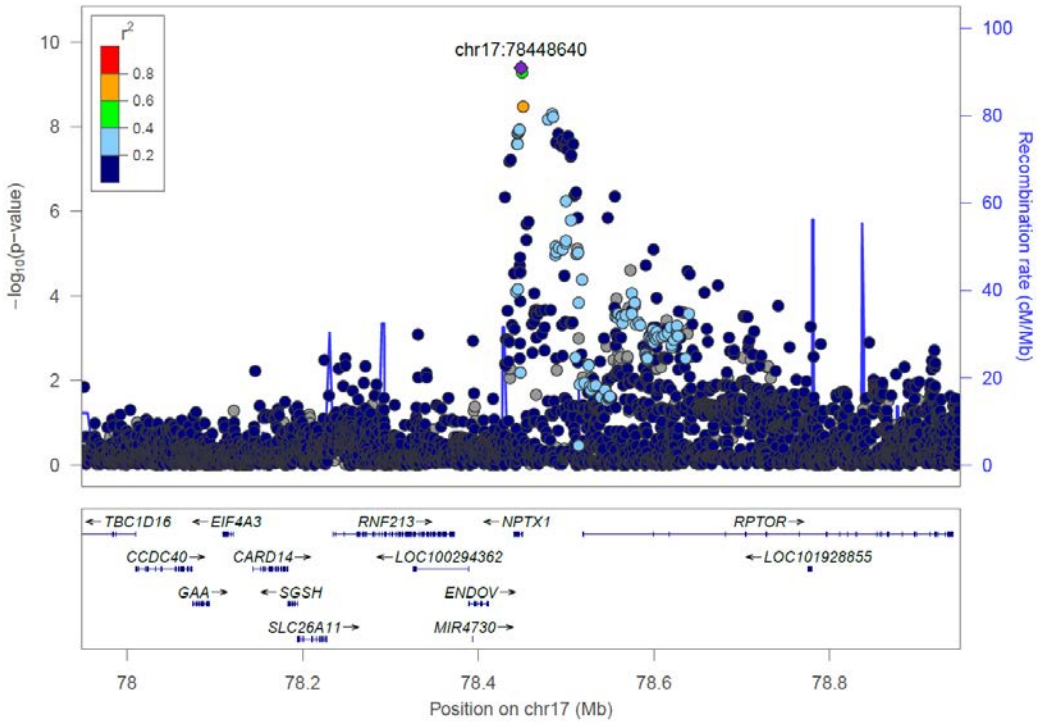
45. Putamen (rs2410767)



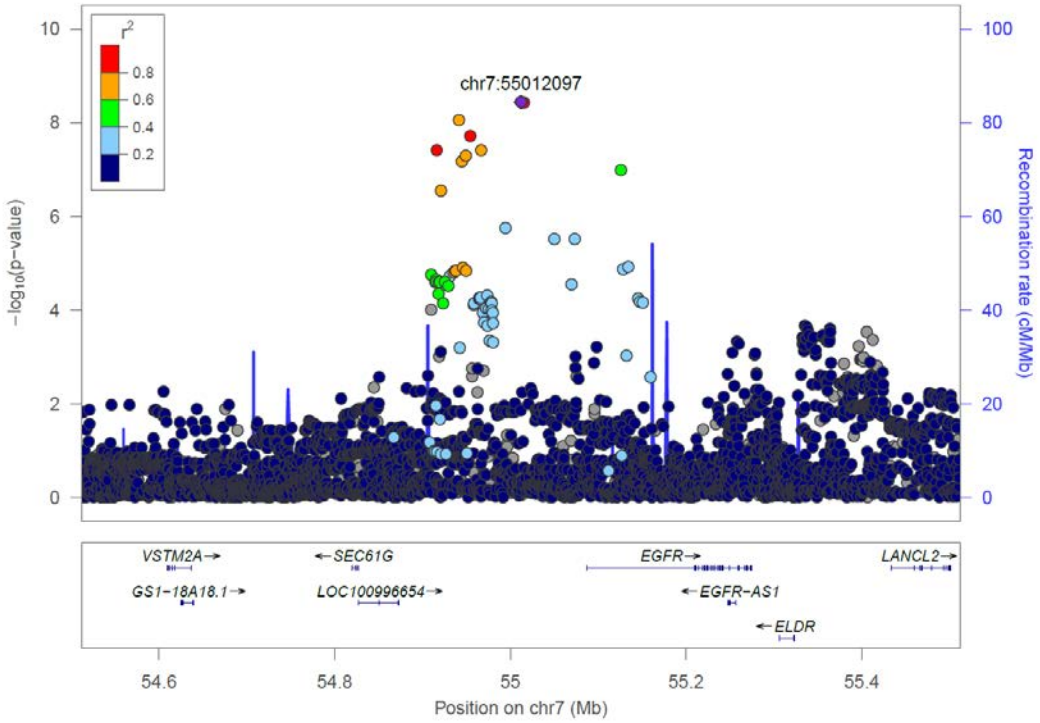
46. Putamen (rs1187162)



47. Thalamus (rs12600720)

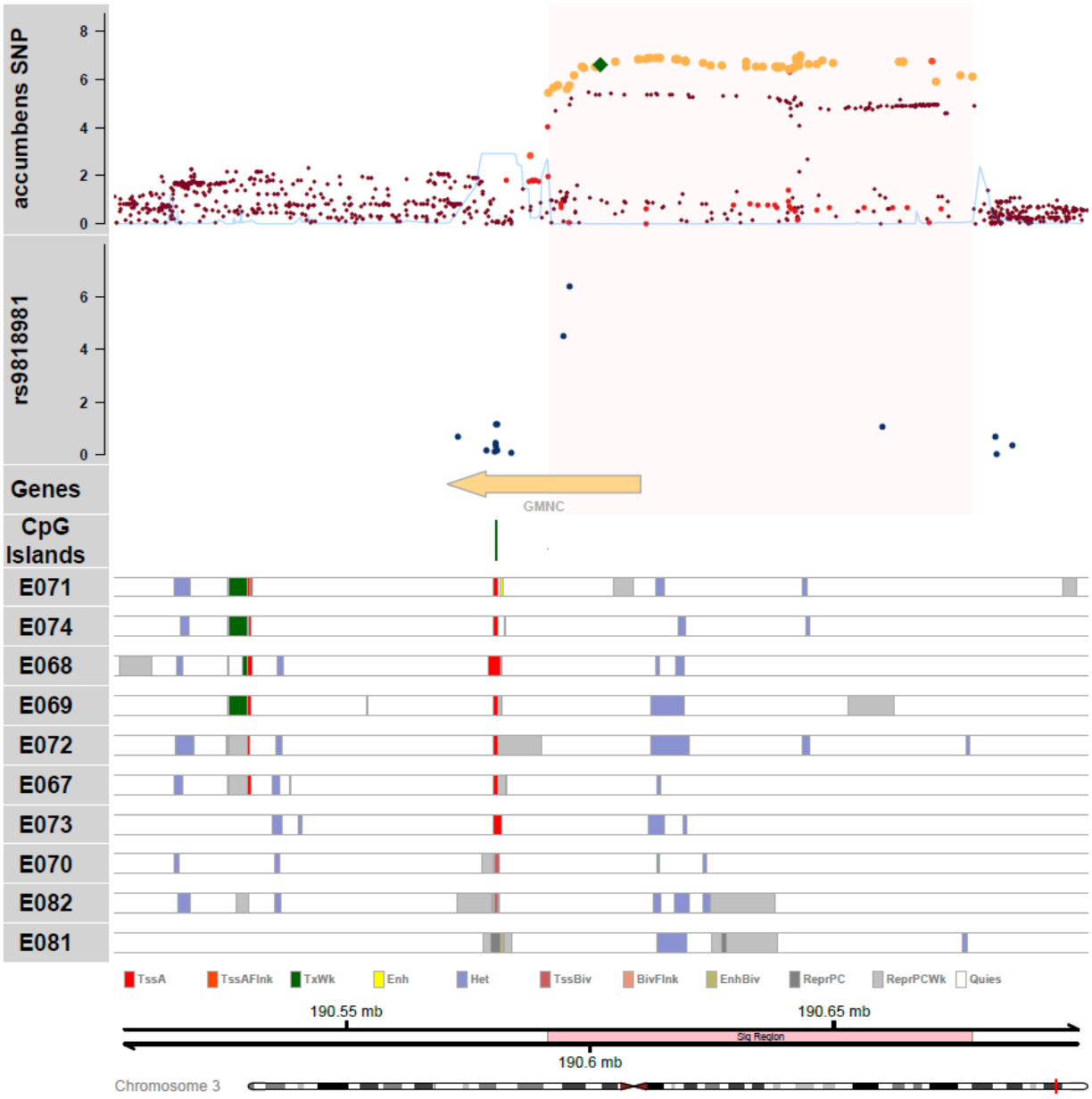


48. Thalamus (rs142461330)

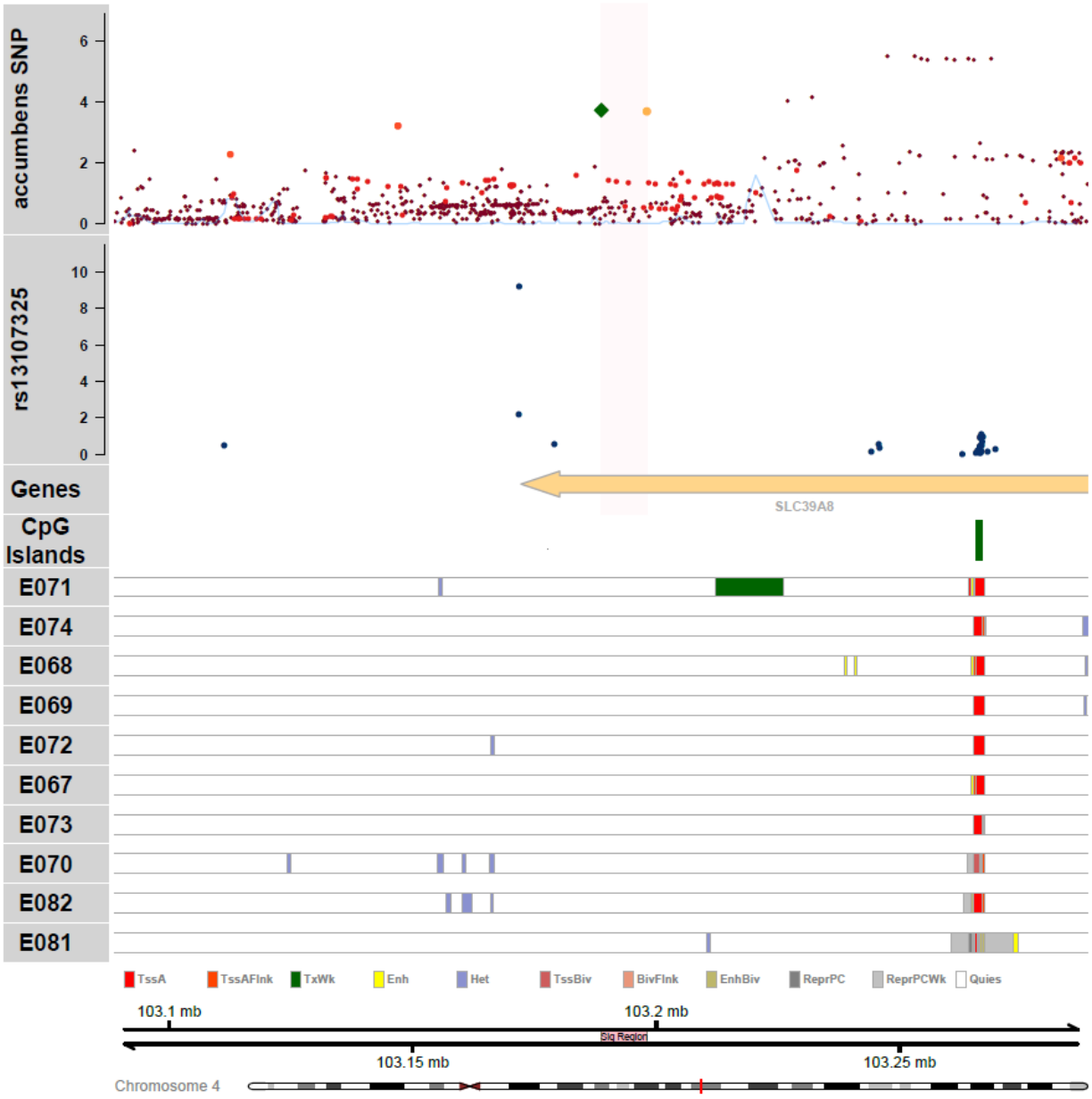


Supplementary Figure 3. **Methylation QTL, gene annotations and chromatin states in ROSMAP**. The first track presents genome-wide associations, where the index SNP is symbolized by a yellow square. The second track presents CpG sites associated with the index SNP. The third track displays gene USGC annotations. The fourth track presents the location of CpG islands. The fifth track presents chromatin states in different brain tissues from the Roadmap Epigenomics Project (E071 = Brain Hippocampus Middle, E074 = Brain Substantia Nigra, E068 = Brain Anterior Caudate, E069 = Brain Cingulate Gyrus, E072 = Brain Inferior Temporal Lobe, E067 = Brain Angular Gyrus, E073 = Brain Mid Frontal Lobe, E070 = Brain Germinal Matrix, E082 = Female Fetal Brain, E081 = Male Fetal Brain). Chromatin states are coded by color according to the labels. The sixth track presents the genomic region and the seventh track the position on the chromosome. Refer to Supplementary Table S12.

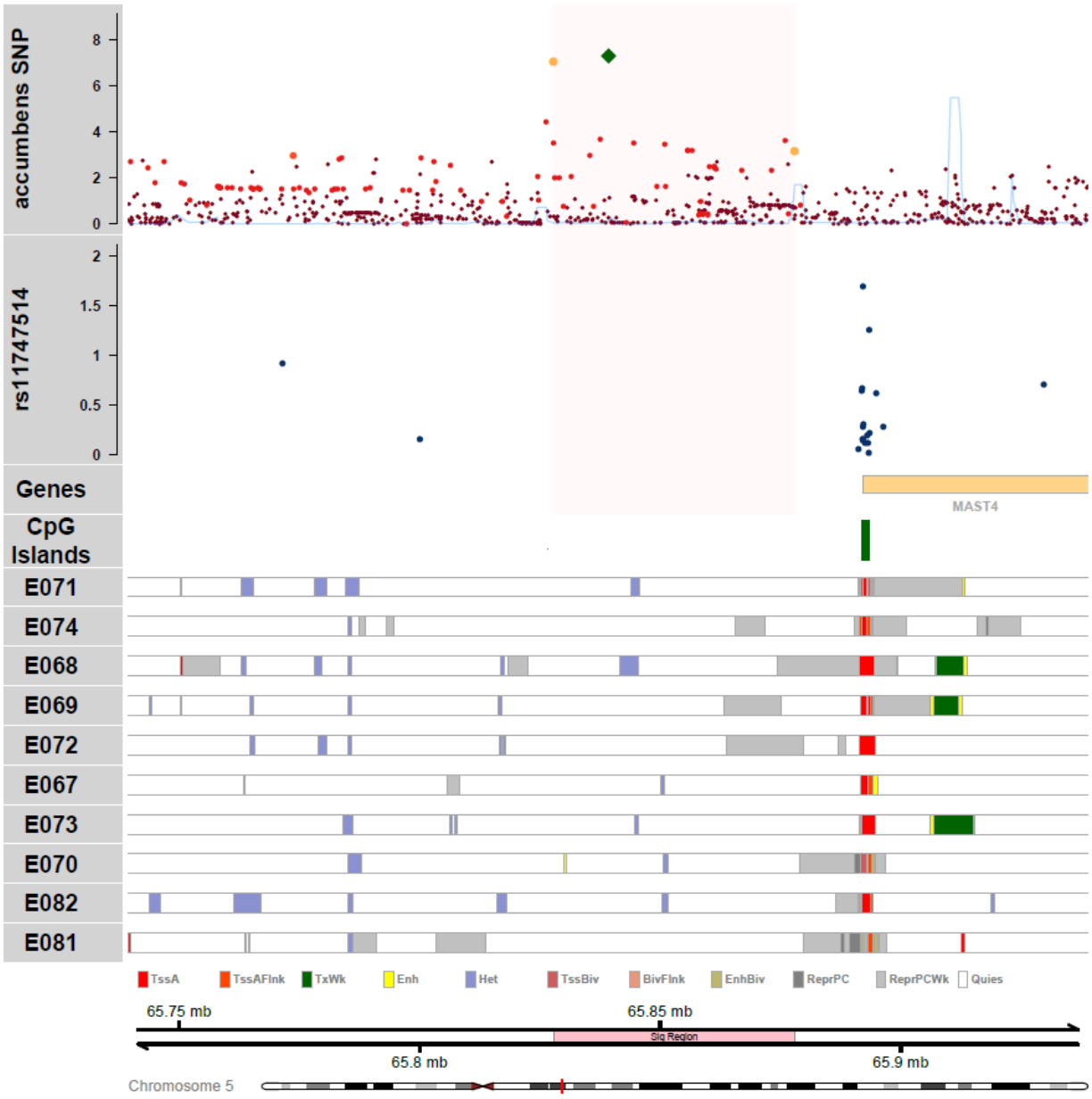
1. Nucleus accumbens (rs9818981)



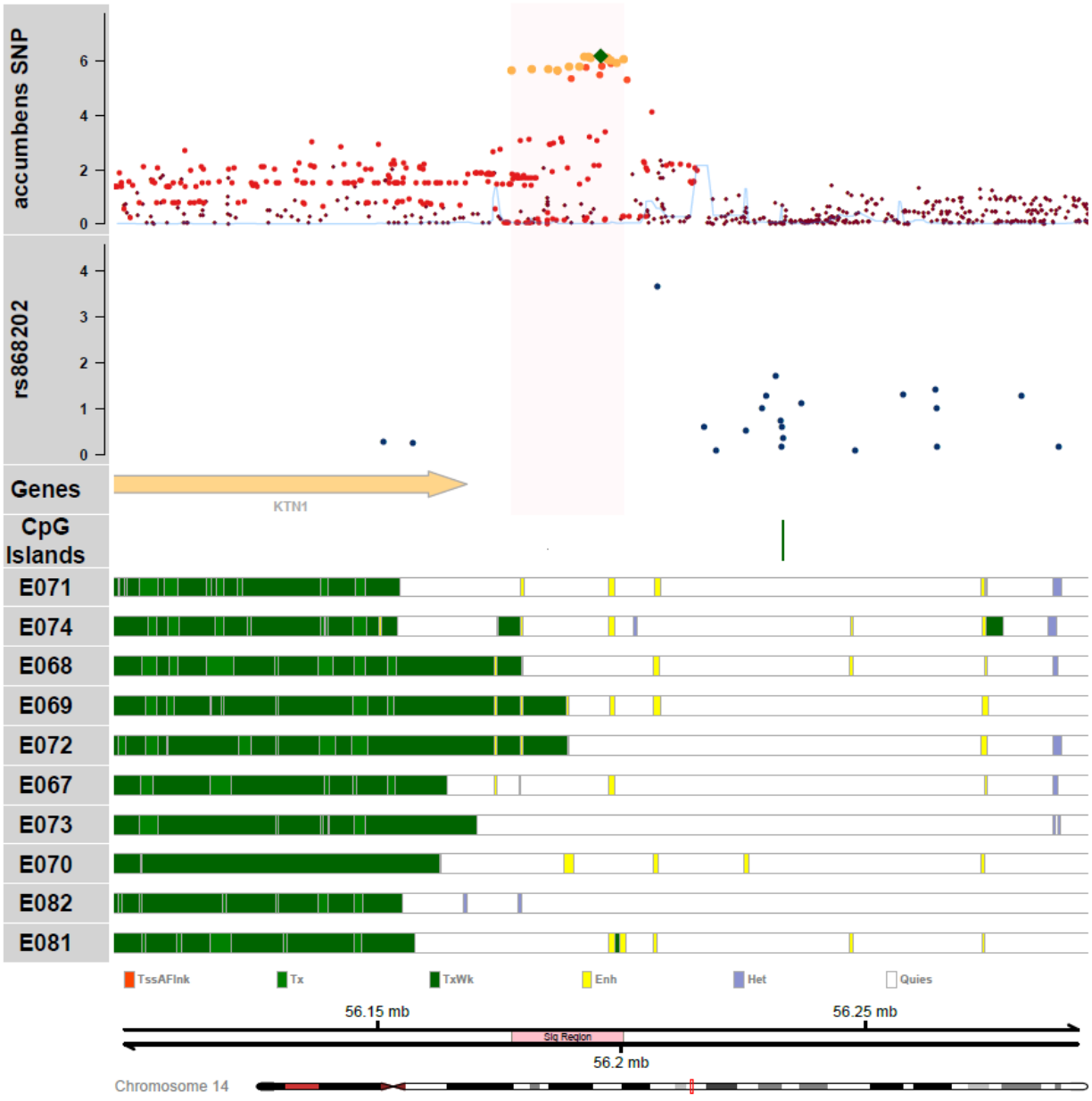
2. Nucleus accumbens (rs13107325)



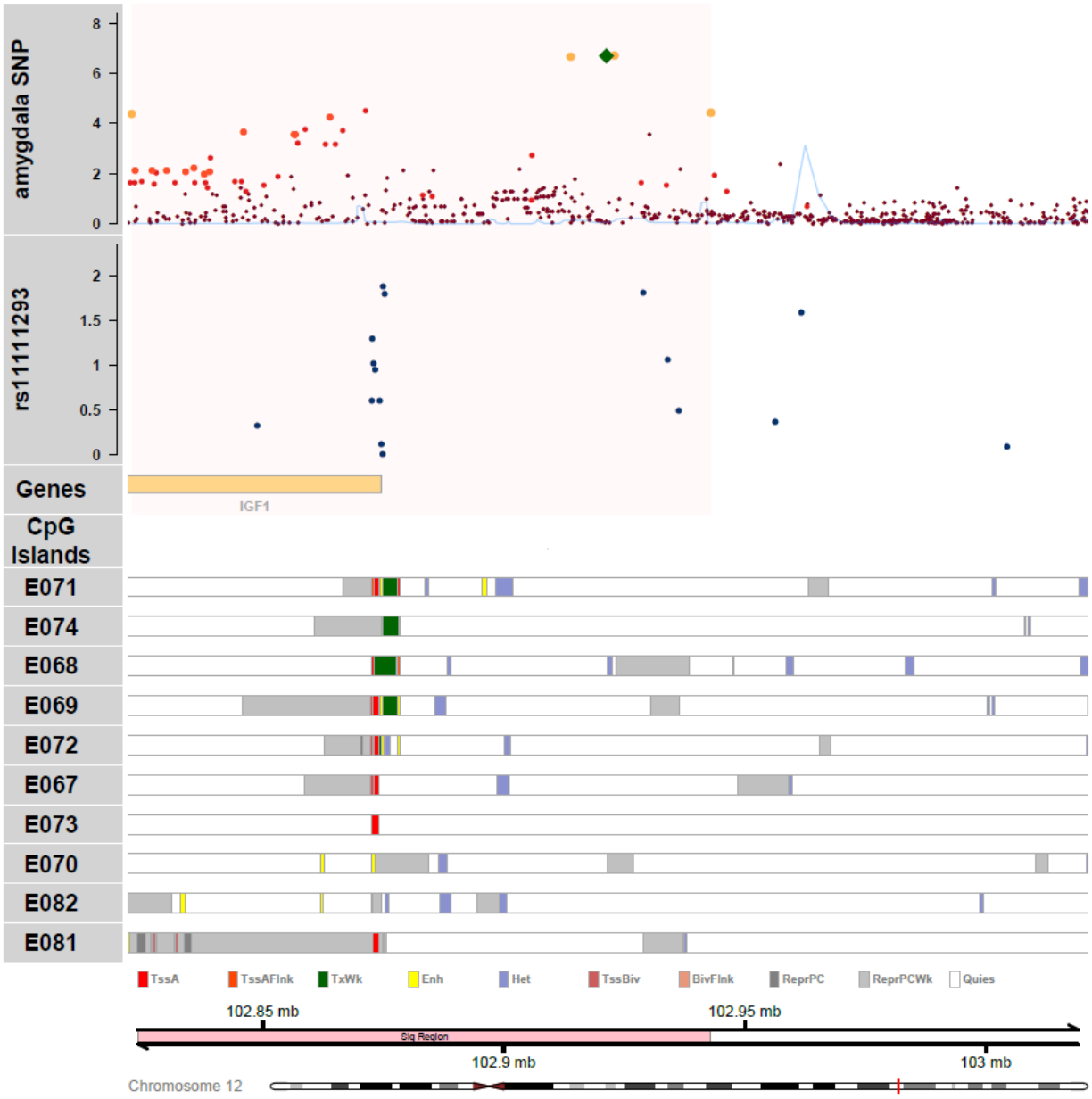
3. Nucleus accumbens (rs11747514)



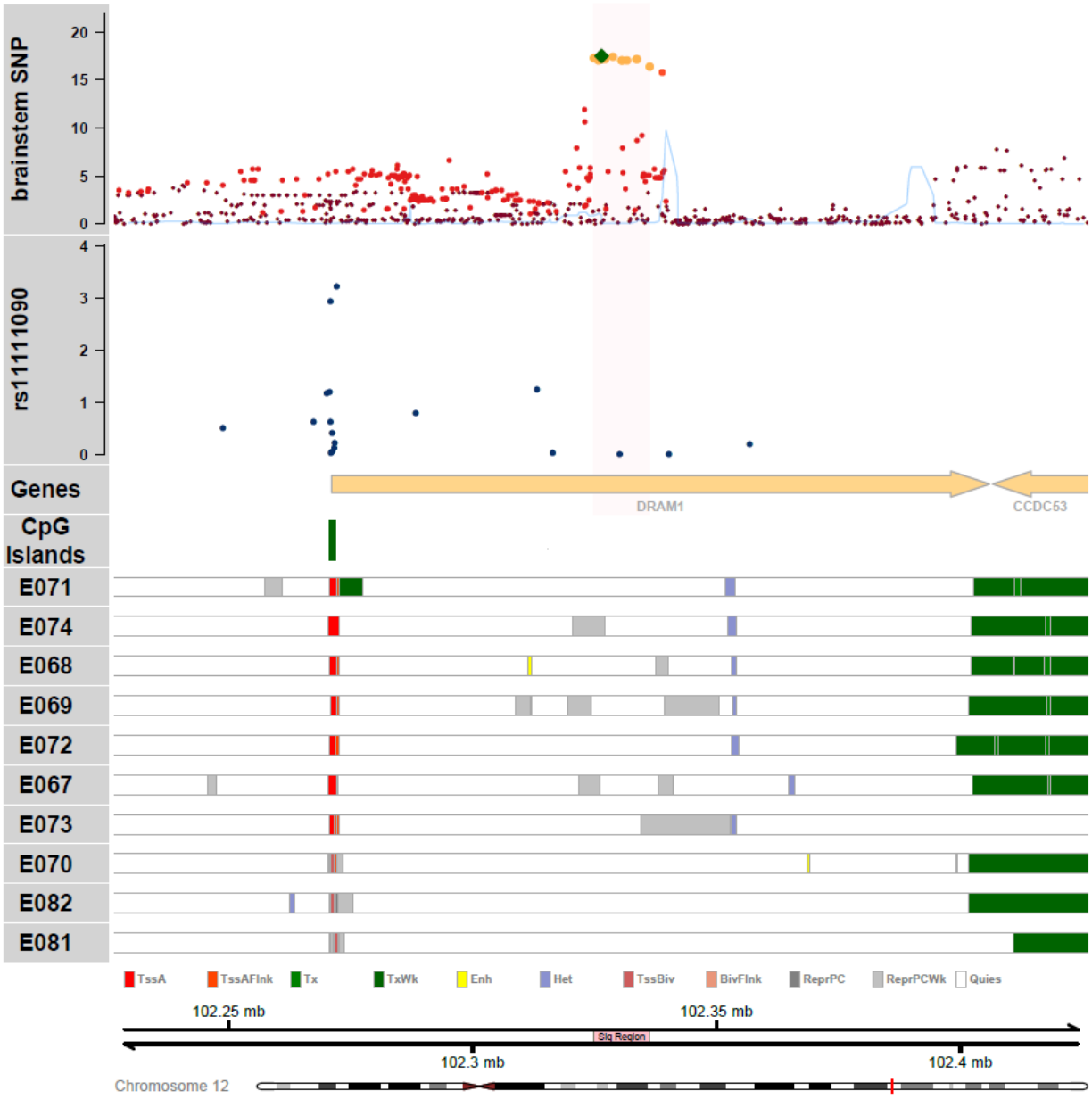
4. Nucleus accumbens (rs868202)



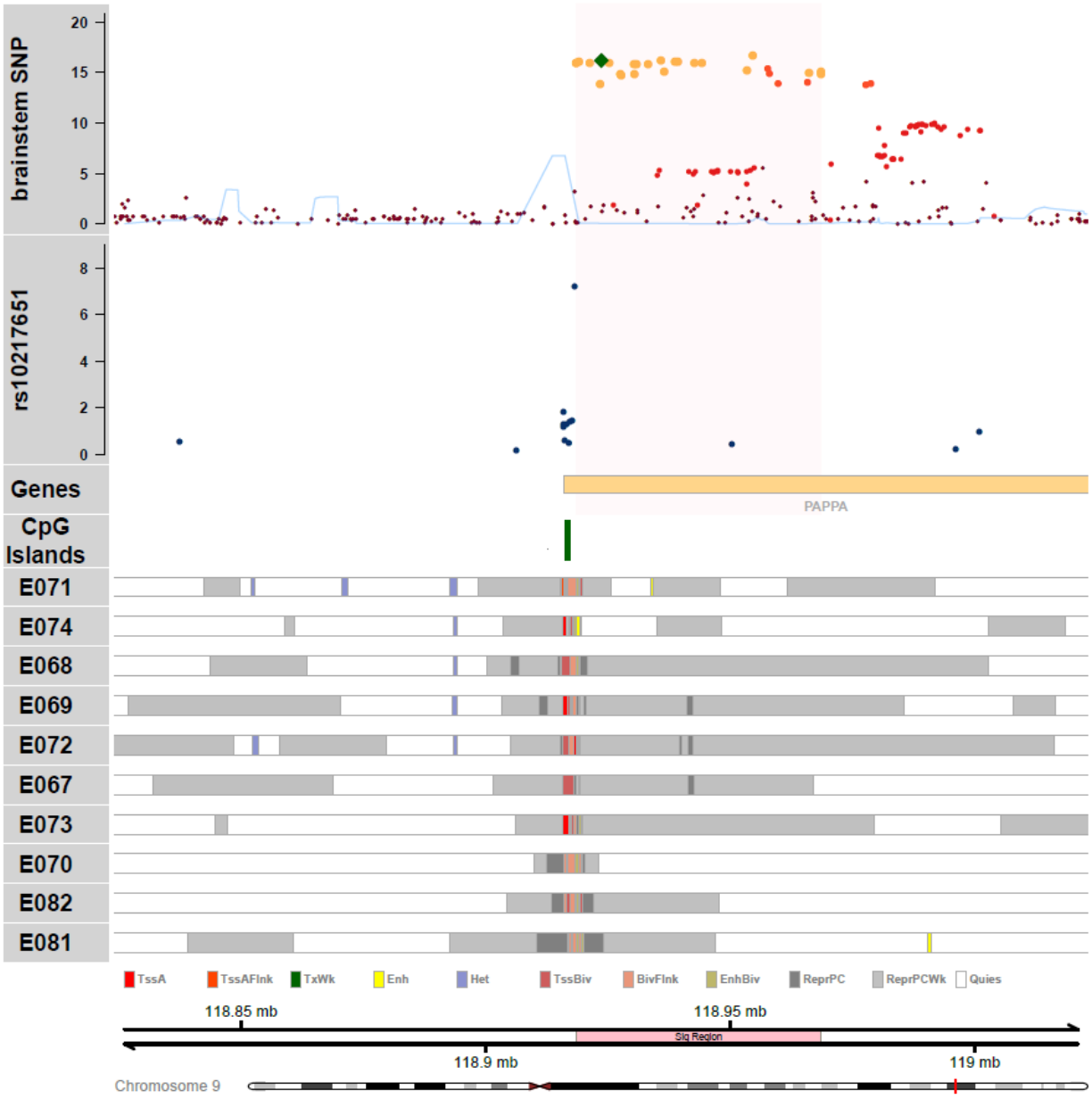
5. Amygdala (rs11111293)



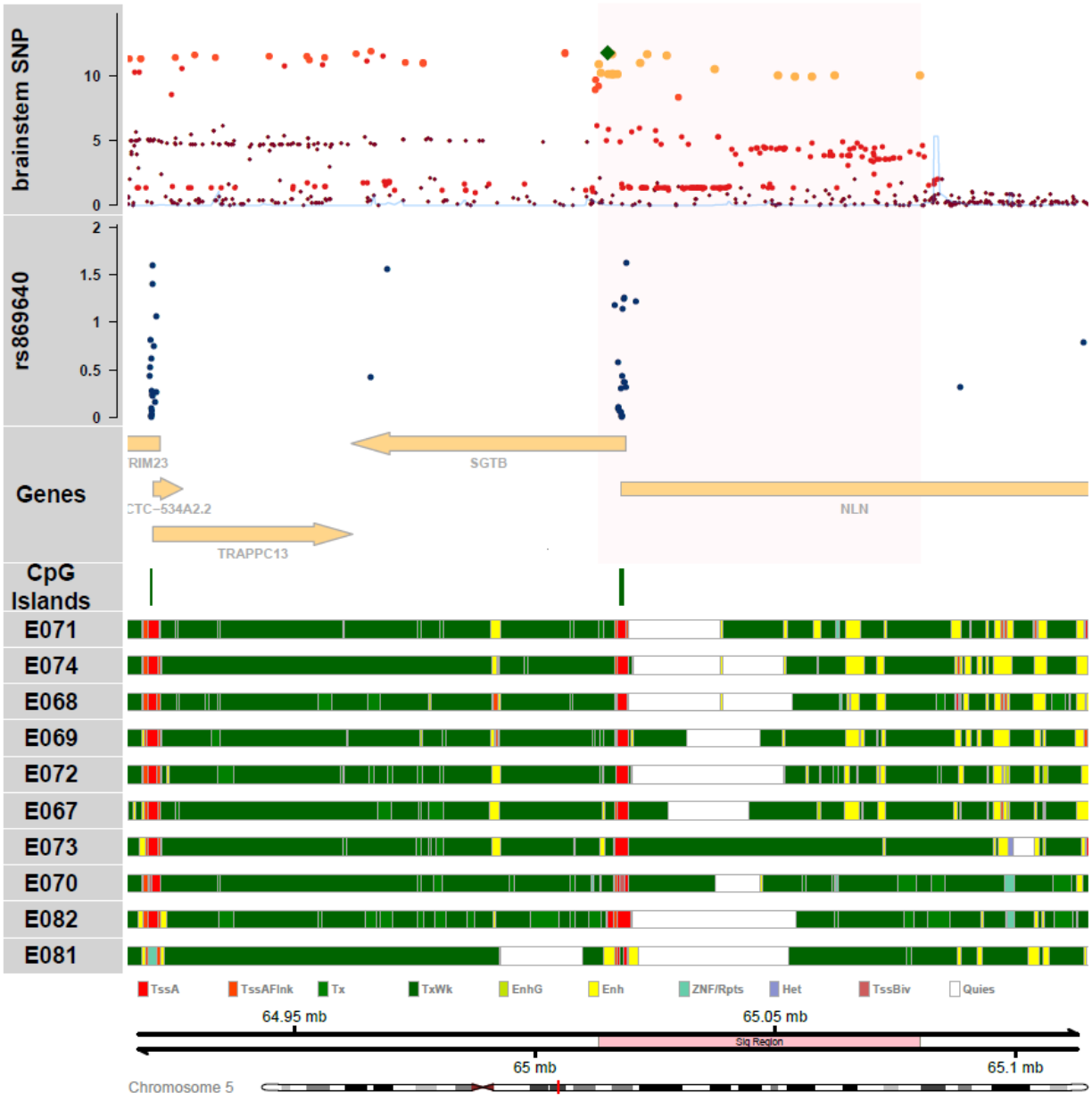
6. Brainstem (rs11111090)



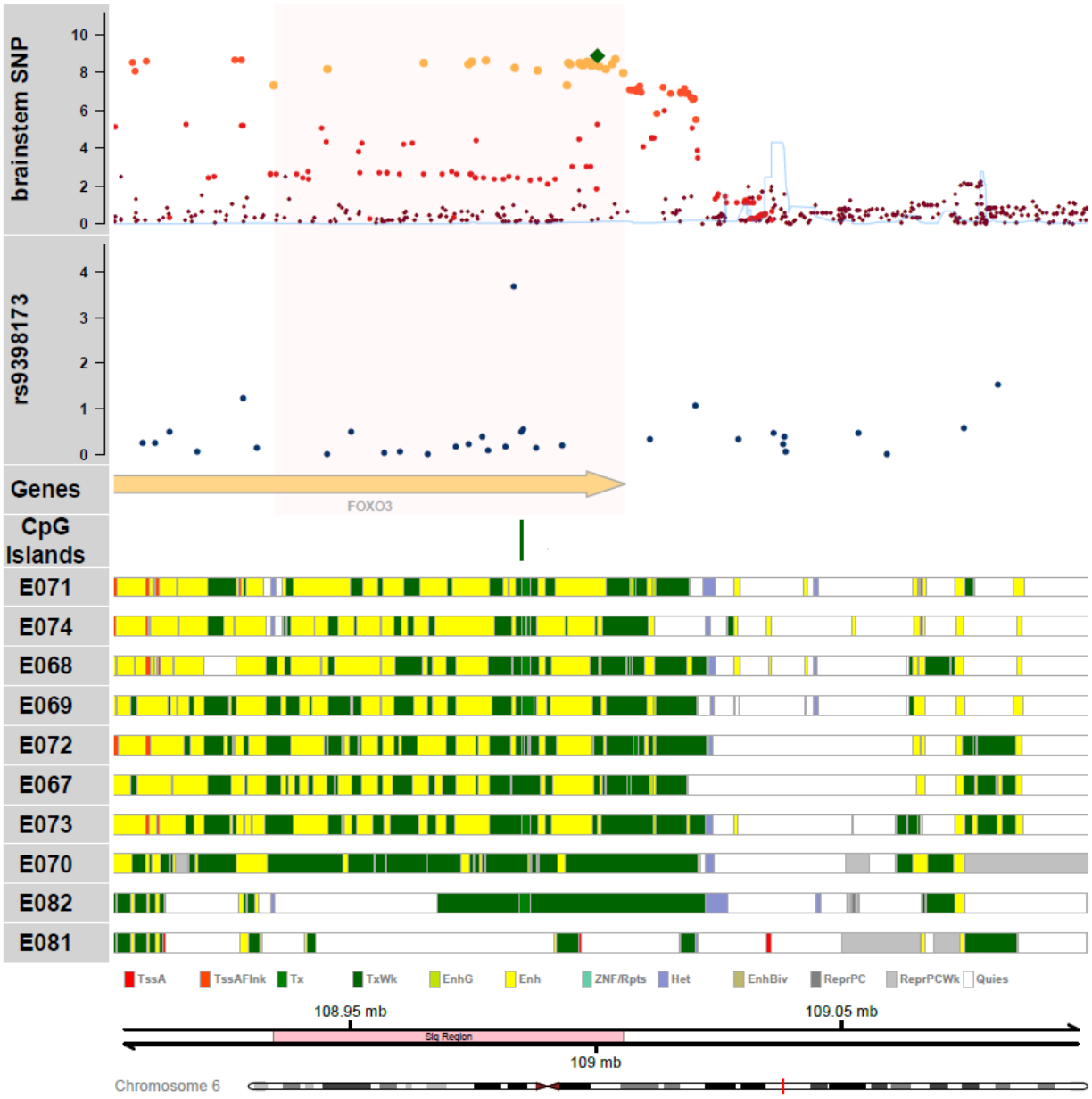
7. Brainstem (rs10217651)



8. Brainstem (rs869640)



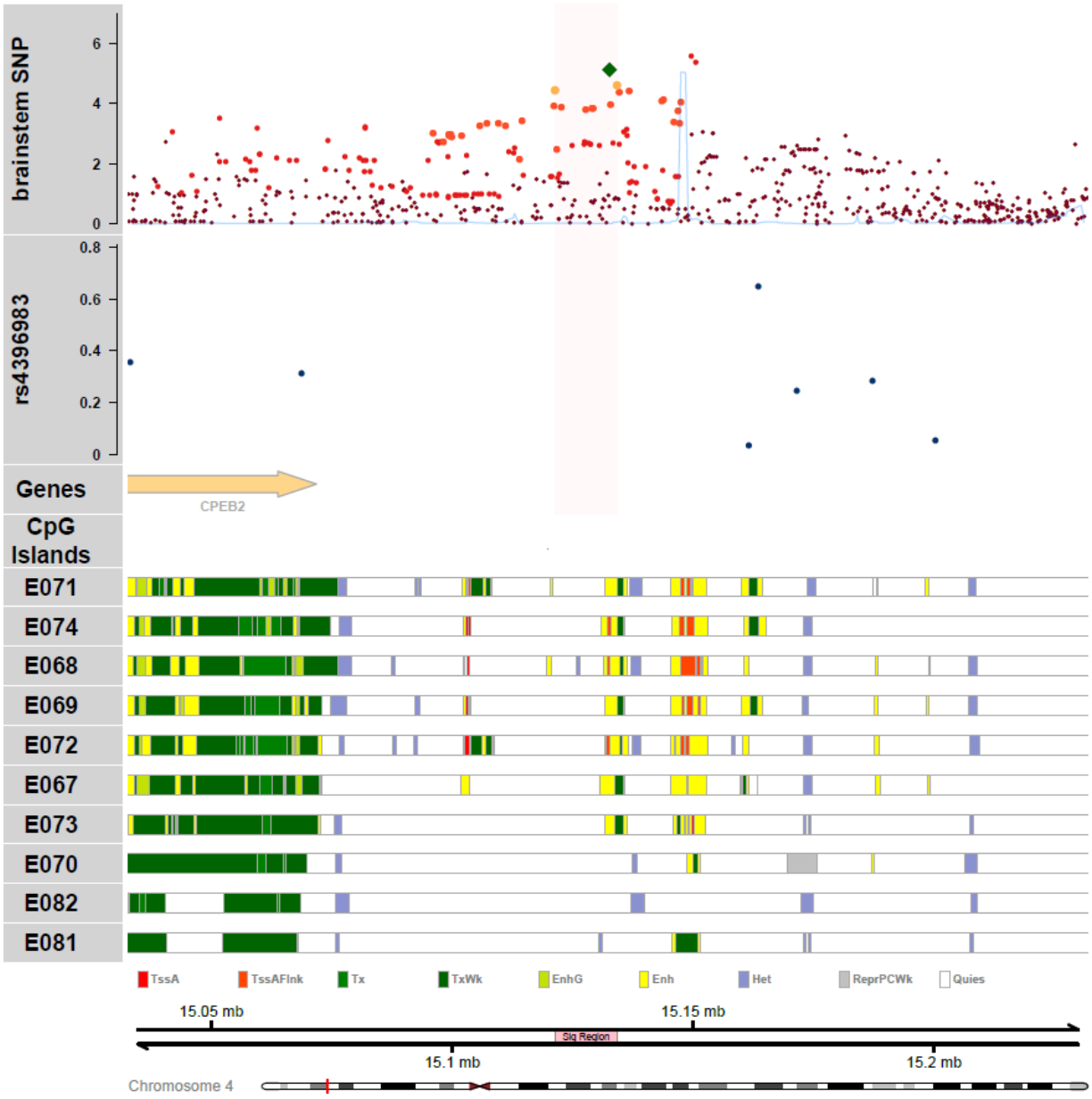
9. Brainstem (rs9398173)



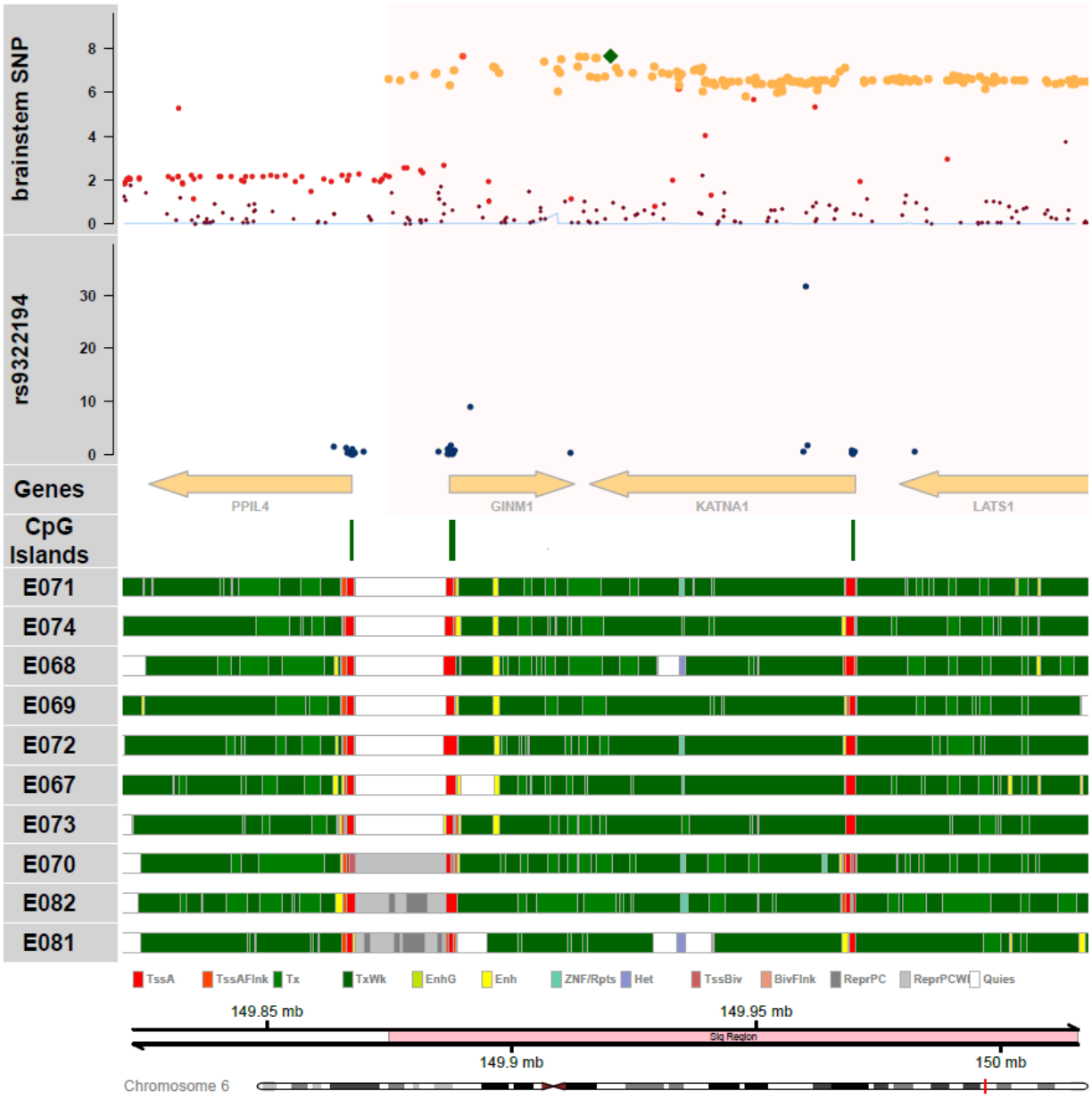
10. Brainstem (rs10792032)

Information was not available

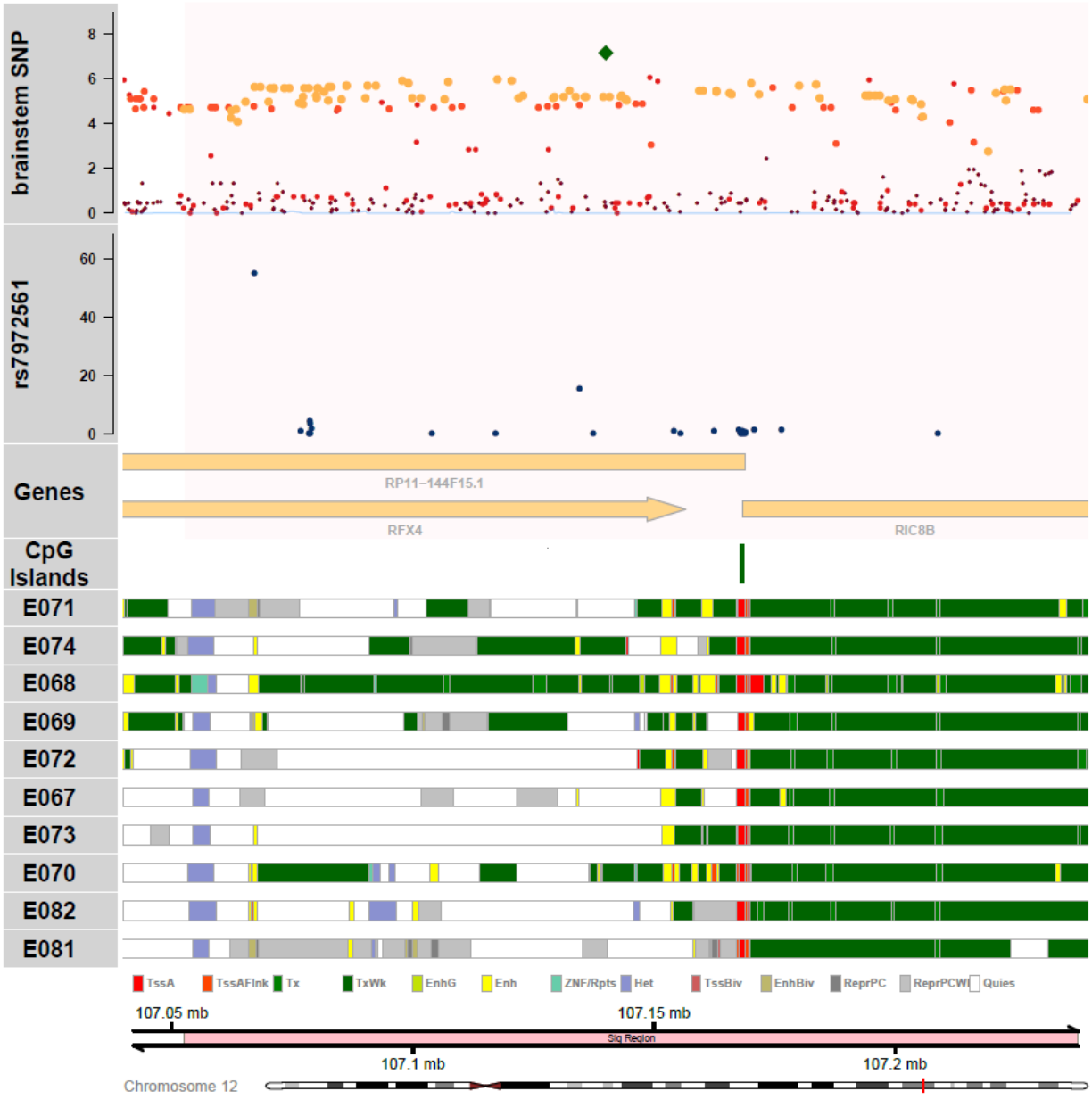
11. Brainstem (rs4396983)



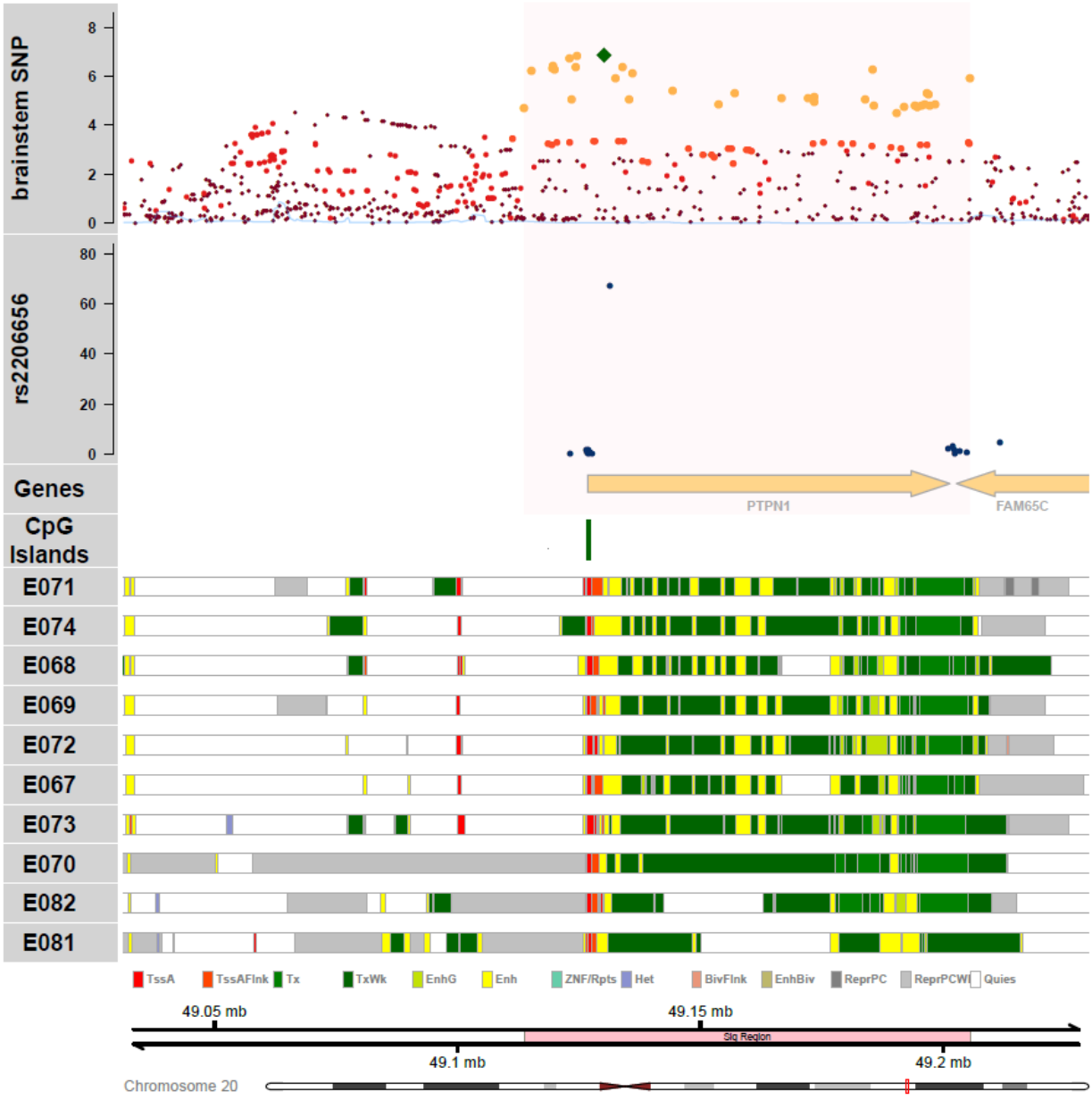
12. Brainstem (rs9322194)



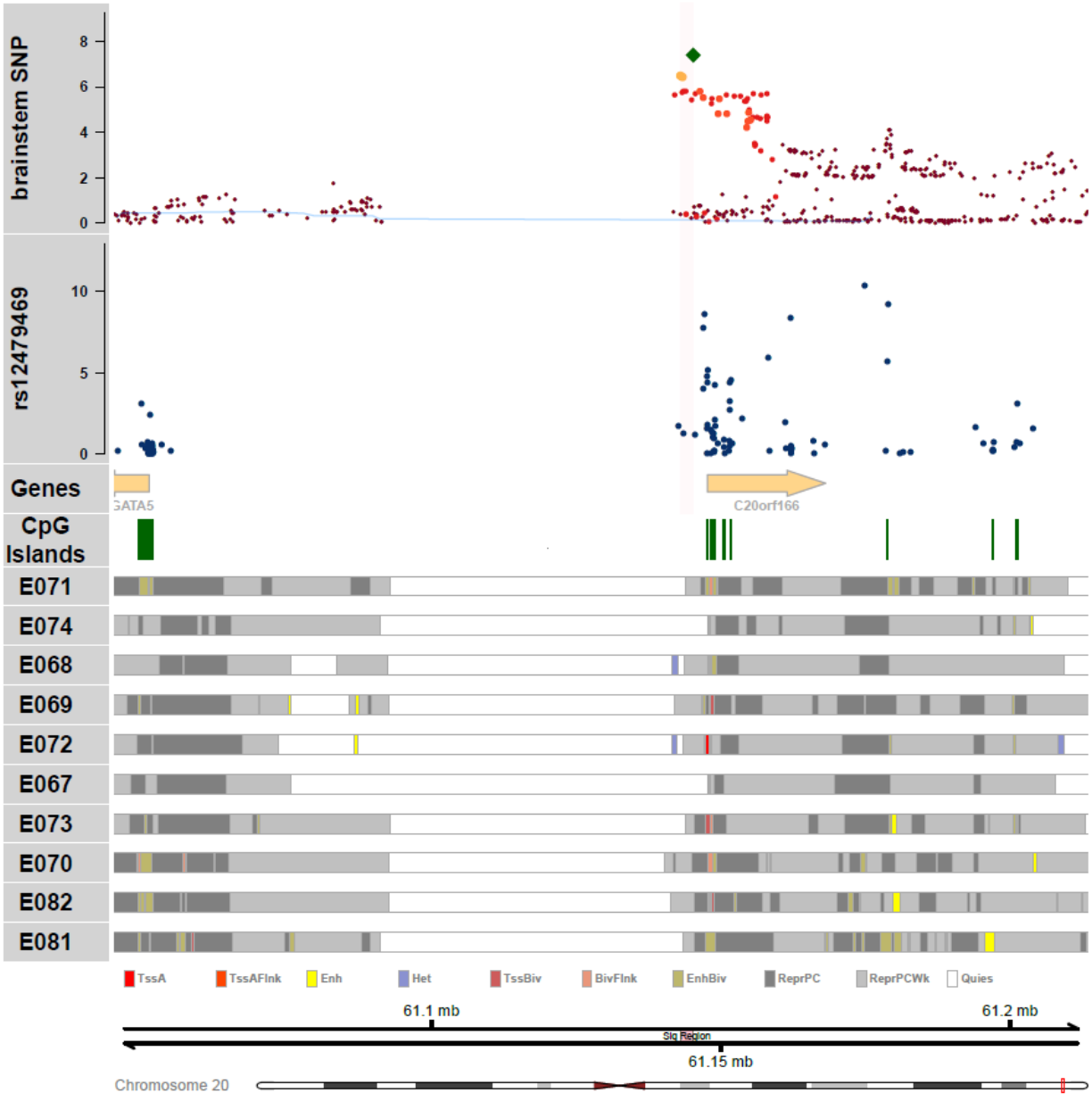
13. Brainstem (rs7972561)



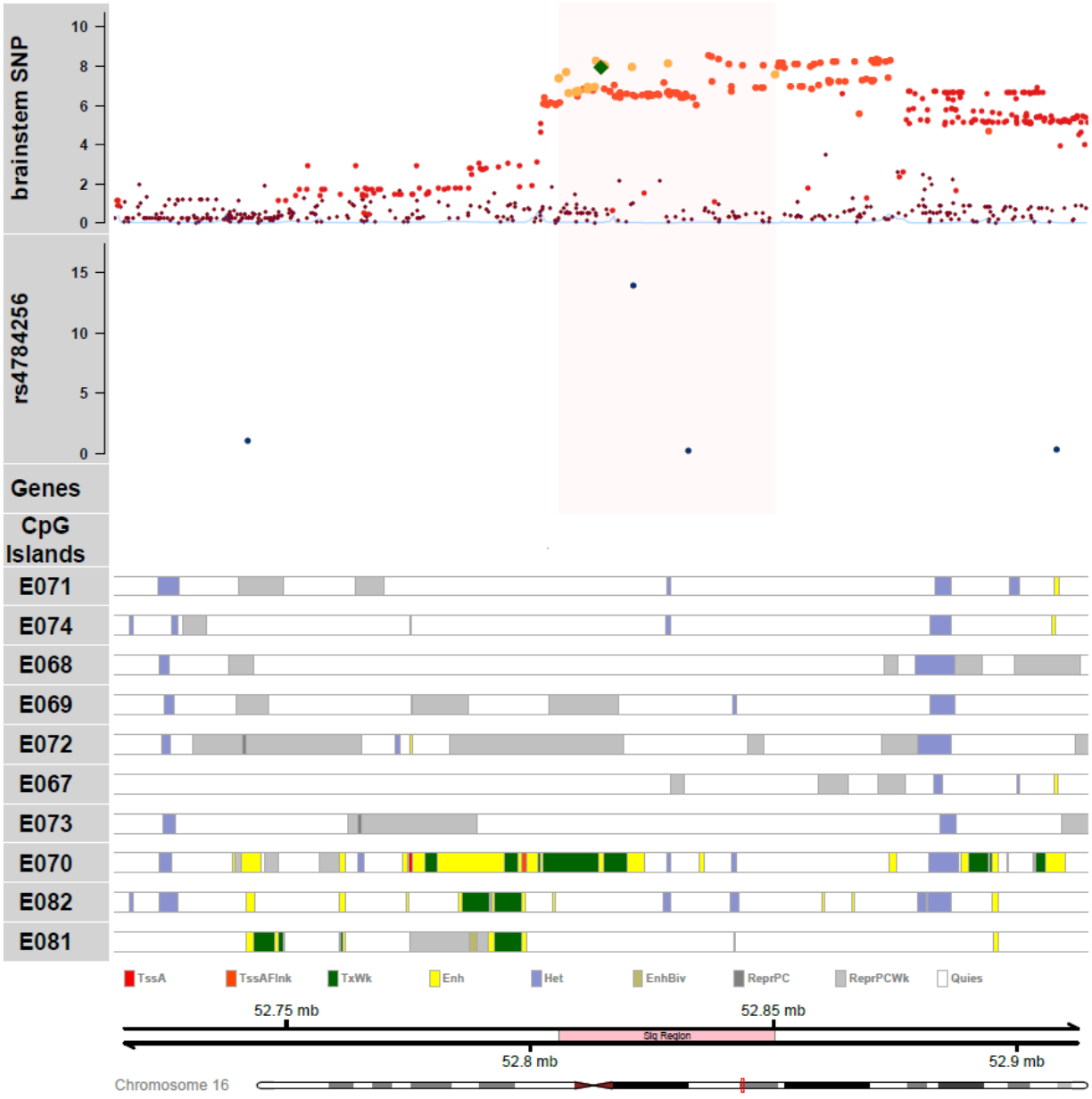
14. Brainstem (rs2206656)



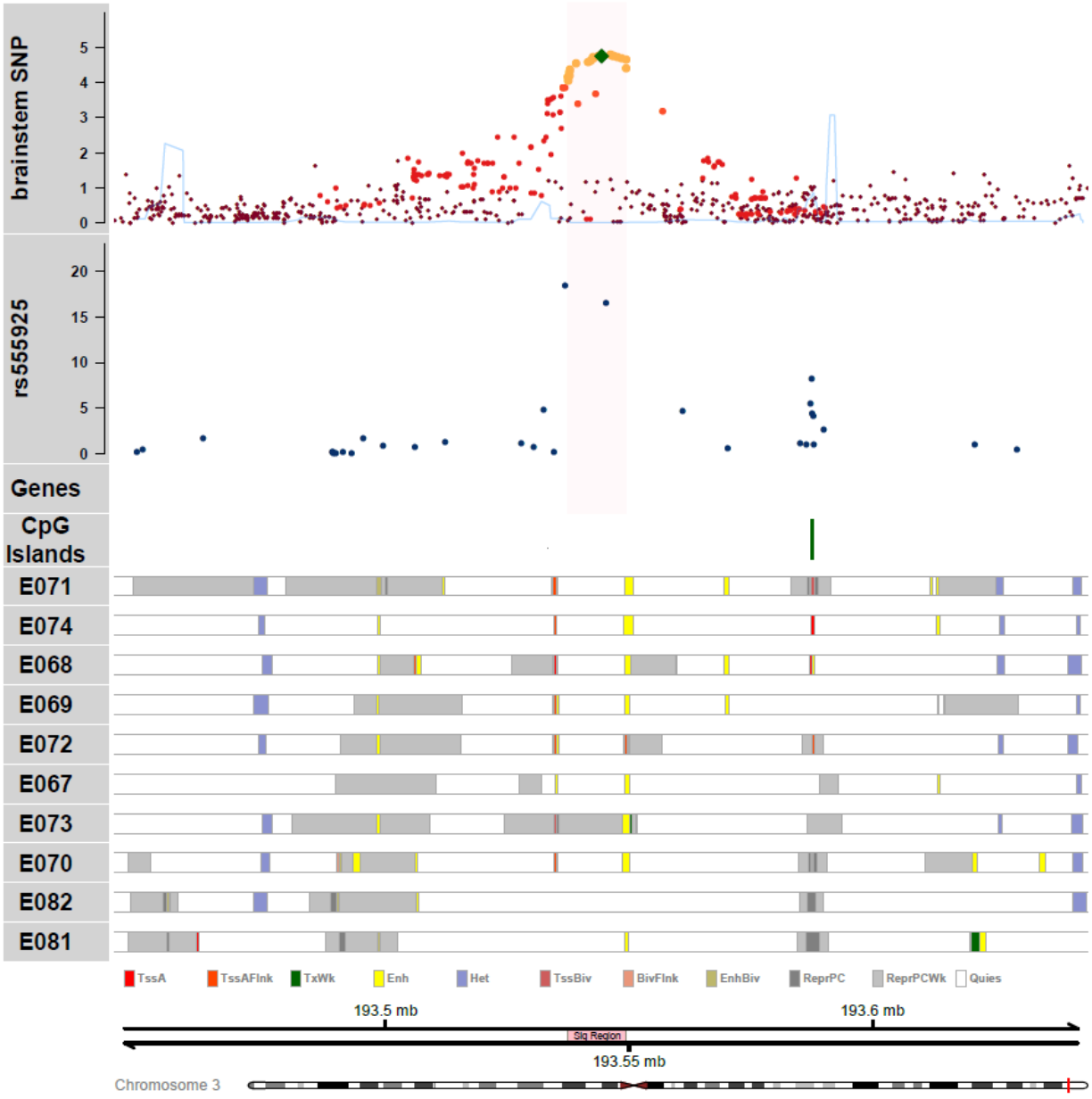
15. Brainstem (rs12479469)



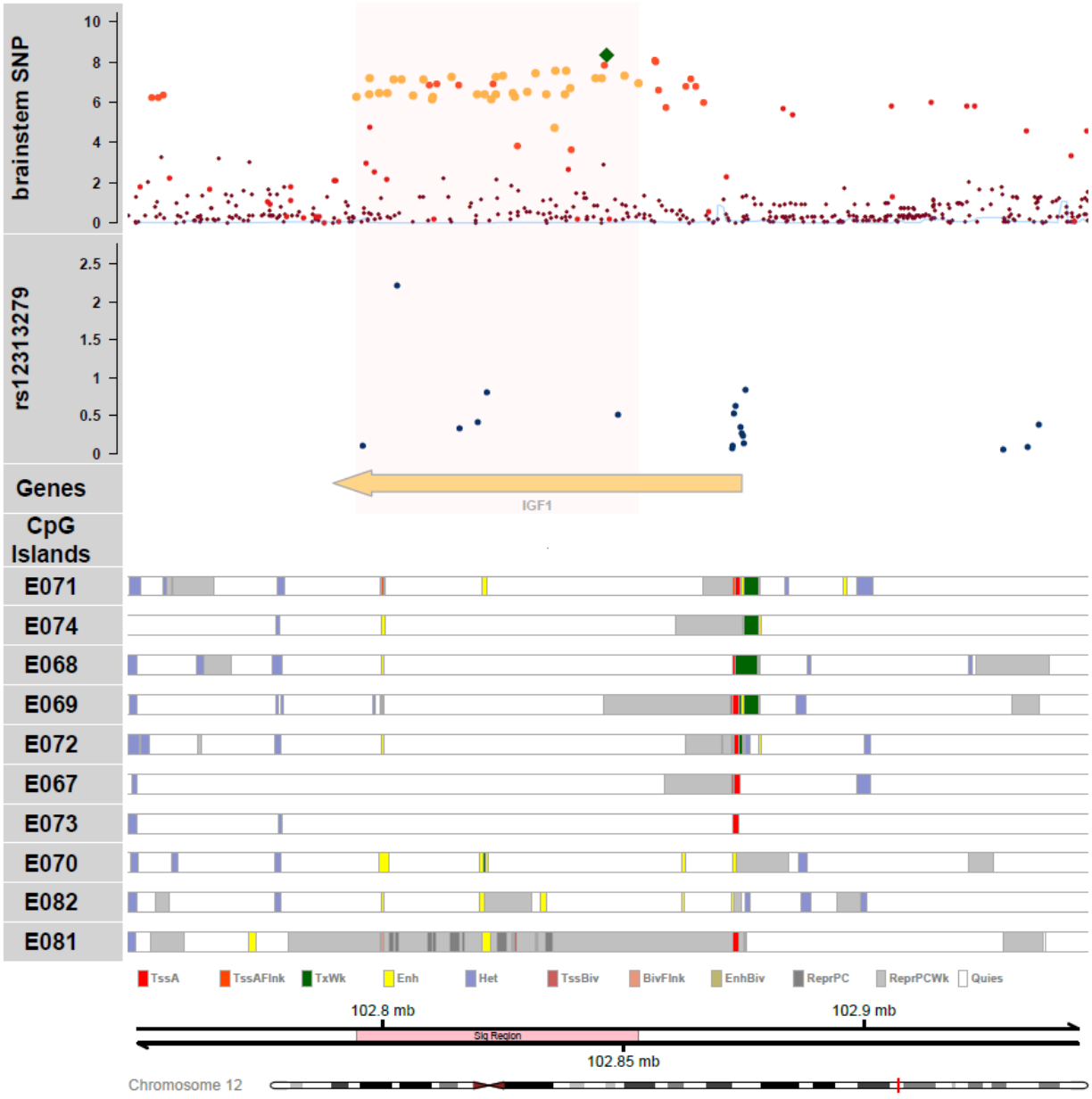
16. Brainstem (rs4784256)



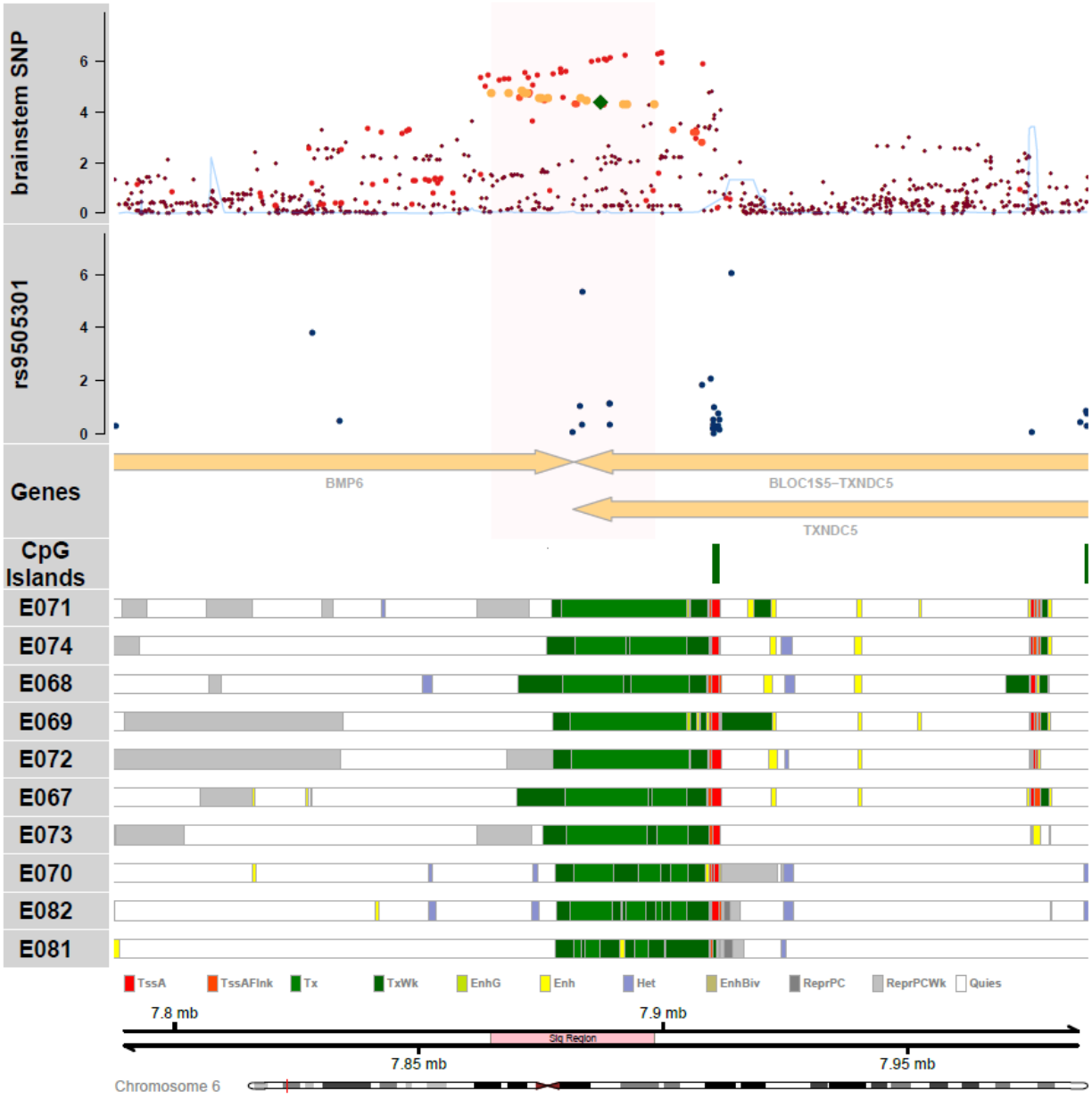
17. Brainstem (rs555925)



18. Brainstem (rs12313279)



19. Brainstem (rs9505301)



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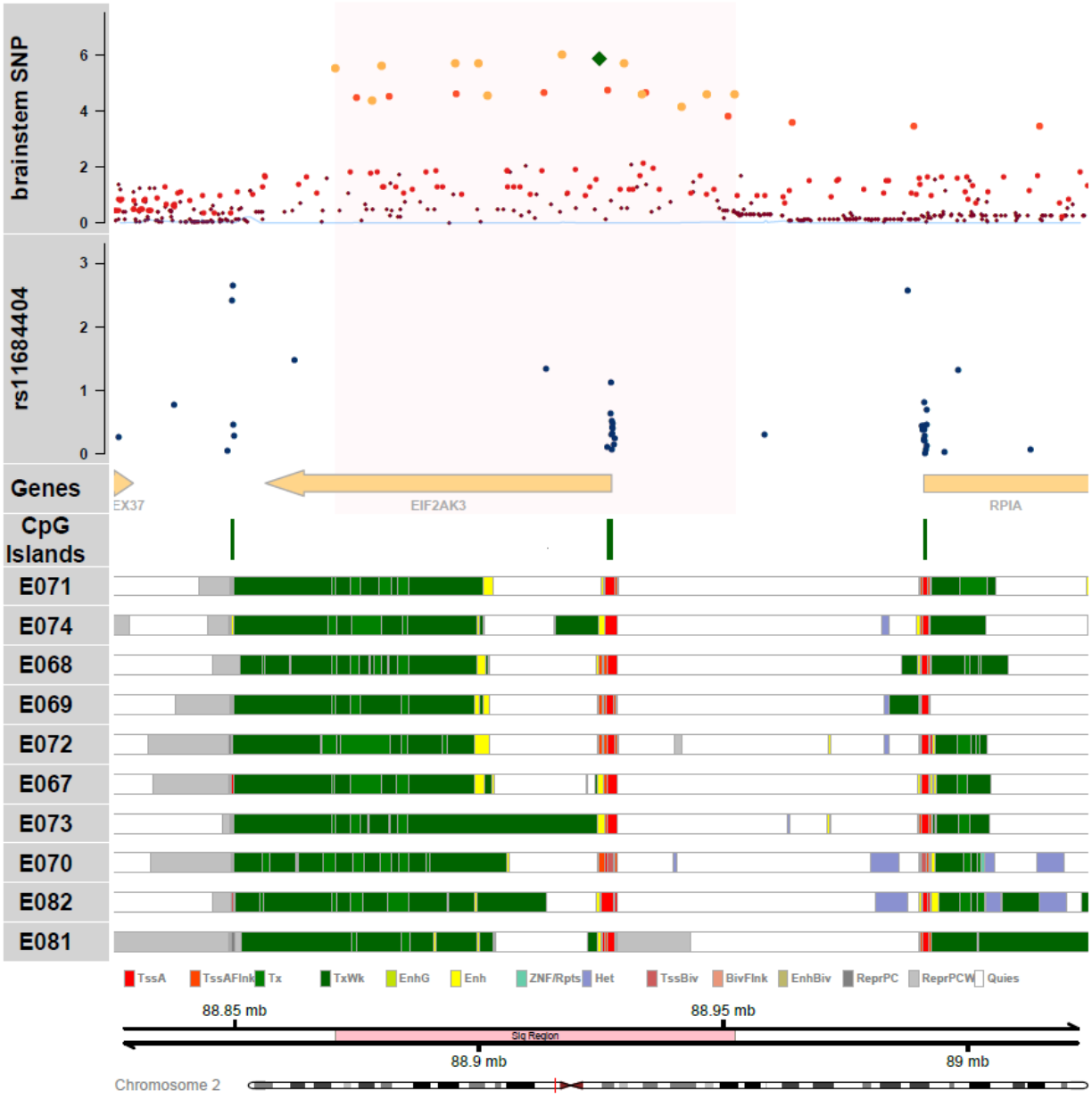
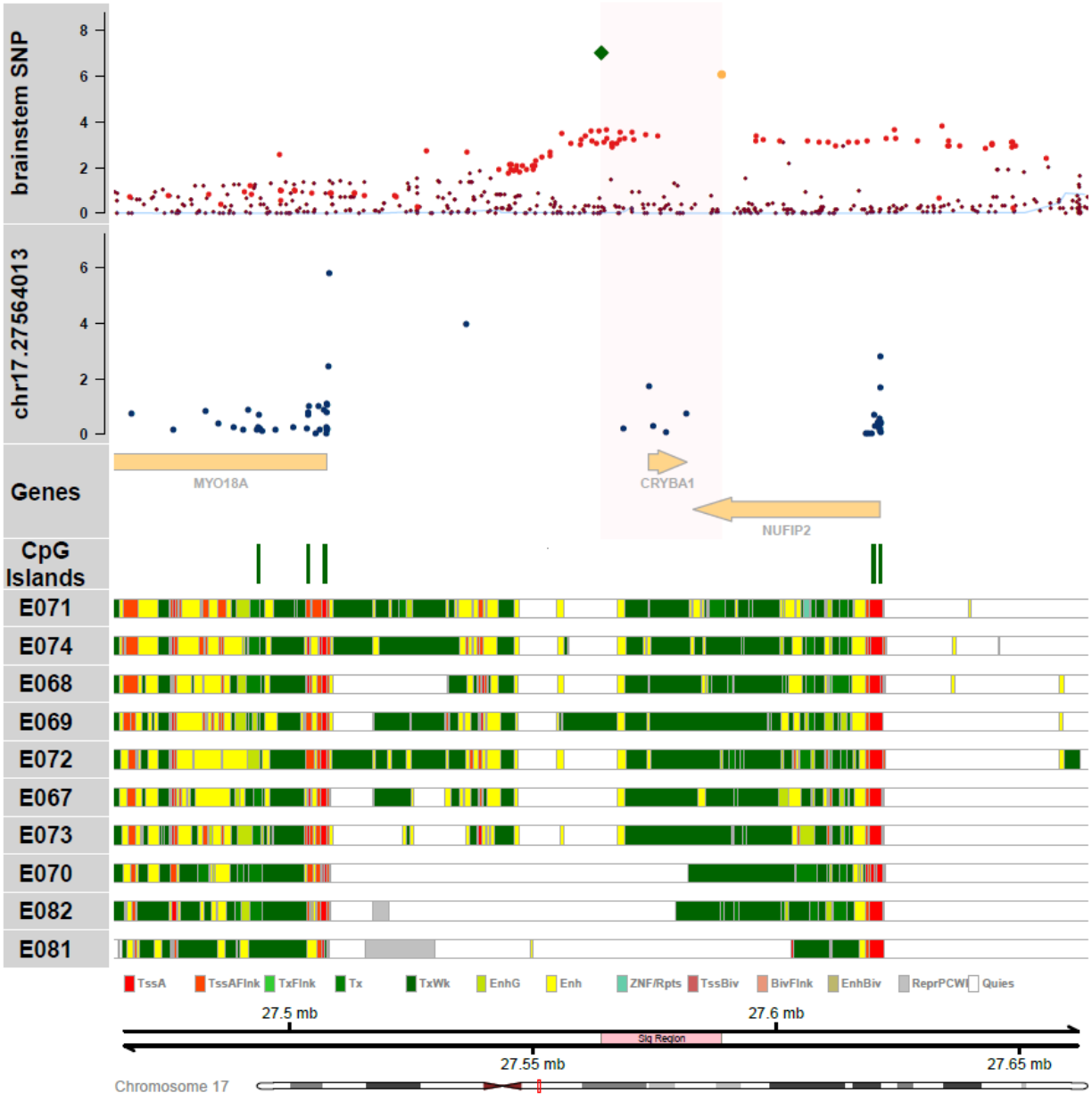
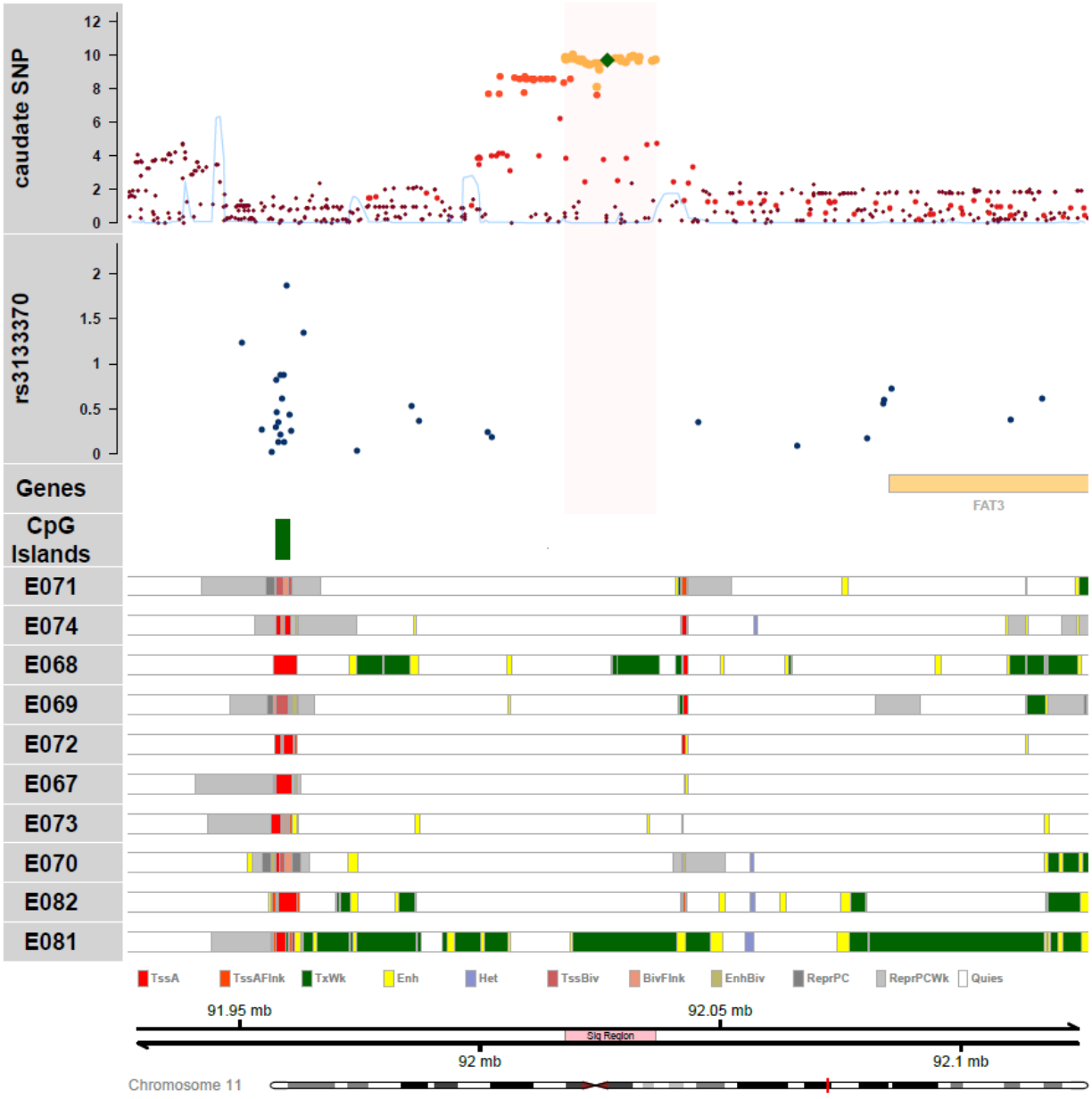


21. Brainstem (rs112178027)



22. Caudate nucleus (rs3133370)



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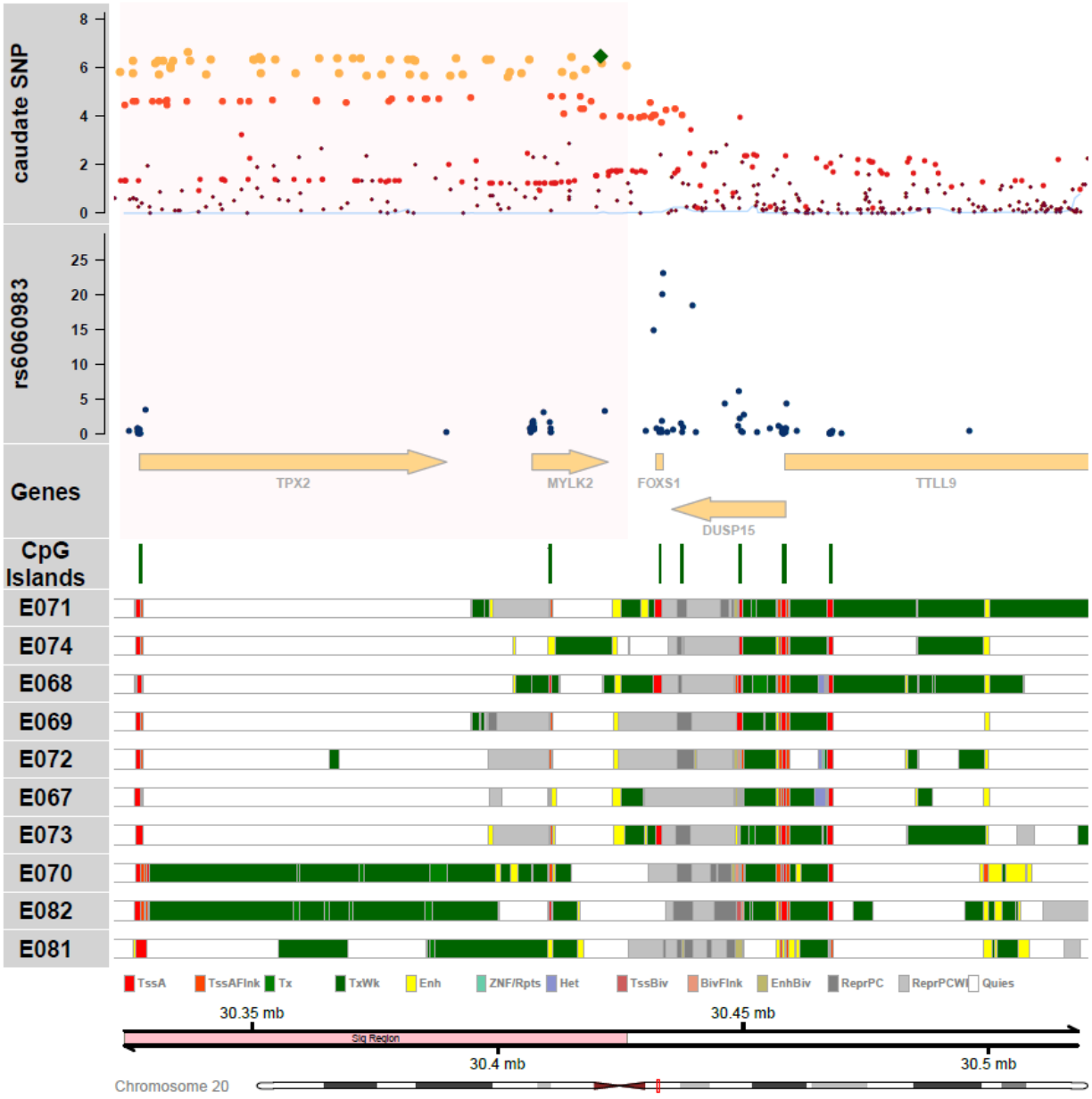

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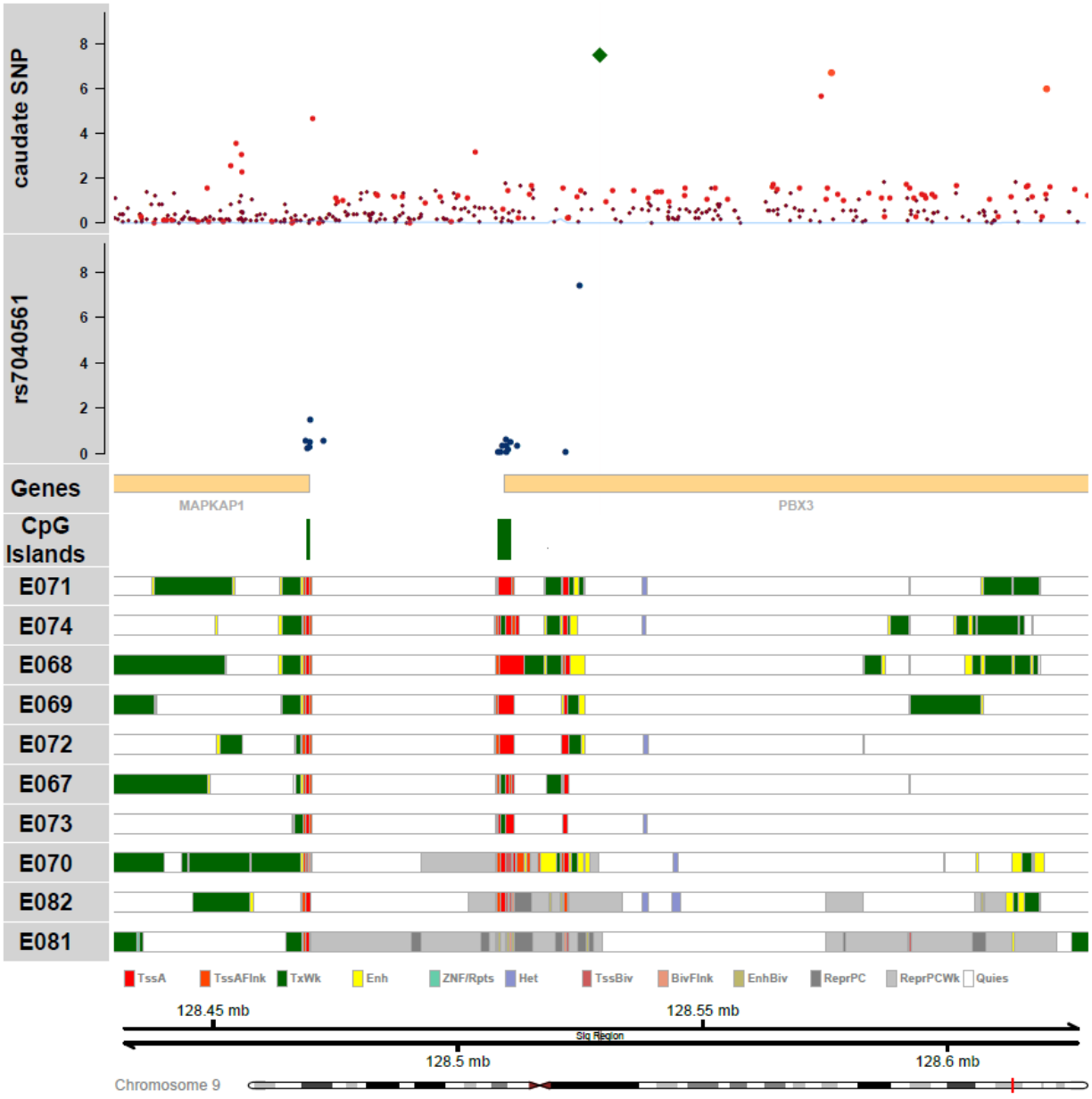
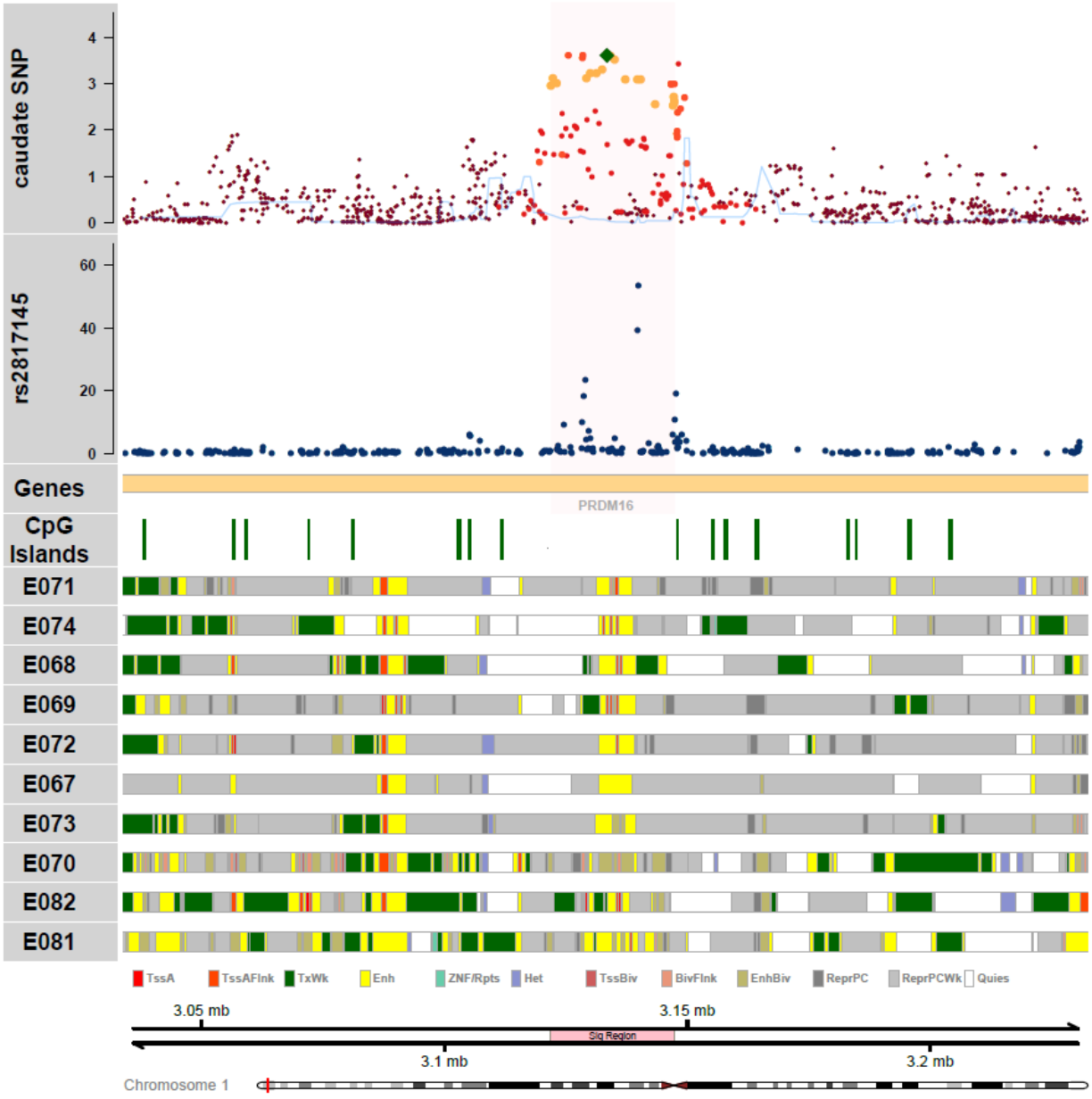


25. Caudate nucleus (rs2817145)



26. Caudate nucleus (rs148470213)

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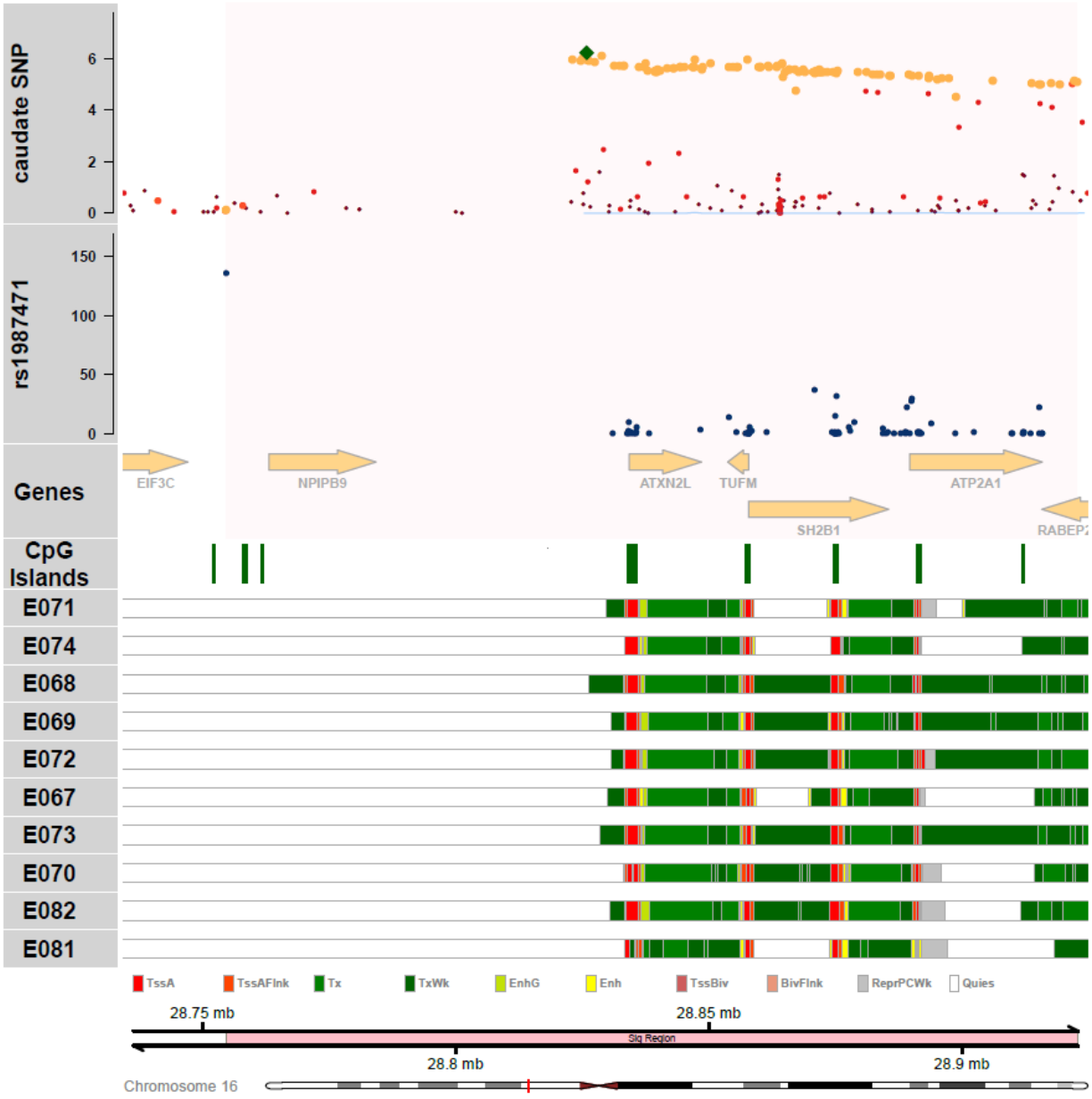
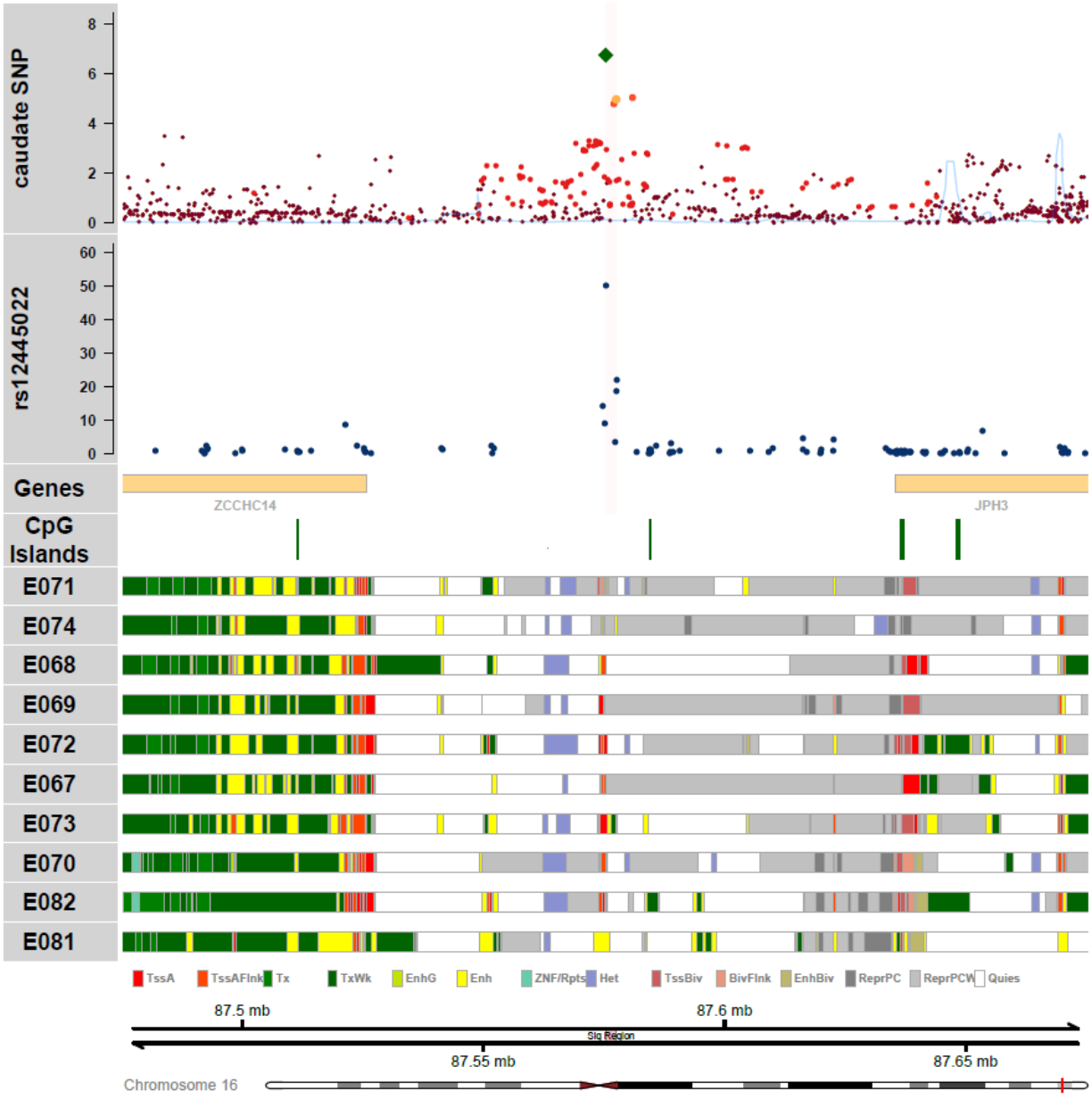
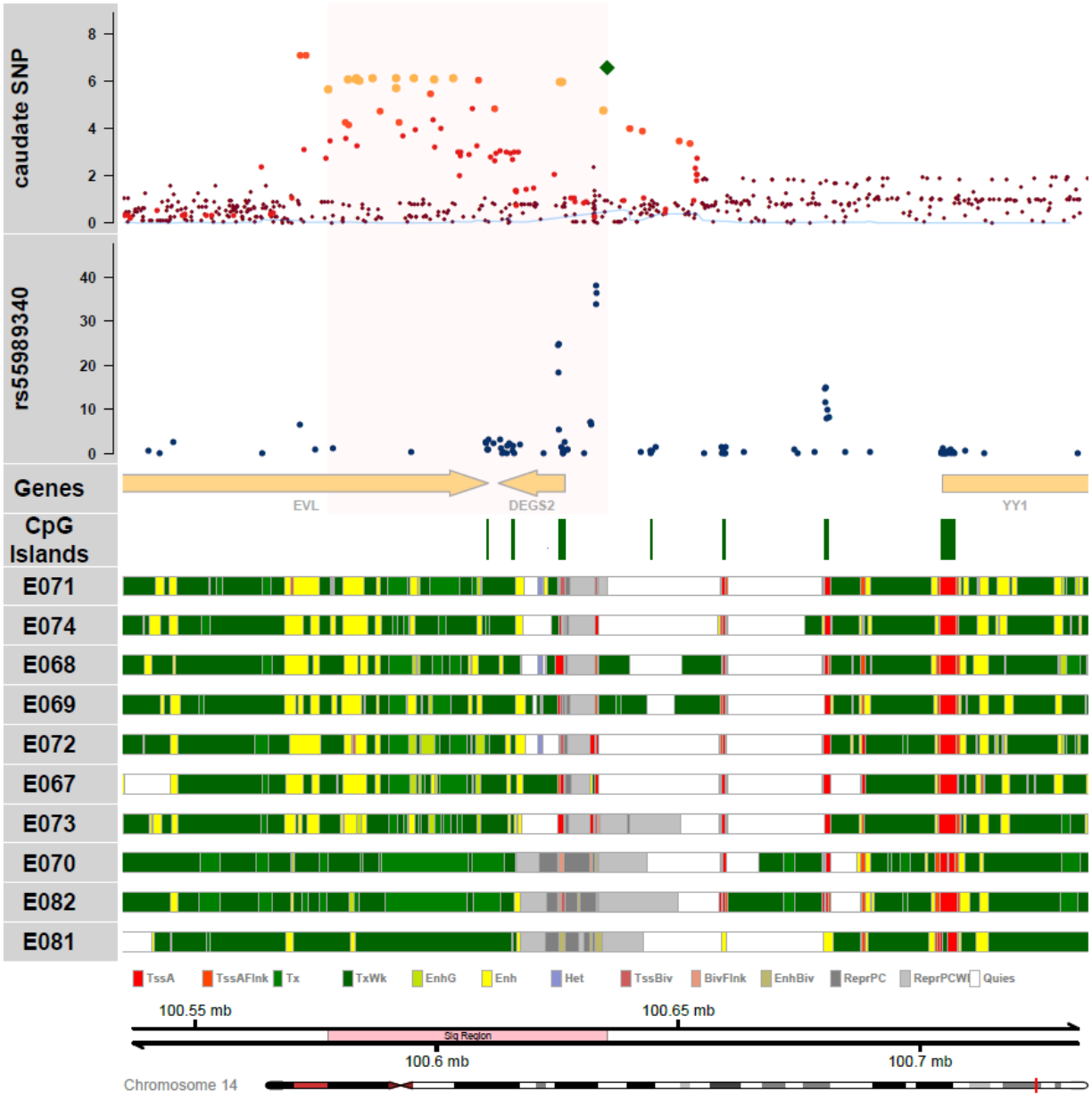
27. Caudate nucleus (rs1987471)



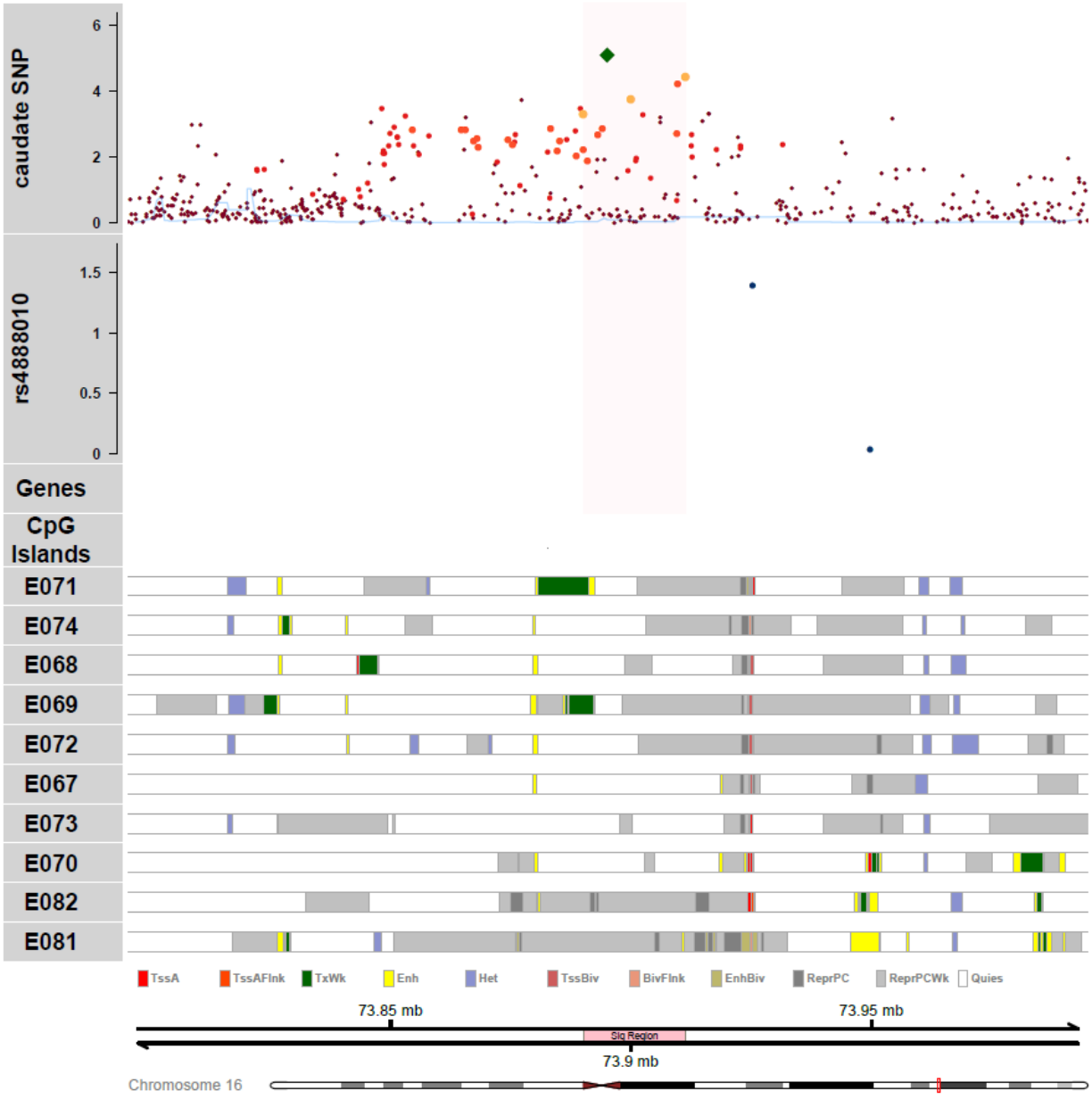
28. Caudate nucleus (rs12445022)



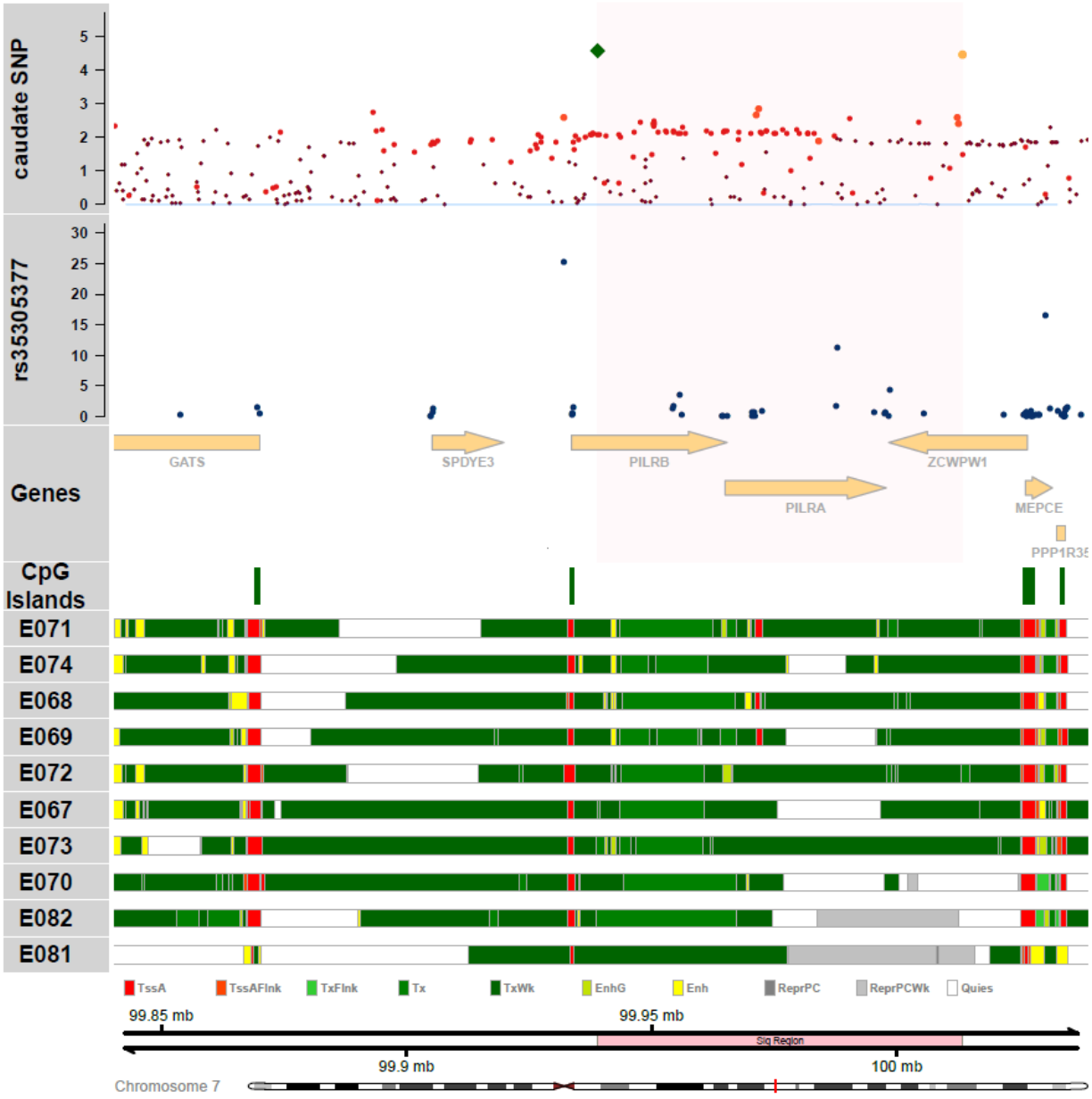
29. Caudate nucleus (rs55989340)



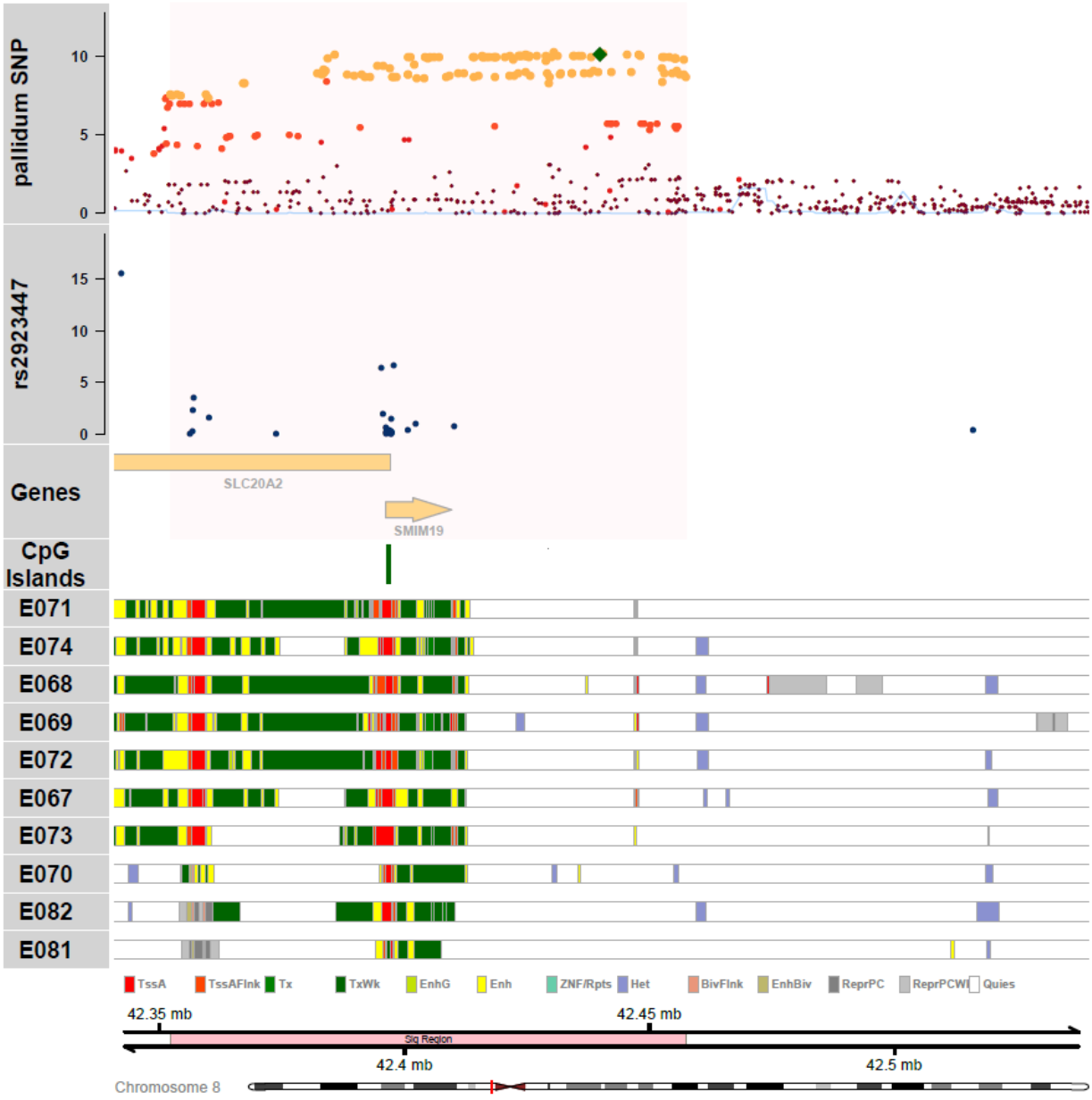
30. Caudate nucleus (rs4888010)



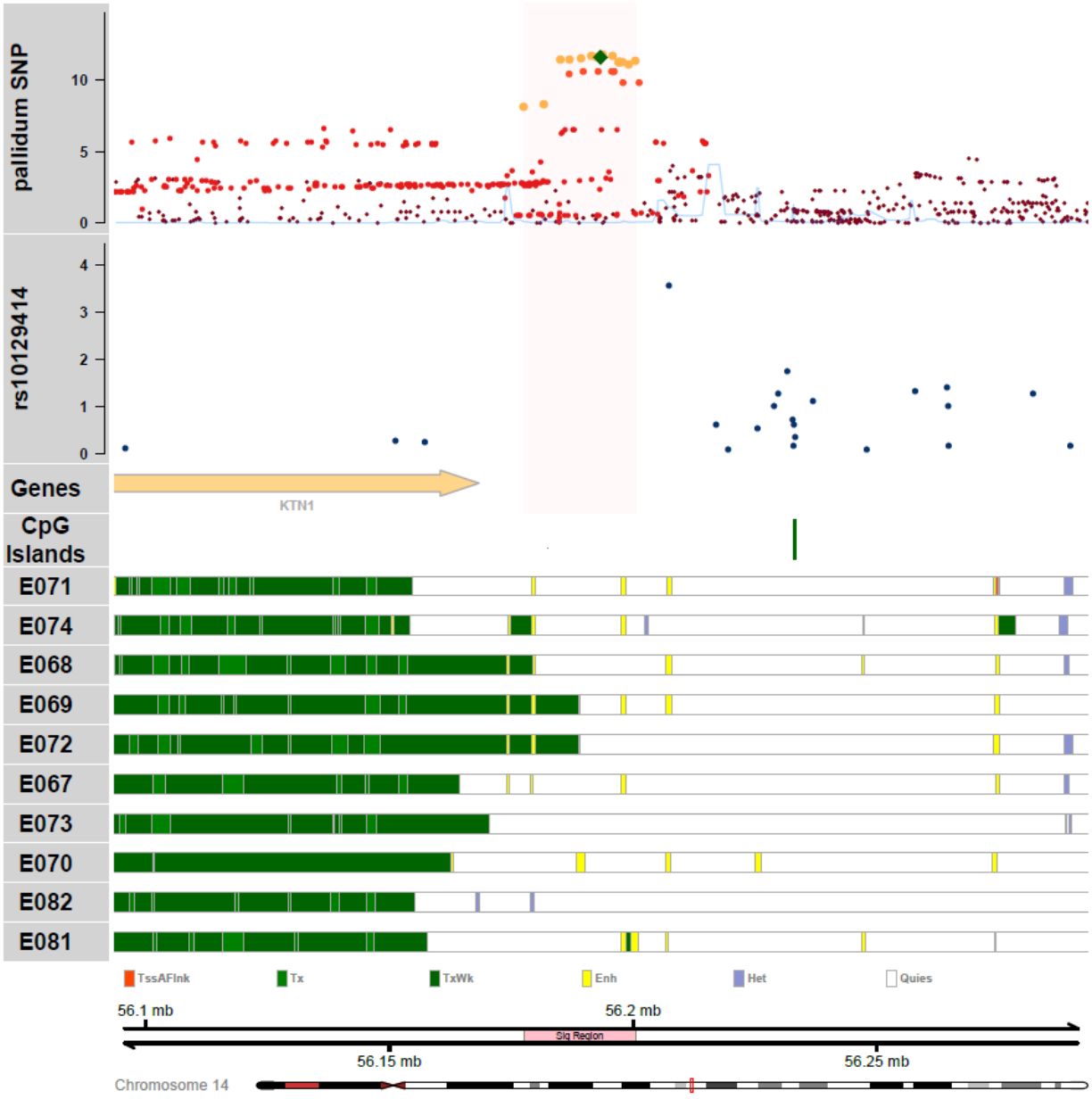
31. Caudate nucleus (rs35305377)



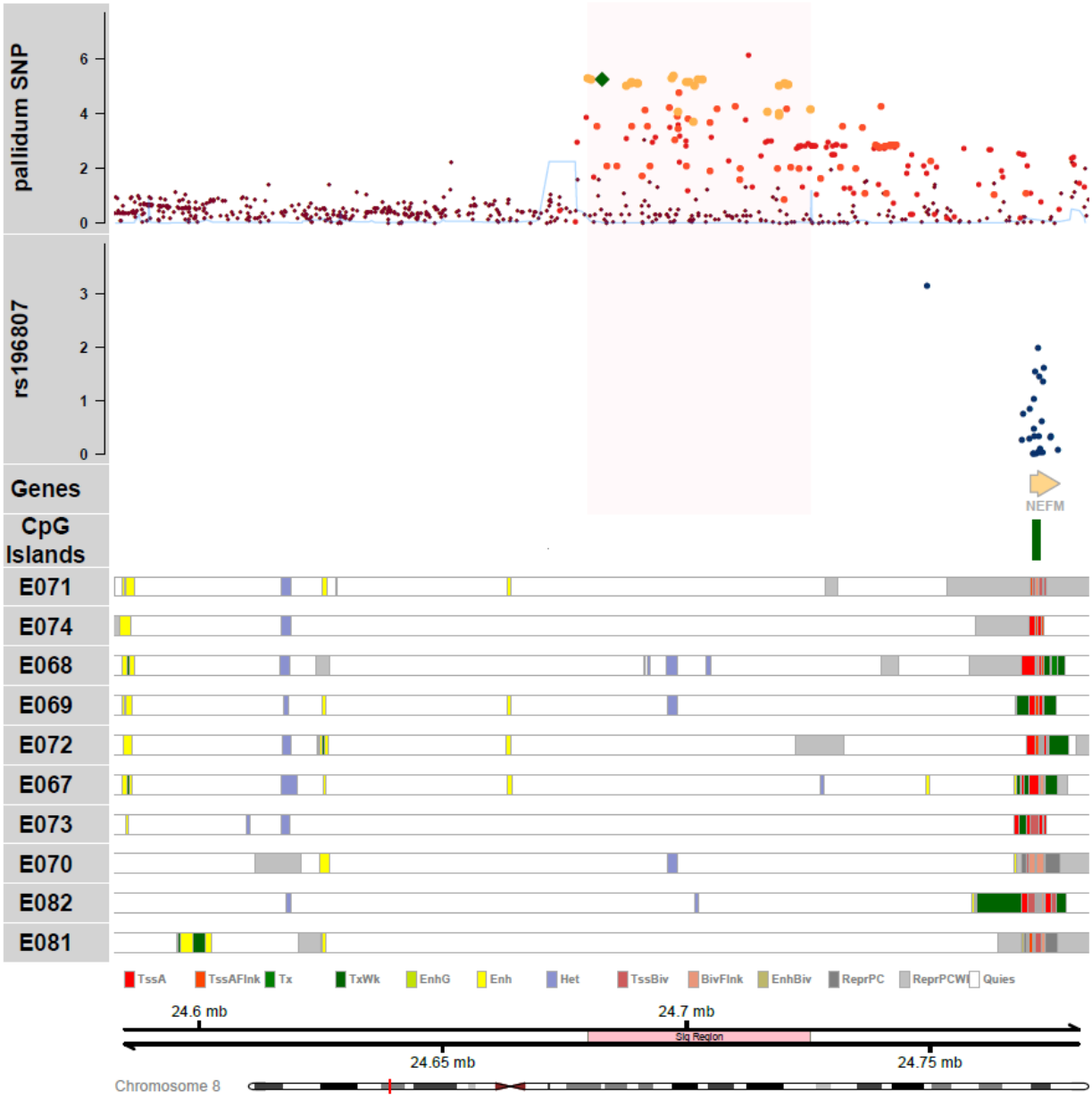
32. Globus pallidus (rs2923447)



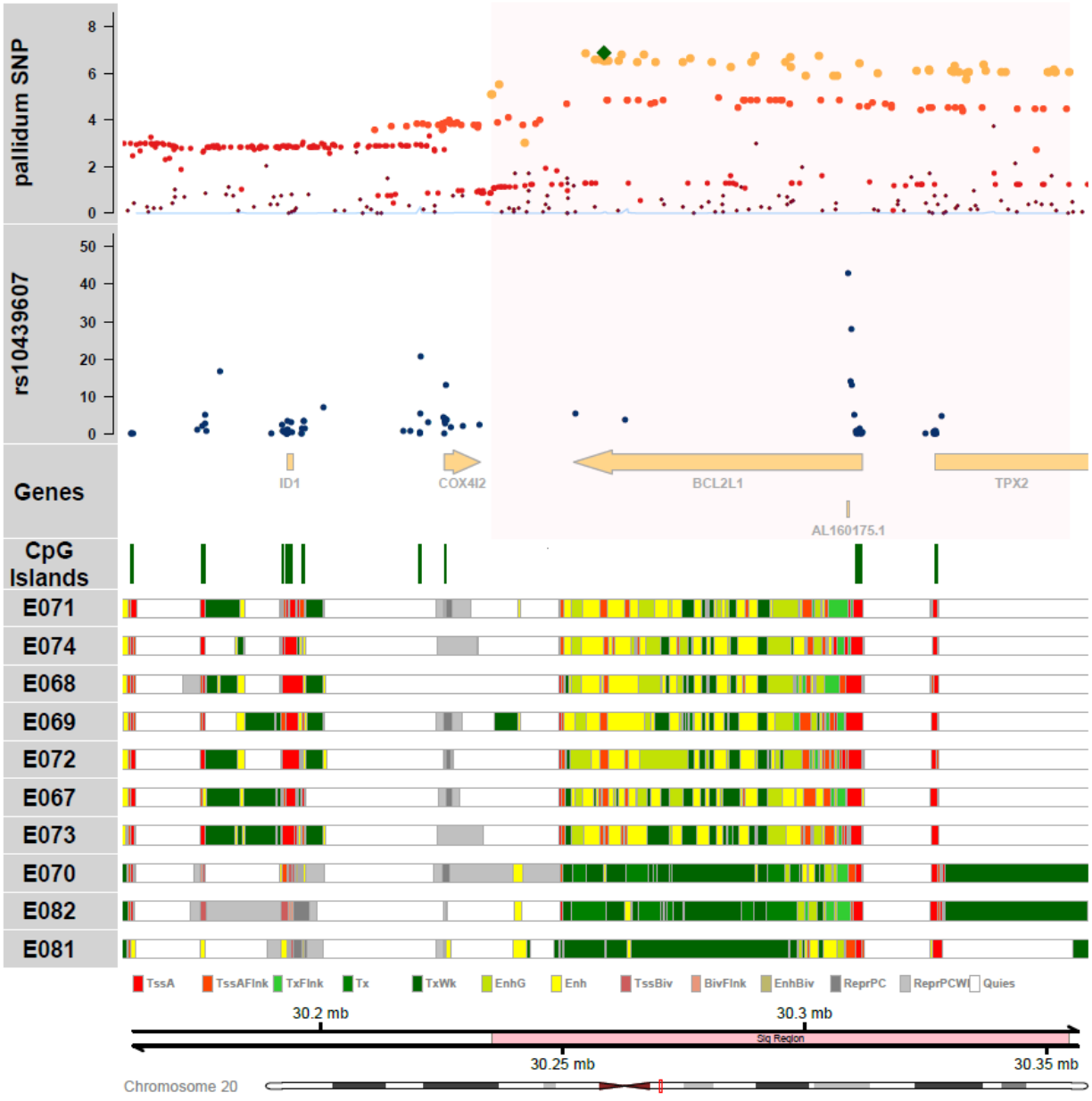
33. Globus pallidus (rs10129414)



34. Globus pallidus (rs196807)



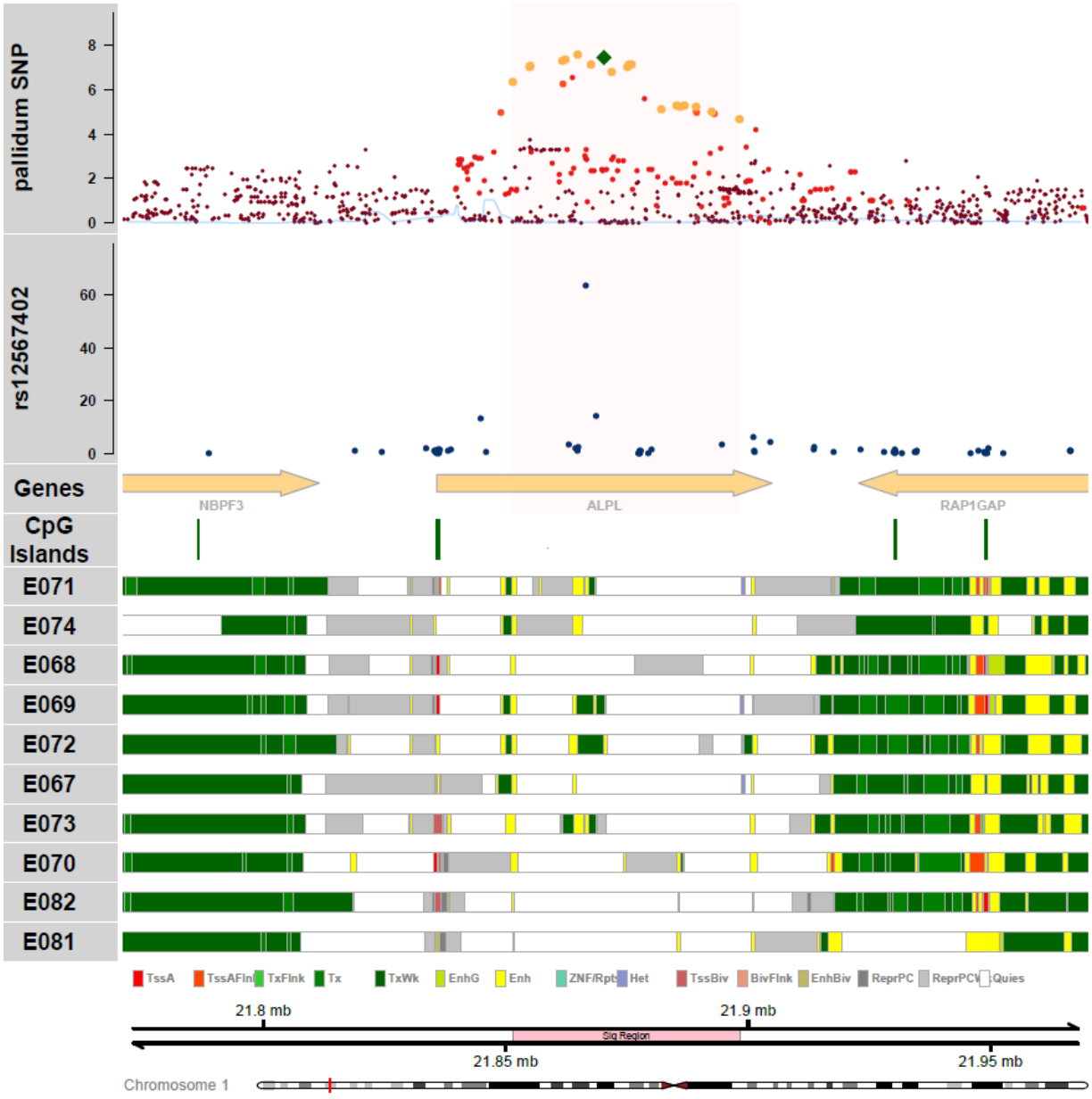
35. Globus pallidus (rs10439607)



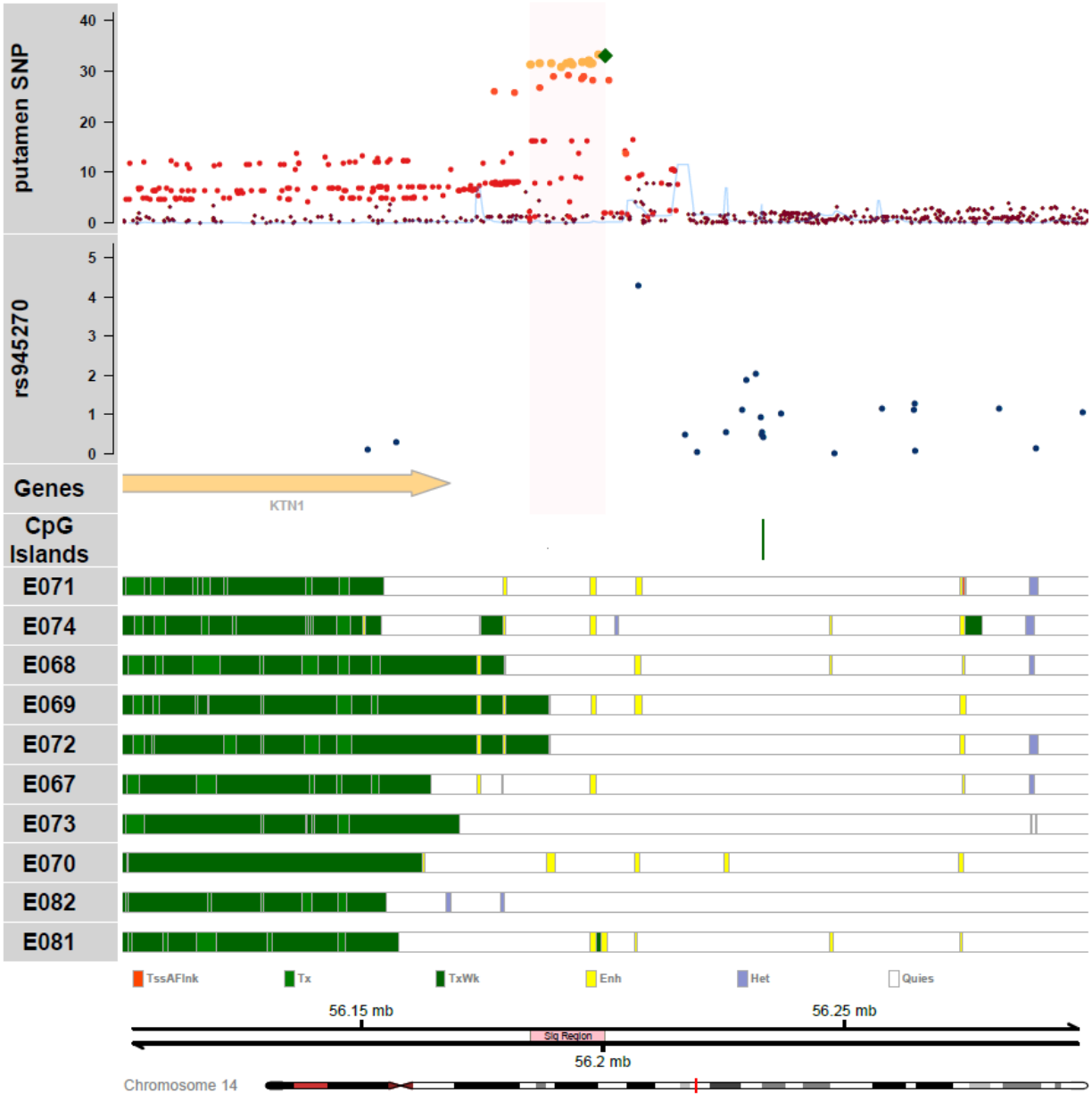
36. Globus pallidus (rs4952211)

Information was not available

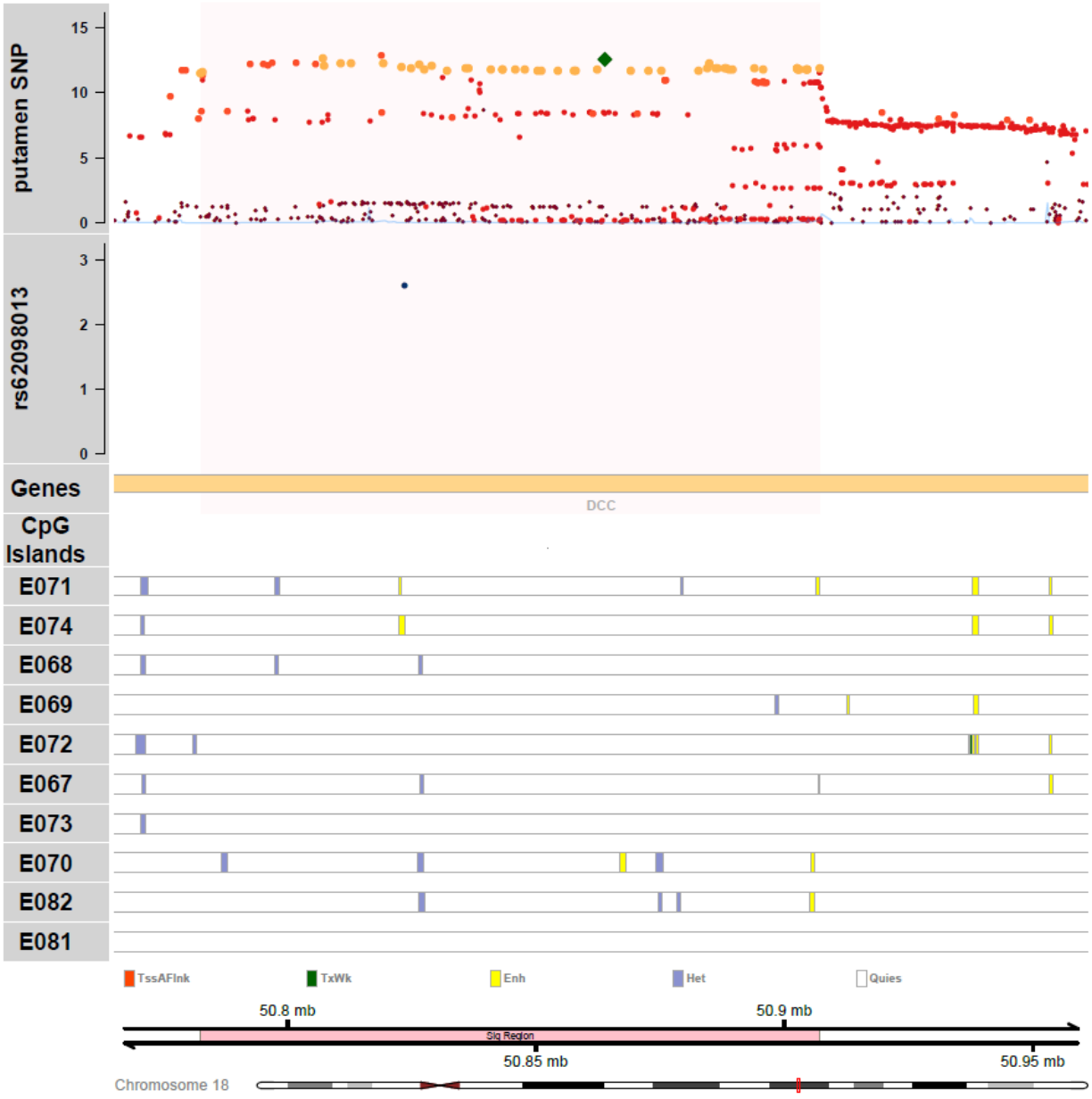
37. Globus pallidus (rs12567402)



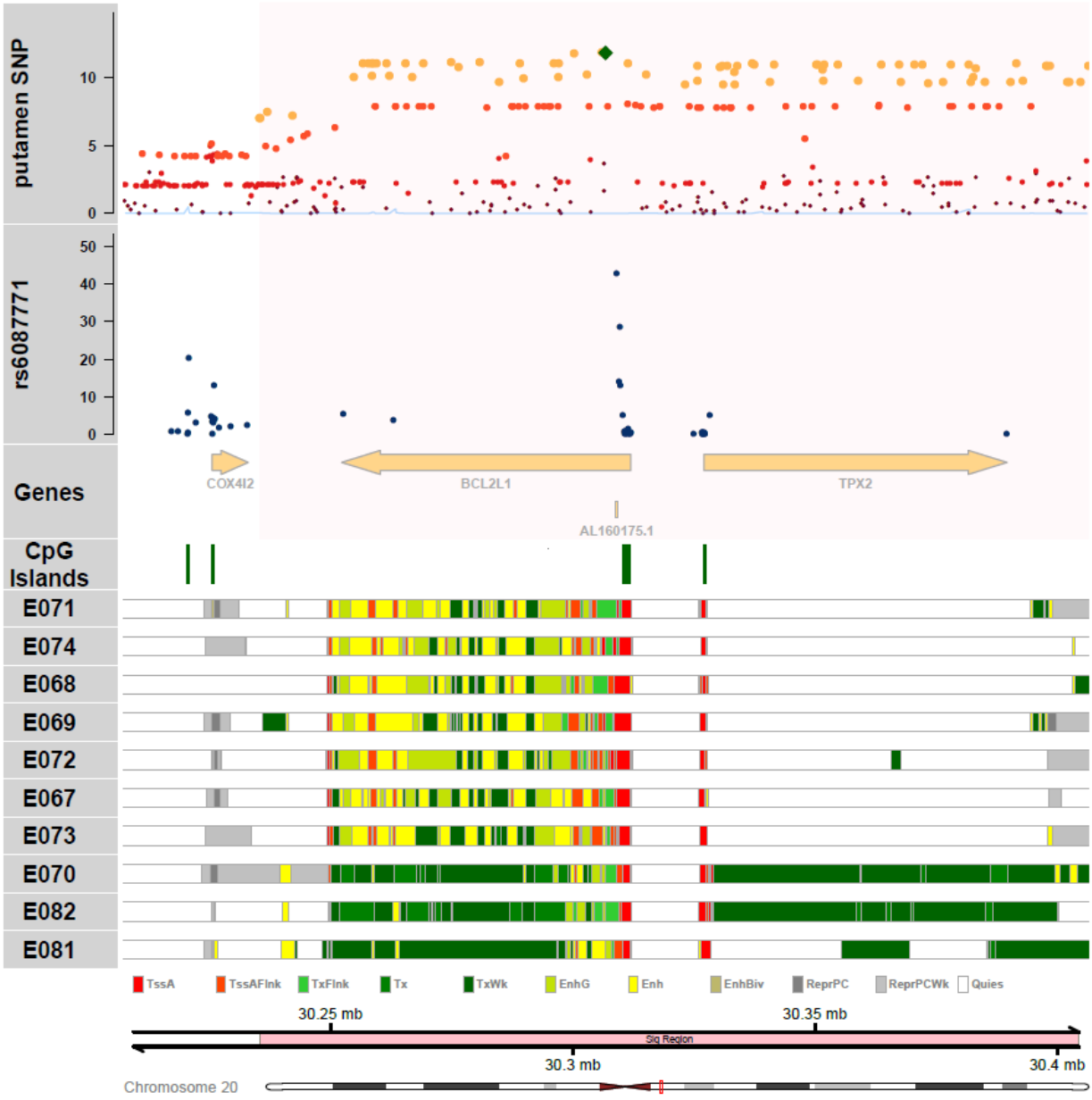
38. Putamen (rs945270)



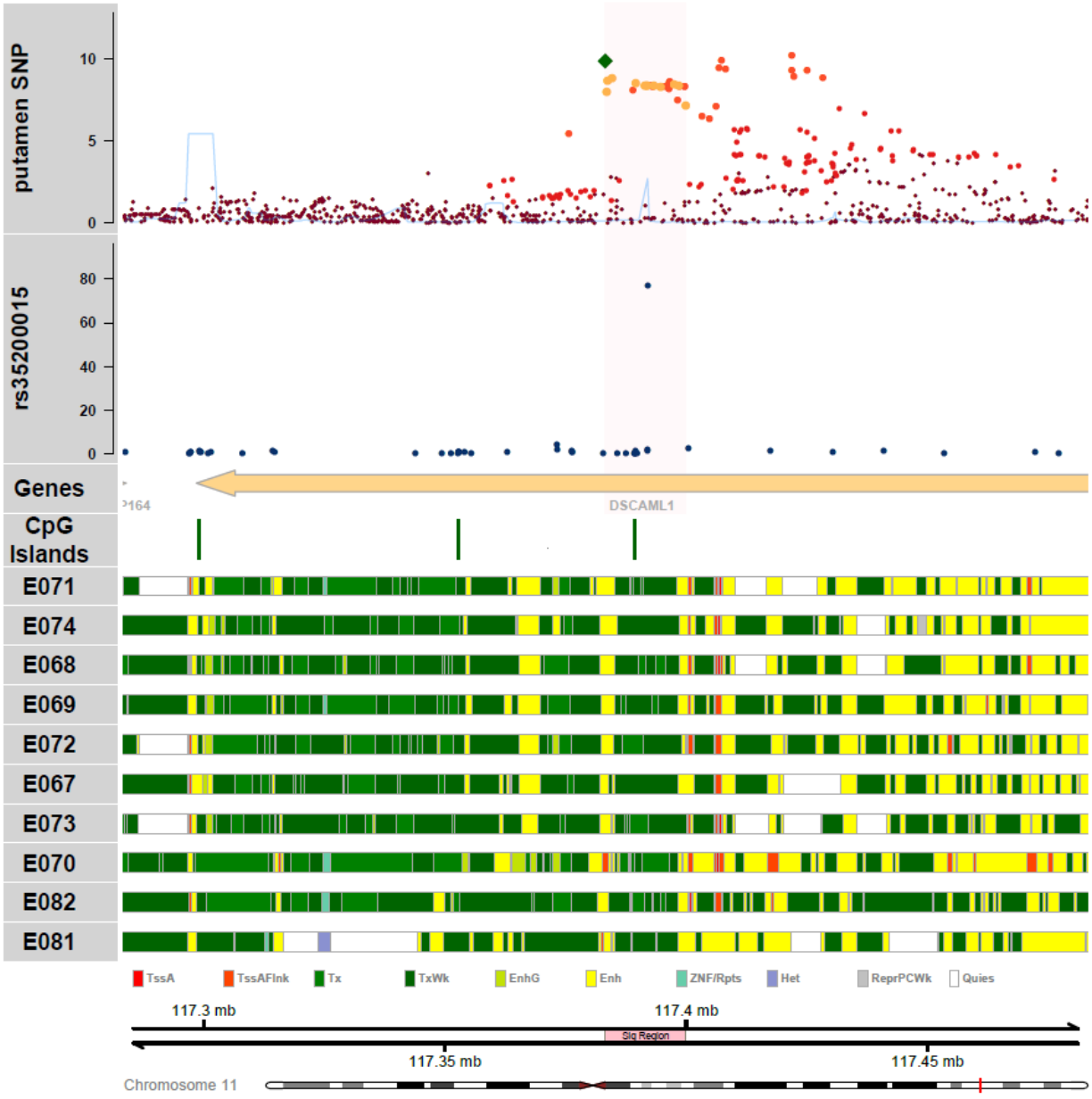
39. Putamen (rs62098013)



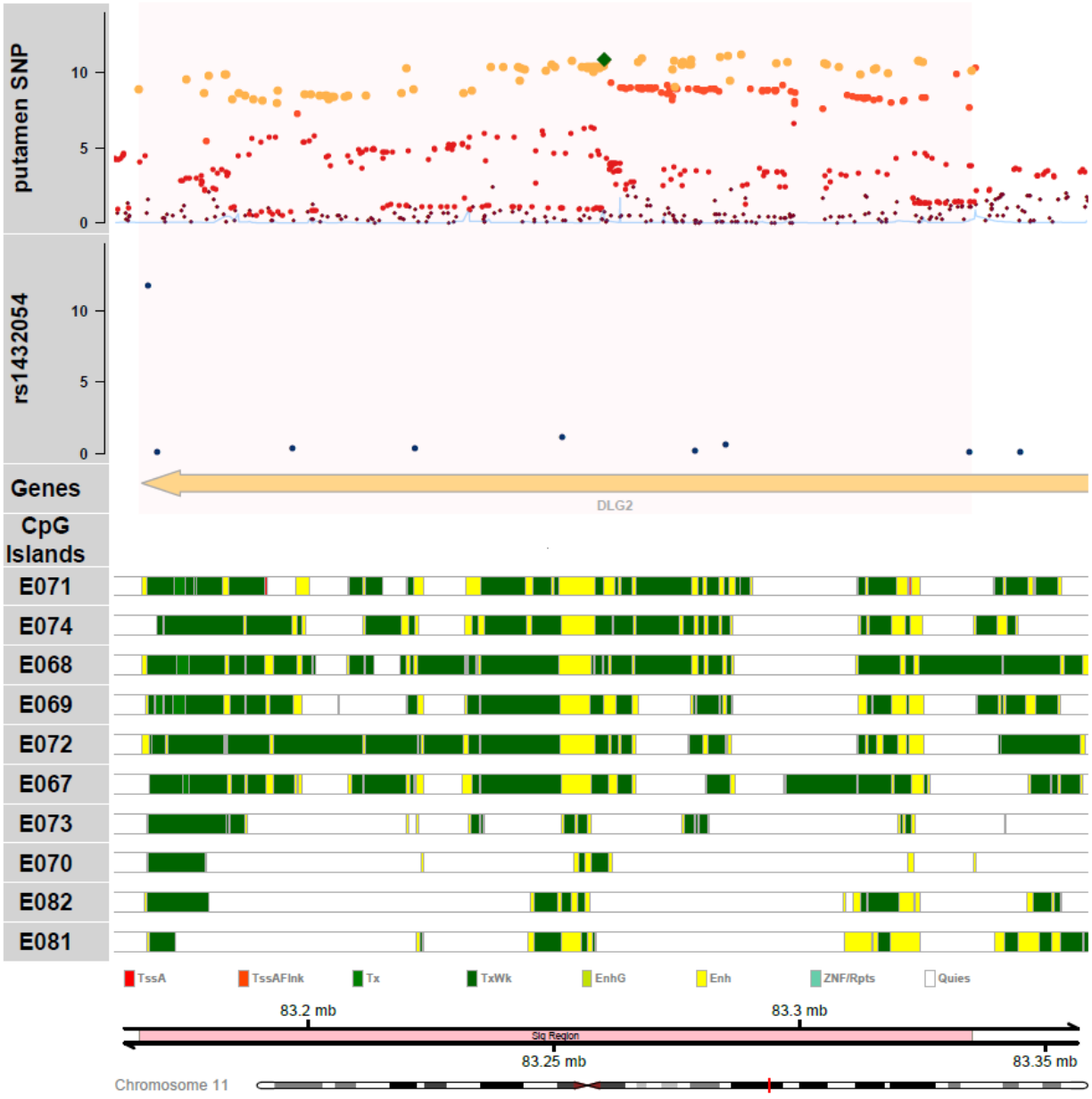
40. Putamen (rs6087771)



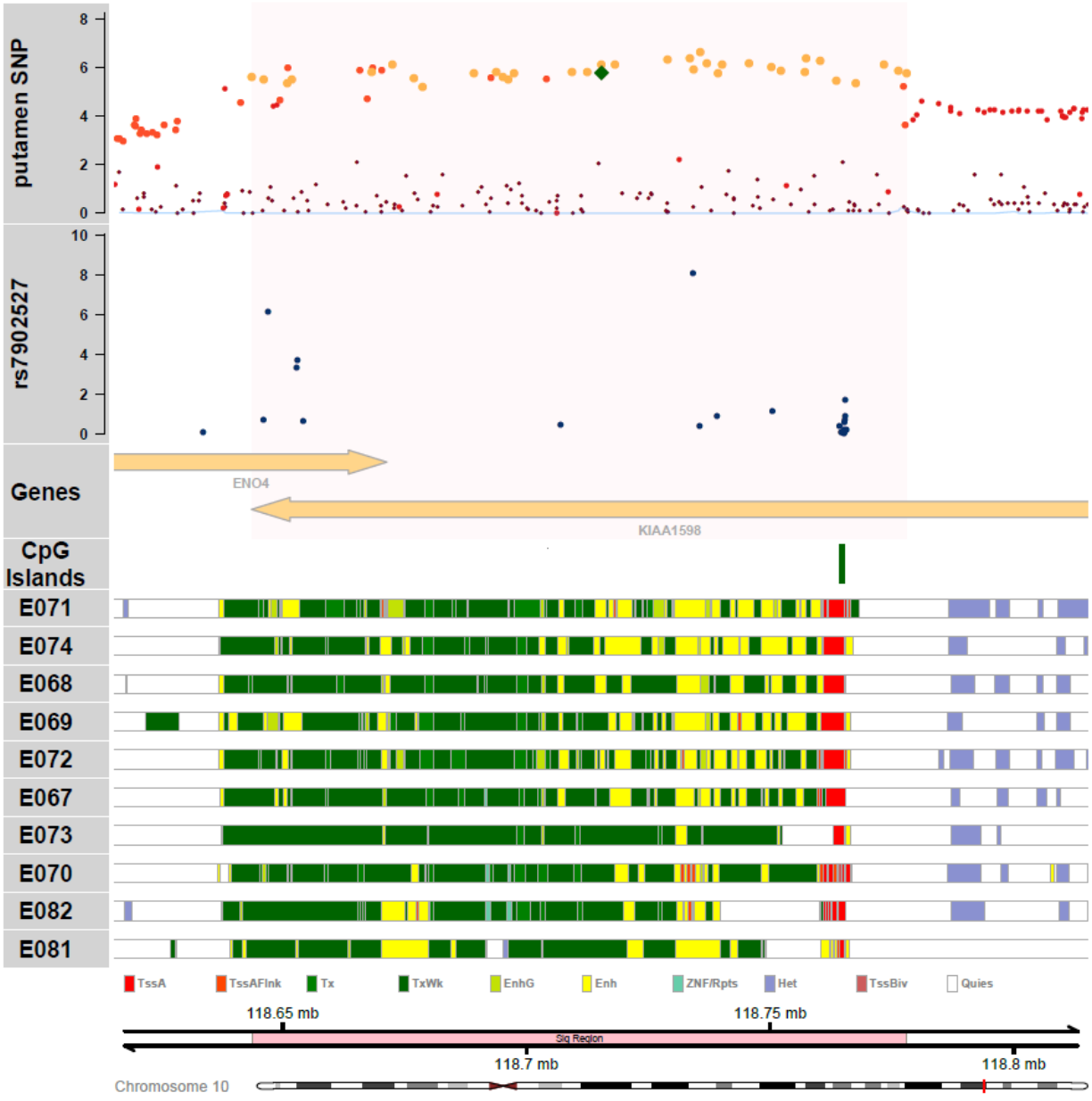
41. Putamen (rs35200015)



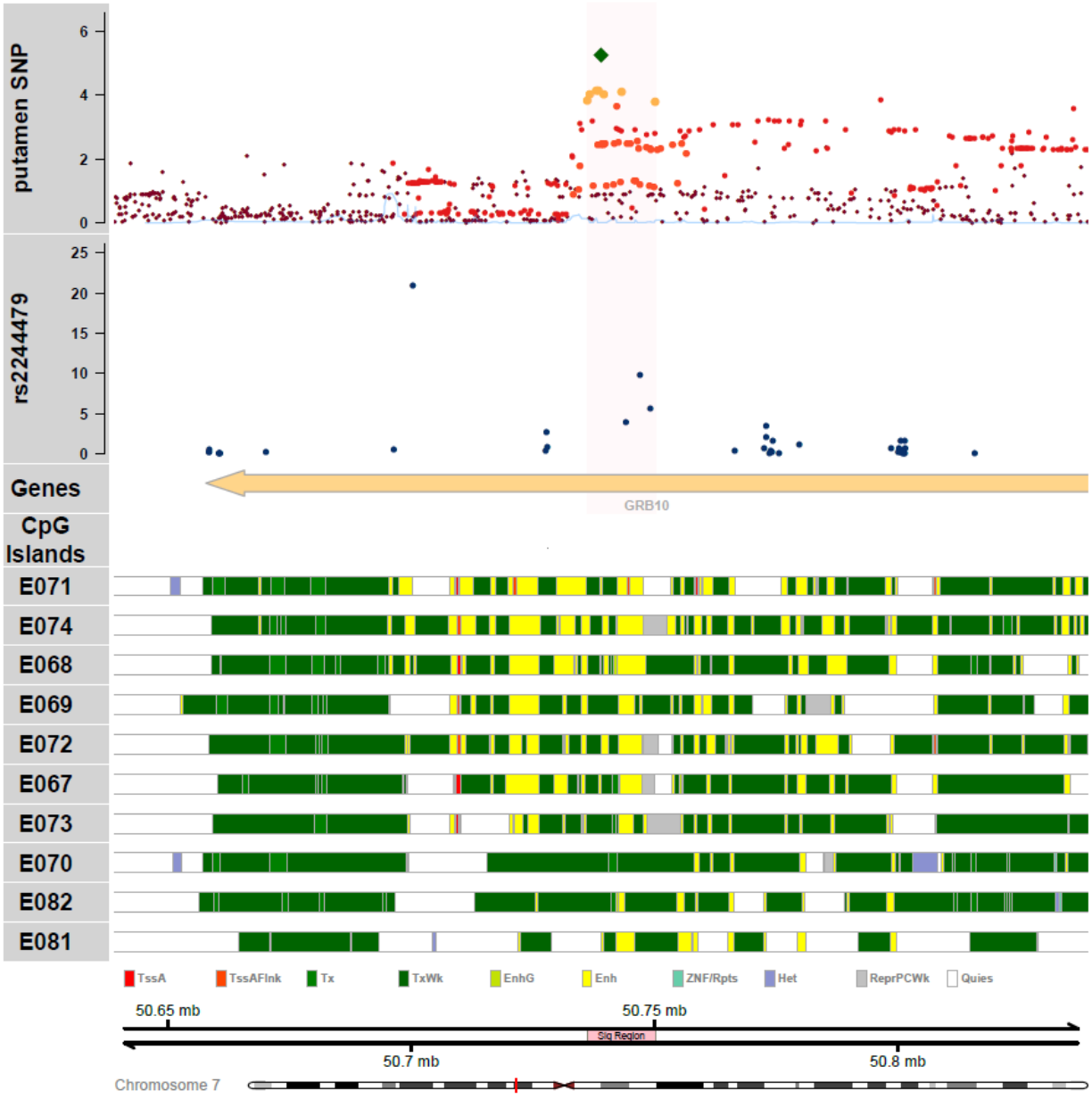
42. Putamen (rs1432054)



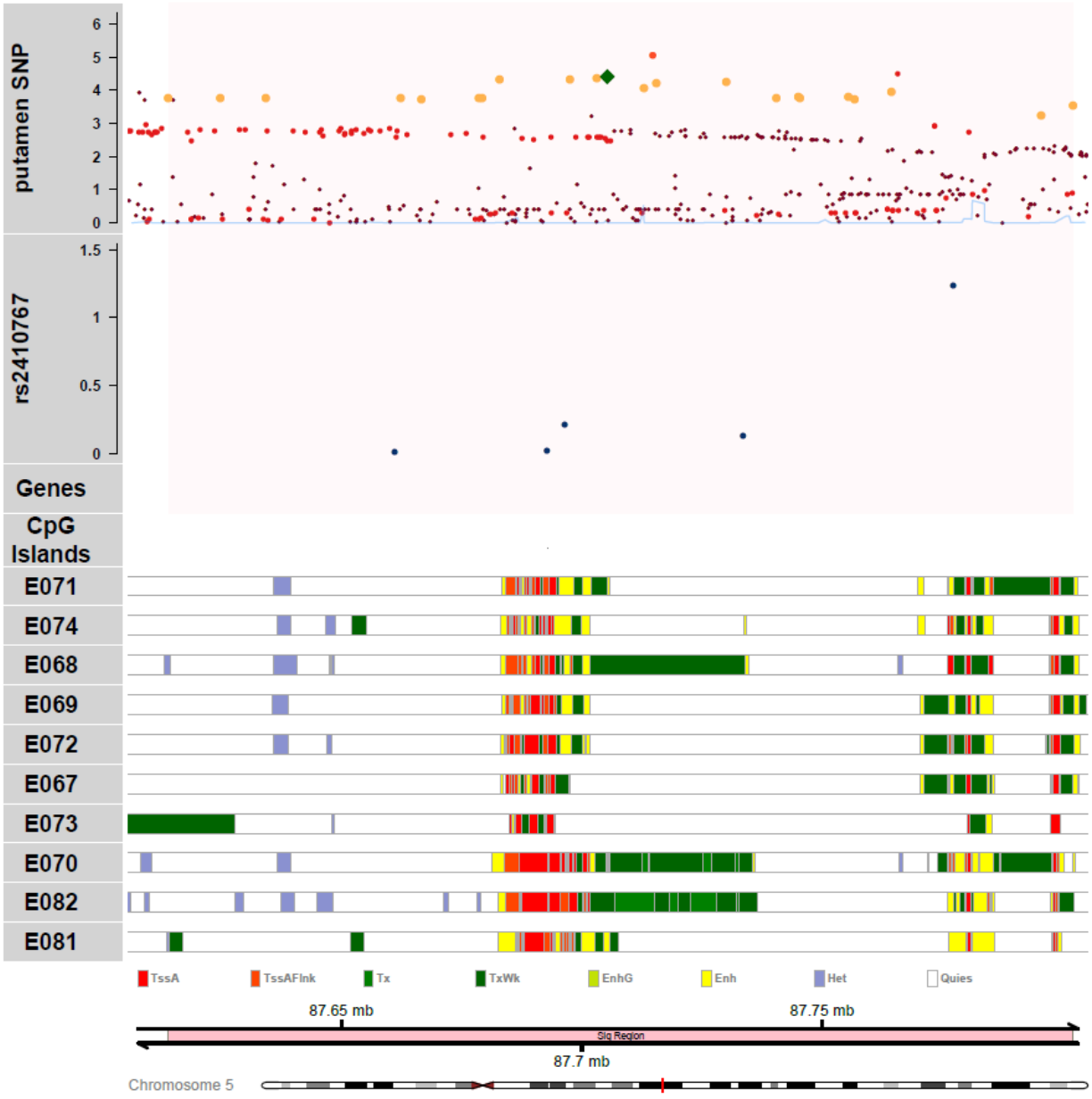
43. Putamen (rs7902527)



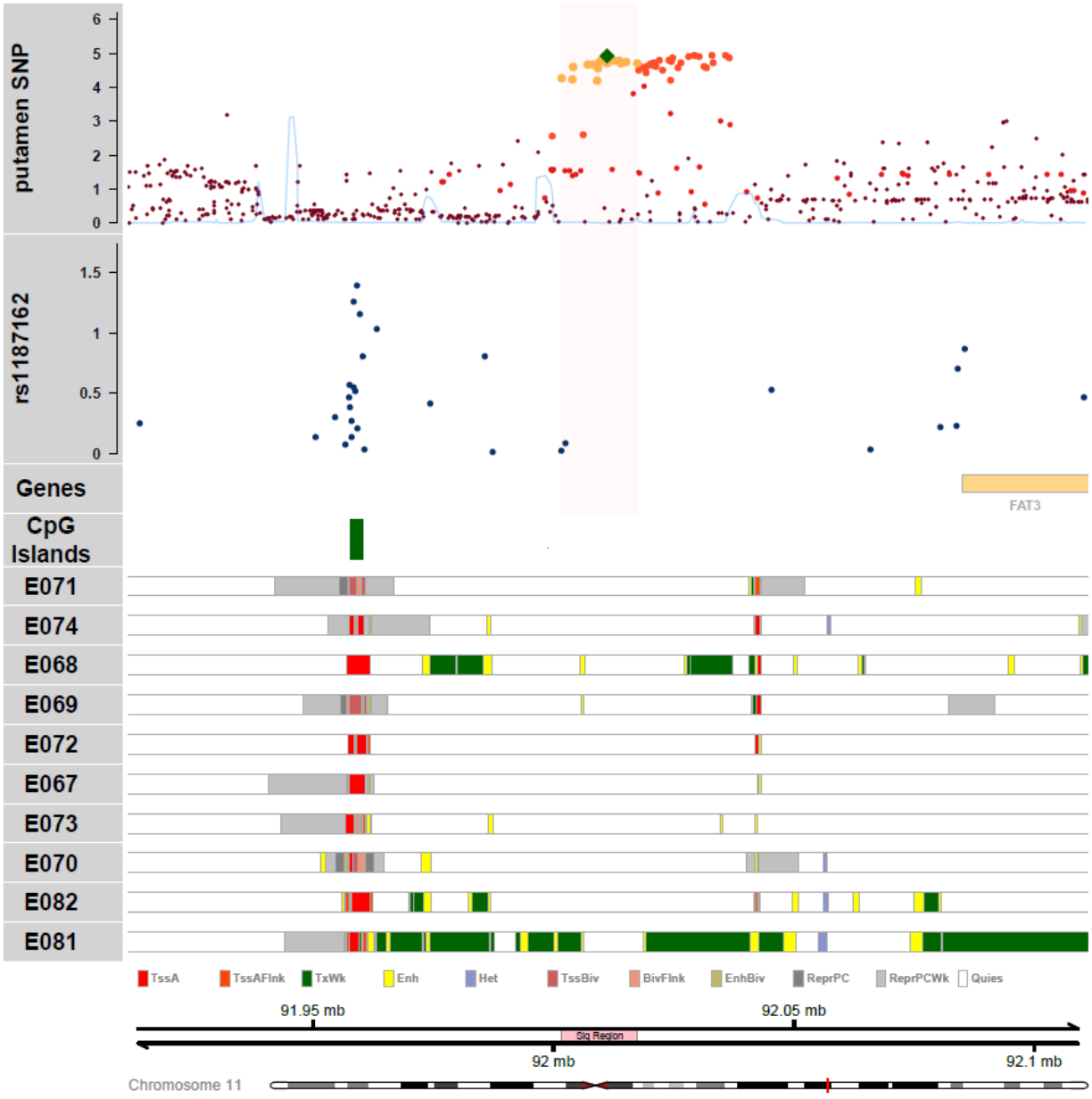
44. Putamen (rs2244479)



45. Putamen (rs2410767)

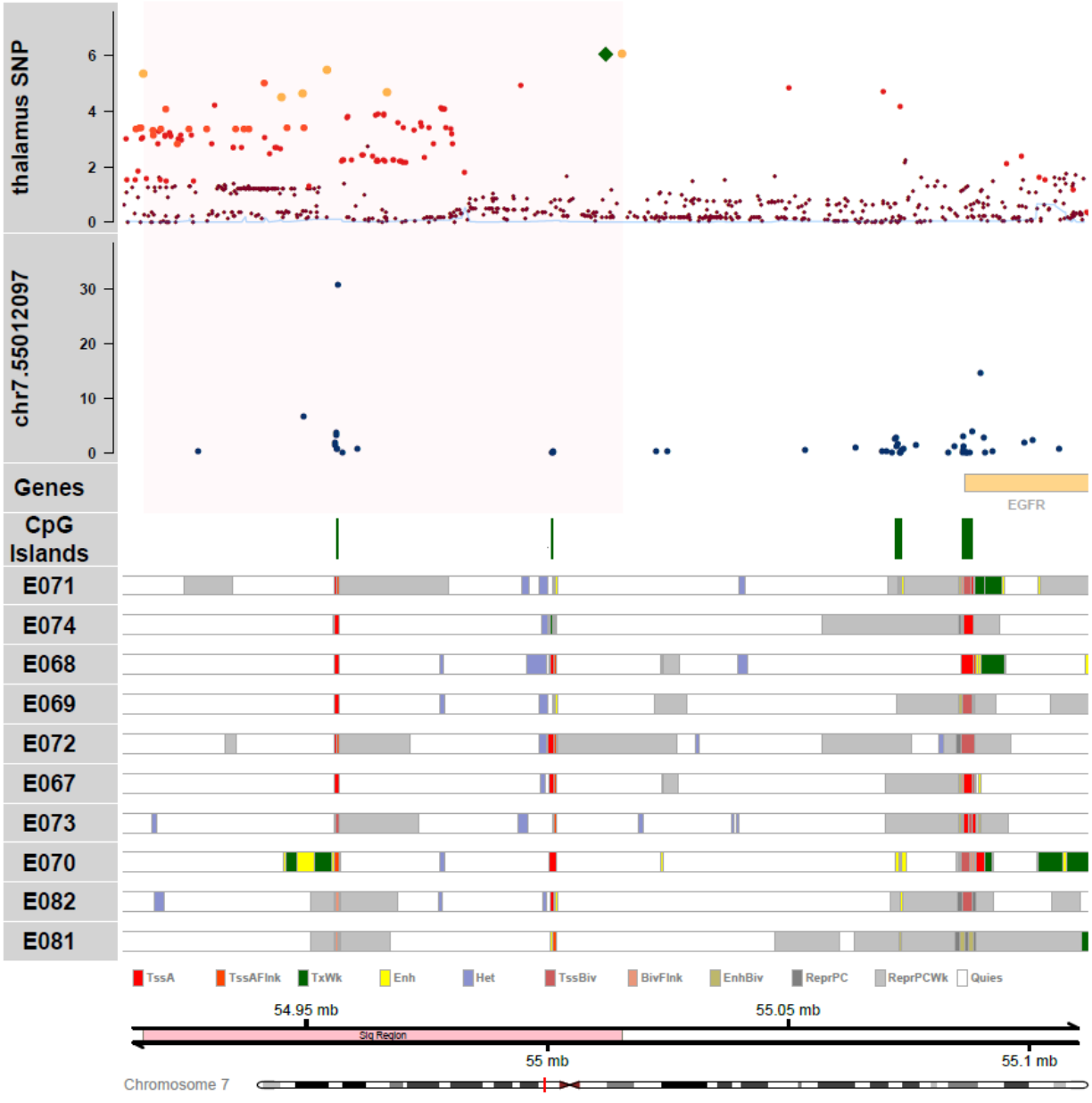


46. Putamen (rs1187162)



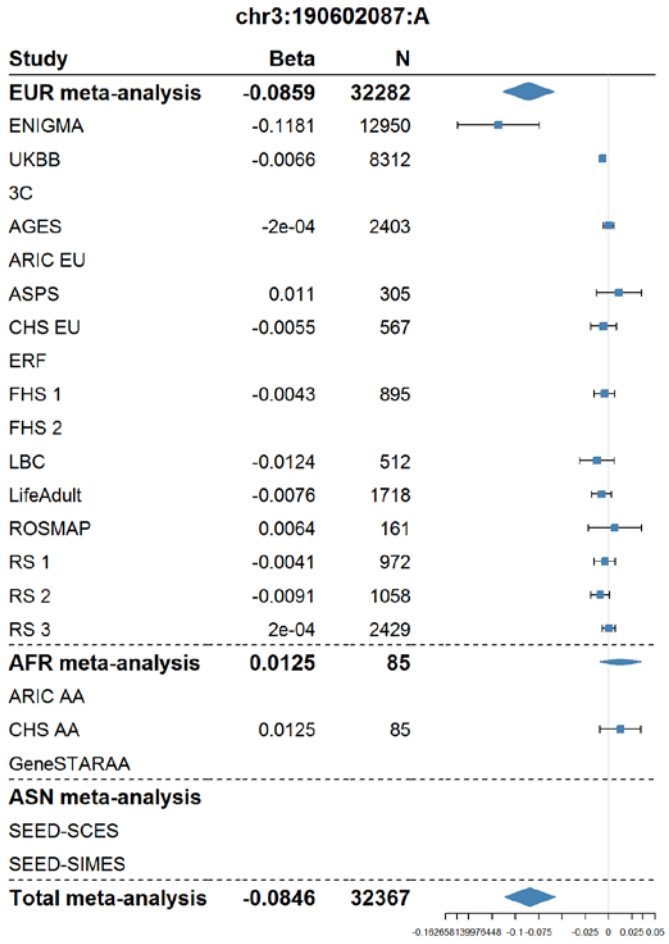
47. Thalamus (rs12600720)

48. Thalamus (rs142461330)

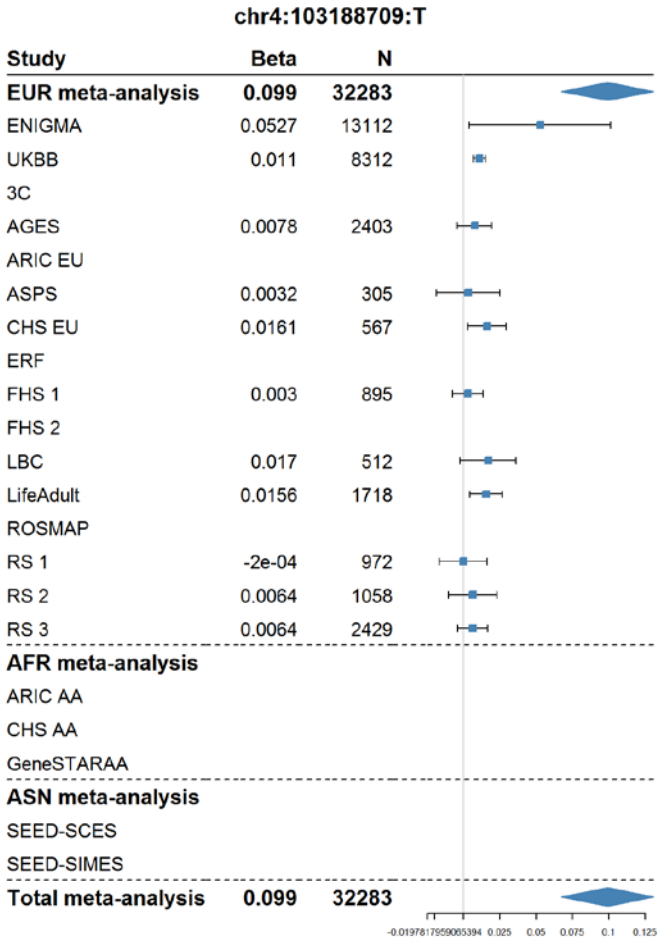


Supplementary Figure 4. **Forest plots for variants influencing the volume of subcortical brain structures**. Forest plots show the contribution from each participating study and summary estimates per ethnicity (European, African-American, and Asian), and their combined effect. The center measure represents beta coefficients, and the error bars 95% confidence intervals. Estimates were re-calculated from Z-scores, sample size, and allele frequencies as previously described[1].

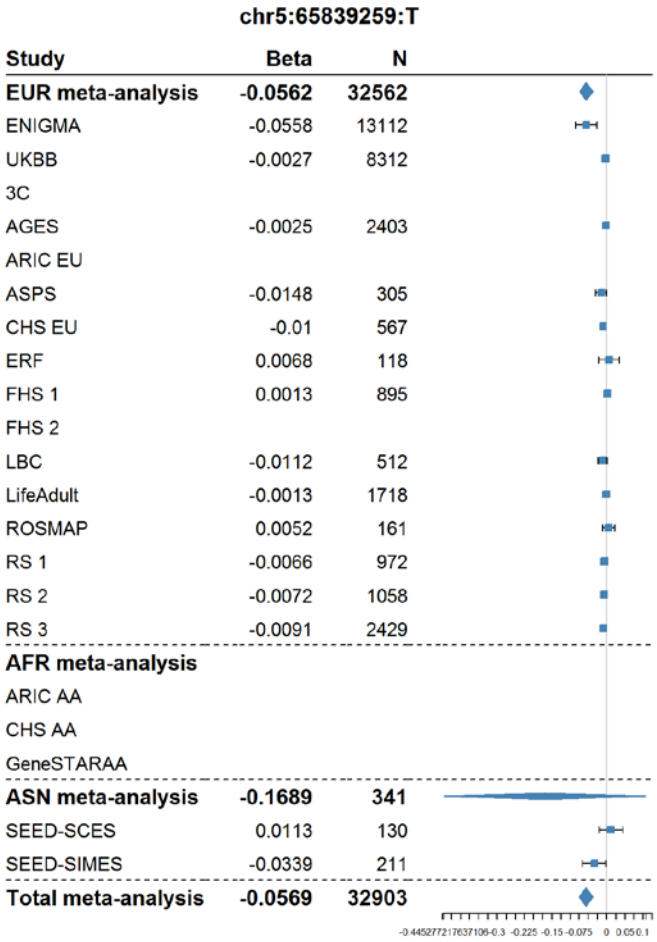
1. Nucleus accumbens (rs9818981)



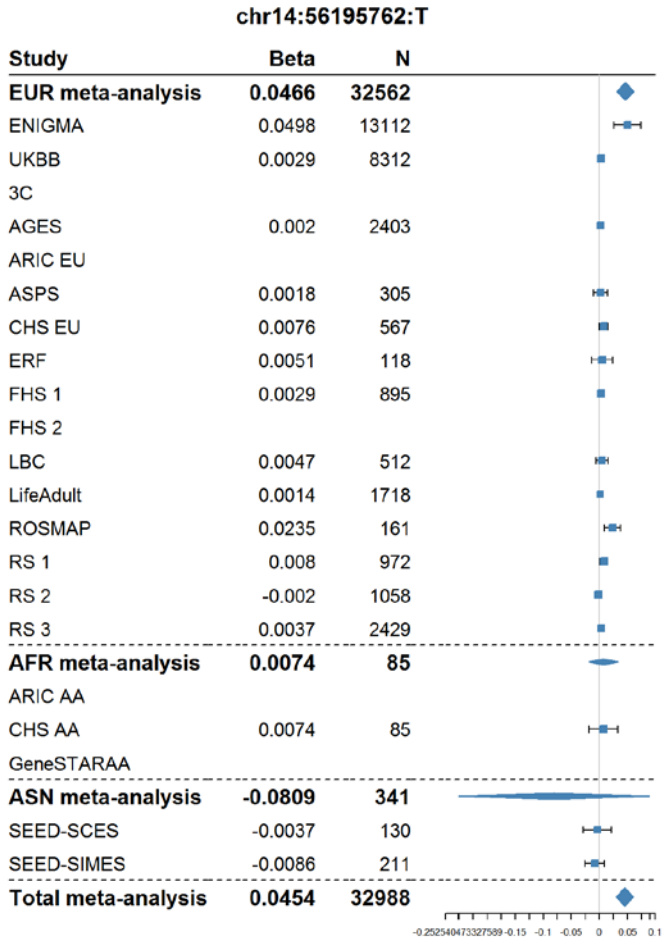
2. Nucleus accumbens (rs13107325)



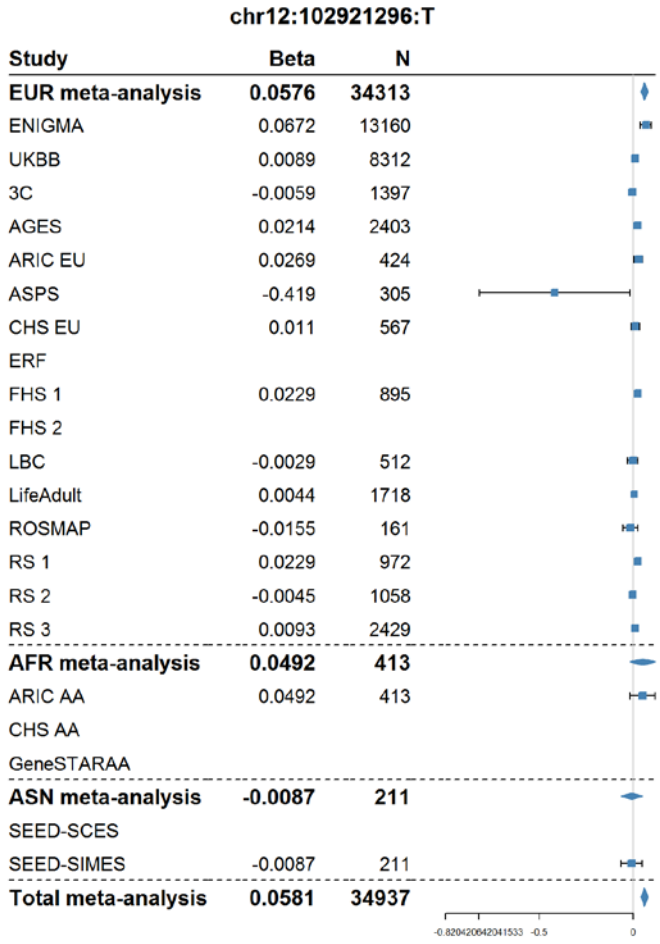
3. Nucleus accumbens (rs11747514)



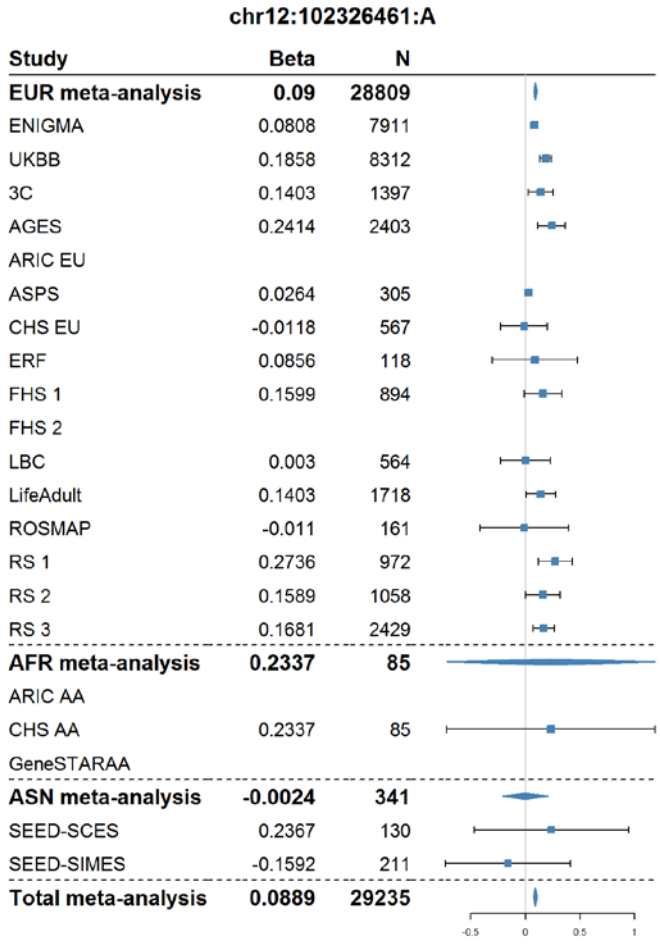
4. Nucleus accumbens (rs868202)



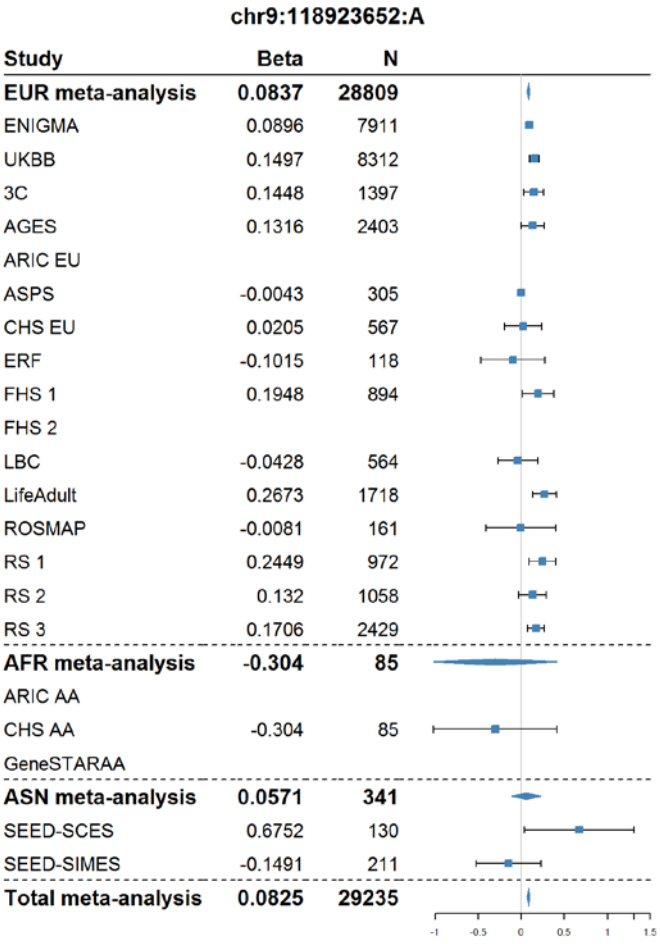
5. Amygdala (rs11111293)



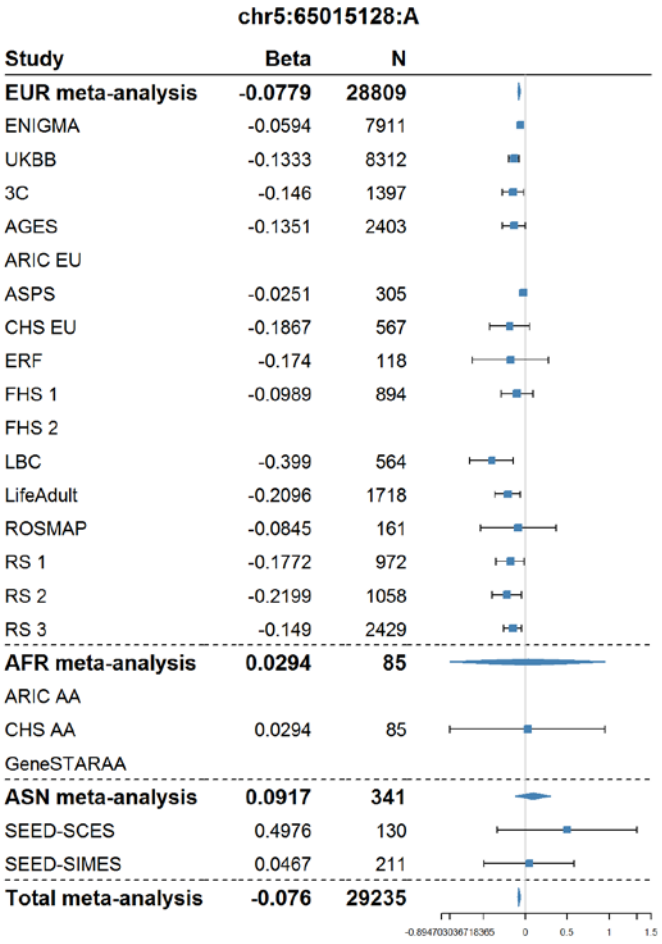
6. Brainstem (rs11111090)



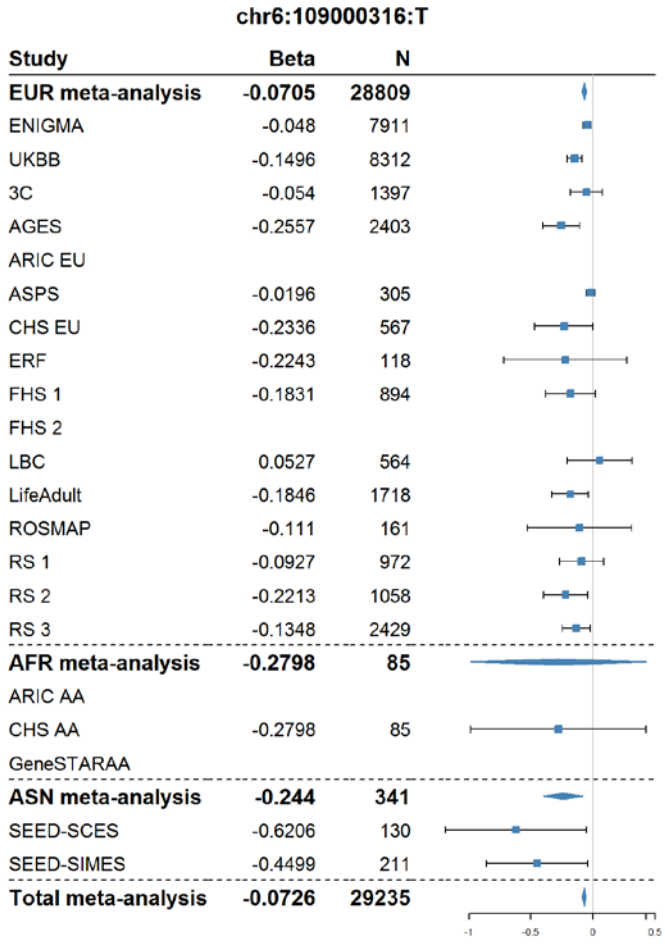
7. Brainstem (rs10217651)



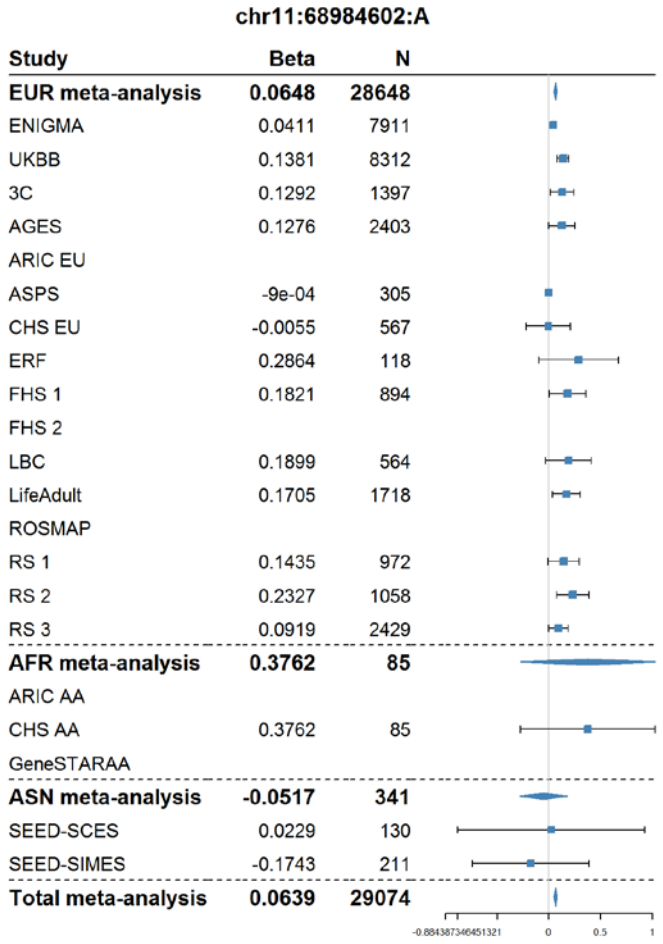
8. Brainstem (rs869640)



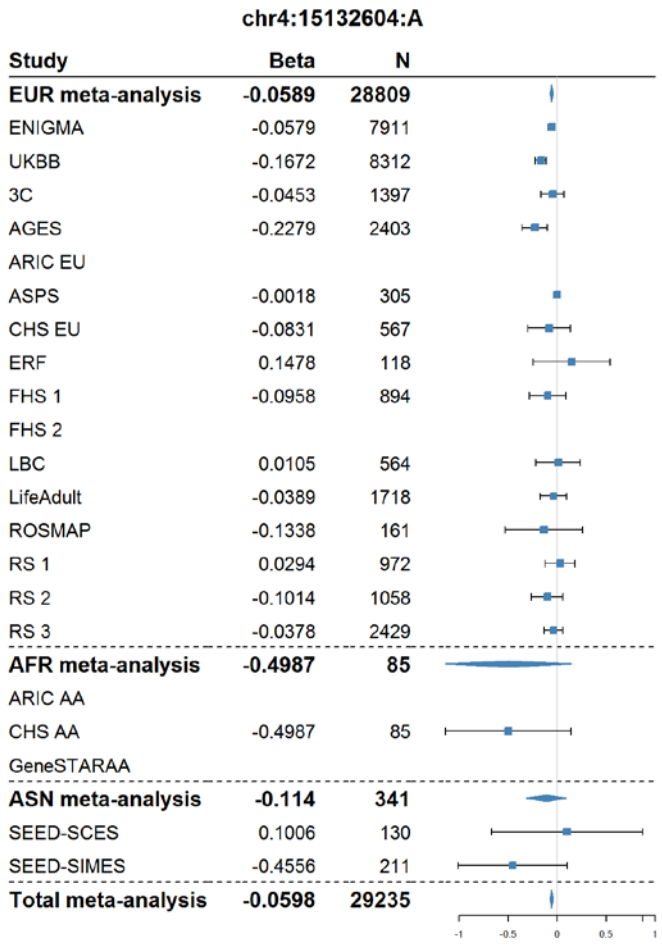
9. Brainstem (rs9398173)



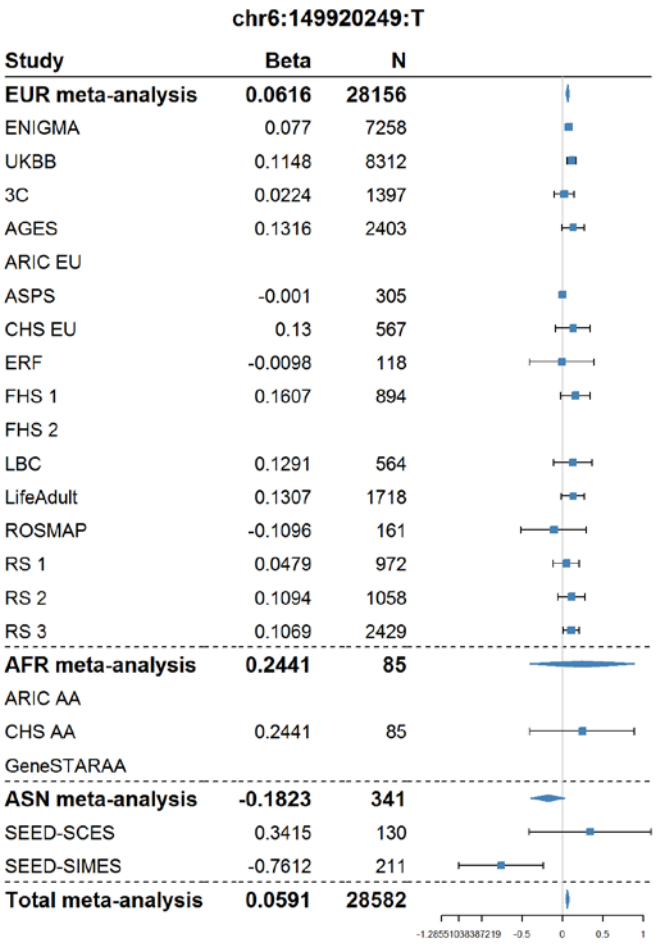
10. Brainstem (rs10792032)



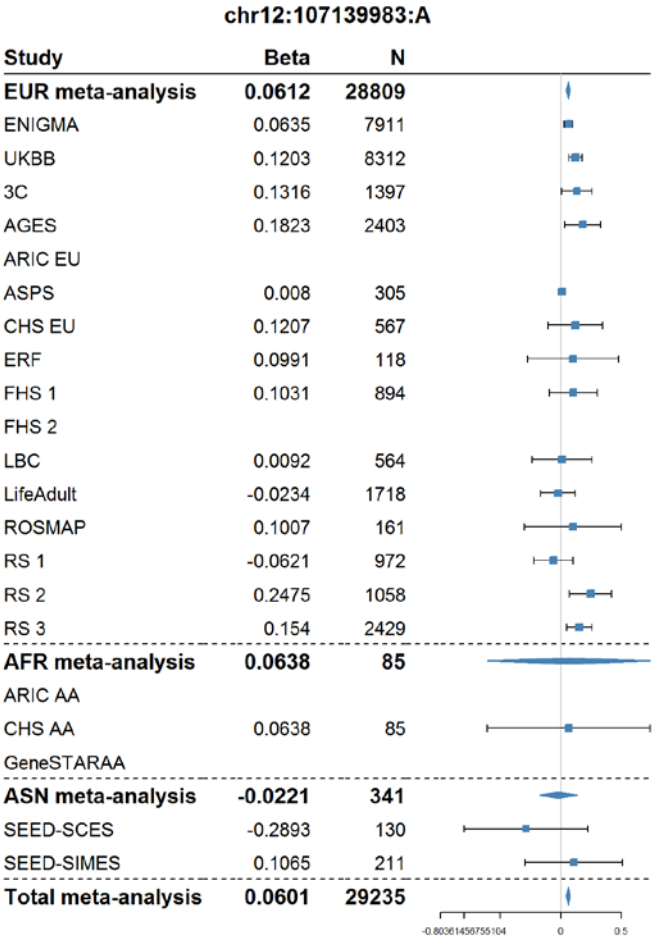
11. Brainstem (rs4396983)



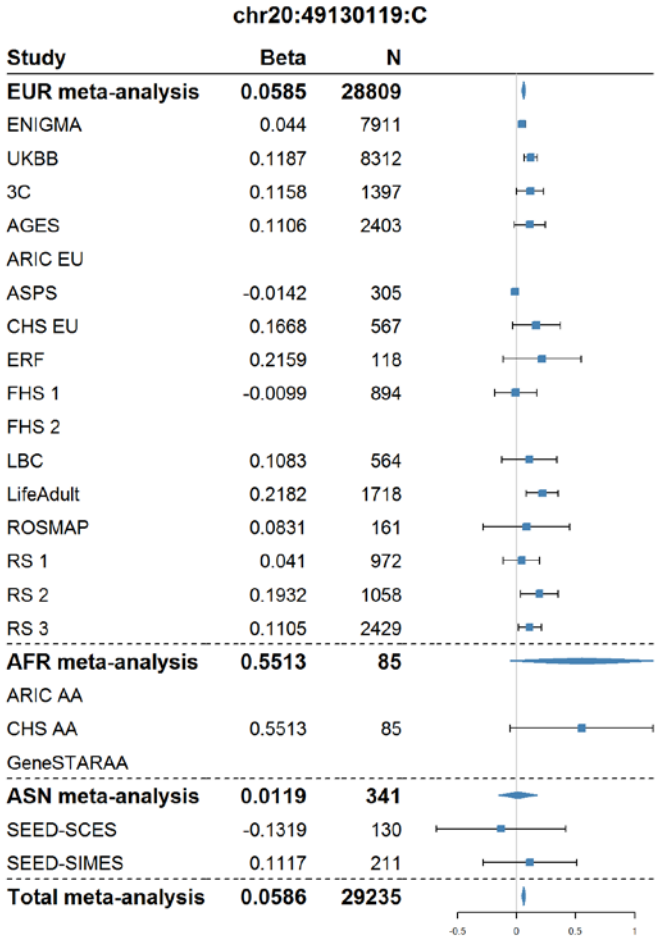
12. Brainstem (rs9322194)



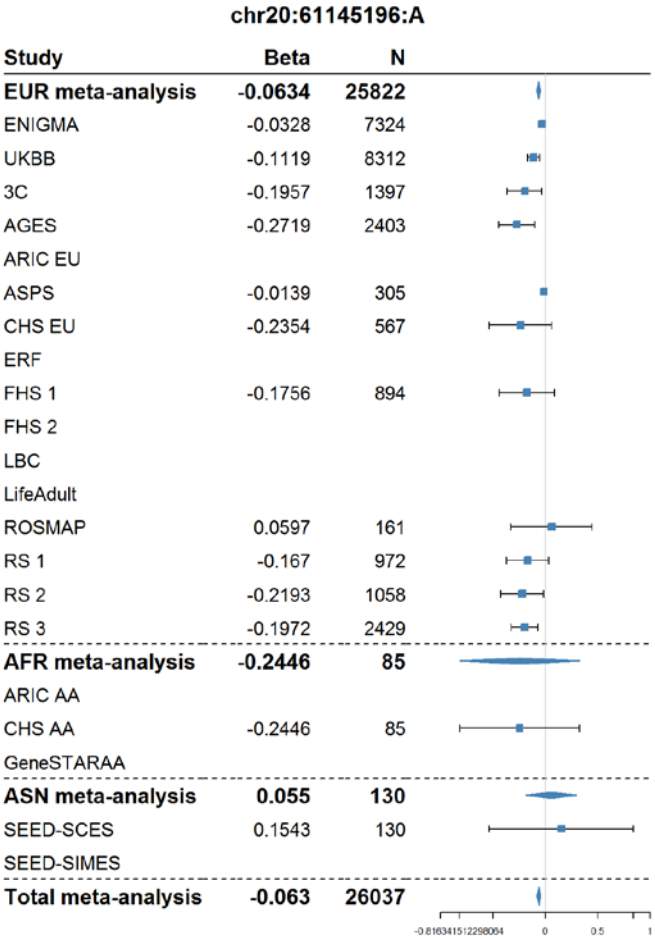
13. Brainstem (rs7972561)



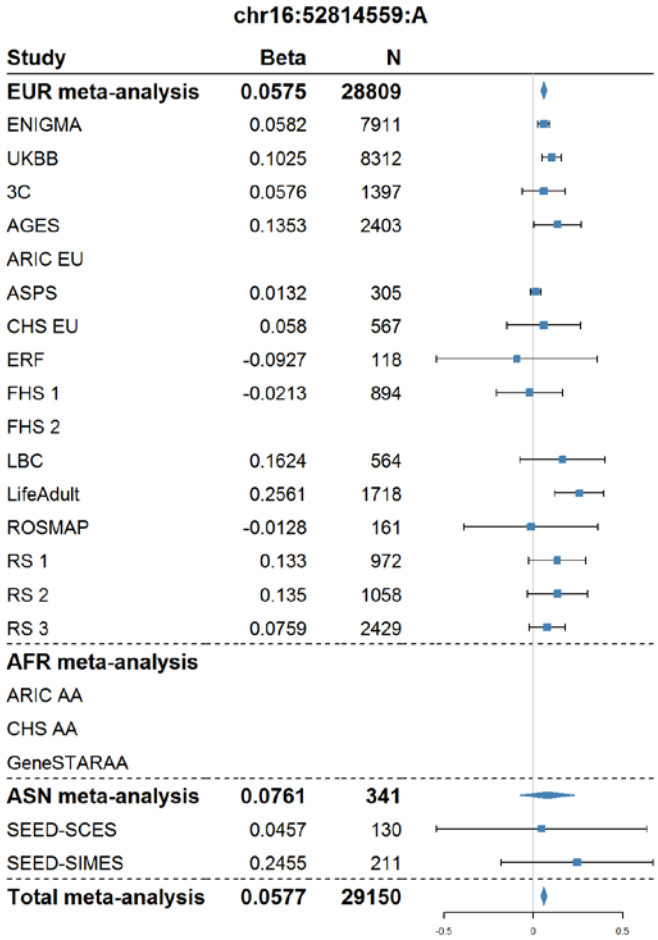
14. Brainstem (rs2206656)



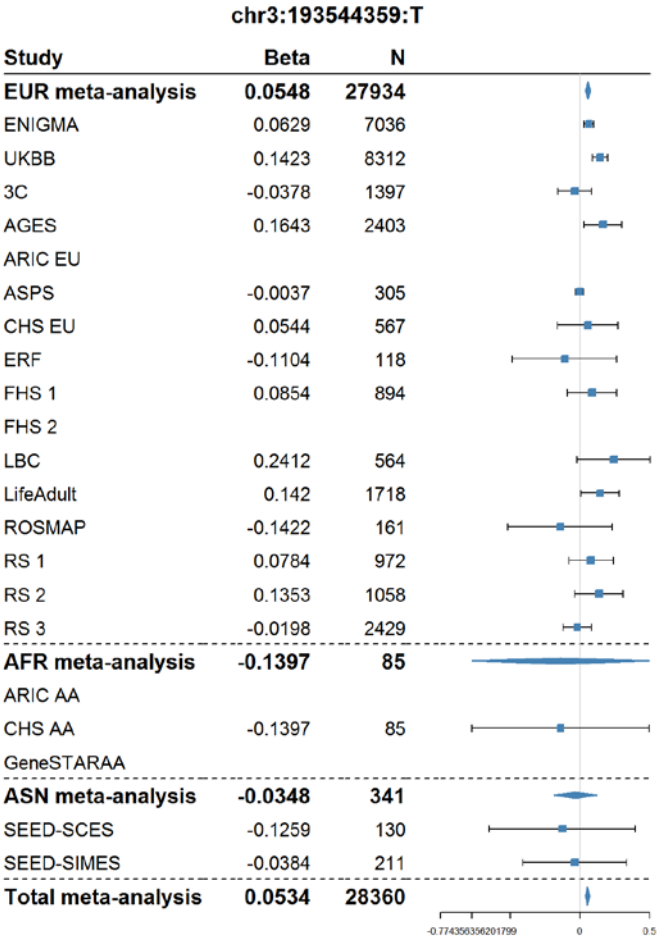
15. Brainstem (rs12479469)



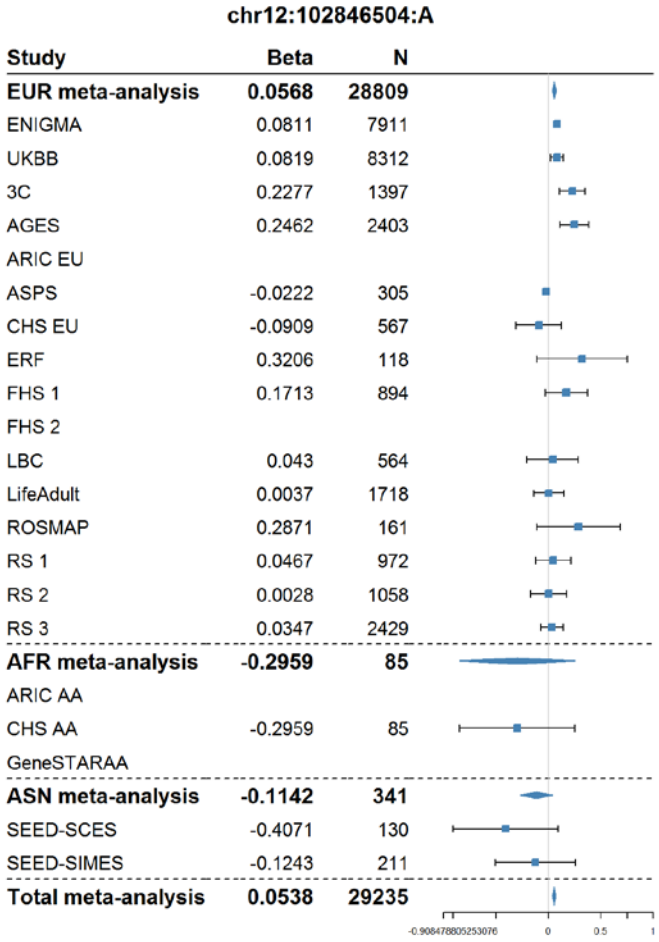
16. Brainstem (rs4784256)



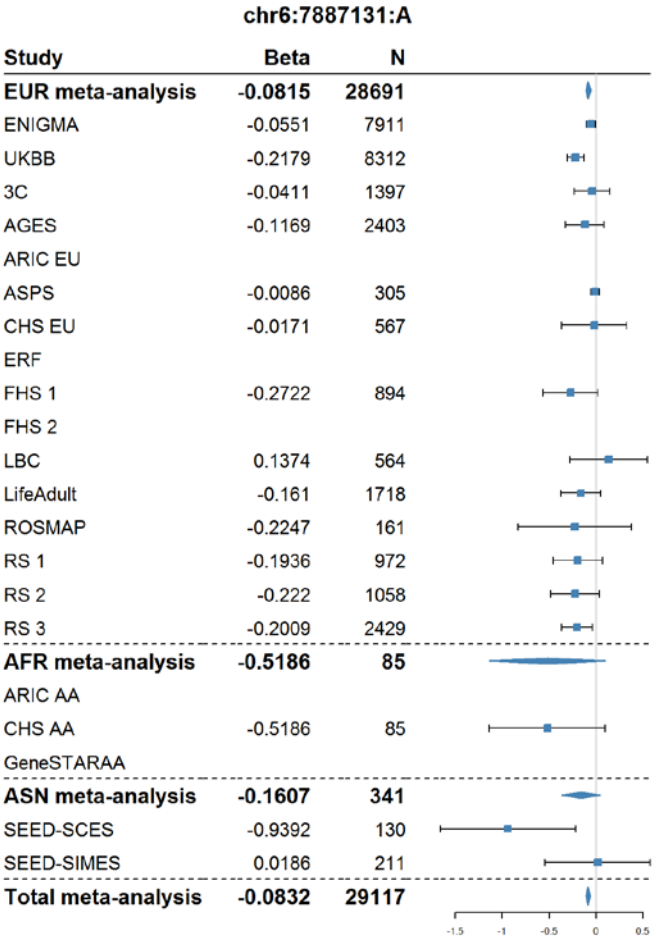
17. Brainstem (rs555925)



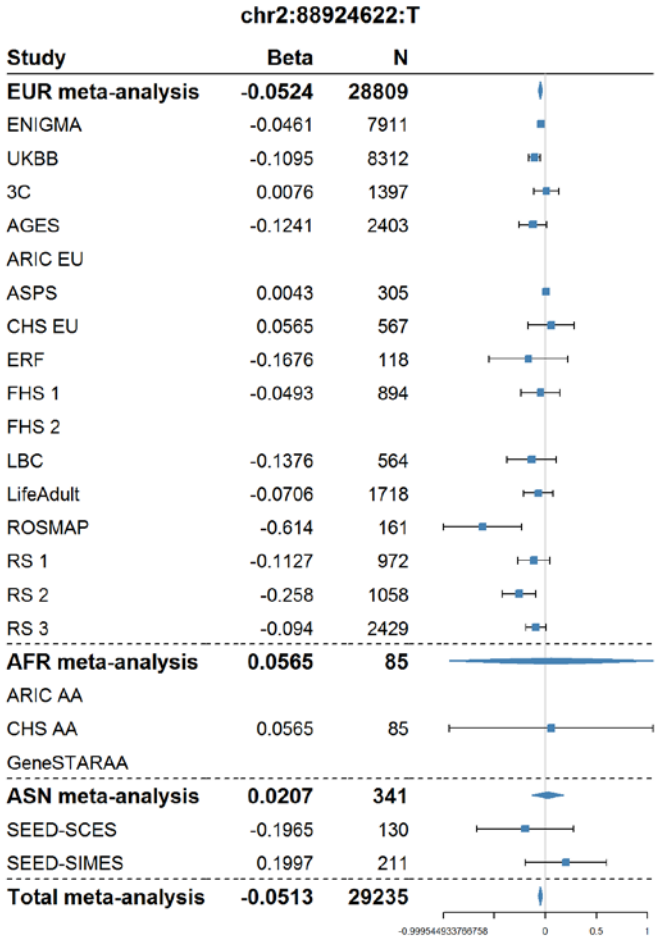
18. Brainstem (rs12313279)



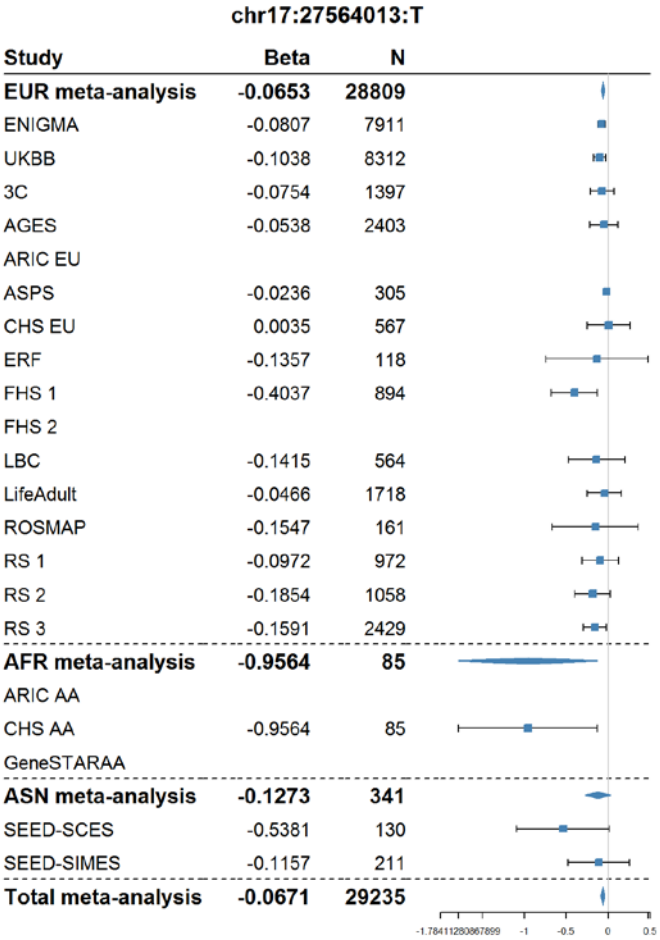
19. Brainstem (rs9505301)



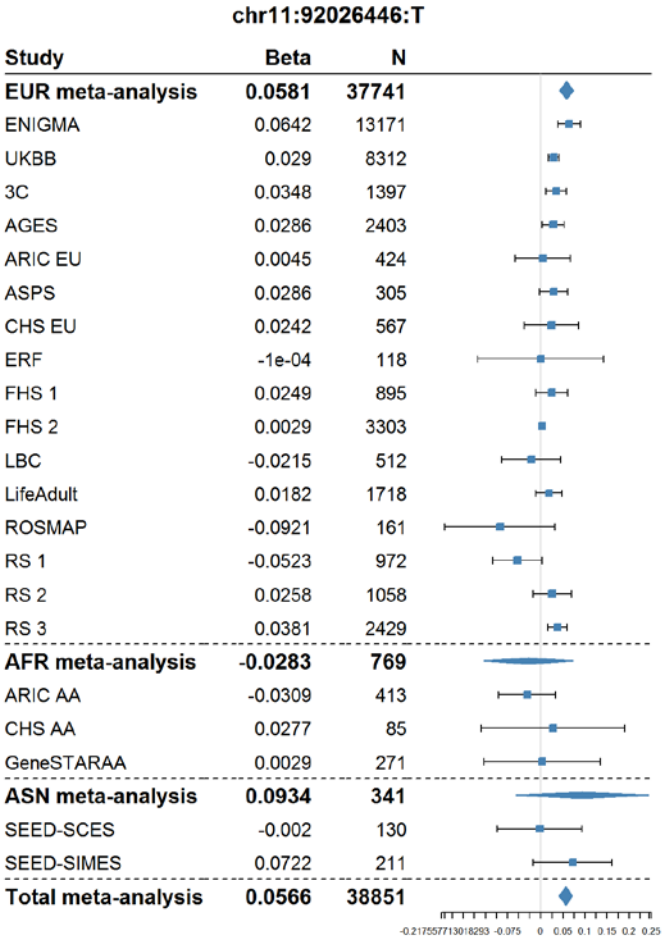
20. Brainstem (rs11684404)



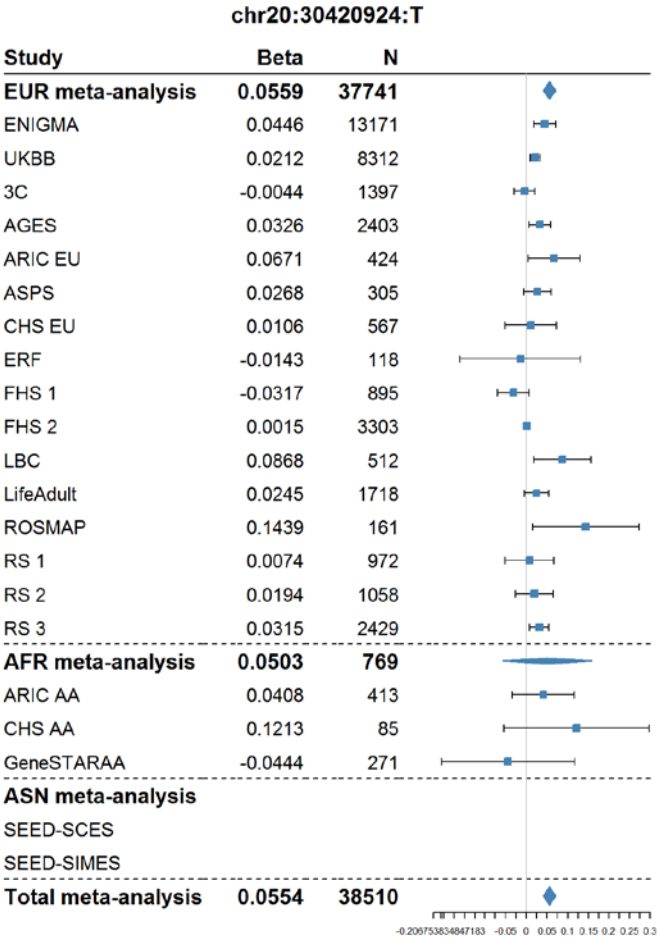
21. Brainstem (rs112178027)



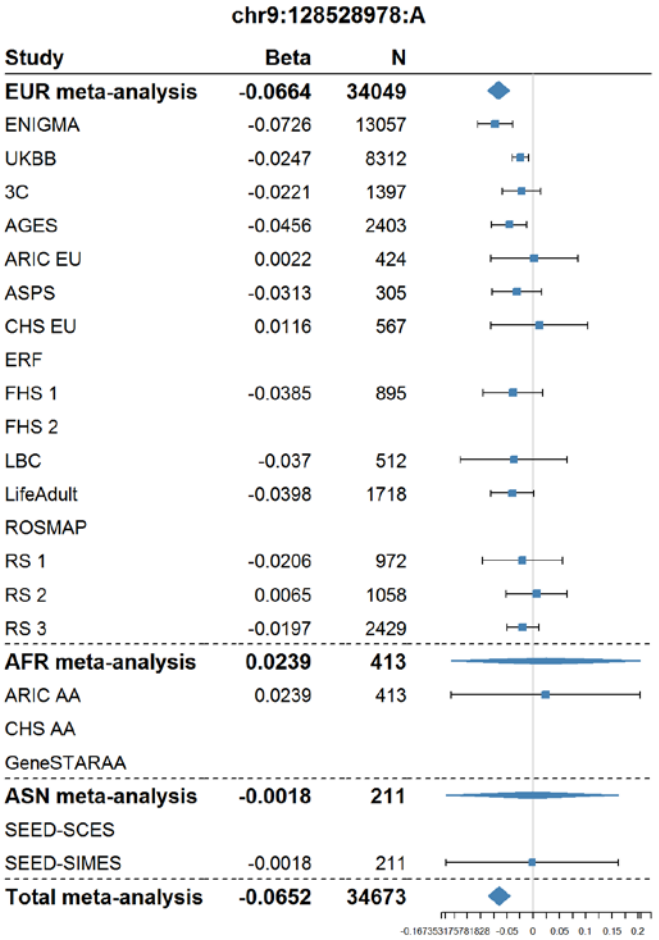
22. Caudate nucleus (rs3133370)



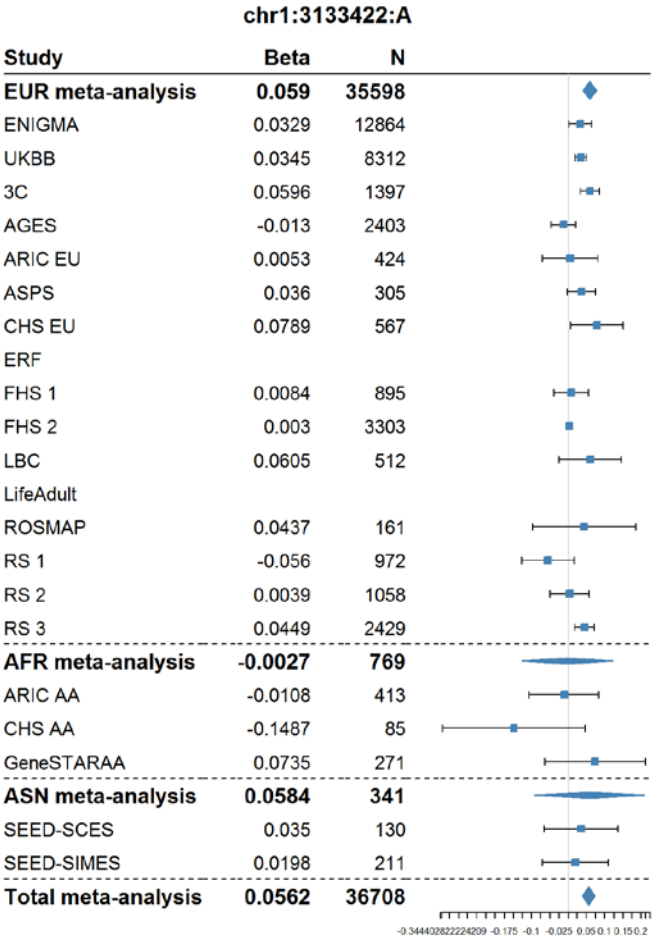
23. Caudate nucleus (rs6060983)



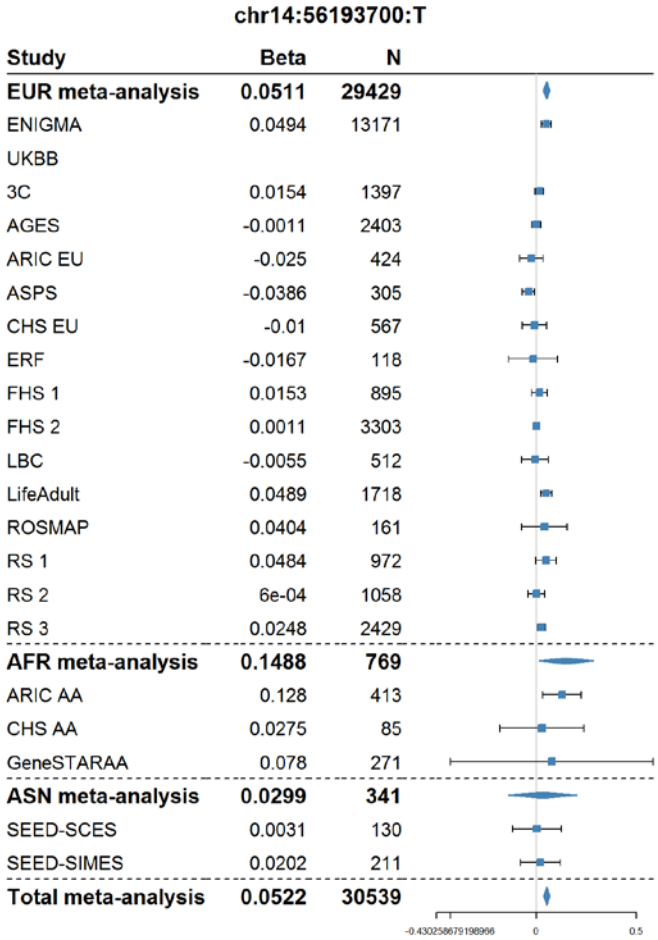
24. Caudate nucleus (rs7040561)



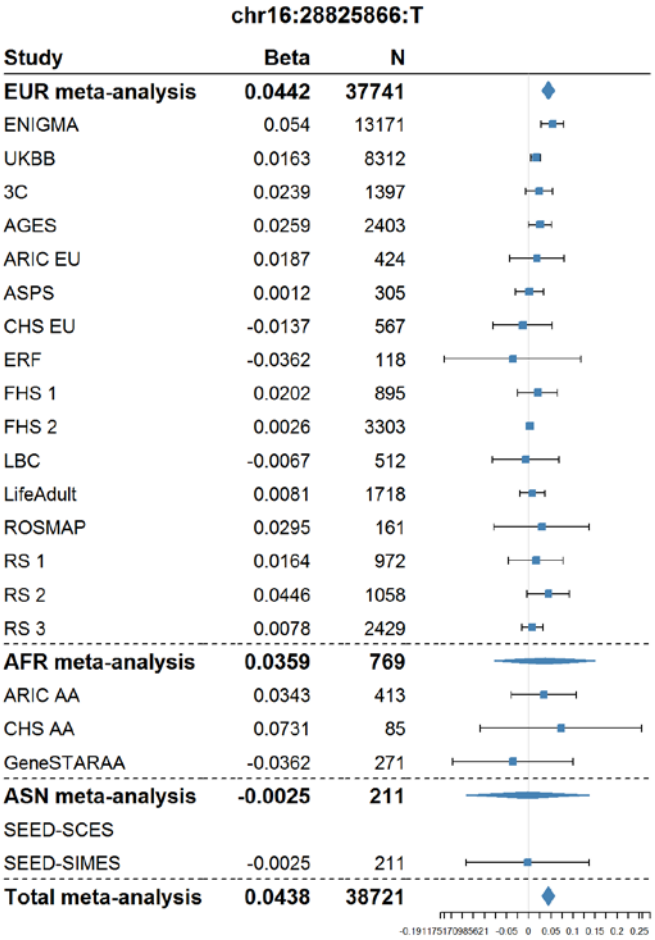
25. Caudate nucleus (rs2817145)



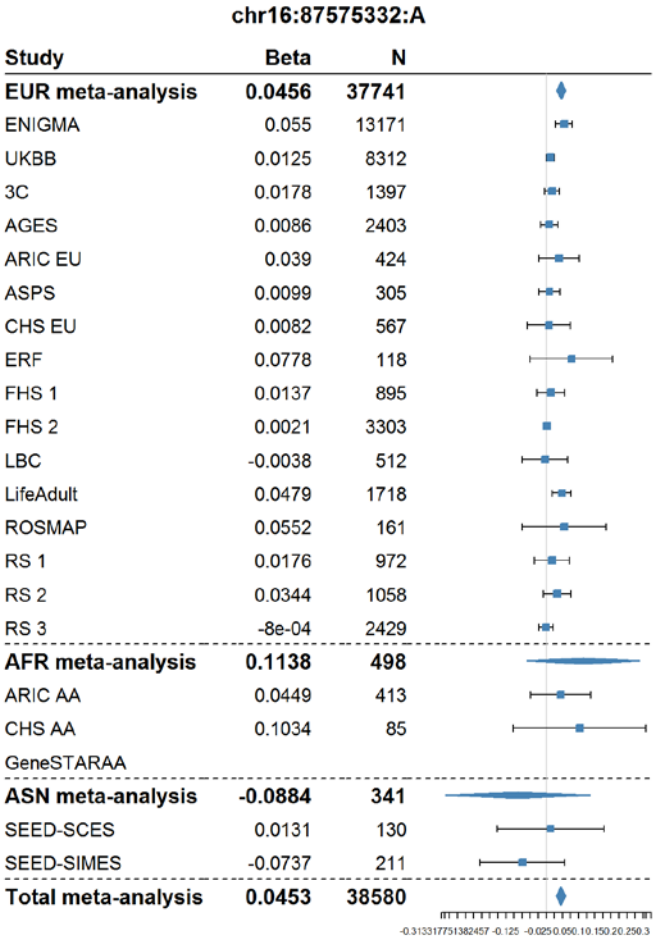
26. Caudate nucleus (rs148470213)



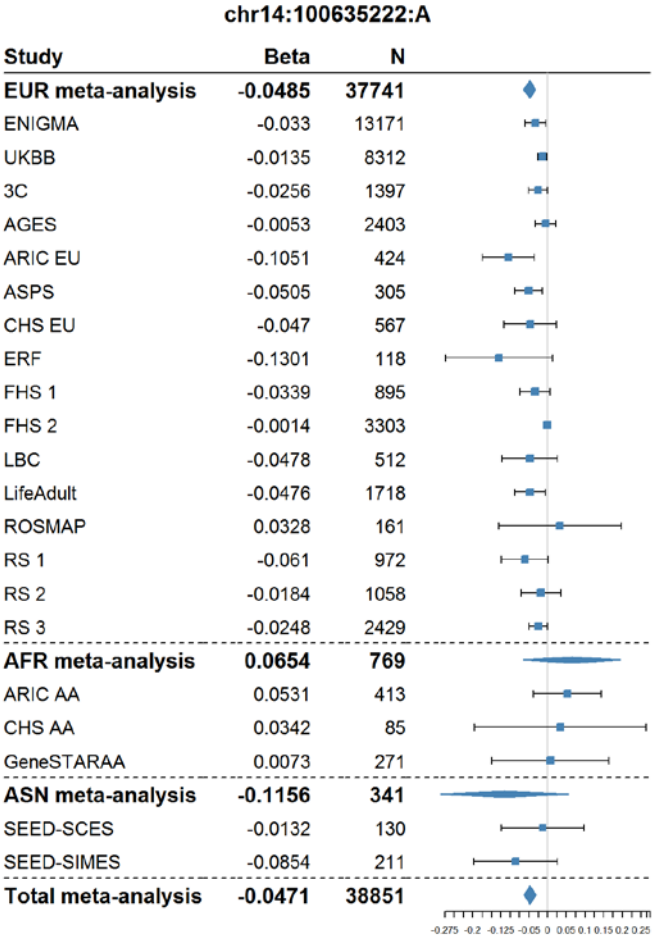
27. Caudate nucleus (rs1987471)



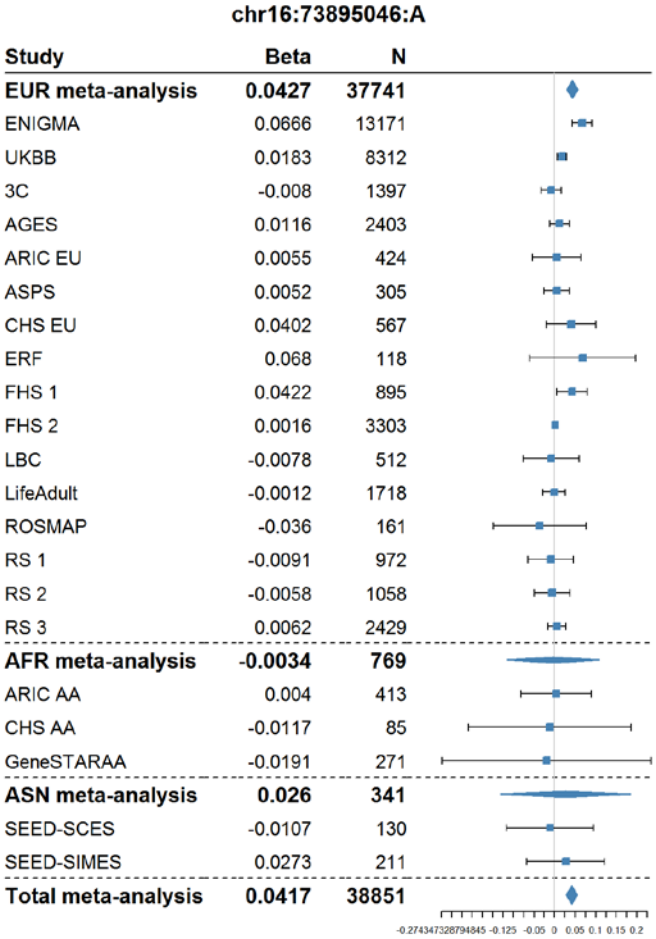
28. Caudate nucleus (rs12445022)



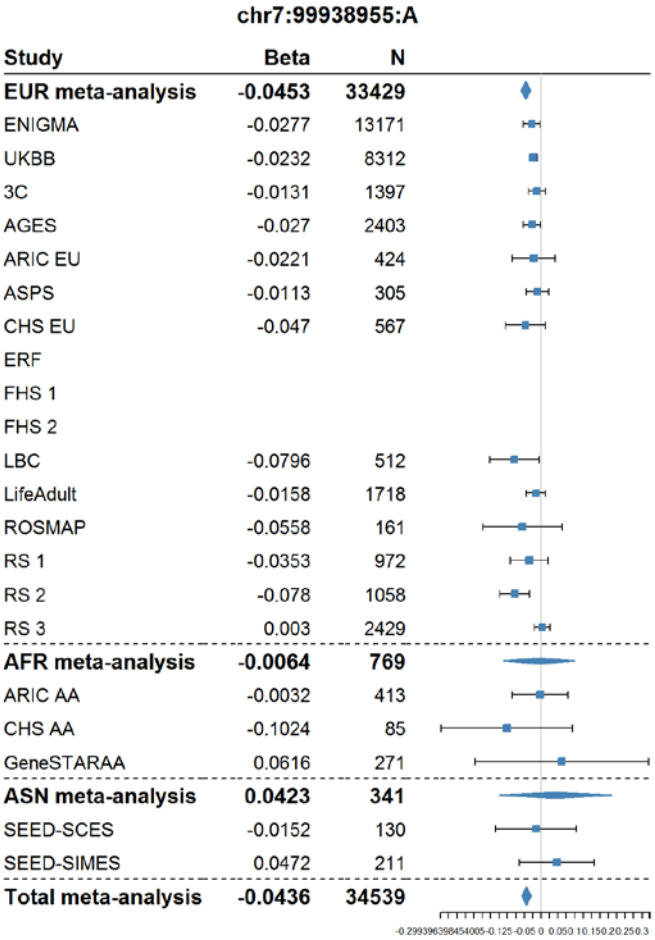
29. Caudate nucleus (rs55989340)



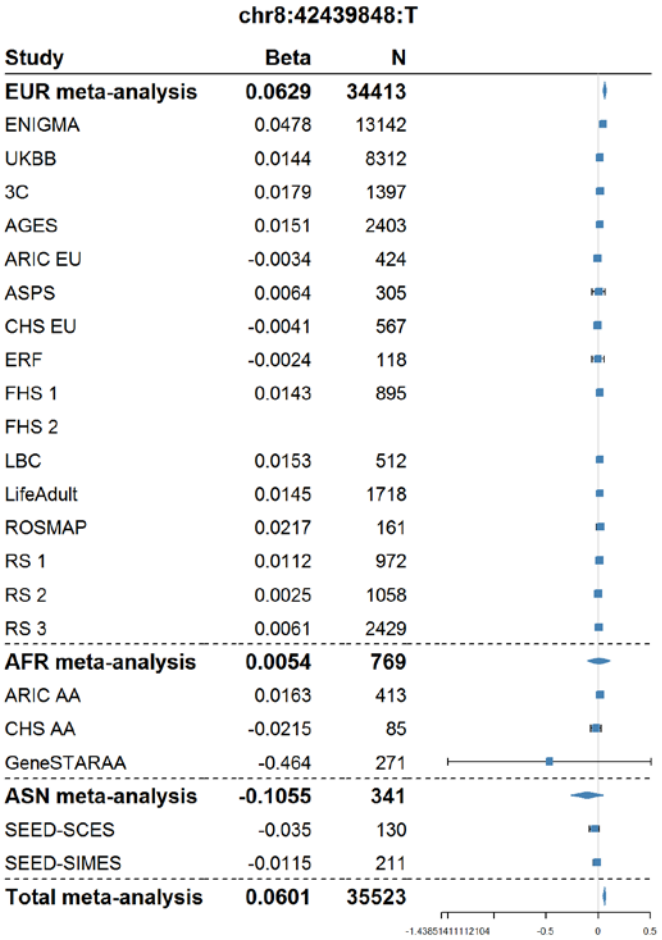
30. Caudate nucleus (rs4888010)



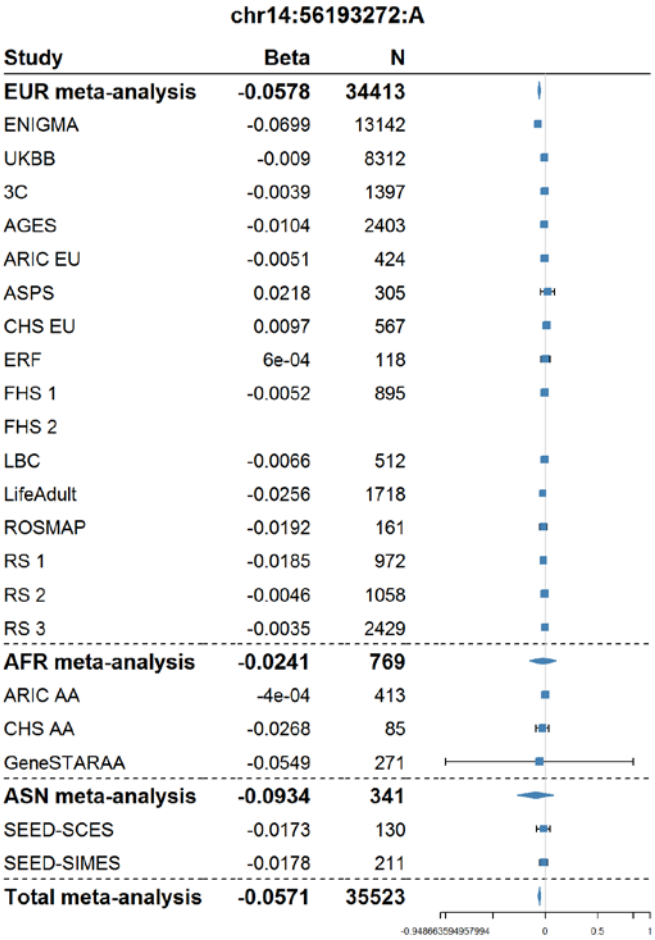
31. Caudate nucleus (rs35305377)



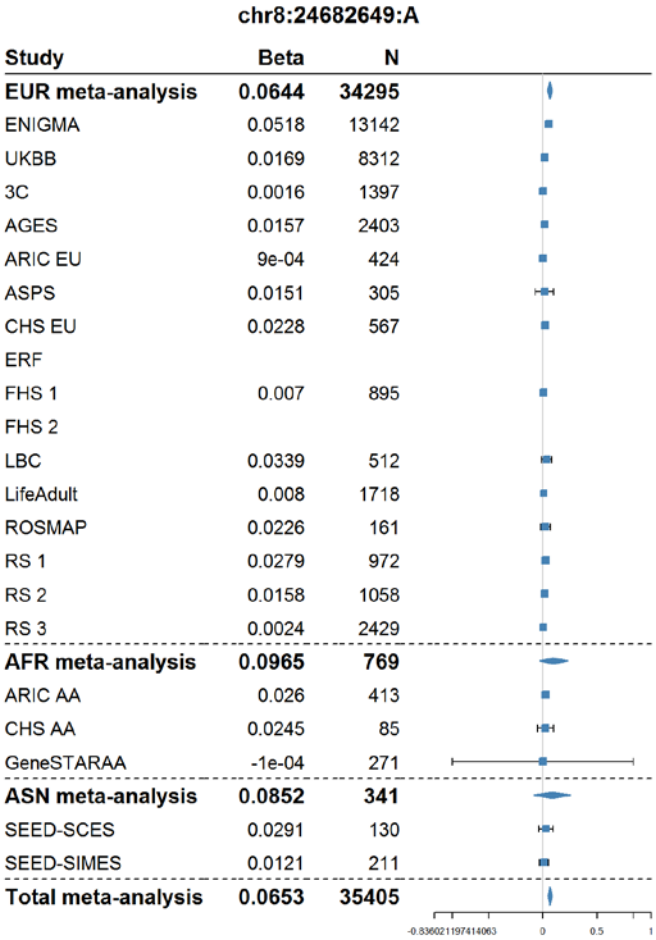
32. Globus pallidus (rs2923447)



33. Globus pallidus (rs10129414)



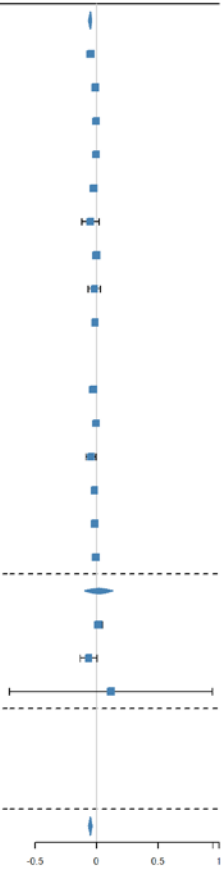
34. Globus pallidus (rs196807)



35. Globus pallidus (rs10439607)

chr20:30258541:A

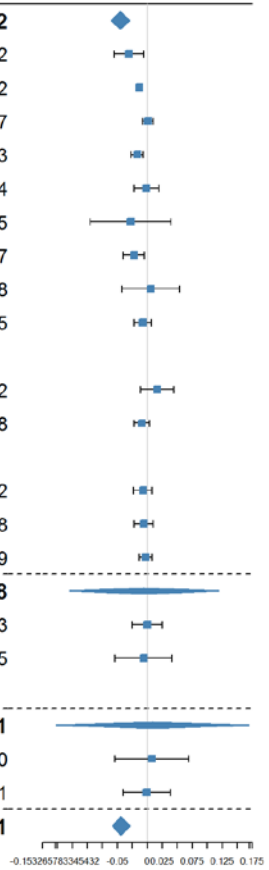
Study	Beta	N
EUR meta-analysis	**-0.0523**	**34413**
ENIGMA	-0.0475	13142
UKBB	-0.0105	8312
3C	-0.0027	1397
AGES	-0.0031	2403
ARIC EU	-0.0242	424
ASPS	-0.0494	305
CHS EU	0	567
ERF	-0.0164	118
FHS 1	-0.0126	895
FHS 2		
LBC	-0.0283	512
LifeAdult	-0.0031	1718
ROSMAP	-0.0446	161
RS 1	-0.0173	972
RS 2	-0.015	1058
RS 3	-0.0059	2429
AFR meta-analysis	**0.0167**	**769**
ARIC AA	0.0148	413
CHS AA	-0.064	85
GeneSTARAA	0.1173	271
ASN meta-analysis		
SEED-SCES		
SEED-SIMES		
Total meta-analysis	**-0.0504**	**35182**



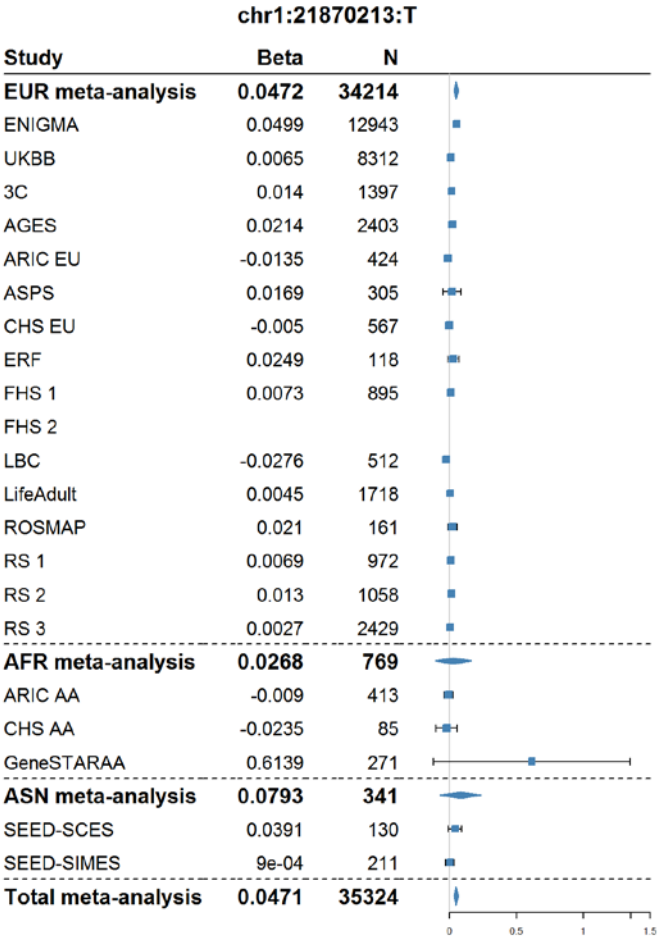
36. Globus pallidus (rs4952211)

chr2:32611512:T

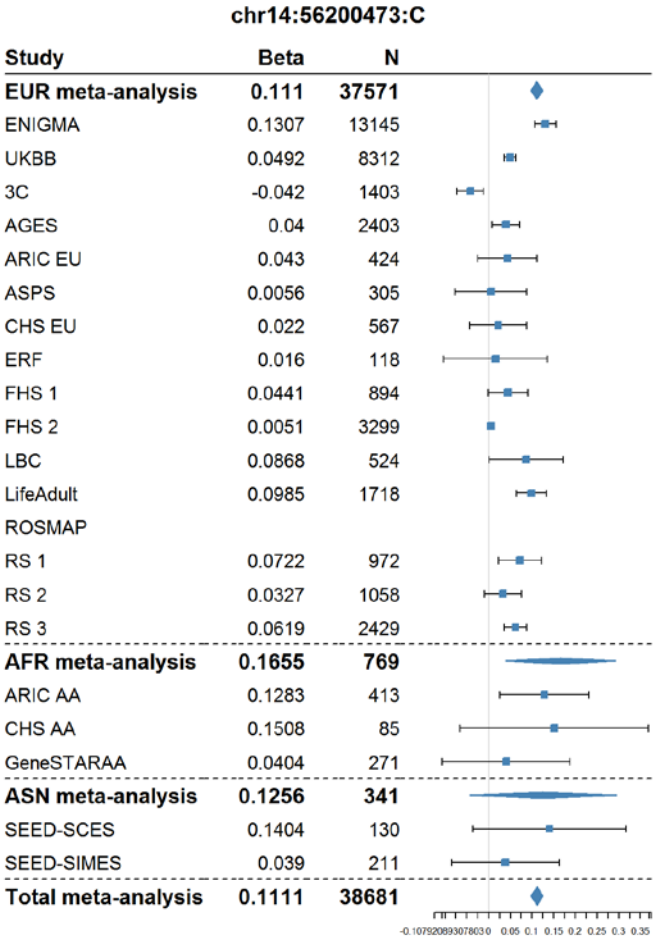
Study	Beta	N
EUR meta-analysis	**-0.0451**	**34252**
ENIGMA	-0.0304	13142
UKBB	-0.0137	8312
3C	9e-04	1397
AGES	-0.0169	2403
ARIC EU	-0.0014	424
ASPS	-0.0278	305
CHS EU	-0.0223	567
ERF	0.0056	118
FHS 1	-0.0076	895
FHS 2		
LBC	0.0165	512
LifeAdult	-0.0092	1718
ROSMAP		
RS 1	-0.0073	972
RS 2	-0.0062	1058
RS 3	-0.0026	2429
AFR meta-analysis	**-0.0055**	**498**
ARIC AA	3e-04	413
CHS AA	-0.0063	85
GeneSTARAA		
ASN meta-analysis	**0.0084**	**341**
SEED-SCES	0.0074	130
SEED-SIMES	-0.0011	211
Total meta-analysis	**-0.044**	**35091**



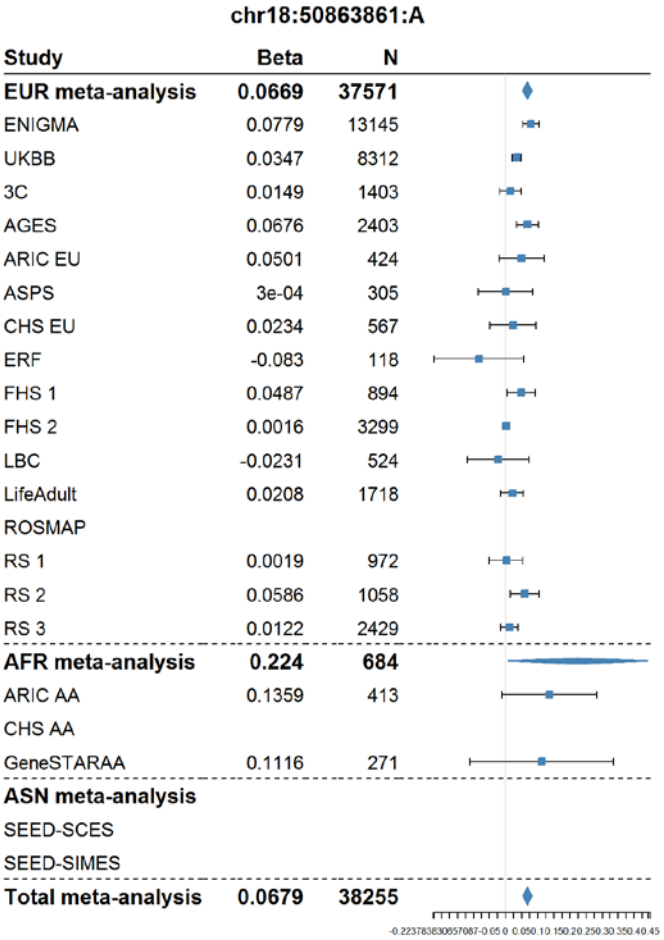
37. Globus pallidus (rs12567402)



38. Putamen (rs945270)



39. Putamen (rs62098013)



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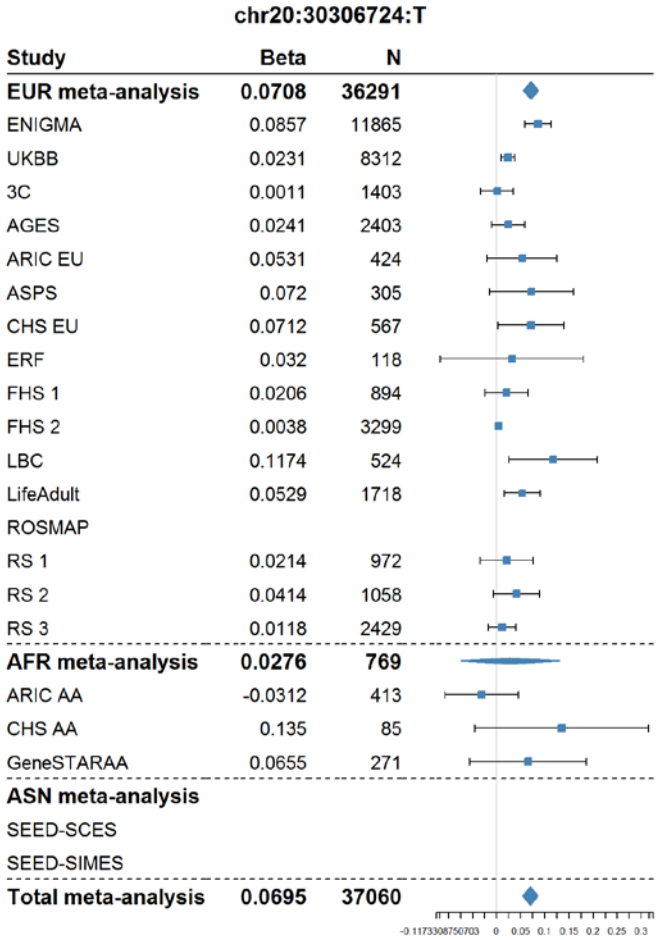
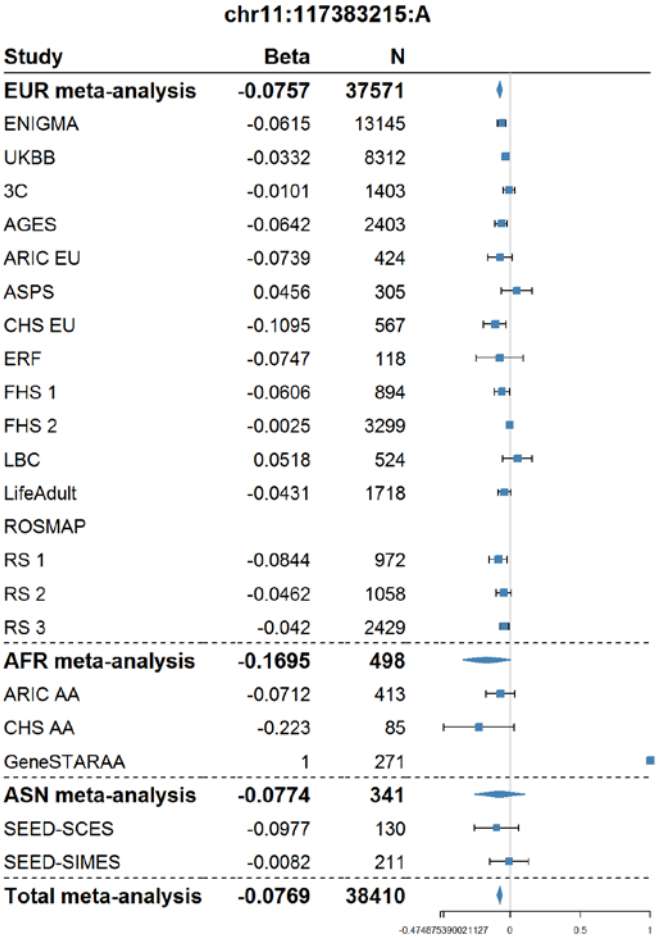
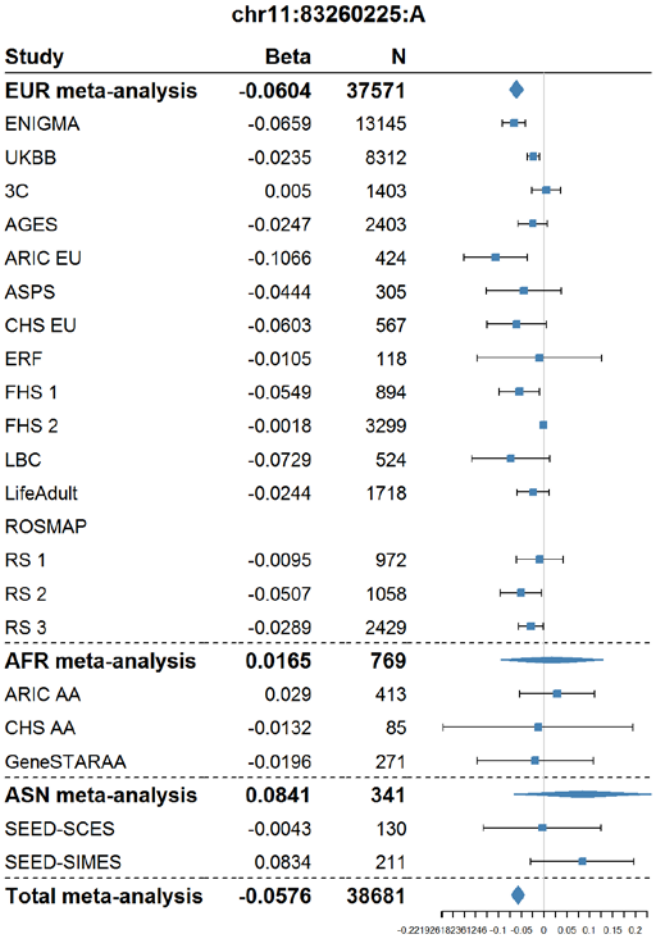


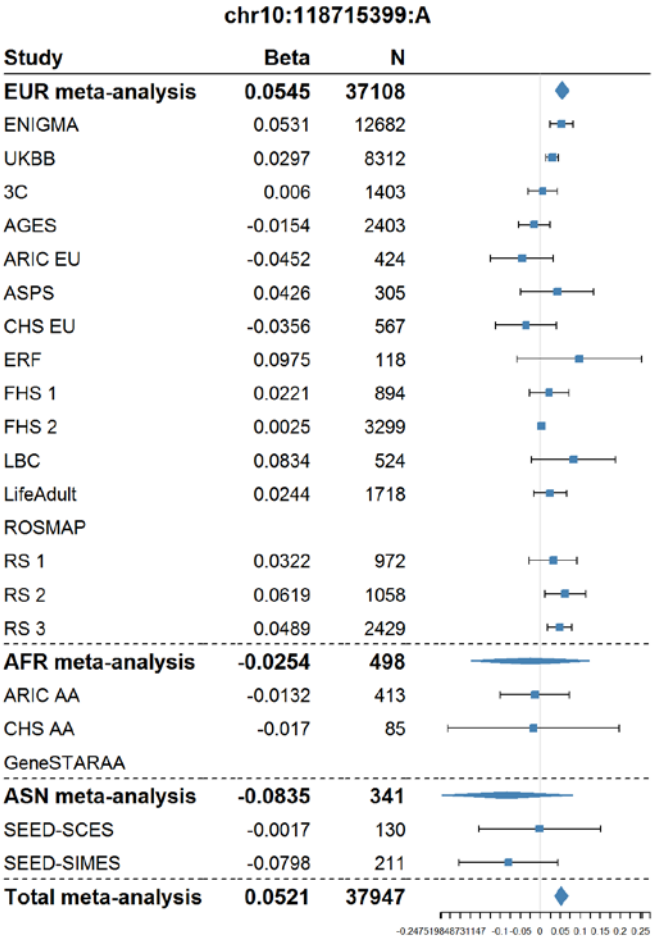
41. Putamen (rs35200015)



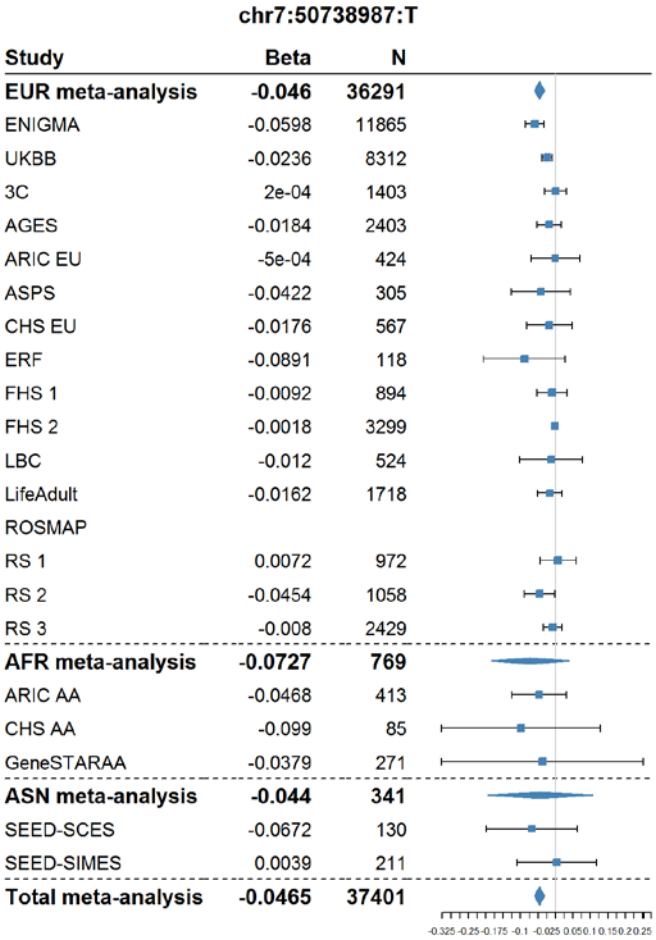
42. Putamen (rs1432054)



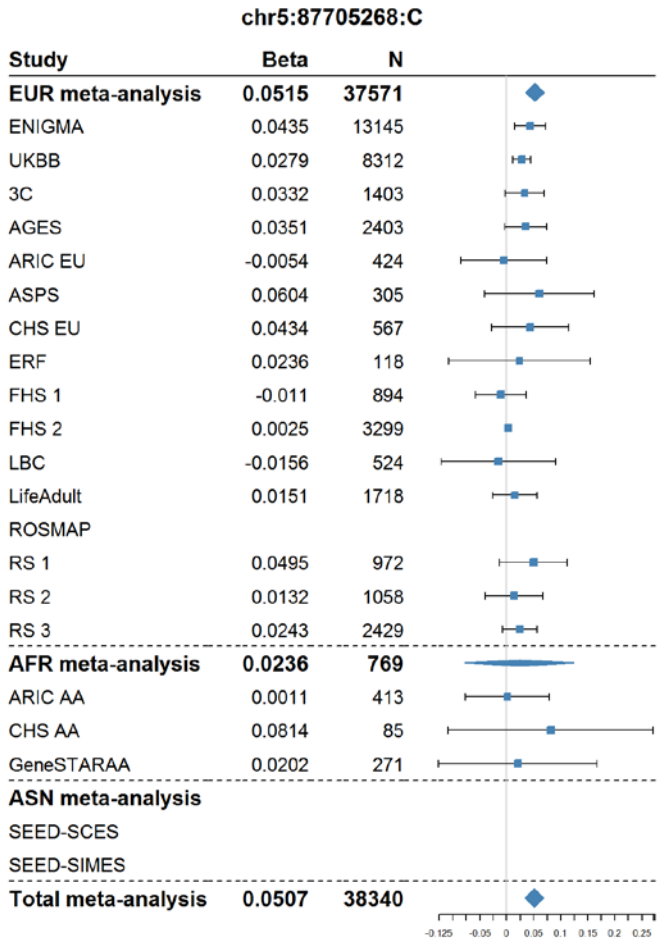
43. Putamen (rs7902527)



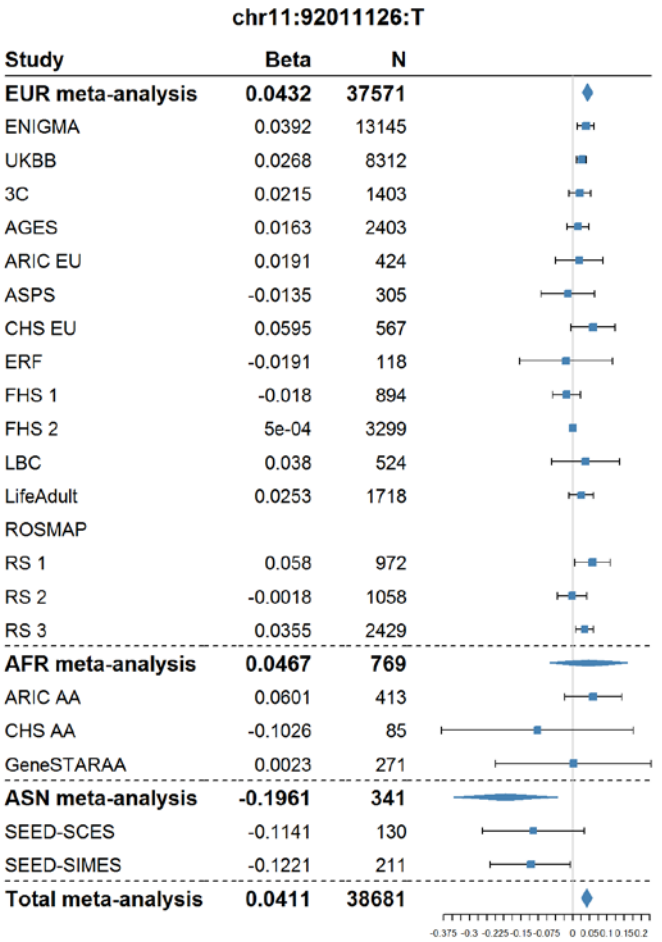
44. Putamen (rs2244479)



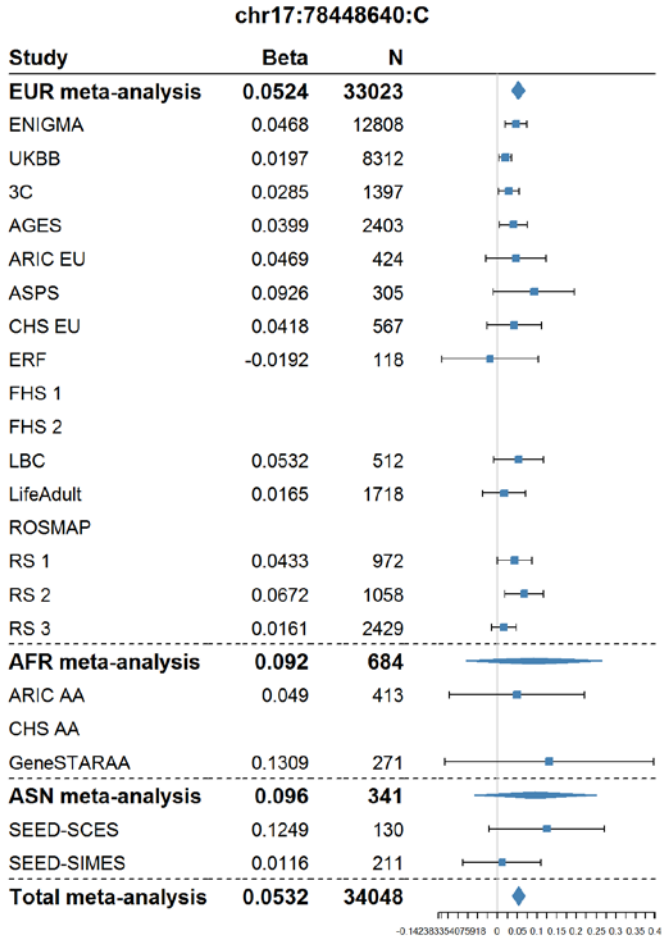
45. Putamen (rs2410767)



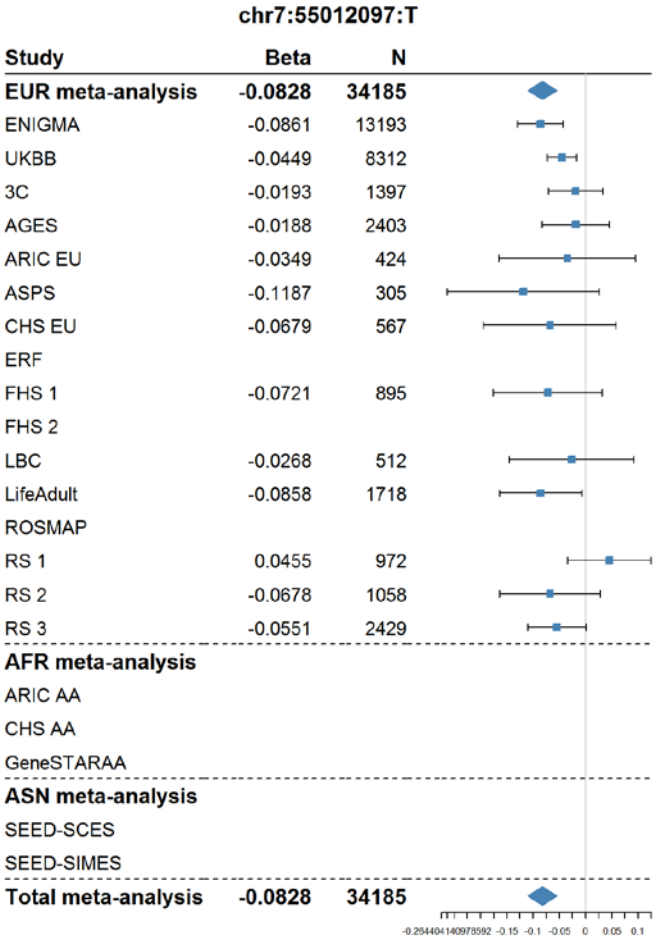
46. Putamen (rs1187162)



47. Thalamus (rs12600720)



48. Thalamus (rs142461330)



STUDY DESIGN

Three-City Dijon (3C-Dijon): The 3C study is a cohort study conducted in three French cities (Bordeaux, Dijon, and Montpellier), comprising 9,294 participants, designed to estimate the risk of dementia and cognitive impairment attributable to vascular factors[2]. Eligibility criteria included living in the city and being registered on the electoral rolls in 1999, 65 years or older, and not institutionalized. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre and each participant signed an informed consent.

Data reported in this article were obtained in Dijon (3C-Dijon study), where 4,931 individuals were recruited (1999–2001). The overall design of the 3C-Dijon study is detailed elsewhere[2-4]. Participants aged less than 80 years and enrolled between June 1999 and September 2000 (n=2,763) were invited to undergo a brain MRI. Although 2,285 subjects agreed to participate (82.7%), because of financial limitations, 1,924 MRI scans were performed, of which 120 were not interpretable. Volume measurements for subcortical structures were available in 1,397 participants with genome-wide genotypes, after exclusion of participants with a diagnosis of dementia, stroke, or brain tumor at the time of MRI. DNA samples of 3C-Dijon participants were genotyped at the Centre National de Génotypage, Evry, France (www.cng.fr) with Illumina Human610-Quad® BeadChips[5,6].

Alzheimer's Disease Neuroimaging Initiative (ADNI): Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many co-investigators from a broad range of academic institutions and private corporations, and subjects have been recruited

from over 50 sites across the U.S. and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these three protocols have recruited over 1500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2. For up-to-date information, see www.adni-info.org.

Age, Gene/Environment Susceptibility-Reykjavik Study (AGES): The AGES cohort originally comprised a random sample of 30,795 men and women born in 1907–1935 and living in Reykjavik in 1967[7]. A total of 19381 attended, resulting in 71% recruitment rate. The study sample was divided into six groups by birth year and birth date within month. One group was designated for longitudinal follow-up and was examined in all stages. One group was designated a control group and was not included in examinations until 1991. Other groups were invited to participate in specific stages of the study. Between 2002 and 2006, the AGES-Reykjavik study re-examined 5764 survivors of the original cohort who had participated before in the Reykjavik Study. MR images were acquired on a single research-dedicated 1.5 T Signa Twinspeed EXCITE system (GE Medical Systems, Waukesha, WI) using a multi-channel phased array head cap coil. The structural image protocol included a T1-weighted three dimensional spoiled gradient echo (3D-SPGR) sequence (TE (time to echo), 8 ms; TR (time repetition), 21 ms; FA (flip angle), 30°; FOV (field of view), 240 mm; matrix, 256 × 256). Each volume consisted of 110 slices with 1.5 mm slice thickness,, in-plane 0.94 x 0.94 mm. A proton density (PD)/T2 - weighted fast spin echo (FSE) sequence (TE1, 22 ms; TE2, 90 ms; TR, 3220 ms; echo train length, 8; FA, 90°; FOV, 220 mm; 256 × 256), and a fluid attenuated inversion recovery (FLAIR) sequence (TE, 100 ms; TR, 8000 ms, inversion time, 2000 ms, FA, 90°; FOV, 220 mm; matrix, 256 × 256). These latter two sequences were acquired with 3-mm thick slices and in-plane pixel size of 0.86 x 0.86 mm. All images were acquired to give full brain coverage and were localized at the AC/PC commissure line.

Avon Longitudinal Study of Parents and Children (ALSPAC): The initial ALPSAC cohort consisted of 14,062 children born to women who resided in the former Avon Health Authority area who had an expected delivery date between April 1991 and December 1992 (www.alspac.bris.ac.uk). The cohort was set up with the goal of determining ways in which genetic and environmental factors influence health and development in parents and children (see http://ije.oxfordjournals.org/content/early/2012/04/14/ije.dys064.full.pdf for a detailed description of the cohort and http://www.bris.ac.uk/alspac/researchers/data-access/data-

dictionary for all available data). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Between November 2011 and October 2012, a subset of 510 male participants was recruited for an MRI study. These individuals were selected based on the availability of multiple (> 3) blood samples obtained during their early and mid-puberty (9, 11, 13 and 15 yr), and their current residence being in the South-West of England. T1-weighted images were acquired on a General Electric 3.0-T magnet (General Electric Medical Systems, Milwaukee, WI) using the following parameters: 3D fast spoiled gradient echo scan with 180 oblique-axial slices, 1-mm isotropic resolution, TR-7.9 ms, TE=3.0 ms, TI=450ms and flip angle=20°. Genetic data were acquired using the Illumina HumanHap550 quad genome-wide single nucleotide polymorphism (SNP) genotyping platform from 9912 ALSPAC children. Individuals were excluded from analysis on the basis of gender mismatches, minimal or excessive heterozygosity, disproportionate levels of individual missingness (>3%), evidence of cryptic relatedness (>10% of alleles identical by descent), and being of non-European ancestry (assessed by multidimensional scaling analysis including HapMap 2 individuals). SNPs with a minor allele frequency (MAF) of < 1%, Impute2 information quality metric of < 0.8, a call rate of < 95% or evidence for violations of Hardy-Weinberg equilibrium (p value < 5 x 10-7) were removed. Imputation of the target data was performed using Impute V2.2.2 against the 1000 genomes reference panel (Phase 1, Version 3; all polymorphic SNPs excluding singletons), using 2,186 reference haplotypes (including non-Europeans). Following quality control assessment, 405 individuals had phenotypic and genetic data available for inclusion into the current study.

Atherosclerosis Risk in Communities (ARIC) Study: The ARIC study is a population-based cohort study of atherosclerosis and clinical atherosclerotic diseases[8]. At its inception (1987-1989), 15,792 men and women, including 11,478 white and 4,266 black participants were recruited from four U.S. communities: Suburban Minneapolis, Minnesota; Washington County, Maryland; Forsyth County, North Carolina; and Jackson, Mississippi. In the first 3 communities, the sample reflects the demographic composition of the community. In Jackson, only black residents were enrolled. Participants were between age 45 and 64 years at their baseline examination in 1987-1989 when blood was drawn for DNA extraction and participants consented to genetic testing. Vascular risk factors and outcomes, including transient ischemic attack, stroke and dementia, were determined in a standard fashion. During the first 2 years (1993-1994) of the third ARIC examination (V3), participants aged 55 and older from the Forsyth County and Jackson sites were invited to undergo cranial MRI. This subgroup of individuals with MRI scanning represents a random sample of the full cohort because examination dates were allocated at baseline through randomly selected induction

cycles. After excluding individuals with prevalent stroke at V3, a total of 424 white and 413 black participants had phenotypic and genome-wide genotypic data.

Austrian Stroke Prevention-Family Study (ASPS-Fam): The ASPS-Fam is a prospective single-center community-based study on the cerebral effects of vascular risk factors in the normal aged population of the city of Graz, Austria[9,10]. ASPS-Fam represents an extension of the ASPS, which was established in 1991[11,12]. Between 2006 and 2013, study participants of the ASPS and their first-grade relatives were invited to enter ASPS-Fam. Inclusion criteria were no history of previous stroke or dementia and a normal neurologic examination. The study protocol was approved by the ethics committee of the Medical University of Graz, Austria, and written informed consent was obtained from all subjects. The entire cohort of 419 individuals underwent an extended diagnostic work- up including clinical history, blood tests, cognitive testing, and a thorough vascular risk factor assessment. Those 305 ASPS-Fam individuals who underwent MRI scanning and passed genotyping quality control were available for these analyses. They were all European Caucasians.

Cardiovascular Health Study (CHS): The CHS is a population-based cohort study of risk factors for coronary heart disease and stroke in adults ≥ 65 years conducted across four field centers[13]. The original predominantly European ancestry cohort of 5,201 persons was recruited in 1989-1990 from random samples of the Medicare eligibility lists; subsequently, an additional predominantly African-American cohort of 687 persons was enrolled for a total sample of 5,888. Blood samples were drawn from all participants at their baseline examination and DNA was subsequently extracted from available samples. Genotyping was performed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai among CHS participants who consented to genetic testing and had DNA. European ancestry participants were excluded from the GWAS study sample due to the presence at study baseline of coronary heart disease, congestive heart failure, peripheral vascular disease, valvular heart disease, stroke or transient ischemic attack or lack of available DNA. Among those with successful GWAS, 567 European ancestry and 85 African-American participants had available FreeSurfer measures for this analysis. CHS was approved by institutional review committees at each field center and individuals in the present analysis had available DNA and gave informed consent including consent to use of genetic information for the study of cardiovascular disease.

Epidemiology of Dementia In Singapore (EDIS): The EDIS study draws subjects from the on-going population-based community-dwelling study of Chinese, Malays and Indians cohorts aged ≥40 years who participated in the Singapore Epidemiology of Eye Disease (SEED; n=10,033), which

comprises the Singapore Chinese Eye Study (SCES; n=3,353), Singapore Malay Eye Study-2 (SiMES-2; n=3,280) and Singapore Indian Eye Study-2 (SINDI-2; n=3,400)[14]. As part of the baseline examinations in the SEED cohorts, genotyping was done in 2,587 SCES participants and 3,072 SiMES participants[15,16]. In the present study we restricted analysis to the Chinese (EDIS-SCES) and Malay (EDIS-SiMES) component of EDIS, as the recruitment of the Indians has recently ended. In the first phase of the EDIS Study, participants from SEED aged ≥ 60 years (n=1,538 Chinese and n=1,014 Malay) were screened using the 10-point Abbreviated Mental Test (AMT) and a self-report of progressive forgetfulness. Screen-positives were defined as AMT score ≤ 6, among those with ≤ 6 years of formal education, or ≤ 8 among those with > 6 years of formal education; or if the subject or caregiver reported progressive forgetfulness [yes/no]. A total of 300 Chinese and 308 Malay screen-positive subjects agreed to take part in the second phase of this study, which included an extensive neuropsychological test battery and brain MRI. Of these 130 Chinese and 211 Malay were included in the current analyses, who had genotyping and MRI data. Ethics approval for EDIS study was obtained from the Singapore Eye Research Institute (SERI) and National Healthcare Group Domain-Specific Review Board (DSRB). The study is being conducted in accordance with the Declaration of Helsinki. Written informed consent is obtained, in the preferred language of the participants, by bilingual study coordinators prior to their recruitment in the study.

Erasmus Rucphen Family study (ERF): The Erasmus Rucphen Family (ERF) study is a family-based cohort study in a genetically isolated population from a community in the South-West of the Netherlands (Rucphen municipality) including 3000 participants. Participants are all descendents of a limited number of founders living in the 19th century, and all of Caucasian European descent. Extensive genealogical data is available for this population. The study population is described in detail elsewhere. As part of the protocol, genomic DNA was collected from all participants. Genotyping was done at the Human Genotyping Facility, Genetic Laboratory Department of Internal Medicine, Erasmus MC, Rotterdam, and at the Genotyping Center of Leiden University, The Netherlands. All participants gave informed consent and the study was approved by the medical ethics committee at Erasmus MC University Medical Center. In a follow-up analysis, 135 nondemented hypertensive (SBP ≥ 160, DBP ≥ 100 or use of antihypertensive medication) subjects aged 55-75 years were included for a new battery of tests including MRI scanning. Of these, 4 subjects were excluded because of physical constraints impeding the MRI scanning, and 2 subjects were excluded from analysis because large brain tumors were incidentally discovered. Full genotype and phenotype data were available for 118 subjects after QC of the automated segmentations.

The Framingham Heart Study (FHS): The FHS is a three-generation, single-site, community-based, ongoing cohort study that was initiated in 1948 to investigate the risk factors for cardiovascular disease. It now comprises 3 generations of participants: the Original cohort followed since 1948[17]; their Offspring and spouses of the Offspring (Gen 2), followed since 1971[18]; and children from the largest Offspring families enrolled in 2000 (Gen 3)[19]. The Original cohort enrolled 5,209 men and women who comprised two-thirds of the adult population then residing in Framingham, MA. Survivors continue to receive biennial examinations. The Offspring cohort comprises 5,124 persons (including 3,514 biological offspring) who have been examined approximately once every 4 years. The Third-generation includes 4,095 participants with at least one parent in the Offspring Cohort. The first two generations were invited to undergo an initial brain MRI in 1999-2005, and for Gen 3, brain MRI began in 2009. The population of Framingham was virtually entirely white (Europeans of English, Scots, Irish and Italian descent) in 1948 when the Original cohort was recruited. Self-reports of ethnicity across all three generations were 99.7% whites, reflecting the ethnicity of the population of Framingham in 1948. FHS participants had DNA extracted and provided consent for genotyping, and eligible participants underwent genome-wide genotyping.
In 1,035 participants from the Offspring cohort we had FreeSurfer measures processed at the Athinoula A. Martinos Center for Biomedical Imaging at the MGH/HST. Form this sample, 896 had genotyping and constituted the European sample contributing to the GWAS of all subcortical structures (FHS-1). Additionally, a larger sample of FHS including all three generations had caudate and putamen measures processed by the Imaging of Dementia (IDeA) laboratory at UC Davis. After exclusion of Offspring participants with FreeSurfer data, a sample of 3,303 participants with genotyping was used for replication of the caudate and putamen findings (FHS-2).

Genetic Study of Atherosclerosis Risk (GeneSTAR): is an ongoing prospective study designed to determine environmental, phenotypic, and genetic causes of premature cardiovascular disease[20,21]. Participants (n=3533) came from European- and African-American families (n=891) identified from 1983-2006 from probands with a premature coronary disease event prior to 60 years of age who were identified at the time of hospitalization in any of 10 Baltimore area hospitals. Apparently healthy siblings of the probands and offspring of the siblings and probands were screened for traditional coronary disease and stroke risk factors. A random subset of this study population underwent MRI with a Philips 3T imaging unit according to standardized protocols between 2009 and 2013. Siblings and offspring were excluded if they had a history of chronic corticosteroid use, life-threatening diseases, neurologic diseases that would preclude accurate MRI interpretation, and implanted metals that prohibited MRI scans. Participants with atrial fibrillation or symptomatic

cardiovascular disease of any kind were excluded from the study. MPRAGE images were skull-stripped and co-registered to FLAIR images. Spatial normalization of the co-registered MPRAGE and FLAIR images into MNI space was performed via affine transformation. We segmented the brain in native MPRAGE space using an automated probabilistic methodology that employs a topology-preserving algorithm and mapped the resulting tissue mask to MNI space. We measured total brain, intracranial, and subcortical volumes. Intracranial volume was defined (in cubic millimeters) as the sum of all meningeal material, soft tissue, and sulcal and ventricular cerebrospinal volumes inferior to bone from the vertex to the foramen magnum.

The Lothian Birth Cohort (LBC) -1936: LBC participants (n = 1091; 49.8% women) were born in the Edinburgh area of Scotland in 1936 and represent a relatively healthy cohort who live independently in the community. Most members of this cohort had been tested for general cognitive ability at age 11[22] and their structural MRI assessments were performed as part of a second wave of data collection in adulthood at age 73 (n = 724)[23]. Following relevant exclusions (e.g., stroke, poor data acquisition), subcortical measures were available for a reduced sample of 512, who also had genome-wide data (genotyped using DNA from venesected whole blood). Ethical approval was obtained from Scotland's Multicentre Research Ethics Committee and local research ethics committee.

LIFE-Adult: LIFE-Adult is a population-based cohort of 10,000 randomly selected adults of the city of Leipzig, Germany. Details of the study can be found elsewhere[24]. About 2,600 subjects underwent magnetic resonance imaging (MRI) of the head at 3T. Exclusion criteria of the current study were dementia, stroke and major brain pathology. LIFE-Adult has been approved by the Ethics Committee of the Medical Faculty of the University Leipzig, Germany (Reg. No 263-2009-14122009). Written informed consent including agreement with genetic analyses was obtained from all participants.

The Religious Orders Study and The Rush Memory and Aging Project (ROSMAP): The ROS, started in 1994, enrolled Catholic priests, nuns, and brothers, from about 40 groups in 12 states[25]. Since January 1994, 1321 participants completed their baseline evaluation, of whom 1259 were non-Hispanic white. The follow-up rate of survivors exceeds 90%. Participants were free of known dementia at enrollment, agreed to annual clinical evaluations, and signed both an informed consent and an Anatomic Gift Act form donating their brains at time of death[25]. A more detailed description of ROS has been published previously[25]. Participants take a neuropsychological test battery. DNA was extracted from whole blood, lymphocytes, or frozen post-mortem brain tissue. Genotyping was

performed at the Broad Institute's Center for Genotyping and the Translational Genomics Research Institute and the Children's Hospital of Philadelphia[26]. The Rush Memory and AP, started in 1997, enrolled older men and women from assisted living facilities in the Chicago area with no evidence on dementia at baseline[1]. Since October 1997, 1815 participants completed their baseline evaluation, of whom 1701 were non-Hispanic white people. The follow-up rate of survivors exceeds 90%. Participants agreed to annual clinical evaluations, and signed both an informed consent and an Anatomic Gift Act form donating their brains at time of death. A more detailed description of the MAP has been published previously[1]. Participants were invited to take a neuropsychological test battery. DNA was extracted from whole blood, lymphocytes, or frozen postmortem brain tissue. Genotyping was performed at the Broad Institute's Center for Genotyping and the Translational Genomics Research Institute and the Children's Hospital of Philadelphia[2]. Participants underwent their initial MRI beginning in 2009. In 493 participants from ROS and MAP, we have FreeSurfer measures processed at Rush. After excluding subjects with dementia or history of stroke at the time of MRI-scan, 161 subjects with genotype data were included in the present analysis.

Rotterdam Study (RSI, RSII, RSIII): The Rotterdam Study is a prospective, population-based cohort study among individuals living in the well-defined Ommoord district in the city of Rotterdam in The Netherlands[27]. The aim of the study is to determine the occurrence of cardiovascular, neurological, ophthalmic, endocrine, hepatic, respiratory, and psychiatric diseases in elderly people. The cohort was initially defined in 1990 among approximately 7,900 persons, aged 55 years and older, who underwent a home interview and extensive physical examination at the baseline and during follow-up rounds every 3-4 years (RS-I). The cohort was extended in 2000/2001 (RS-II, 3,011 individuals aged 55 years and older) and 2006/2008 (RS-III, 3,932 subjects, aged 45 and older). Written informed consent was obtained from all participants and the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, approved the study.

United Kingdom Biobank (UKBB): The UKBB is a large-scale epidemiological study of over 500,000 individuals aged 40-69 years from the United Kingdom (http://www.ukbiobank.ac.uk). The analyses presented here use data that were accessed via application 1155. Genetic data are available for the majority of these individuals[28] and as of 15 July 2017 13,269 of these participants had participated in a multimodal imaging sub-study [29,30]. The analyses presented here use the subcortical volumes of the unrelated participants released by the UKBB which are derived from the T1 Brain MRI, the extraction of these measures using FIRST is described in Alfaro-Almagro *et al* (2017). These data were not visually QCed (as the required files were not available for download).

However, we removed outliers by setting data points more than 3 standard deviations from the mean to missing. The genetic data used for these analyses uses only those variants imputed using the HRC reference panel. Imputation accuracy and allele frequency were recalculated in the subset of participants with imaging from the raw imputed data using HASE software, quality control filters used in the meta-analyses were applied to the UKBB data prior to analysis. To account for ethnicity, we included only subjects with white British ancestry (base on provided by UKBB information). To avoid correct cryptic relationship we excluded all subject with >=3rd degree of genetic relationship.

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