

Genome-wide analyses identify a role for SLC17A4 and AADAT in thyroid hormone regulation

Teumer *et al.*

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Supplementary Note 1: Detailed results of mouse candidate analyses

In this candidate gene approach we selected genes that are linked to abnormal thyroid physiology (i.e., hormone levels, $n=26$) or morphology ($n=51$) in mice to assess whether their human homologs contained SNPs significantly associated with FT4 and TSH in our GWAS. For FT4, variants in 6 and 3 genes and for TSH in 4 and 5 genes (**Supplementary Data 2**) from the abnormal murine thyroid physiology and morphology list, respectively, showed significant association (**Supplementary Figure 7A**). Four of them (*TPO*, *CGA*, *TRHR*, and *FOXE1*) did not reach genome-wide significance in the full TSH or FT4 GWAS. Notably, *CGA* and *TRHR* were never been detected by previous GWAS of thyroid function or thyroid diseases. Both *CGA* and *TRHR* represent excellent biological candidates; *CGA* codes for the alpha chain of TSH, and *TRHR* for the thyrotropin (TSH) releasing hormone receptor expressed in the pituitary. To validate these four additional associations, we sought replication of the variants in 9,011 (TSH) and 4,532 (FT4) independent samples. As shown in **Supplementary Figure 7B and C**, both *CGA* and *TPO* achieved genome-wide significance for TSH ($p < 5 \times 10^{-8}$), whereas *TRHR* approached this threshold for FT4 ($p = 5.7 \times 10^{-8}$, **Supplementary Data 2**).

Supplementary Note 2: Pathway analyses results

Top canonical pathways identified for the TSH hits included G-protein signaling and ephrin receptor signaling, both important for neurogenesis and neuronal sustainability during development, as well as cardiac beta-adrenergic signaling (**Supplemental Figure 12A**), which overlap with the top pathways revealed for hyperthyroidism. The top canonical pathways identified for FT4 did not overlap with those for TSH but partially with those for hypothyroidism and included thyroid hormone metabolism and biosynthesis, and thyroid hormone receptor/retinoid-X receptor activation. The canonical pathway related to tRNA splicing overlapped with both hypo- and hyperthyroidism, whereas other pathways like

cAMP-mediated signaling and T-cell receptor signaling were specific for hyperthyroidism and hypothyroidism, respectively. For TSH, the top networks incorporated genes involved in embryonic development, cell cycle control and cell fate decision. For FT4, the top networks incorporated genes encoding proteins involved in endocrine system development and function as well as molecular transport and small molecule biochemistry.

The DEPICT results assessing tissue-specificity of the GWAS results did not reveal any associations that passed the significance level after multiple testing correction (all false discovery rates were ≥ 0.2). However, the only thyroid tissue related association with a nominal significant p-value was found for the TSH GWAS results with thyroid gland, which was also the strongest tissue enrichment for this trait (**Supplemental Figure 12B**). Additionally, nominally significant tissue enrichment was revealed in the pancreas in which also AADAT and SLC17A4 co-localized.

Supplementary Note 3: Lookup for pleiotropy of novel loci

Pleiotropic effects of the novel loci associated with TSH included body height (*ADCY9*, *MIR365A*), waist circumference (*ADCY9*), type II diabetes (*IGF2BP2*), as well as age at menarche (*MIR365A*) and ovarian cancer (*NSF*), and intracranial volume and Parkinson's disease (*NSF*). Loci associated with FT4 were also associated with body height, body mass index, proinsulin and high-density lipoprotein (*FNBP4*), with blood metabolite levels (*ACMSD*: N1-methyl-3-pyridone-4-carboxamide, *SLCO1B1*: isoleucine), and serum urate and hemoglobin levels (*SLC17A4*). The loci associated with hypo- or hyperthyroidism were almost exclusively additionally associated with thyroid related traits including TSH levels, thyroid volume and thyroid cancer. The detailed results of genome-wide significant pleiotropic effects are provided in **Supplementary Data 5**, and a description of the new loci with respect to gene function is provided in **Supplementary Data 6**.

Supplementary Note 4: Extended acknowledgements

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ASKLEPIOS

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BHS

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CHRIS

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GARP

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LLS

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NBS

The Nijmegen Biomedical Study is a population-based survey conducted at the Department for Health Evidence and the Department of Laboratory Medicine of the Radboud university medical center. Principal investigators of the Nijmegen Biomedical Study are L.A.L.M.

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Rotterdam Study

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The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered in the Netherlands National Trial Register (NTR; <http://www.trialregister.nl>) and in the WHO International Clinical Trials Registry Platform (ICTRP; <http://www.who.int/ictip/network/primary/en/>) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

The generation and management of GWAS genotype data for the Rotterdam Study (RS I, RS

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This study makes use of sequence reference data generated by the UK10K Consortium, derived from samples from the ALSPAC and TwinsUK datasets. A full list of the investigators who contributed to the generation of the data is available from www.UK10K.org. Funding for UK10K was provided by the Wellcome Trust under award WT091310. We thank Jie Huang at the Wellcome Trust's Sanger Institute, at Hinxton, U.K. for the creation of imputed data, with the support of Marijn Verkerk, Carolina Medina-Gomez, MSc, and Anis Abuseiris and their input for the analysis setup.

This study makes use of an extended dataset of RS II and RS III samples based on Illumina Omni 2.5 and 5.0 GWAS genotype data, imputed to 1KG using the two-phase imputation method³. This dataset was funded by the Genetic Laboratory of the Department of Internal Medicine, the department of Forensic Molecular Biology, and the department of Dermatology, Erasmus MC, Rotterdam, The Netherlands. This work was supported by a grant from the Netherlands Organisation for Health Research and Development (project number

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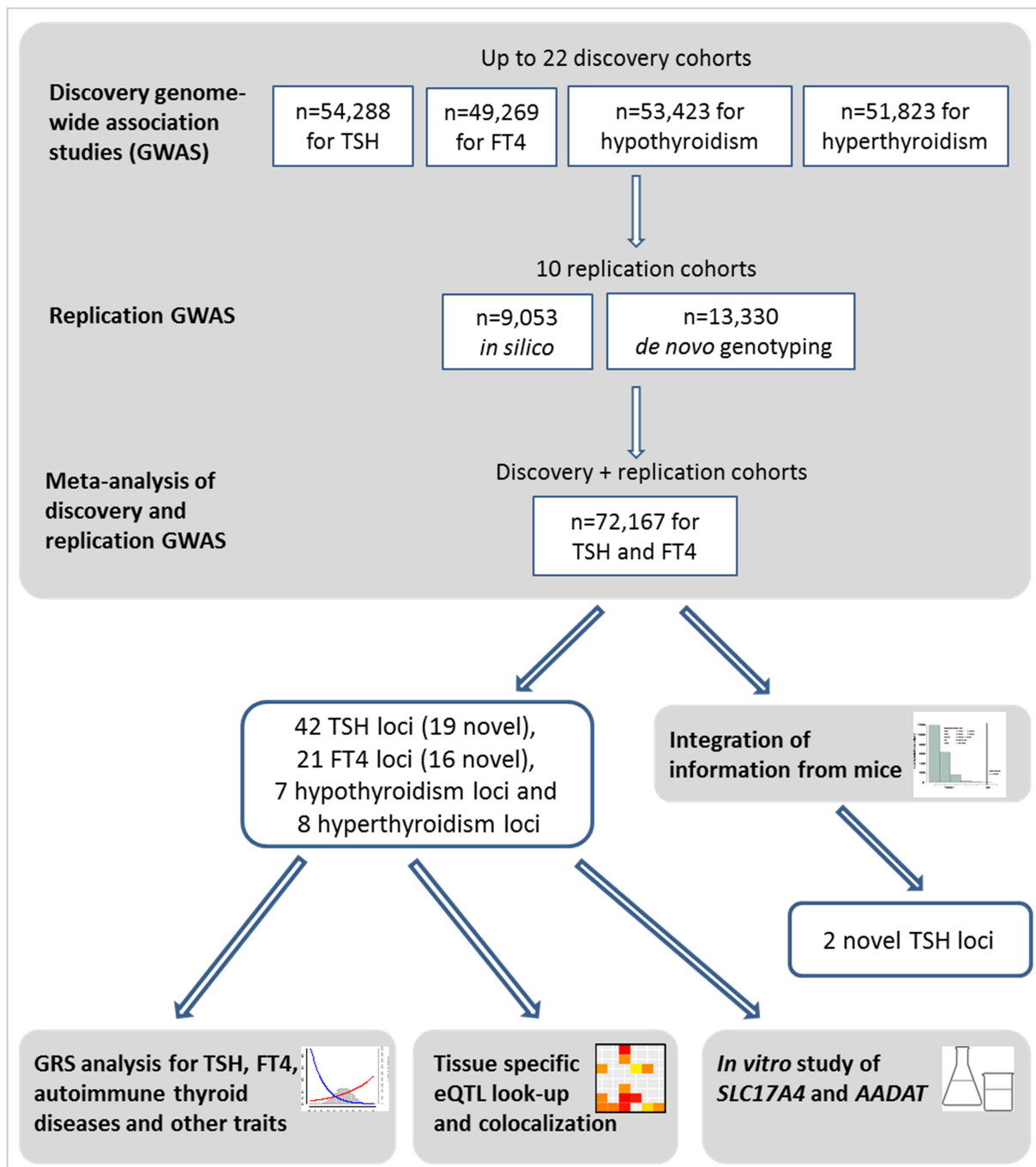
TwinsUK

TwinsUK is funded by the Wellcome Trust, Medical Research Council, European Union, the National Institute for Health Research (NIHR)-funded BioResource, Clinical Research Facility and Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London. This research was also supported by the Australian National Health and Medical Research Council (Project Grant 1087407), the Sir Charles Gairdner Hospital RAC (SGW) and the iVEC/Pawsey Supercomputing Centre (Project Grants: Pawsey0162, Director2025 (SGW)).

Val Borbera

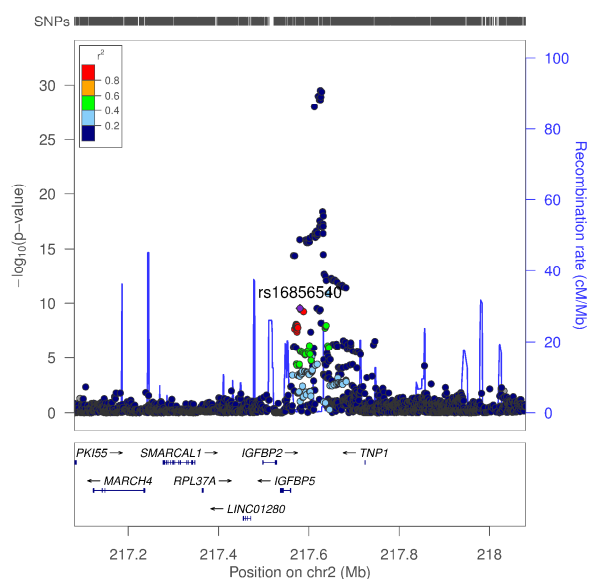
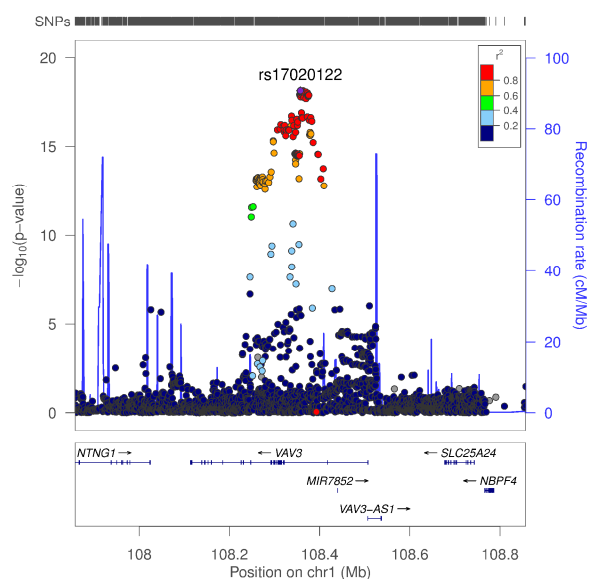
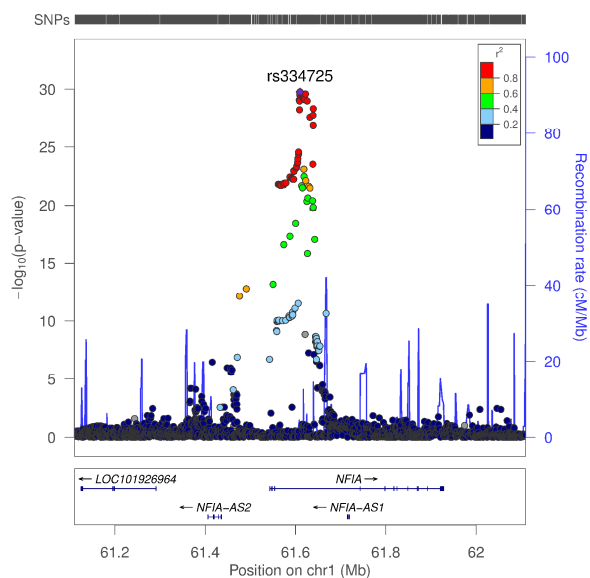
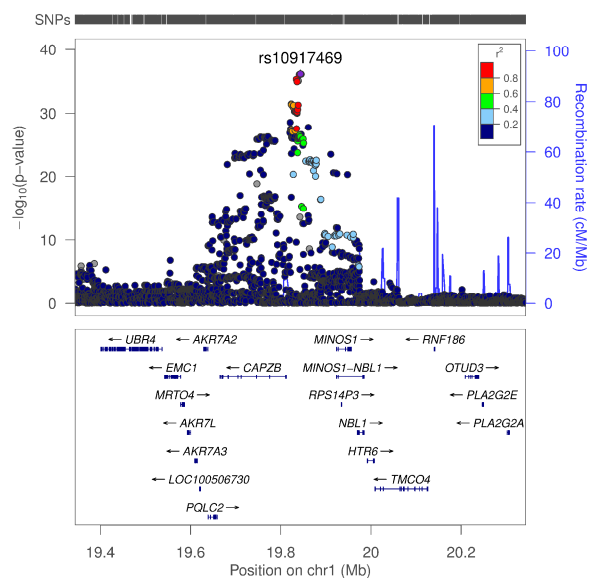
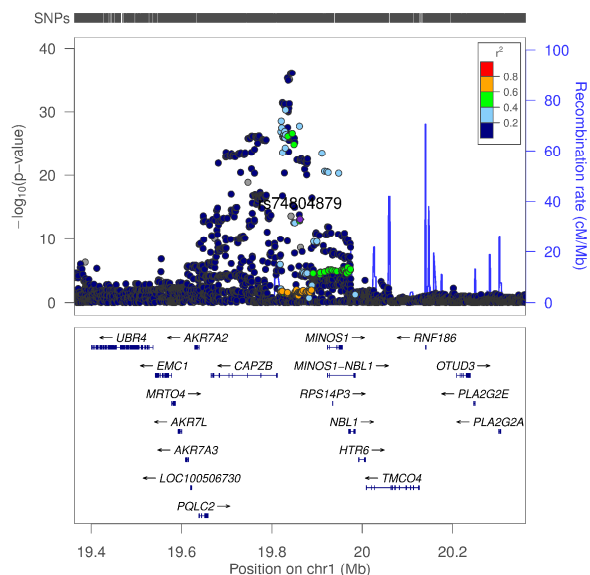
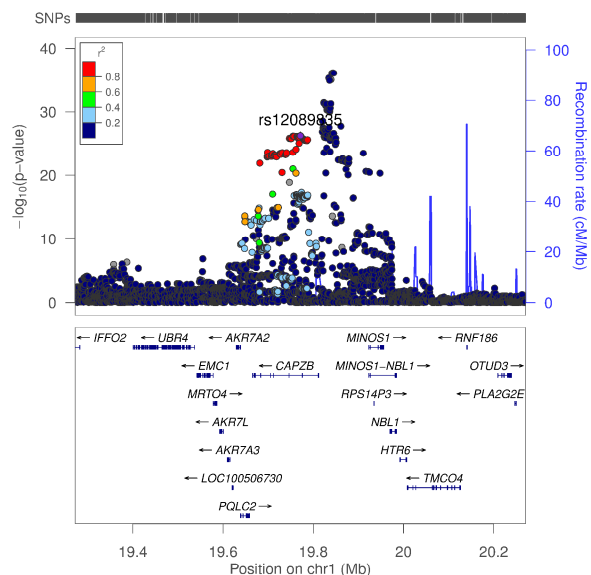
Val Borbera is an isolated valley in North Western Italy. We thank all the participants in the project, the San Raffaele Hospital MDs who contributed to clinical data collection, Prof. Clara Camaschella who coordinated the data collection, Corrado Masciullo and Massimiliano Cocca for the database informatics. The research was supported by funds from Compagnia di San Paolo, Torino, Italy; Fondazione Cariplo, Italy; Telethon Italy; Ministry of Health, Ricerca Finalizzata 2008 and 2011-2012 and Public Health Genomics Project 2010.

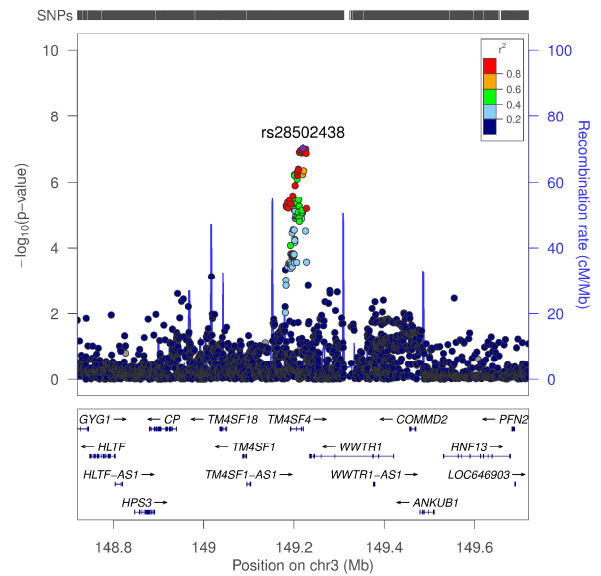
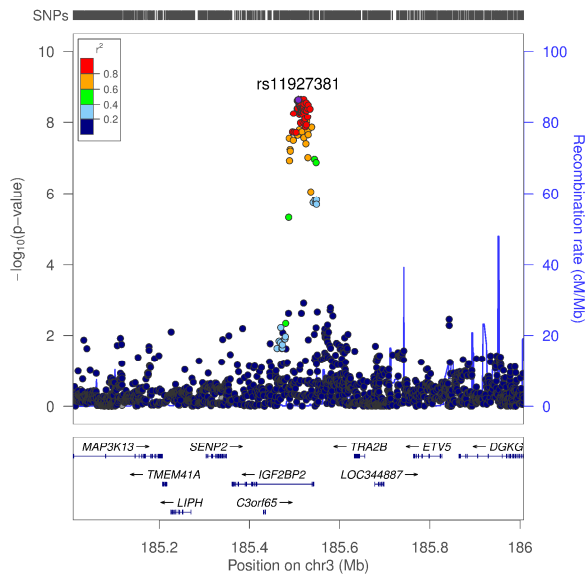
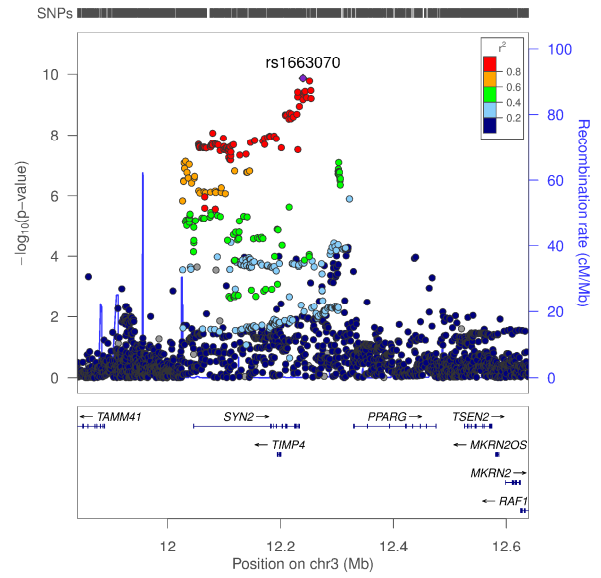
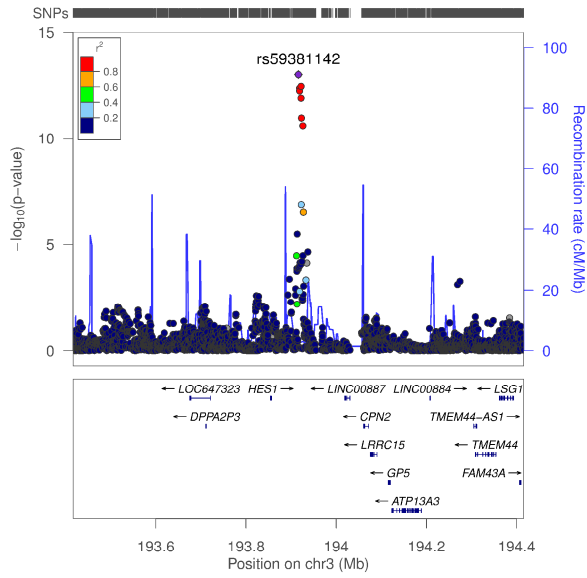
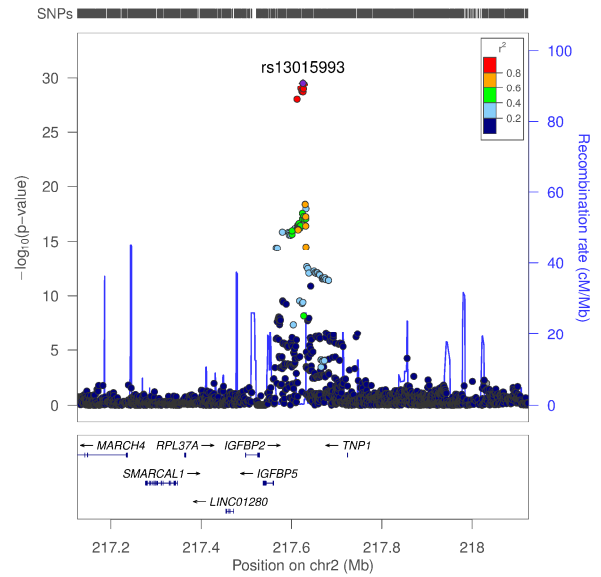
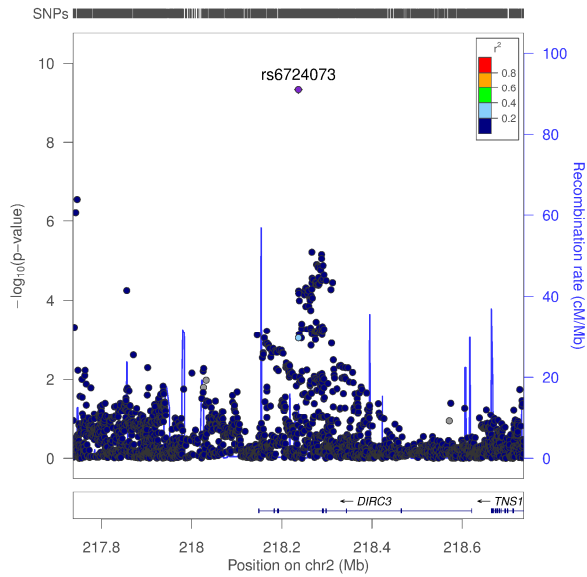
Supplementary Figure 1: Schematic of the project

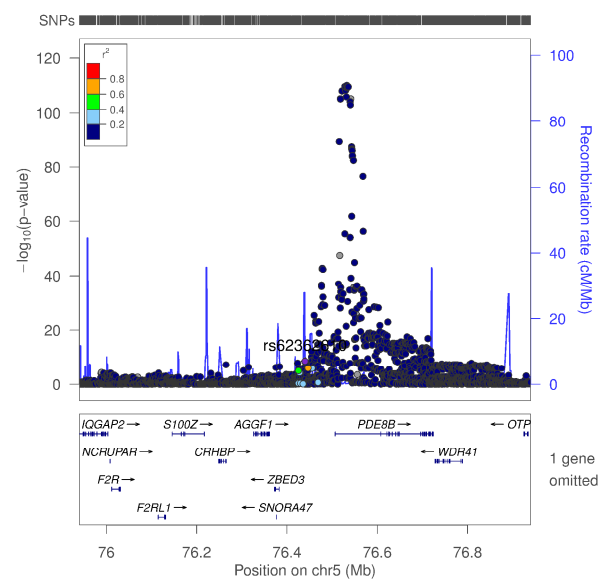
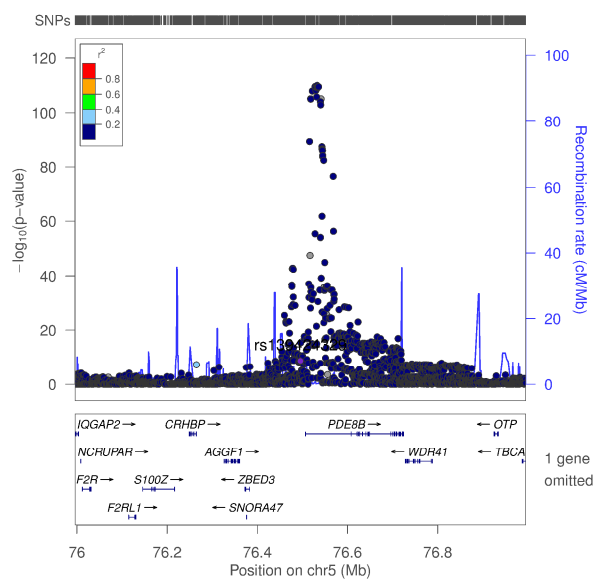
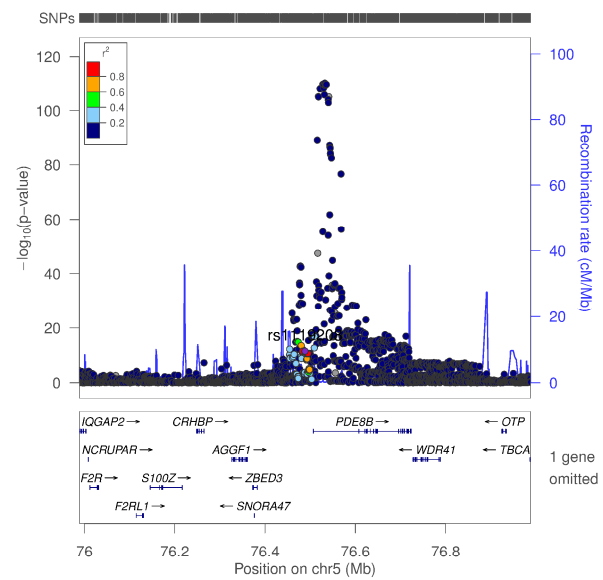
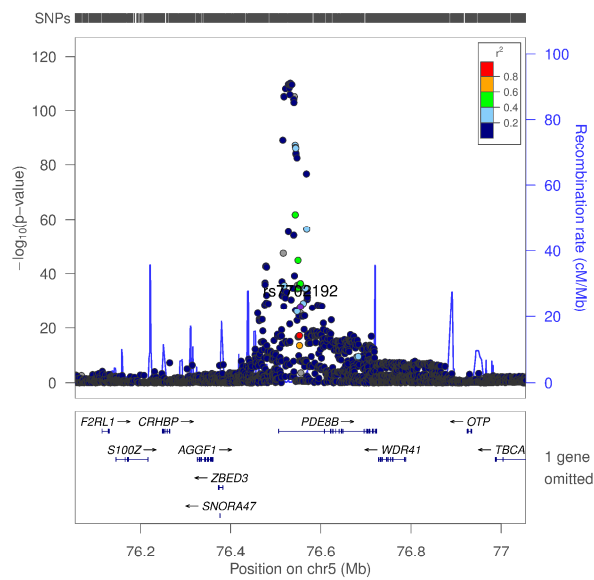
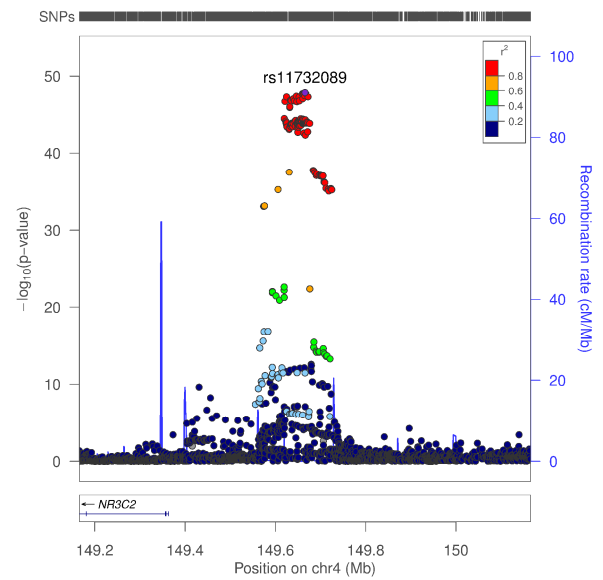
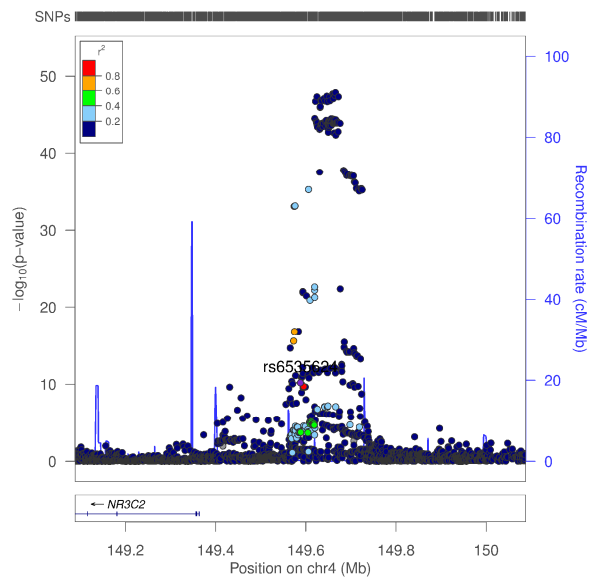


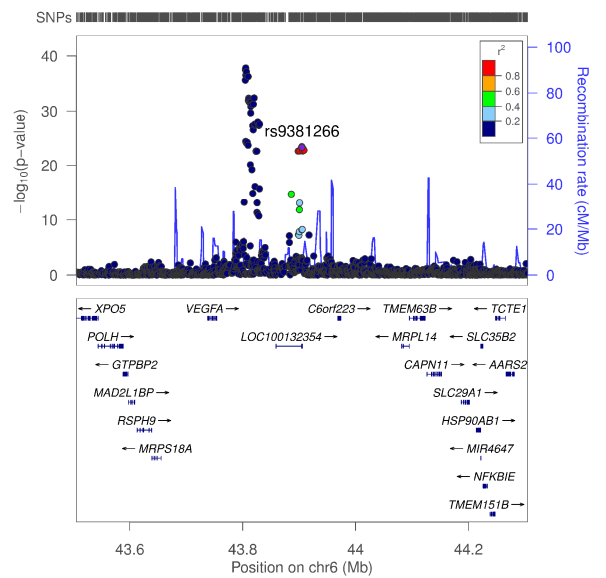
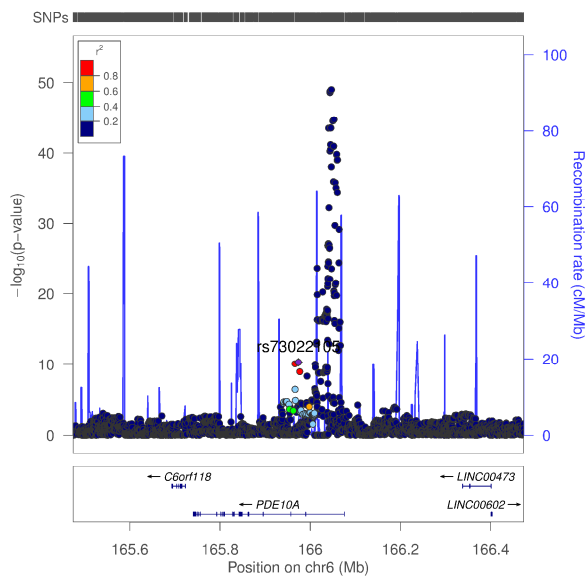
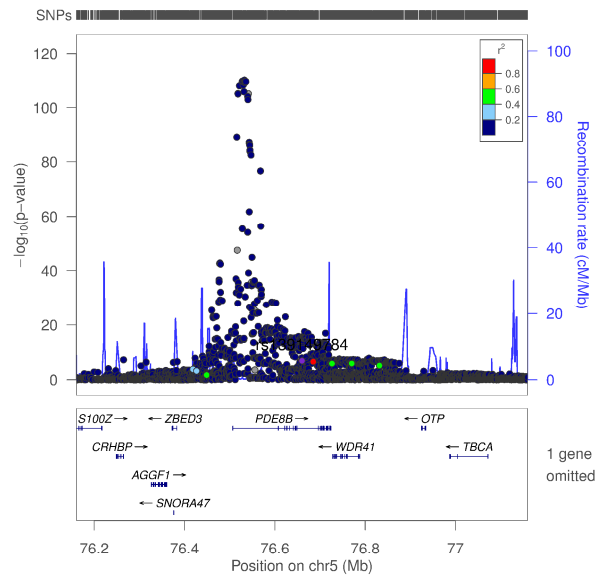
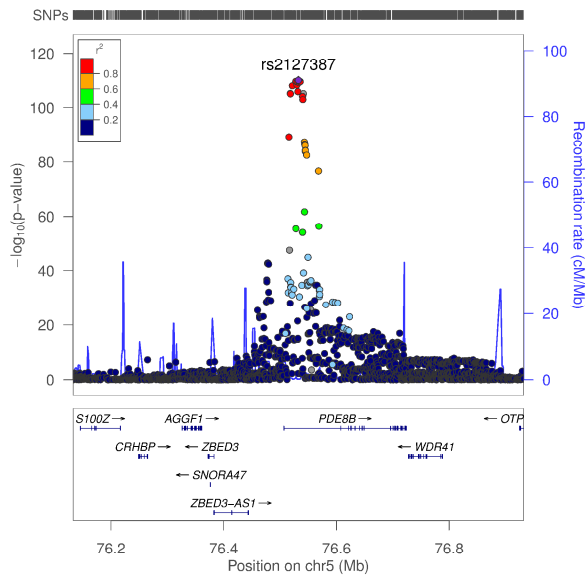
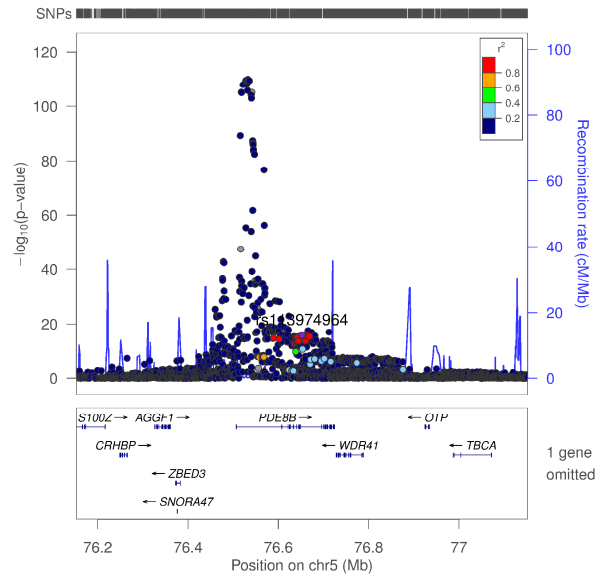
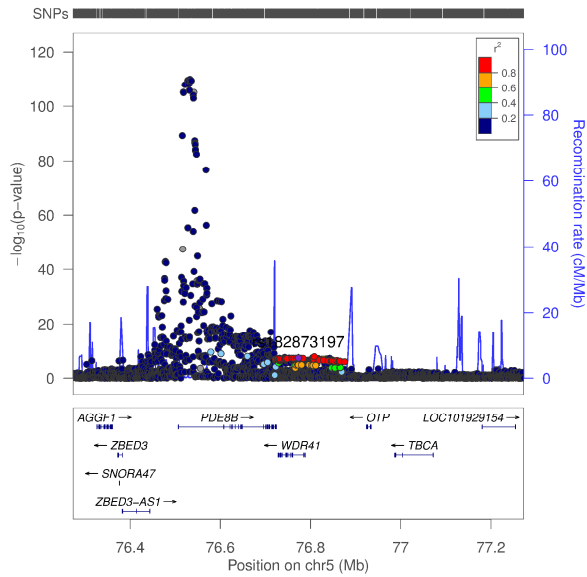
Overview of the workflow of the project showing its major sub-analyses.

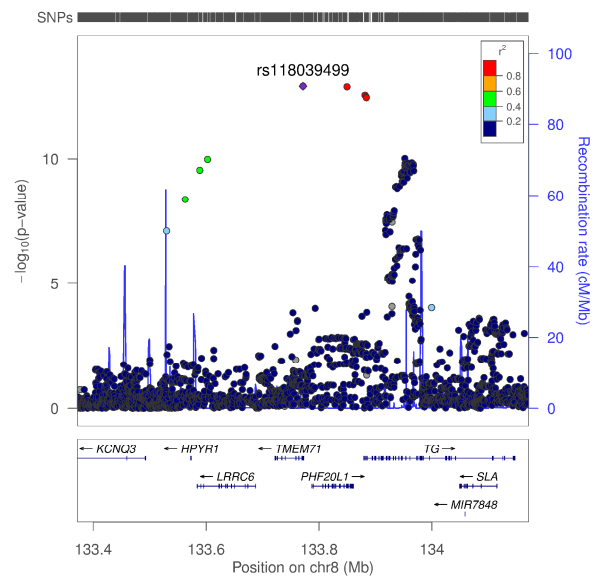
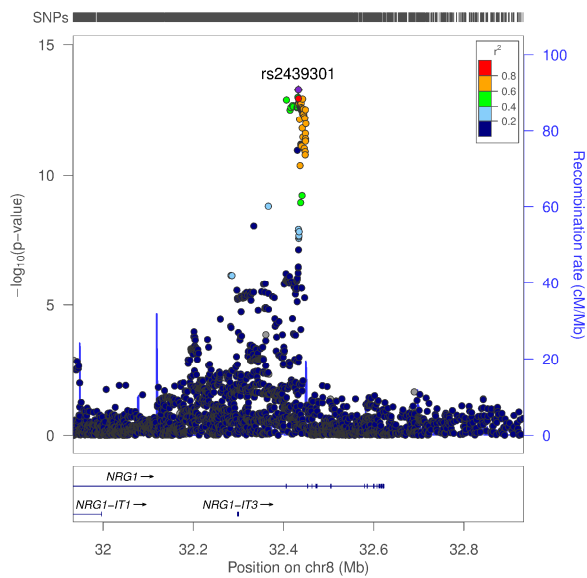
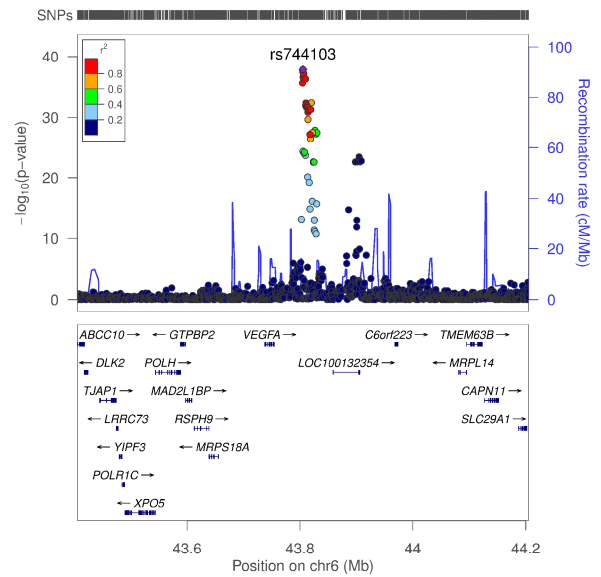
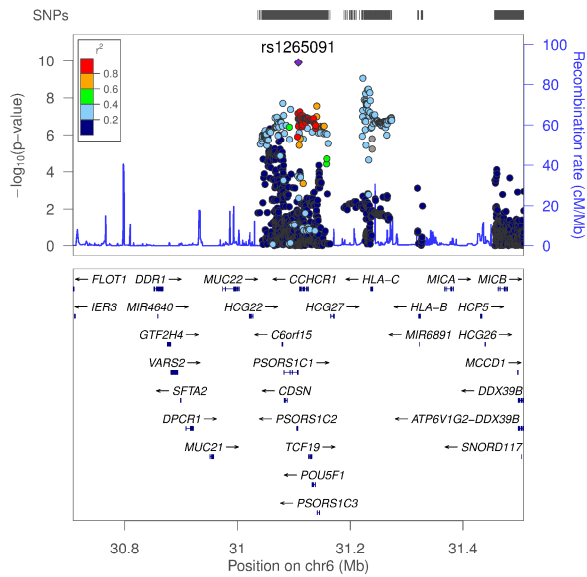
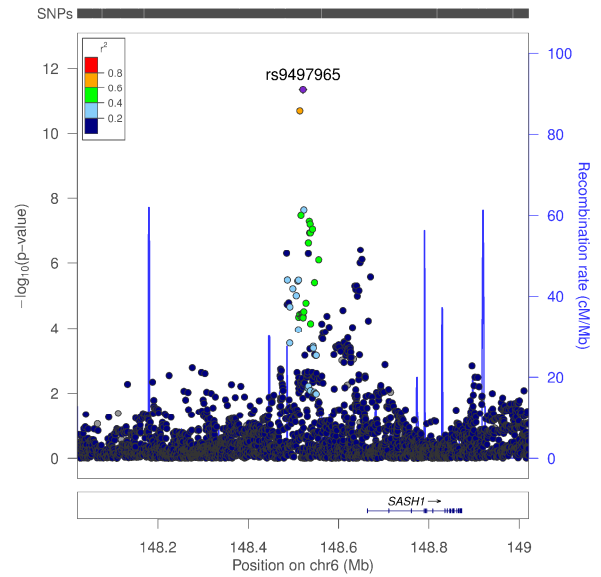
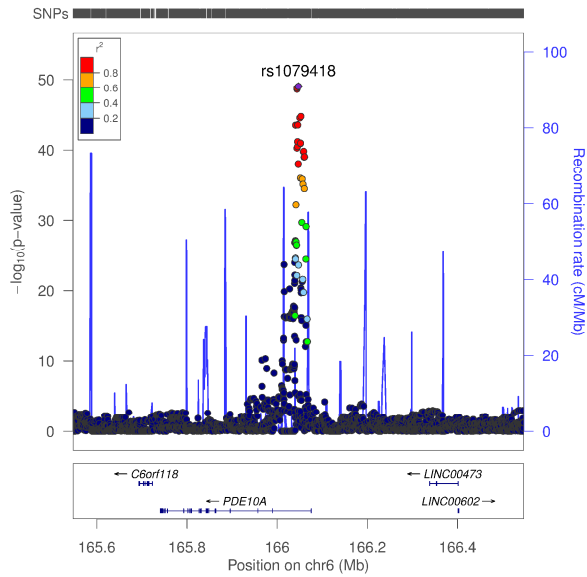
Supplementary Figure 2: Regional association plots for TSH

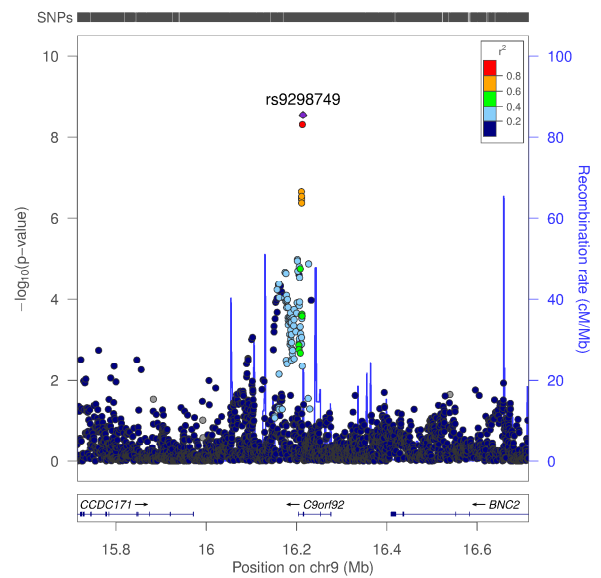
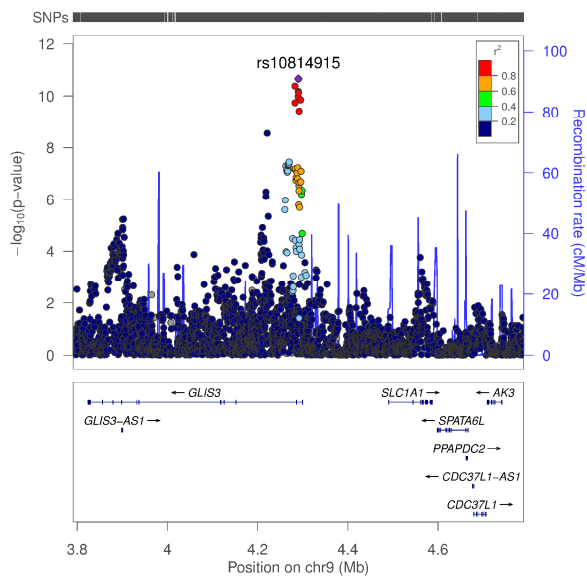
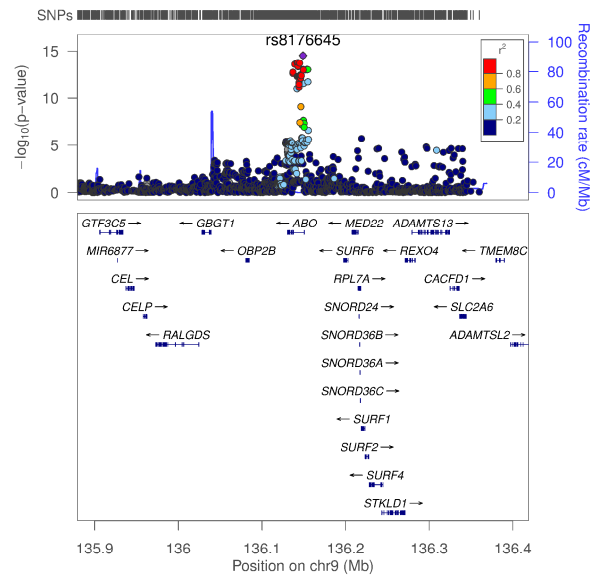
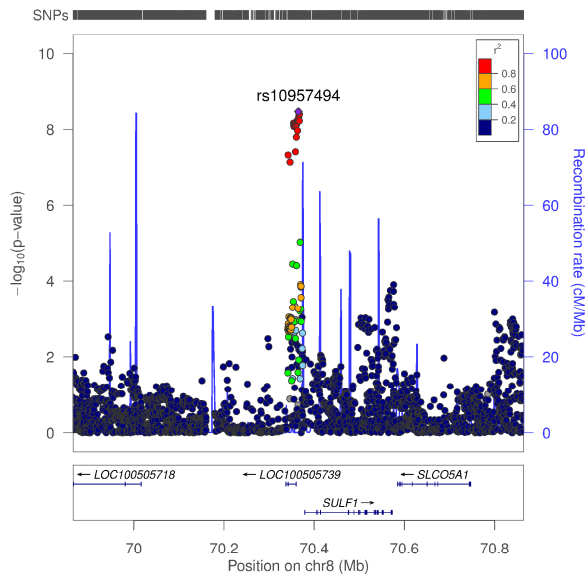
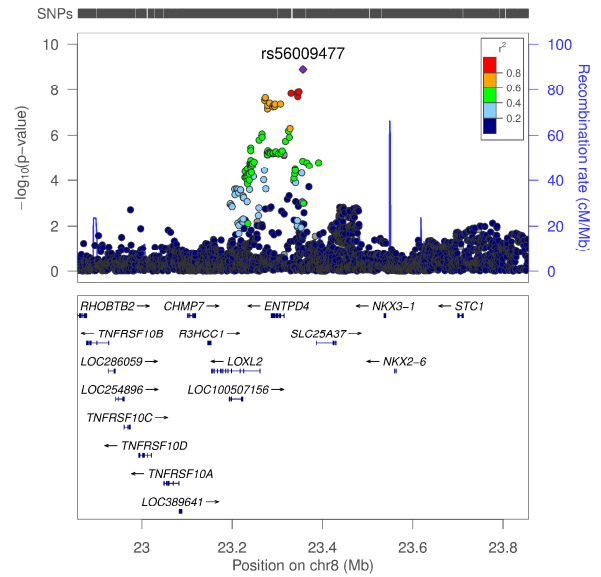
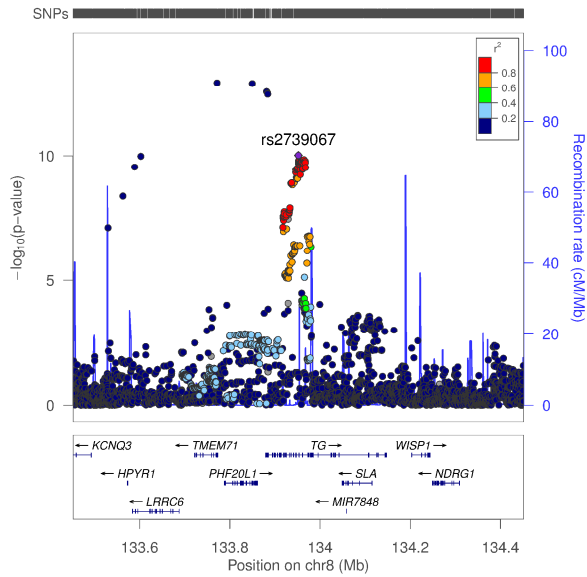


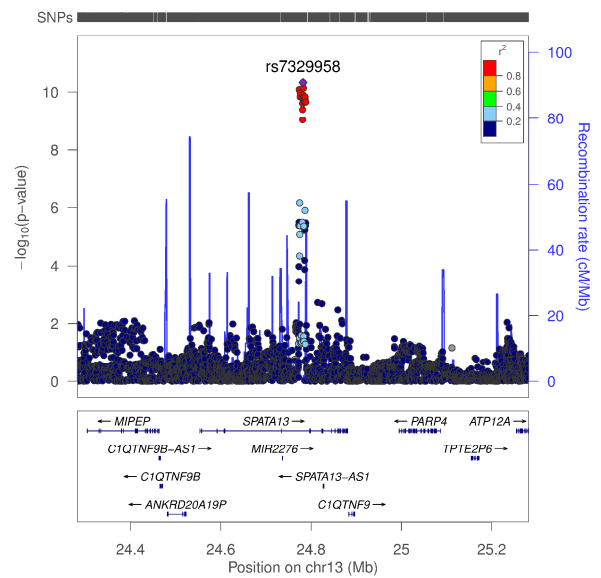
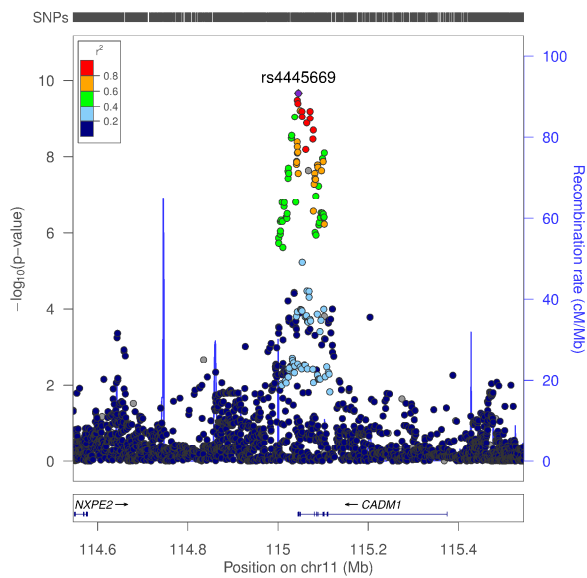
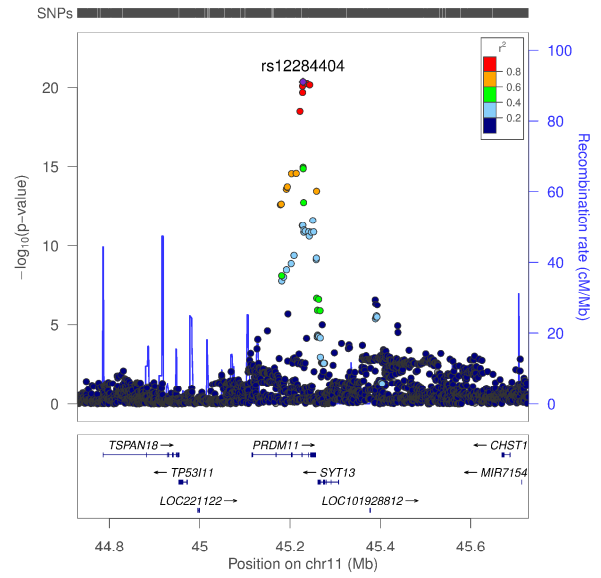
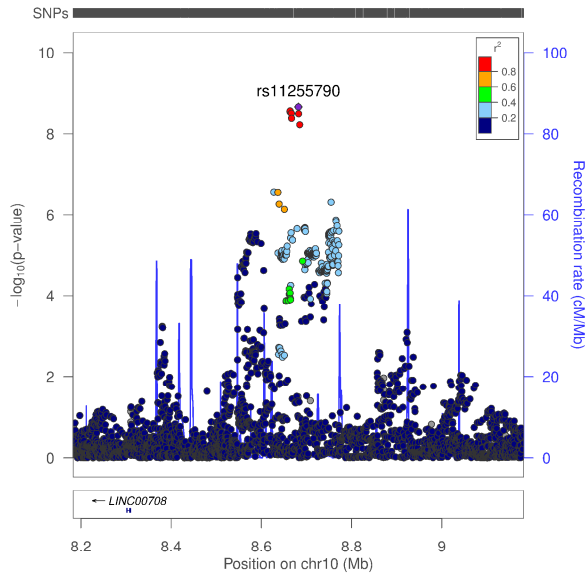
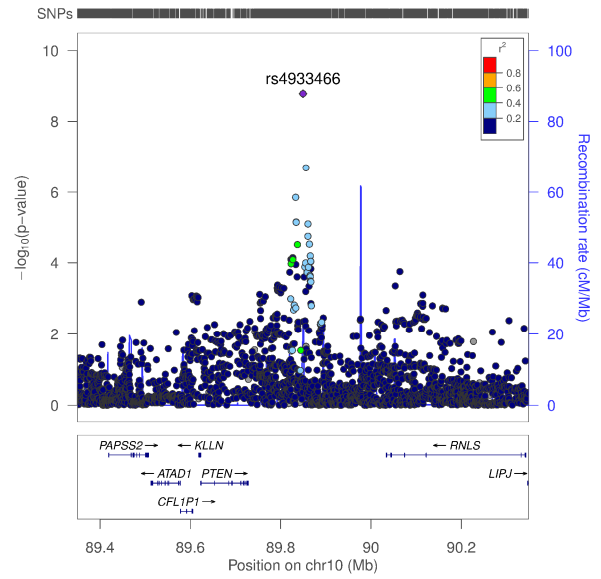
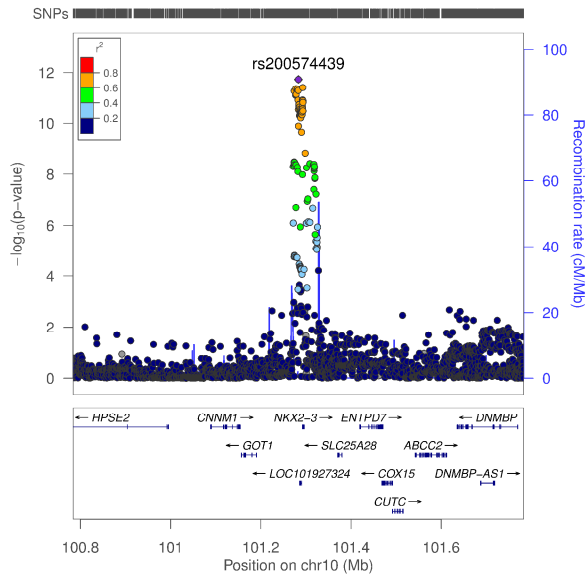


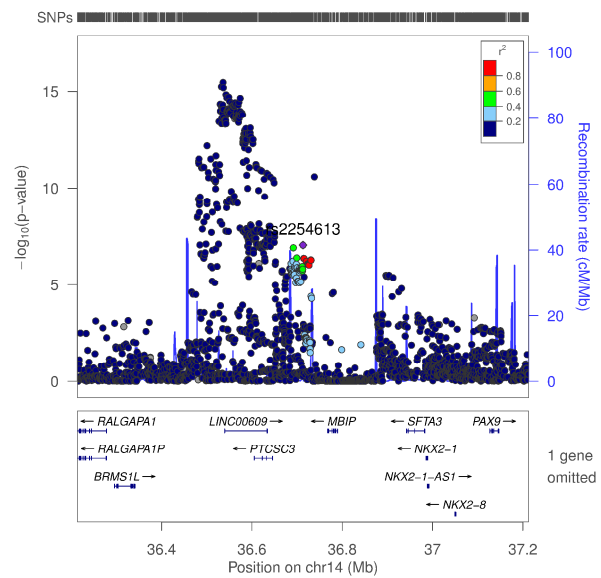
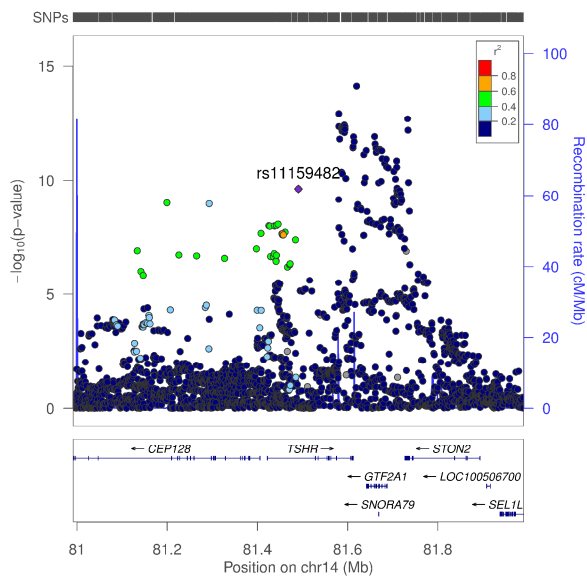
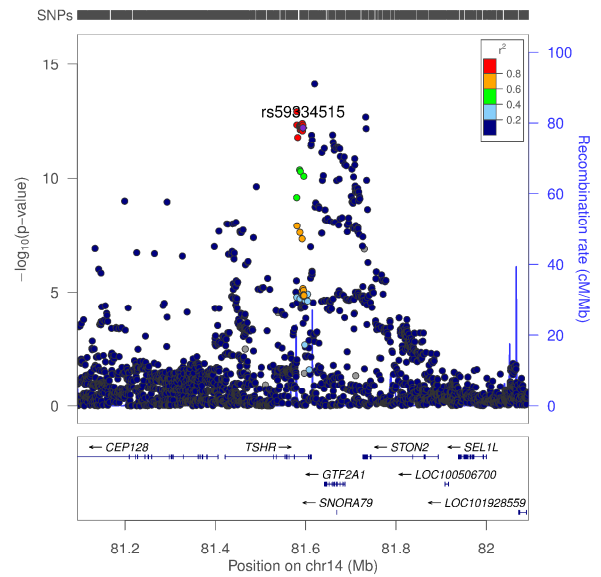
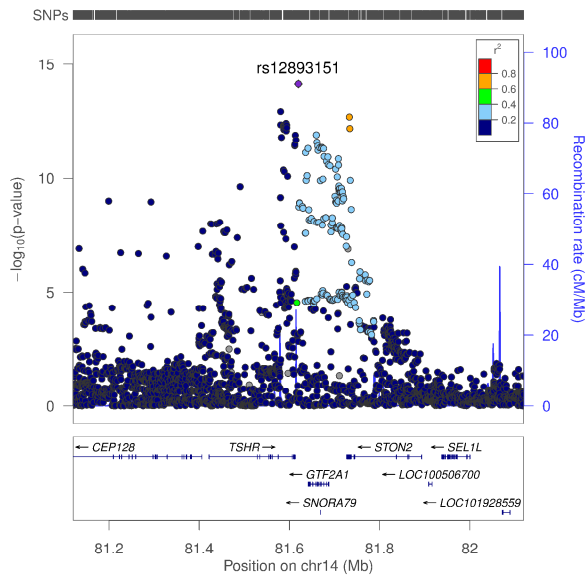
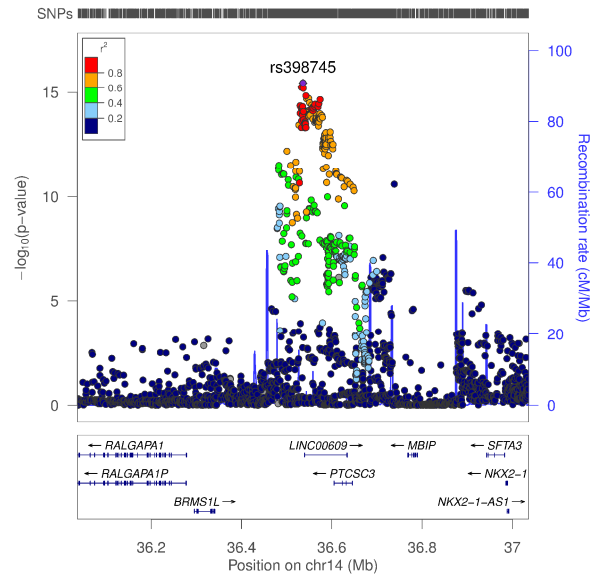
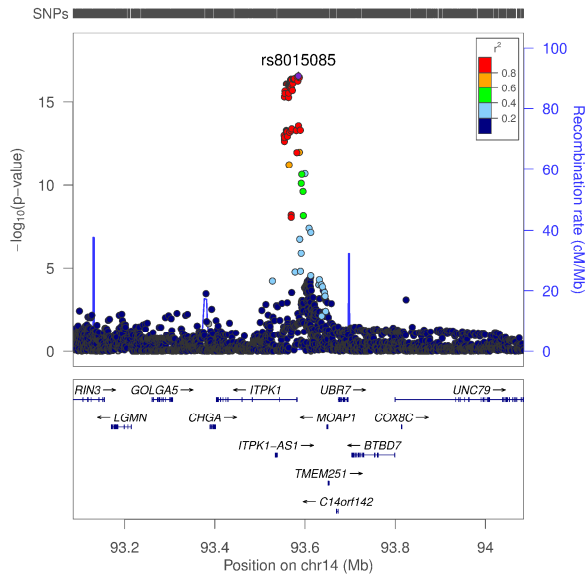


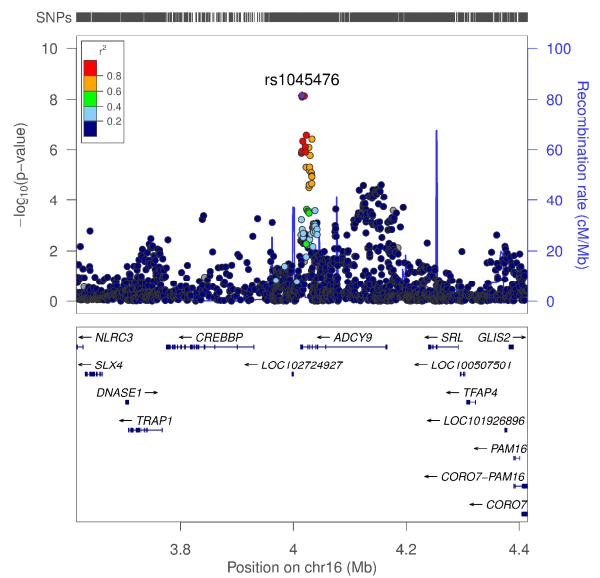
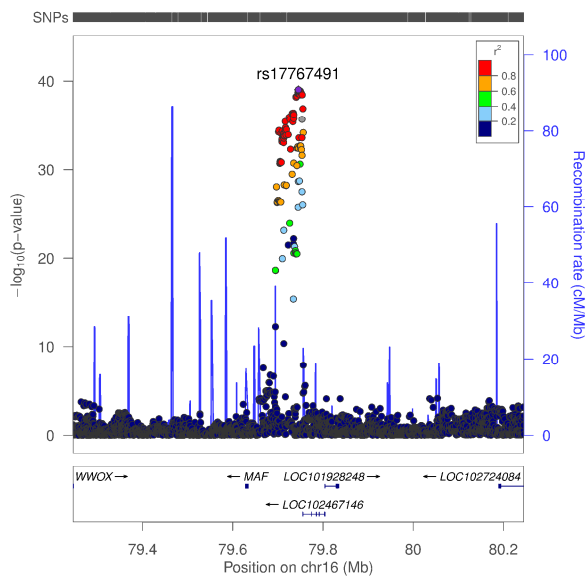
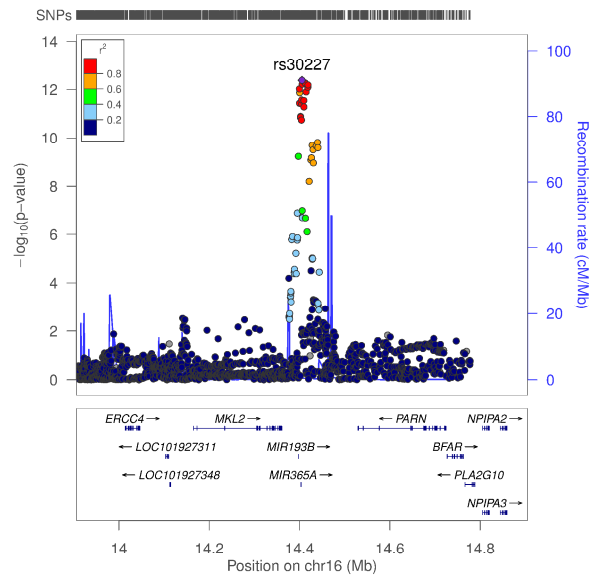
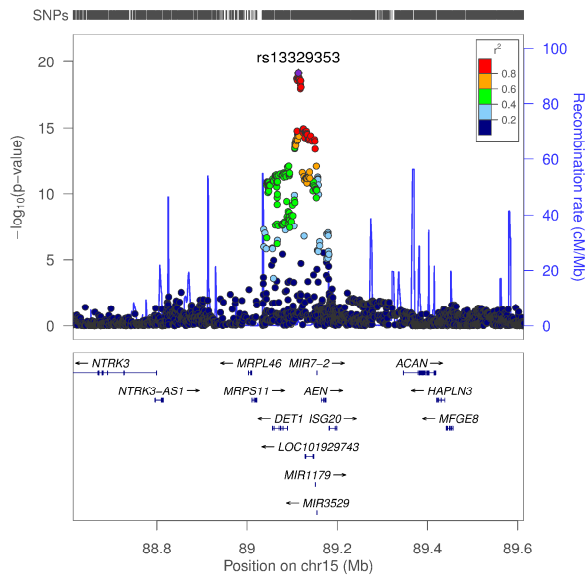
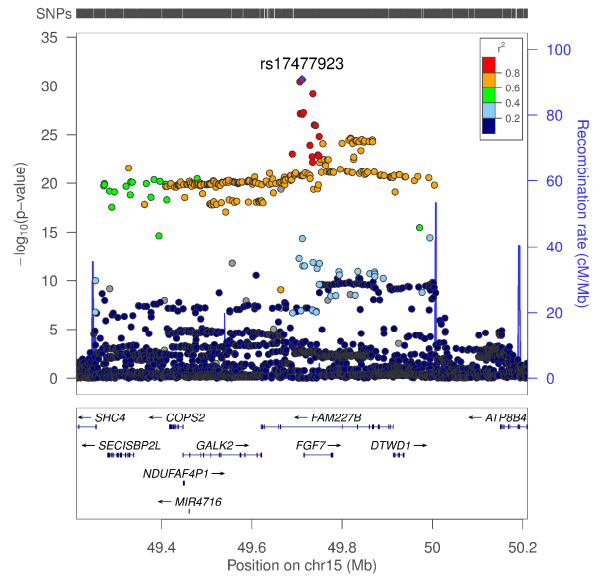
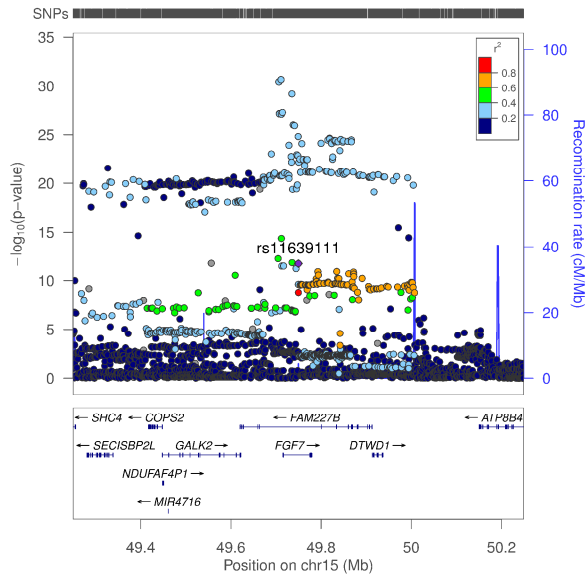


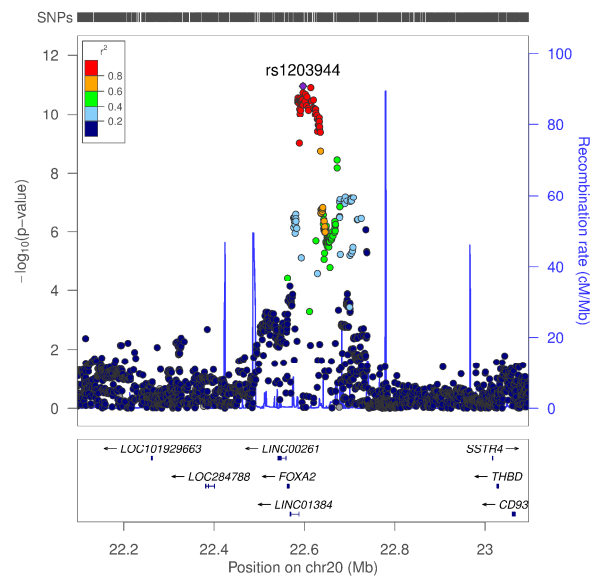
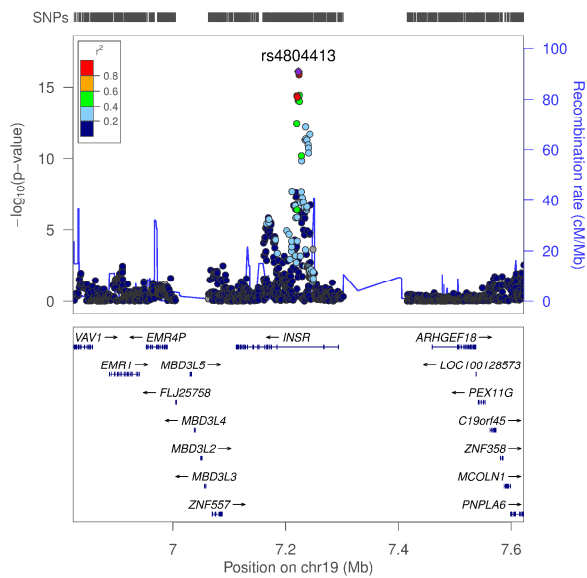
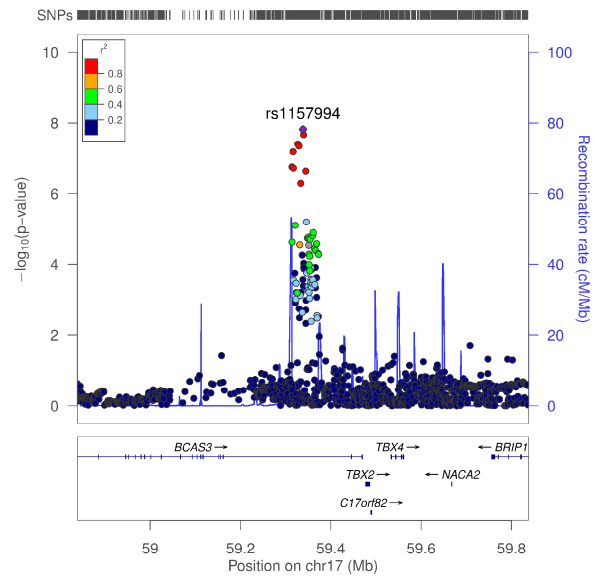
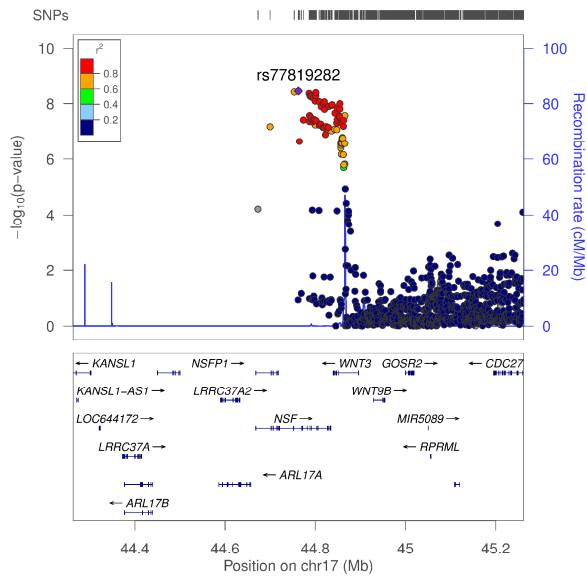
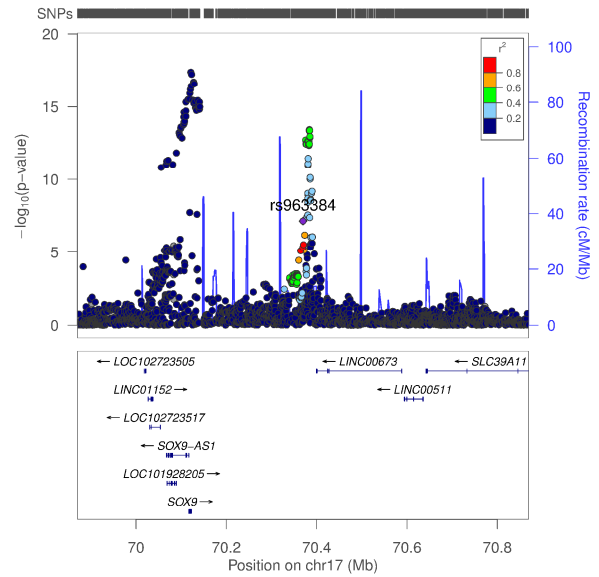
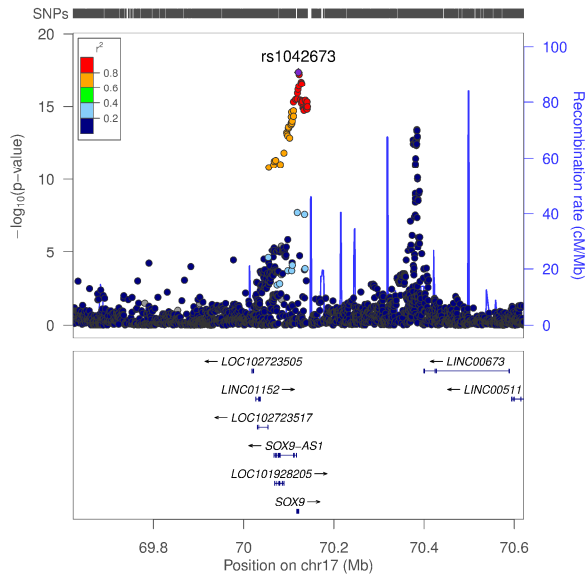


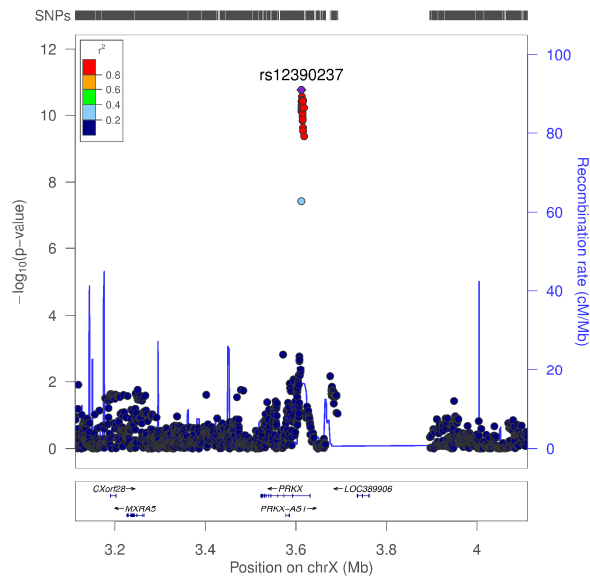






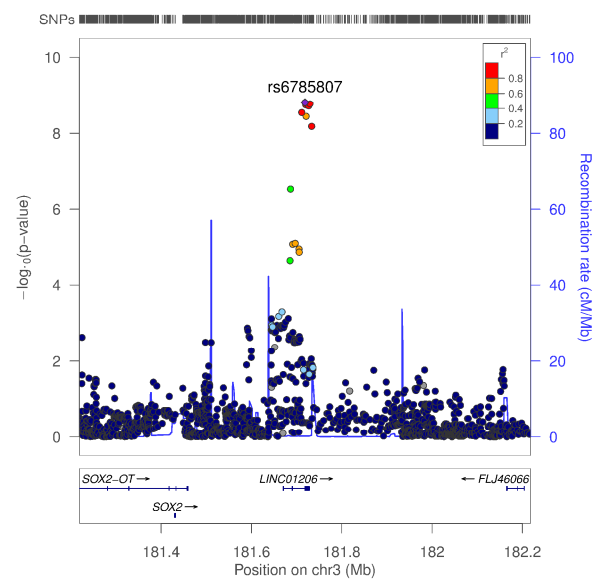
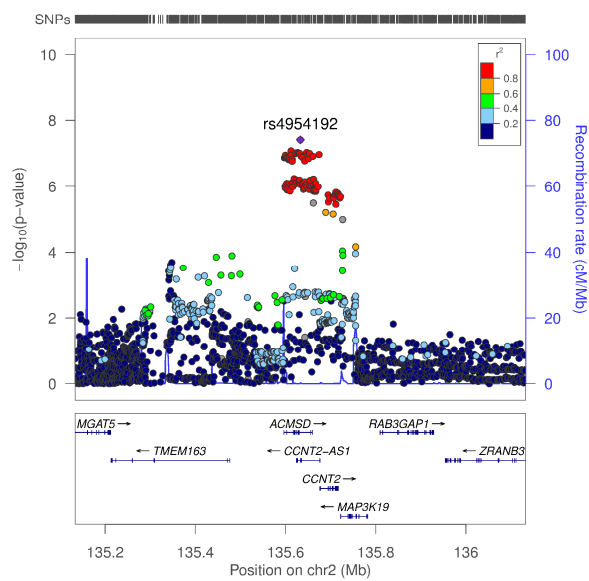
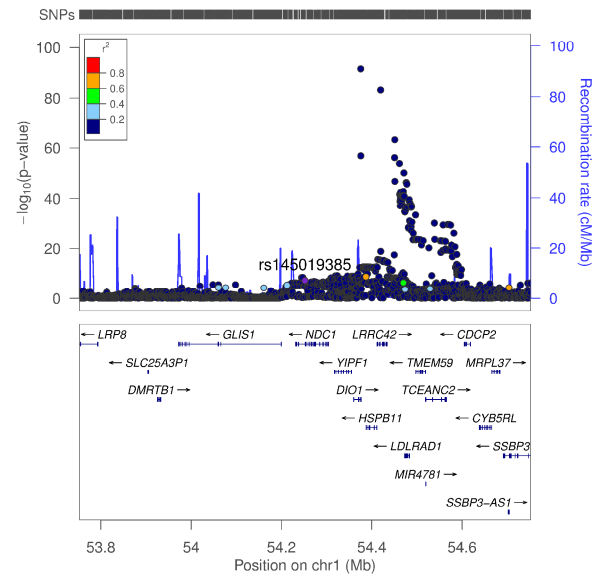
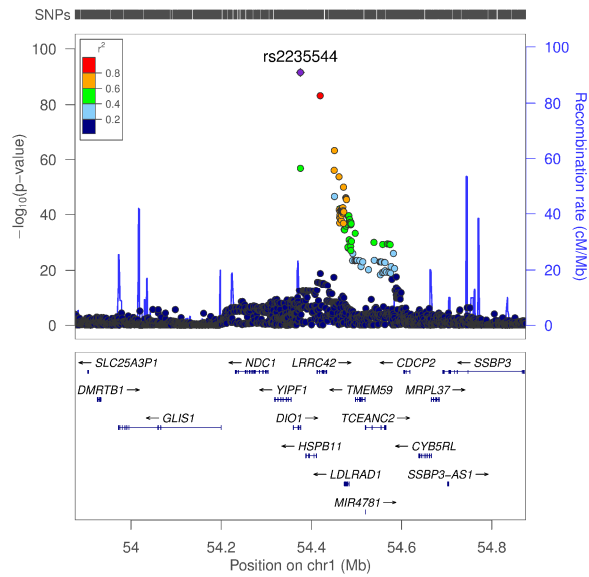
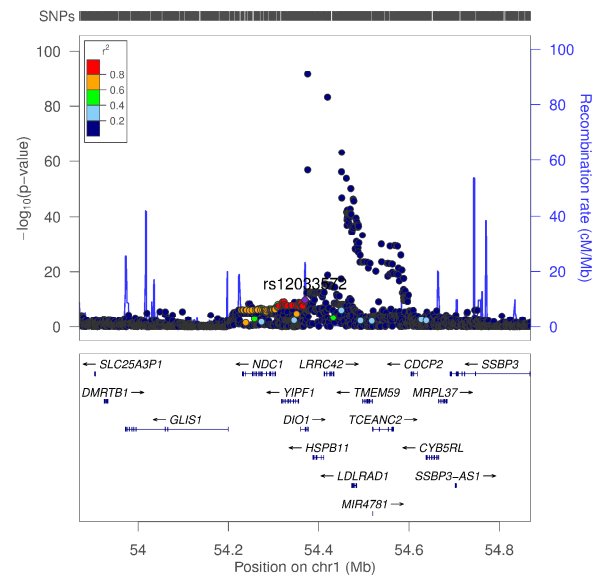
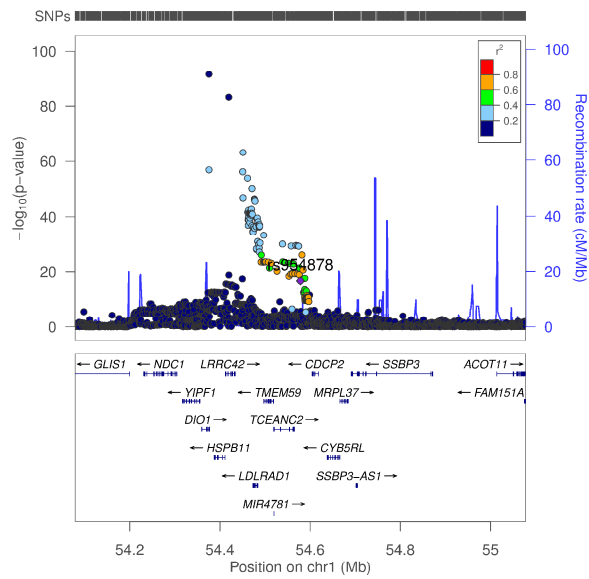


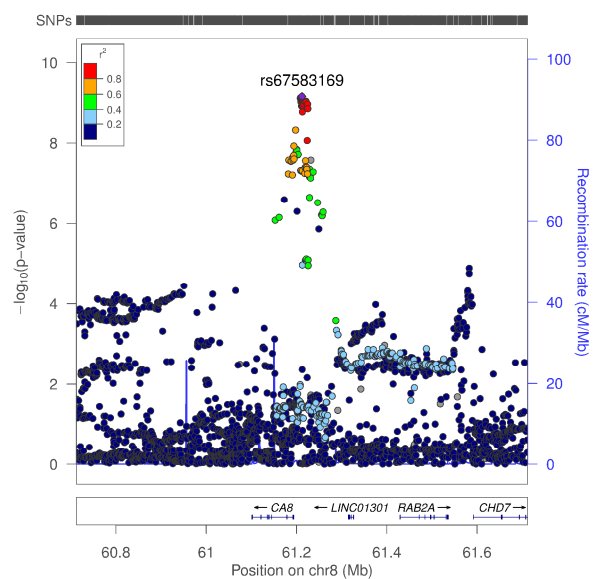
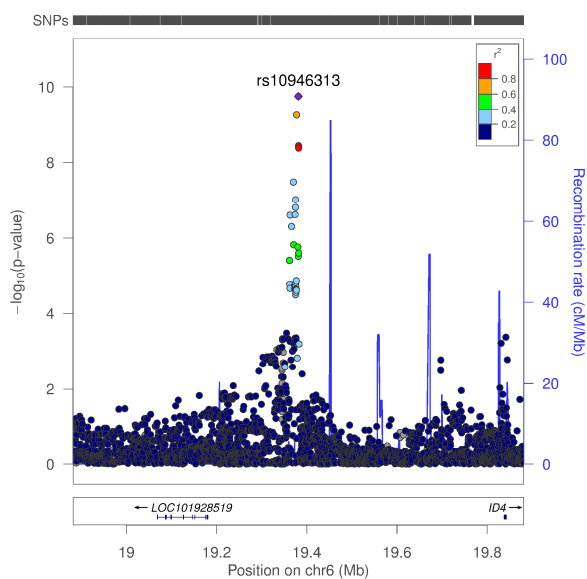
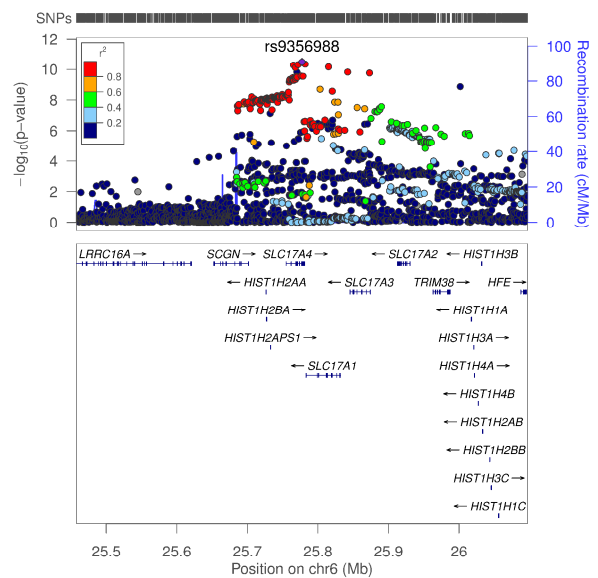
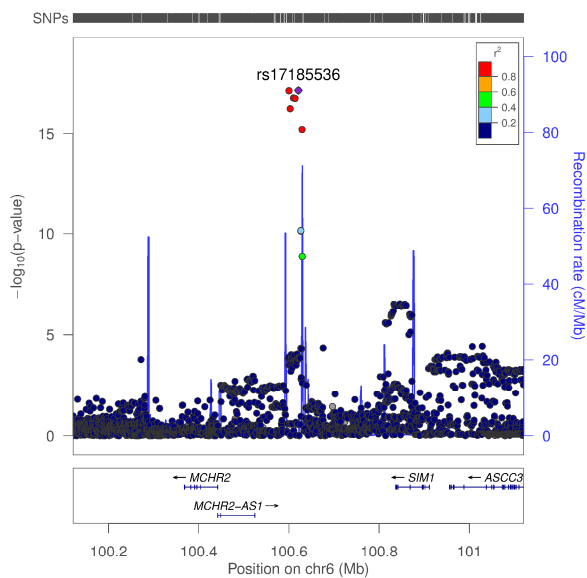
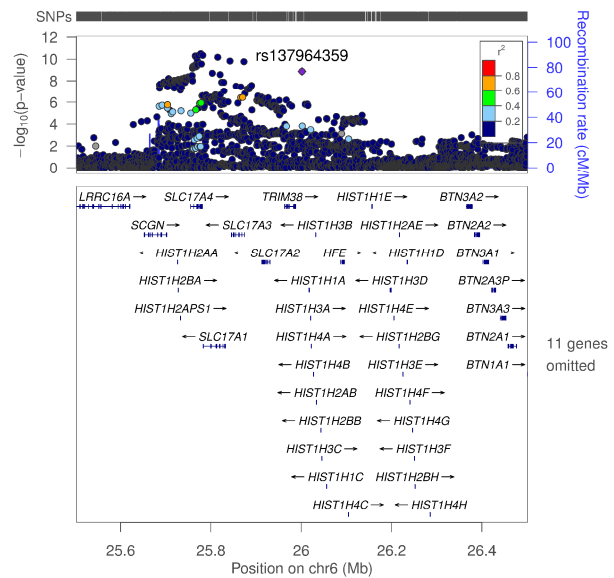
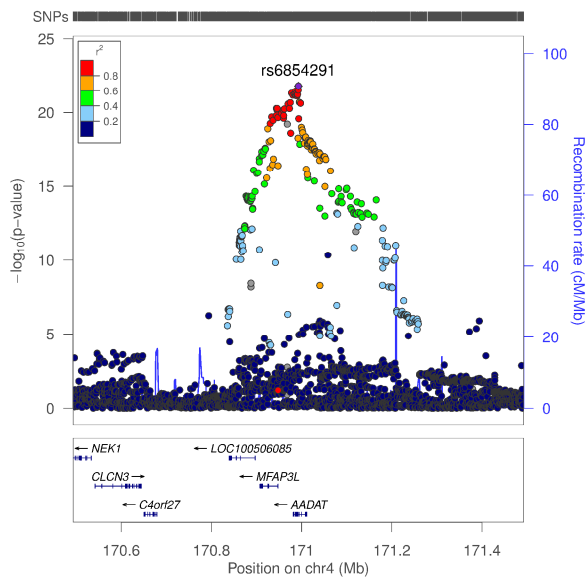


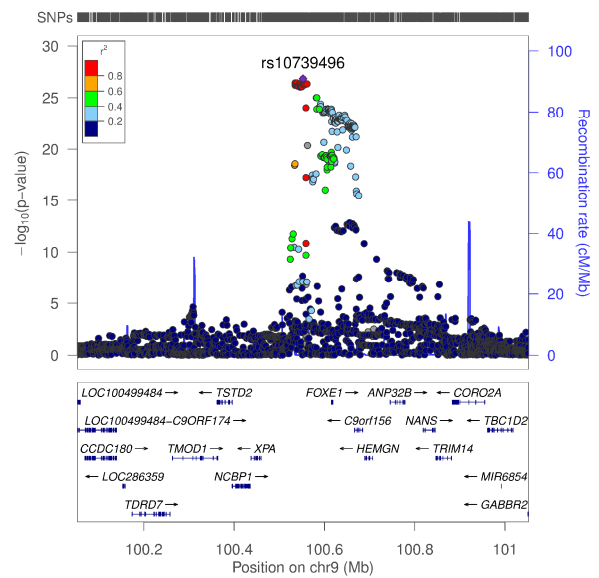
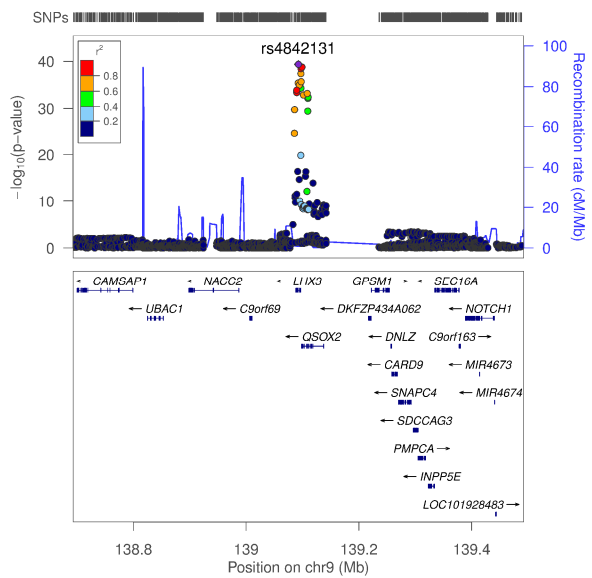
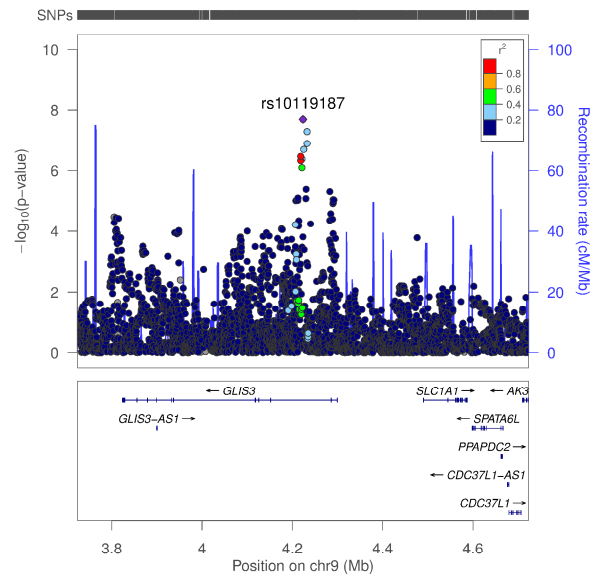
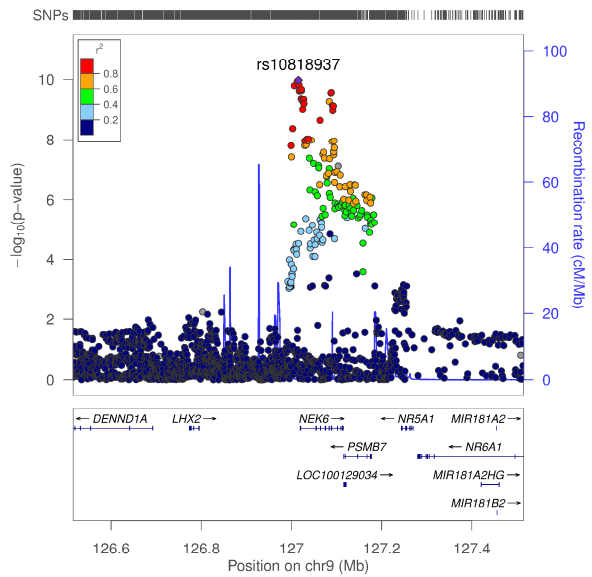
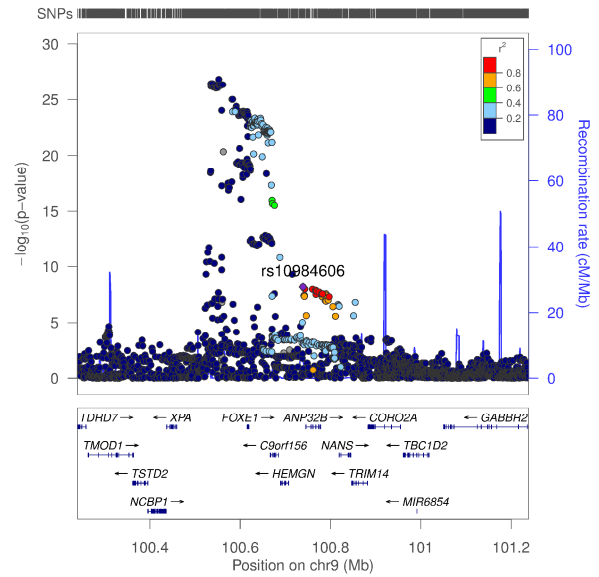
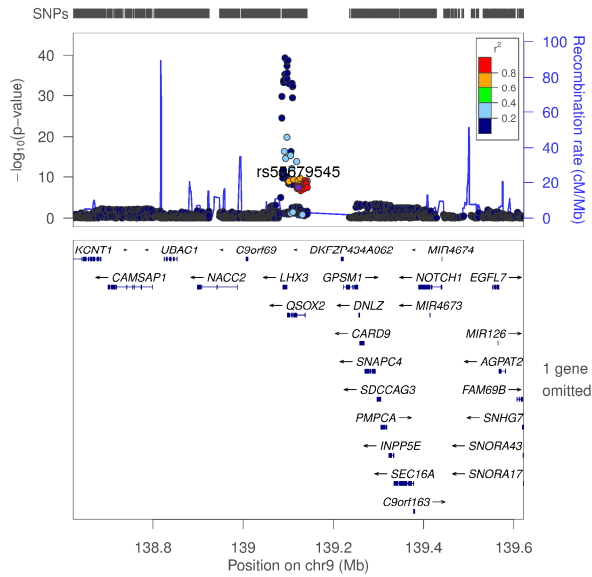


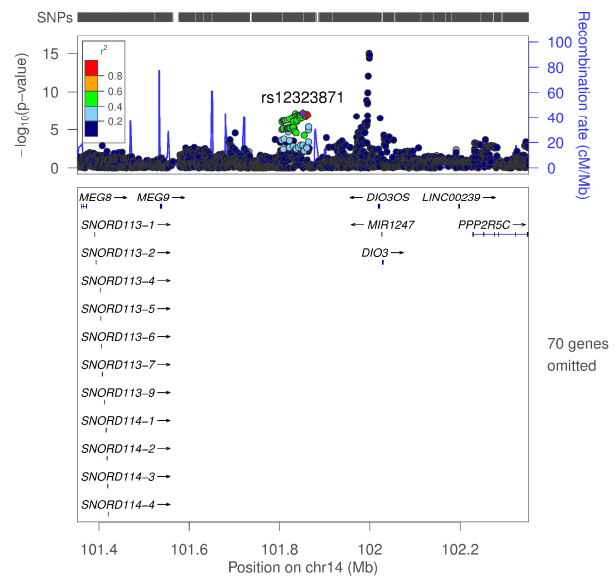
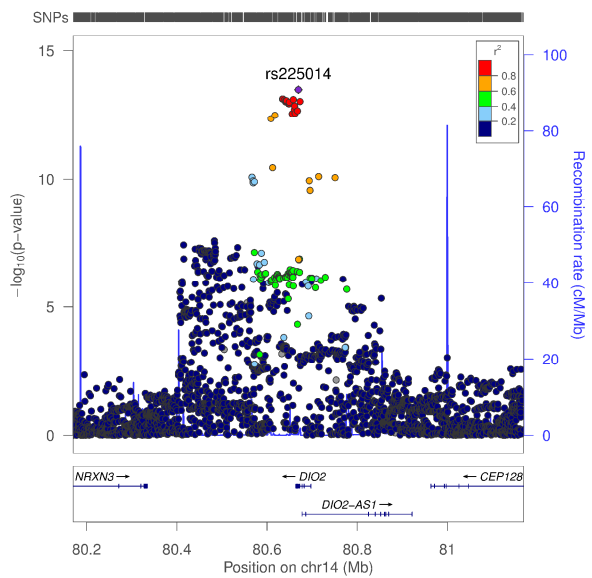
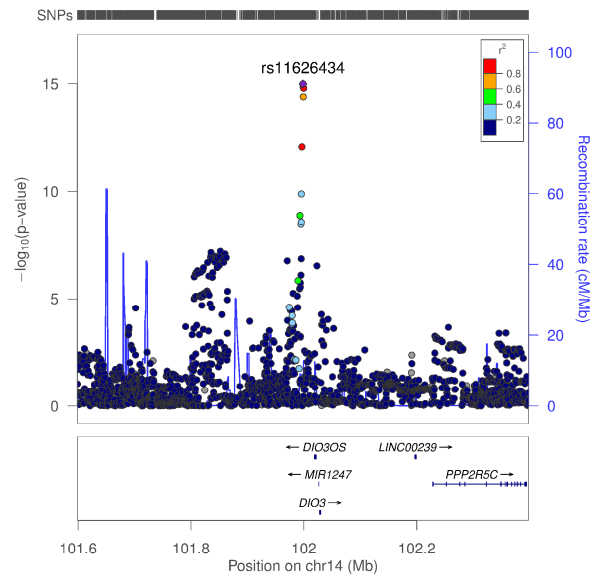
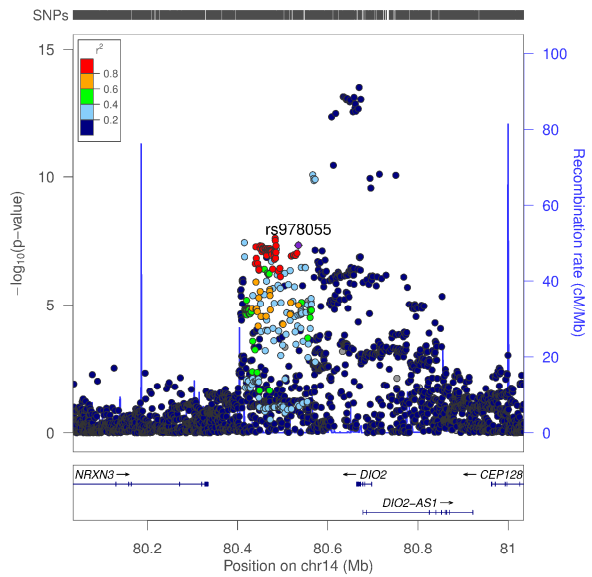
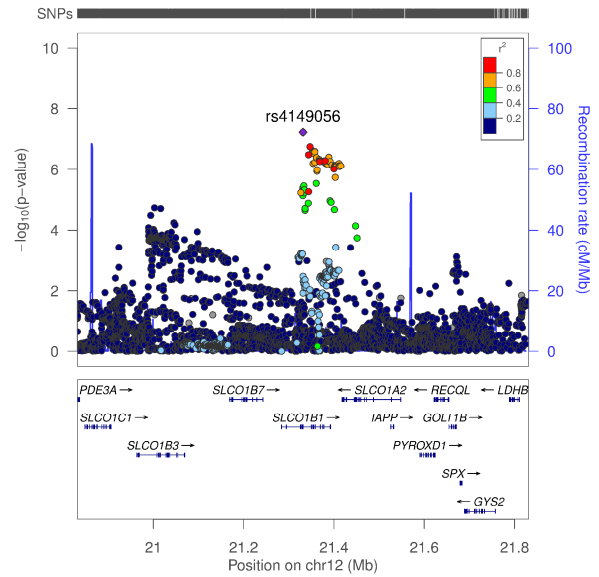
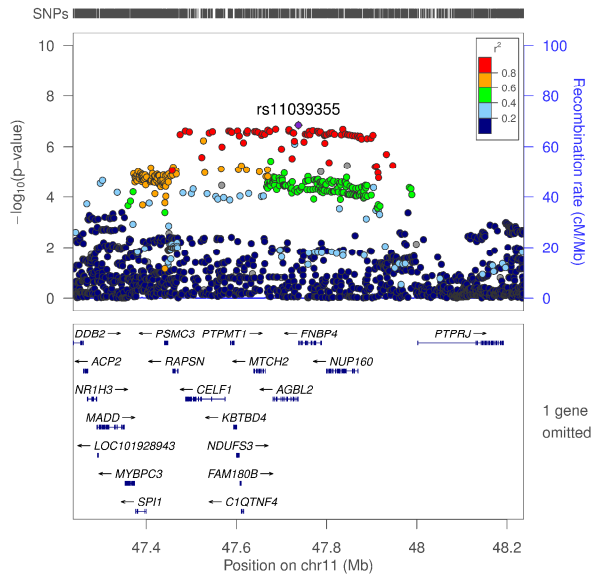
Regional association plots are shown for all genome-wide significant independent SNPs after the final stage meta-analyses. Correlation with the index SNP is estimated based on the 1000 Genomes reference samples. Plots were generated using the stand-alone version of LocusZoom⁵. Genetic positions refer to GRCh37/hg19 coordinates.

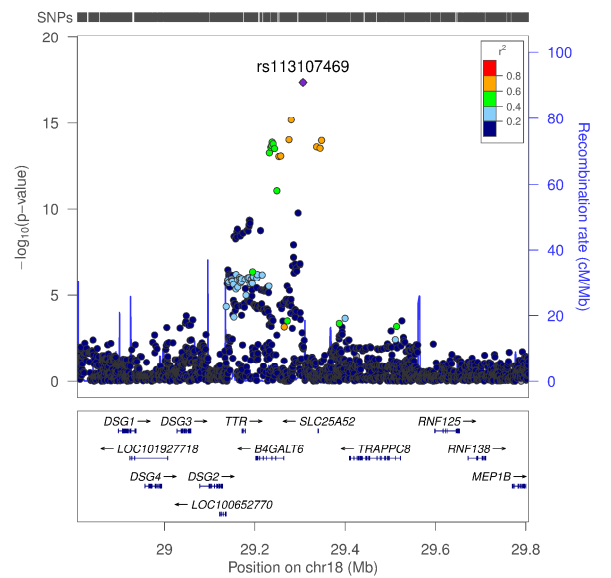
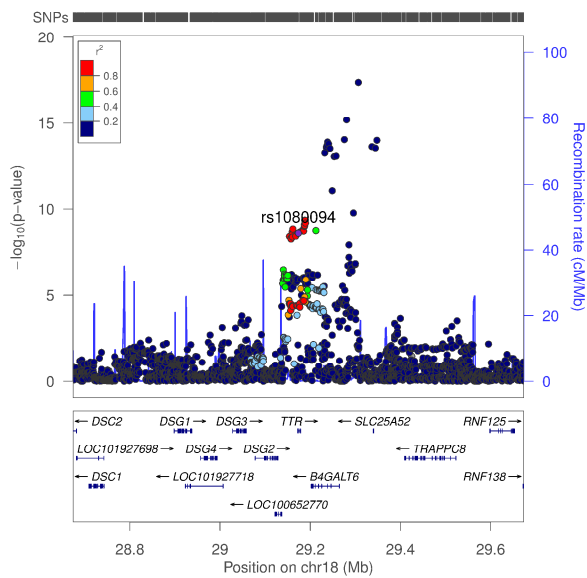
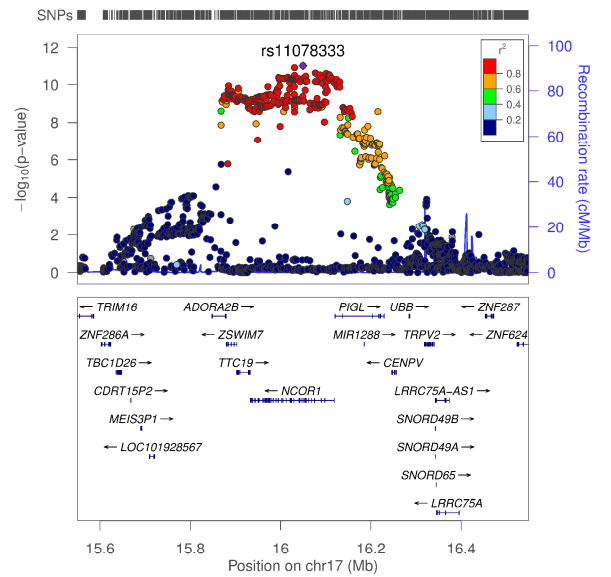
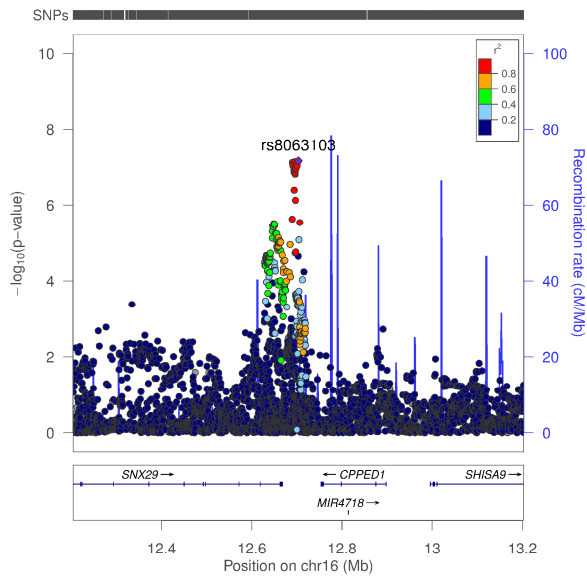
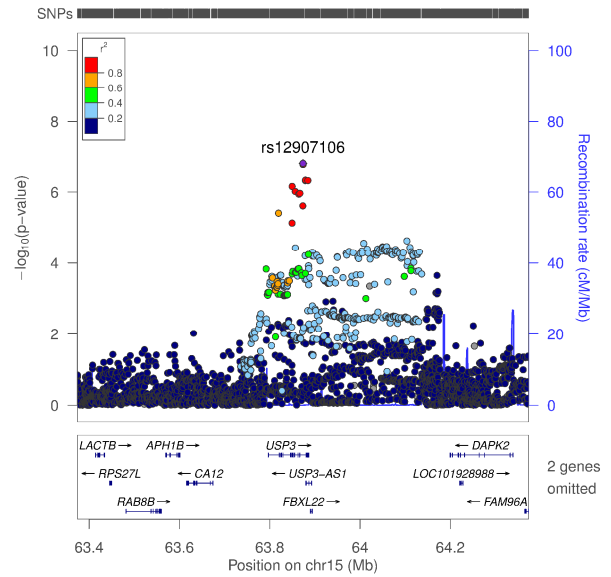
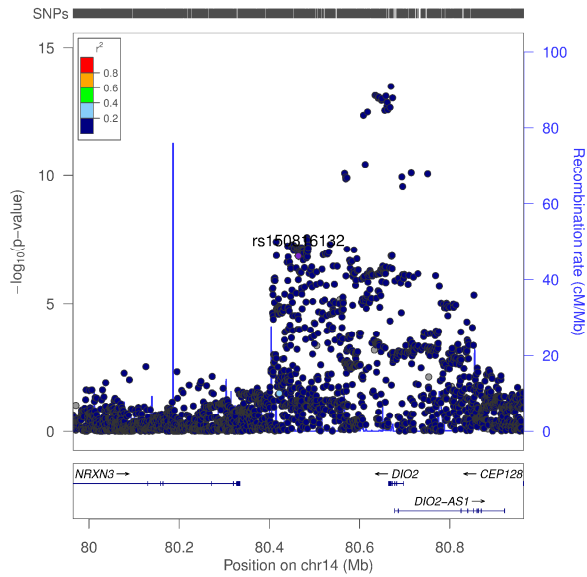
Supplementary Figure 3: Regional association plots for FT4

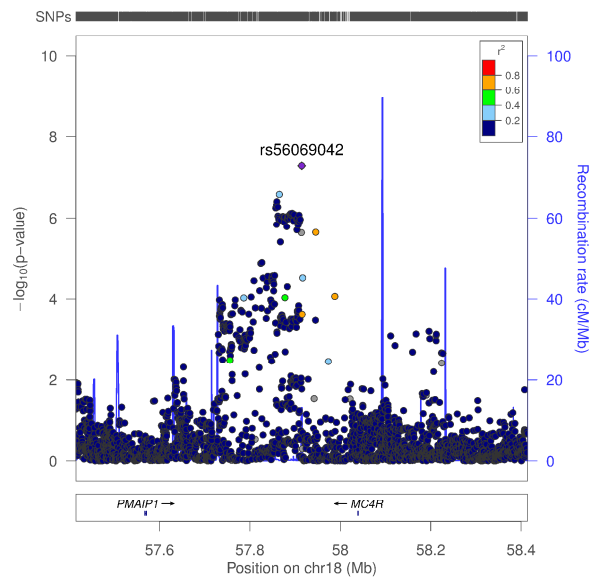








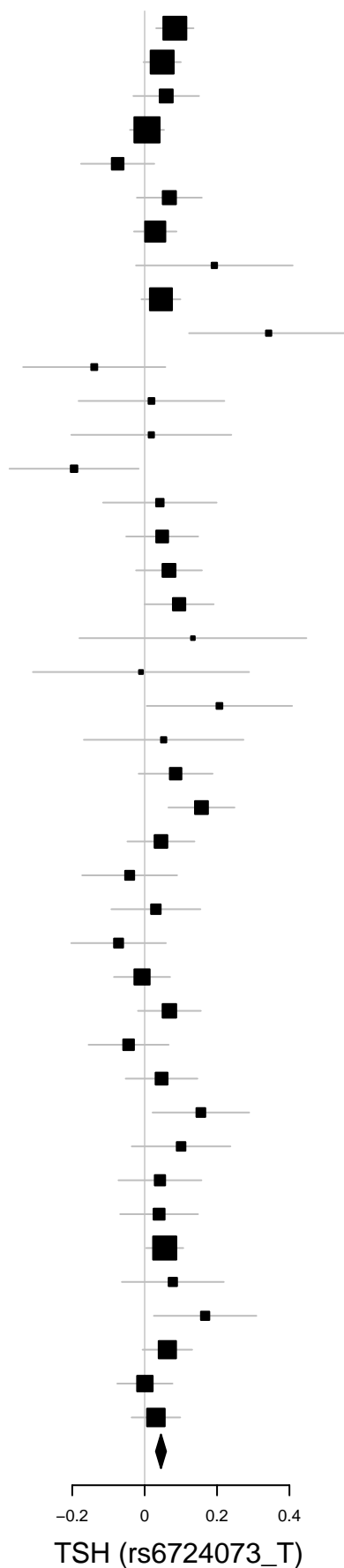


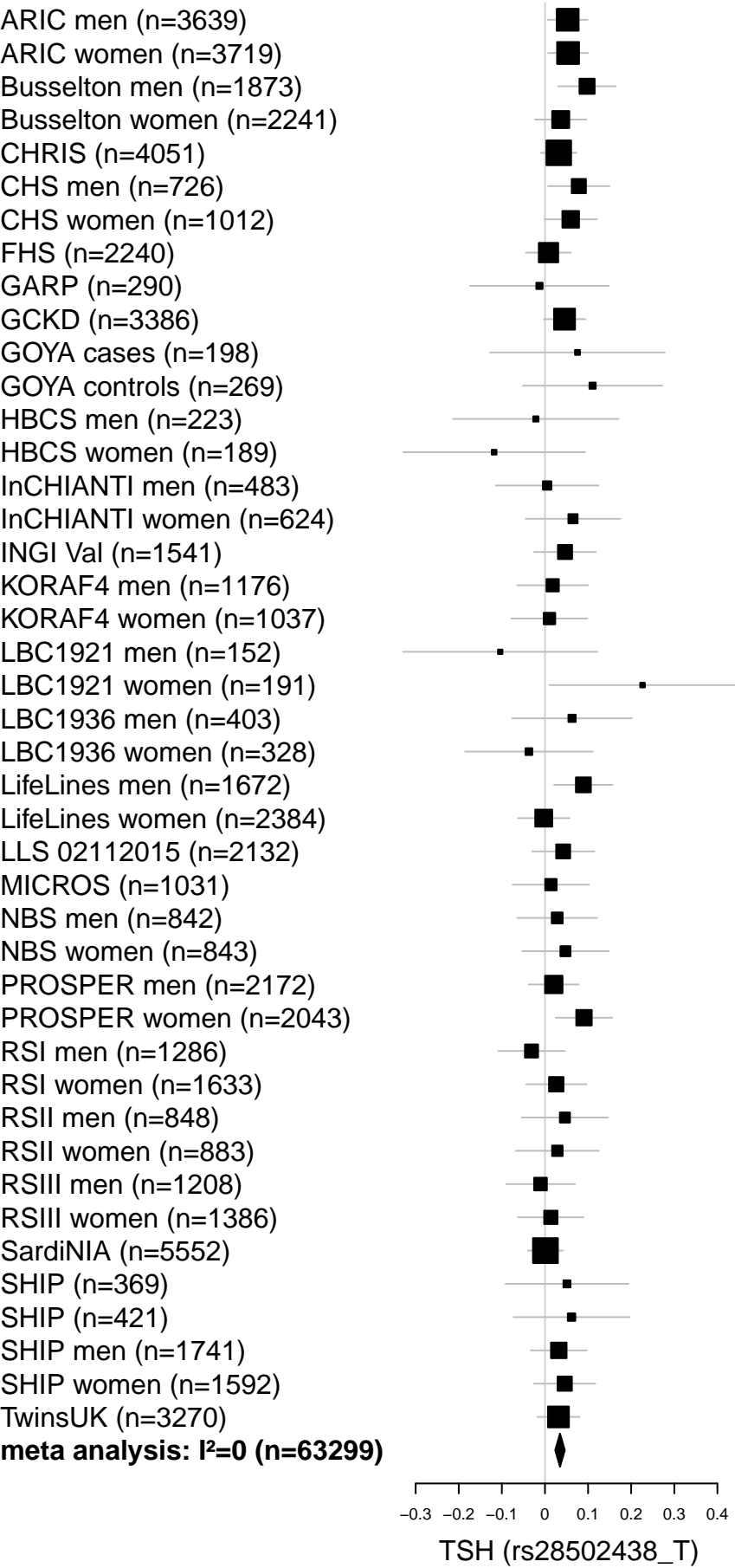


Regional association plots are shown for all genome-wide significant independent SNPs after the final stage meta-analyses. Correlation with the index SNP is estimated based on the 1000 Genomes reference samples. Plots were generated using the stand-alone version of LocusZoom⁵. Genetic positions refer to GRCh37/hg19 coordinates.

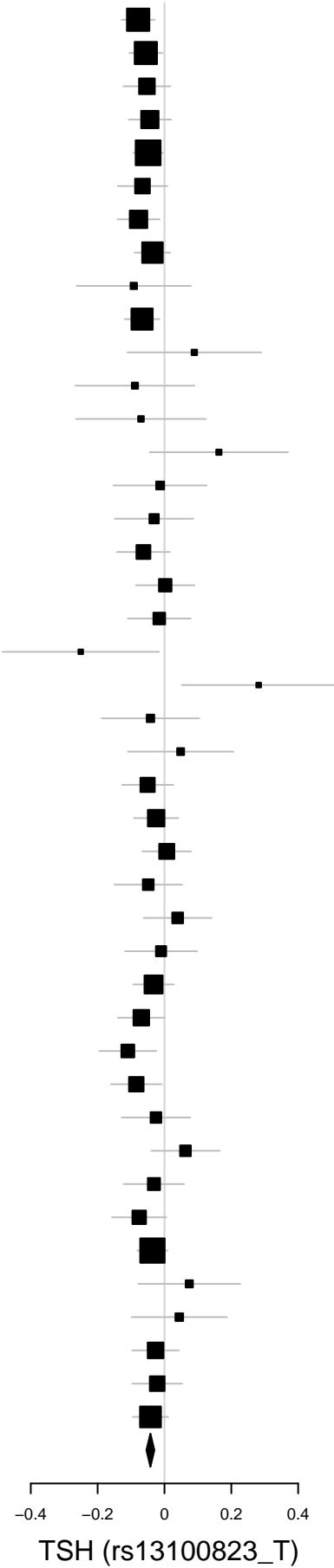
Supplementary Figure 4: Forest plots for TSH

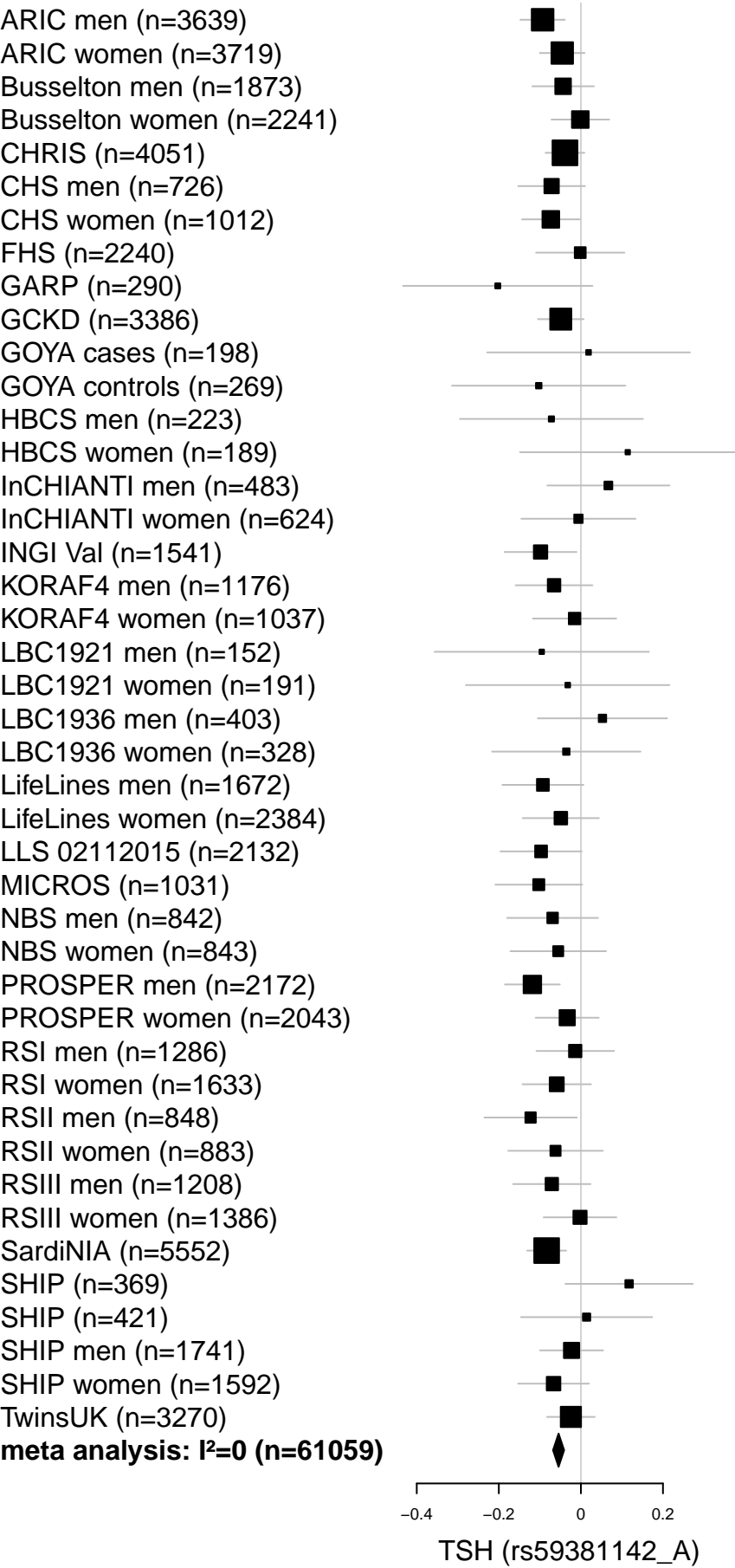
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 ARIC women (n=3719)
 Busselton men (n=1873)
 CHRIS (n=4051)
 CHS men (n=726)
 CHS women (n=1012)
 FHS (n=2240)
 GARP (n=290)
 GCKD (n=3386)
 GOYA cases (n=198)
 GOYA controls (n=269)
 HBCS men (n=223)
 HBCS women (n=189)
 InCHIANTI men (n=483)
 InCHIANTI women (n=624)
 INGI Val (n=1541)
 KORAF4 men (n=1176)
 KORAF4 women (n=1037)
 LBC1921 men (n=152)
 LBC1921 women (n=191)
 LBC1936 men (n=403)
 LBC1936 women (n=328)
 LifeLines men (n=1672)
 LifeLines women (n=2384)
 LLS 02112015 (n=2132)
 MICROS (n=1031)
 NBS men (n=842)
 NBS women (n=843)
 PROSPER men (n=2172)
 PROSPER women (n=2043)
 RSI men (n=1286)
 RSI women (n=1633)
 RSII men (n=848)
 RSII women (n=883)
 RSIII men (n=1208)
 RSIII women (n=1386)
 SardiNIA (n=5552)
 SHIP (n=369)
 SHIP (n=421)
 SHIP men (n=1741)
 SHIP women (n=1592)
 TwinsUK (n=3270)
meta analysis: $I^2=29.4$ (n=61058)



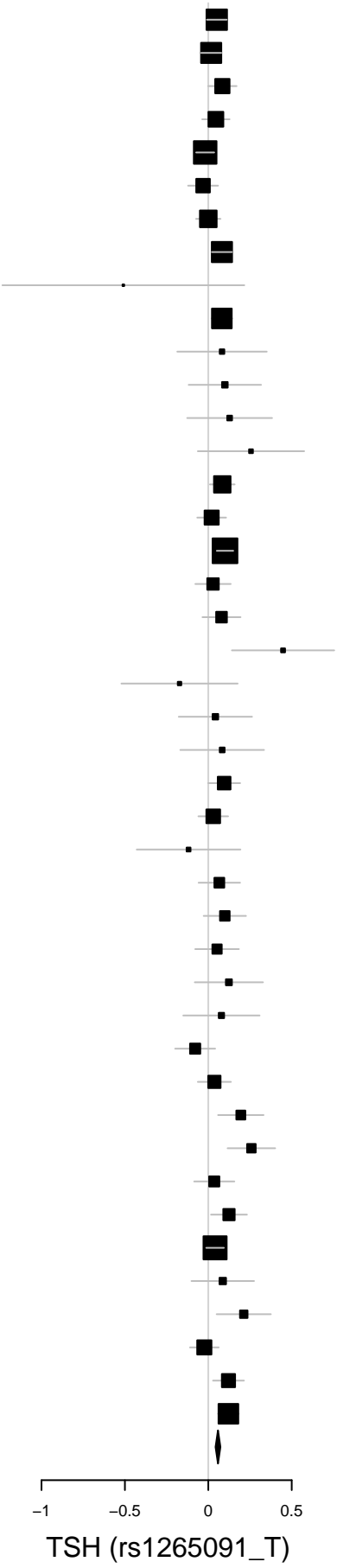


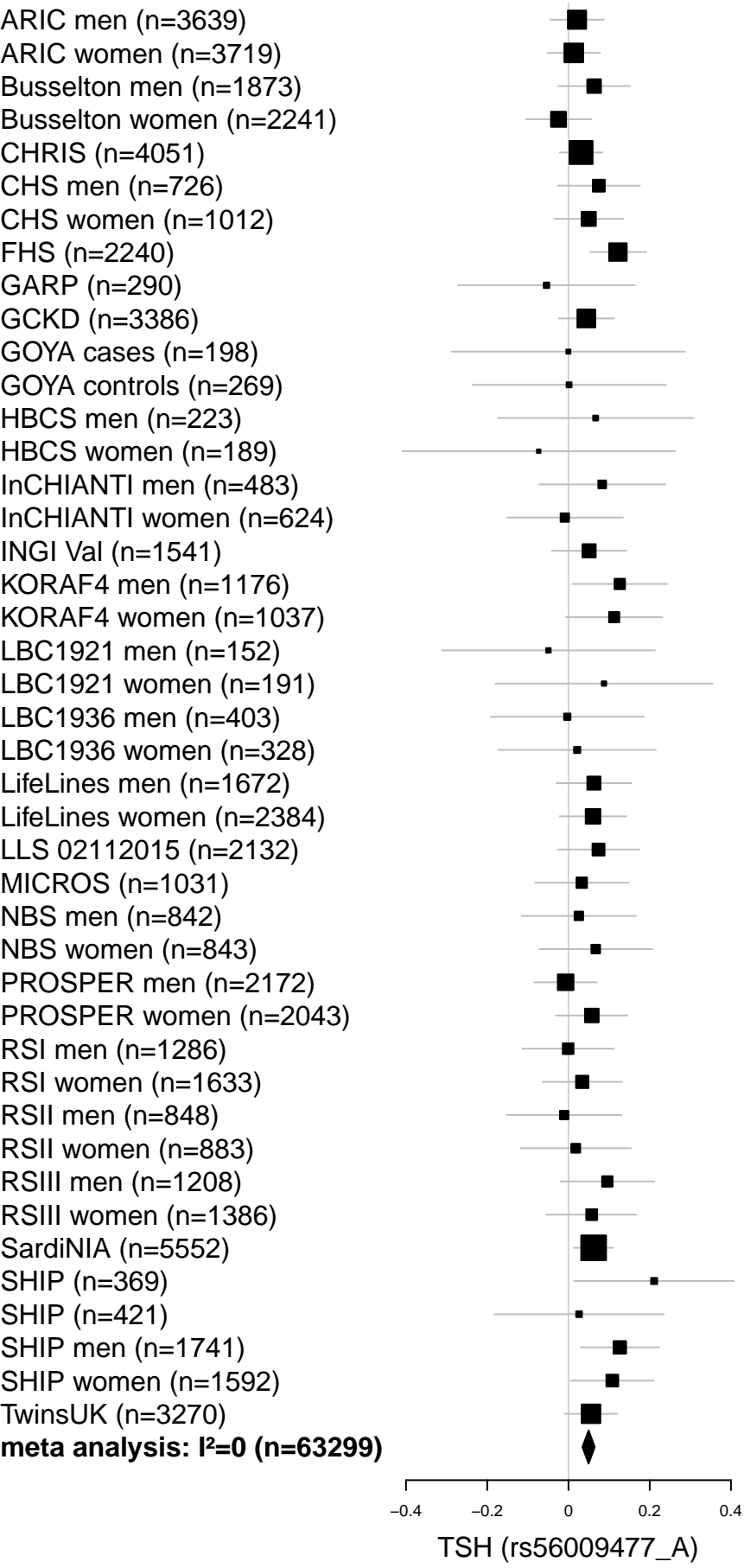
ARIC men (n=3639)
 ARIC women (n=3719)
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 Busselton women (n=2241)
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 CHS men (n=726)
 CHS women (n=1012)
 FHS (n=2240)
 GARP (n=290)
 GCKD (n=3386)
 GOYA cases (n=198)
 GOYA controls (n=269)
 HBCS men (n=223)
 HBCS women (n=189)
 InCHIANTI men (n=483)
 InCHIANTI women (n=624)
 INGI Val (n=1541)
 KORAF4 men (n=1176)
 KORAF4 women (n=1037)
 LBC1921 men (n=152)
 LBC1921 women (n=191)
 LBC1936 men (n=403)
 LBC1936 women (n=328)
 LifeLines men (n=1672)
 LifeLines women (n=2384)
 LLS 02112015 (n=2132)
 MICROS (n=1031)
 NBS men (n=842)
 NBS women (n=843)
 PROSPER men (n=2172)
 PROSPER women (n=2043)
 RSI men (n=1286)
 RSI women (n=1633)
 RSII men (n=848)
 RSII women (n=883)
 RSIII men (n=1208)
 RSIII women (n=1386)
 SardiNIA (n=5552)
 SHIP (n=369)
 SHIP (n=421)
 SHIP men (n=1741)
 SHIP women (n=1592)
 TwinsUK (n=3270)
meta analysis: I²=2.1 (n=63299)



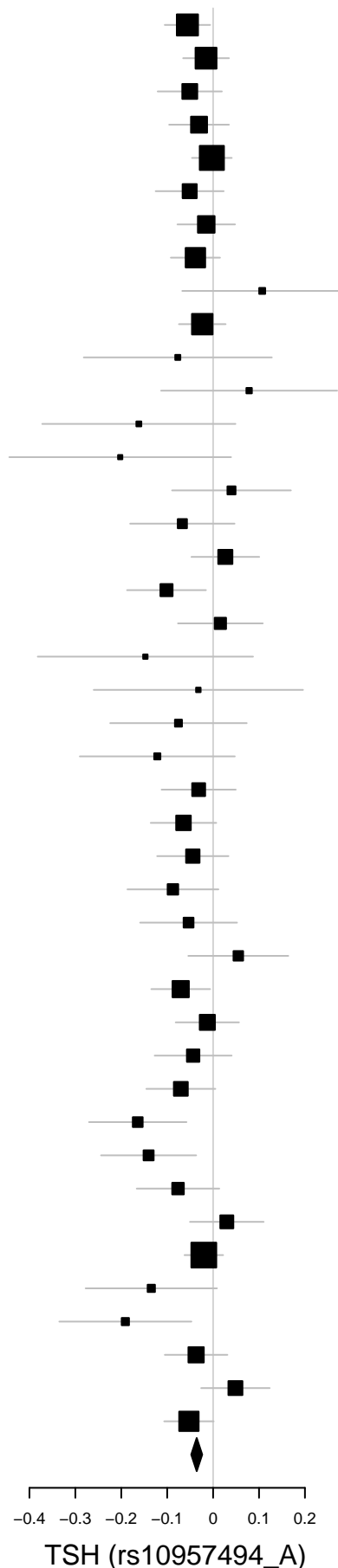


ARIC men (n=3639)
 ARIC women (n=3719)
 Busselton men (n=1873)
 Busselton women (n=2241)
 CHRIS (n=4051)
 CHS men (n=726)
 CHS women (n=1012)
 FHS (n=2240)
 GARP (n=290)
 GCKD (n=3386)
 GOYA cases (n=198)
 GOYA controls (n=269)
 HBCS men (n=223)
 HBCS women (n=189)
 Health2006 (n=2890)
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 Inter99 (n=5978)
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 LBC1921 men (n=152)
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 LBC1936 men (n=403)
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 LifeLines women (n=2384)
 LLS 02112015 (n=2132)
 MICROS (n=1031)
 NBS men (n=842)
 NBS women (n=843)
 PROSPER men (n=2172)
 PROSPER women (n=2043)
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 RSI women (n=1633)
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 SHIP (n=421)
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 SHIP women (n=1592)
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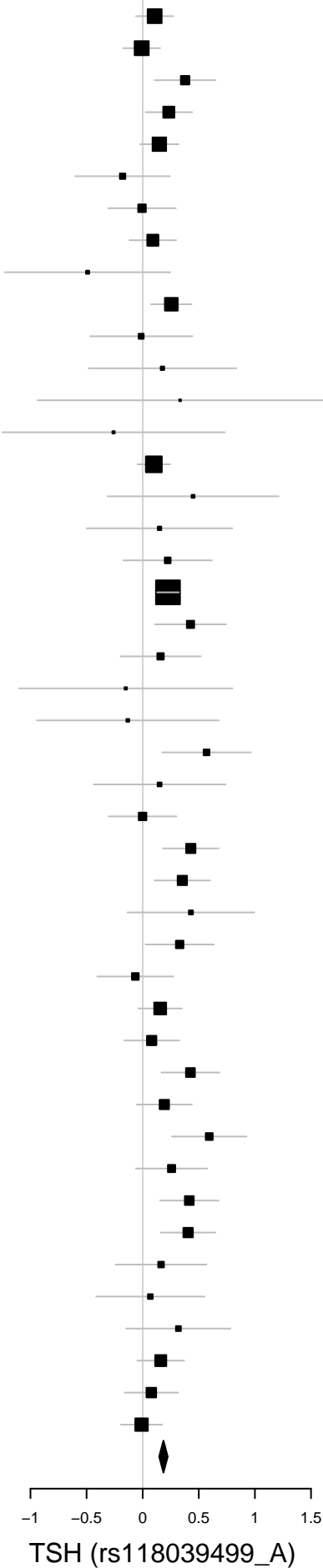




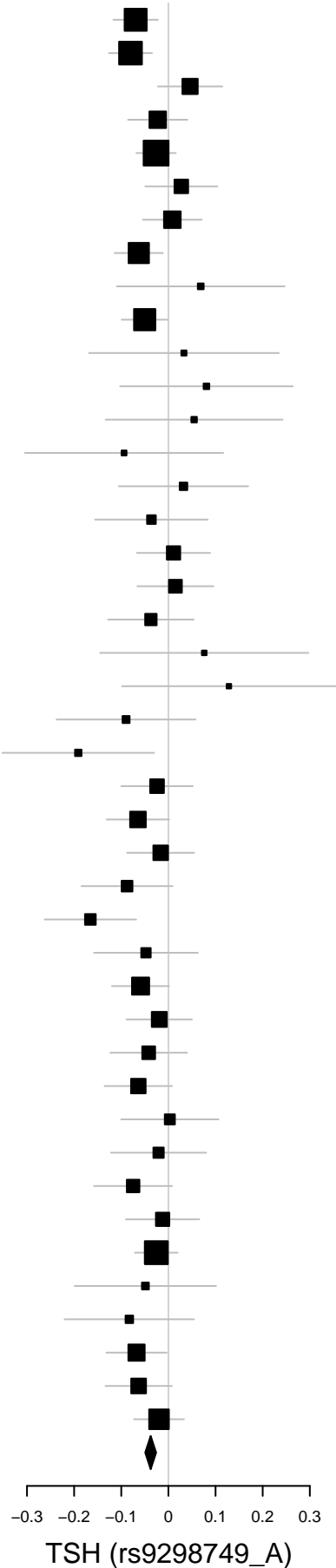
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 GCKD (n=3386)
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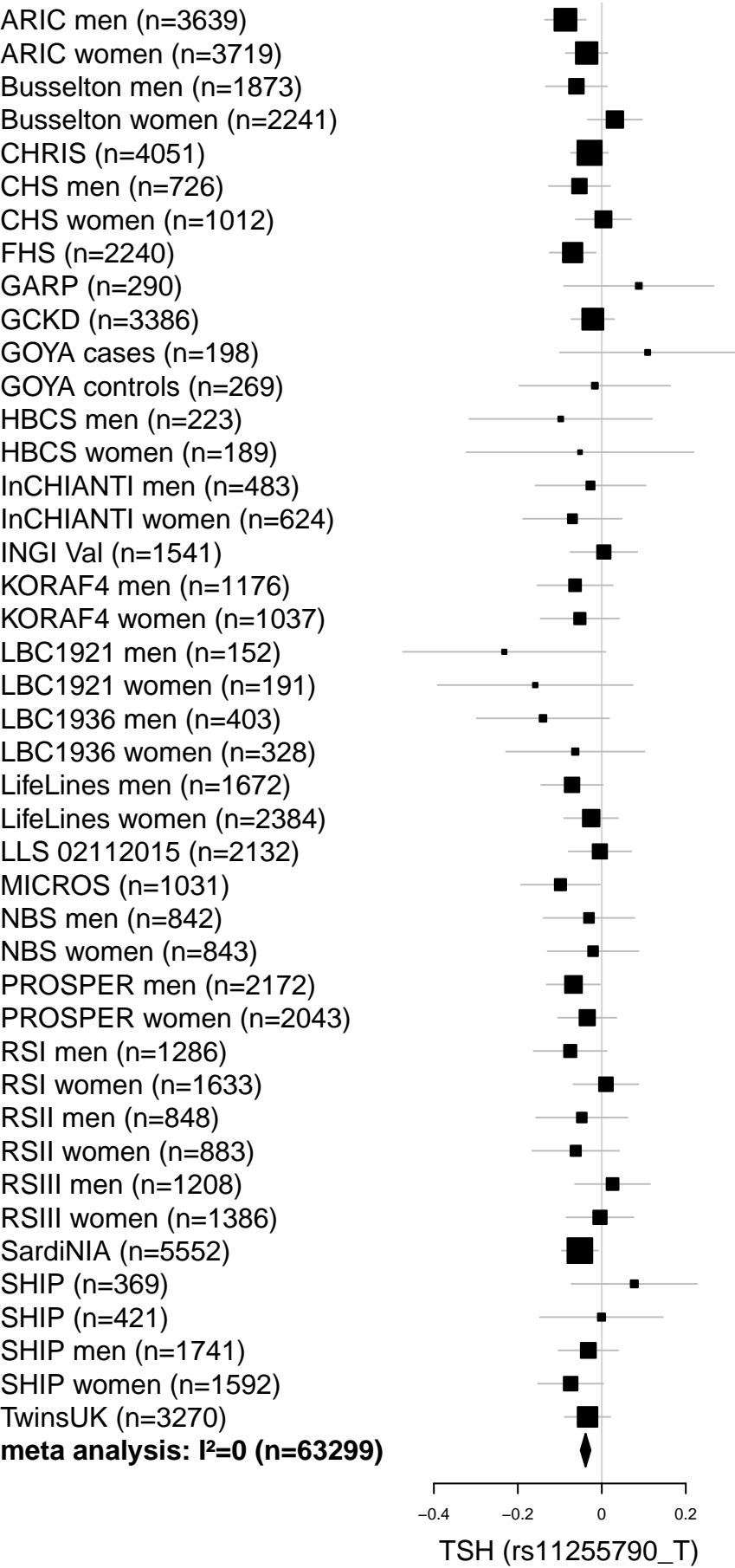


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NBS women (n=843)
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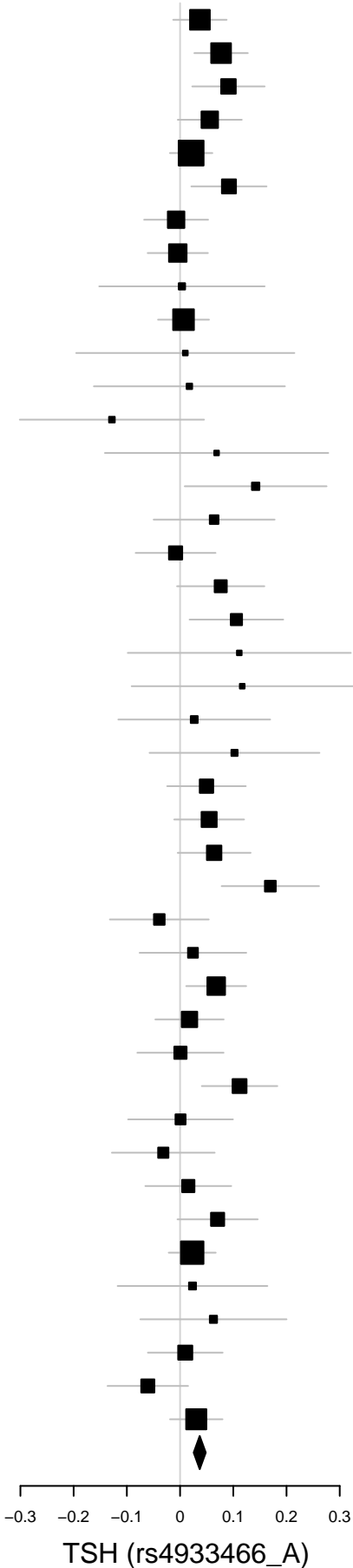


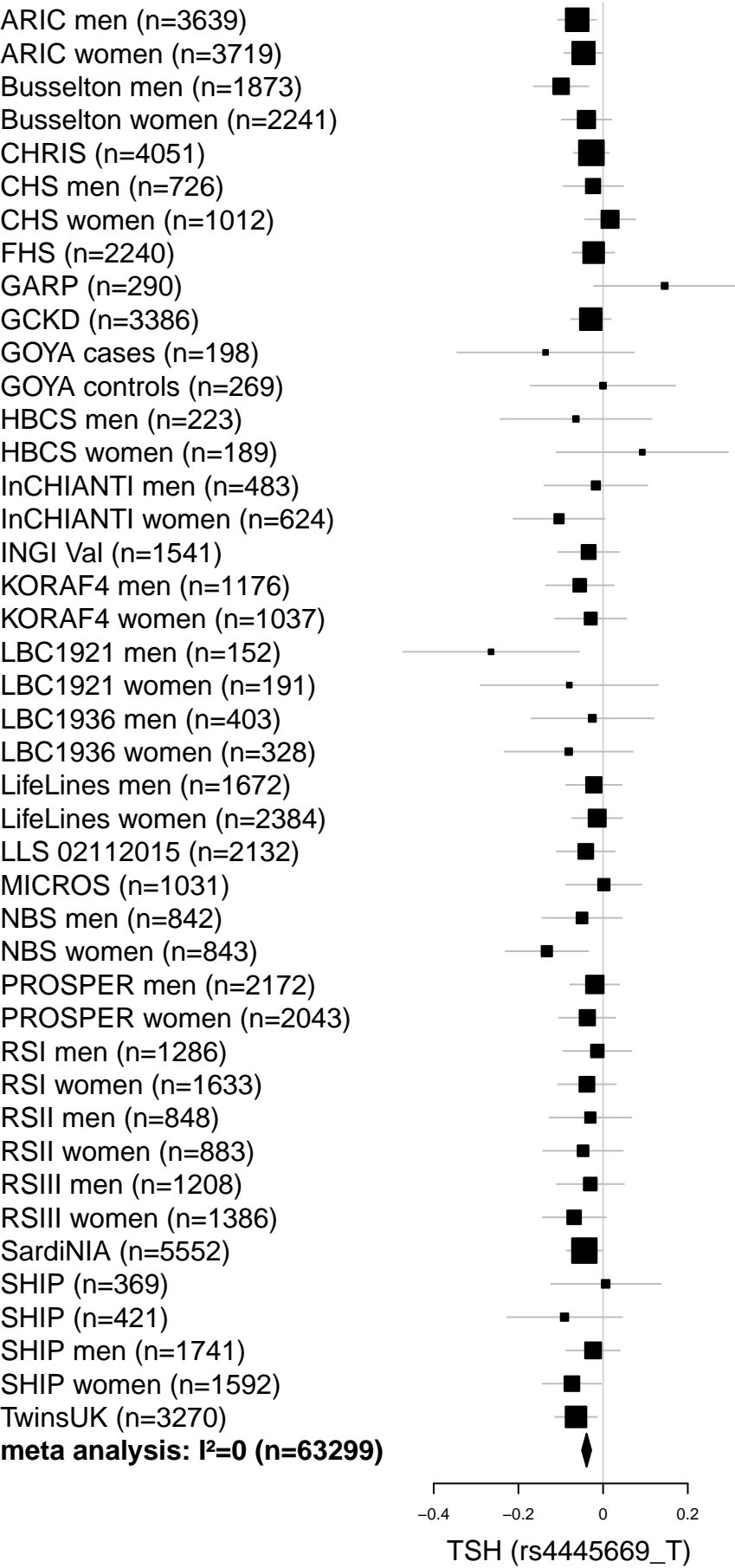
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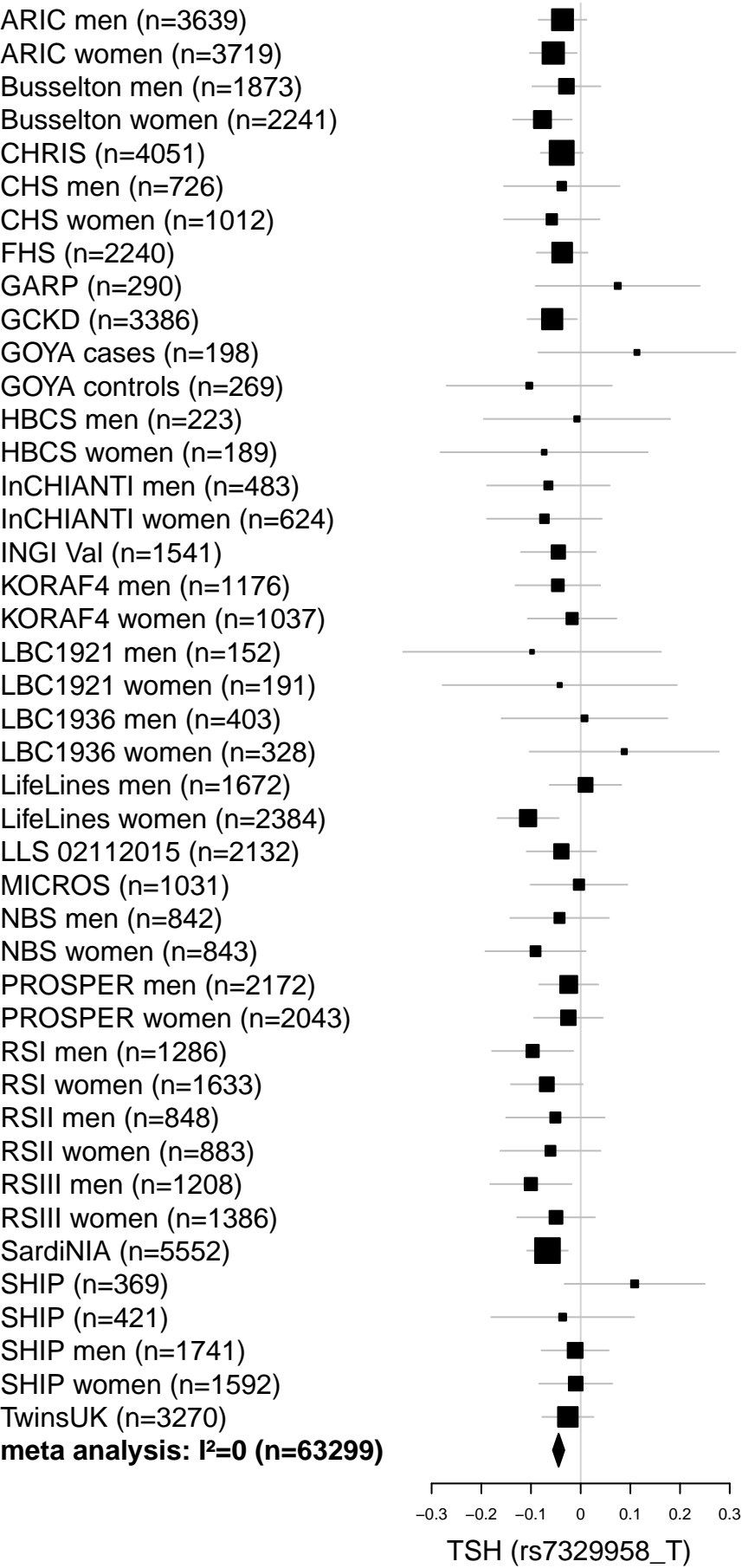




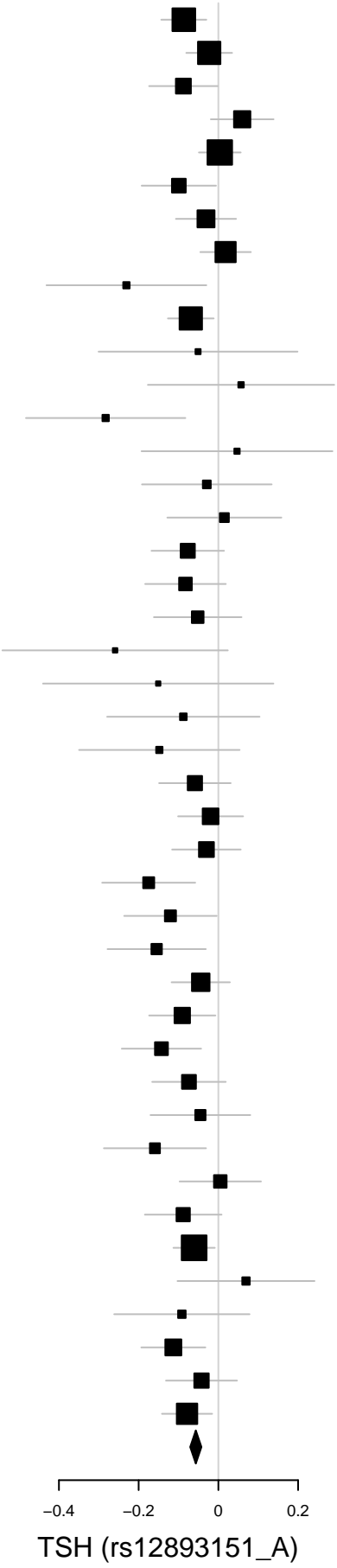
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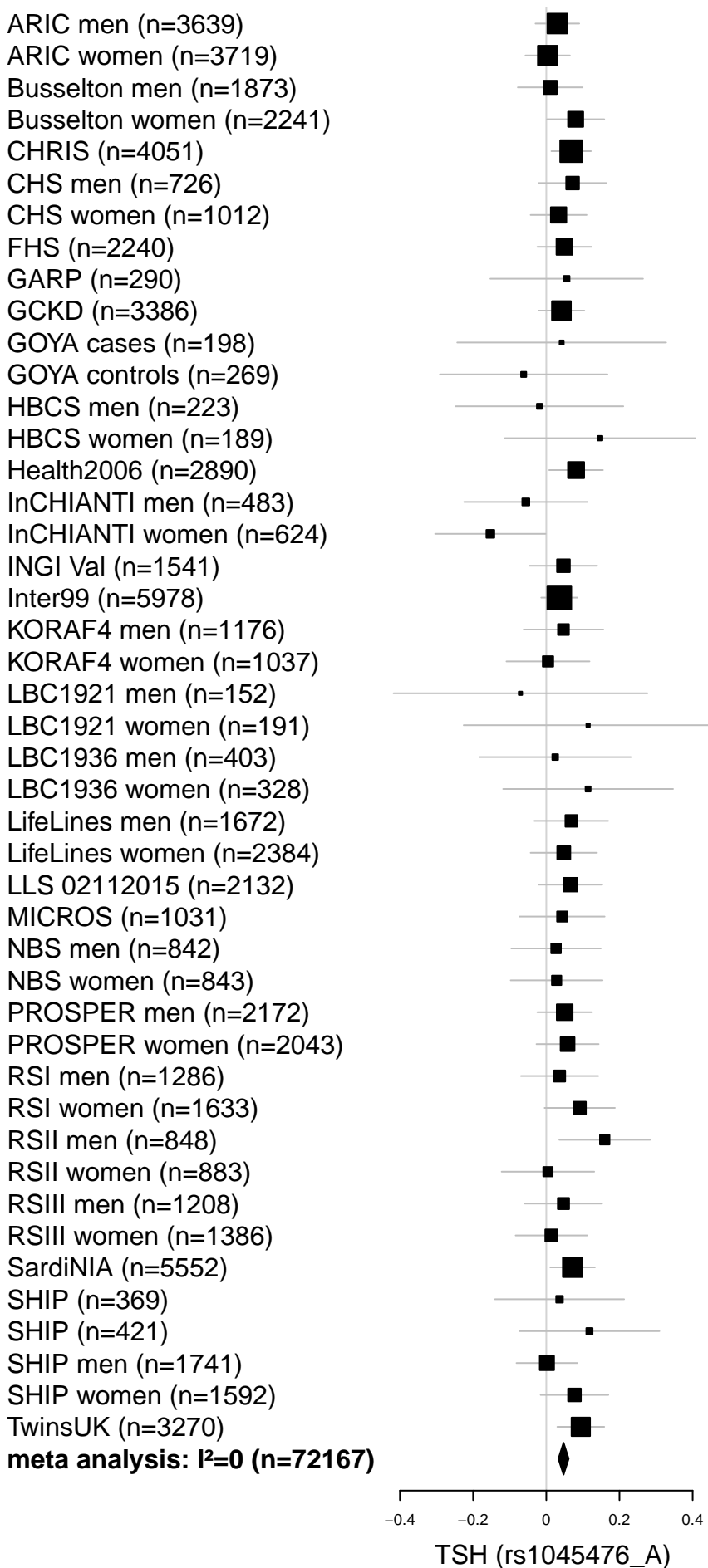




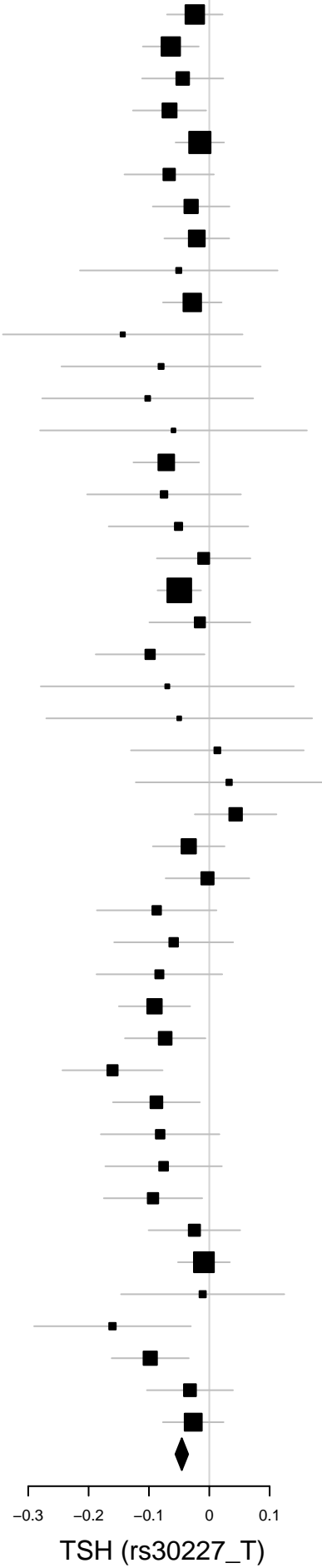


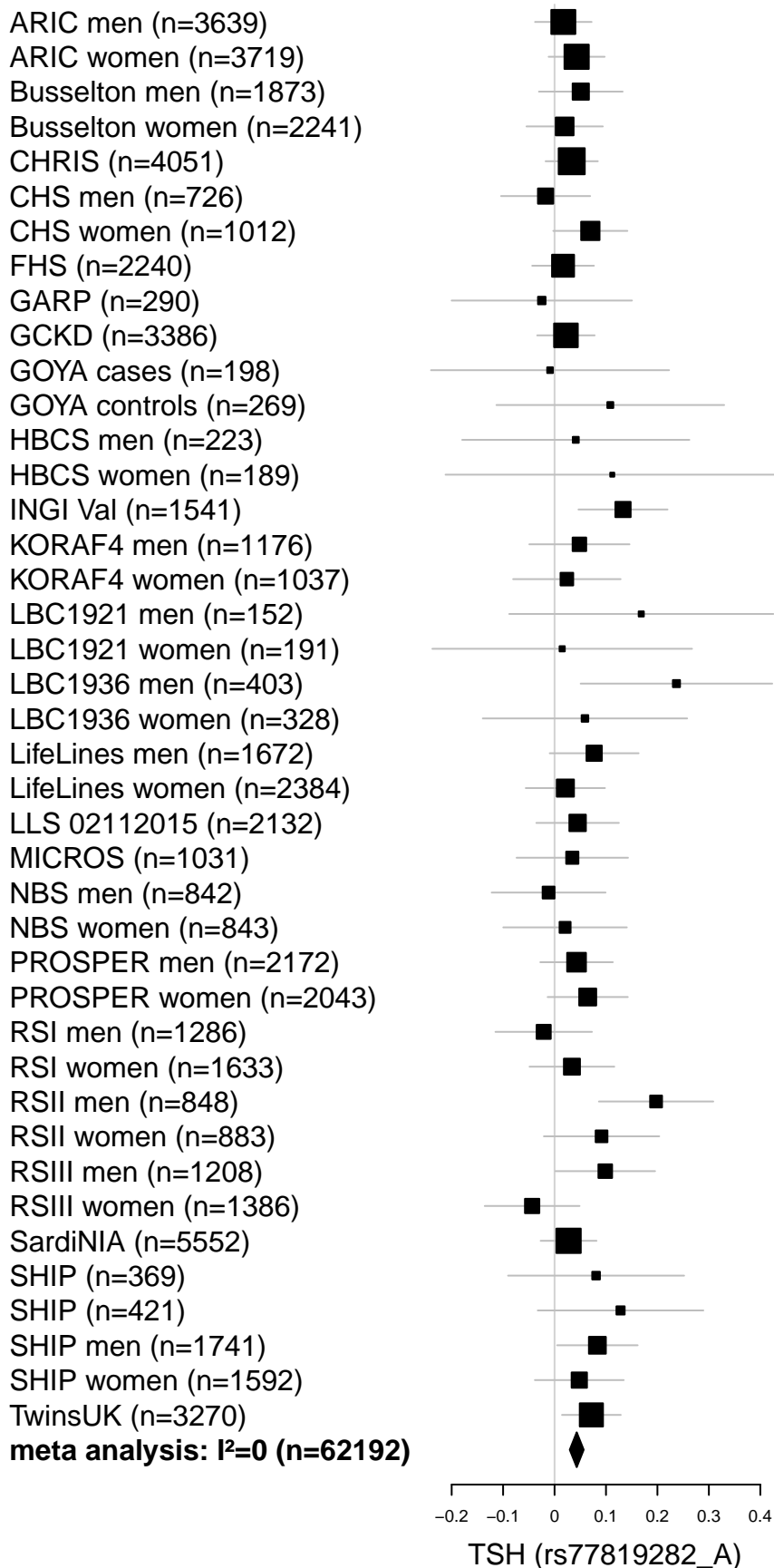
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meta analysis: $I^2=27.4$ (n=63299)



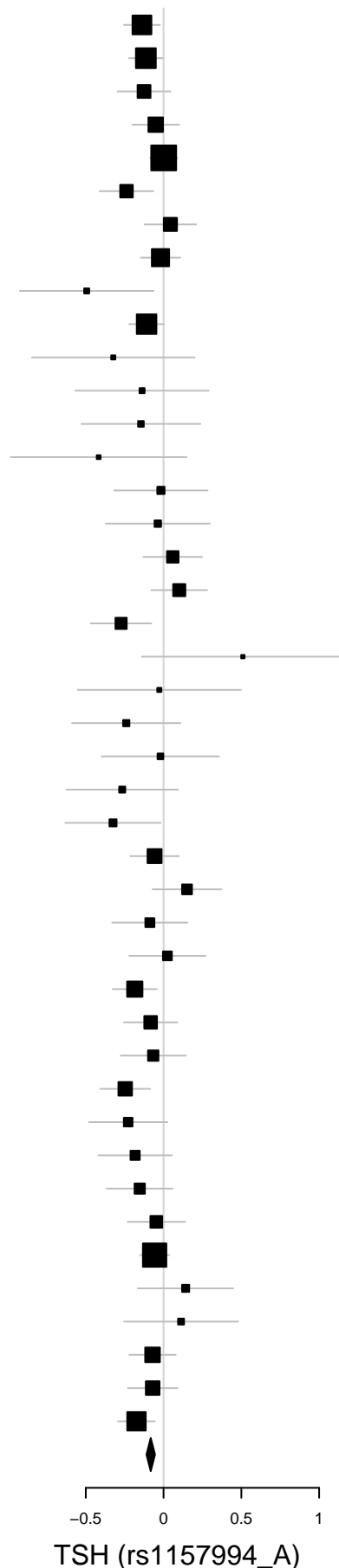


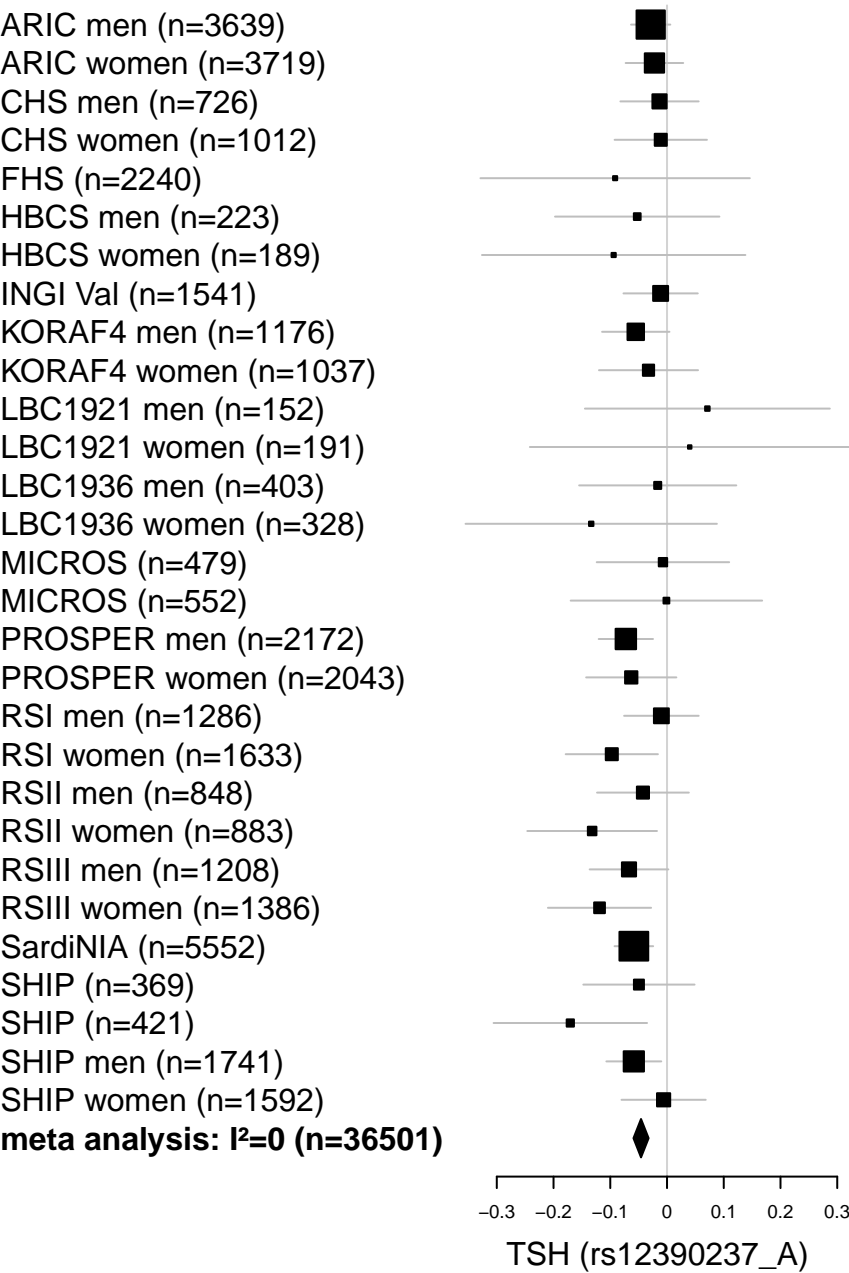
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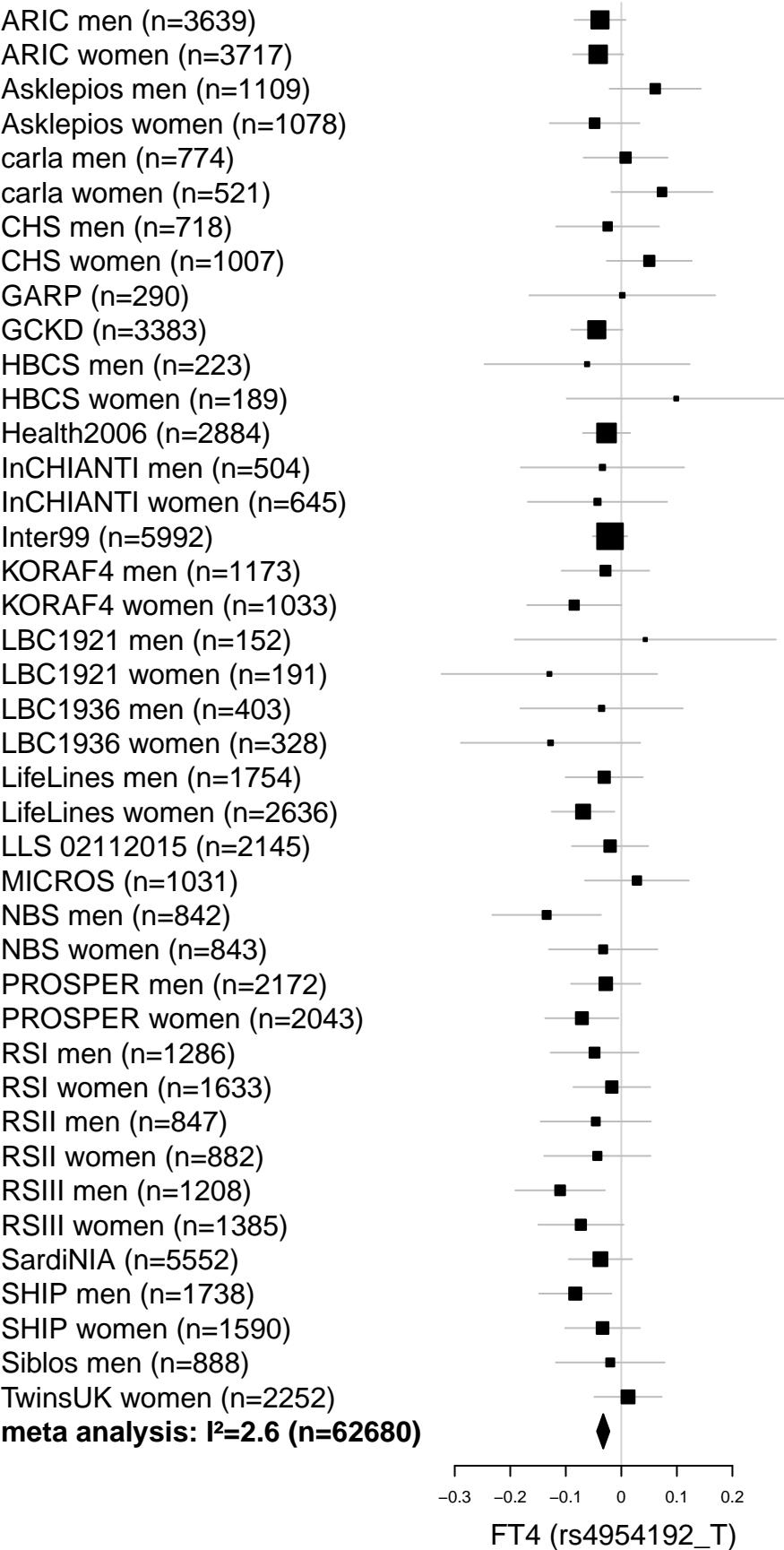
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meta analysis: I²=21 (n=59243)



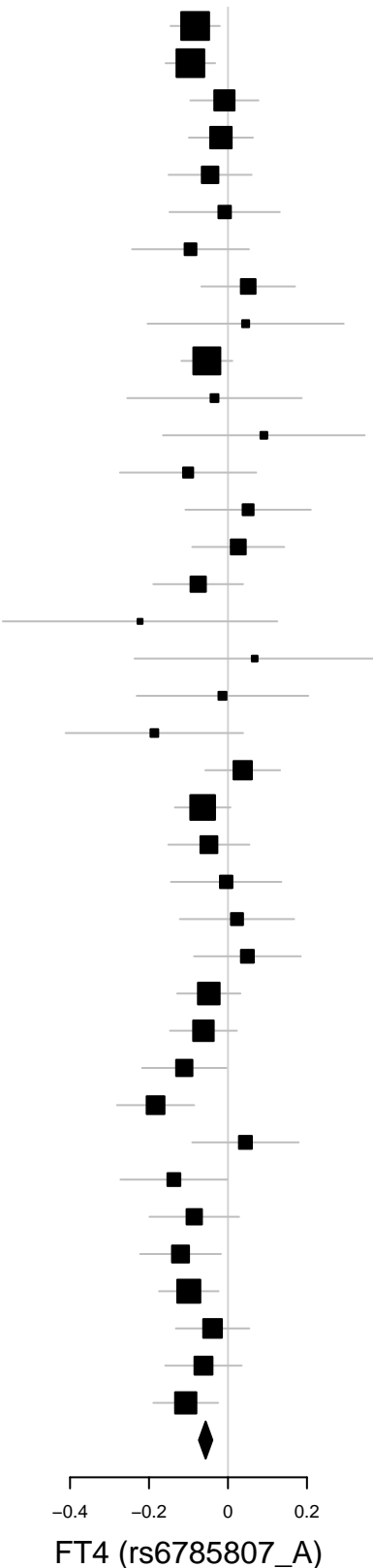


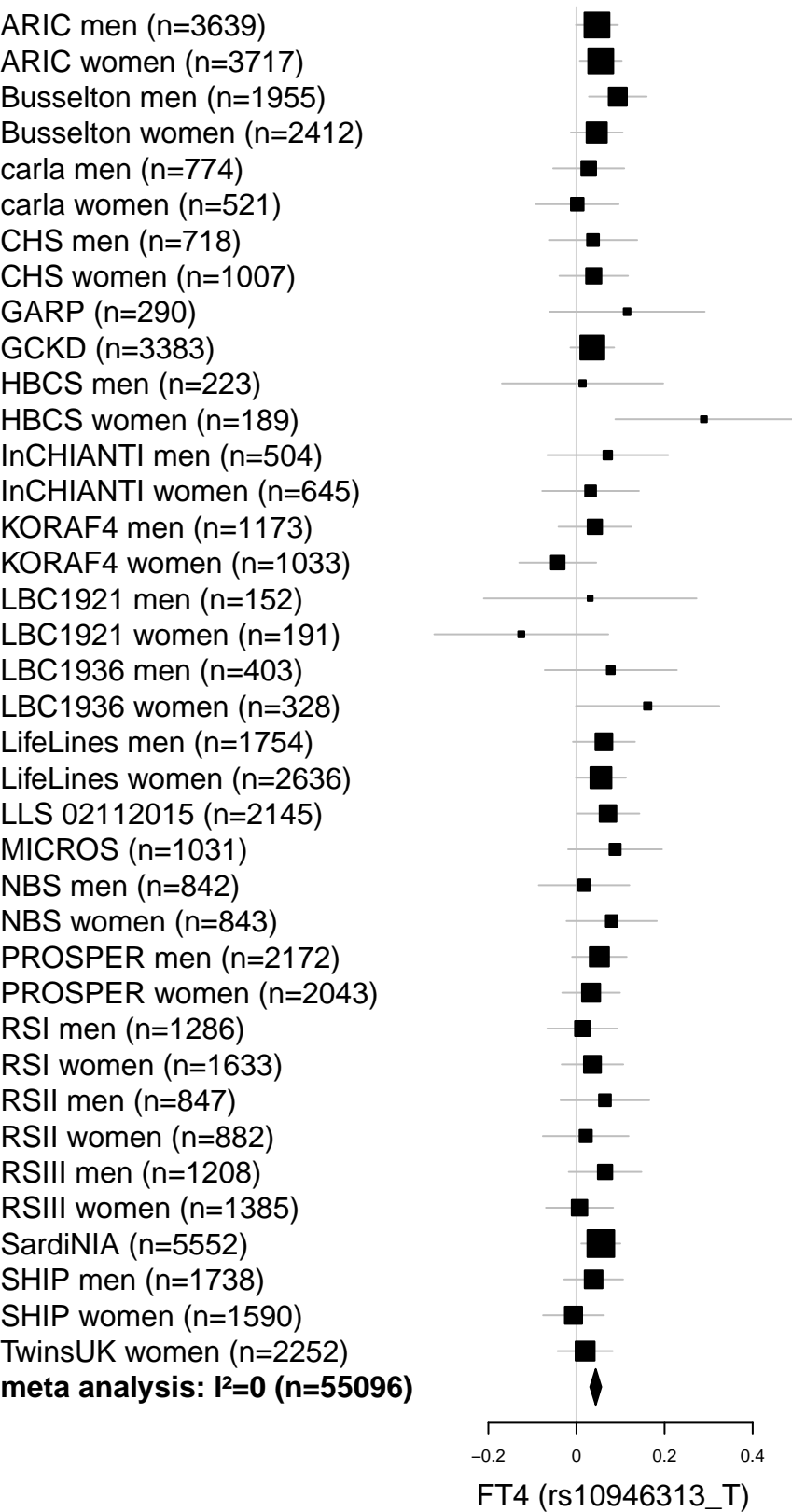
Forest plots of the 19 index SNPs of replicated susceptibility loci for TSH in the combined discovery and replication samples. Effects and their 95% confidence intervals are based on inverse normalized TSH values. I^2 is the percentage of total variation across studies that is due to heterogeneity.

Supplementary Figure 5: Forest plots for FT4

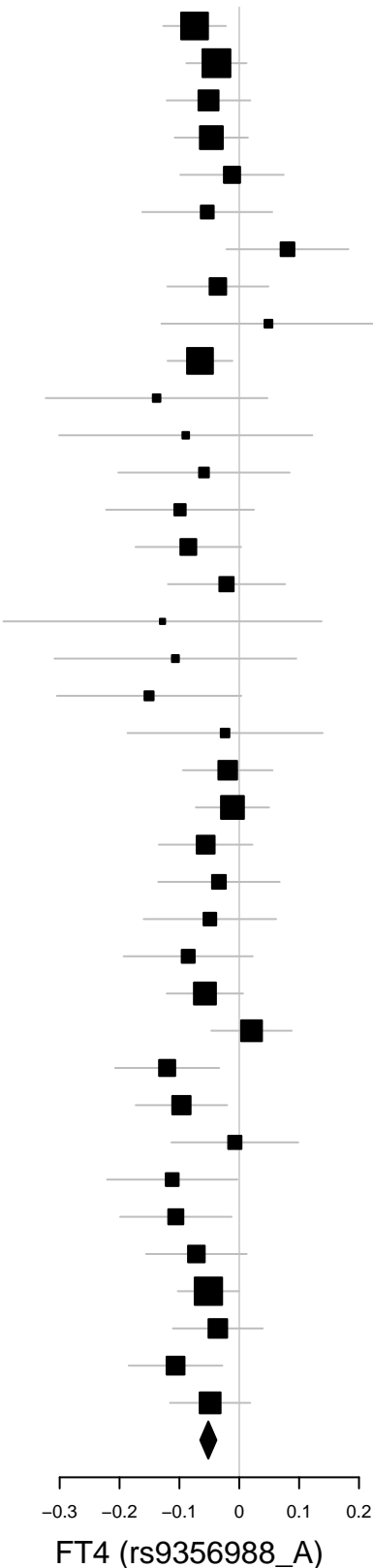


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Busselton women (n=2412)
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CHS women (n=1007)
GARP (n=290)
GCKD (n=3383)
HBCS men (n=223)
HBCS women (n=189)
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KORAF4 women (n=1033)
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LBC1921 women (n=191)
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MICROS (n=1031)
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RSII women (n=882)
RSIII men (n=1208)
RSIII women (n=1385)
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meta analysis: I²=7.4 (n=55096)

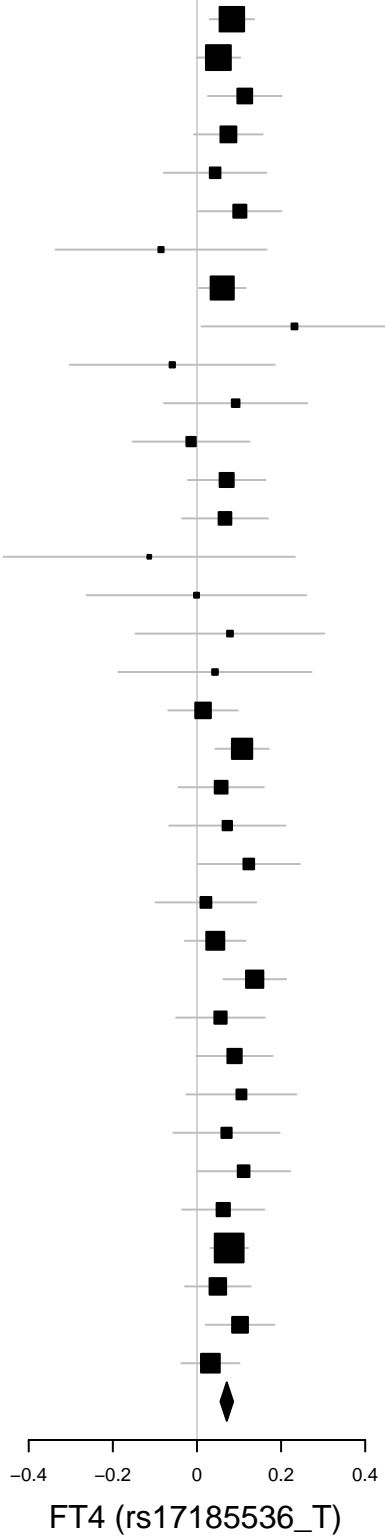




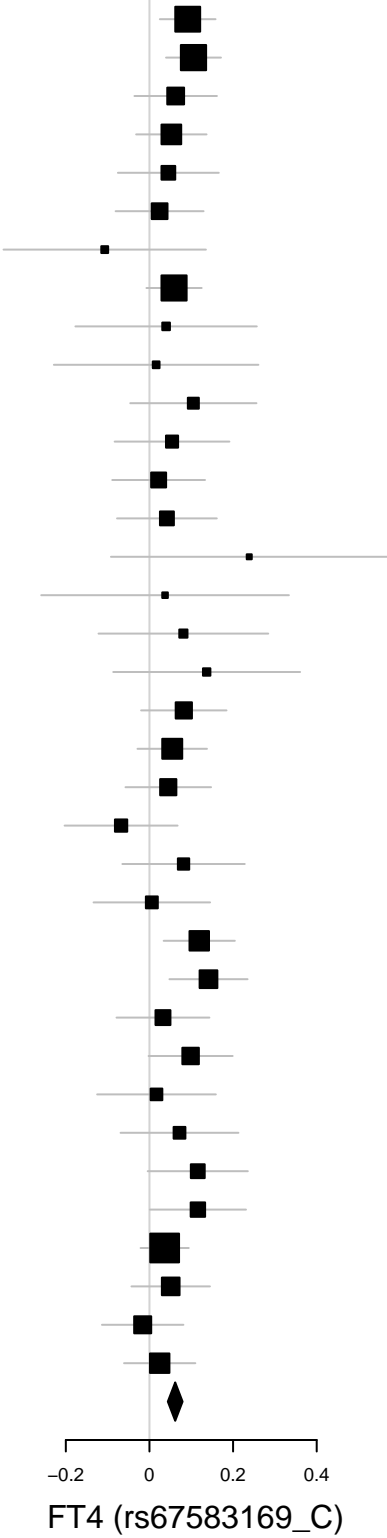
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RSI women (n=1633)
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RSIII women (n=1385)
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SHIP men (n=1738)
SHIP women (n=1590)
TwinsUK women (n=2252)
meta analysis: I²=0 (n=55096)



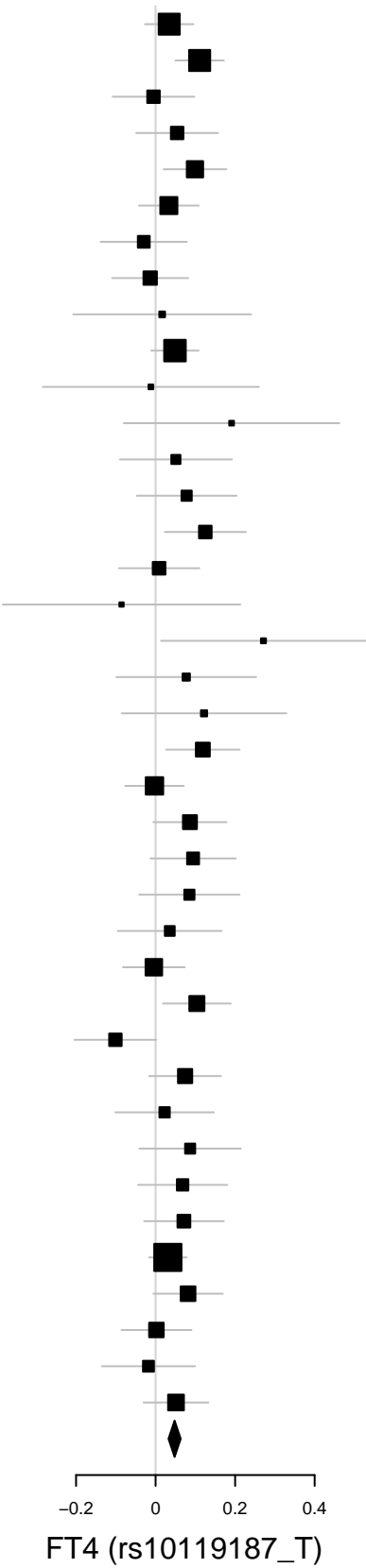
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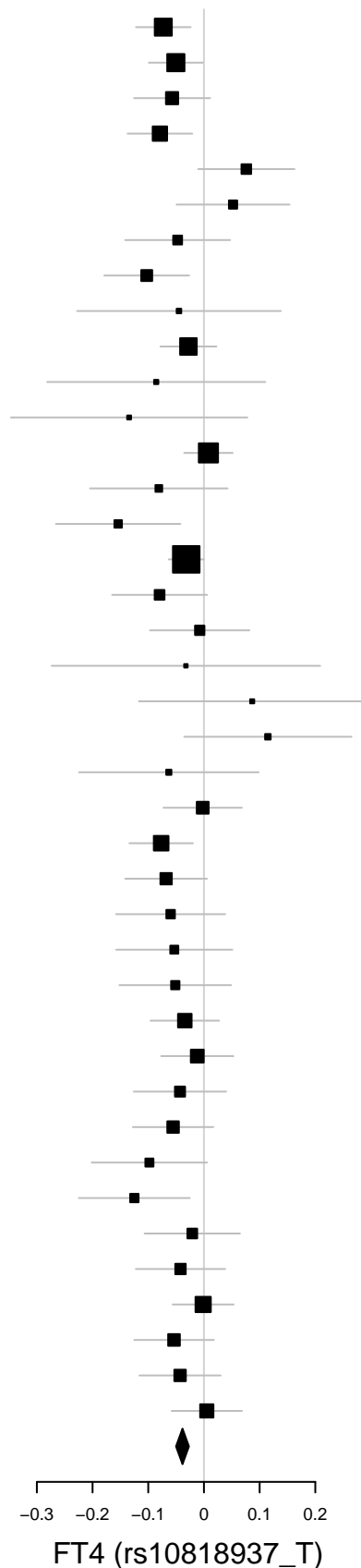
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HBCS women (n=189)
InCHIANTI men (n=504)
InCHIANTI women (n=645)
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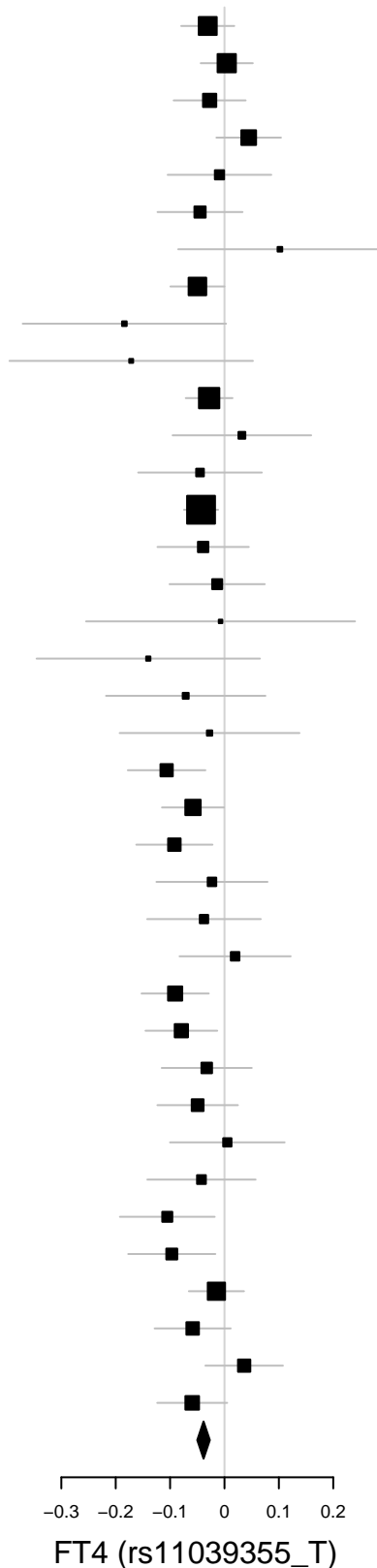
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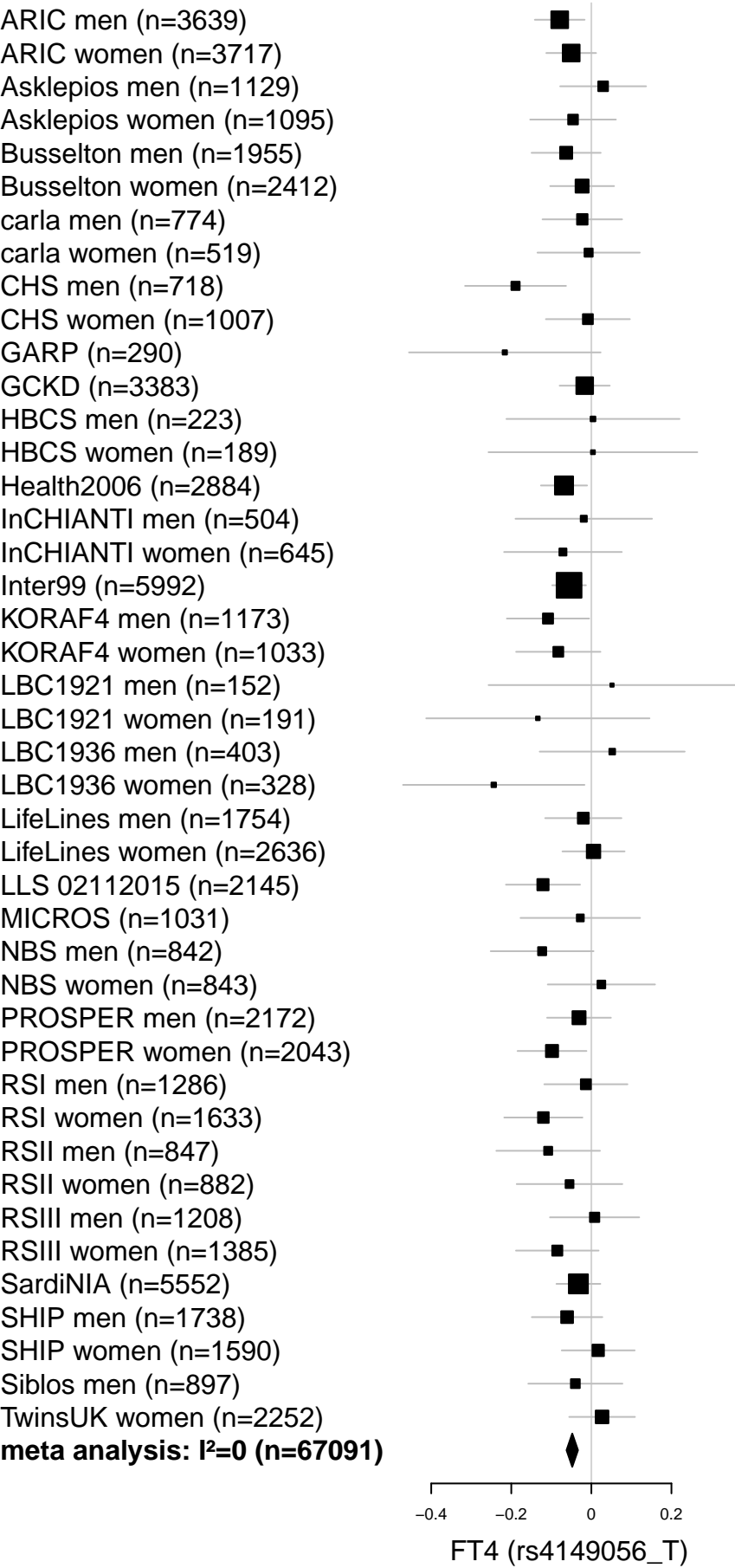


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 PROSPER men (n=2172)
 PROSPER women (n=2043)
 RSI men (n=1286)
 RSI women (n=1633)
 RSII men (n=847)
 RSII women (n=882)
 RSIII men (n=1208)
 RSIII women (n=1385)
 SardiNIA (n=5552)
 SHIP men (n=1738)
 SHIP women (n=1590)
 TwinsUK women (n=2252)
meta analysis: $I^2=15.8$ (n=63971)

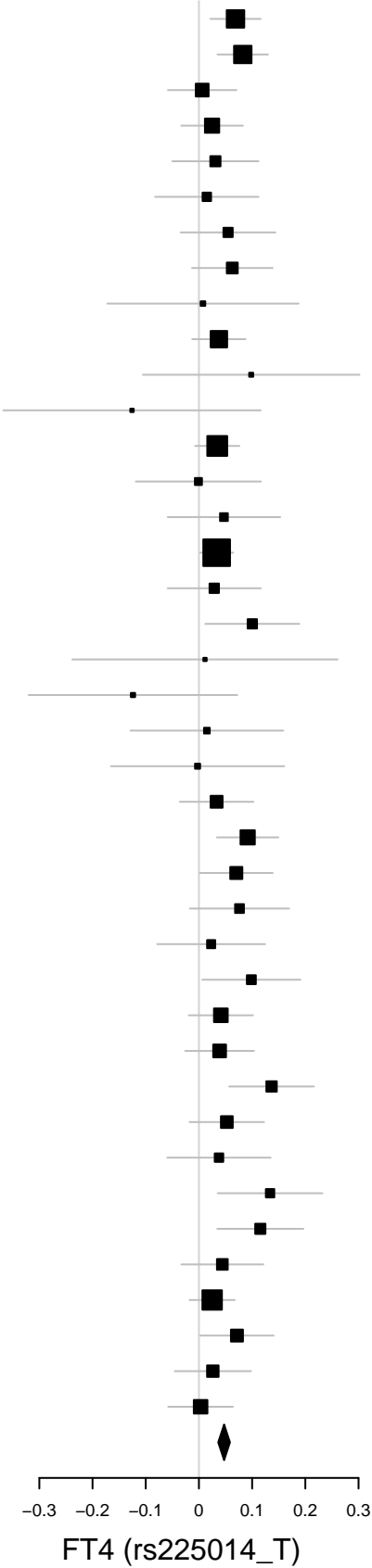


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 HBCS women (n=189)
 Health2006 (n=2884)
 InCHIANTI men (n=504)
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 Inter99 (n=5992)
 KORAF4 men (n=1173)
 KORAF4 women (n=1033)
 LBC1921 men (n=152)
 LBC1921 women (n=191)
 LBC1936 men (n=403)
 LBC1936 women (n=328)
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 LifeLines women (n=2636)
 LLS 02112015 (n=2145)
 MICROS (n=1031)
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 NBS women (n=843)
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 RSIII men (n=1208)
 RSIII women (n=1385)
 SardiNIA (n=5552)
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 SHIP women (n=1590)
 TwinsUK women (n=2252)
meta analysis: $I^2=12.2$ (n=62677)

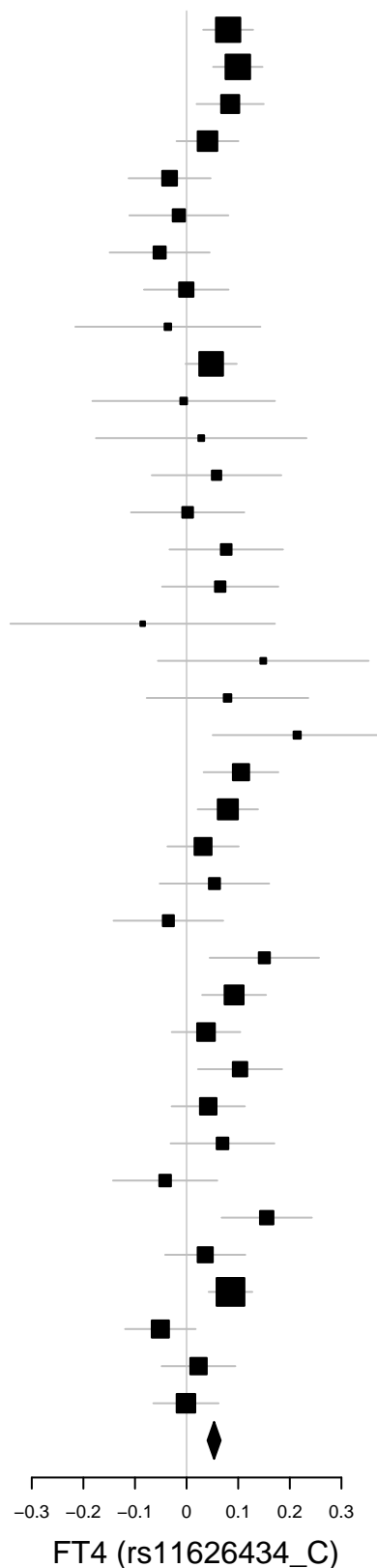


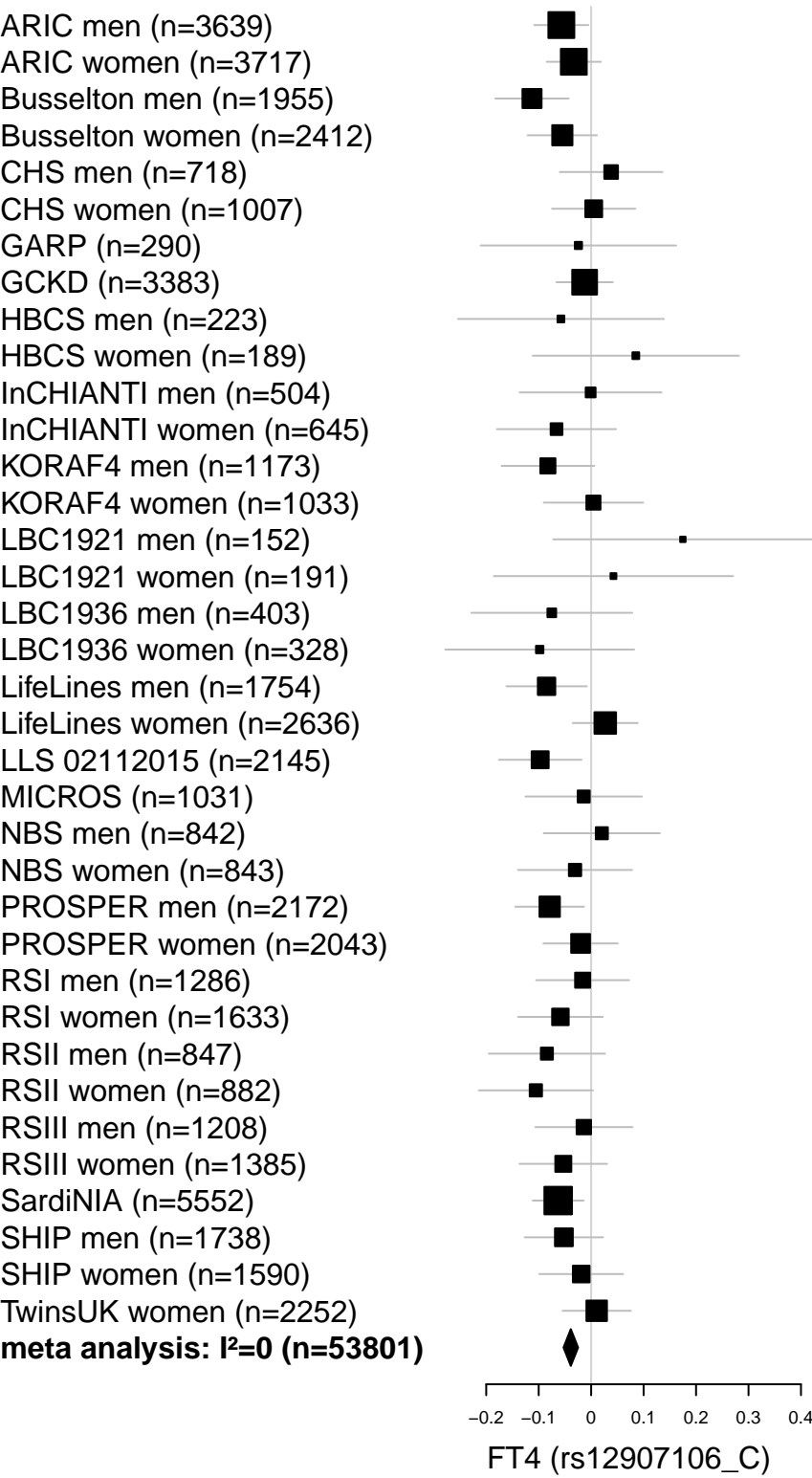


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GCKD (n=3383)
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Health2006 (n=2884)
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Inter99 (n=5992)
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KORAF4 women (n=1033)
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RSII women (n=882)
RSIII men (n=1208)
RSIII women (n=1385)
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meta analysis: $I^2=0$ (n=63971)

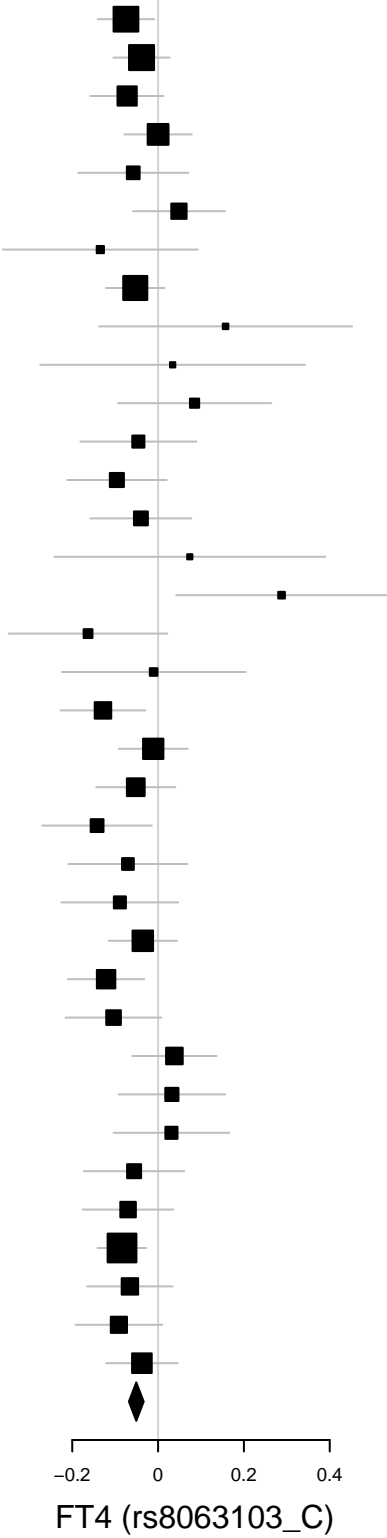


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 InCHIANTI women (n=645)
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 KORAF4 women (n=1033)
 LBC1921 men (n=152)
 LBC1921 women (n=191)
 LBC1936 men (n=403)
 LBC1936 women (n=328)
 LifeLines men (n=1754)
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 RSII men (n=847)
 RSII women (n=882)
 RSIII men (n=1208)
 RSIII women (n=1385)
 SardiNIA (n=5552)
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 SHIP women (n=1590)
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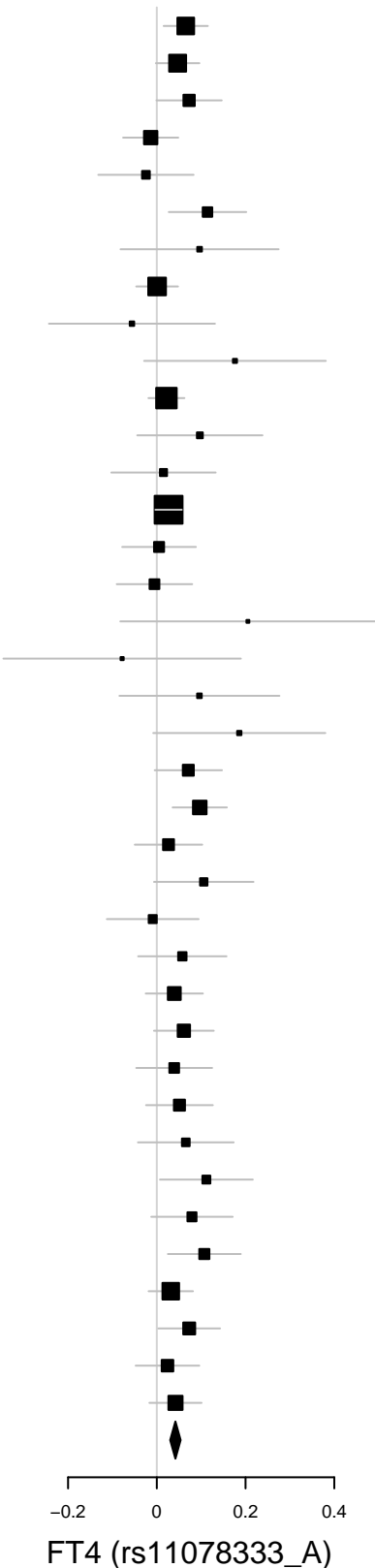




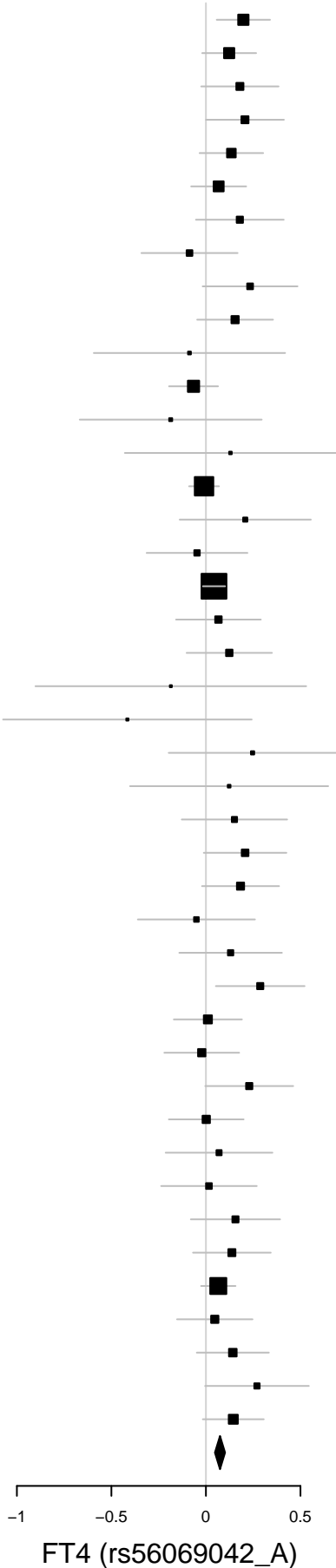
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MICROS (n=1031)
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NBS women (n=843)
PROSPER men (n=2172)
PROSPER women (n=2043)
RSI men (n=1286)
RSI women (n=1633)
RSII men (n=847)
RSII women (n=882)
RSIII men (n=1208)
RSIII women (n=1385)
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SHIP women (n=1590)
TwinsUK women (n=2252)
meta analysis: I²=7.9 (n=53801)



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 Busselton women (n=2412)
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 CHS women (n=1007)
 GARP (n=290)
 GCKD (n=3383)
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 HBCS women (n=189)
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meta analysis: $I^2=0$ (n=62677)

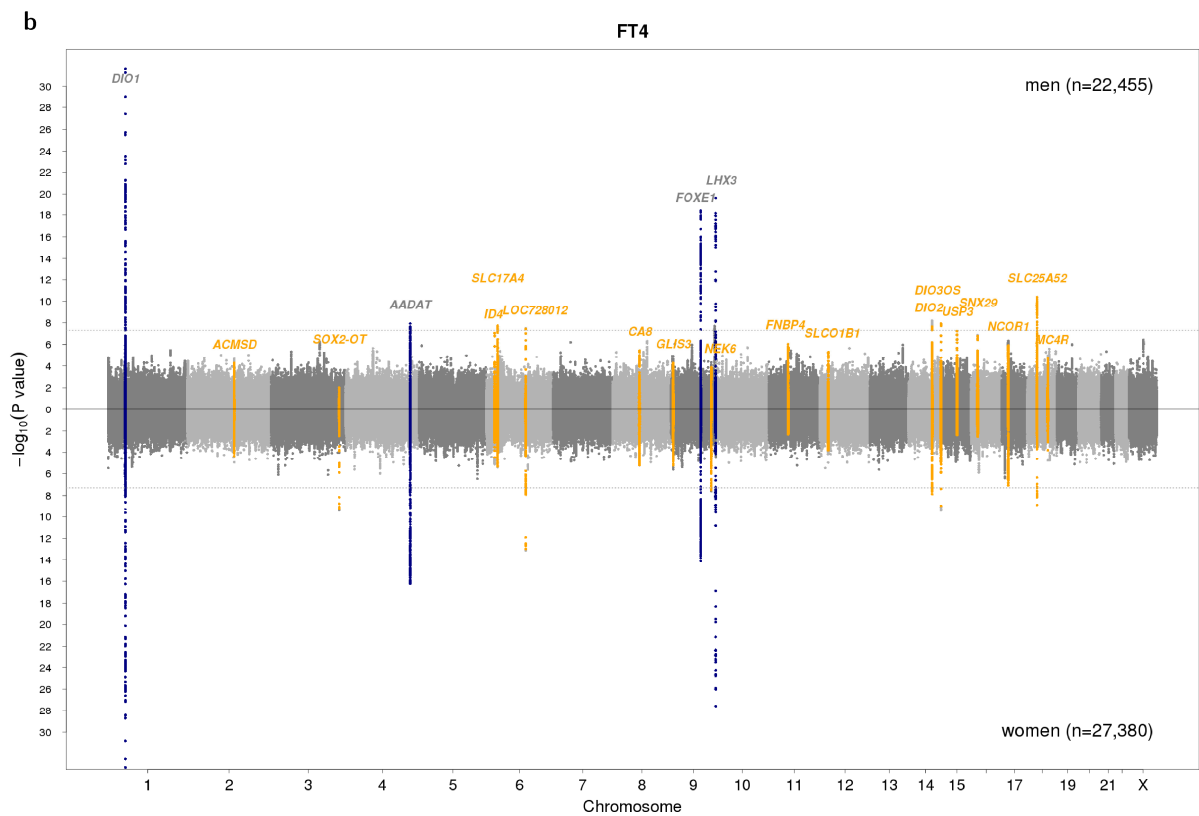
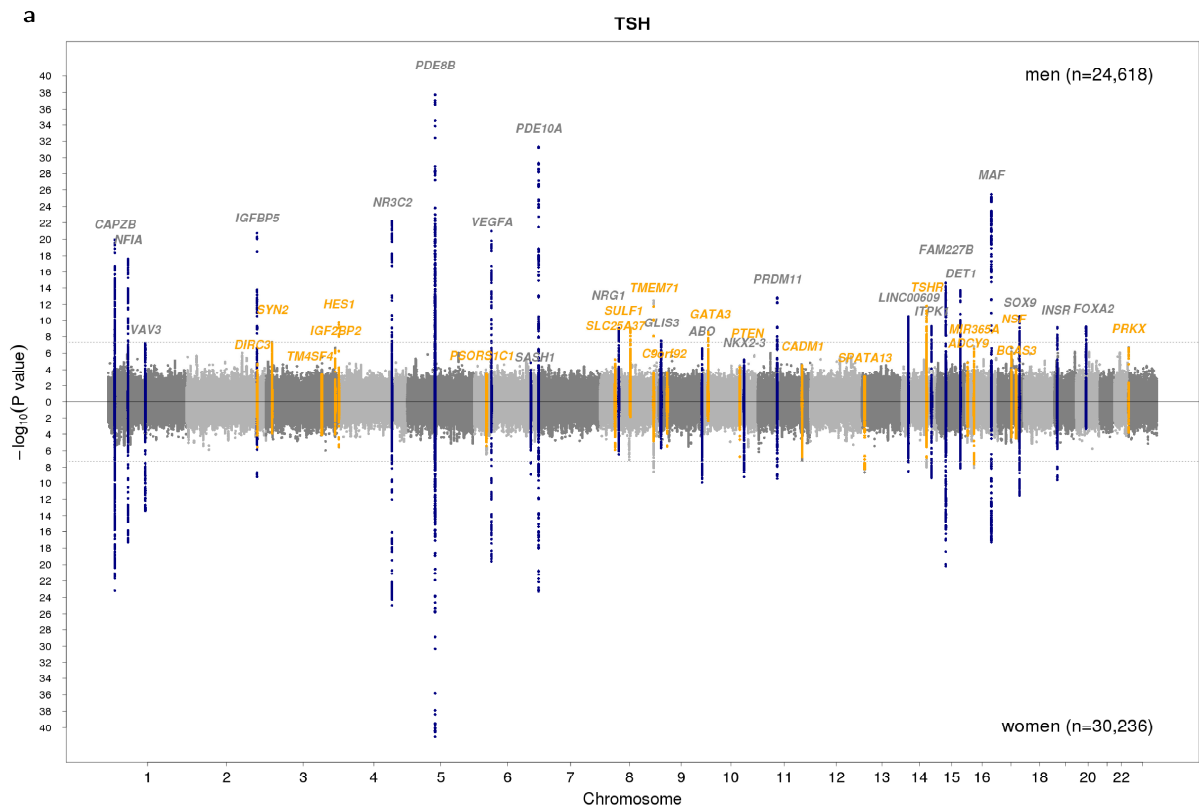


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 SardiNIA (n=5552)
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meta analysis: $I^2=0$ (n=67073)



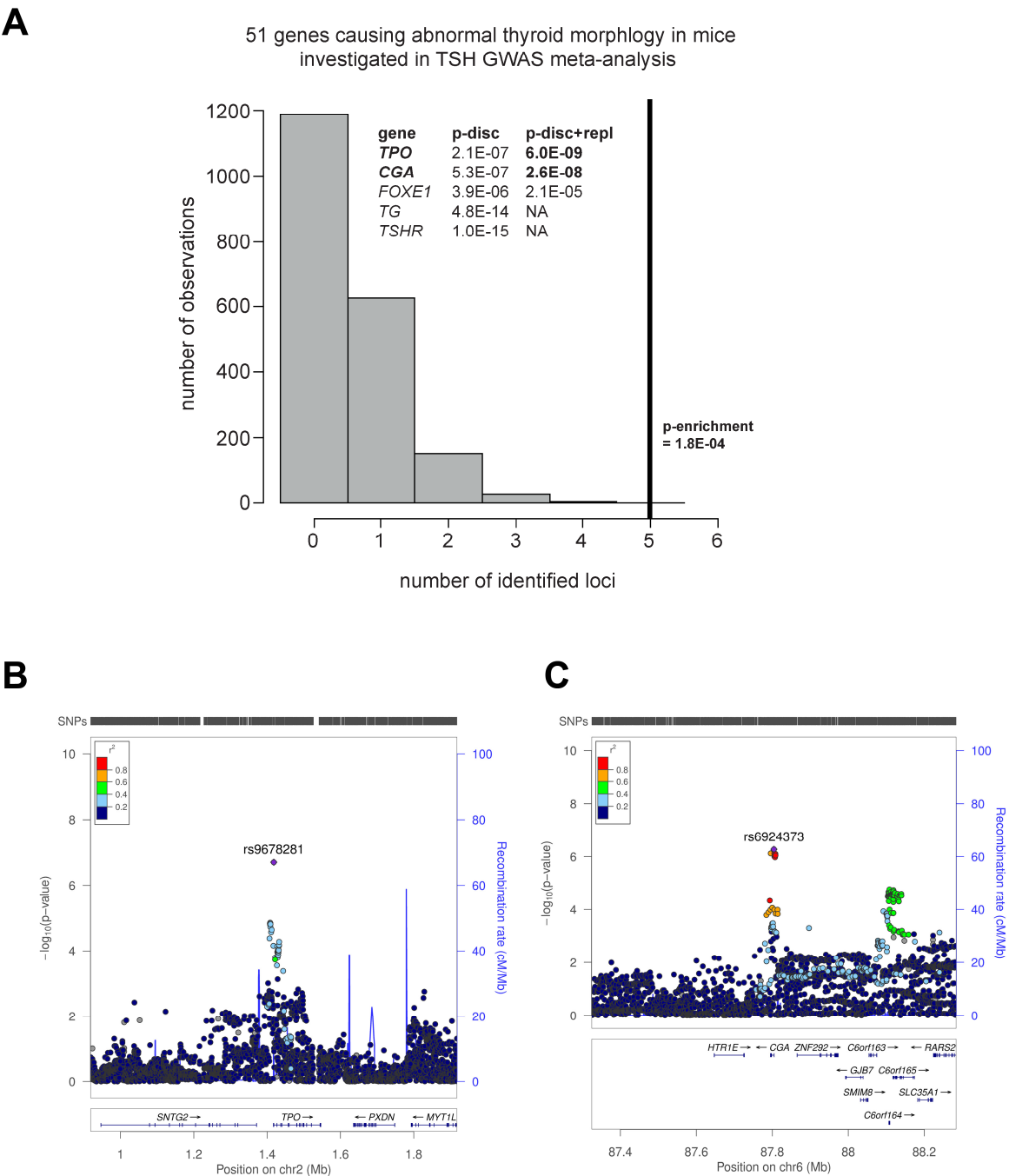
Forest plots of the 16 index SNPs of replicated susceptibility loci for FT4 in the combined discovery and replication samples. Effects and their 95% confidence intervals are based on inverse normalized FT4 values. I^2 is the percentage of total variation across studies that is due to heterogeneity.

Supplementary Figure 6: Manhattan plots for GWAS meta-analyses in the sex-stratified samples



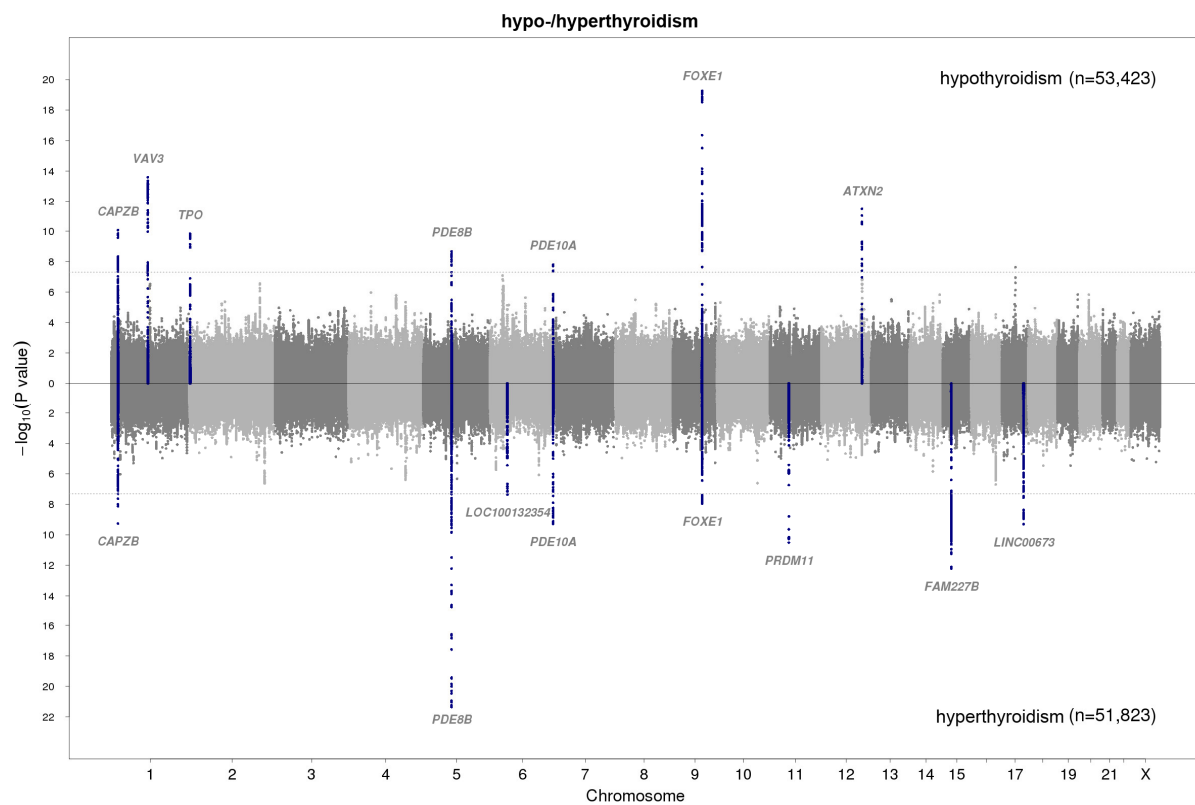
Manhattan plots of the GWAS meta-analysis results for (a) TSH and (b) FT4 contrasted for the men vs. women stratum. SNPs are plotted on the x-axis according to their position on each chromosome with the $-\log_{10}(\text{p-value})$ of the association test on the y-axis. The upper solid horizontal line indicates the threshold for genome-wide significance, 5×10^{-8} . Genomic loci previously known to contain trait-associated variants are colored in blue, new findings in orange (based on the overall sample).

Supplementary Figure 7: Genes related to abnormal thyroid morphology in genetically manipulated mice are enriched for SNPs significantly associated with TSH concentrations in humans



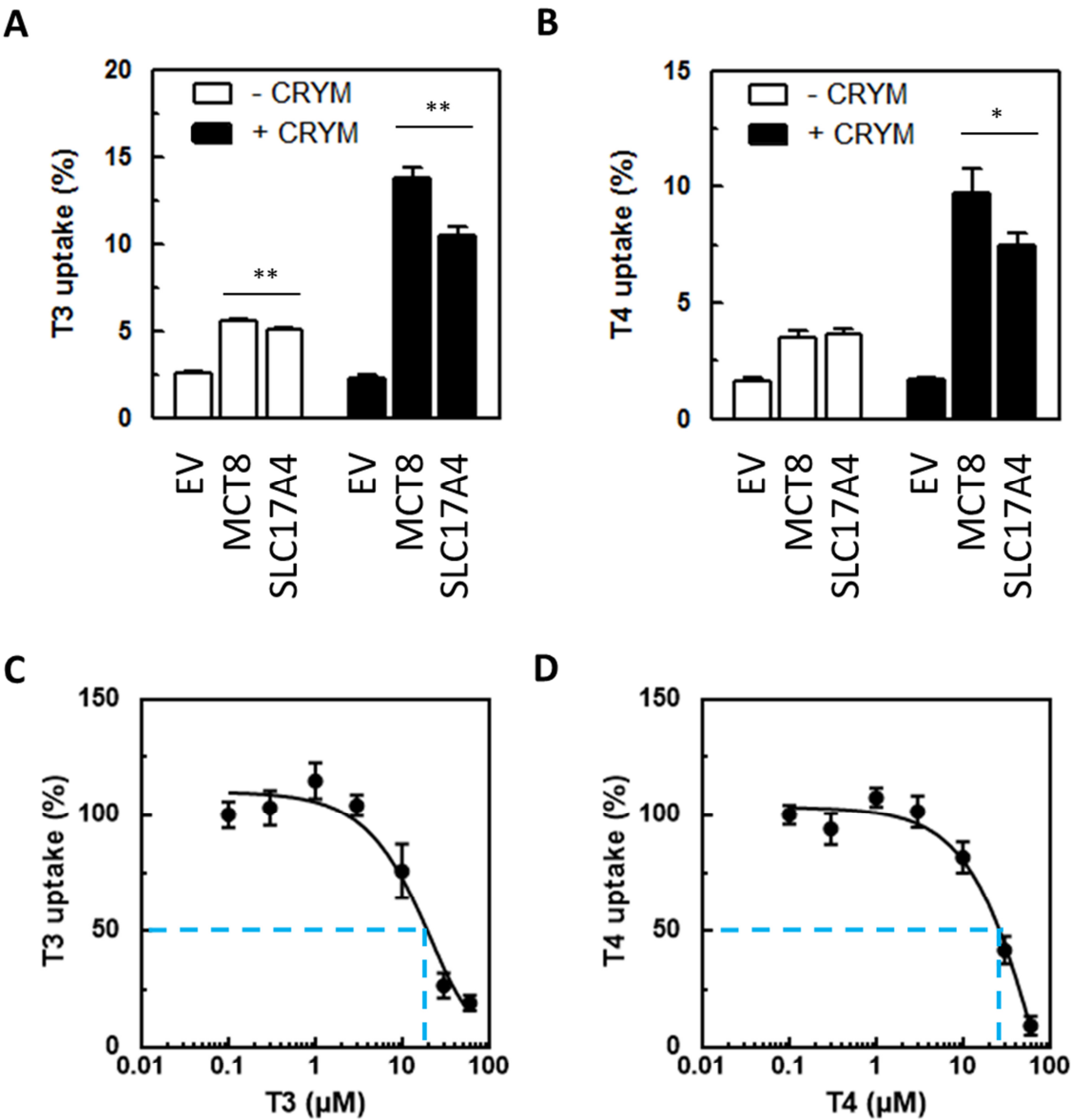
The line indicates the number of observed genes that contain significant SNPs in the TSH meta-analysis based on the human orthologs of 51 genes that cause abnormal thyroid morphology in mice. The histogram depicts the distribution of genes that contain significant SNPs in the TSH meta-analysis based on 2,000 randomly drawn lists of 51 genes. The inset shows the 5 genes that contained significantly associated SNPs in the TSH discovery meta-analysis (p-disc: association test p-value of the index SNP) as well as their evidence for replication in independent samples for SNPs (p-disc+repl: association test p-value in the combined discovery and replication sample) that did not achieve genome-wide significance in the GWAS (Panel A). Panels B and C show the regional association plots for the SNPs that reached genome-wide significance based on the candidate gene approach.

Supplementary Figure 8: Manhattan plot for GWAS meta-analyses for hypo- vs. hyperthyroidism



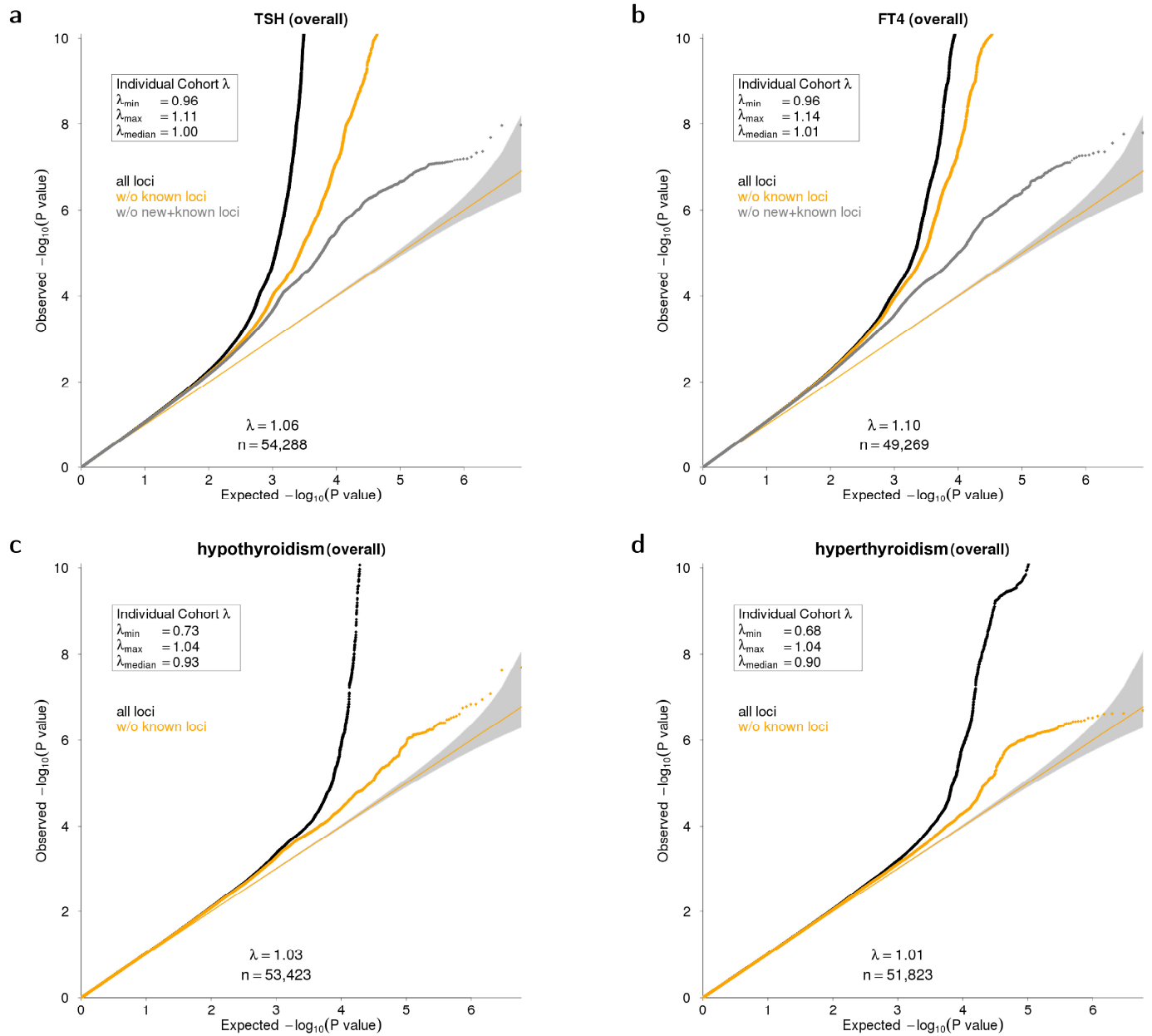
Manhattan plot of the GWAS meta-analysis results for hypo- and hyperthyroidism contrasted with each other. SNPs are plotted on the x-axis according to their position on each chromosome with the $-\log_{10}(\text{p-value})$ of the association test on the y-axis. The upper solid horizontal line indicates the threshold for genome-wide significance, 5×10^{-8} . Genomic loci previously known to contain trait-associated variants are colored in blue.

Supplementary Figure 9: Thyroid hormone transport by MCT8 in comparison to hSLC17A4



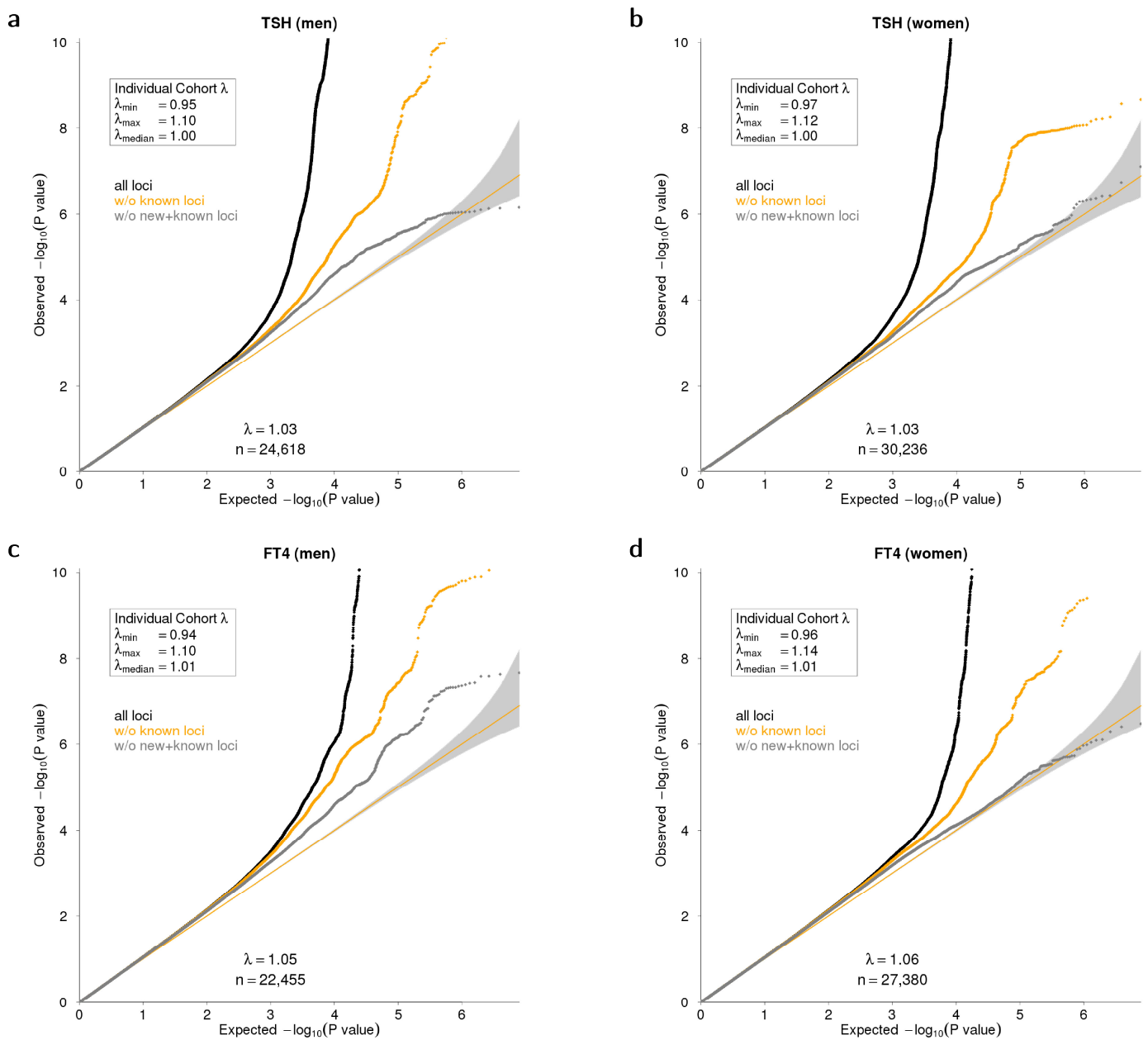
Cellular T3 (Panel A) and T4 (Panel B) accumulation in COS-1 cells, transiently transfected with empty vector (EV), wild-type hMCT8 or wild-type hSLC17A4 in the absence (white bars) or presence (black bars) of the intracellular thyroid hormone binding protein CRYM, after 10 minutes incubation at 37°C. All uptake levels are expressed relative to the amount of radio-labeled T3 or T4 added to the cells at the start of the incubation (1 nM (5x10E4 cpm) [¹²⁵I]-T3 or [¹²⁵I]-T4). All results are presented as means ± SEM (n=3). In the presence and absence of CRYM, T3 and T4 accumulation in MCT8 and hSLC17A4 transfected cells was significantly higher compared to empty vector control cells (one-way ANOVA with a Bonferroni corrected post hoc test, P<0.001). In the presence and absence of CRYM, T3 accumulation in hMCT8-transfected cells was slightly, but significantly, higher than in hSLC17A4-transfected cells; which was also the case for T4 uptake in the presence of CRYM. T3 (Panel C) and T4 (Panel D) saturation curves in COS-1 cells transiently transfected with hMCT8 in the absence of CRYM. All data points are corrected for background thyroid hormone uptake in control cells and presented relatively to the amount of internalized thyroid hormone in the presence of the lowest substrate concentration (0.1 μM for T3 and T4). Apparent IC₅₀ values were determined by standard second order polynomial regression analyses implemented in GraphPad Prism (La Jolla, USA). * P<0.05; ** P<0.01.

Supplementary Figure 10: QQ plots for all GWAS meta-analyses in the overall samples



Quantile-quantile (QQ) plots of the GWAS meta-analysis results for (a) TSH, (b) FT4, (c) hypothyroidism, and (d) hyperthyroidism in the overall sample. The observed p-values of the association test are plotted on the y-axis against their expected distribution under the null hypothesis of no association on the x-axis. Results for all SNPs are shown in black, results after removal of loci previously known to contain trait-associated variants are shown in yellow, and results after removal of known and novel loci are shown in gray. Gray bands represent 95% confidence intervals. λ : lambda, genomic control parameter; n: sample size.

Supplementary Figure 11: QQ plots for all GWAS meta-analyses in the sex-stratified samples



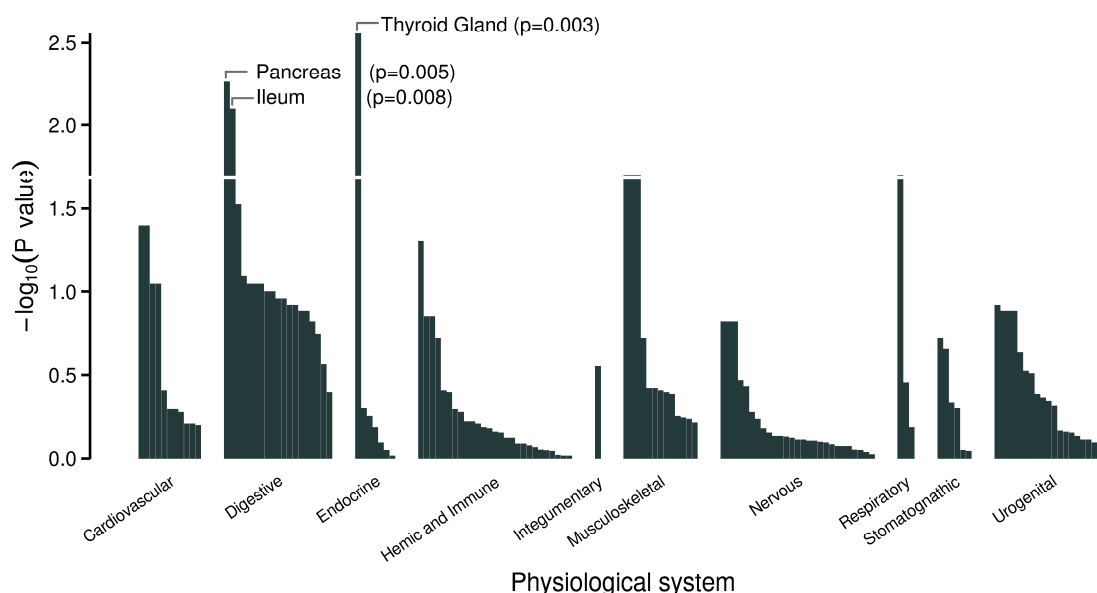
Quantile-quantile (QQ) plots of the GWAS meta-analysis results for TSH in the (a) men and (b) women, and for FT4 in the (c) men and (d) women stratum. The observed p-values of the association test are plotted on the y-axis against their expected distribution under the null hypothesis of no association on the x-axis. Results for all SNPs are shown in black, results after removal of loci previously known to contain trait-associated variants are shown in yellow, and results after removal of known and novel loci are shown in gray. Gray bands represent 95% confidence intervals. λ : lambda, genomic control parameter; n: sample size.

Supplementary Figure 12: Results of pathway analyses

A

Canonical Pathway	TSH	FT4	hyperthyroidism	hypothyroidism
G Protein Signaling Mediated by Tubby	1.21E-05		3.79E-03	
Ephrin Receptor Signaling	1.30E-05			
Cardiac Beta-adrenergic Signaling	3.26E-04		4.47E-03	
Protein Kinase A Signaling	3.33E-04			
Relaxin Signaling	3.49E-04			
Thyronamine and Iodothyronamine Metabolism		1.90E-05		5.89E-03
Thyroid Hormone Metabolism I (via Deiodination)		1.90E-05		5.89E-03
Thyroid Hormone Biosynthesis				5.89E-03
TR/RXR Activation		6.48E-05		
2-amino-3-carboxymuconate Semialdehyde Degradation to Glytaryl-CoA		2.56E-03		
Thyroid Hormone Metabolism II (via conjugation and/or degradation)		3.58E-03		
cAMP-mediated signaling			2.16E-03	
Gustation Pathway			3.43E-03	
tRNA Splicing			3.45E-03	2.16E-03
T Cell Receptor Signaling				9.17E-04

B



Panel A shows the top canonical pathways of the respective GWAS obtained by the IPA tool. The p-value for each pathway is calculated using a right-tailed Fisher Exact test. Tissue enrichment results based on the TSH GWAS (overall sample) obtained by the DEPICT software are shown in panel B. The nominal p-values <0.01 of the corresponding tissues are provided in the figure.

Supplementary Table 1: Genome-wide significant index SNPs for TSH after final stage

SNP	Chr	Position	Locus	A1	A2	AF1	Effect	SE	P	I2	N total	P GxSex	P hyperthyroidism	P hypothyroidism	P FT4
known loci															
rs12089835*	1	19,771,438	CAPZB	t	c	0.35	0.073	0.007	1.3E-28	5.3	51018	0.734	7.7E-04	1.5E-06	0.015
rs10917469	1	19,843,576	CAPZB	a	g	0.84	0.111	0.009	4.0E-39	26.5	51018	0.793	1.0E-08	1.9E-10	0.001
rs74804879*	1	19,862,320	CAPZB	t	c	0.65	0.050	0.007	1.2E-14	5.3	51018	0.287	6.8E-04	3.8E-04	0.034
rs334725	1	61,610,049	NFIA	a	g	0.95	0.174	0.015	2.4E-32	39.2	51018	0.750	1.6E-04	6.7E-05	1.1E-04
rs17020122	1	108,357,391	VAV3	t	c	0.09	0.104	0.011	5.3E-20	11.6	51018	0.093	1.1E-01	6.4E-14	0.142
rs16856540*	2	217,580,413	IGFBP5	t	c	0.84	-0.055	0.008	7.8E-11	0.0	52047	0.805	6.8E-04	8.0E-01	0.603
rs13015993	2	217,625,523	IGFBP5	a	g	0.73	0.082	0.007	4.5E-32	0.0	52047	0.034	3.5E-07	5.4E-02	0.043
rs1663070	3	12,239,852	SYN2	t	c	0.74	-0.046	0.007	3.5E-11	0.0	54288	0.243	1.3E-01	3.1E-03	0.889
rs6535624*	4	149,587,905	NR3C2	a	g	0.44	0.042	0.006	1.6E-11	0.0	52047	0.441	3.3E-03	2.8E-02	0.387
rs11732089	4	149,665,602	NR3C2	t	c	0.80	0.115	0.008	1.7E-51	8.4	52047	0.673	1.7E-06	2.8E-05	0.563
rs62362610*	5	76,439,961	PDE8B	g	c	0.08	0.073	0.012	7.7E-10	0.0	53074	0.205	1.3E-02	7.5E-02	0.156
rs1119208*	5	76,488,613	PDE8B	t	c	0.37	0.046	0.006	6.6E-13	13.6	53074	0.835	4.8E-05	9.5E-01	0.150
rs139424329*	5	76,495,539	PDE8B	a	g	0.01	-0.200	0.032	5.1E-10	0.0	45981	0.640	1.4E-02	5.5E-01	0.574
rs2127387	5	76,532,571	PDE8B	a	g	0.41	0.104	0.006	1.1E-117	25.0	53074	0.012	5.5E-22	4.2E-09	2.4E-06
rs7702192*	5	76,554,807	PDE8B	a	c	0.47	0.070	0.006	2.6E-30	0.0	53074	0.177	2.7E-07	3.6E-03	6.1E-02
rs113974964*	5	76,652,403	PDE8B	t	c	0.05	-0.124	0.015	2.1E-17	41.5	53074	0.656	4.2E-04	2.7E-01	0.224
rs139149784*	5	76,660,193	PDE8B	a	g	0.03	0.156	0.029	5.0E-08	2.3	49018	0.552	1.0E-01	7.9E-03	0.979
rs182873197*	5	76,773,148	PDE8B	t	c	0.05	-0.080	0.014	1.7E-08	14.4	53074	0.667	2.5E-01	1.9E-01	0.408
rs744103	6	43,805,362	VEGFA/LOC100132354	a	t	0.69	0.092	0.007	6.7E-41	40.9	54288	0.802	3.7E-05	5.7E-05	3.3E-05
rs9381266*	6	43,905,037	VEGFA/LOC100132354	t	c	0.74	0.073	0.007	1.8E-25	27.1	54288	0.390	1.5E-07	3.3E-03	5.6E-03
rs9497965	6	148,521,292	SASH1	t	c	0.40	0.044	0.006	9.8E-13	21.9	54288	0.069	3.5E-01	1.6E-05	0.327
rs73022105*	6	165,973,757	PDE10A	t	c	0.95	0.005	0.016	1.2E-11	0.0	52424	0.087	2.2E-02	2.4E-01	0.406
rs1079418	6	166,047,034	PDE10A	a	g	0.69	0.101	0.007	8.2E-53	20.9	52424	0.206	3.6E-09	4.3E-08	0.019
rs2439301	8	32,433,013	NRG1	a	g	0.23	-0.059	0.008	8.2E-15	13.9	54288	0.177	7.9E-03	3.5E-02	0.308
rs10814915	9	4,290,544	GLIS3	t	c	0.44	0.042	0.006	5.1E-12	6.4	54288	0.547	3.2E-04	2.5E-03	5.6E-05
rs8176645	9	136,149,098	ABO	a	t	0.34	0.052	0.006	3.9E-16	51.2	54288	0.383	2.1E-02	2.2E-04	0.806
rs200574439	10	101,283,330	NKX2-3	a	c	0.58	-0.047	0.006	3.7E-13	13.8	54288	0.311	3.2E-05	1.4E-04	0.007
rs12284404	11	45,228,686	PRDM11	a	g	0.27	-0.067	0.007	2.5E-22	0.0	54288	0.250	6.0E-11	9.5E-01	0.414
rs398745	14	36,536,181	MBIP	a	c	0.59	-0.052	0.006	4.0E-17	0.0	54288	0.236	1.7E-03	2.2E-02	1.8E-04
rs2254613*	14	36,713,154	MBIP	t	g	0.55	-0.035	0.006	3.4E-08	27.0	54288	0.754	2.4E-02	4.2E-01	0.008
rs8015085	14	93,585,331	ITPK1	a	g	0.21	0.067	0.008	2.4E-18	16.9	54288	0.875	3.5E-04	4.5E-03	2.5E-05
rs17477923	15	49,711,185	FAM227B/FGF7	t	c	0.74	0.083	0.007	2.6E-33	40.3	54288	0.503	6.1E-13	1.6E-02	1.2E-06
rs11639111*	15	49,749,735	FAM227B/FGF7	t	c	0.41	0.045	0.006	3.6E-13	11.0	54288	0.858	9.7E-04	1.3E-01	0.047
rs13329353	15	89,113,877	DET1	t	c	0.68	0.061	0.007	5.2E-21	19.2	54288	0.110	3.4E-03	7.9E-01	3.6E-06
rs17767491	16	79,745,487	MAF	a	g	0.68	0.088	0.007	3.4E-42	40.5	54288	0.069	7.0E-07	5.6E-03	0.054
rs1042673	17	70,121,339	SOX9	a	g	0.52	-0.055	0.006	3.6E-19	0.0	54288	0.563	3.2E-06	8.7E-01	0.672
rs963384*	17	70,369,758	SOX9	t	c	0.46	0.035	0.006	2.8E-08	0.0	54288	0.370	2.7E-08	2.5E-01	0.643
rs4804413	19	7,222,655	INSR	t	c	0.44	0.053	0.006	8.6E-18	0.6	51942	0.865	9.7E-03	1.8E-03	0.030
rs1203944	20	22,596,879	FOXA2	t	c	0.23	-0.051	0.007	2.4E-12	0.0	54288	0.040	3.8E-02	6.2E-05	0.145
novel loci															
rs6724073	2	218,236,786	DIRC3	t	c	0.74	0.051	0.008	1.3E-10	6.8	52047	0.690	1.1E-01	6.3E-02	0.005
rs28502438	3	149,220,109	TM4SF4	t	c	0.57	0.034	0.006	3.7E-08	0.0	54288	0.803	7.6E-01	7.2E-02	0.183
rs13100823	3	185,514,088	IGF2BP2	t	c	0.31	-0.041	0.007	6.8E-10	9.5	54288	0.367	8.5E-04	1.7E-04	0.003
rs59381142	3	193,916,181	HES1	a	g	0.24	-0.058	0.008	1.7E-14	0.0	52048	0.225	1.8E-03	2.4E-02	0.353
rs1265091	6	31,108,129	PSORS1C1	t	c	0.20	0.057	0.009	3.2E-11	38.5	47651	0.483	3.0E-01	3.0E-02	0.047
rs56009477	8	23,356,964	SLC25A37	a	g	0.84	0.052	0.008	3.7E-10	0.0	54288	0.869	9.2E-03	3.5E-02	0.085
rs10957494	8	70,365,025	SULF1	a	g	0.69	-0.040	0.007	1.1E-09	24.1	54288	0.008	3.5E-02	2.5E-01	0.221
rs118039499	8	133,771,635	TG	a	c	0.98	0.184	0.024	2.0E-14	37.8	48736	0.065	1.8E-12	4.0E-01	0.401
rs2739067*	8	133,951,991	TG	a	g	0.60	-0.042	0.006	2.4E-11	0.0	54288	0.125	1.2E-01	1.3E-01	0.026
rs9298749	9	16,214,340	C9orf92	a	c	0.59	-0.039	0.006	8.8E-10	16.7	54288	0.524	9.0E-01	6.9E-03	0.039
rs11255790	10	8,682,180	GATA3	t	c	0.30	-0.041	0.007	6.8E-10	0.0	54288	0.016	1.3E-02	7.9E-01	0.358
rs4933466	10	89,849,519	PTEN	a	g	0.60	0.040	0.006	5.1E-10	28.6	54288	0.557	2.6E-01	6.6E-03	0.028
rs4445669	11	115,045,237	CADM1	t	c	0.46	-0.040	0.006	5.8E-11	0.0	54288	0.600	5.1E-02	9.4E-02	0.158
rs7329958	13	24,782,080	SPATA13	t	c	0.35	-0.044	0.007	1.1E-11	0.0	54288	0.138	6.1E-01	4.5E-03	0.137
rs11159482*	14	81,490,842	TSHR	t	c	0.09	0.085	0.013	6.3E-11	0.0	54288	0.397	1.9E-01	1.8E-04	0.210
rs59334515*	14	81,594,143	TSHR	t	c	0.22	-0.054	0.007	1.1E-13	25.7	54288	0.697	1.4E-02	3.1E-03	0.082
rs12893151	14	81,619,945	TSHR	a	c	0.22	-0.062	0.008	1.0E-15	28.2	54288	0.124	3.2E-04	1.9E-04	0.931
rs1045476	16	4,015,313	ADCY9	a	g	0.18	0.049	0.008	2.4E-09	0.0	54288	0.660	1.7E-01	4.6E-03	0.745
rs30227	16	14,405,428	MIR365A	t	c	0.61	-0.047	0.006	7.6E-14	11.1	54288	0.955	2.6E-02	1.1E-01	0.087
rs77819282	17	44,762,589	NSF	a	g	0.24	0.045	0.007	1.1E-09	0.0	54288	0.419	5.2E-01	7.1E-03	0.715
rs1157994	17	59,338,574	BCAS3	a	g	0.05	-0.090	0.016	5.3E-09	25.4	50232	0.990	1.8E-01	4.1E-01	0.003
rs12390237	X	3,612,081	PRKX	a	g	0.62	-0.046	0.007	1.7E-11	0.0	36501	0.894	1.0E-02	6.6E-01	0.705

Effects, standard errors (SE), p-values (P) and N total are provided for the discovery stage. (*) additional independent hits of a locus. A1: effect allele; AF1: allele frequency of A1; I2: percentage of total variation across studies that is due to heterogeneity; P GxSex: p-values of gene-by-sex interaction. Bold values of the increased and decreased TSH p-values indicate significance after Bonferroni correction for the 61 independent TSH-associated SNPs tested ($p < 8.2E-4$). Bold values of the FT4 p-values indicate significance after Bonferroni correction for the 91 independent FT4+TSH SNPs tested ($p < 5.5E-4$).

Supplementary Table 2: Genome-wide significant index SNPs for FT4 after final stage

SNP	Chr	Position	Locus	A1	A2	AF1	Effect	SE	P	I2	N total	P GxSex	P TSH
known loci													
rs145019385*	1	54,252,139	<i>DIO1</i>	t	c	0.98	0.181	0.032	1.1E-08	0.0	42463	0.799	0.708
rs12033572*	1	54,369,674	<i>DIO1</i>	c	g	0.05	0.115	0.017	1.4E-11	0.0	49269	0.371	0.377
rs2235544	1	54,375,570	<i>DIO1</i>	a	c	0.52	0.139	0.007	4.2E-101	0.0	49269	0.950	0.062
rs954878*	1	54,578,401	<i>DIO1</i>	a	g	0.45	-0.058	0.007	4.8E-19	0.0	49269	0.468	0.799
rs6854291	4	170,992,760	<i>AADAT</i>	a	g	0.10	0.117	0.011	1.3E-24	4.5	47314	0.257	0.030
rs10739496	9	100,552,559	<i>FOXE1</i>	t	c	0.66	0.078	0.007	4.2E-30	20.1	49269	0.181	4.8E-07
rs10984606*	9	100,739,117	<i>FOXE1</i>	t	g	0.50	-0.040	0.007	1.2E-09	0.0	49269	0.405	0.030
rs4842131	9	139,092,679	<i>LHX3</i>	t	c	0.45	-0.104	0.008	7.7E-44	4.4	44811	0.285	0.315
rs55679545*	9	139,122,363	<i>LHX3</i>	a	g	0.27	0.044	0.008	8.4E-09	0.0	49269	0.428	0.321
rs1080094*	18	29,173,795	<i>SLC25A52</i>	a	g	0.60	-0.042	0.007	4.1E-10	14.5	49269	0.008	0.272
rs113107469	18	29,306,737	<i>SLC25A52</i>	t	c	0.03	0.200	0.022	1.0E-19	34.3	49269	0.431	0.510
novel loci													
rs4954192	2	135,632,981	<i>ACMSD</i>	t	c	0.43	-0.041	0.007	8.4E-09	0.0	44902	0.826	0.333
rs6785807	3	181,718,601	<i>SOX2-OT</i>	a	g	0.15	-0.059	0.009	2.5E-10	14.4	49269	0.026	0.297
rs10946313	6	19,381,386	<i>ID4</i>	t	c	0.63	0.046	0.007	2.3E-11	0.0	49269	0.243	0.002
rs9356988	6	25,777,481	<i>SLC17A4</i>	a	g	0.27	-0.051	0.007	3.6E-12	0.0	49269	0.273	0.802
rs137964359*	6	26,001,742	<i>SLC17A4</i>	t	c	0.99	-0.200	0.032	2.1E-10	0.0	49269	0.175	0.335
rs17185536	6	100,620,931	<i>LOC728012</i>	t	c	0.24	0.073	0.008	1.9E-19	0.0	49269	0.368	0.707
rs67583169	8	61,212,179	<i>CA8</i>	c	g	0.87	0.061	0.010	1.0E-10	0.0	49269	0.718	0.169
rs10119187	9	4,223,660	<i>GLIS3</i>	t	c	0.81	0.050	0.009	4.1E-09	15.9	49269	0.933	2.2E-06
rs10818937	9	127,015,440	<i>NEK6</i>	t	c	0.31	-0.048	0.007	1.3E-11	0.0	49269	0.388	6.3E-04
rs11039355	11	47,737,501	<i>FNBP4</i>	t	c	0.34	-0.039	0.007	3.5E-08	20.9	49269	0.080	0.764
rs4149056	12	21,331,549	<i>SLCO1B1</i>	t	c	0.84	-0.051	0.009	1.3E-08	5.2	49269	0.432	0.094
rs150816132*	14	80,464,293	<i>DIO2</i>	a	g	0.01	-0.220	0.040	3.5E-08	24.1	38640	0.453	0.435
rs978055*	14	80,534,869	<i>DIO2</i>	a	t	0.38	0.038	0.007	1.1E-08	10.5	49269	0.350	0.642
rs225014	14	80,669,580	<i>DIO2</i>	t	c	0.64	0.054	0.007	1.8E-15	0.0	49269	0.759	0.006
rs12323871*	14	101,852,075	<i>DIO3OS</i>	t	c	0.82	-0.047	0.008	1.4E-08	25.7	49269	0.829	0.144
rs11626434	14	101,998,443	<i>DIO3OS</i>	c	g	0.36	0.058	0.007	4.1E-17	40.7	49269	0.908	0.340
rs12907106	15	63,873,658	<i>USP3</i>	c	g	0.27	-0.041	0.007	3.7E-08	0.7	49269	0.038	0.494
rs8063103	16	12,703,395	<i>SNX29</i>	c	g	0.85	-0.052	0.009	1.6E-08	10.4	49269	0.064	0.934
rs11078333	17	16,049,626	<i>NCOR1</i>	a	t	0.53	0.051	0.007	9.9E-13	0.0	49269	0.956	0.746
rs56069042	18	57,914,644	<i>MC4R</i>	a	g	0.96	0.106	0.019	1.2E-08	0.0	49269	0.516	0.499

Effects, standard errors (SE), p-values (P) and N total are provided for the discovery stage. (*) additional independent hits of a locus. A1: effect allele; AF1: allele frequency of A1; I2: percentage of total variation across studies that is due to heterogeneity; P GxSex: p-values of gene-by-sex interaction. Bold values of the TSH p-values indicate significance after Bonferroni correction for the 91 independent FT4+TSH SNPs tested ($p < 5.5E-4$).

Supplementary Table 3: Distribution of sex and age group for hypo- and hyperthyroidism GWAS cases and controls

hypothyroidism				hyperthyroidism			
age	sex	cases	controls	age	sex	cases	controls
0-19	male	0.0%	0.7%	0-19	male	0.0%	0.7%
0-19	female	0.0%	0.8%	0-19	female	0.0%	0.8%
20-39	male	0.2%	6.9%	20-39	male	0.2%	7.1%
20-39	female	0.4%	7.7%	20-39	female	0.3%	8.0%
40-59	male	0.6%	17.5%	40-59	male	0.6%	18.0%
40-59	female	1.3%	17.7%	40-59	female	0.7%	18.2%
60-79	male	1.0%	20.0%	60-79	male	0.7%	20.6%
60-79	female	2.1%	18.6%	60-79	female	0.8%	19.2%
80+	male	0.2%	1.5%	80+	male	0.1%	1.6%
80+	female	0.3%	2.3%	80+	female	0.1%	2.4%

The % values correspond to the total number of samples in the hypo- and hyperthyroidism analysis, respectively.

Supplementary Table 4: Genome-wide significant index SNPs for hypo- and hyperthyroidism

<i>hypothyroidism</i>														
SNP	Chr	Position	Locus	A1	A2	AF1	Effect	SE	P	I2	N total	P TSH	Reference	
rs7032019*	9	100,548,144	<i>FOXE1</i>	a	g	0.66	0.248	0.027	5.5E-20	11.8	53241	0.000001229	1, 2	
rs78495697	1	108,355,719	<i>VAV3</i>	t	c	0.09	0.316	0.041	2.6E-14	12.6	53241	9.278E-20	2	
rs597808	12	111,973,358	<i>ATXN2/SH2B3</i>	a	g	0.51	0.180	0.026	3.5E-12	21.9	53241	2.29E-06	2	
rs75491569	1	19,836,221	<i>CAPZB</i>	t	c	0.16	-0.238	0.037	8.7E-11	0.0	53241	7.805E-38	1	
rs11675342	2	1,407,628	<i>TPO</i>	t	c	0.43	0.160	0.025	1.5E-10	0.0	53241	7.88E-06	3	
rs1382879	5	76,521,868	<i>PDE8B</i>	t	c	0.59	-0.153	0.026	2.1E-09	0.0	48969	1.51E-115	1	
rs2983514	6	166,050,119	<i>PDE10A</i>	a	g	0.67	0.154	0.027	1.6E-08	15.5	51313	4.745E-48	1	
rs12449792**	17	43,302,259	<i>FMNL1</i>	t	c	0.46	0.157	0.028	2.4E-08	0.0	46314	4.619E-08		
<i>hyperthyroidism</i>														
SNP	Chr	Position	Locus	A1	A2	AF1	Effect	SE	P	I2	N total	P TSH	Reference	
rs2046045	5	76,535,811	<i>PDE8B</i>	t	g	0.60	0.329	0.034	4.4E-22	57.3	50420	3.72E-117	1	
rs17477923	15	49,711,185	<i>FAM227B/FGF7</i>	t	c	0.72	-0.245	0.034	6.1E-13	28.7	48508	2.572E-33	1	
rs11038357	11	45,237,858	<i>PRDM11</i>	a	t	0.28	0.235	0.035	3.1E-11	42.1	48508	3.244E-22	1	
rs8077245	17	70,376,177	<i>SOX9</i>	t	g	0.58	0.205	0.033	5.0E-10	0.0	48508	6.231E-14	1	
rs2983514	6	166,050,119	<i>PDE10A</i>	a	g	0.65	-0.199	0.032	5.2E-10	37.7	49745	4.745E-48	1	
rs12138950	1	19,839,115	<i>CAPZB</i>	a	c	0.85	-0.258	0.042	5.5E-10	64.3	51668	5.789E-38	1	
rs925488*	9	100,546,391	<i>FOXE1</i>	a	g	0.65	0.190	0.033	1.1E-08	66.0	48508	6.482E-07	1, 2, 3	
rs66760320	6	43,906,255	<i>VEGFA/LOC100132354</i>	t	c	0.27	0.192	0.035	4.4E-08	22.6	51668	1.011E-24	3	

(*) FT4 locus (p=3E-29). (**) discovered also in TSH, but did not replicate. SE: standard errors; A1: effect allele; AF1: allele frequency of A1; I2: percentage of total variation across studies that is due to heterogeneity. Bold values of TSH indicate genome-wide significance.

References: 1) Porcu et al. 2012 2) Eriksson et al. 2012 3) Gudmundsson et al. 2012

Supplementary Table 5: Lookup of TSH associated SNPs in Graves' disease and TPOab positivity

<i>Graves' disease</i>							
SNP	Chr	Position	Nearest gene	A1	A2	Effect direction	P
rs12089835	1	19,771,438	CAPZB	t	c	-	0.090
rs10917469	1	19,843,576	CAPZB	a	g	-	0.005
rs74804879	1	19,862,320	CAPZB	t	c	-	0.823
rs334725	1	61,610,049	NFIA	a	g	+	0.206
rs17020122	1	108,357,391	VAV3	t	c	-	0.112
rs16856540	2	217,580,413	IGFBP5	t	c	+	0.021
rs13015993	2	217,625,523	IGFBP5	a	g	-	0.008
rs6724073	2	218,236,786	DIRC3	t	c	+	0.503
rs1663070	3	12,239,852	SYN2	t	c	-	0.035
rs28502438	3	149,220,109	TM4SF4	t	c	-	0.423
rs13100823	3	185,514,088	IGF2BP2	t	c	+	0.018
rs59381142	3	193,916,181	HES1	a	g	-	0.924
rs6535624	4	149,587,905	NR3C2	a	g	-	0.736
rs11732089	4	149,665,602	NR3C2	t	c	-	0.934
rs1119208	5	76,488,613	PDE8B	t	c	+	0.407
rs2127387	5	76,532,571	PDE8B	a	g	-	0.192
rs7702192	5	76,554,807	PDE8B	a	c	-	0.599
rs1265091	6	31,108,129	PSORS1C1	t	c	-	1.3E-12
rs744103	6	43,805,362	VEGFA	a	t	+	0.332
rs9381266	6	43,905,037	LOC100132354	t	c	-	0.290
rs9497965	6	148,521,292	SASH1	t	c	+	0.048
rs73022105	6	165,973,757	PDE10A	t	c	-	0.707
rs1079418	6	166,047,034	PDE10A	a	g	+	0.854
rs56009477	8	23,356,964	SLC25A37	a	g	-	0.269
rs2439301	8	32,433,013	NRG1	a	g	+	0.321
rs10957494	8	70,365,025	SULF1	a	g	-	0.287
rs2739067	8	133,951,991	TG	a	g	-	0.148
rs10814915	9	4,290,544	GLIS3	t	c	+	0.284
rs9298749	9	16,214,340	C9orf92	a	c	+	0.377
rs8176645	9	136,149,098	ABO	a	t	-	0.722
rs11255790	10	8,682,180	GATA3	t	c	+	0.110
rs4933466	10	89,849,519	PTEN	a	g	+	0.420
rs12284404	11	45,228,686	PRDM11	a	g	+	0.986
rs4445669	11	115,045,237	CADM1	t	c	+	0.055
rs7329958	13	24,782,080	SPATA13	t	c	-	0.223
rs398745	14	36,536,181	LINC00609	a	c	+	0.350
rs2254613	14	36,713,154	MBIP	t	g	+	0.570
rs11159482	14	81,490,842	TSHR	t	c	+	0.215
rs59334515	14	81,594,143	TSHR	t	c	+	0.017
rs12893151	14	81,619,945	TSHR	a	c	-	0.193
rs8015085	14	93,585,331	ITPK1	a	g	+	0.912
rs17477923	15	49,711,185	FAM227B	t	c	+	0.764
rs11639111	15	49,749,735	FAM227B	t	c	-	0.089
rs13329353	15	89,113,877	DET1	t	c	-	0.795
rs1045476	16	4,015,313	ADCY9	a	g	+	0.344
rs30227	16	14,405,428	MIR365A	t	c	+	0.966
rs17767491	16	79,745,487	MAF	a	g	-	0.001
rs77819282	17	44,762,589	NSF	a	g	-	0.867
rs1042673	17	70,121,339	SOX9	a	g	+	0.651
rs963384	17	70,369,758	LINC00673	t	c	+	0.647
rs4804413	19	7,222,655	INSR	t	c	-	0.230
rs1203944	20	22,596,879	FOXA2	t	c	+	0.060

TPOab positivity							
SNP	Chr	Position	Nearest gene	A1	A2	Effect direction	P
rs12091047	1	19,771,925	CAPZB	t	c	-	0.187
rs10917469	1	19,843,576	CAPZB	a	g	-	0.836
rs334725	1	61,610,049	NFIA	a	g	-	0.788
rs17020122	1	108,357,391	VAV3	t	c	+	7.4E-04
rs16856540	2	217,580,413	IGFBP5	t	c	+	0.313
rs13015993	2	217,625,523	IGFBP5	a	g	-	0.052
rs6724073	2	218,236,786	TNS1	t	c	-	0.003
rs1663070	3	12,239,852	SYN2	t	c	+	0.821
rs9828967	3	149,226,442	TM4SF4	a	t	+	0.319
rs6767484	3	185,520,578	IGF2BP2	a	g	+	0.916
rs4578973	3	193,918,634	HES1	t	c	+	0.524
rs6535624	4	149,587,905	NR3C2	a	g	+	0.017
rs11732089	4	149,665,602	NR3C2	t	c	+	0.089
rs1119208	5	76,488,613	PDE8B	t	c	-	0.957
rs6885099	5	76,530,349	PDE8B	a	g	-	0.736
rs7702192	5	76,554,807	PDE8B	a	c	+	0.219
rs12189200	5	76,658,640	PDE8B	t	c	-	0.080
rs6869902	5	76,783,252	WDR41	a	c	-	0.810
rs1063646	6	31,107,648	PSORS1C1	t	c	+	0.528
rs744103	6	43,805,362	VEGFA	a	t	-	0.991
rs9381266	6	43,905,037	C6orf223	t	c	-	0.460
rs9497965	6	148,521,292	SASH1	t	c	+	0.122
rs4709949	6	165,966,099	PDE10A	t	c	-	0.447
rs1079418	6	166,047,034	PDE10A	a	g	-	0.128
rs17770799	8	23,347,851	ENTPD4	t	c	+	0.766
rs2439300	8	32,433,104	NRG1	t	c	+	0.115
rs7011706	8	70,362,479	SULF1	t	c	-	0.077
rs2739068	8	133,952,435	TG	t	g	-	0.055
rs10758594	9	4,295,583	GLIS3	a	g	+	0.447
rs9298749	9	16,214,340	BNC2	a	c	-	0.385
rs644234	9	136,142,217	ABO	t	g	+	0.069
rs11255790	10	8,682,180	GATA3	t	c	-	0.287
rs4933466	10	89,849,519	PTEN	a	g	+	0.989
rs7077040	10	101,281,014	NKX2-3	c	g	-	0.286
rs17723470	11	45,227,567	PRDM11	t	c	+	0.112
rs4445669	11	115,045,237	CADM1	t	c	+	0.849
rs4770628	13	24,782,064	SPATA13	a	g	-	1.1E-04
rs398745	14	36,536,181	BRMS1L	a	c	+	0.291
rs2254613	14	36,713,154	MBIP	t	g	+	0.656
rs2268476	14	81,592,717	TSHR	a	g	+	0.192
rs9672082	14	93,572,855	ITPK1	t	c	+	0.114
rs17477923	15	49,711,185	C15orf33	t	c	-	0.013
rs11639111	15	49,749,735	C15orf33	t	c	-	0.095
rs13329353	15	89,113,877	DET1	t	c	+	0.338
rs2072346	16	4,027,423	ADCY9	t	c	+	0.930
rs30227	16	14,405,428	MKL2	t	c	+	0.932
rs17767491	16	79,745,487	MAF	a	g	-	2.2E-05
rs183211	17	44,788,310	NSF	a	g	+	0.963
rs17597856	17	59,314,176	BCAS3	c	g	-	0.215
rs9915657	17	70,127,536	SOX9	t	c	+	0.283
rs759563	17	70,370,888	SOX9	t	c	+	0.287
rs4804416	19	7,223,848	INSR	t	g	+	0.100
rs1203944	20	22,596,879	FOXA2	t	c	+	0.623

A1: effect allele. Bold values indicate significance ($p < 0.05$) after Bonferroni correction for the number of SNPs per trait tested.

Supplementary Table 6: Association of *SLC17A4* and *AADAT* hits with T3 and T3/T4 ratio

SNP	Locus	A1	A2	Effect	SE	P	I ²	N total	N cohorts
FT3									
rs9356988	SLC17A4	a	g	0.022	0.015	0.143	0	10803	3
rs137964359	SLC17A4	t	c	0.012	0.062	0.849	23.5	10803	3
rs6854291	AADAT	a	g	-0.068	0.023	0.003	0	10803	3
TT3									
rs9356988	SLC17A4	a	g	0.019	0.016	0.238	0	9083	2
rs137964359	SLC17A4	t	c	-0.114	0.074	0.125	0	9083	2
rs6854291	AADAT	a	g	-0.049	0.025	0.047	64.2	9083	2
T3*									
rs9356988	SLC17A4	a	g	0.021	0.011	0.06	0	19886	5
rs137964359	SLC17A4	t	c	-0.04	0.048	0.401	14.4	19886	5
rs6854291	AADAT	a	g	-0.059	0.017	4.46E-04	10.6	19886	5
FT3/FT4 ratio									
rs9356988	SLC17A4	a	g	0.008	0.003	0.004	54.9	10800	3
rs137964359	SLC17A4	t	c	0.016	0.012	0.204	0	10800	3
rs6854291	AADAT	a	g	-0.028	0.004	1.15E-10	3.8	10800	3
TT3/FT4 ratio									
rs9356988	SLC17A4	a	g	0.009	0.003	0.007	0	9082	2
rs137964359	SLC17A4	t	c	0.019	0.016	0.221	55.6	9082	2
rs6854291	AADAT	a	g	-0.018	0.005	7.77E-04	0	9082	2
T3/FT4 ratio*									
rs9356988	SLC17A4	a	g	0.009	0.002	8.42E-05	11.4	19882	5
rs137964359	SLC17A4	t	c	0.017	0.01	0.079	0	19882	5
rs6854291	AADAT	a	g	-0.024	0.003	1.24E-12	25.5	19882	5

SE: standard errors; A1: effect allele; AF1: allele frequency of A1. Bold p values of TSH indicate statistical significance (p<0.05) after Bonferroni correction. FT3: free T3; TT3: total T3;

* indicates a combined analysis of FT3 and TT3 of disjunct samples.

Supplementary Table 7: GRS association with hypo- and hyperthyroidism

GRS	outcome:quantile	Effect	SE	p	OR
TSH	hypothyroidism:1	reference			
TSH	hypothyroidism:2	0.272	0.087	1.82E-03	1.31
TSH	hypothyroidism:3	0.566	0.084	1.26E-11	1.76
TSH	hypothyroidism:4	0.929	0.079	6.76E-32	2.53
TSH	hyperthyroidism:1	reference			
TSH	hyperthyroidism:2	-0.746	0.101	1.34E-13	0.47
TSH	hyperthyroidism:3	-1.090	0.112	1.45E-22	0.34
TSH	hyperthyroidism:4	-1.649	0.143	9.81E-31	0.19
FT4	hypothyroidism:1	reference			
FT4	hypothyroidism:2	-0.034	0.075	0.649	0.97
FT4	hypothyroidism:3	0.041	0.074	0.580	1.04
FT4	hypothyroidism:4	0.034	0.074	0.642	1.03
FT4	hyperthyroidism:1	reference			
FT4	hyperthyroidism:2	-0.064	0.114	0.575	0.94
FT4	hyperthyroidism:3	-0.064	0.114	0.575	0.94
FT4	hyperthyroidism:4	0.035	0.112	0.752	1.04
TSH	hypothyroidism:Genescore	0.100	0.007	4.47E-45	1.11
TSH	hyperthyroidism:Genescore	-0.179	0.011	7.90E-60	0.84
FT4	hypothyroidism:Genescore	0.004	0.006	0.535	1.00
FT4	hyperthyroidism:Genescore	0.004	0.009	0.642	1.00

Association results of the genetic risk score (GRS) based on TSH and FT4 with hypo- and hyperthyroidism contrasting the respective quartile of the GRS distribution against the lowest quartile (1). Genescore corresponds to the association results on the continuous GRS scale (0-100). SE: standard error; OR: odds ratio

Supplementary Table 8: Association results of TSH-based genetic risk score

Trait	#SNPs in GRS	Effect (SE)	P	FDR	Reference
Graves' disease	52	-0.443 (0.104)	2.00E-05	8.50E-05	
hypothyroidism	61	1.203 (0.060)	6.20E-89	1.10E-87	
hyperthyroidism	61	-1.957 (0.074)	4.00E-156	1.40E-154	
TPO antibody (case/control)	53	-0.137 (0.081)	8.90E-02	2.00E-01	Medici et al. (2014)
goiter	53	-1.190 (0.110)	3.90E-27	3.40E-26	Teumer et al. (2011)
thyroid volume	53	-0.262 (0.020)	1.30E-37	1.60E-36	Teumer et al. (2011)
anxiety (case/control)	53	-0.116 (0.071)	1.00E-01	2.10E-01	Otowa et al. (2016)
anxiety (factor score)	52	0.002 (0.013)	8.80E-01	9.30E-01	Otowa et al. (2016)
type 2 diabetes (DIAGRAM)	50	-0.110 (0.045)	1.60E-02	5.00E-02	Morris et al. (2012)
forearm BMD (GEFOS)	59	-0.051 (0.037)	1.70E-01	3.10E-01	Zheng et al. (2015)
femoral neck BMD (GEFOS)	60	-0.010 (0.018)	5.70E-01	7.40E-01	Zheng et al. (2015)
lumbar spine BMD (GEFOS)	60	-0.004 (0.021)	8.50E-01	9.30E-01	Zheng et al. (2015)
body mass index (GIANT)	51	0.006 (0.009)	5.00E-01	7.20E-01	Locke et al. (2015)
waist circumference adjBMI (GIANT)	51	-0.022 (0.010)	3.30E-02	8.80E-02	Shungin et al. (2015)
waist-hip-ratio adjBMI (GIANT)	51	4.8E-04 (0.010)	9.60E-01	9.80E-01	Shungin et al. (2015)
body height (GIANT)	51	-0.050 (0.007)	2.00E-11	1.40E-10	Wood et al. (2014)
obesity class 1 (GIANT)	50	0.026 (0.032)	4.20E-01	6.30E-01	Berndt et al. (2013)
obesity class 2 (GIANT)	50	0.032 (0.049)	5.10E-01	7.20E-01	Berndt et al. (2013)
obesity class 3 (GIANT)	50	0.046 (0.092)	6.20E-01	7.70E-01	Berndt et al. (2013)
gout (GUGC)	50	0.149 (0.078)	5.50E-02	1.40E-01	Köttgen et al. (2013)
uric acid (GUGC)	50	0.021 (0.014)	1.20E-01	2.40E-01	Köttgen et al. (2013)
IGF-I	50	-4.2E-04 (0.022)	9.80E-01	9.80E-01	Teumer et al. (2016)
IGFBP3	50	-0.045 (0.026)	8.00E-02	1.90E-01	Teumer et al. (2016)
HDL (GLGC)	48	0.011 (0.012)	3.60E-01	6.00E-01	Willer et al. (2013)
LDL (GLGC)	48	0.035 (0.013)	4.90E-03	1.90E-02	Willer et al. (2013)
total cholesterol (GLGC)	48	0.054 (0.012)	1.10E-05	6.50E-05	Willer et al. (2013)
triglyceride (GLGC)	48	-0.004 (0.011)	7.50E-01	9.00E-01	Willer et al. (2013)
fasting glucose (MAGIC)	50	0.005 (0.009)	5.70E-01	7.40E-01	Dupuis et al. (2010)
HbA1C (MAGIC)	52	0.010 (0.009)	2.40E-01	4.20E-01	Soranzo et al. (2010)
bipolar disorder (PGC)	49	-0.050 (0.060)	4.10E-01	6.30E-01	PGC BD WG (2011)
major depressive disorder (PGC)	34	-0.011 (0.068)	8.70E-01	9.30E-01	PGC MDD WG (2011)
kidney function eGFR (CKDGen)	48	-0.010 (0.002)	1.40E-05	7.20E-05	Pattaro et al. (2016)
kidney function UACR (CKDGen)	48	-0.035 (0.016)	3.00E-02	8.80E-02	Teumer et al. (2015)
schizophrenia (PGC)	61	-0.064 (0.025)	1.10E-02	3.80E-02	Schizophrenia PGC (2011)
education years (SSGAC)	49	-0.009	8.10E-01	9.30E-01	Rietveld et al. (2013)

Bold values indicate significant associations of GRS with the respective trait (false discovery rate < 0.05). Effect provides the change of the unit of the corresponding trait (or log of odd ratio for binary traits) per increase in standard deviation of TSH.

Supplementary Table 9: Association results of FT4-based genetic risk score

Trait	#SNPs in GRS	Effect (SE)	P	FDR	Reference
Graves' disease	25	-0.225 (0.151)	1.37E-01	3.49E-01	
hypothyroidism	31	0.078 (0.084)	3.52E-01	5.60E-01	
hyperthyroidism	31	0.179 (0.105)	8.79E-02	3.42E-01	
goiter	27	0.417 (0.157)	7.90E-03	4.61E-02	Teumer et al. (2011)
thyroid volume	27	0.084 (0.029)	3.84E-03	3.36E-02	Teumer et al. (2011)
TPO antibody (case/control)	27	0.004 (0.113)	9.72E-01	9.72E-01	Medici et al. (2014)
anxiety (case/control)	27	-0.238 (0.099)	1.64E-02	8.19E-02	Otowa et al. (2016)
anxiety (factor score)	27	-0.012 (0.018)	4.78E-01	6.69E-01	Otowa et al. (2016)
type 2 diabetes (DIAGRAM)	27	-0.056 (0.065)	3.90E-01	5.69E-01	Morris et al. (2012)
forearm BMD (GEFOS)	30	0.055 (0.053)	2.98E-01	5.48E-01	Zheng et al. (2015)
femoral neck BMD (GEFOS)	31	0.012 (0.025)	6.37E-01	7.50E-01	Zheng et al. (2015)
lumbar spine BMD (GEFOS)	31	0.044 (0.029)	1.29E-01	3.49E-01	Zheng et al. (2015)
body mass index (GIANT)	27	-0.039 (0.013)	2.74E-03	3.19E-02	Locke et al. (2015)
waist circumference adjBMI (GIANT)	27	-0.001 (0.015)	9.42E-01	9.72E-01	Shungin et al. (2015)
waist-hip-ratio adjBMI (GIANT)	27	-0.019 (0.015)	1.94E-01	4.54E-01	Shungin et al. (2015)
body height (GIANT)	27	0.039 (0.011)	2.92E-04	5.50E-03	Wood et al. (2014)
obesity class 1 (GIANT)	27	-0.044 (0.045)	3.31E-01	5.51E-01	Berndt et al. (2013)
obesity class 2 (GIANT)	27	-0.014 (0.069)	8.45E-01	9.24E-01	Berndt et al. (2013)
obesity class 3 (GIANT)	27	0.008 (0.126)	9.50E-01	9.72E-01	Berndt et al. (2013)
gout (GUGC)	27	0.173 (0.117)	1.40E-01	3.49E-01	Köttgen et al. (2013)
uric acid (GUGC)	27	-0.029 (0.020)	1.32E-01	3.49E-01	Köttgen et al. (2013)
IGF-I	27	0.036 (0.031)	2.41E-01	4.68E-01	Teumer et al. (2016)
IGFBP3	27	0.008 (0.037)	8.19E-01	9.24E-01	Teumer et al. (2016)
HDL (GLGC)	27	0.020 (0.016)	2.17E-01	4.68E-01	Willer et al. (2013)
LDL (GLGC)	27	-0.063 (0.017)	3.14E-04	5.50E-03	Willer et al. (2013)
total cholesterol (GLGC)	27	-0.047 (0.017)	6.07E-03	4.25E-02	Willer et al. (2013)
triglyceride (GLGC)	27	-0.010 (0.016)	5.32E-01	7.16E-01	Willer et al. (2013)
fasting glucose (MAGIC)	27	-0.013 (0.013)	3.27E-01	5.51E-01	Dupuis et al. (2010)
HbA1C (MAGIC)	27	0.015 (0.012)	2.32E-01	4.68E-01	Soranzo et al. (2010)
bipolar disorder (PGC)	27	-0.162 (0.085)	5.57E-02	2.44E-01	PGC BD WG (2011)
major depressive disorder (PGC)	10	-0.086 (0.098)	3.78E-01	5.69E-01	PGC MDD WG (2011)
kidney function eGFR (CKDGen)	25	0.002 (0.003)	6.11E-01	7.50E-01	Pattaro et al. (2016)
kidney function UACR (CKDGen)	26	-0.034 (0.023)	1.36E-01	3.49E-01	Teumer et al. (2015)
schizophrenia (PGC)	31	-0.020 (0.035)	5.68E-01	7.37E-01	Schizophrenia PGC (2011)
education years (SSGAC)	27	-0.006 (0.013)	6.43E-01	7.50E-01	Rietveld et al. (2013)

Bold values indicate significant associations of GRS with the respective trait (false discovery rate < 0.05). Effect provides the change of the unit of the corresponding trait (or log of odd ratio for binary traits) per increase in standard deviation of FT4.

Supplementary Table 10: Replication results of GWAS SNPs

TSH														
SNP	Chr	Position	Locus	A1	A2	AF1	Effect discovery	P discovery	Effect replication	P replication	N replication	P combined	N combined	proxy SNP (R2)
rs12893151	14	81,619,945	<i>TSHR</i>	a	c	0.22	-0.062	1.0E-15	-0.025	1.7E-01	9011	2.3E-15	63299	
rs59381142	3	193,916,181	<i>HES1</i>	a	g	0.24	-0.058	1.7E-14	-0.036	3.5E-02	9011	3.6E-15	61059	
rs118039499	8	133,771,635	<i>TG</i>	a	c	0.98	0.184	2.0E-14	0.188	2.5E-08	17879	2.9E-21	66615	rs114322847 (0.87)
rs30227	16	14,405,428	<i>MIR365A</i>	t	c	0.61	-0.047	7.6E-14	-0.042	6.1E-05	17879	2.3E-17	72167	rs30229 (0.91)
rs7329958	13	24,782,080	<i>SPATA13</i>	t	c	0.35	-0.044	1.1E-11	-0.047	1.6E-03	9011	7.1E-14	63299	
rs12390237	X	3,612,081	<i>PRKX</i>	a	g	0.62	-0.046	1.7E-11	NA	NA	0	1.7E-11	36501	
rs1265091	6	31,108,129	<i>PSORS1C1</i>	t	c	0.20	0.057	3.2E-11	0.060	3.3E-05	16772	5.0E-15	64423	rs1063646 (0.89)
rs4445669	11	115,045,237	<i>CADM1</i>	t	c	0.46	-0.040	5.8E-11	-0.034	1.8E-02	9011	3.6E-12	63299	
rs6724073	2	218,236,786	<i>DIRC3</i>	t	c	0.74	0.051	1.3E-10	0.019	2.6E-01	9011	3.1E-10	61058	
rs56009477	8	23,356,964	<i>SLC25A37</i>	a	g	0.84	0.052	3.7E-10	0.034	7.7E-02	9011	1.1E-10	63299	
rs4933466	10	89,849,519	<i>PTEN</i>	a	g	0.60	0.040	5.1E-10	0.024	1.0E-01	9011	2.2E-10	63299	
rs13100823	3	185,514,088	<i>IGF2BP2</i>	t	c	0.31	-0.041	6.8E-10	-0.050	1.3E-03	9011	4.1E-12	63299	
rs11255790	10	8,682,180	<i>GATA3</i>	t	c	0.30	-0.041	6.8E-10	-0.026	9.7E-02	9011	2.5E-10	63299	
rs9298749	9	16,214,340	<i>C9orf92</i>	a	c	0.59	-0.039	8.8E-10	-0.029	5.4E-02	9011	1.6E-10	63299	
rs10957494	8	70,365,025	<i>SULF1</i>	a	g	0.69	-0.040	1.1E-09	-0.012	4.4E-01	9011	3.6E-09	63299	
rs77819282	17	44,762,589	<i>NSF</i>	a	g	0.24	0.045	1.1E-09	0.030	1.1E-01	7904	4.3E-10	62192	
rs1045476	16	4,015,313	<i>ADCY9</i>	a	g	0.18	0.049	2.4E-09	0.042	3.3E-03	17879	3.2E-11	72167	rs2531992 (0.82)
rs1157994	17	59,338,574	<i>BCAS3</i>	a	g	0.05	-0.090	5.3E-09	-0.047	1.6E-01	9011	4.0E-09	59243	
rs28133*	19	8,327,502	<i>CERS4</i>	t	c	0.08	0.072	1.1E-08	0.014	6.0E-01	9011	6.0E-08	58713	
rs55706568*	17	43,292,035	<i>FMNL1</i>	c	g	0.55	-0.038	1.1E-08	0.002	9.2E-01	9011	2.5E-07	63299	
rs28502438	3	149,220,109	<i>TM4SF4</i>	t	c	0.57	0.034	3.7E-08	0.041	5.2E-03	9011	7.3E-10	63299	
rs17398234*	8	66,934,902	<i>DNAJC5B</i>	t	g	0.97	-0.100	4.3E-08	-0.027	5.0E-01	9011	1.4E-07	63299	
FT4														
rs17185536	6	100,620,931	<i>LOC728012</i>	t	c	0.24	0.073	1.9E-19	0.053	3.5E-02	4532	2.7E-20	53801	
rs11626434	14	101,998,443	<i>DIO3OS</i>	c	g	0.36	0.058	4.1E-17	0.020	2.6E-01	5826	1.7E-16	55095	
rs225014	14	80,669,580	<i>DIO2</i>	t	c	0.64	0.054	1.8E-15	0.033	1.5E-03	14702	4.6E-17	63971	
rs11078333	17	16,049,626	<i>NCOR1</i>	a	t	0.53	0.051	9.9E-13	0.021	4.4E-02	13408	2.0E-12	62677	rs3815038 (0.96)
rs9356988	6	25,777,481	<i>SLC17A4</i>	a	g	0.27	-0.051	3.6E-12	-0.056	4.2E-03	5827	5.7E-14	55096	
rs10818937	9	127,015,440	<i>NEK6</i>	t	c	0.31	-0.048	1.3E-11	-0.018	9.3E-02	14702	4.9E-11	63971	
rs10946313	6	19,381,386	<i>ID4</i>	t	c	0.63	0.046	2.3E-11	0.032	7.9E-02	5827	6.2E-12	55096	
rs67583169	8	61,212,179	<i>CA8</i>	c	g	0.87	0.061	1.0E-10	0.064	2.3E-02	4532	7.1E-12	53801	
rs6785807	3	181,718,601	<i>SOX2-OT</i>	a	g	0.15	-0.059	2.5E-10	-0.041	8.5E-02	5827	6.9E-11	55096	
rs10119187	9	4,223,660	<i>GLIS3</i>	t	c	0.81	0.050	4.1E-09	0.037	6.0E-02	7667	8.0E-10	56936	
rs4954192	2	135,632,981	<i>ACMSD</i>	t	c	0.43	-0.041	8.4E-09	-0.018	6.0E-02	17778	9.3E-09	62680	rs6430552 (0.96)
rs56069042	18	57,914,644	<i>MC4R</i>	a	g	0.96	0.106	1.2E-08	0.067	8.0E-02	8928	3.7E-09	58197	
rs4149056	12	21,331,549	<i>SLCO1B1</i>	t	c	0.84	-0.051	1.3E-08	-0.042	1.0E-03	17822	6.3E-11	67091	
rs8063103	16	12,703,395	<i>SNX29</i>	c	g	0.85	-0.052	1.6E-08	-0.038	2.0E-01	4532	7.8E-09	53801	
rs73405691*	6	34,468,767	<i>PACSL1</i>	a	g	0.87	0.056	1.6E-08	-0.002	9.2E-01	7673	2.1E-07	56942	
rs72783371*	10	13,436,195	<i>BEND7</i>	a	c	0.92	0.067	2.8E-08	-0.017	5.7E-01	7596	7.9E-07	56865	
rs11039355	11	47,737,501	<i>FNBP4</i>	t	c	0.34	-0.039	3.5E-08	-0.038	5.7E-04	13408	7.9E-11	62677	rs1064608 (0.95)
rs12907106	15	63,873,658	<i>USP3</i>	c	g	0.27	-0.041	3.7E-08	-0.020	4.0E-01	4532	3.7E-08	53801	
rs951366*	1	205,685,352	<i>NUCKS1</i>	t	c	0.62	0.037	4.4E-08	0.015	2.9E-01	8950	6.1E-08	58219	

(*) did not replicate because not all criteria specified in the methods were fulfilled. SE: standard errors; A1: effect allele; AF1: allele frequency of A1. The proxy SNP and its R2 are provided in case a proxy SNP was used (applies for the Health2006 and Inter99 studies only).

Supplementary References

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