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Supplemental information

Genome-wide association meta-analysis identifies 48 risk variants and highlights the role of the stria vascularis in hearing loss

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Supplementary information

Figure S1. Quantile-Quantile plot of association test results from meta-analysis of hearing impairment

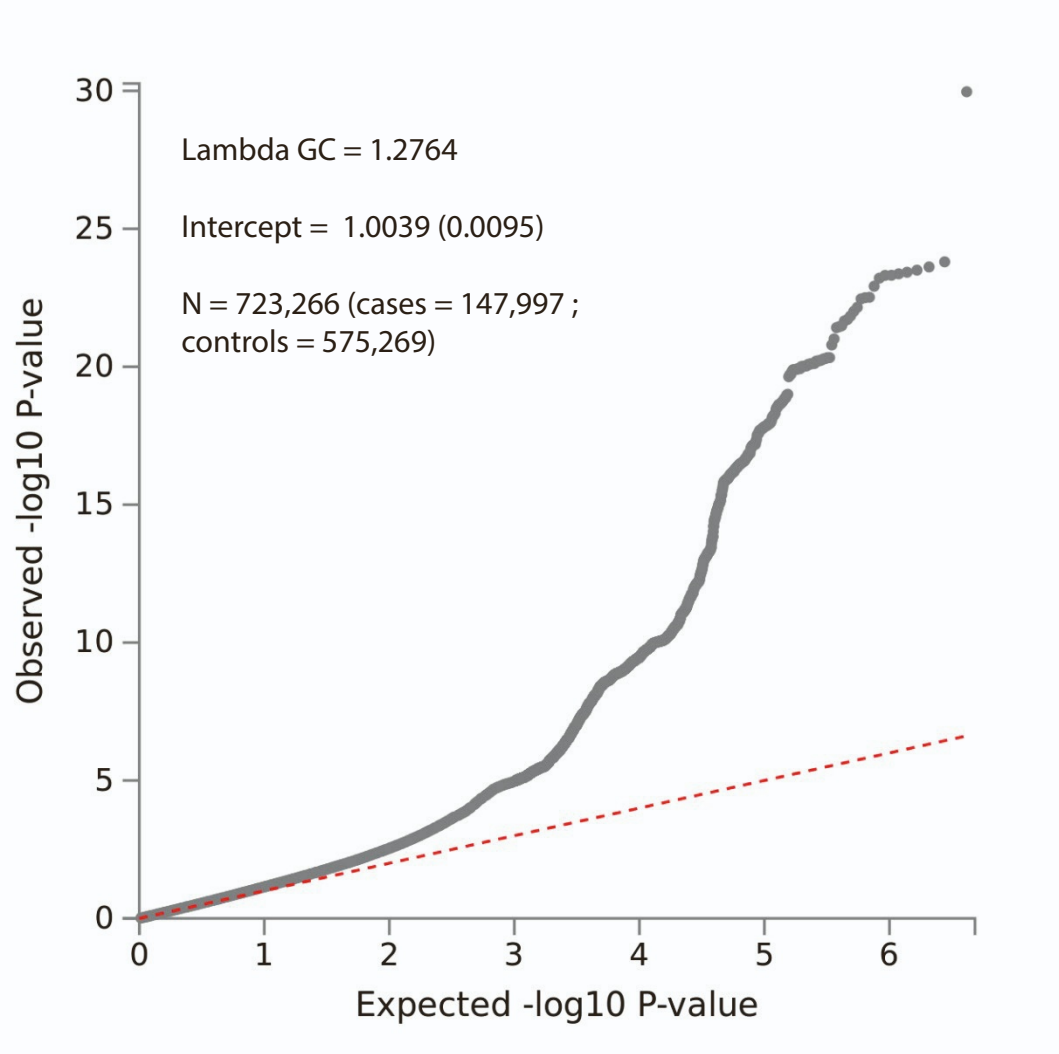
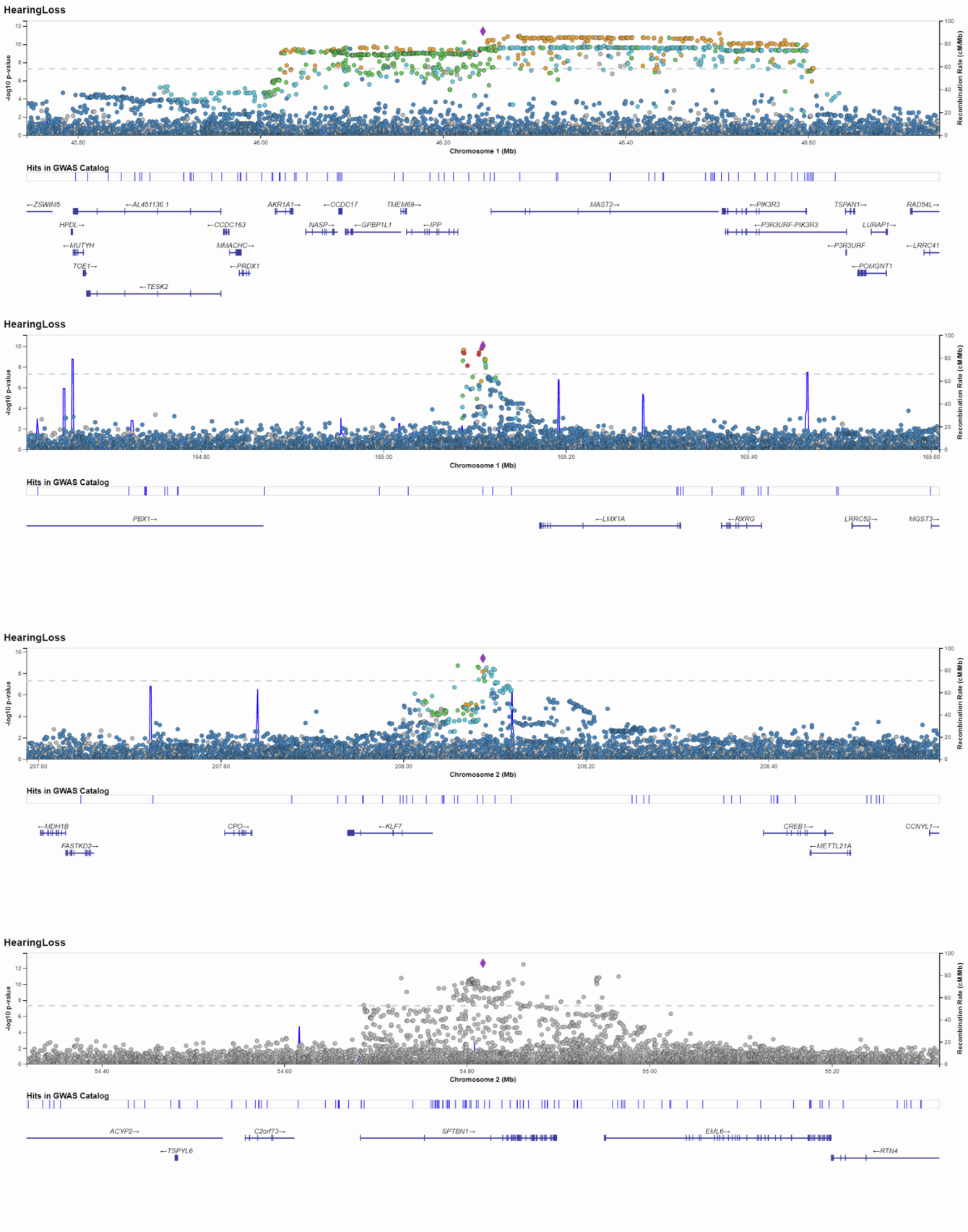
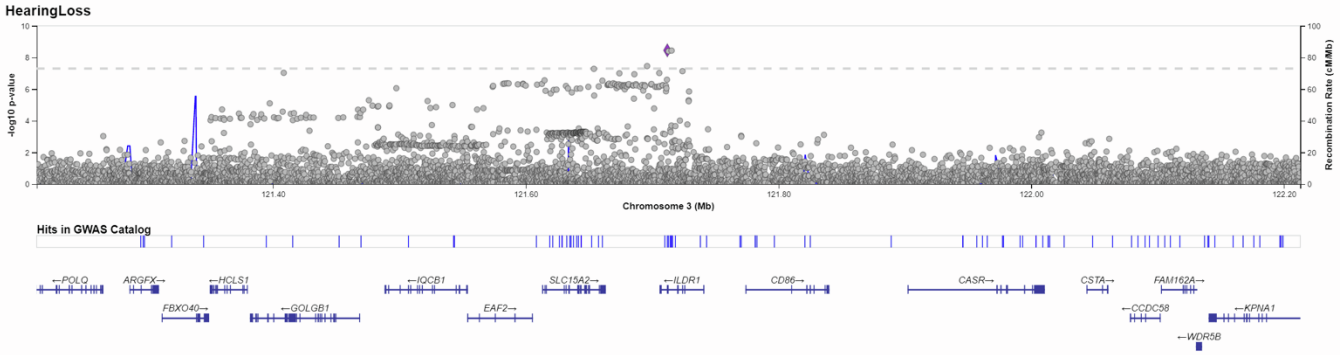
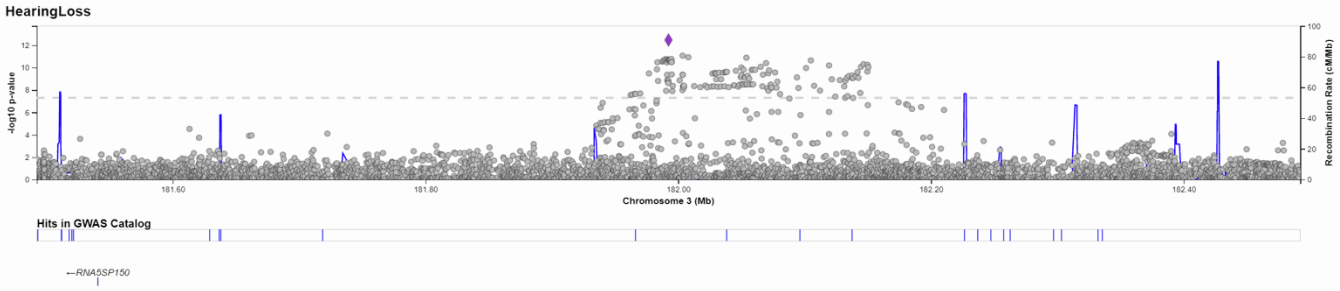


Figure S2 Locus Zoom plot of each statistically significant and independent SNP




HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
121.40
121.60
121.80
122.00
122.20
Chromosome 3 (Mb)
Hits in GWAS Catalog
←POLQ
ARGFX→
←HCLS1
←IQCB1
SLC15A2→
←ILDR1
CD86→
CASR→
CSTA→
FAM162A→
FBXO40→
←GOLGB1
EAF2→
←CCDC58
←KPNA1
←WDR5B


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
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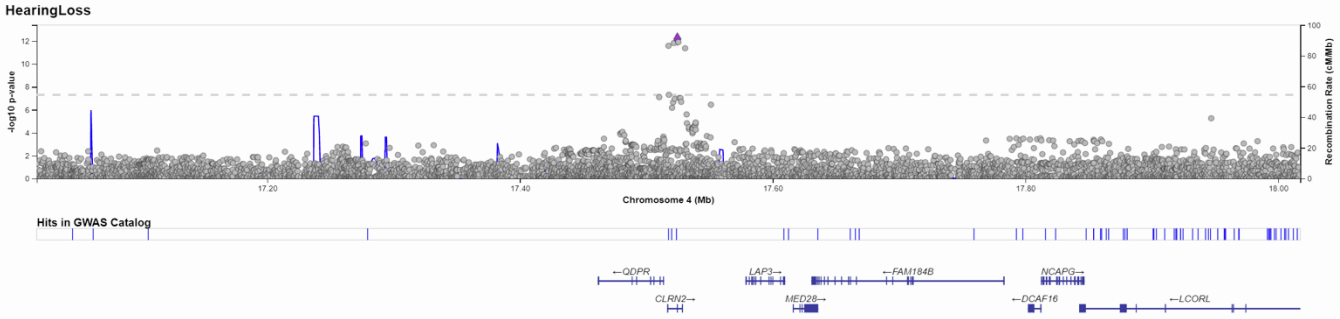
181.80
182.00
182.20
182.40
Chromosome 3 (Mb)
Hits in GWAS Catalog
←RNA5SP150


HearingLoss
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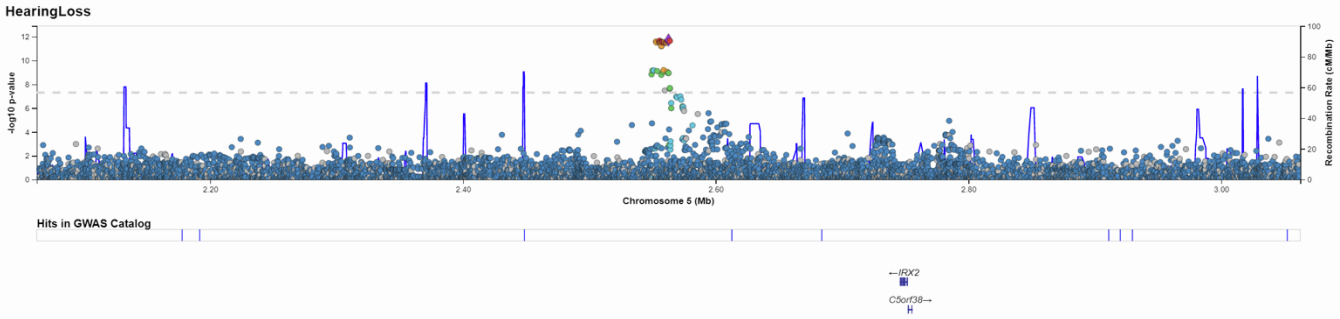
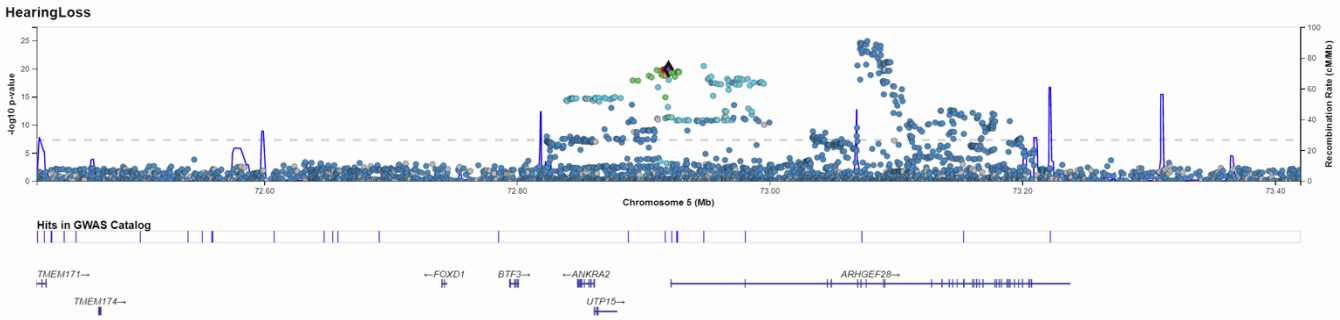
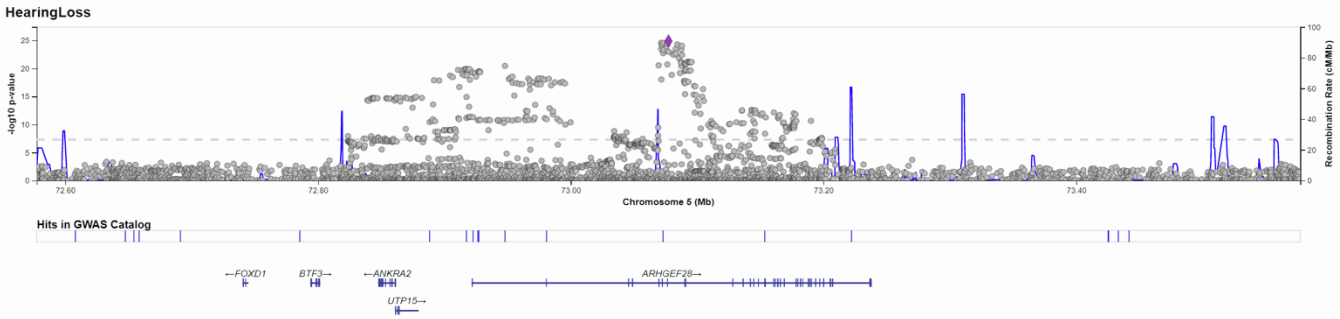
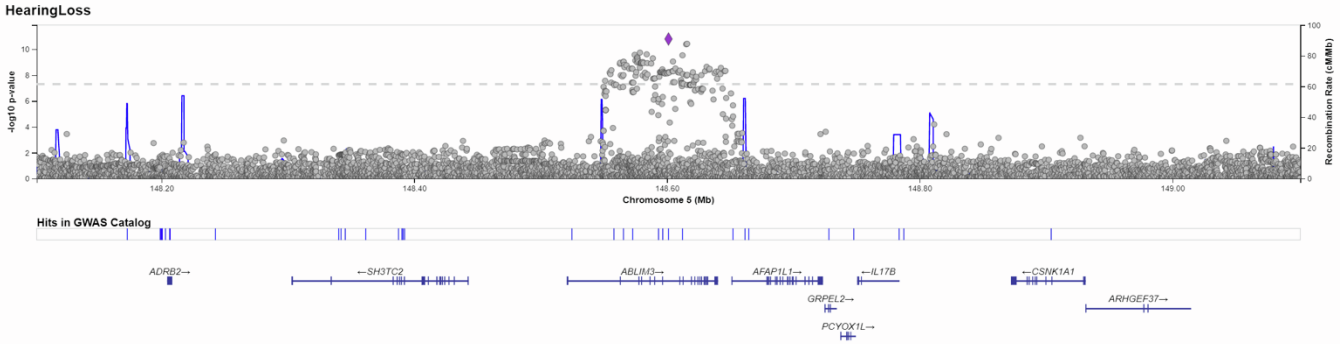
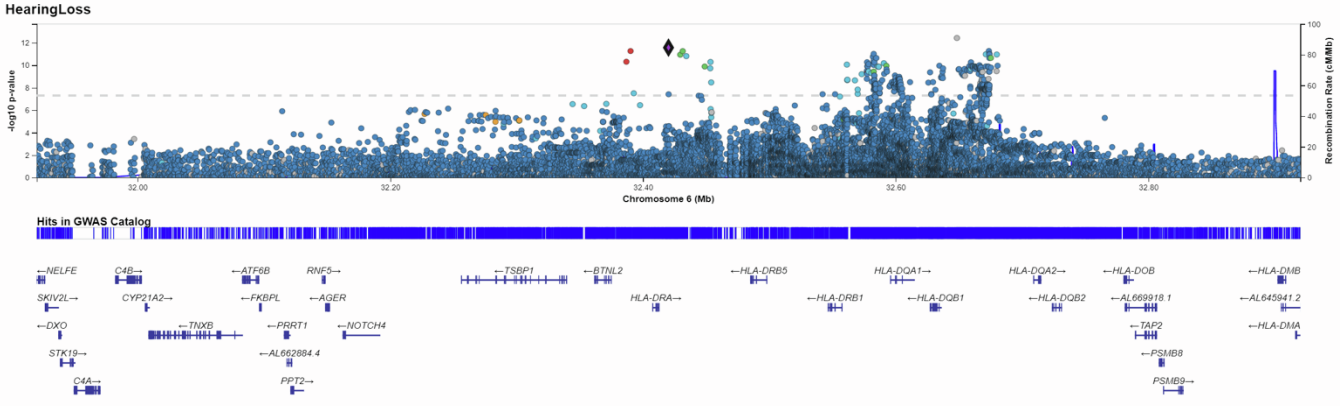
Recombination Rate (cM/Mb)
17.20
17.40
17.60
17.80
18.00
Chromosome 4 (Mb)
Hits in GWAS Catalog
←QDPR
LAP3→
←FAM184B
NCAPG→
CLRN2→
MED28→
←DCAF16
←LCORL

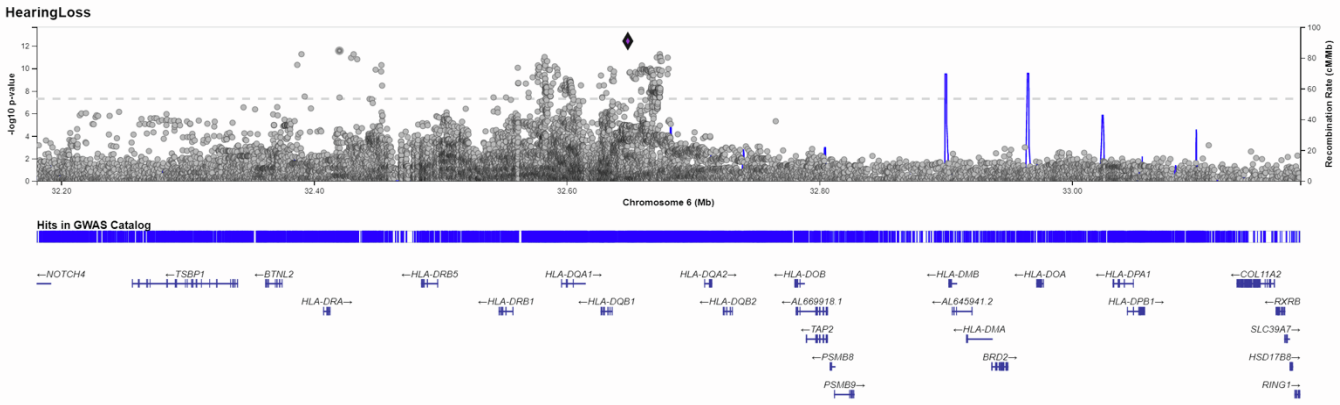

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
2.20
2.40
2.60
2.80
3.00
Chromosome 5 (Mb)
Hits in GWAS Catalog
←IRX2
C5orf38→

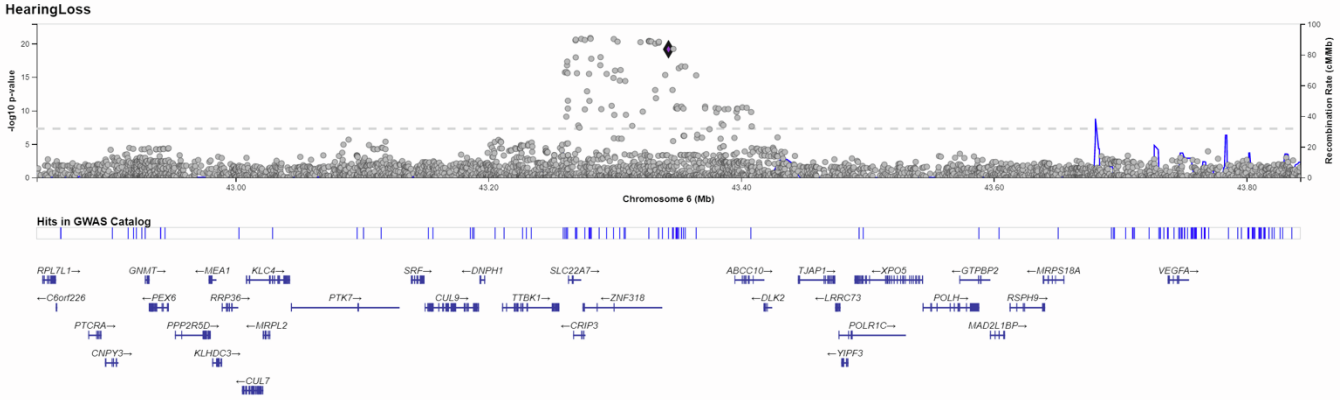

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 5 (Mb)
Hits in GWAS Catalog
TMEM171→
TMEM174→
←FOXD1
BTF3→
←ANKRA2
UTP15→
ARHGEF28→


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 5 (Mb)
Hits in GWAS Catalog
←FOXD1
BTF3→
←ANKRA2
UTP15→
ARHGEF28→


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 5 (Mb)
Hits in GWAS Catalog
ADRB2→
←SH3TC2
ABLIM3→
AFAP1L1→
←IL17B
←CSNK1A1
GRPEL2→
ARHGEF37→
PCYOX1L→


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 6 (Mb)
Hits in GWAS Catalog
←NELFE
C4B→
←ATF6B
RNF5→
←TSBP1
←BTNL2
←HLA-DRB5
HLA-DQA1→
HLA-DQA2→
←HLA-DOB
←HLA-DMB
SKIV2L→
CYP21A2→
←FKBPL
←AGER
HLA-DRA→
←HLA-DRB1
←HLA-DQB1
←HLA-DQB2
←AL669918.1
←AL645941.2
←DXO
←TNXB
←PRRT1
←NOTCH4
←TAP2
←HLA-DMA
STK19→
←AL662684.4
←PSMB8
C4A→
PPT2→
PSMB9→


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 6 (Mb)
Hits in GWAS Catalog
←NOTCH4
←TSBP1
←BTNL2
←HLA-DRB5
HLA-DQA1→
HLA-DQA2→
←HLA-DOB
←HLA-DMB
←HLA-DOA
←HLA-DPA1
←COL11A2
HLA-DRA→
←HLA-DRB1
←HLA-DQB1
←HLA-DQB2
←AL669918.1
←AL645941.2
HLA-DPB1→
←RXRB
←TAP2
←HLA-DMA
SLC39A7→
←PSMB8
BRD2→
HSD17B8→
PSMB9→
RING1→


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 6 (Mb)
Hits in GWAS Catalog
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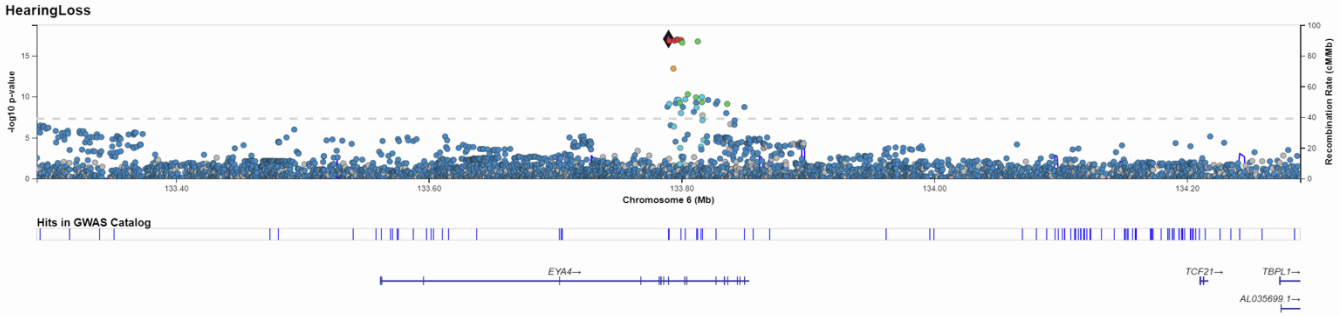
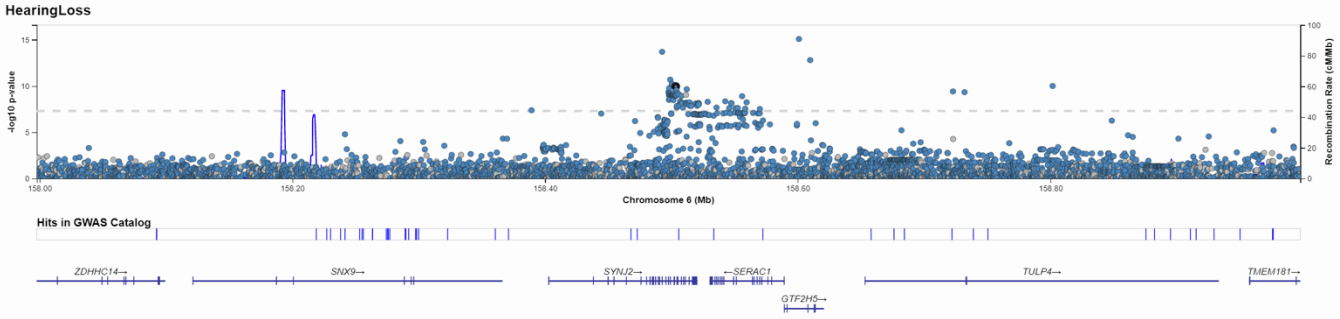
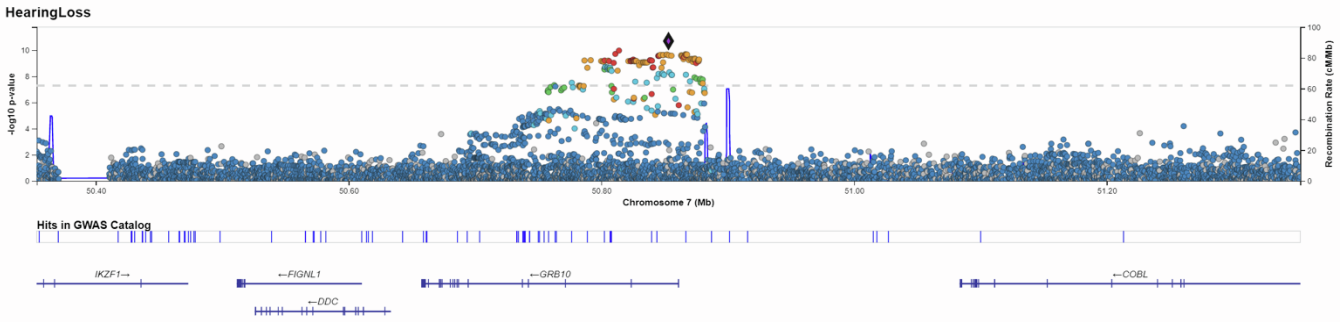
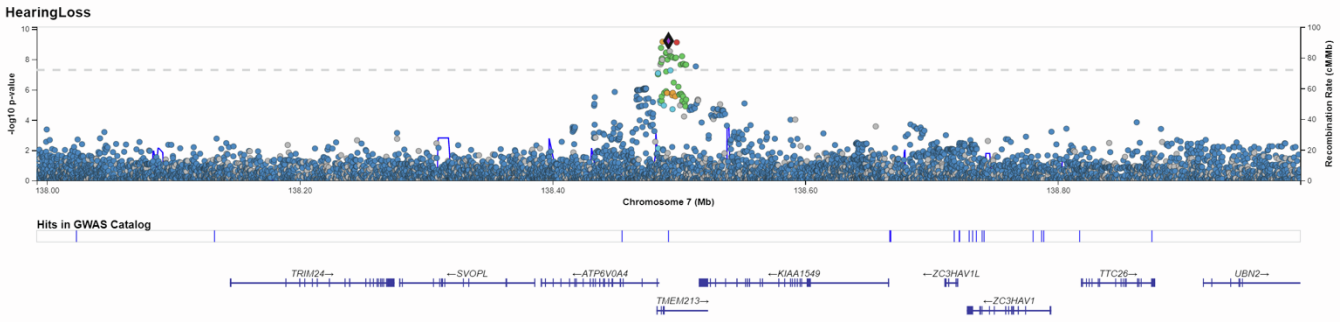
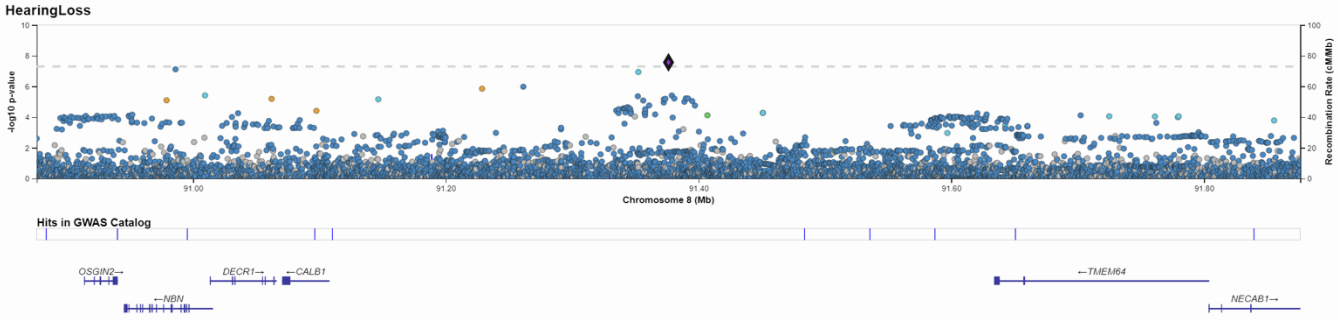
GNMT→
←MEA1
KLC4→
SRF→
←DNPH1
SLC22A7→
ABCC10→
TJAP1→
←XPO5
←GTPBP2
←MRPS18A
VEGFA→
←C6orf226
←PEX6
RRP36→
PTK7→
CUL9→
TTBK1→
←ZNF318
←DLK2
←LRRC73
POLH←
RSPH9→
PTCRA→
PPP2R5D→
←MRPL2
←CRIP3
POLR1C→
MAD2L1BP→
CNPY3→
KLHDC3→
←YIPF3
←CUL7


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 6 (Mb)
Hits in GWAS Catalog
EYA4→
TCF21→
TBPL1→
AL035699.1→


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 6 (Mb)
Hits in GWAS Catalog
ZDHHC14→
SNX9→
SYNJ2→
←SERAC1
TULP4→
TMEM181→
GTF2H5→


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
50.40
50.60
50.80
51.00
51.20
Chromosome 7 (Mb)
Hits in GWAS Catalog
IKZF1→
←FIGNL1
←GRB10
←COBL
←DDC


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
138.00
138.20
138.40
138.60
138.80
Chromosome 7 (Mb)
Hits in GWAS Catalog
TRIM24→
←SVOPL
←ATP6V0A4
←KIAA1549
←ZC3HAV1L
TTC26→
UBN2→
TMEM213→
←ZC3HAV1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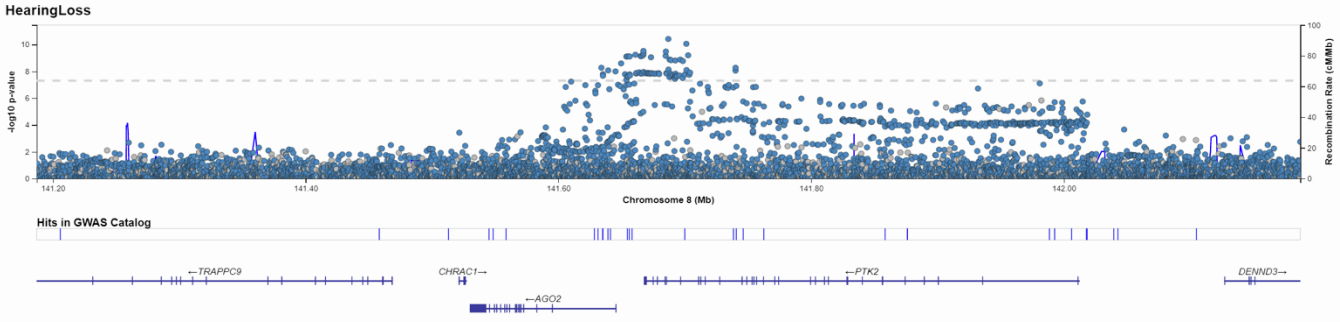
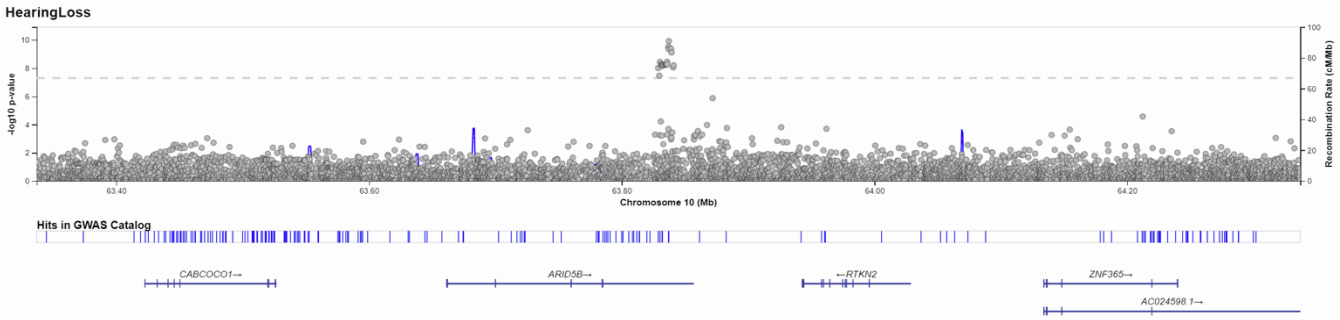
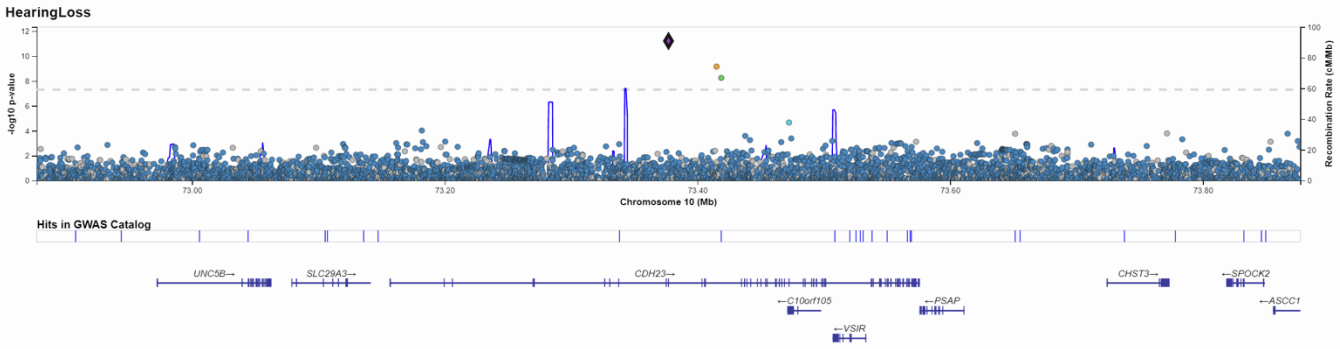
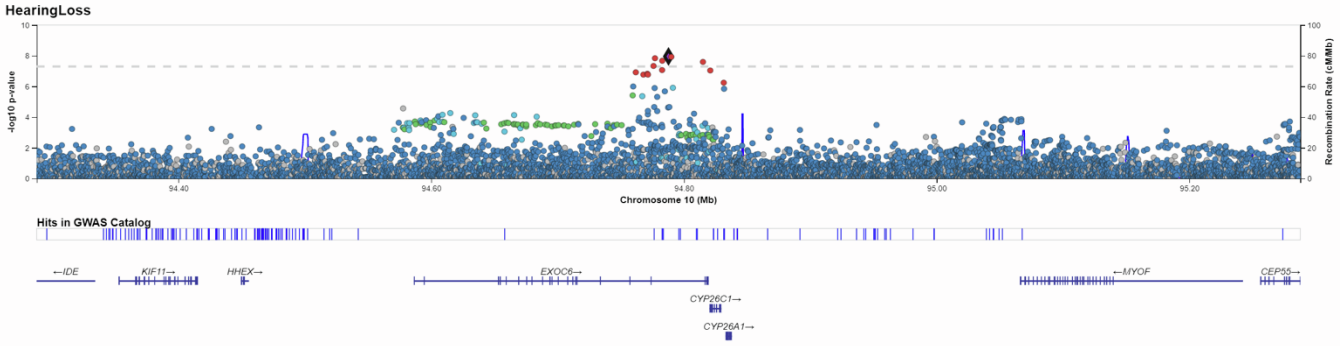
Recombination Rate (cM/Mb)
91.00
91.20
91.40
91.60
91.80
Chromosome 8 (Mb)
Hits in GWAS Catalog
OSGIN2→
DECR1→
←CALB1
←TMEM64
←NBN
NECAB1→


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
141.20
141.40
141.60
141.80
142.00
Chromosome 8 (Mb)
Hits in GWAS Catalog
←TRAPPC9
CHRAC1→
←PTK2
DENND3→
←AGO2


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
63.40
63.60
63.80
64.00
64.20
Chromosome 10 (Mb)
Hits in GWAS Catalog
CABCOCO1→
ARID5B→
←RTKN2
ZNF365→
AC024598.1→


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
73.00
73.20
73.40
73.60
73.80
Chromosome 10 (Mb)
Hits in GWAS Catalog
UNC5B→
SLC29A3→
CDH23→
CHST3→
←SPOCK2
←C10orf105
←PSAP
←ASCC1
←VSIR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-log10 p-value
Recombination Rate (cM/Mb)
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94.60
94.80
95.00
95.20
Chromosome 10 (Mb)
Hits in GWAS Catalog
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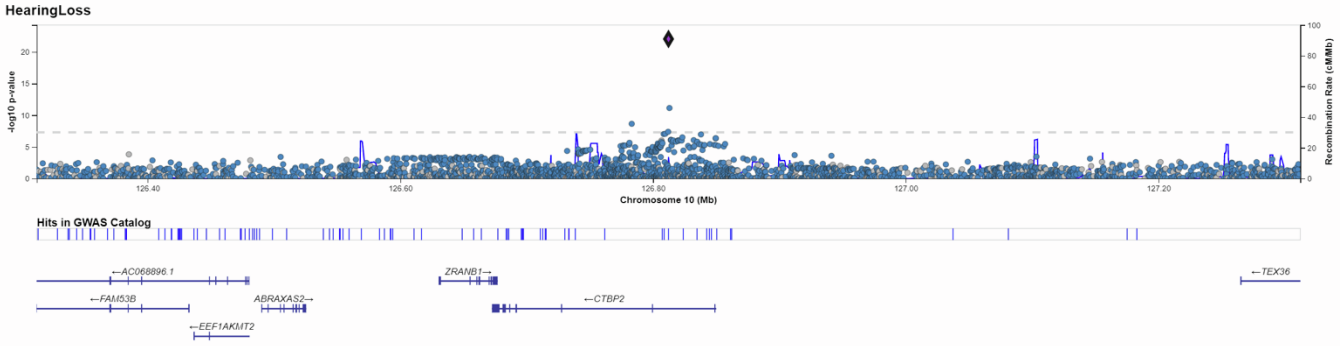
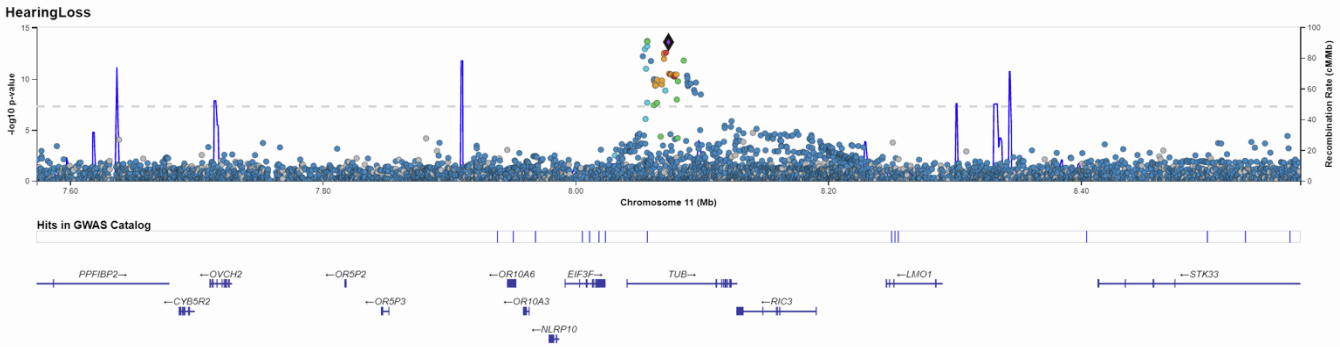
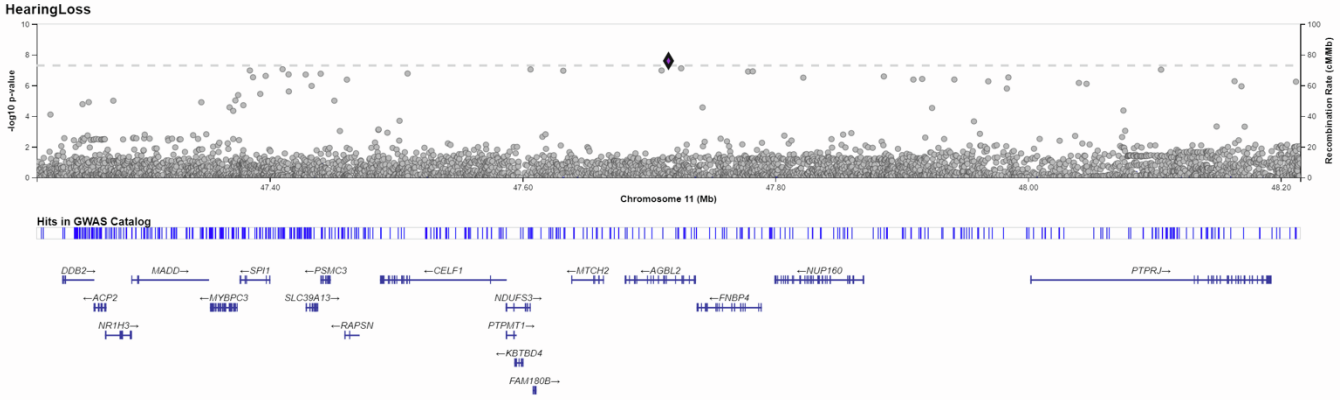
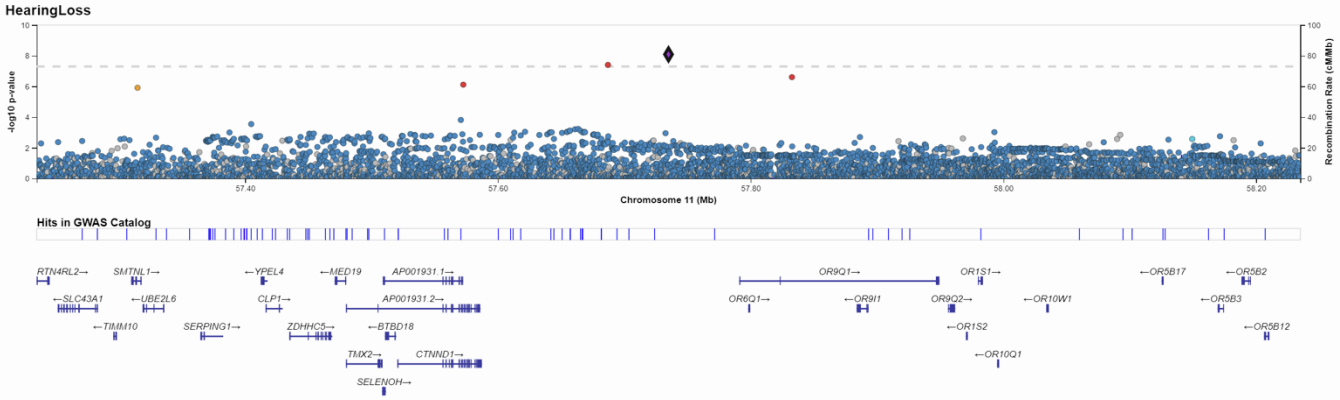
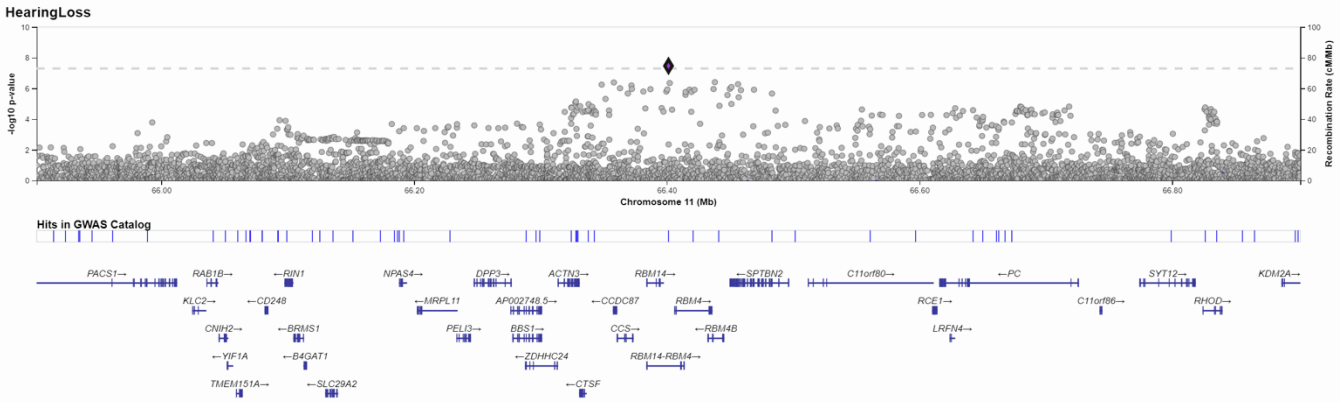
KIF11→
HHEX→
EXOC6→
←MYOF
CEP55→
CYP26C1→
CYP26A1→

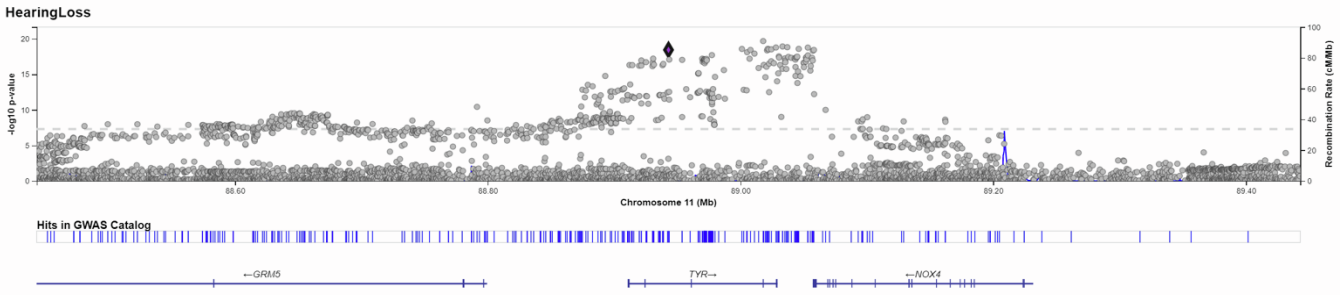

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
126.40
126.60
126.80
127.00
127.20
Chromosome 10 (Mb)
Hits in GWAS Catalog
←AC068896.1
ZRANB1→
←TEX36
←FAM53B
ABRAXAS2→
←CTBP2
←EEF1AKMT2

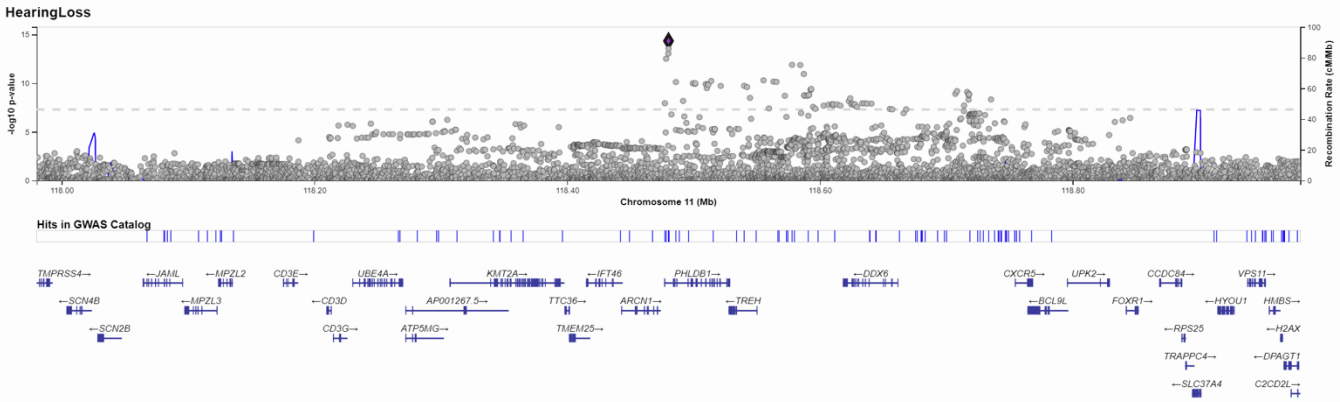

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 11 (Mb)
Hits in GWAS Catalog
PPFIBP2→
←OVCH2
←OR5P2
←OR10A6
EIF3F→
TUB→
←LMO1
←STK33
←CYB5R2
←OR5P3
←OR10A3
←RIC3
←NLRP10

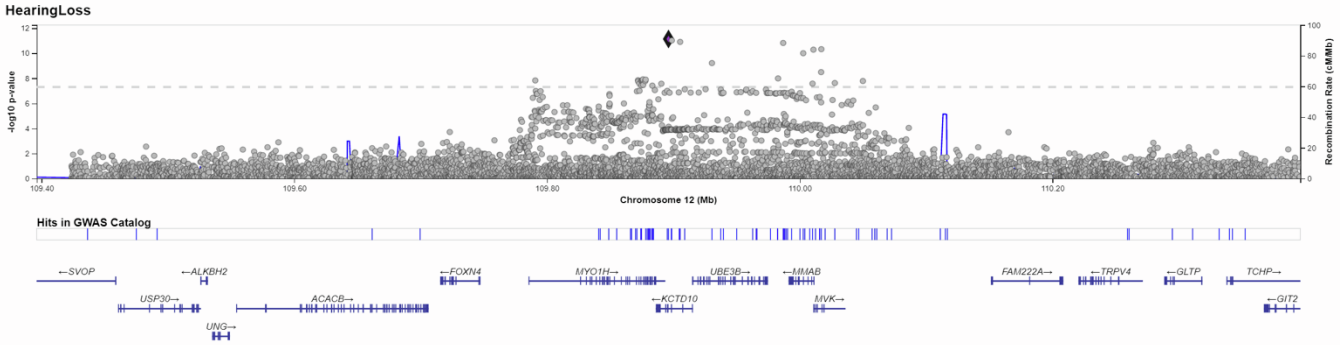

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 11 (Mb)
Hits in GWAS Catalog
DDB2→
MADD→
←SPI1
←PSMC3
←CELF1
←MTCH2
←AGBL2
←NUP160
PTPRJ→
←ACP2
←MYBPC3
SLC39A13→
NDUFS3→
←FNBP4
NR1H3→
←RAPSN
PTPMT1→
←KBTBD4
FAM180B→

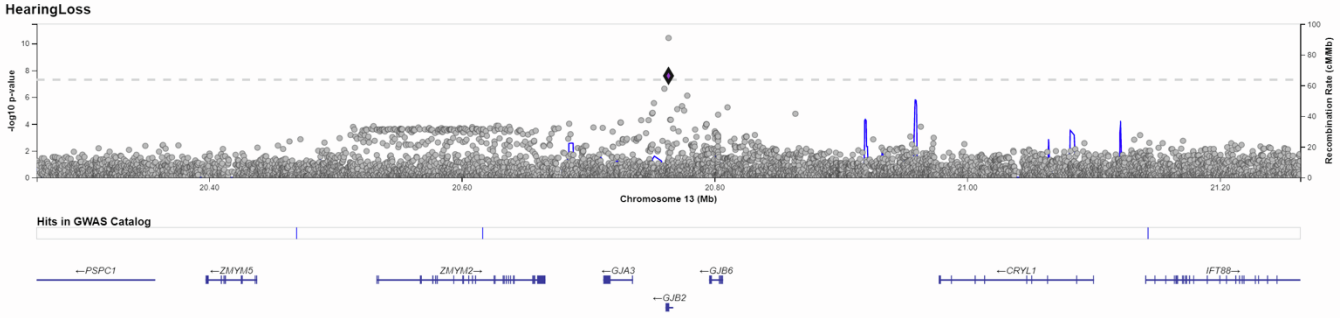

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 11 (Mb)
Hits in GWAS Catalog
RTN4RL2→
SMTNL1→
←YPEL4
←MED19
AP001931.1→
←SLC43A1
←UBE2L6
CLP1→
AP001931.2→
←TIMM10
SERPING1→
ZDHHC5→
←BTBD18
TMX2→
CTNND1→
SELENOH→
OR9Q1→
OR1S1→
←OR5B17
←OR5B2
OR6Q1→
←OR9I1
OR9Q2→
←OR10W1
←OR5B3
←OR1S2
←OR5B12
←OR10Q1

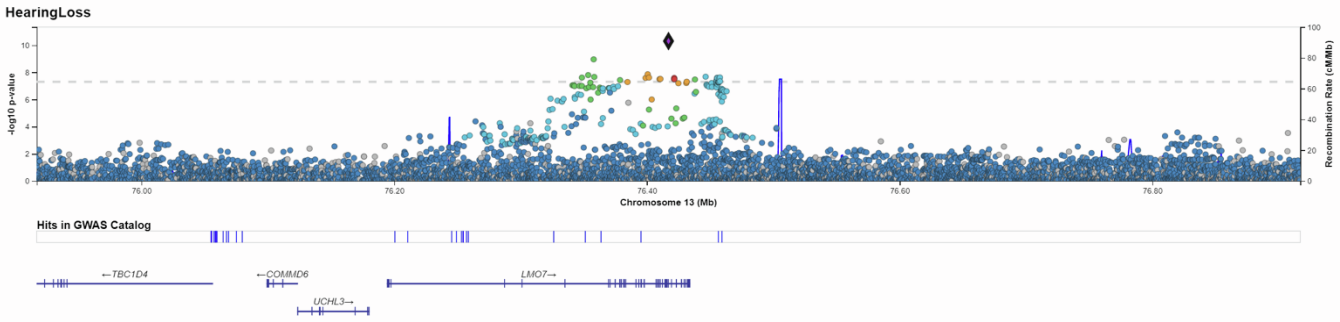

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 11 (Mb)
Hits in GWAS Catalog
PACS1→
RAB1B→
←RIN1
NPAS4→
DPP3→
ACTN3→
RBM14→
←SPTBN2
C11orf80→
←PC
SYT12→
KDM2A→
KLC2→
←CD248
←MRPL11
AP002748.5→
←CCDC87
RBM4→
RCE1→
C11orf86→
RHOD→
CNIH2→
←BRMS1
PELI3→
BBS1→
CCS→
←RBM4B
LRFN4→
←YIF1A
←B4GAT1
←ZDHHC24
RBM14-RBM4→
TMEM151A→
←SLC29A2
←CTSF

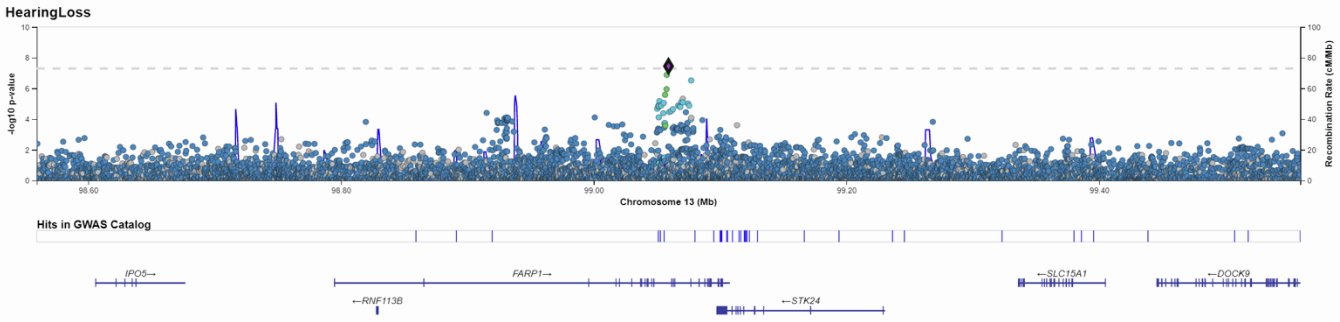

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 11 (Mb)
Hits in GWAS Catalog
←GRM5
TYR→
←NOX4

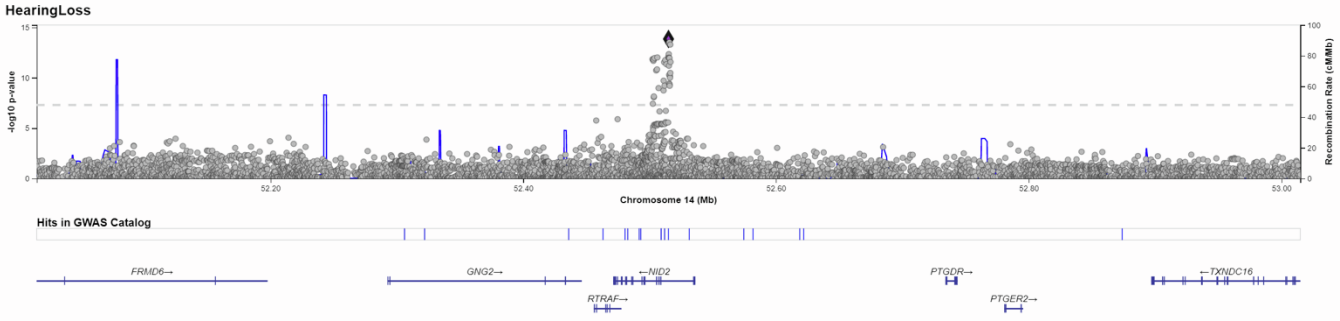

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 11 (Mb)
Hits in GWAS Catalog
TMPRSS4→
←JAML
←MPZL2
CD3E→
UBE4A→
KMT2A→
←IFT46
PHLDB1→
←DDX6
CXCR5→
UPK2→
CCDC84→
VPS11→
←SCN4B
←MPZL3
←CD3D
AP001267.5→
TTC36→
ARCN1→
←TREH
←BCL9L
FOXR1→
←HYOU1
HMBS→
←SCN2B
CD3G→
ATP5MG→
TMEM25→
←RPS25
←H2AX
TRAPPC4→
←DPAGT1
←SLC37A4
C2CD2L→

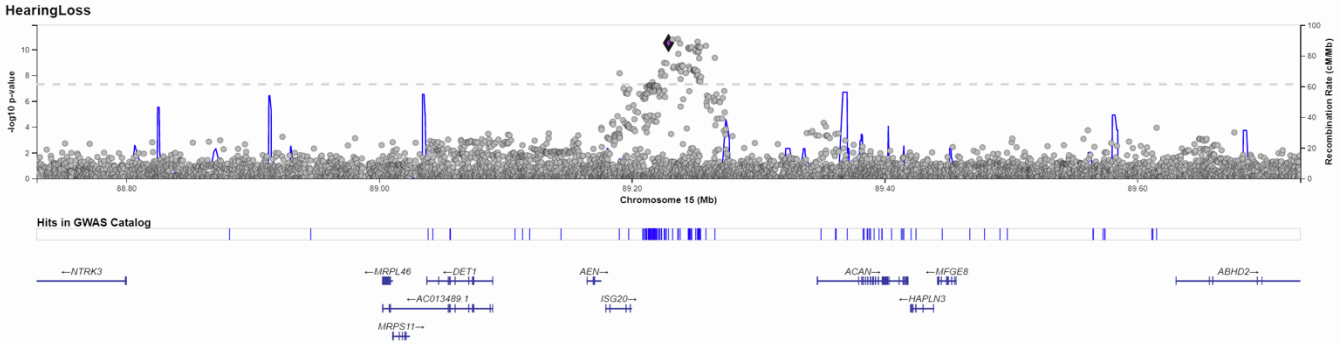

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 12 (Mb)
Hits in GWAS Catalog
←SVOP
←ALKBH2
←FOXN4
MYO1H→
UBE3B→
←MMAB
FAM222A→
←TRPV4
←GLTP
TCHP→
USP30→
ACACB→
←KCTD10
MVK→
←GIT2
UNG→

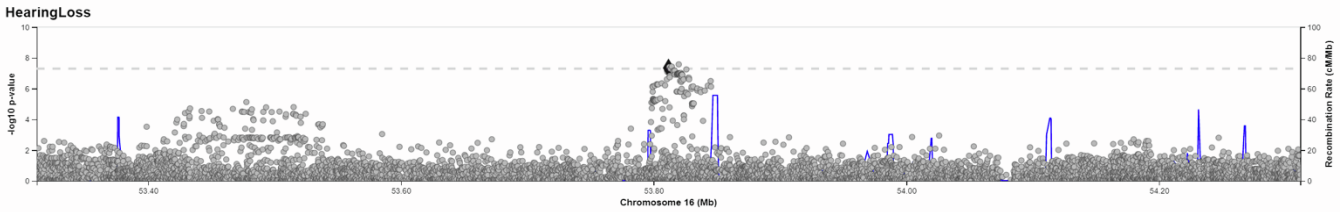

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 13 (Mb)
Hits in GWAS Catalog
←PSPC1
←ZMYM5
ZMYM2→
←GJA3
←GJB6
←GJB2
←CRYL1
IFT88→

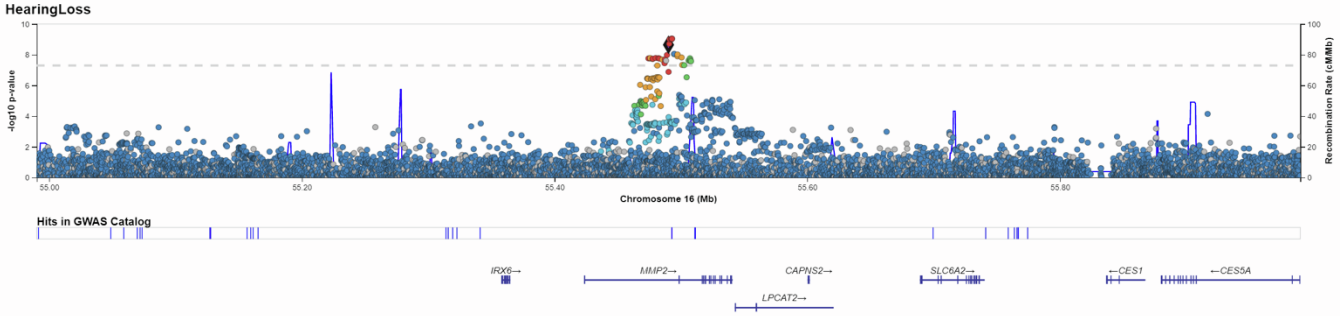

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 13 (Mb)
Hits in GWAS Catalog
←TBC1D4
←COMMD6
LMO7→
UCHL3→

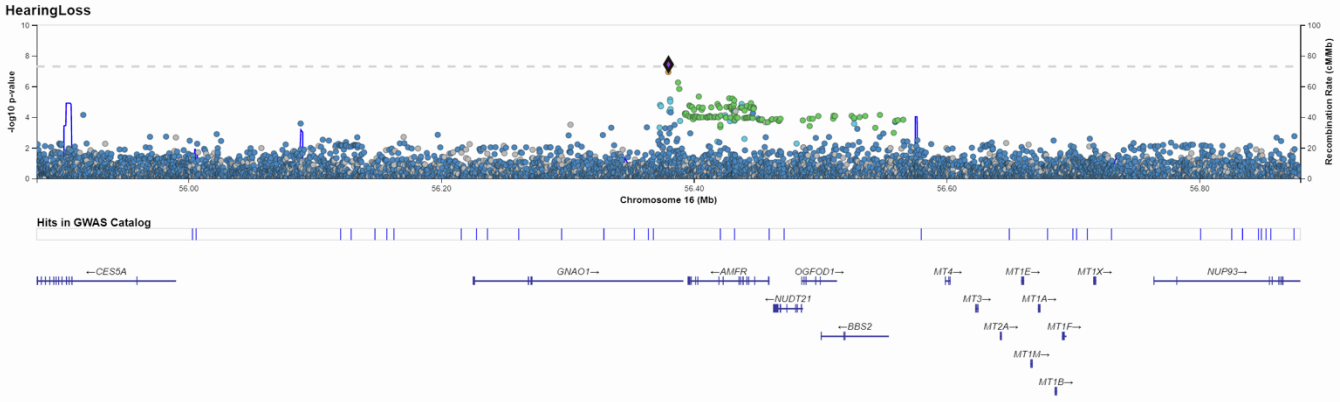

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 13 (Mb)
Hits in GWAS Catalog
IPO5→
FARP1→
←SLC15A1
←DOCK9
←RNF113B
←STK24

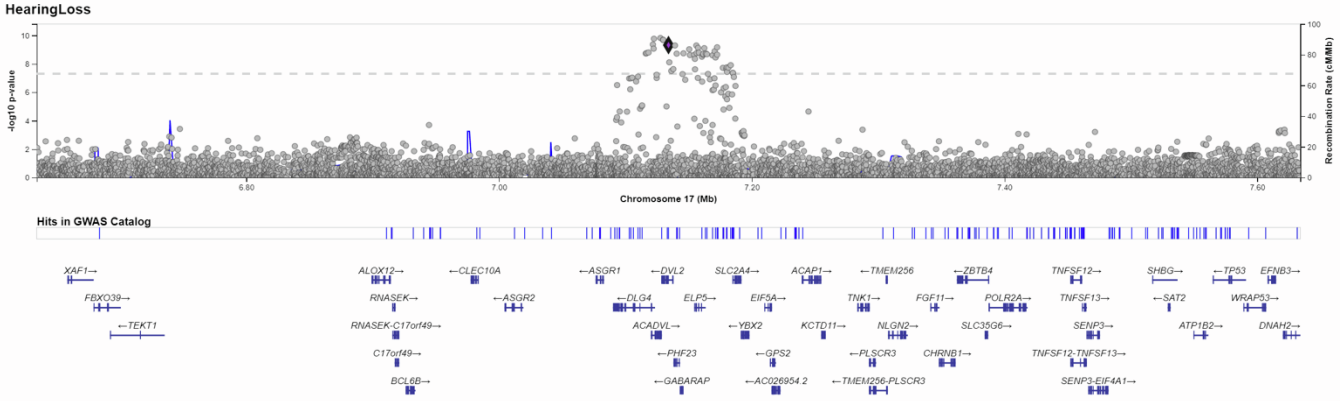

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 14 (Mb)
Hits in GWAS Catalog
FRMD6→
GNG2→
←NID2
PTGDR→
←TXNDC16
RTRAF→
PTGER2→

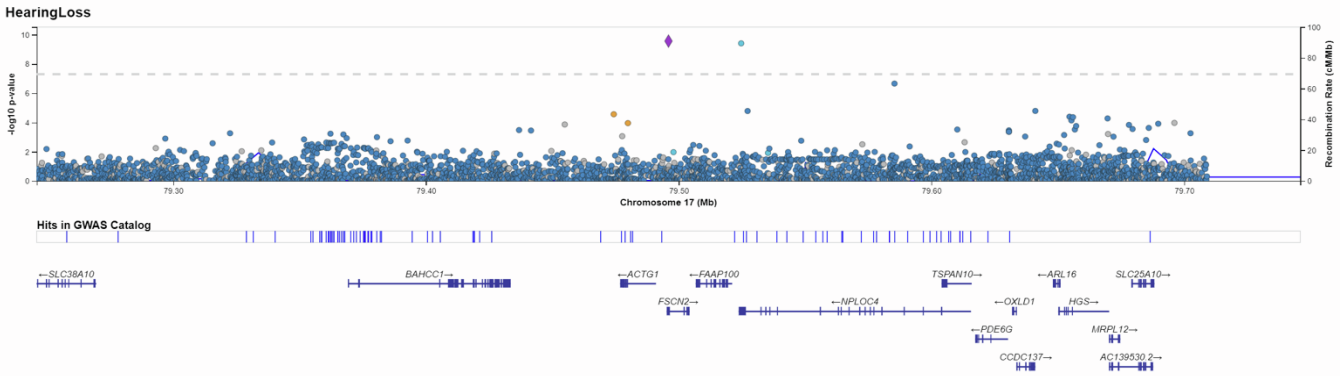

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 15 (Mb)
Hits in GWAS Catalog
←NTRK3
←MRPL46
←DET1
AEN→
ACAN→
←MFGE8
ABHD2→
←AC013489.1
ISG20→
←HAPLN3
MRPS11→

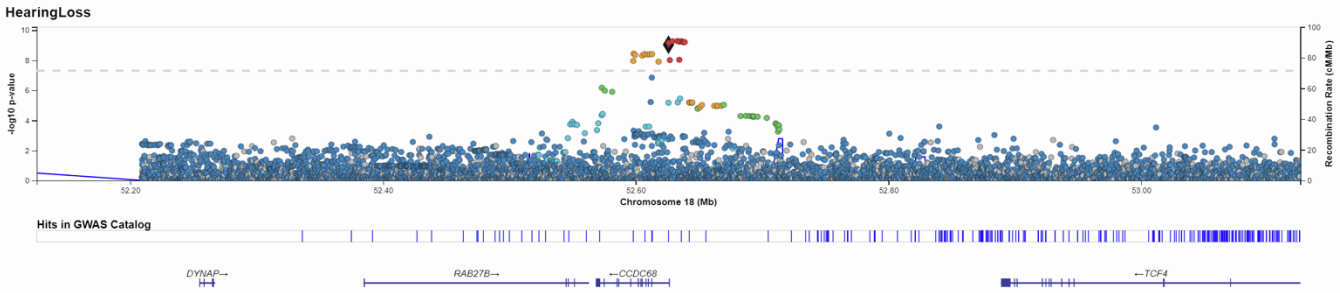

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 16 (Mb)
Hits in GWAS Catalog
CHD9→
RBL2→
←RPGRIP1L
←AKTIP
FTO→

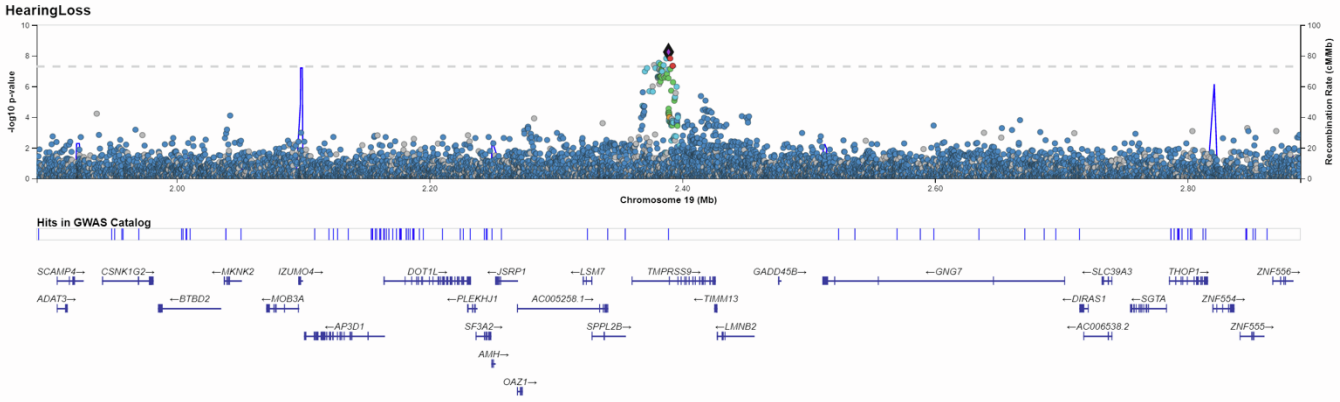

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 16 (Mb)
Hits in GWAS Catalog
IRX6→
MMP2→
CAPNS2→
SLC6A2→
←CES1
←CES5A
LPCAT2→

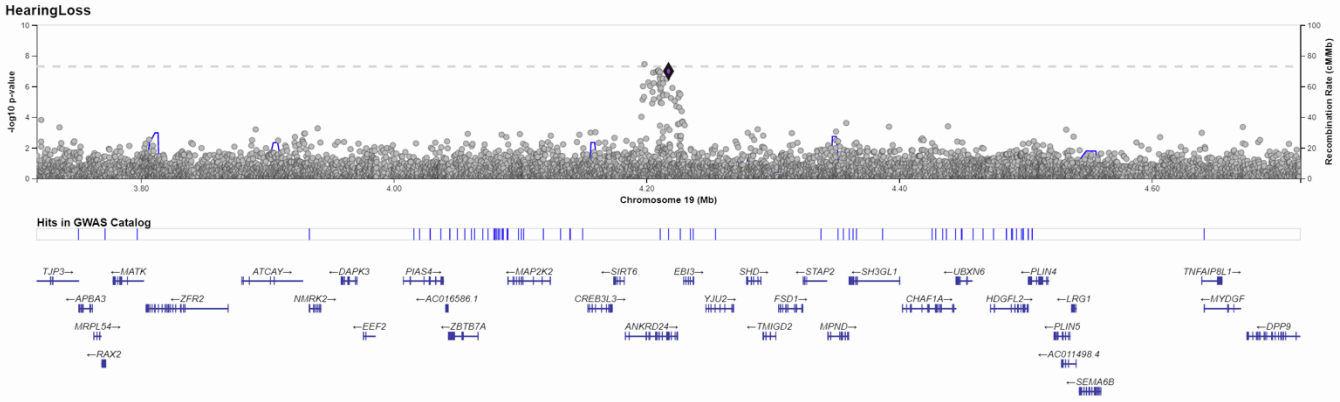

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 16 (Mb)
Hits in GWAS Catalog
←CES5A
GNAO1→
←AMFR
OGFOD1→
←NUDT21
←BBS2
MT4→
MT1E→
MT1X→
NUP93→
MT3→
MT1A→
MT2A→
MT1F→
MT1M→
MT1B→

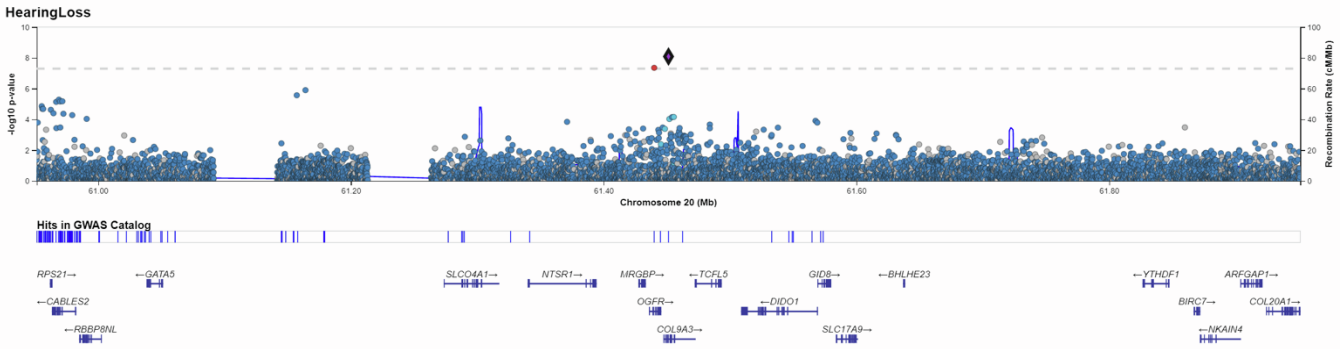

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 17 (Mb)
Hits in GWAS Catalog
XAF1→
FBXO39→
←TEKT1
ALOX12→
←CLEC10A
RNASEK→
←ASGR2
RNASEK-C17orf49→
C17orf49→
BCL6B→
←ASGR1
←DVL2
SLC2A4→
ACAP1→
←TMEM256
←ZBTB4
←DLG4
ELP5→
EIF5A→
TNK1→
FGF11→
POLR2A→
ACADVL→
←YBX2
KCTD11→
NLGN2→
SLC35G6→
←PHF23
←GPS2
←PLSCR3
CHRNB1→
←GABARAP
←AC026954.2
←TMEM256-PLSCR3
TNFSF12→
TNFSF13→
SENP3→
TNFSF12-TNFSF13→
SENP3-EIF4A1→
SHBG→
←SAT2
ATP1B2→
←TP53
EFNB3→
WRAP53→
DNAH2→

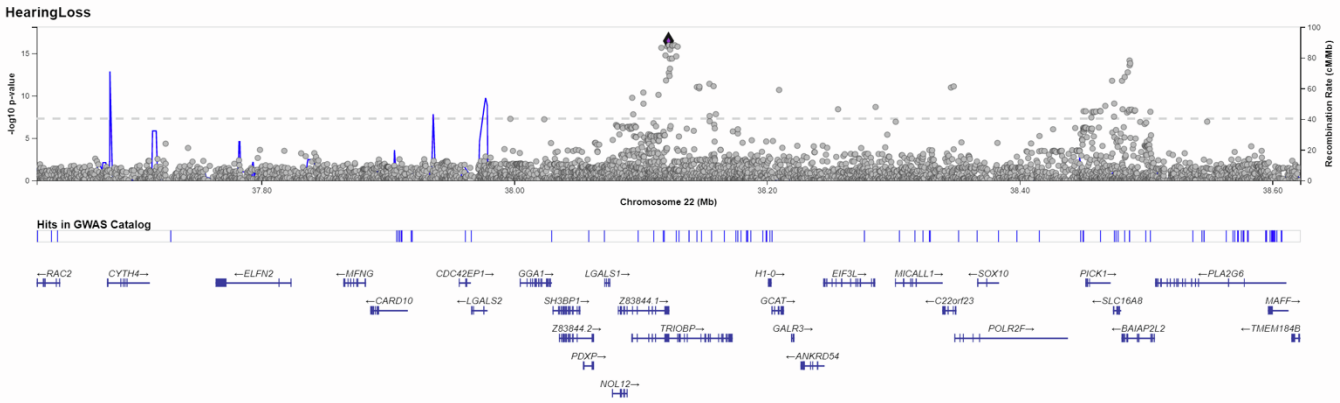

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 17 (Mb)
Hits in GWAS Catalog
←SLC38A10
BAHCC1→
←ACTG1
←FAAP100
TSPAN10→
←ARL16
SLC25A19→
FSCN2→
←NPLOC4
←OXLD1
HGS→
←PDE6G
MRPL12→
CCDC137→
AC139530.2→

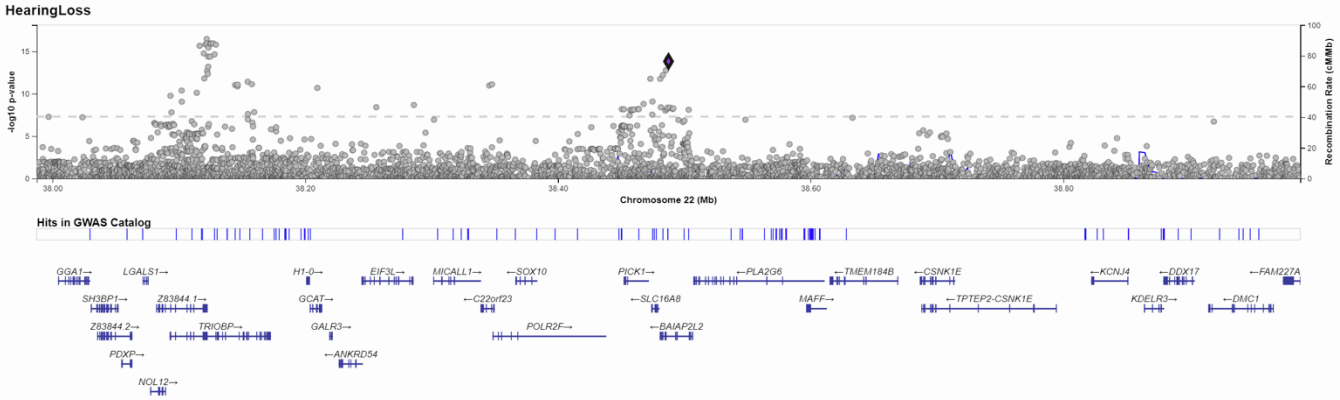

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 18 (Mb)
Hits in GWAS Catalog
DYNAP→
RAB27B→
←CCDC68
←TCF4


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 19 (Mb)
Hits in GWAS Catalog
SCAMP4→
CSNK1G2→
←MKNK2
IZUMO4→
DOT1L→
←JSRP1
←LSM7
TMPRSS9→
GADD45B→
←GNG7
←SLC39A3
THOP1→
ZNF556→
ADAT3→
←BTBD2
←MOB3A
←PLEKHJ1
AC005258.1→
←TIMM13
←DIRAS1
←SGTA
ZNF554→
←AP3D1
SF3A2→
SPPL2B→
←LMNB2
←AC006538.2
ZNF555→
AMH→
OAZ1→


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 19 (Mb)
Hits in GWAS Catalog
TJP3→
←MATK
ATCAY→
←DAPK3
PIAS4→
←MAP2K2
←SIRT6
EBI3→
SHD→
←STAP2
←SH3GL1
←UBXN6
←PLIN4
TNFAIP8L1→
←APBA3
←ZFR2
NMRK2→
←AC016586.1
CREB3L3→
YJU2→
FSD1→
CHAF1A→
HDGFL2→
←LRG1
←MYDGF
MRPL54→
←EEF2
←ZBTB7A
ANKRD24→
←TMIGD2
MPND→
←PLIN5
←DPP9
←RAX2
←AC011498.4
←SEMA6B


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 20 (Mb)
Hits in GWAS Catalog


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 22 (Mb)
Hits in GWAS Catalog


HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 22 (Mb)
Hits in GWAS Catalog

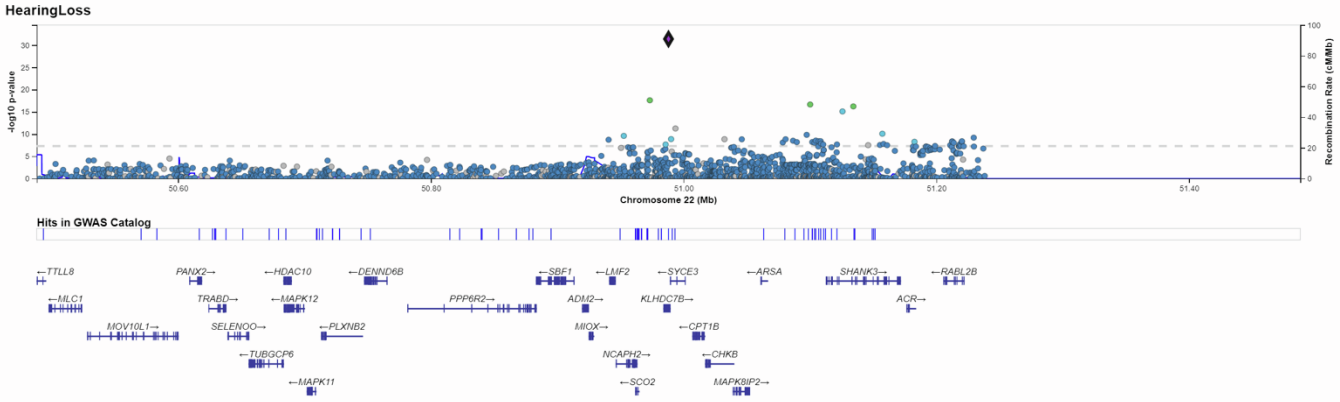
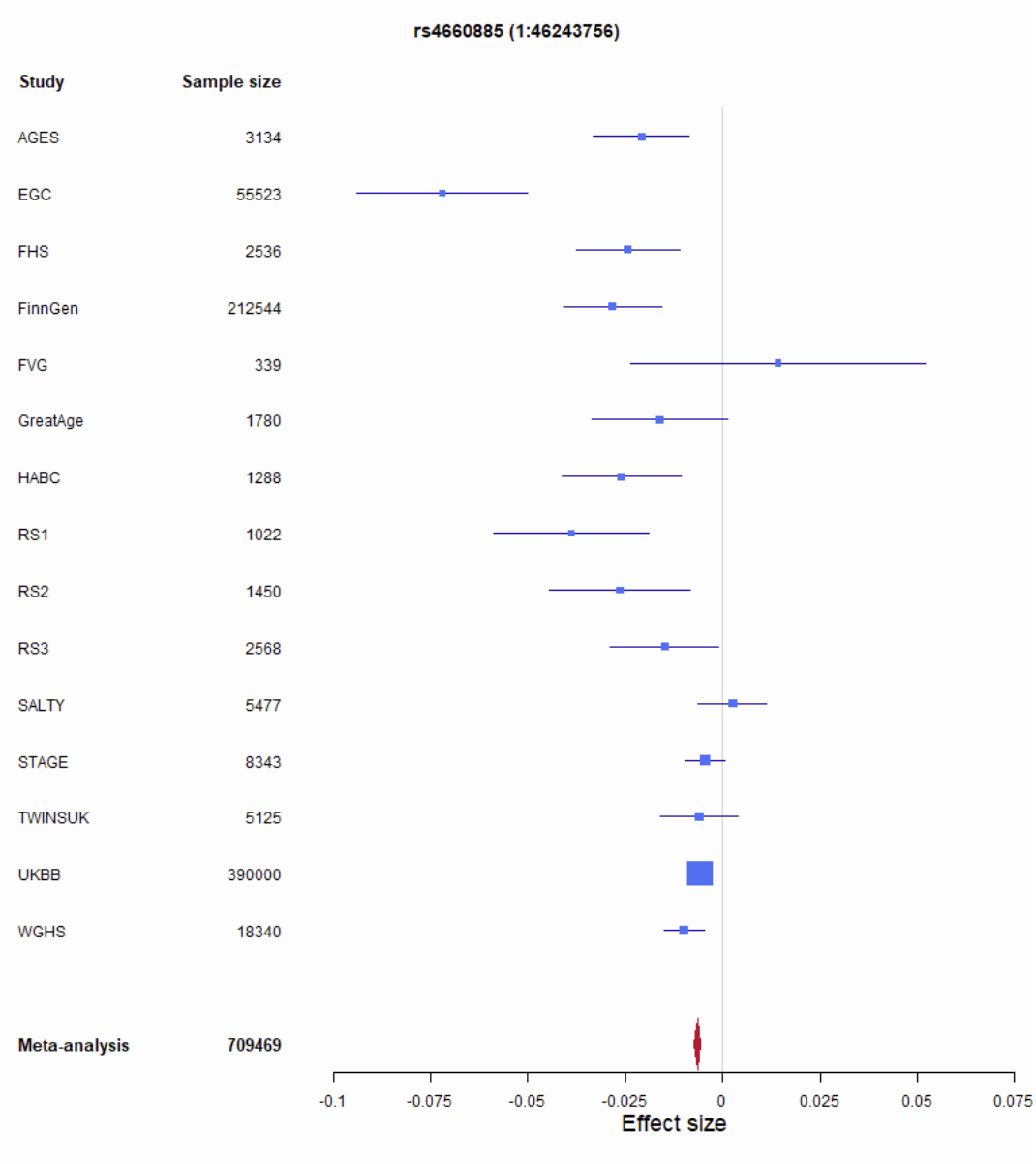
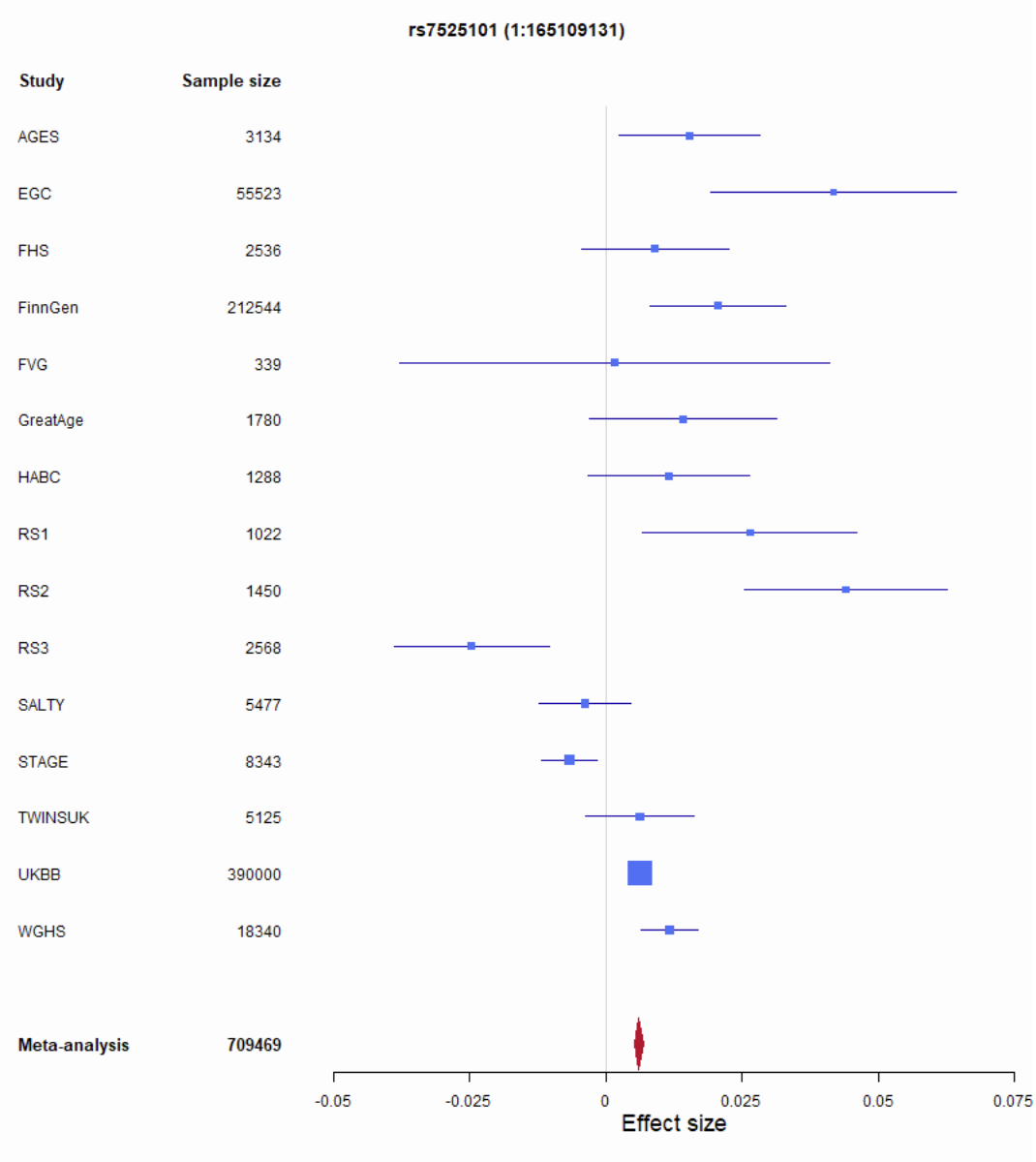

HearingLoss
-log10 p-value
Recombination Rate (cM/Mb)
Chromosome 22 (Mb)
Hits in GWAS Catalog

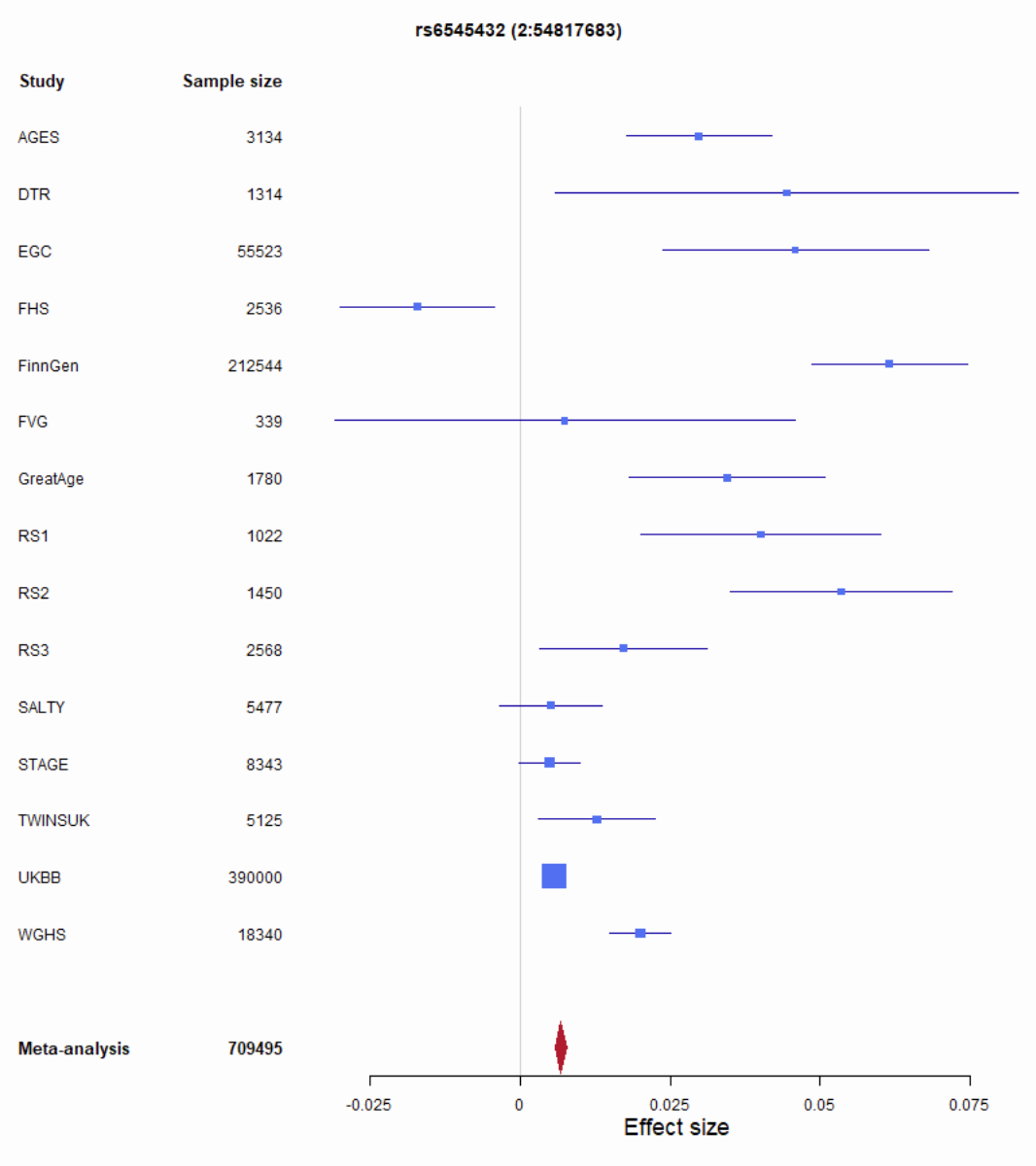
Figure S3. Forest plots for each statistically significant and independent SNP



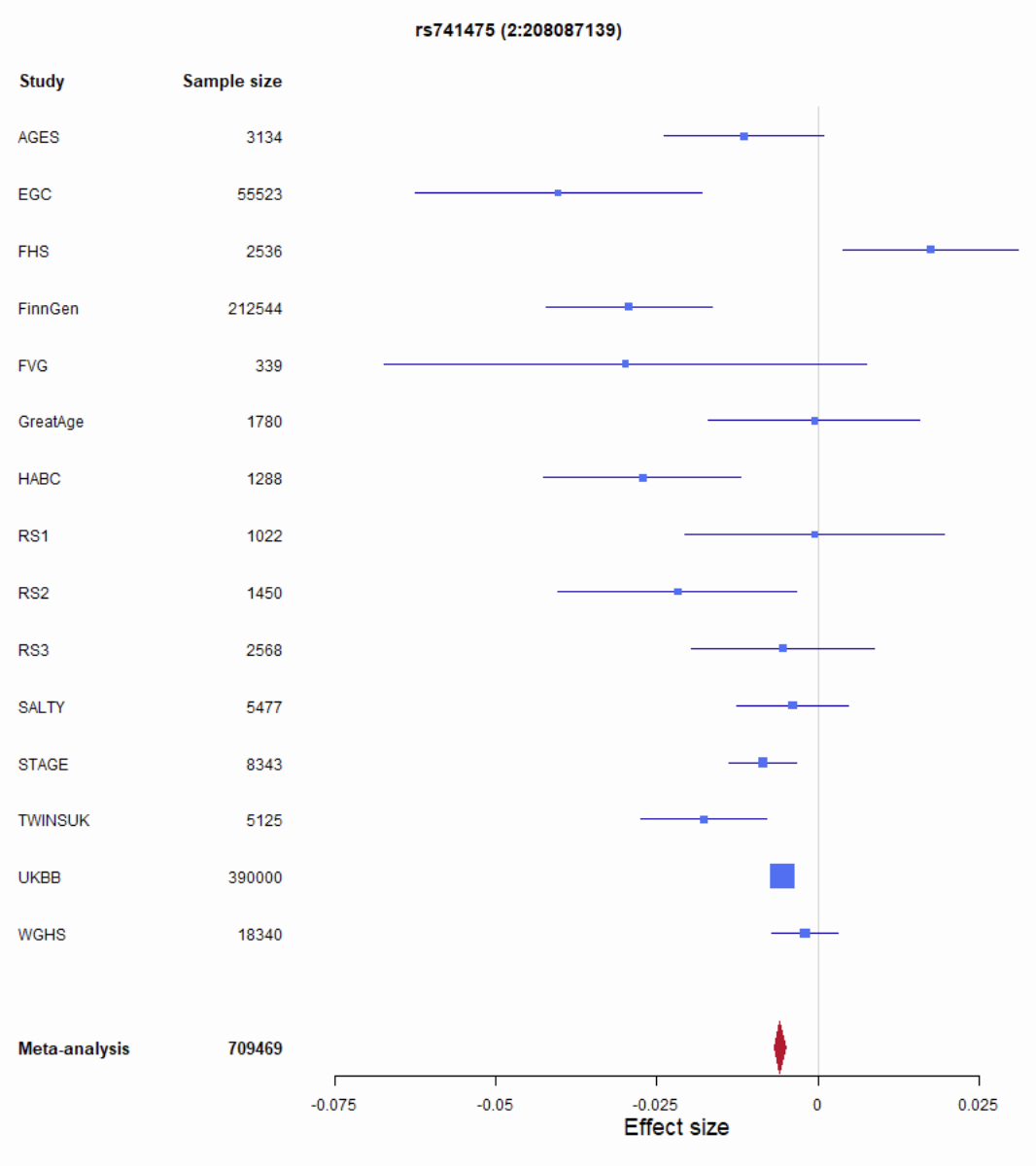
Locus annotation: IPP-[x]-MAST2



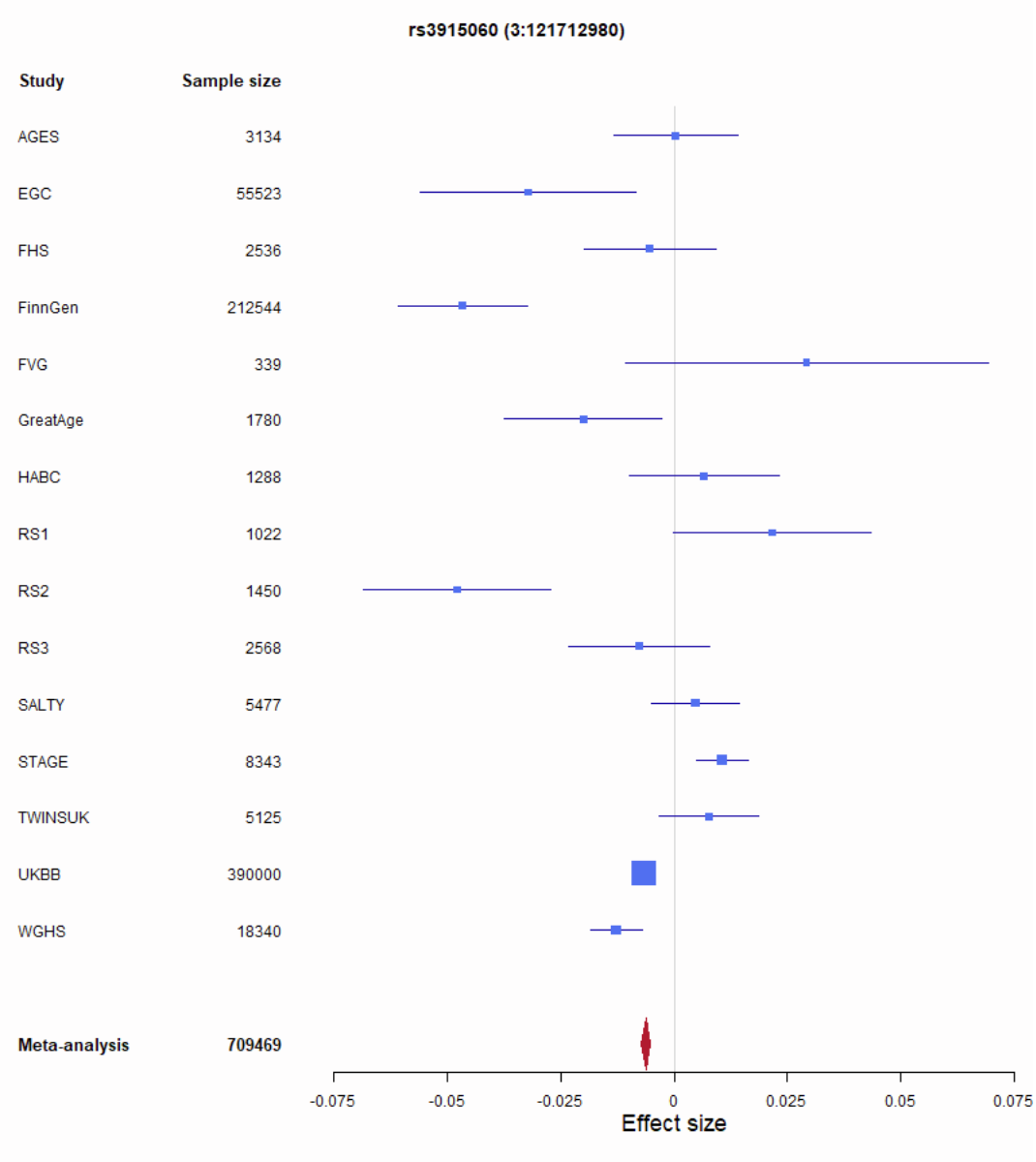
Locus annotation: PBX1---[x]-LMX1A



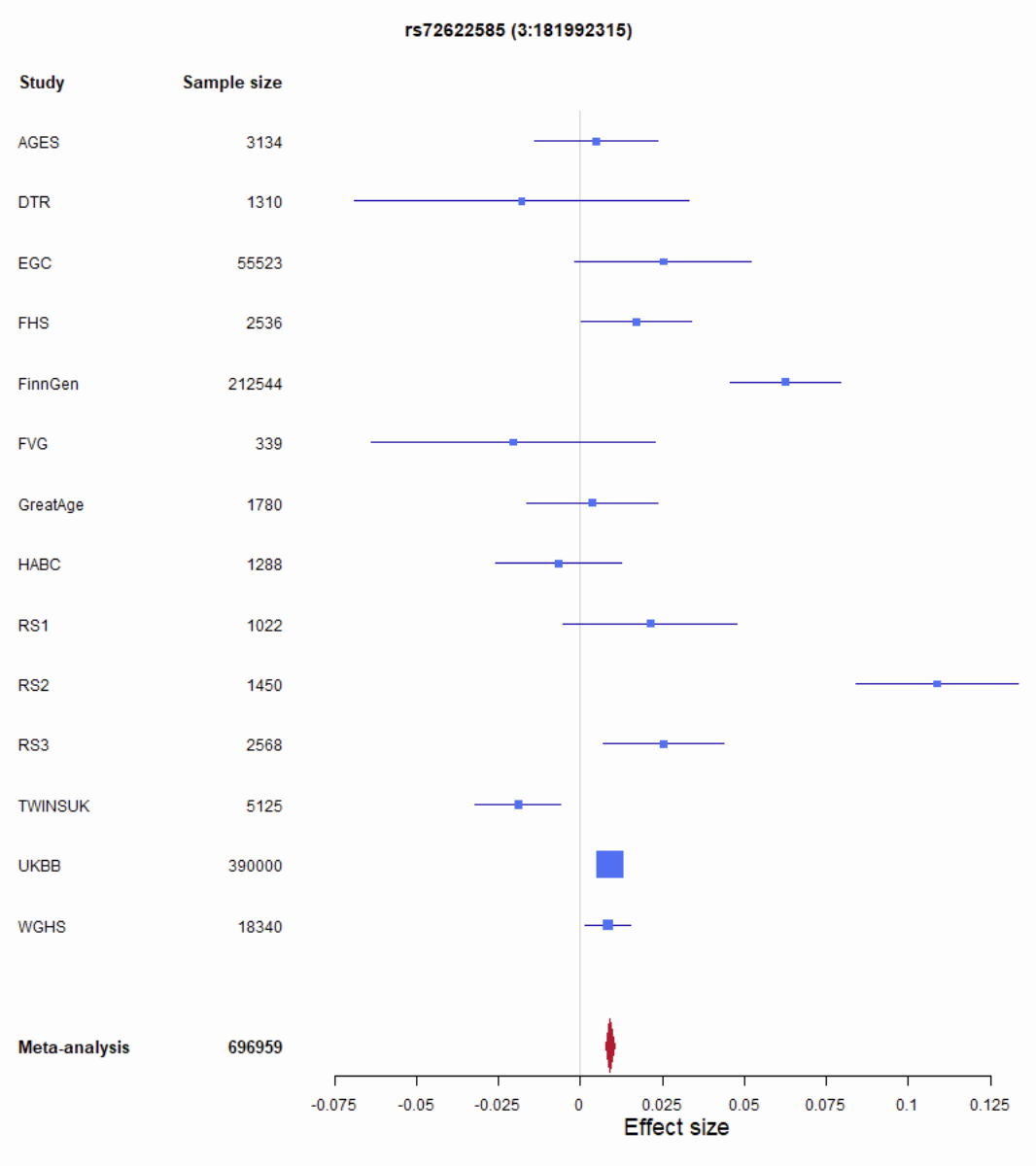
Locus annotation: [SPTBN1] intronic



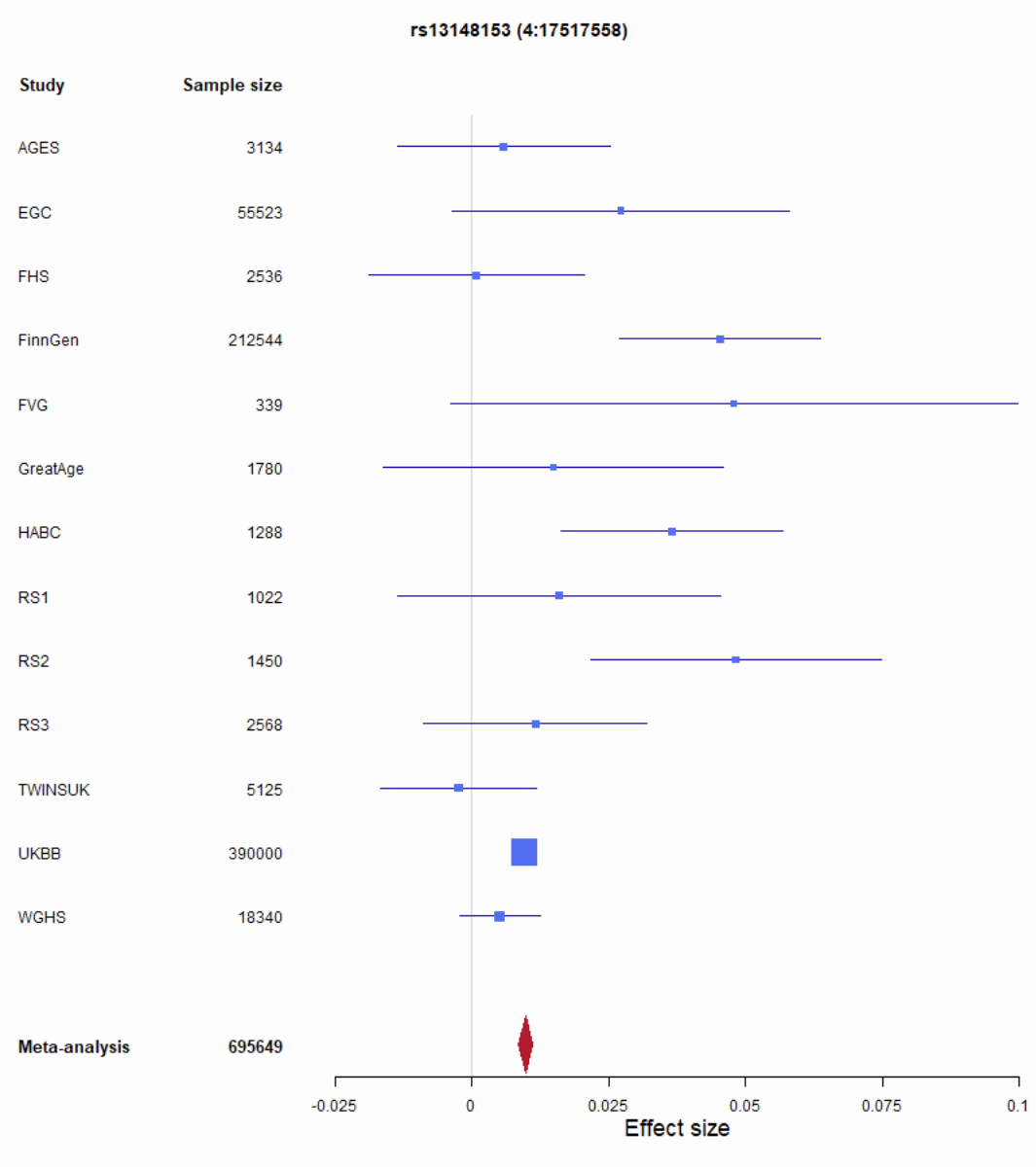
Locus annotation: KLF7-[x]--CREB1



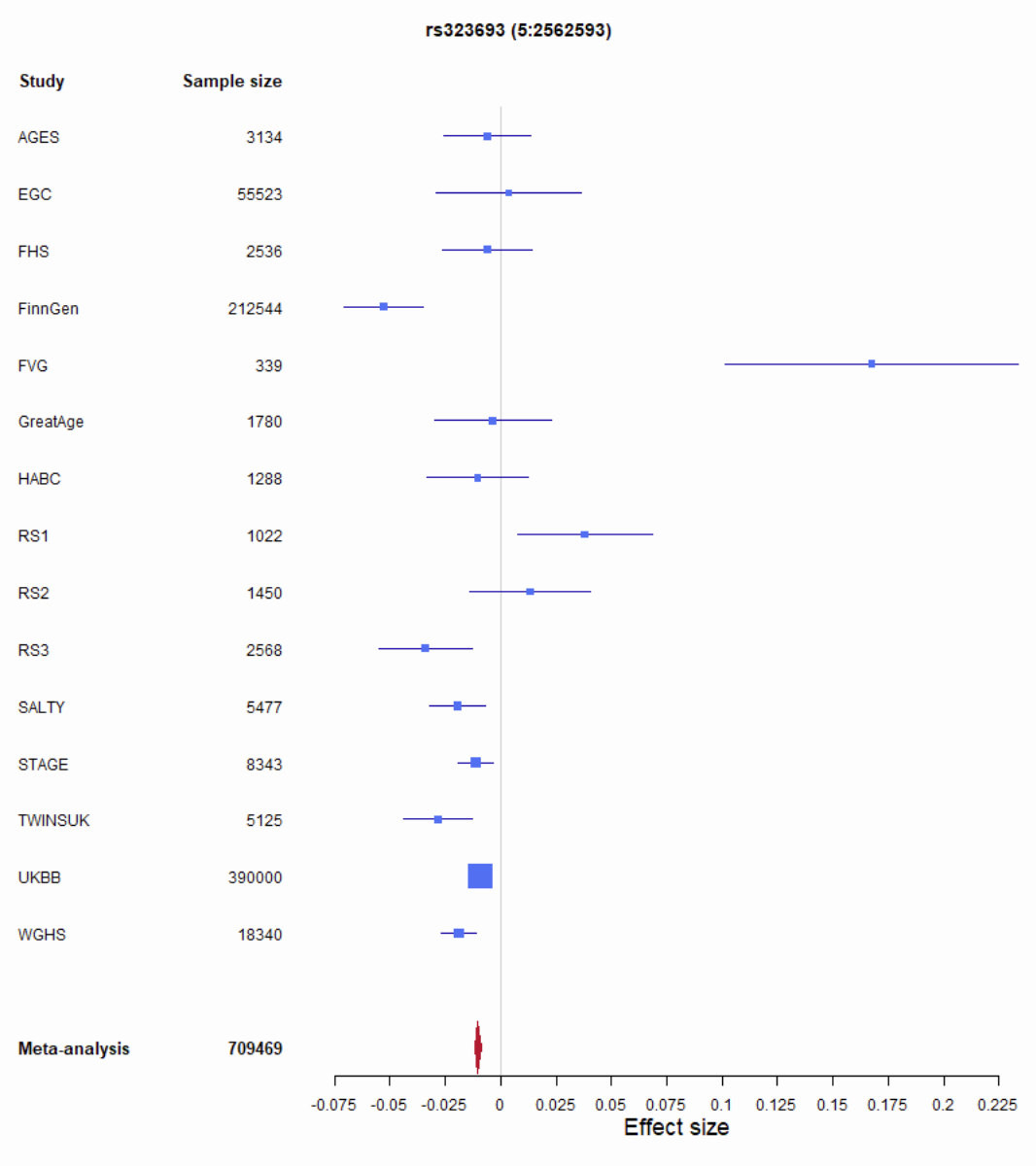
Locus annotation: [ILDR1] intronic



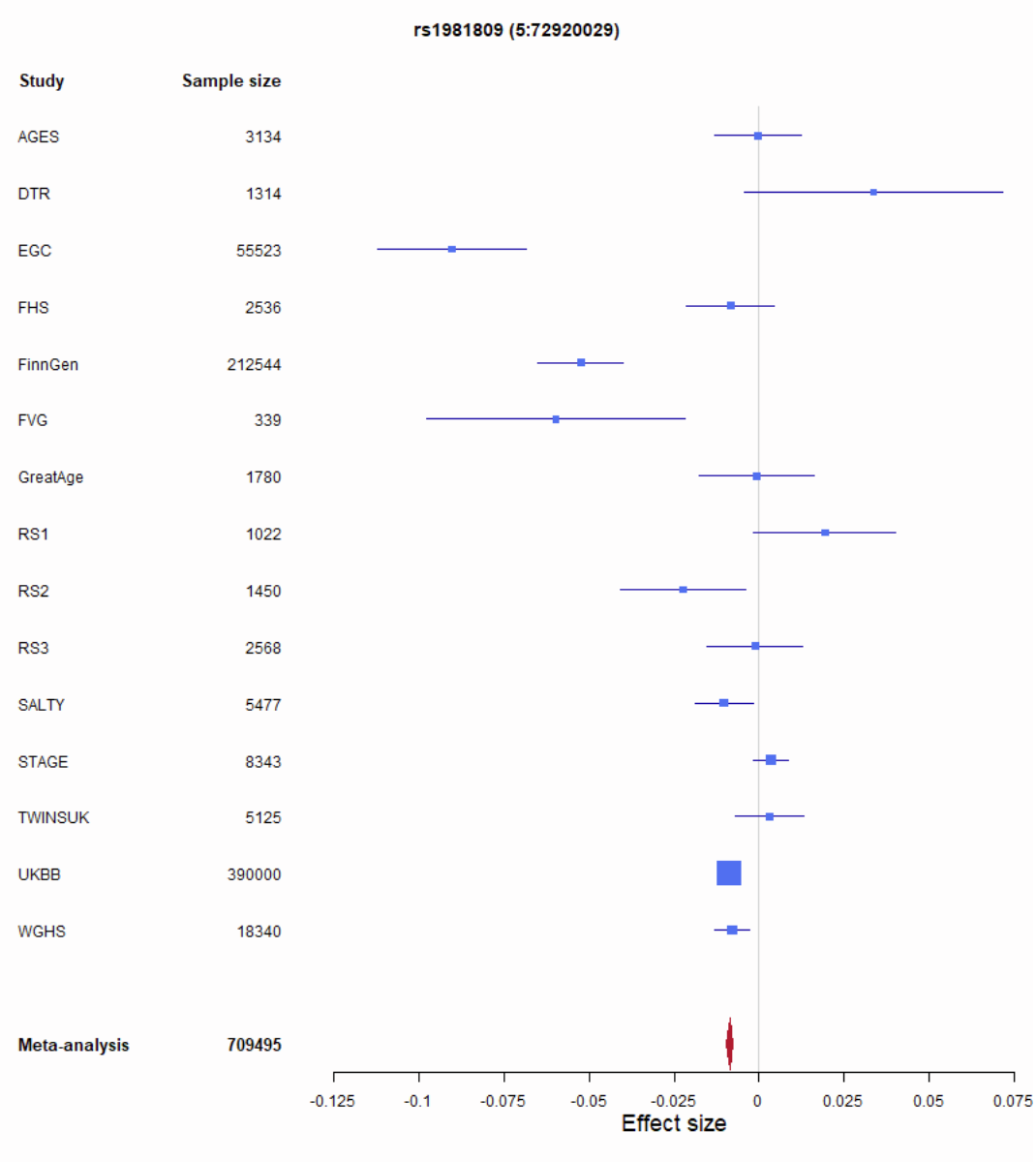
Locus annotation: SOX2---[x]---ATP11B



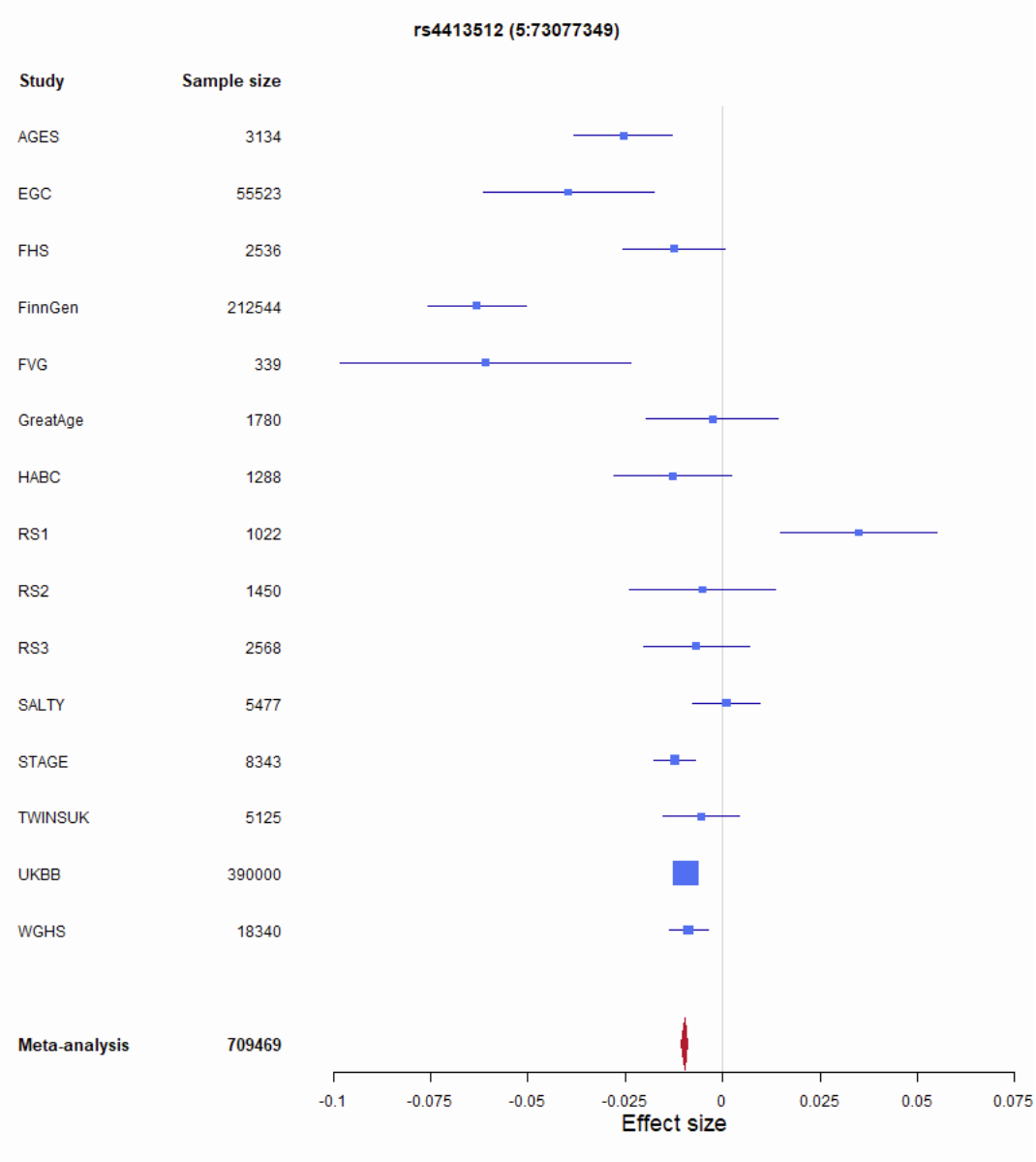
Locus annotation: [CLRN2] intronic



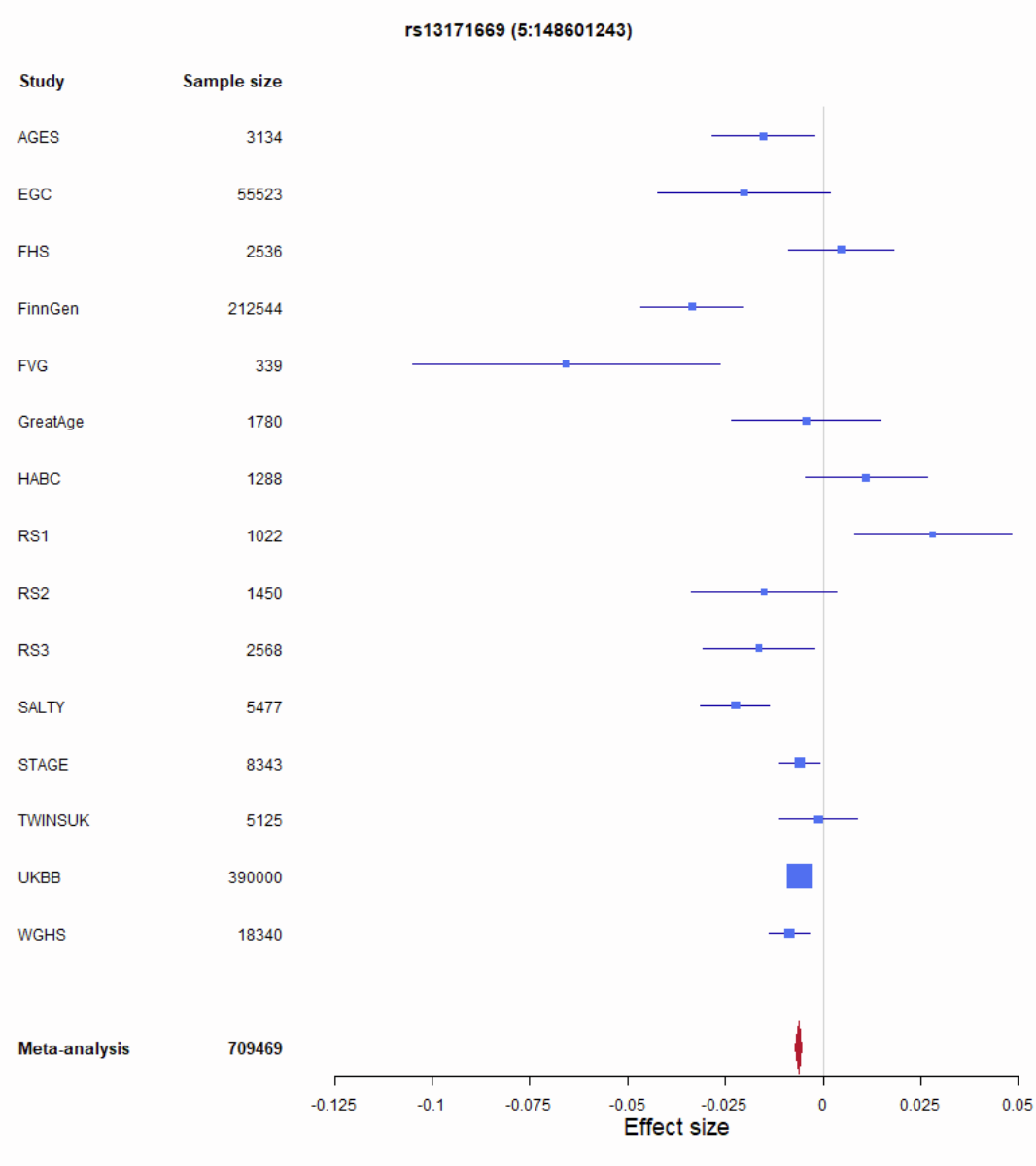
Locus annotation: IRX4---[x]--IRX2



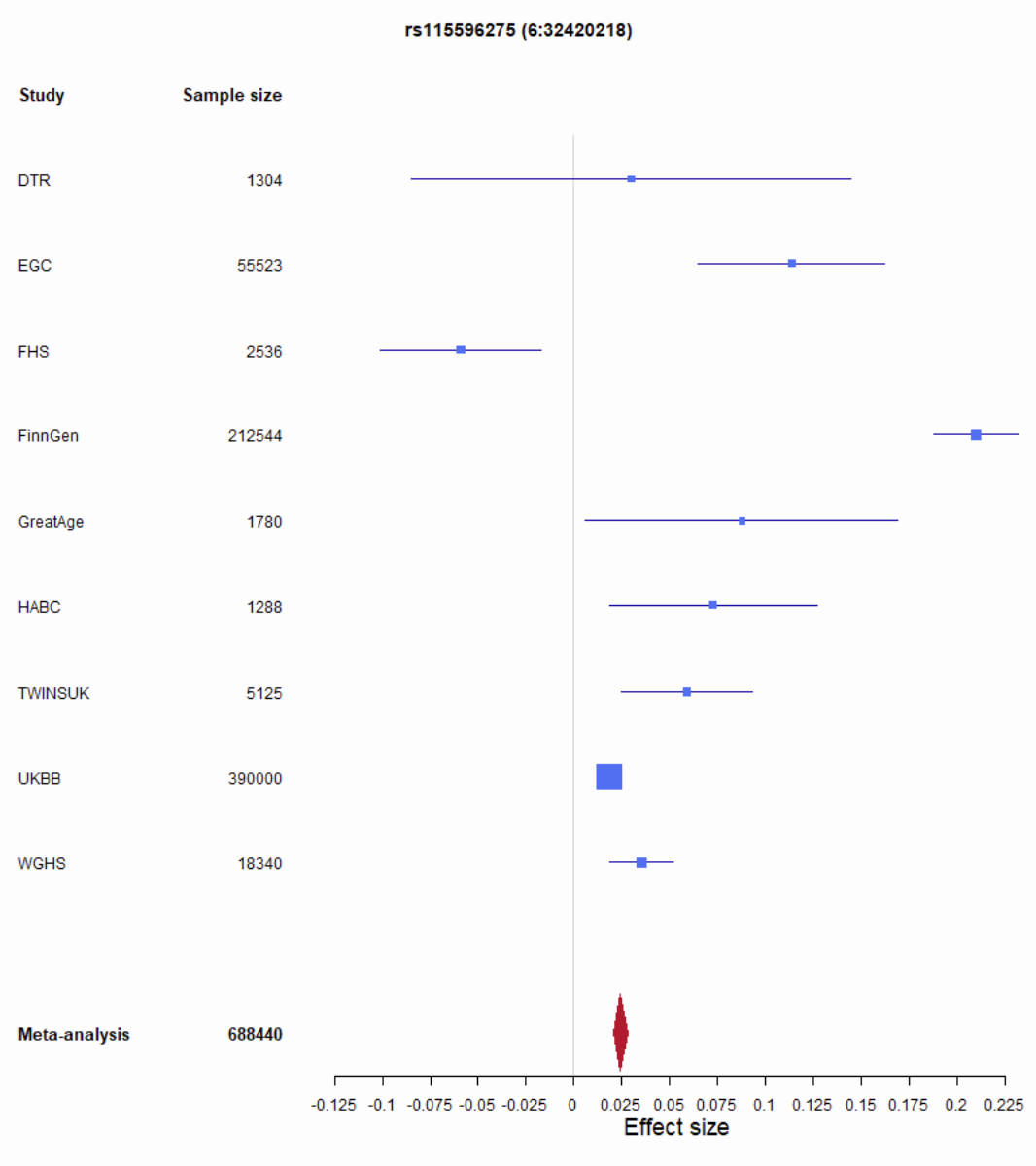
Locus annotation: UTP15-[x]-ARHGEF28



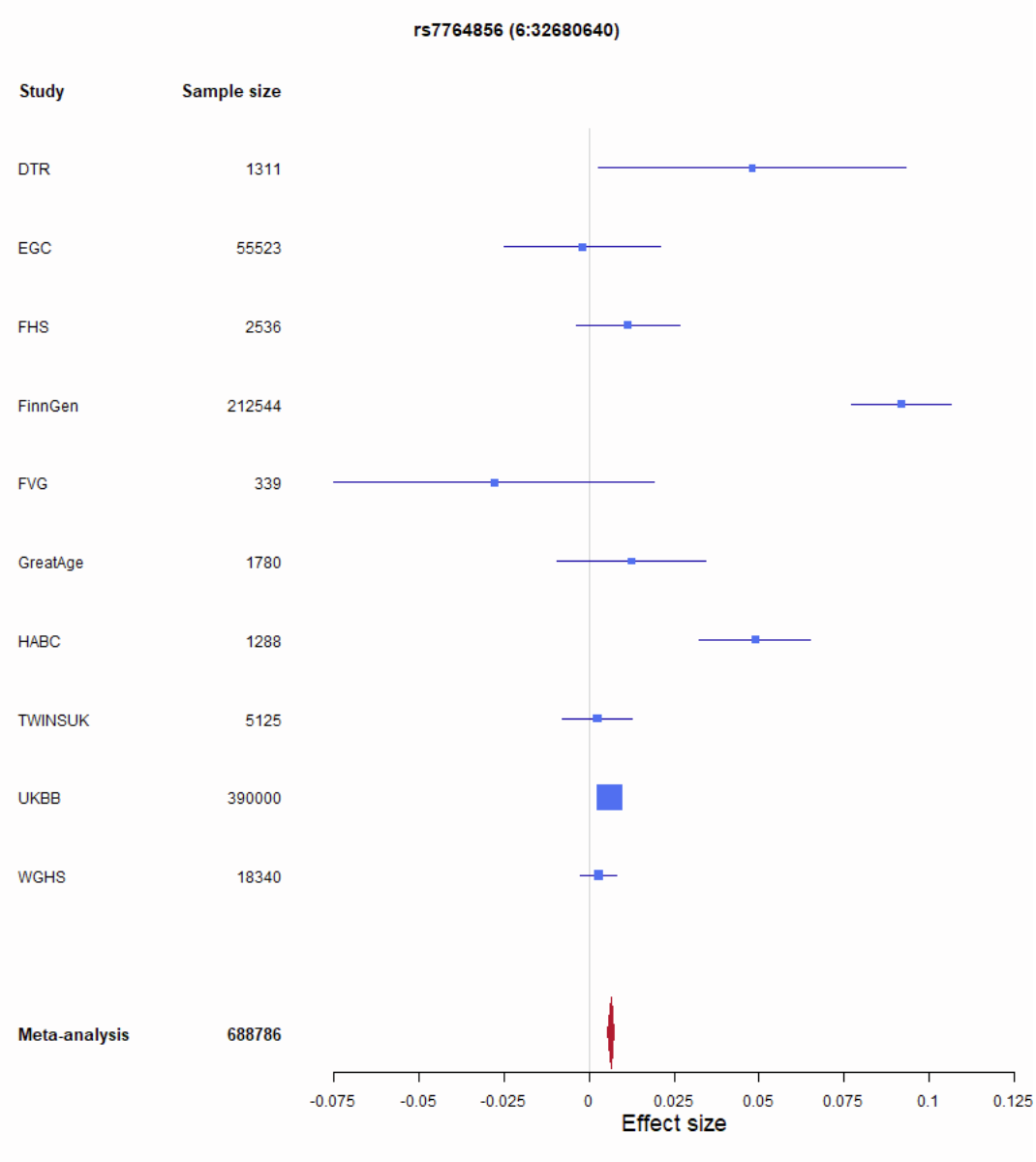
Locus annotation: [ARHGEF28] intronic



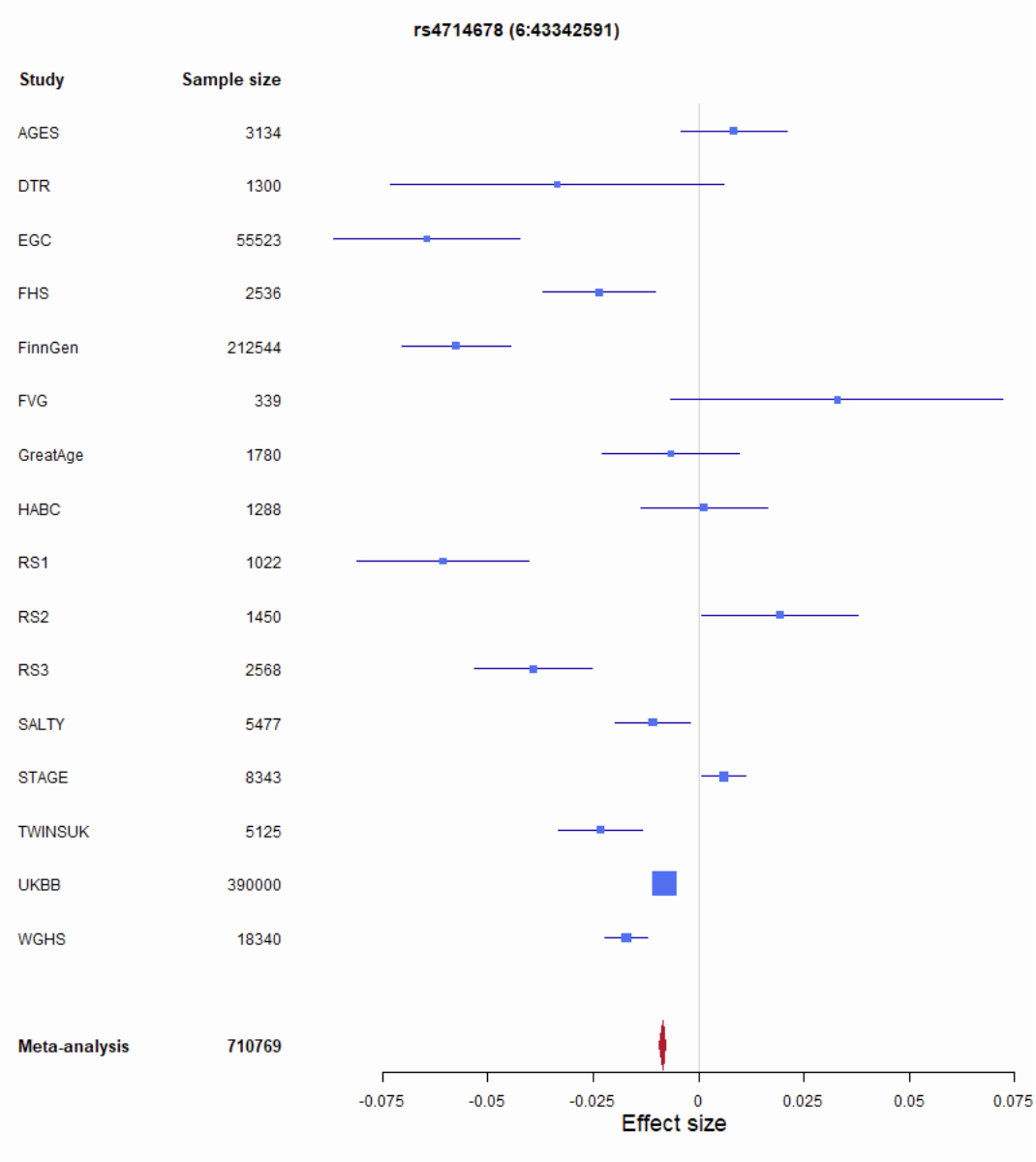
Locus annotation: [ABLIM3] intronic



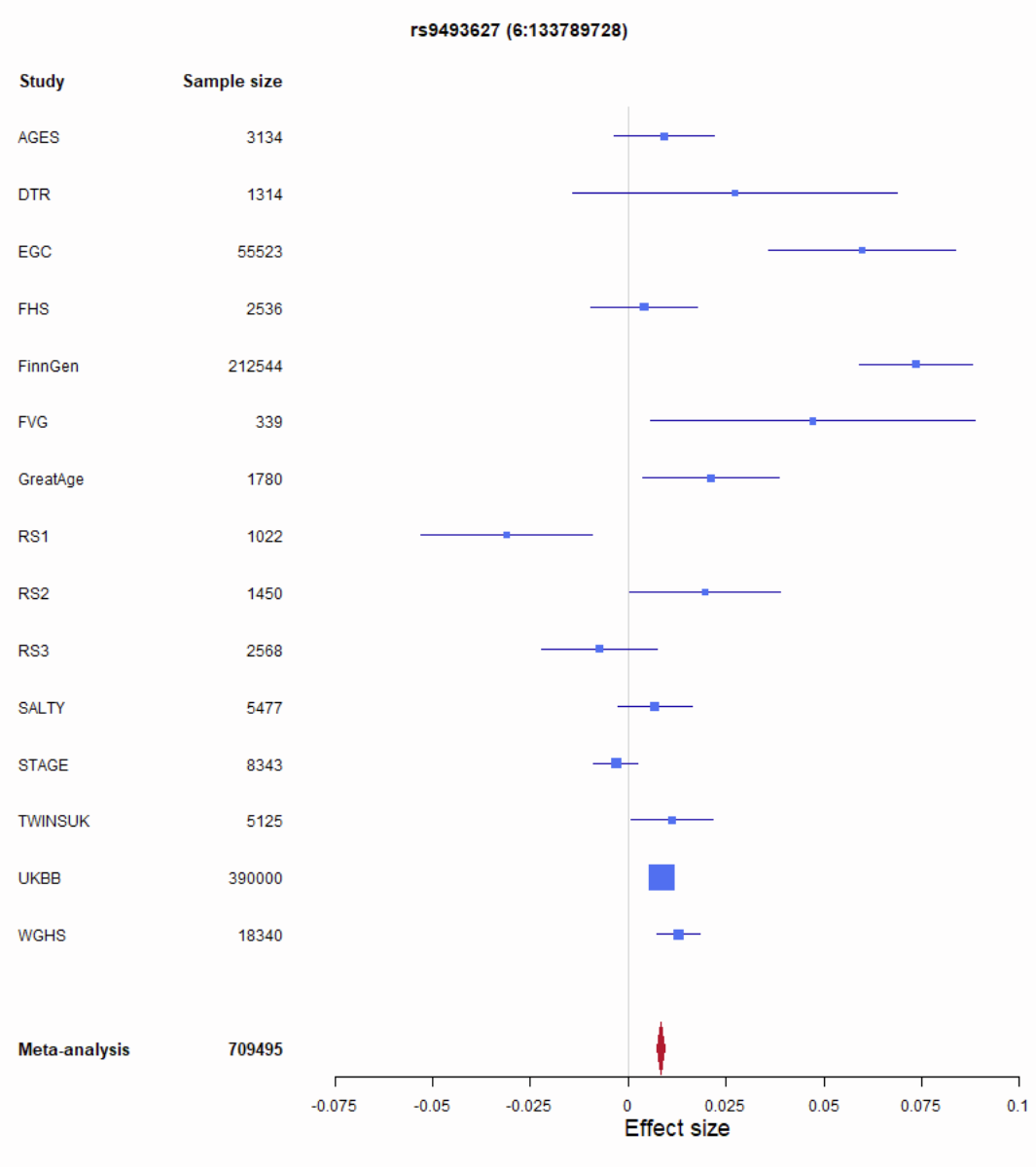
Locus annotation: HLA-DRA-[x]-HLA-DRB5



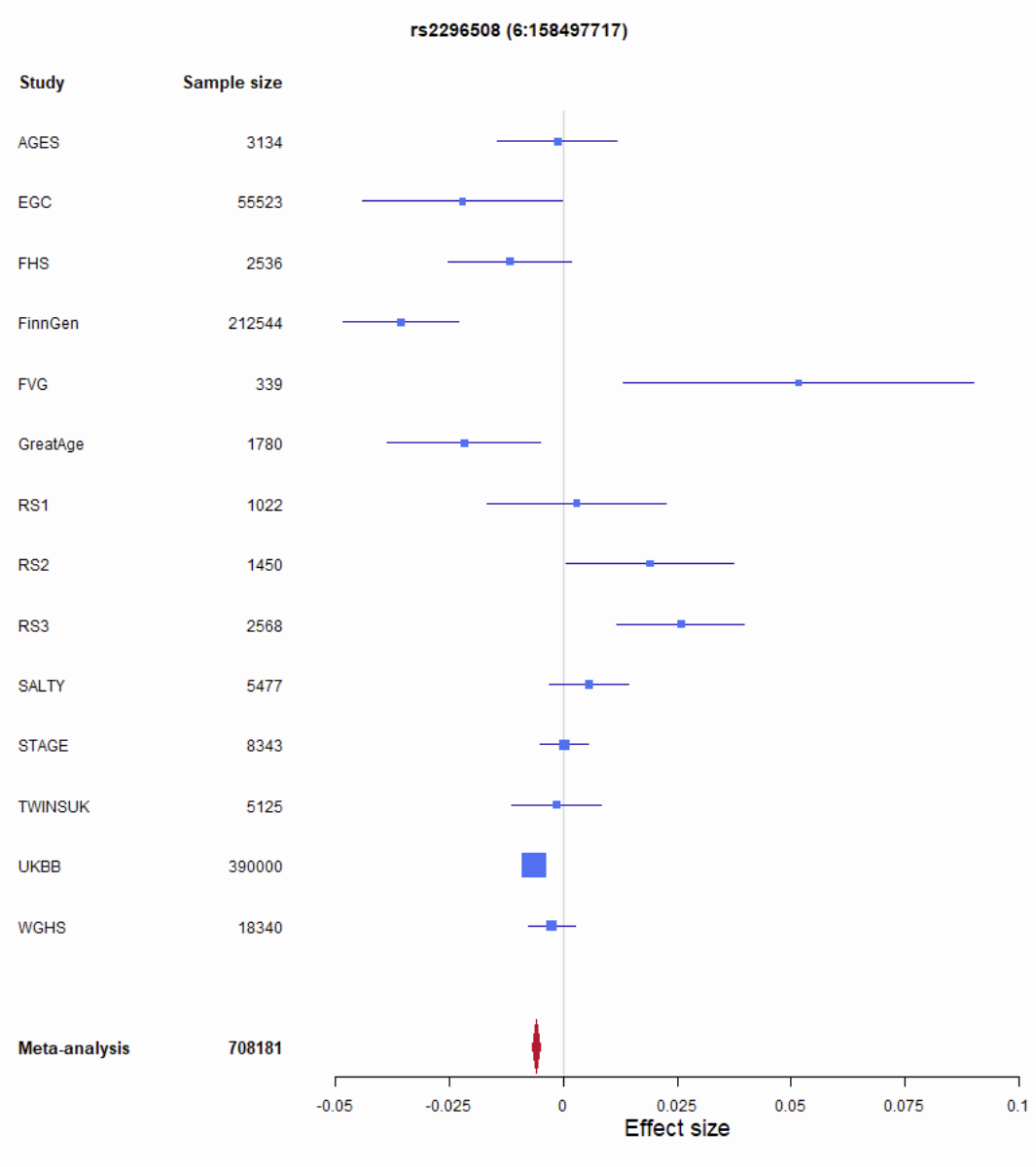
Locus annotation: HLA-DQB1-[x]-HLA-DQA2



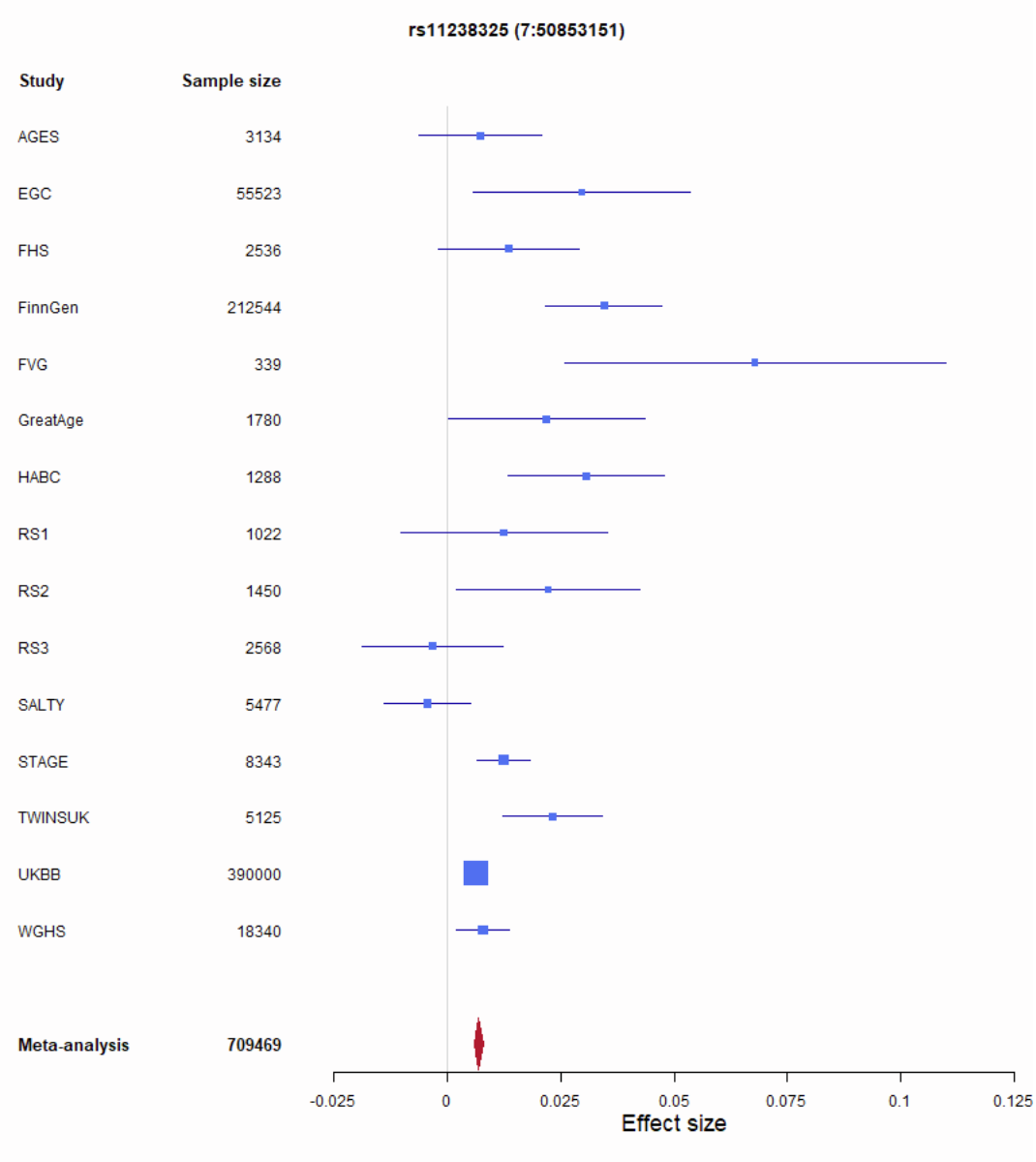
Locus annotation: ZNF318-[x]-ABCC10



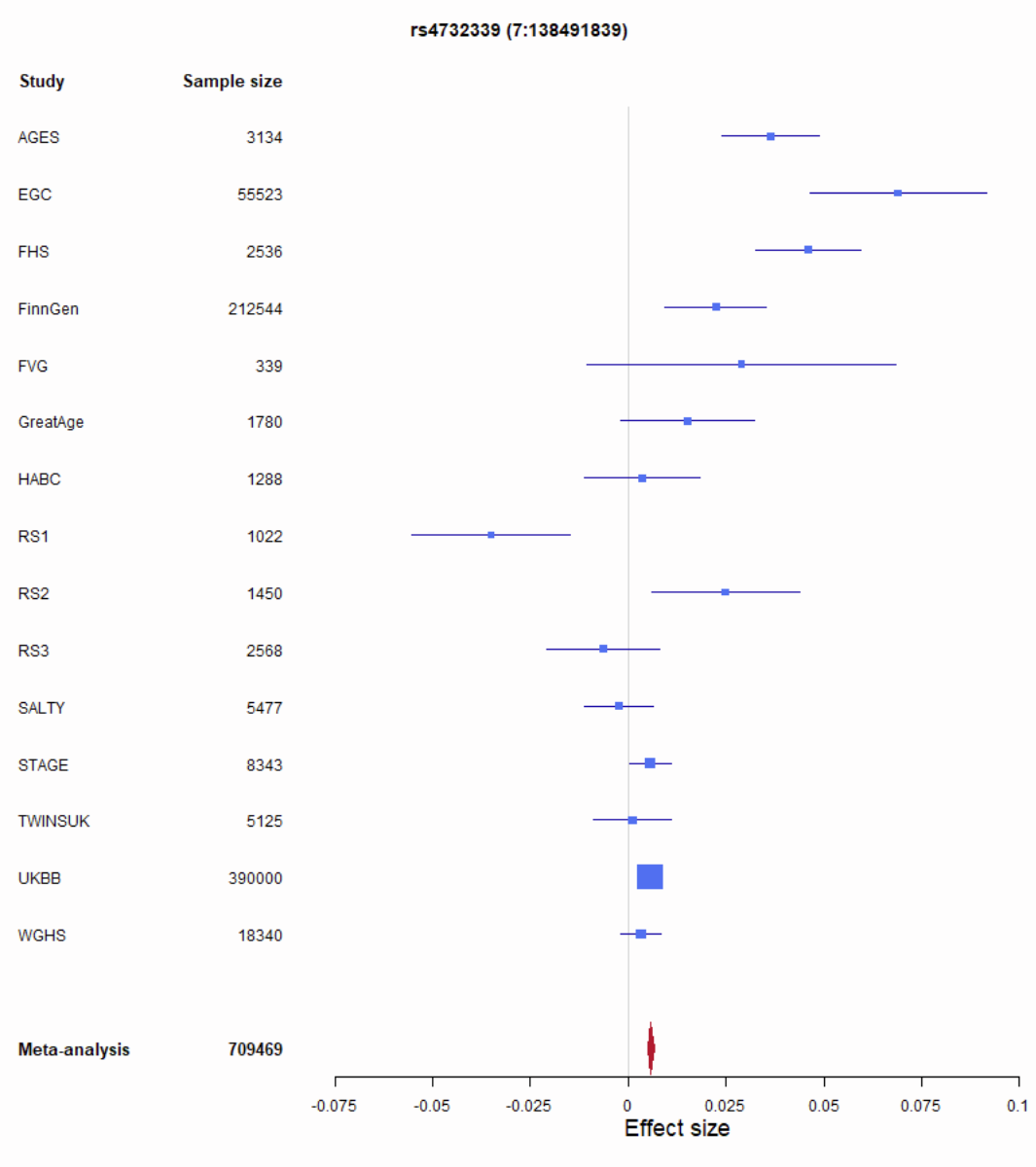
Locus annotation: [EYA4] G>S



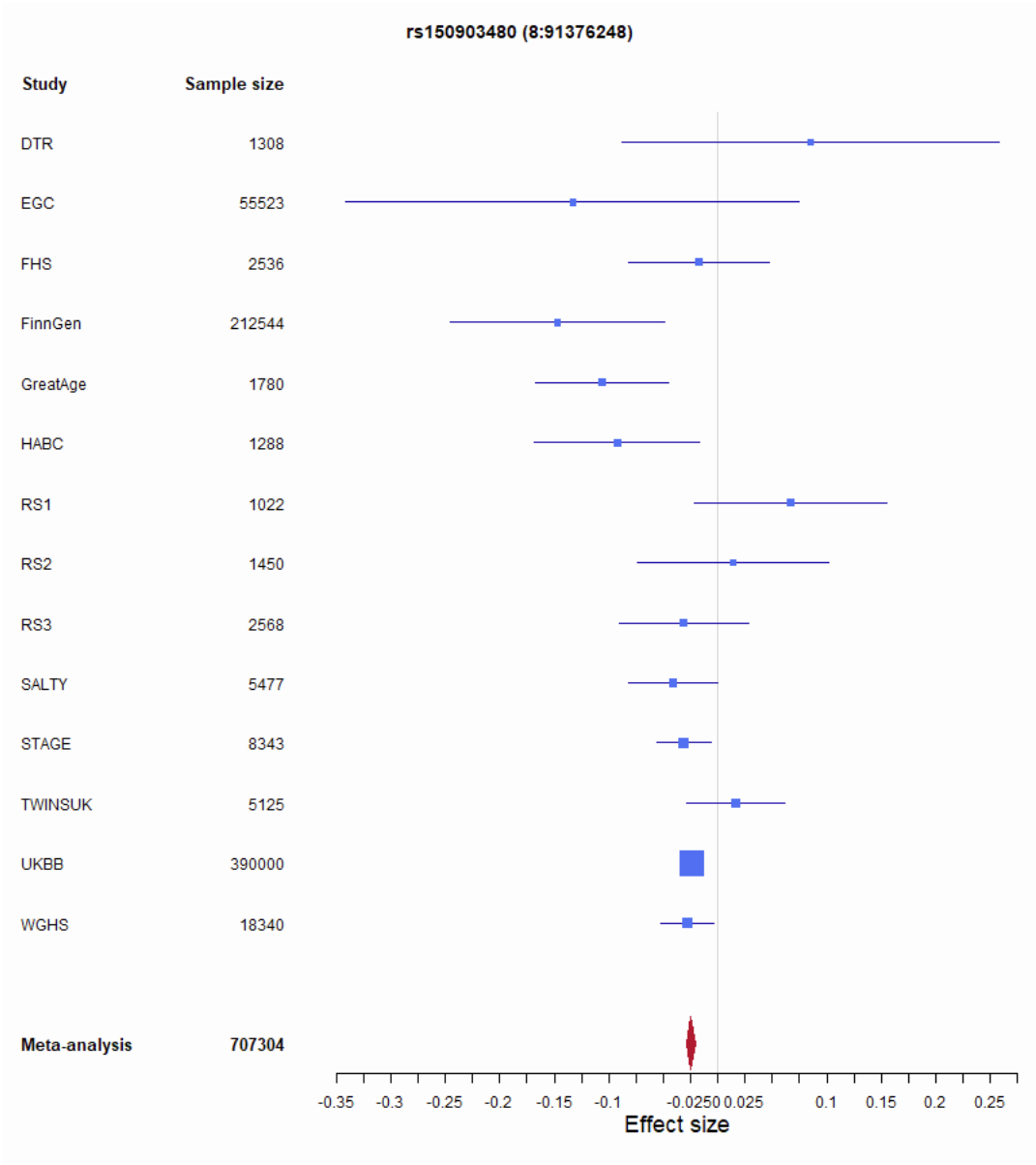
Locus annotation: [SYNJ2] V>V



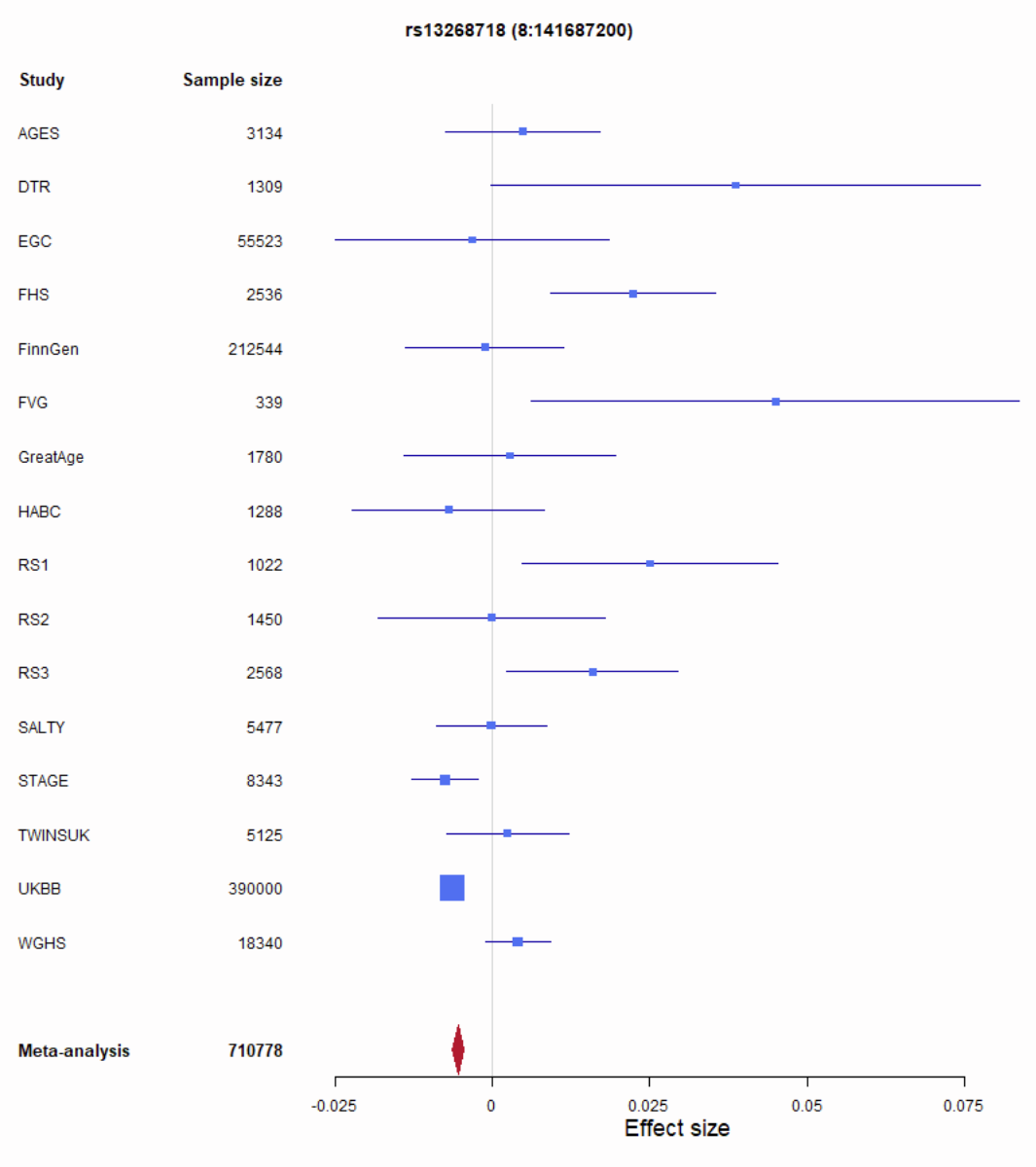
Locus annotation: [GRB10] intronic



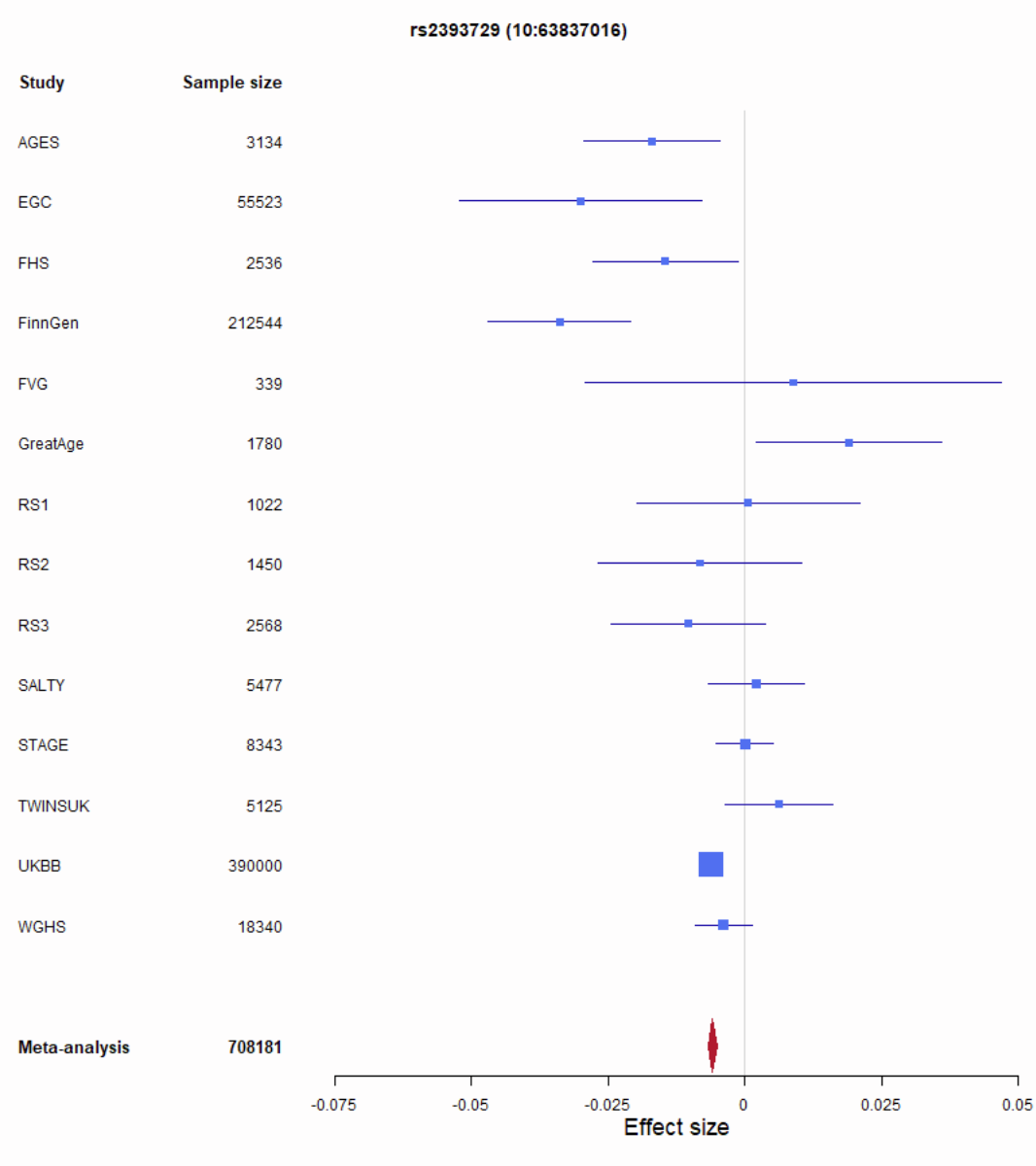
Locus annotation: TMEM213-[x]-KIAA1549



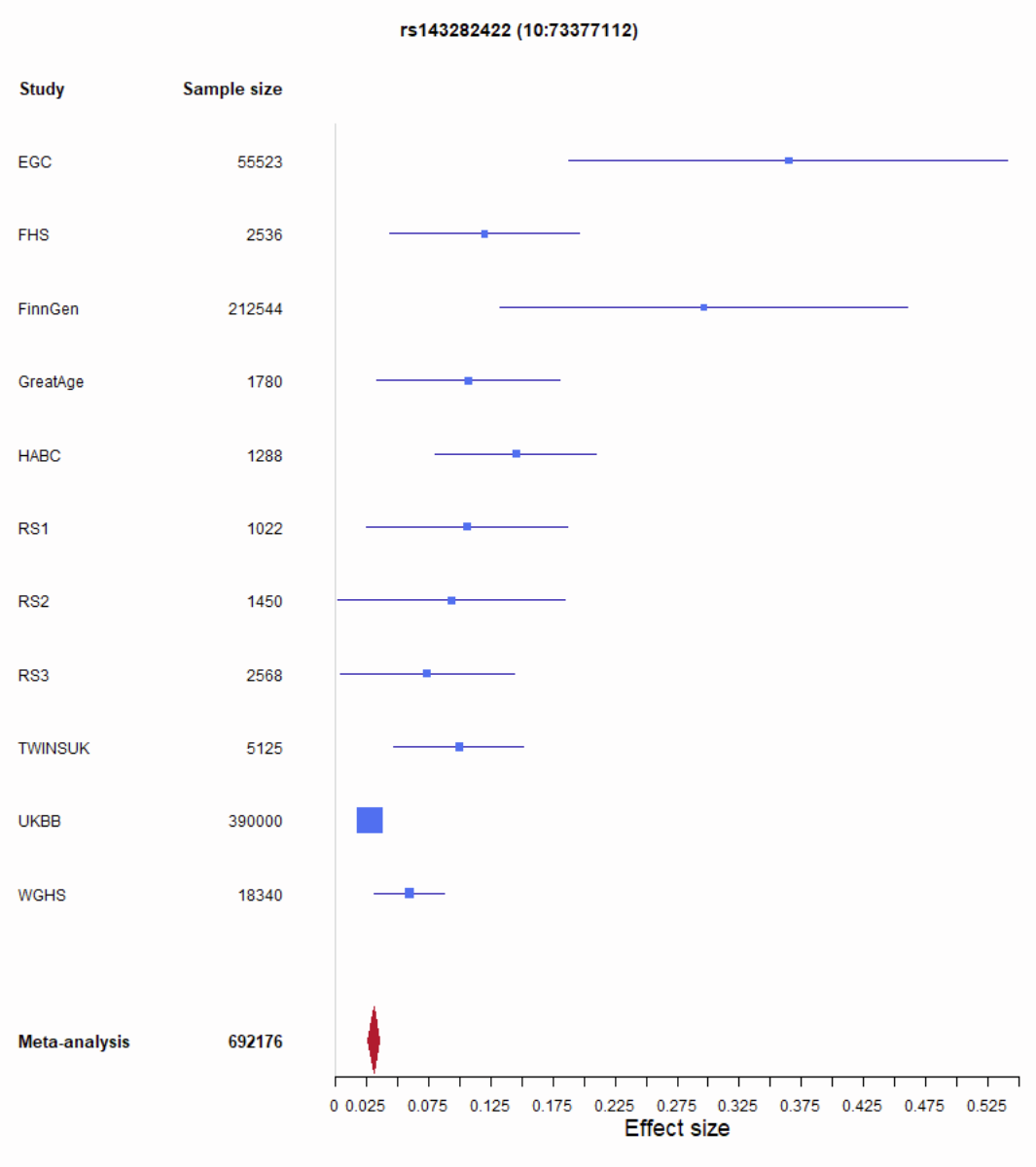
Locus annotation: [LINC00534]



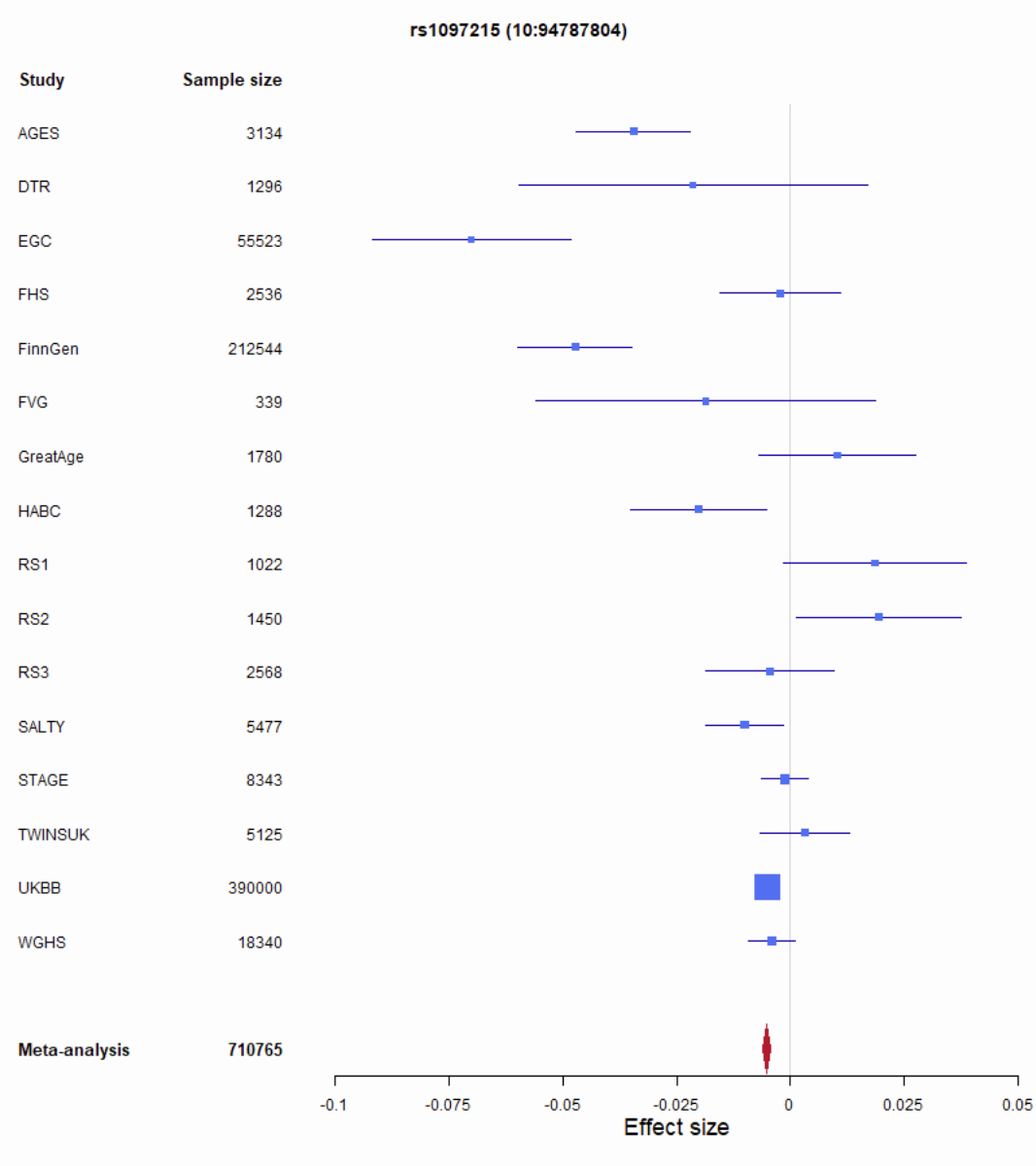
Locus annotation: [PTK2] intronic



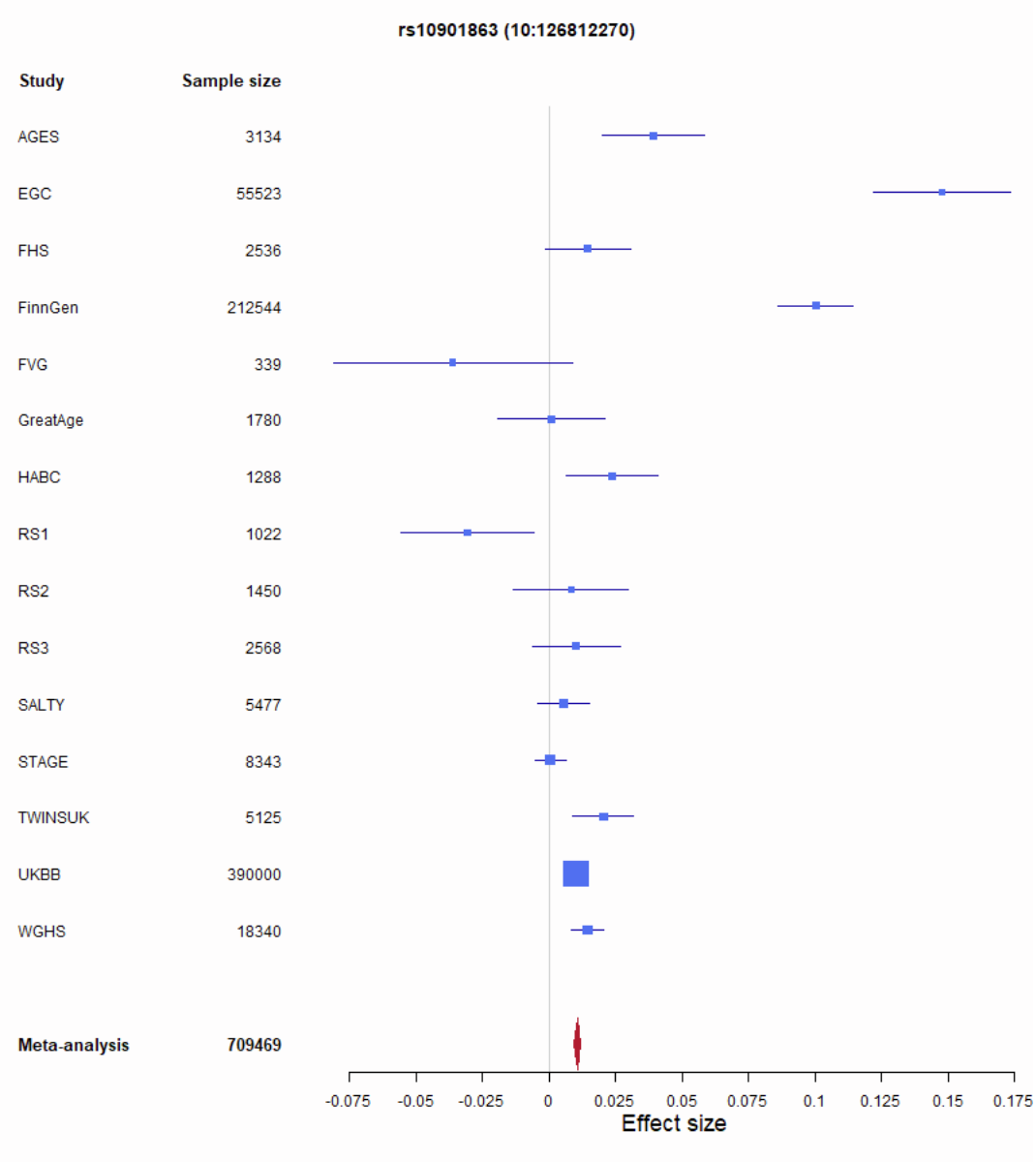
Locus annotation: [ARID5B] intronic



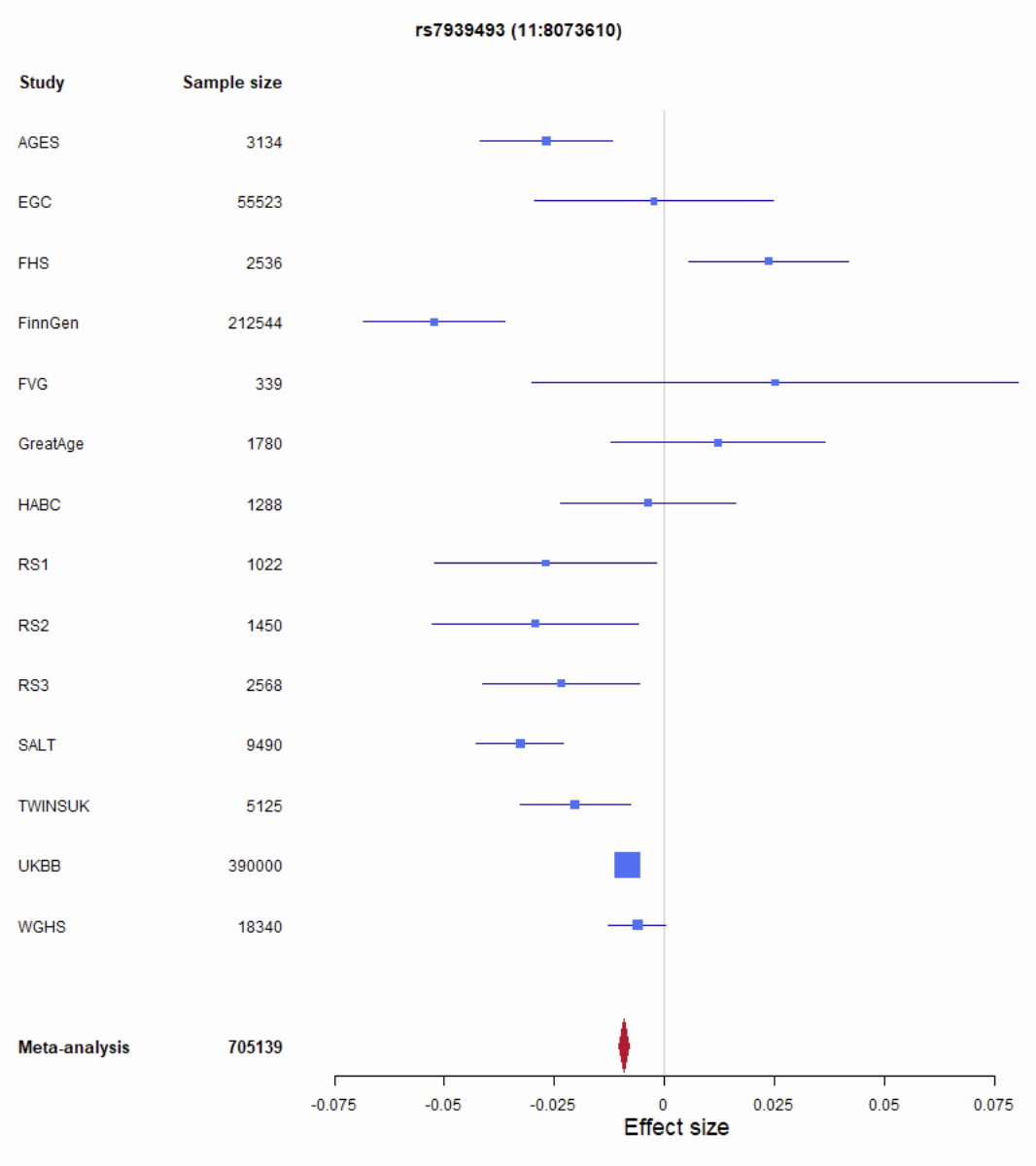
Locus annotation: [CDH23] A>T



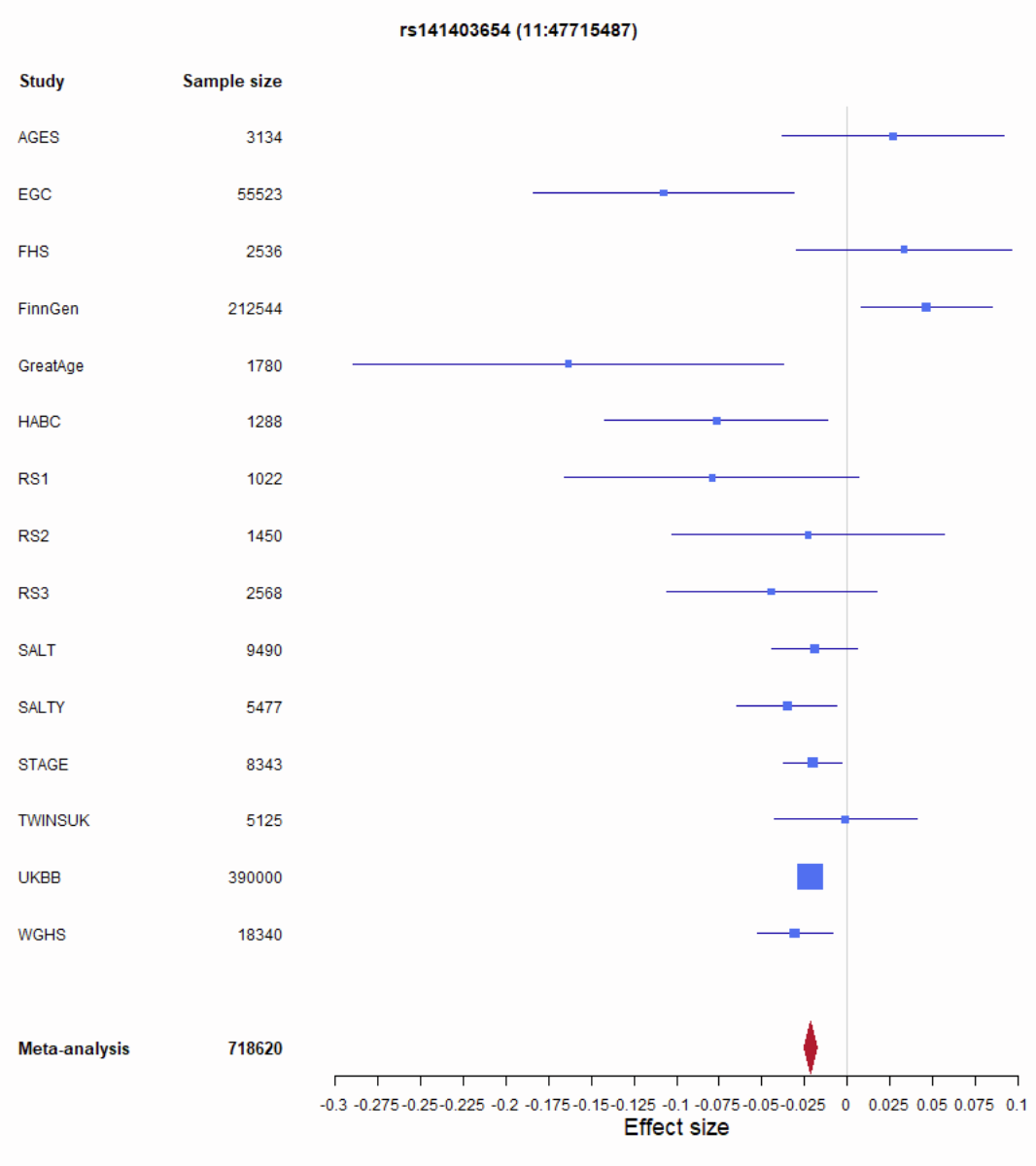
Locus annotation: [EXOC6] intronic



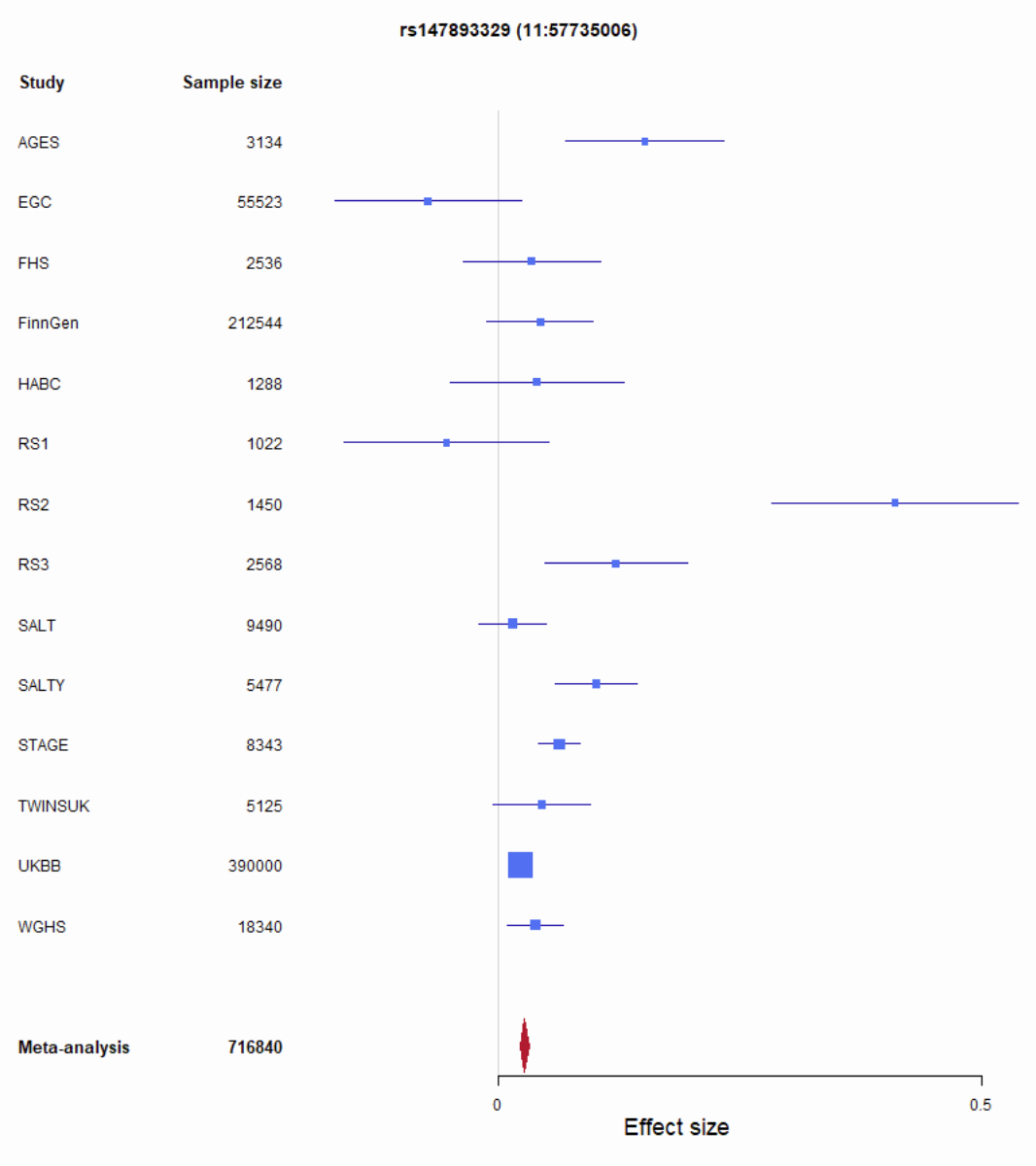
Locus annotation: [CTBP2] 5' UTR



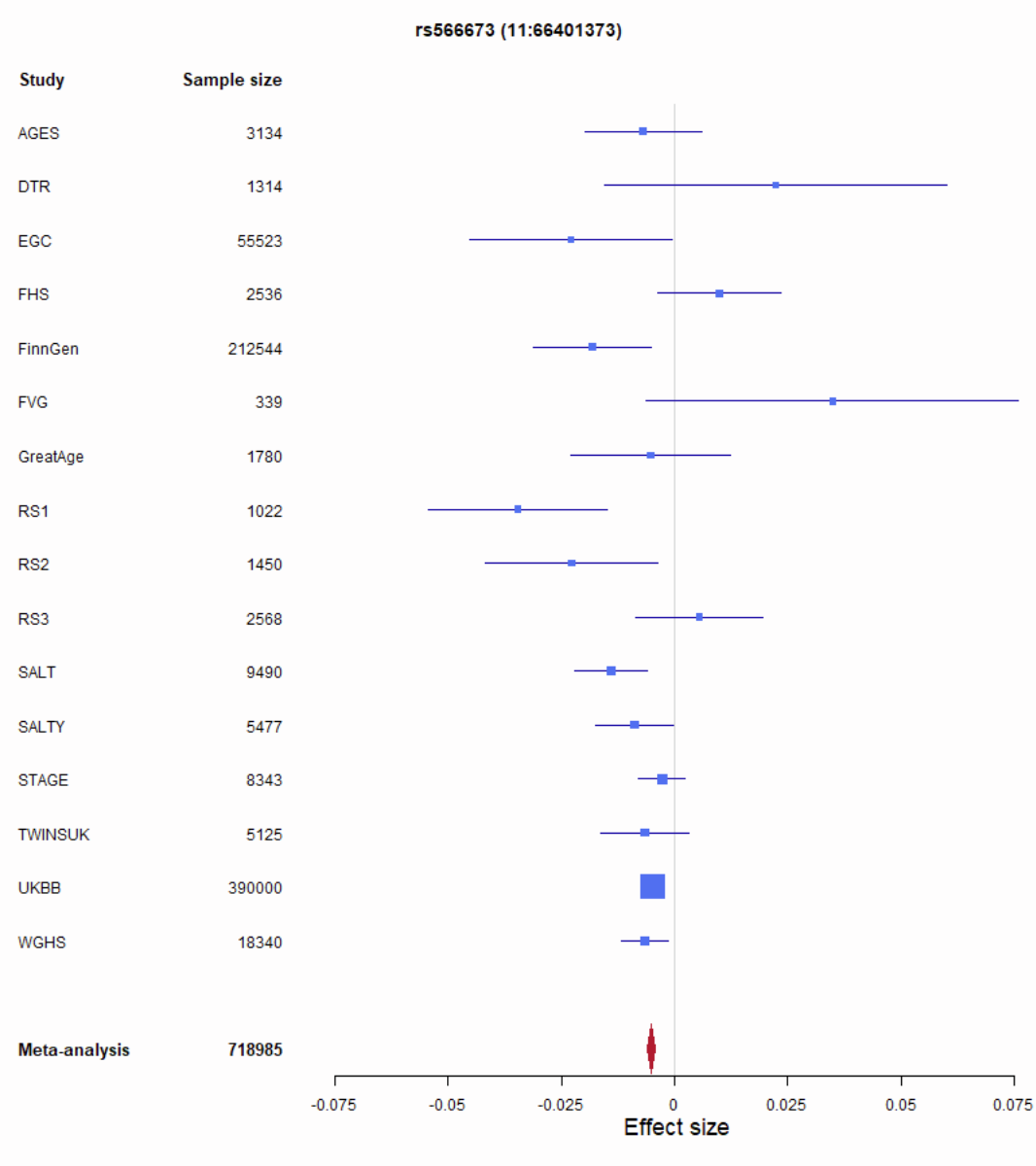
Locus annotation: [TUB] intronic



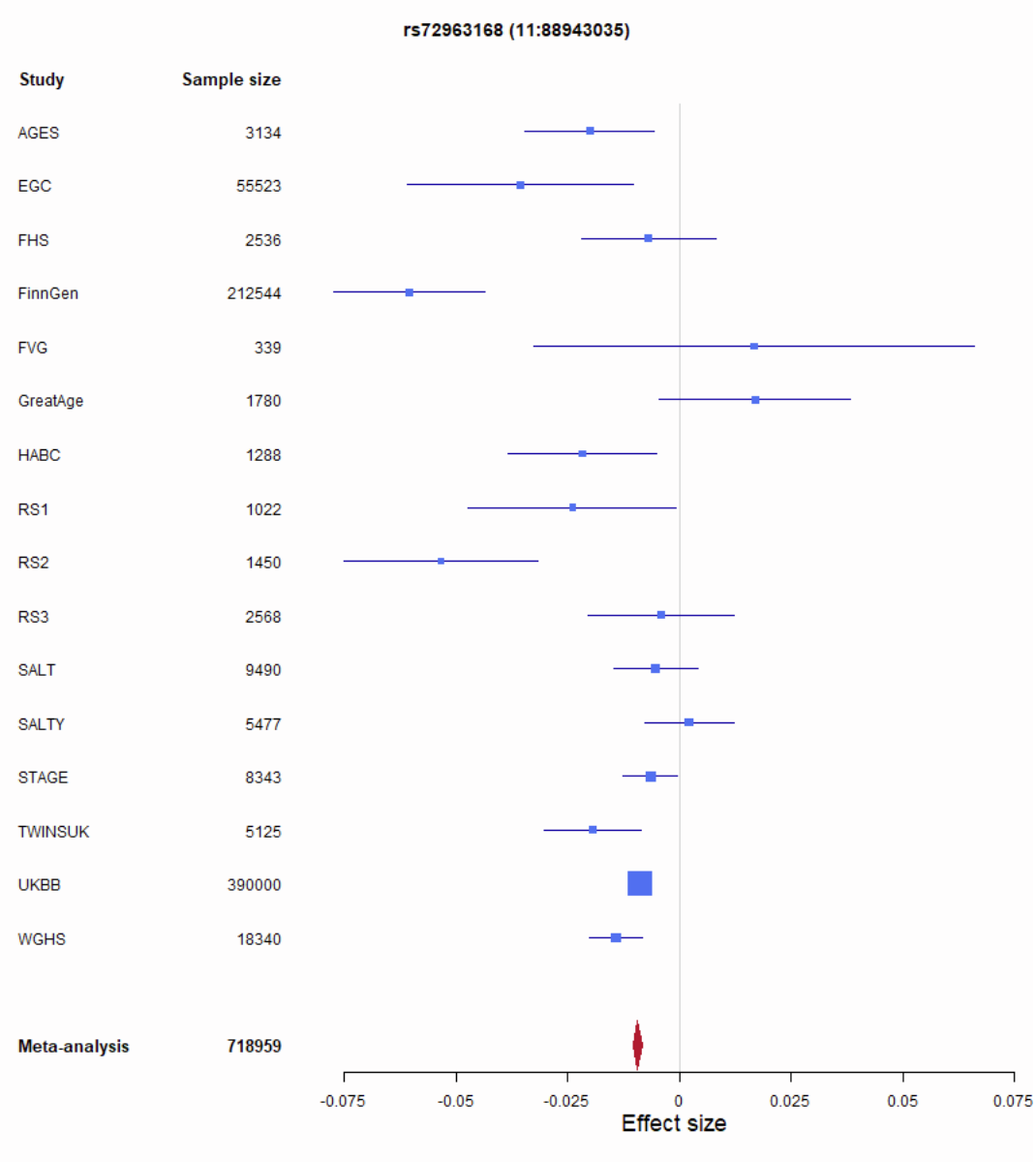
Locus annotation: [AGBL2] intronic



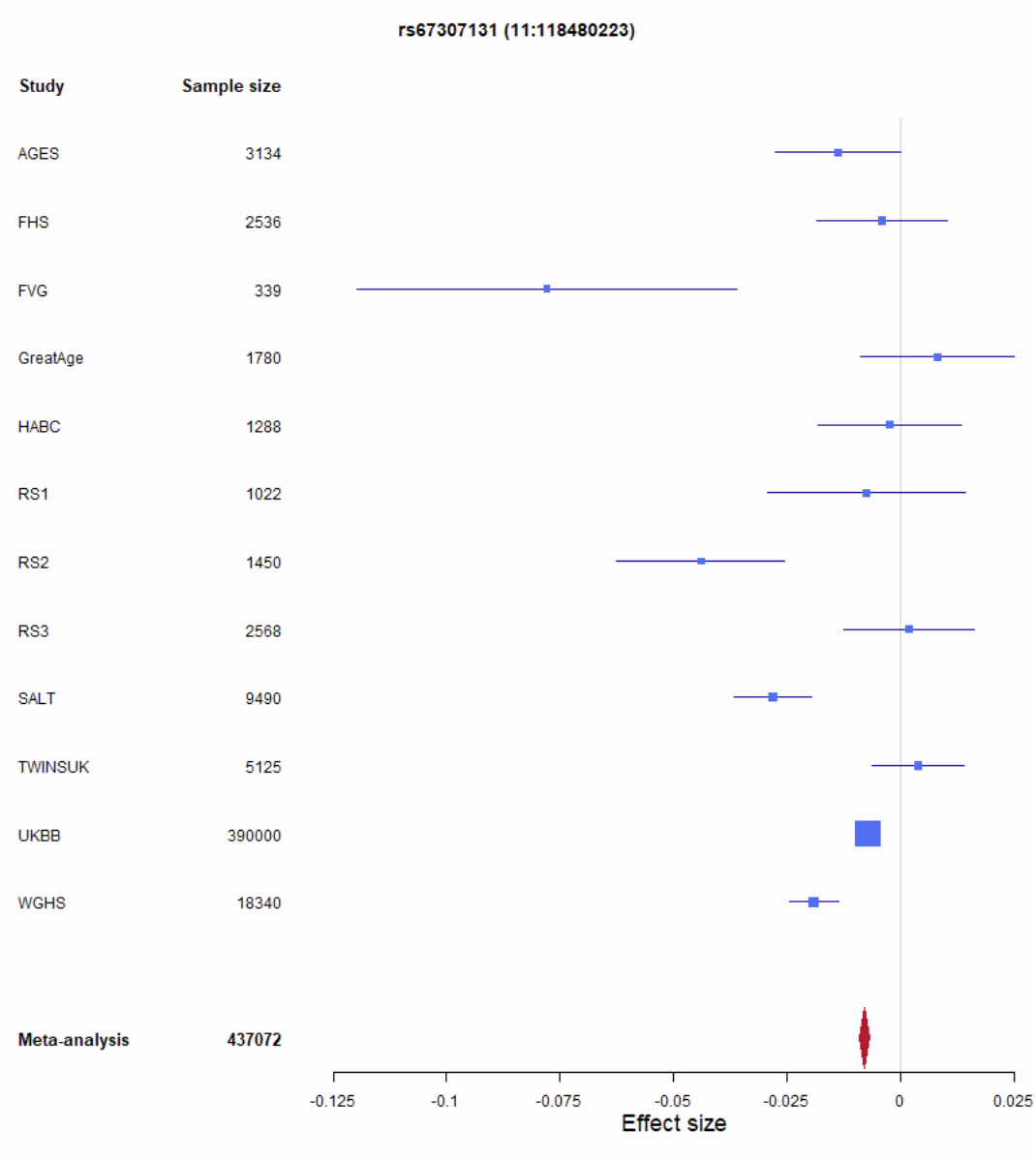
Locus annotation: CTNND1--[x]-OR9Q1



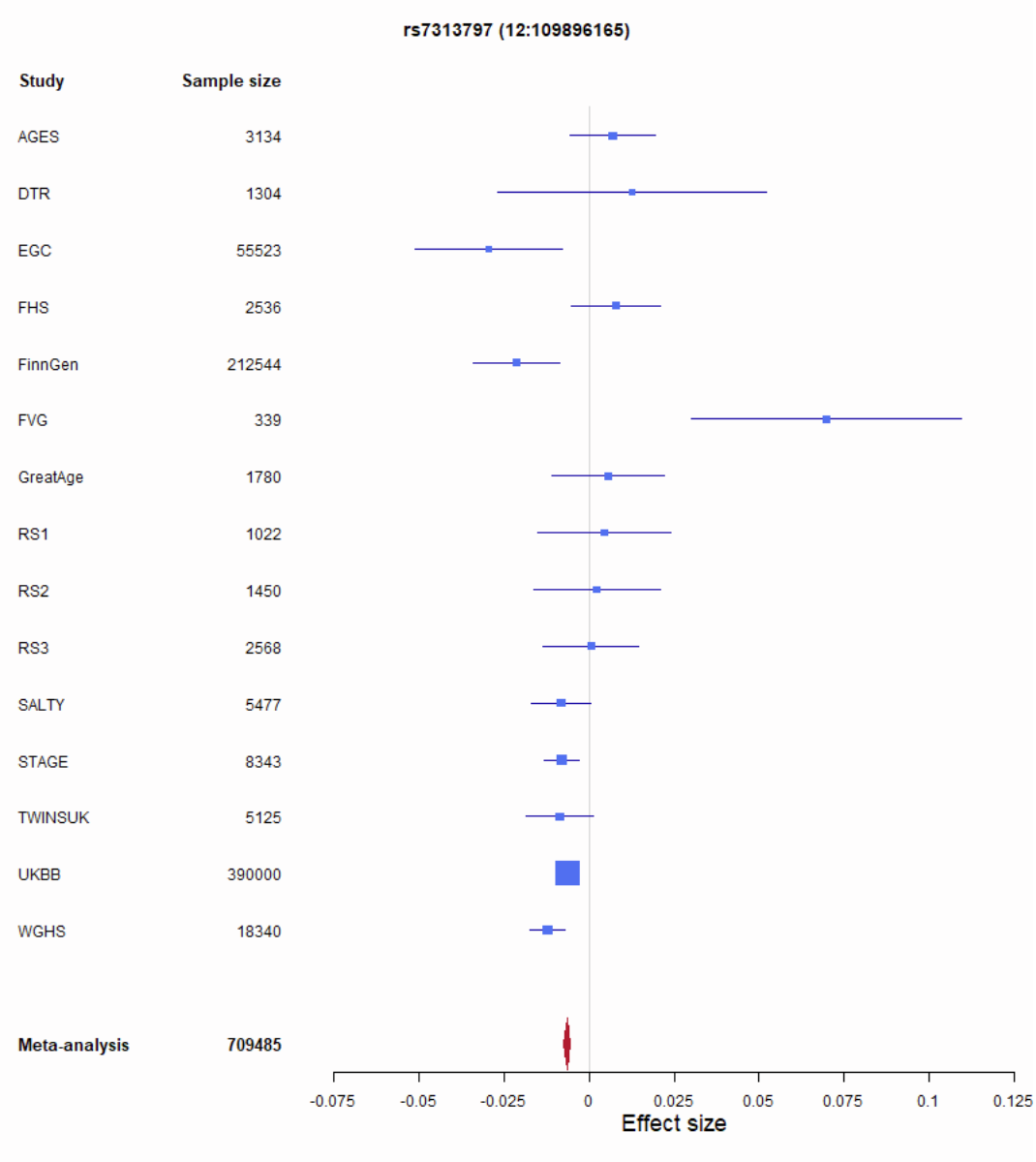
Locus annotation: RBM14-[x]-RBM4



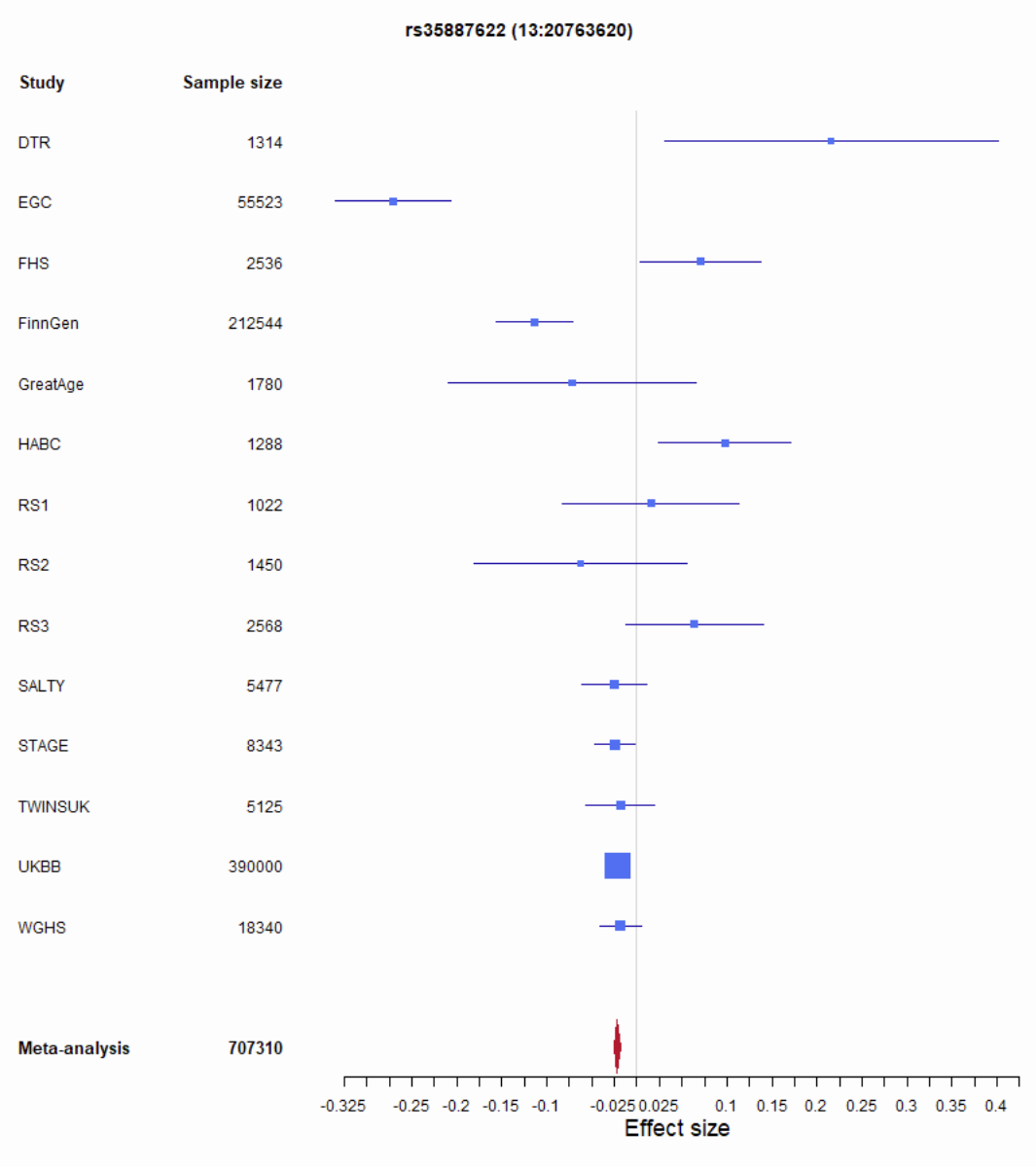
Locus annotation: [TYR] intronic



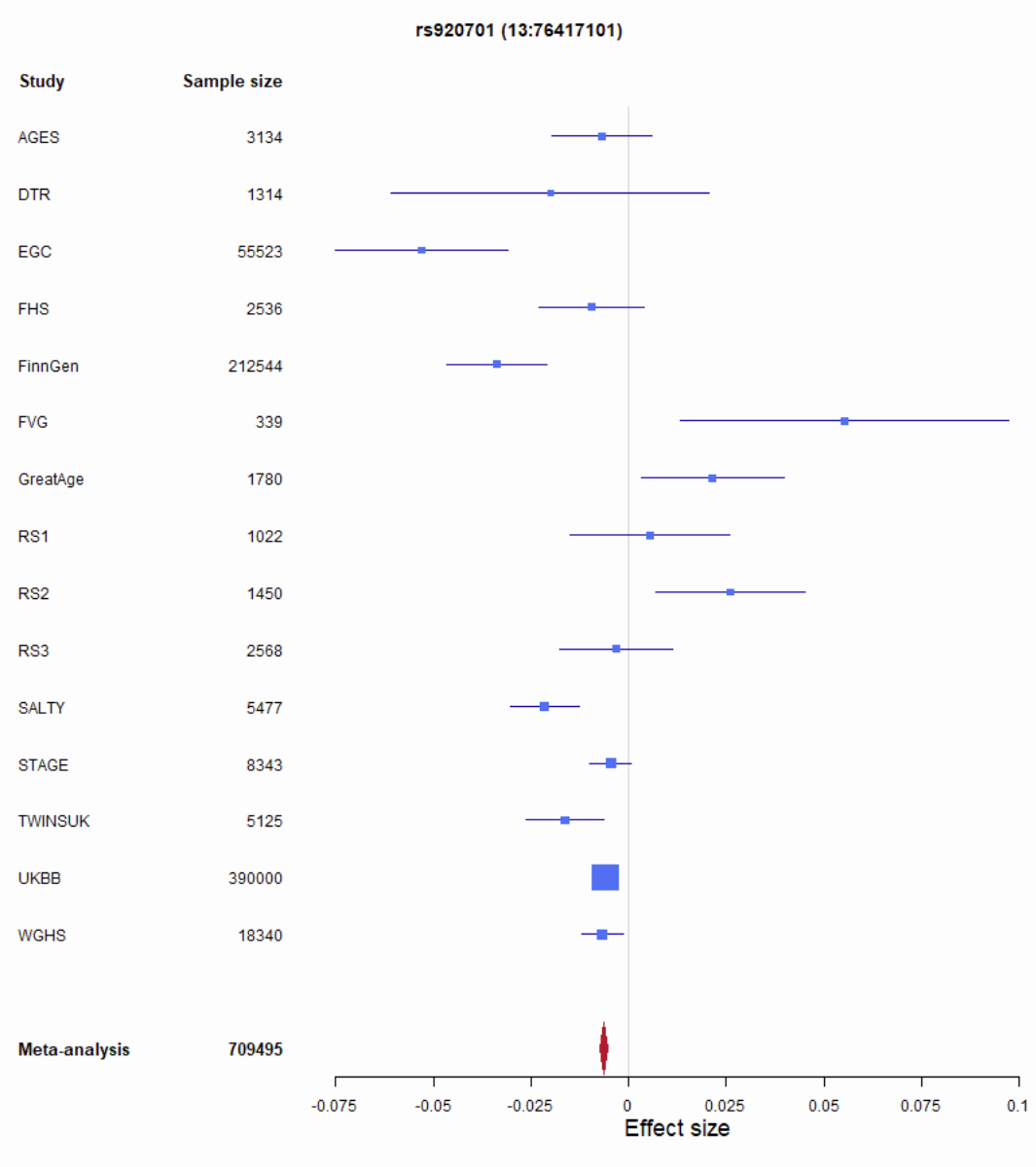
Locus annotation: [PHLDB1] intronic



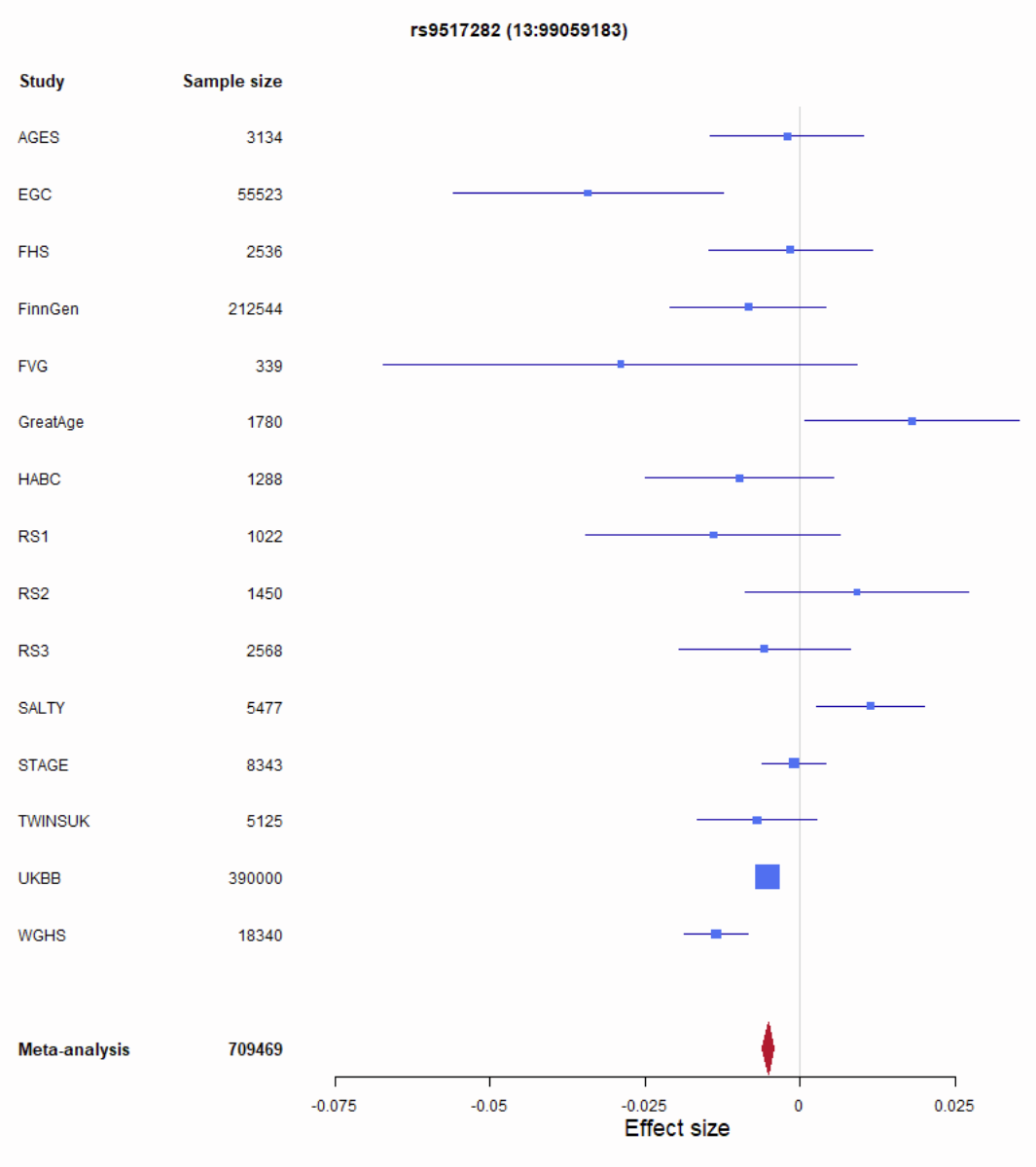
Locus annotation: [KCTD10] intronic



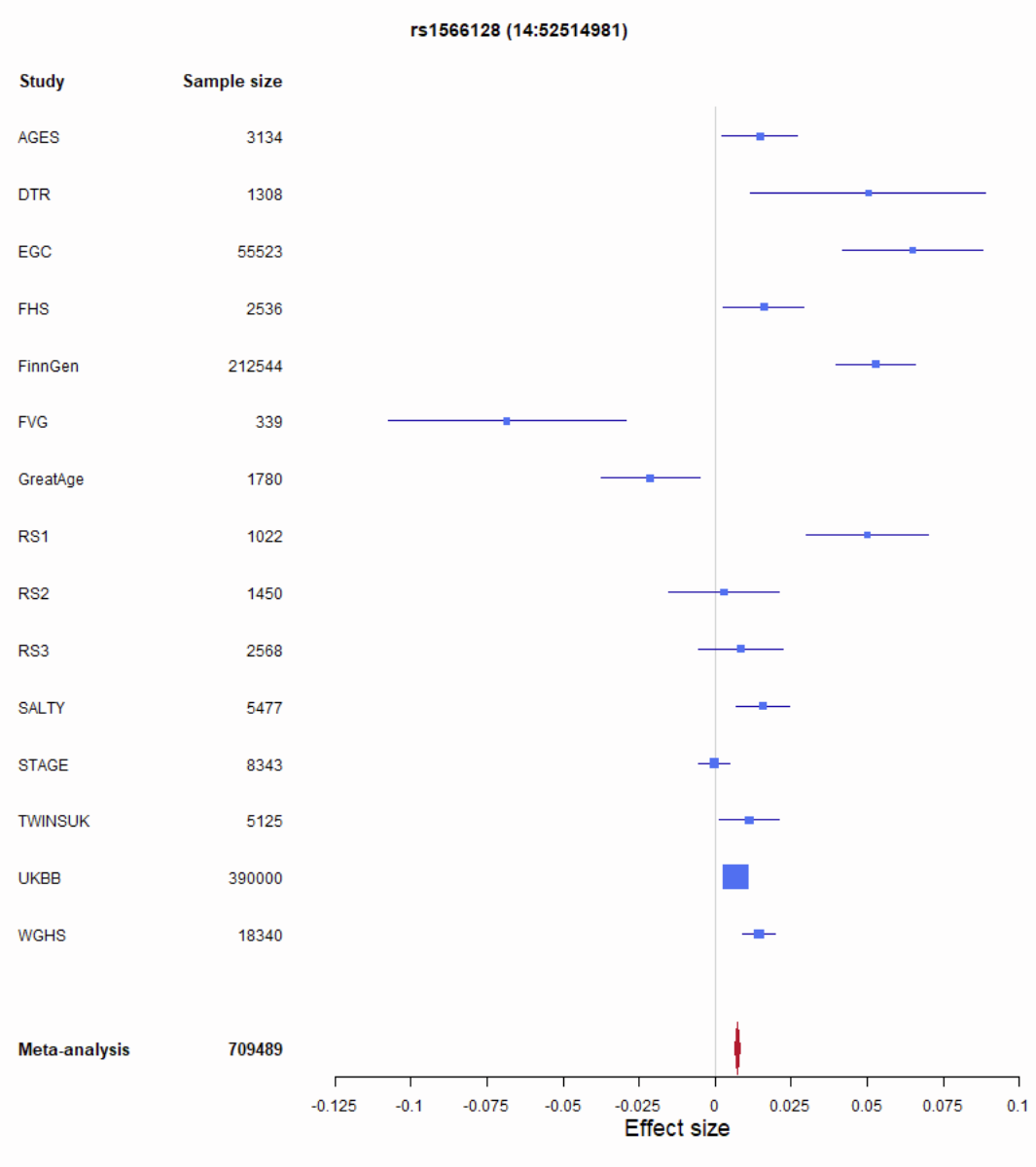
Locus annotation: [GJB2] M>T



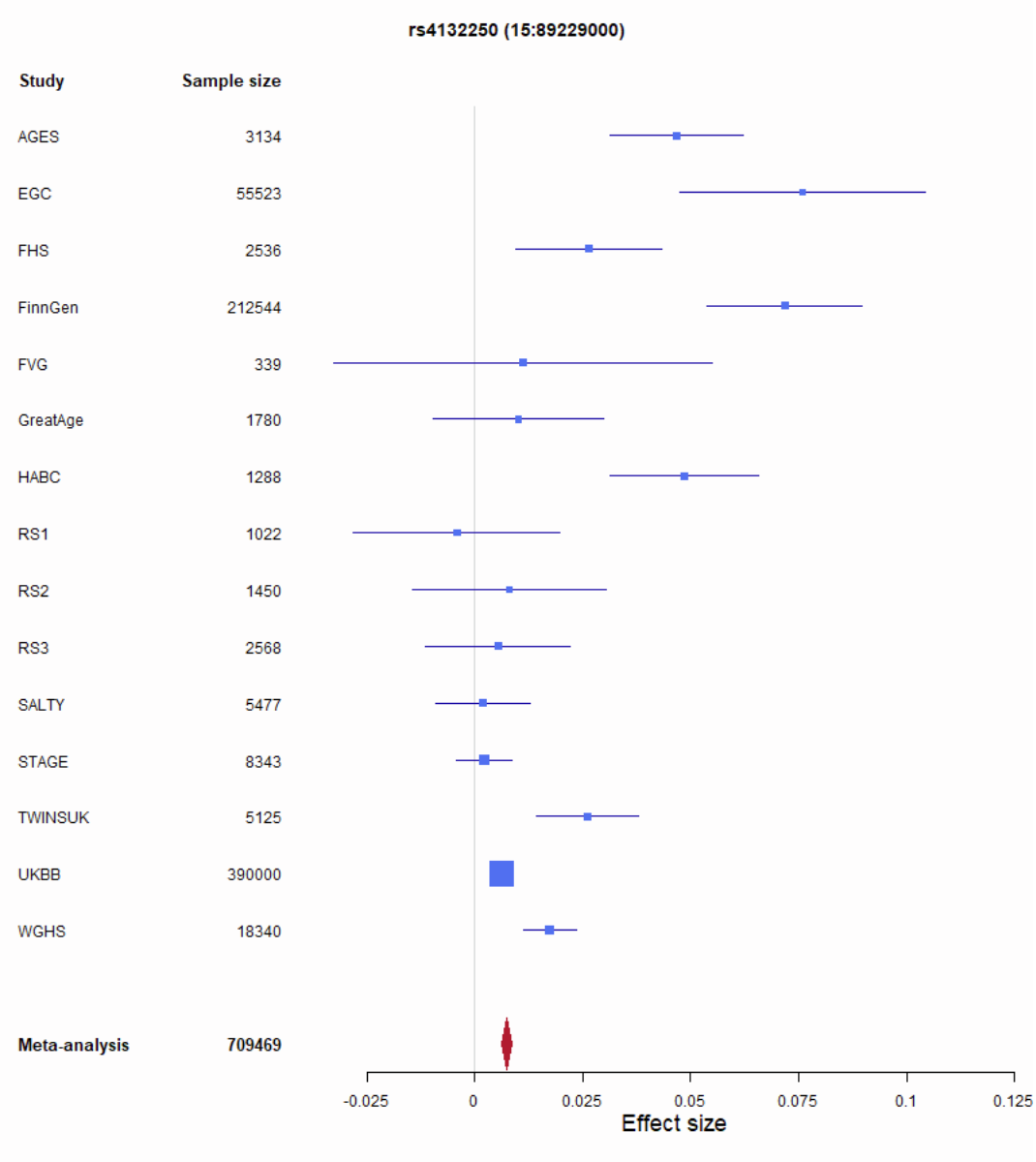
Locus annotation: [LMO7] intronic



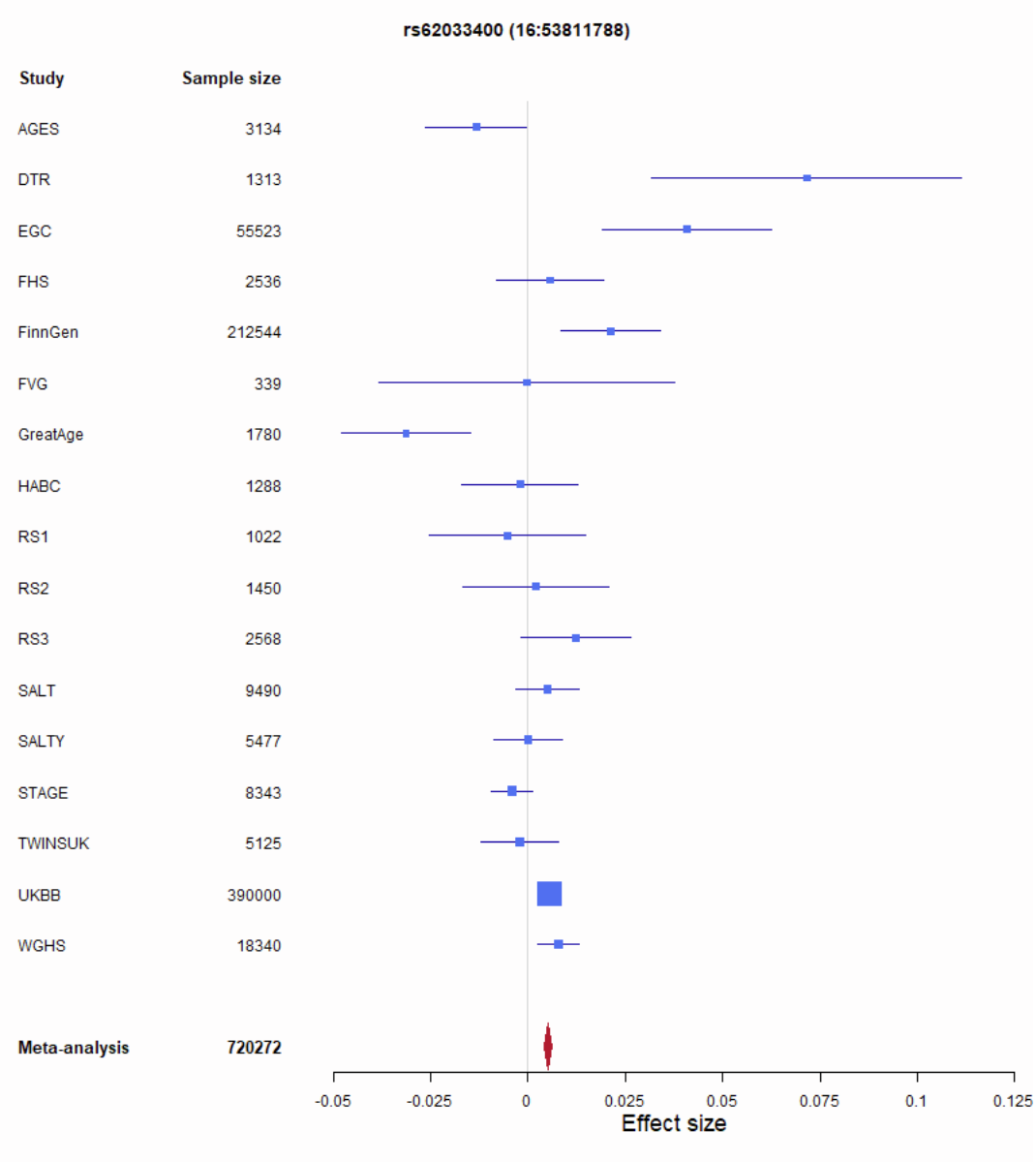
Locus annotation: [FARP1] intronic



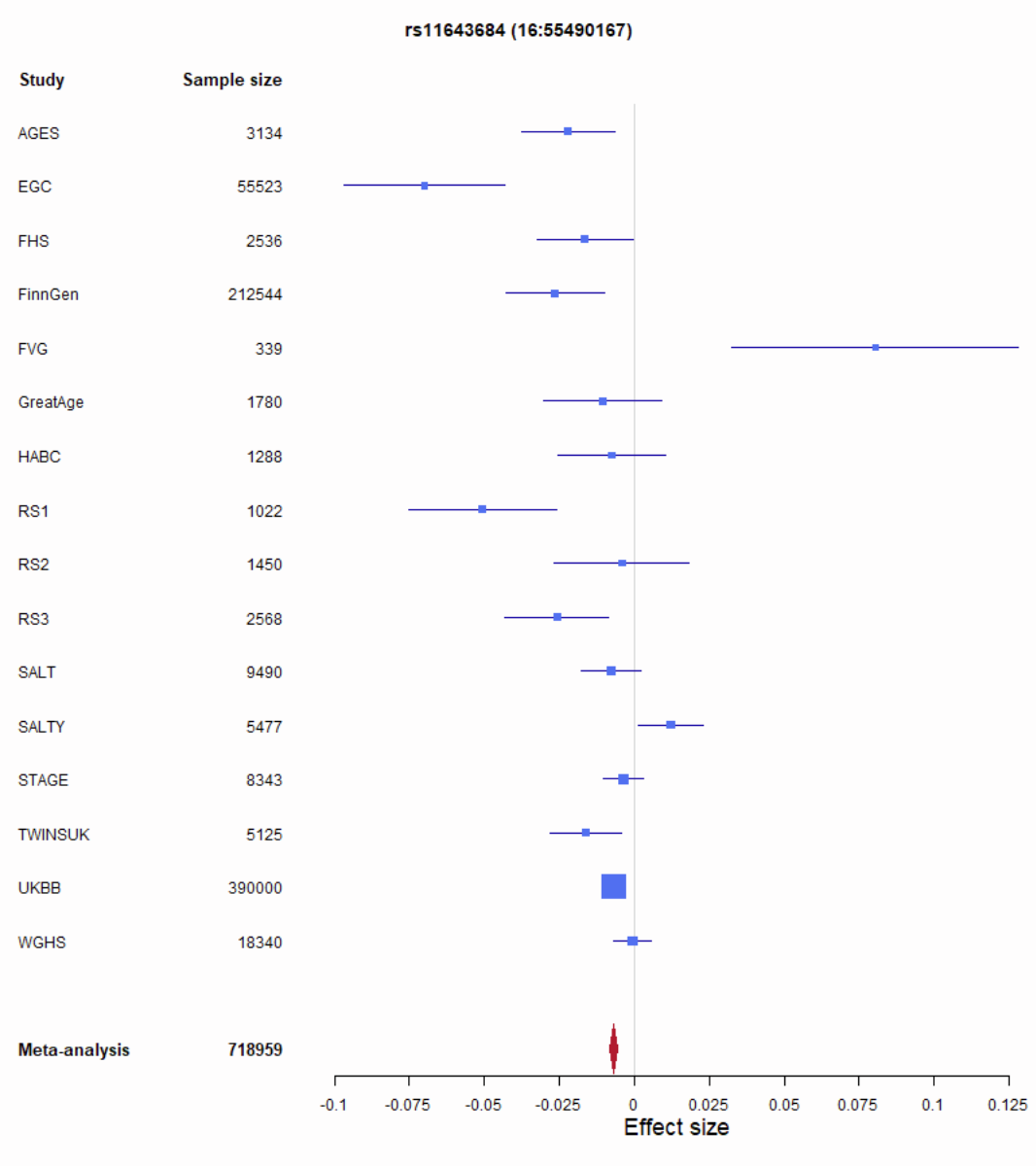
Locus annotation: [NID2] intronic



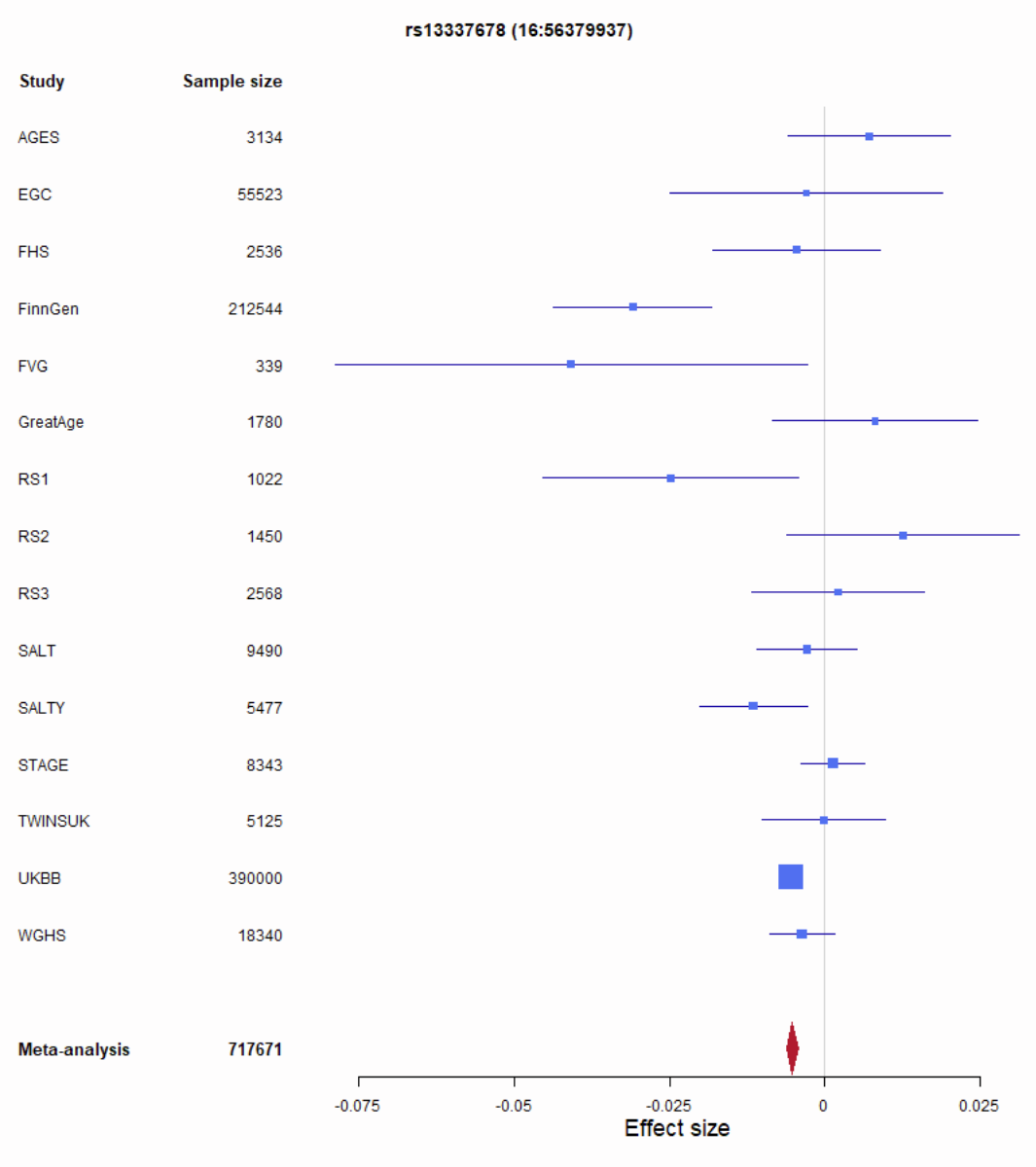
Locus annotation: ISG20-[x]--ACAN



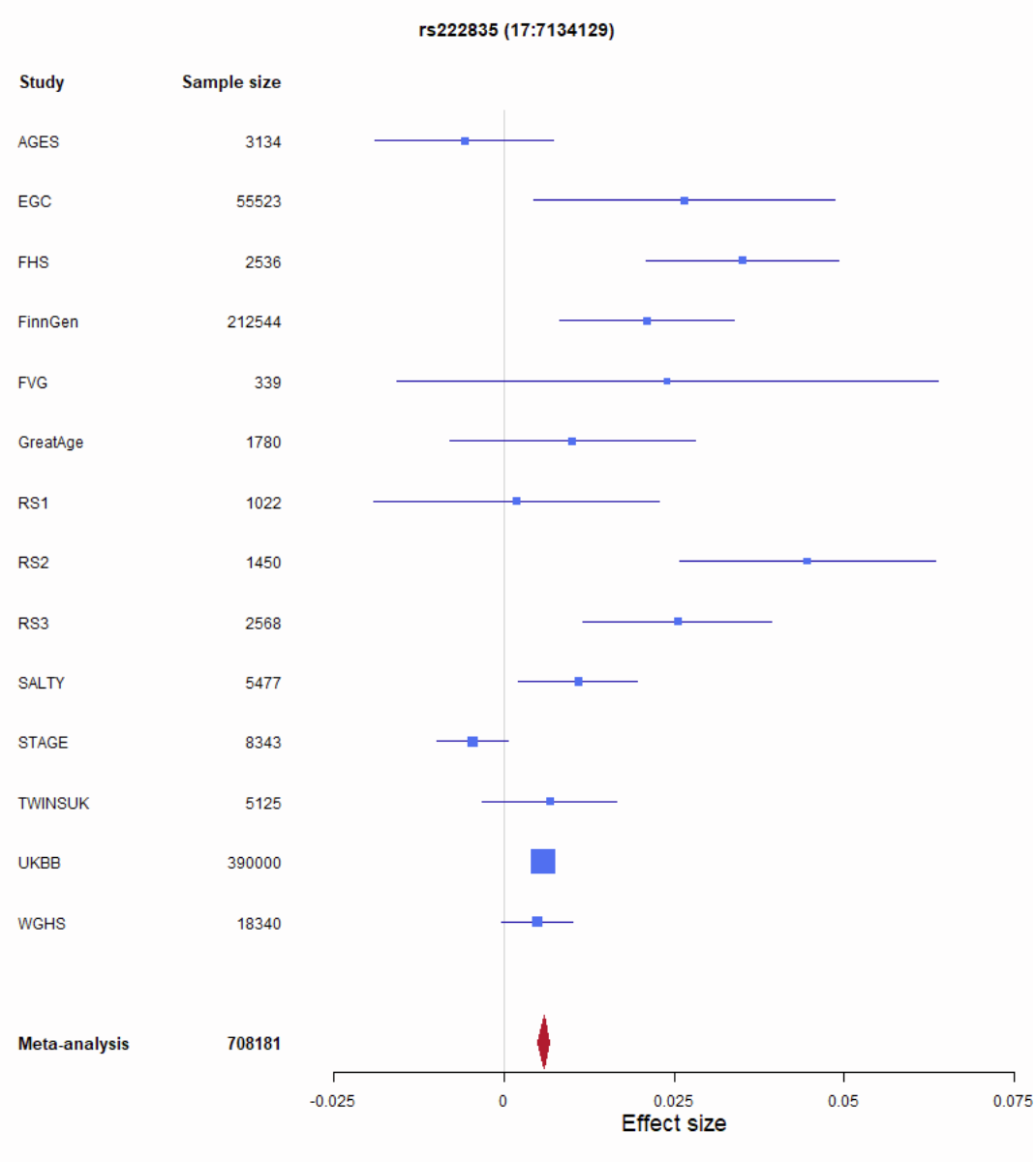
Locus annotation: [FTO] intronic



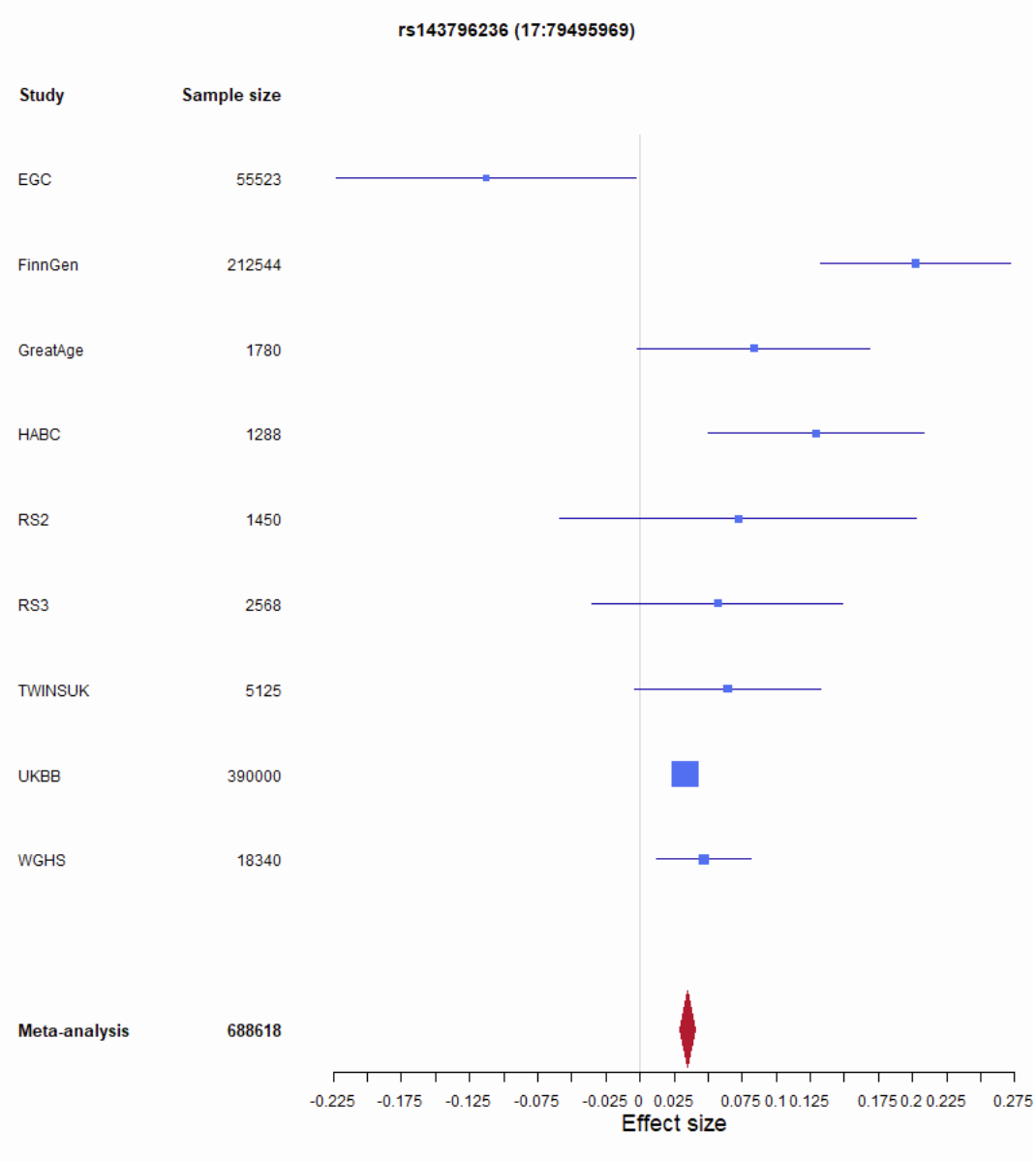
Locus annotation: IRX6--[x]-MMP2



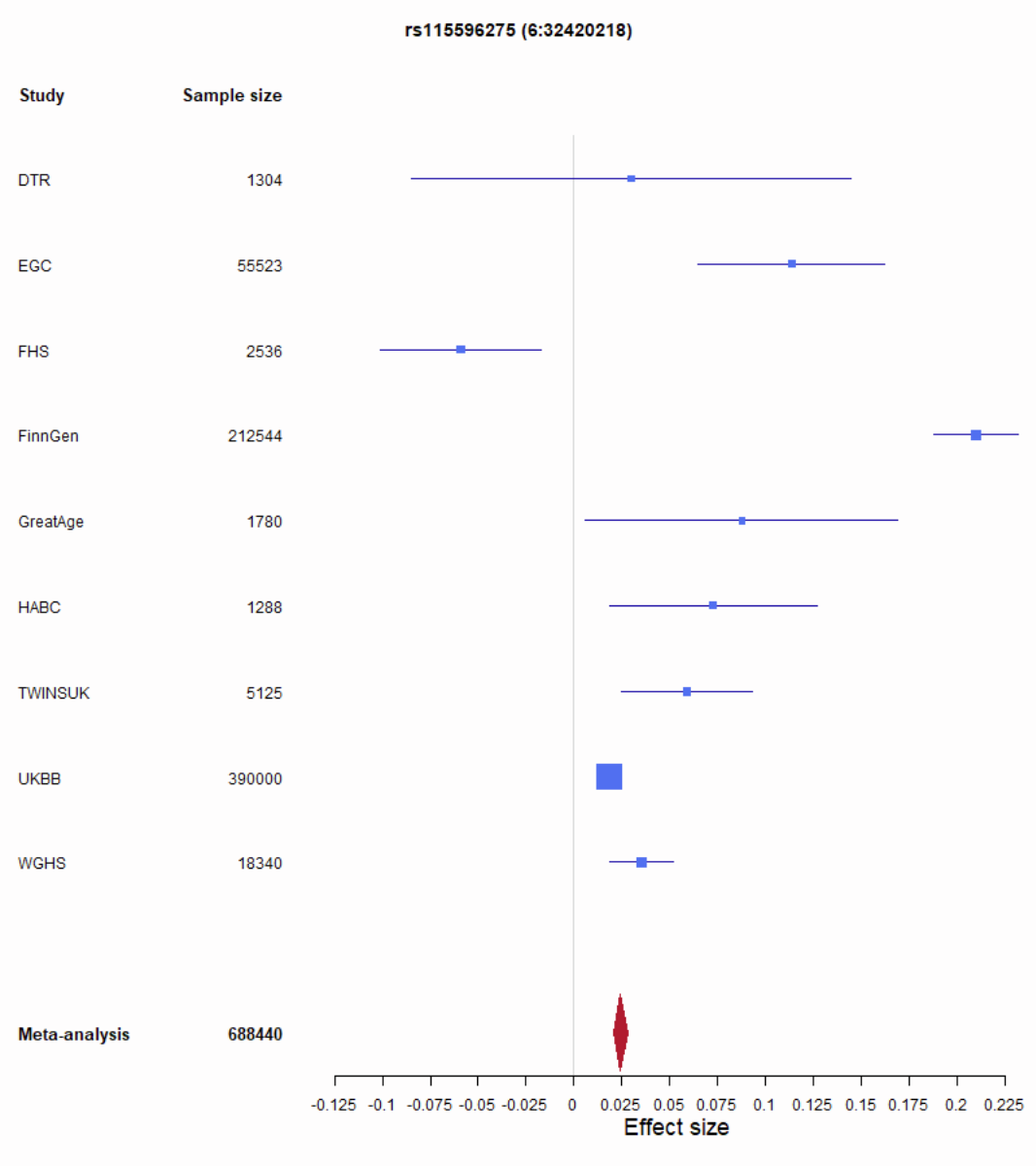
Locus annotation: [GNAO1] 3' UTR



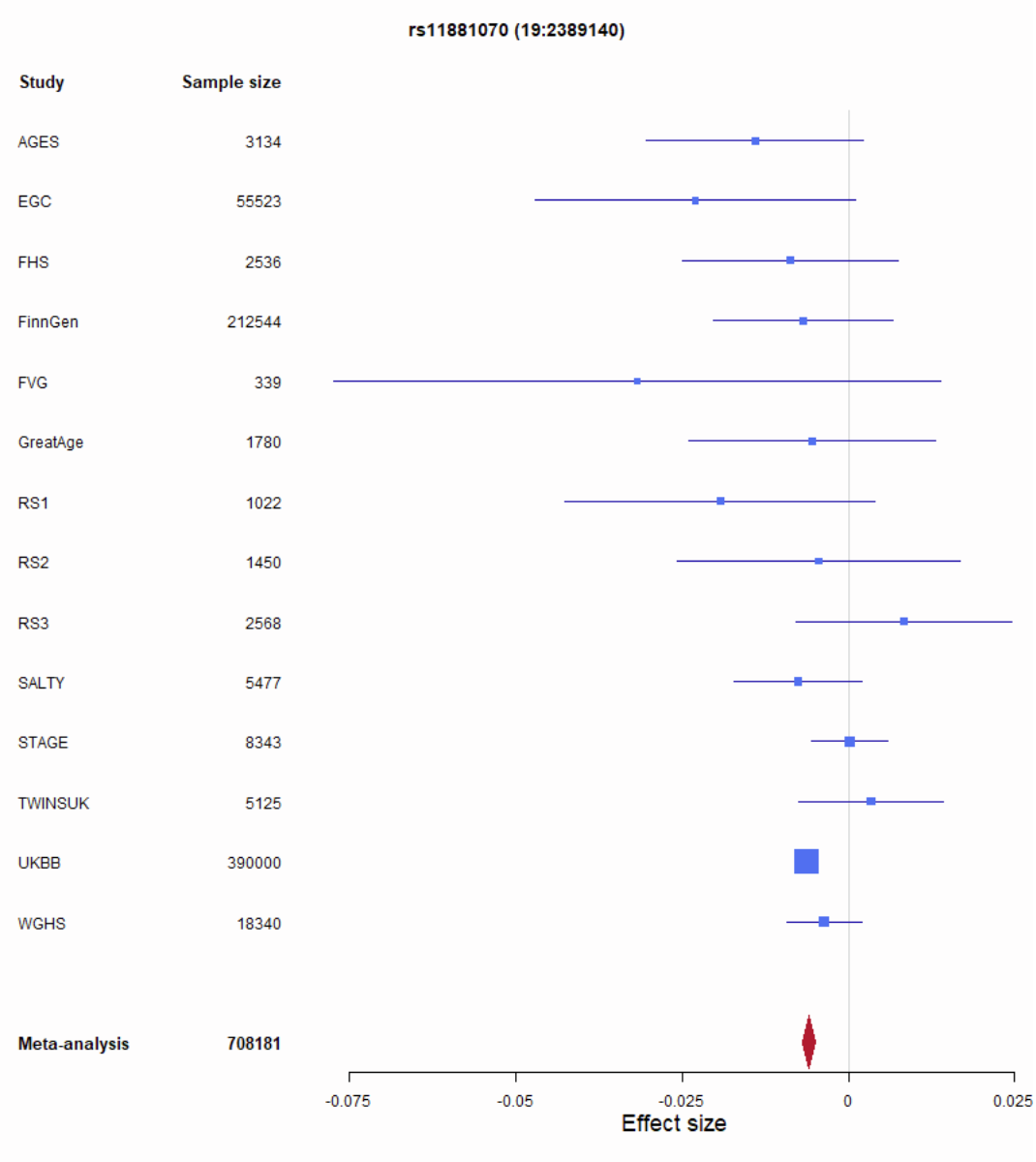
Locus annotation: [DVL2] intronic



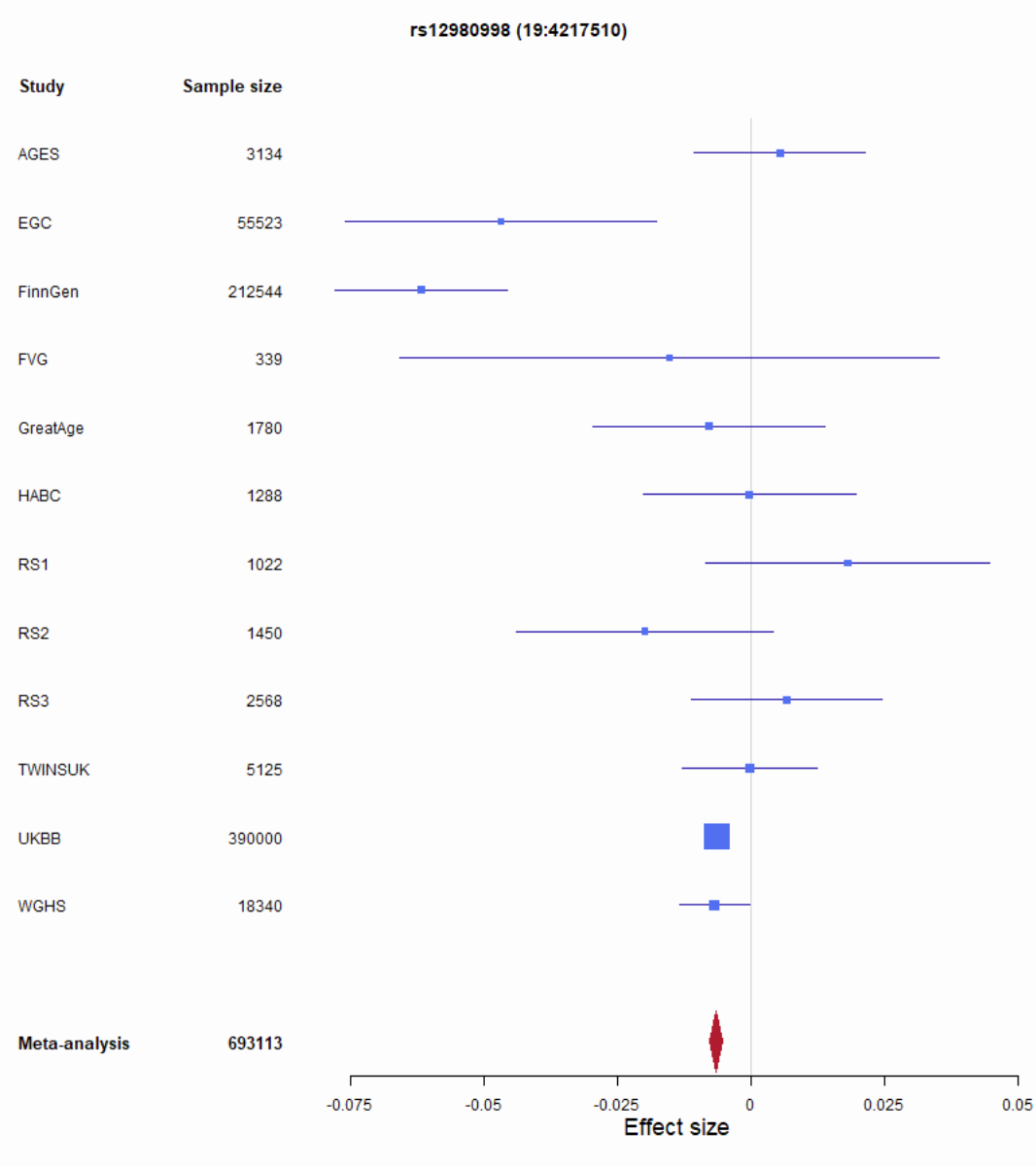
Locus annotation: [FSCN2] H>Y



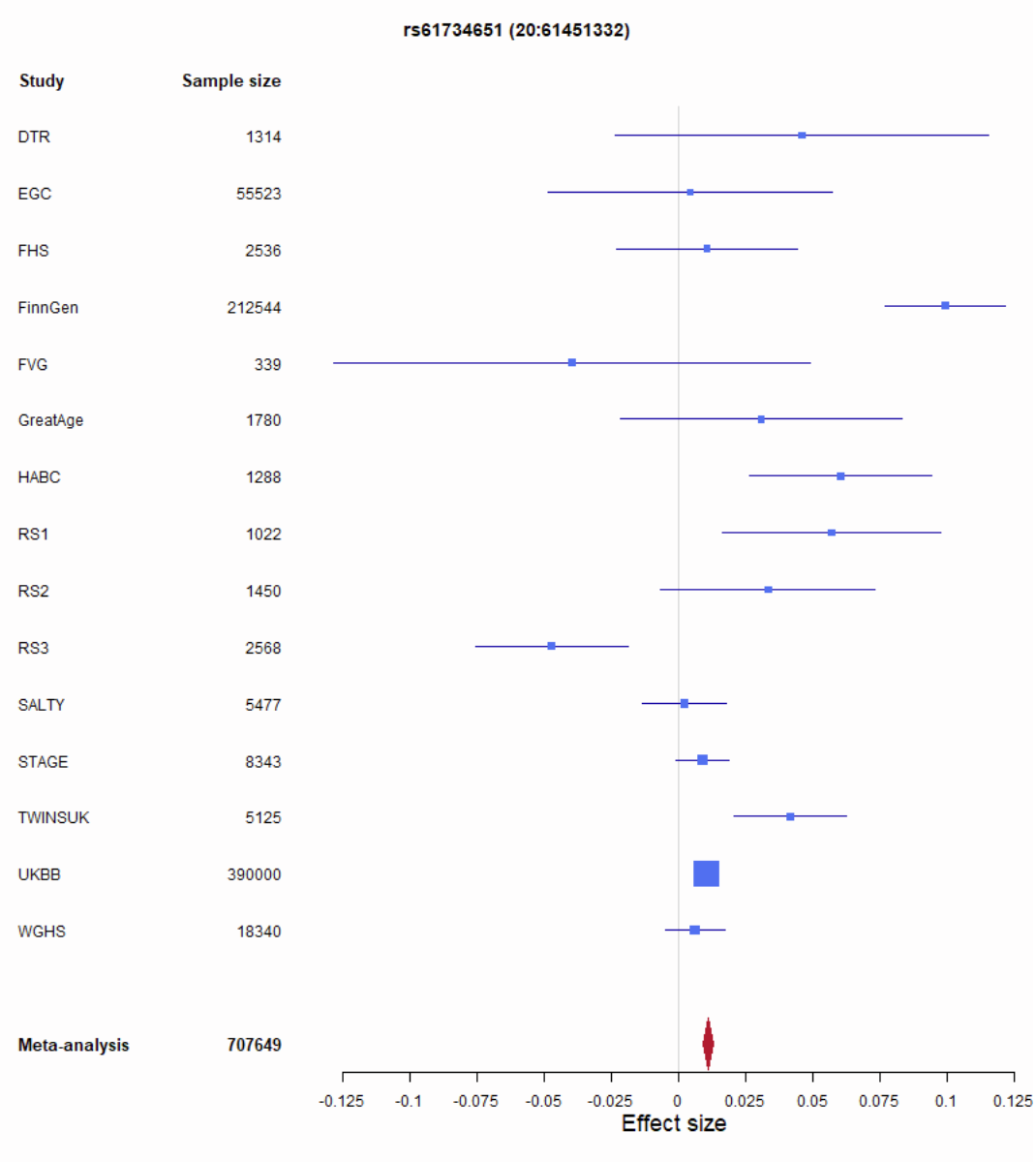
Locus annotation: [CCDC68] 5' UTR



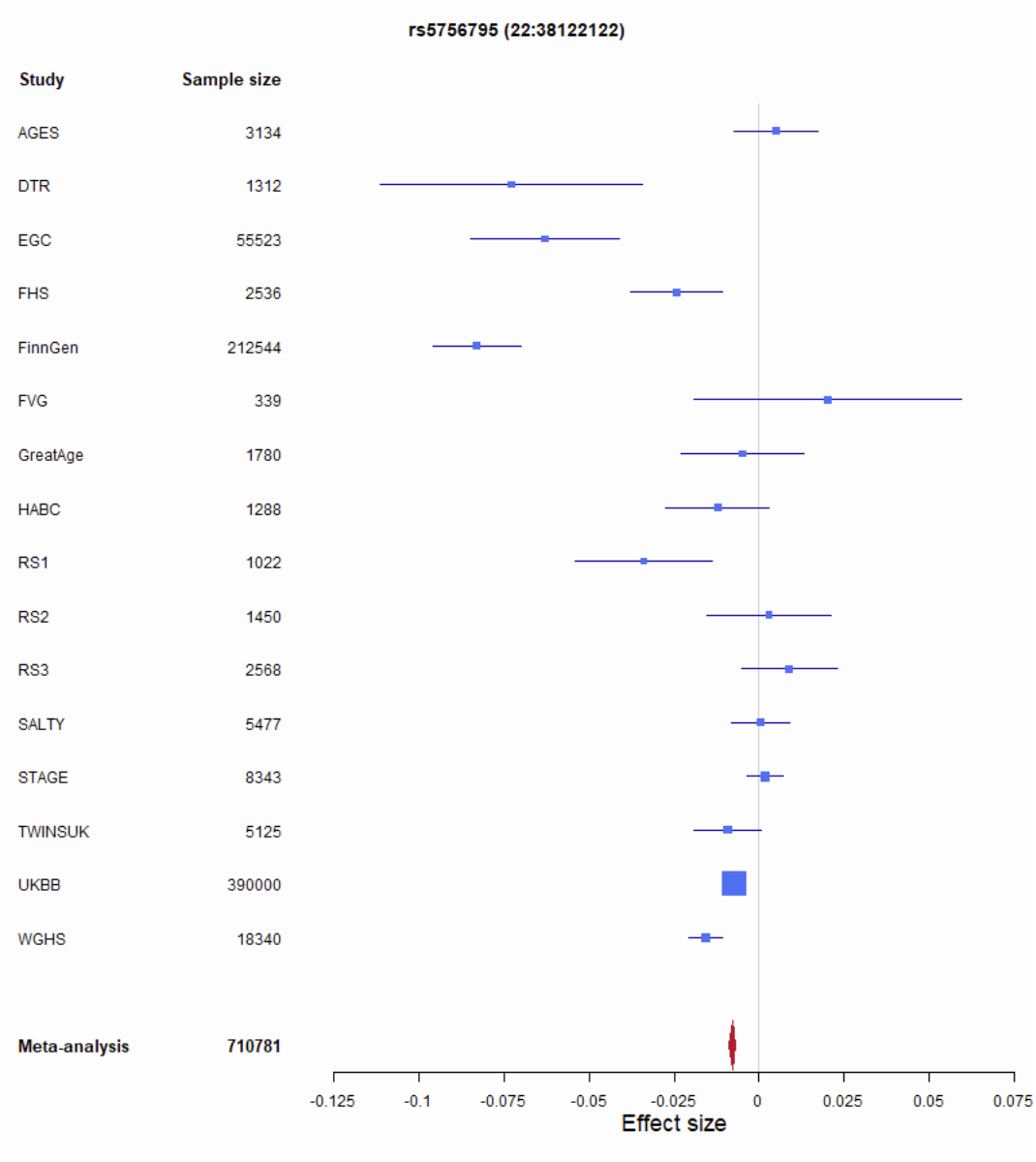
Locus annotation: SPPL2B-[x]-TMRPS9



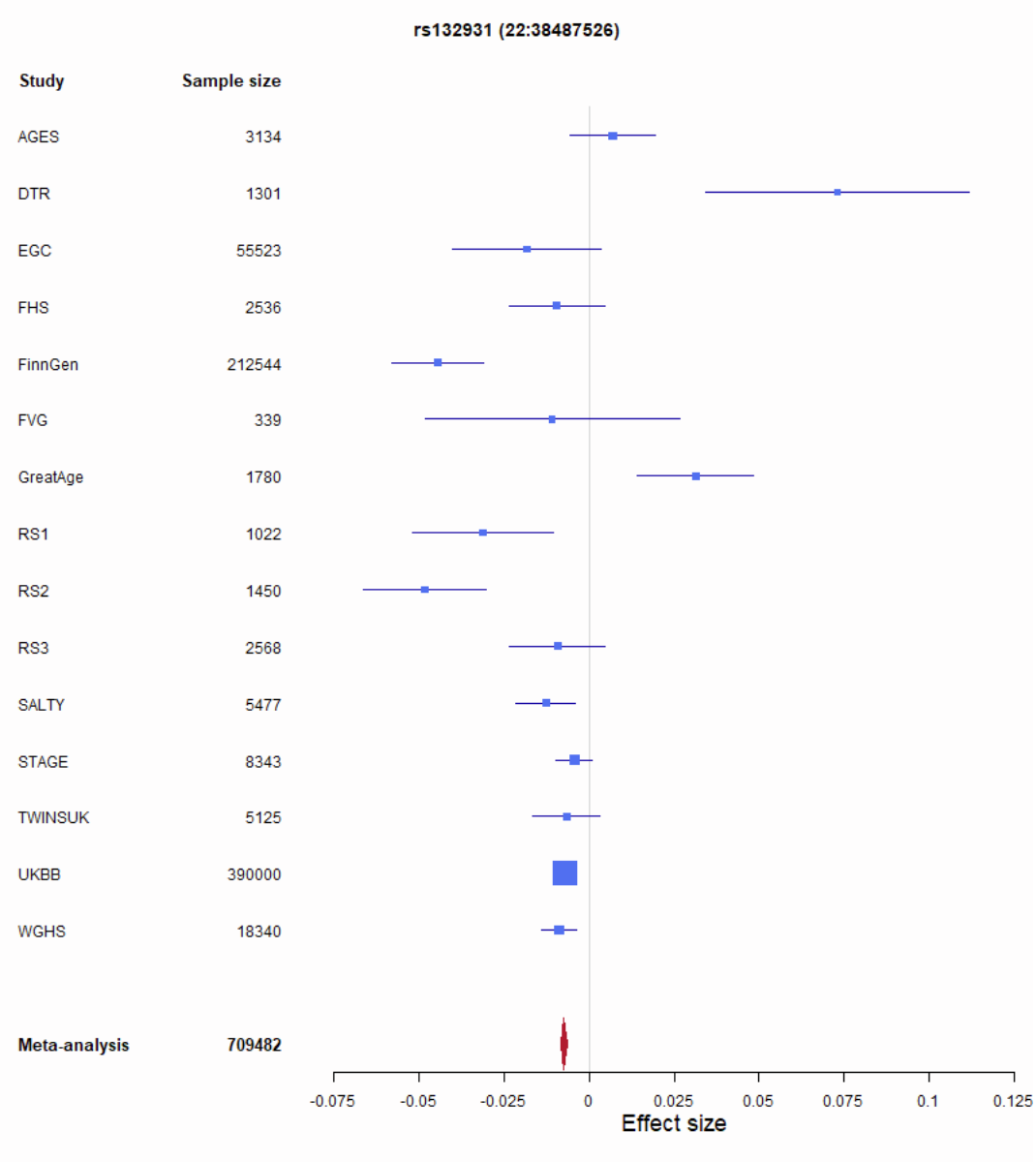
Locus annotation: [ANKRD24] T>S



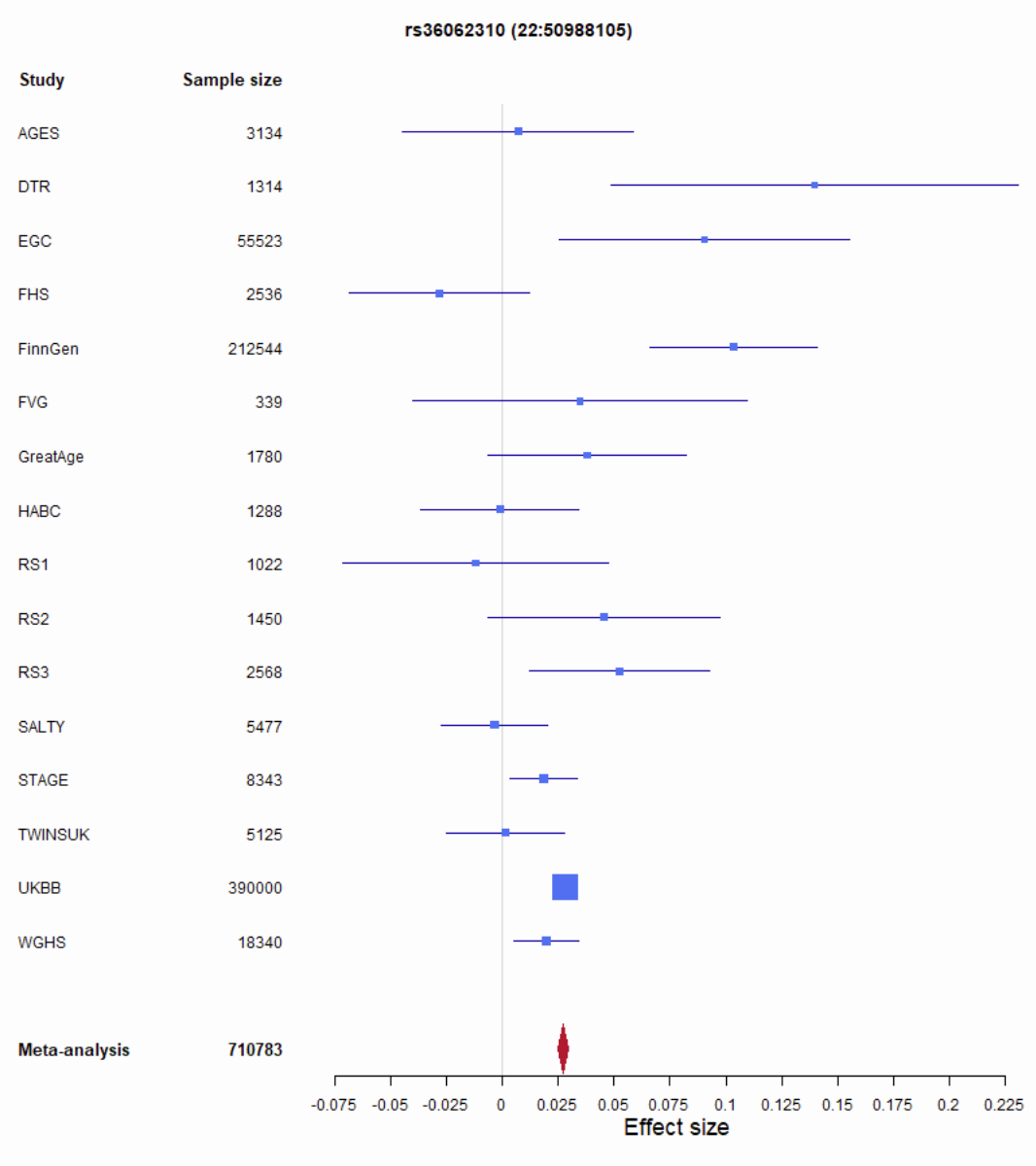
Locus annotation: [COL9A3] R>W



Locus annotation: [TRIOBP] F>I



Locus annotation: [BAIAP2L2] intronic



Locus annotation: [KLHDC7B] V>M

Figure S4. Manhattan plot for gene-based analysis. All significant genes (p<2.66e-6) identified by MAGMA (red) and genes identified by MAGMA and VEGAS simultaneously (blue).

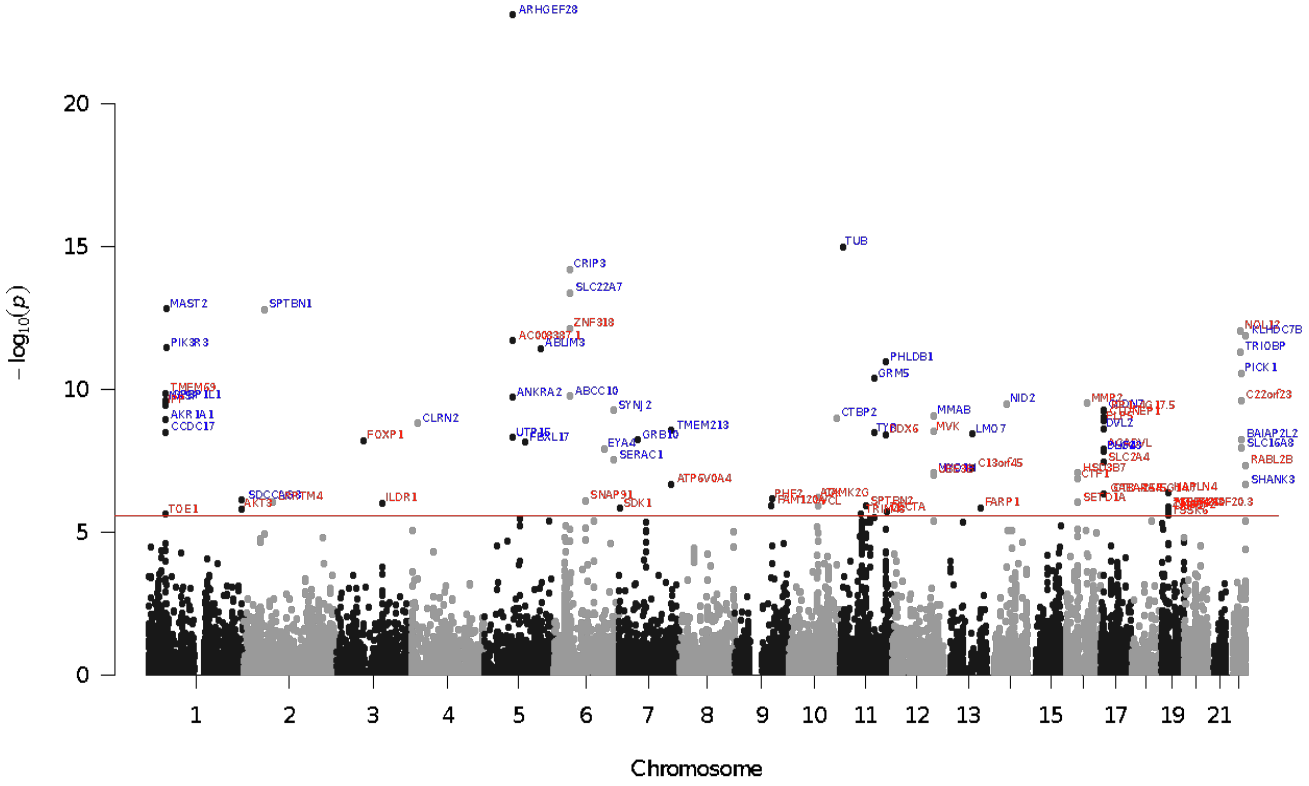


Figure S5. a) Protein structure and modeling of the missense variant effect on GJB2 transporter b) Hydrophilicity/hydrophobicity map

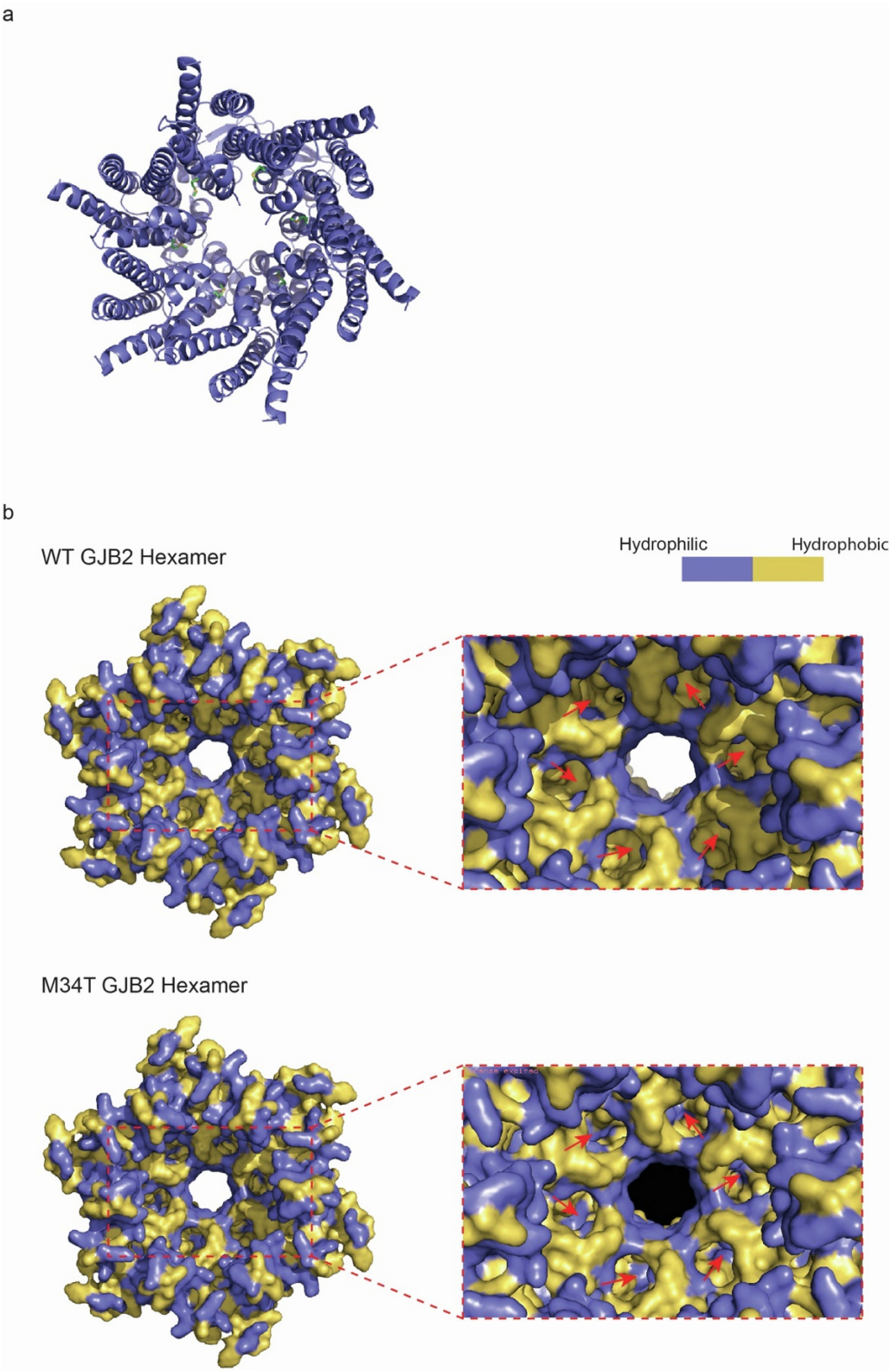


Figure S6. Genetic correlation between age-related hearing impairment and selected number of traits and diseases based on relevance in LDHub. Black filled circles pass the Bonferroni corrected significance threshold (p < 2e-04); bars represent standard error.

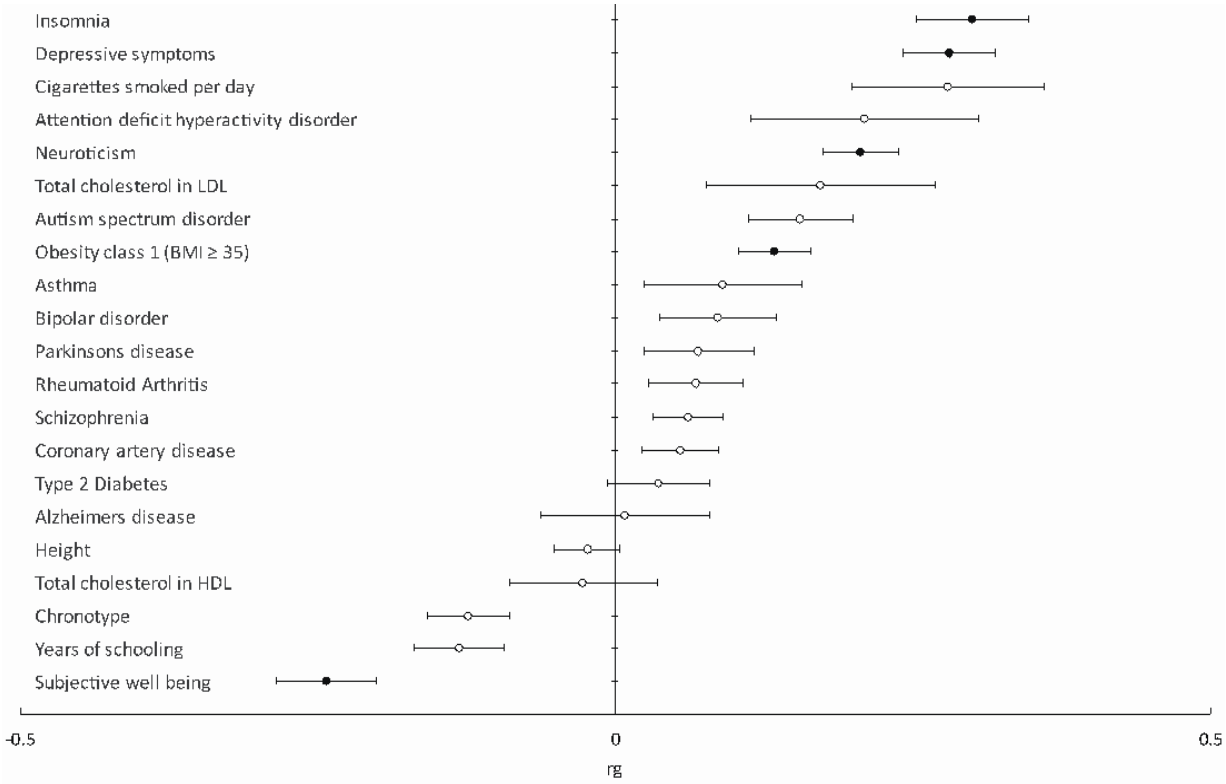


Figure S7. Genetic correlation between age-related hearing impairment and selected GWAS traits based on clinical relevance, collected by the Psychiatric Genomics Consortium. Black filled circles pass the Bonferroni corrected significance threshold ($p < 0.001$); bars represent standard error.

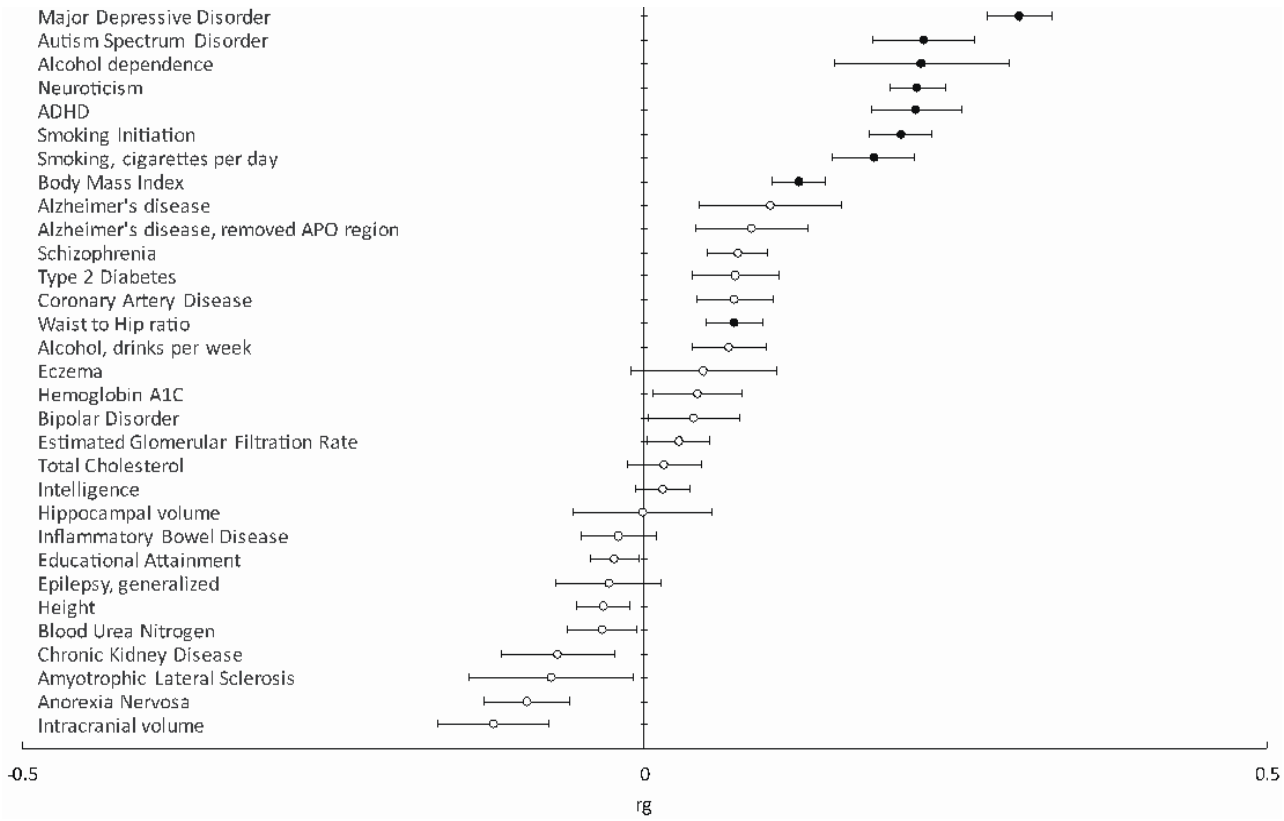


Figure S8. Tissue-set enrichment analysis of GTEx V8 tissues using MAGMA and partitioned LDSC. Bonferroni corrected significance threshold of -log10P-mean > 2.86. Bonferroni corrected significance threshold for MAGMA and LDSC P < 0.001

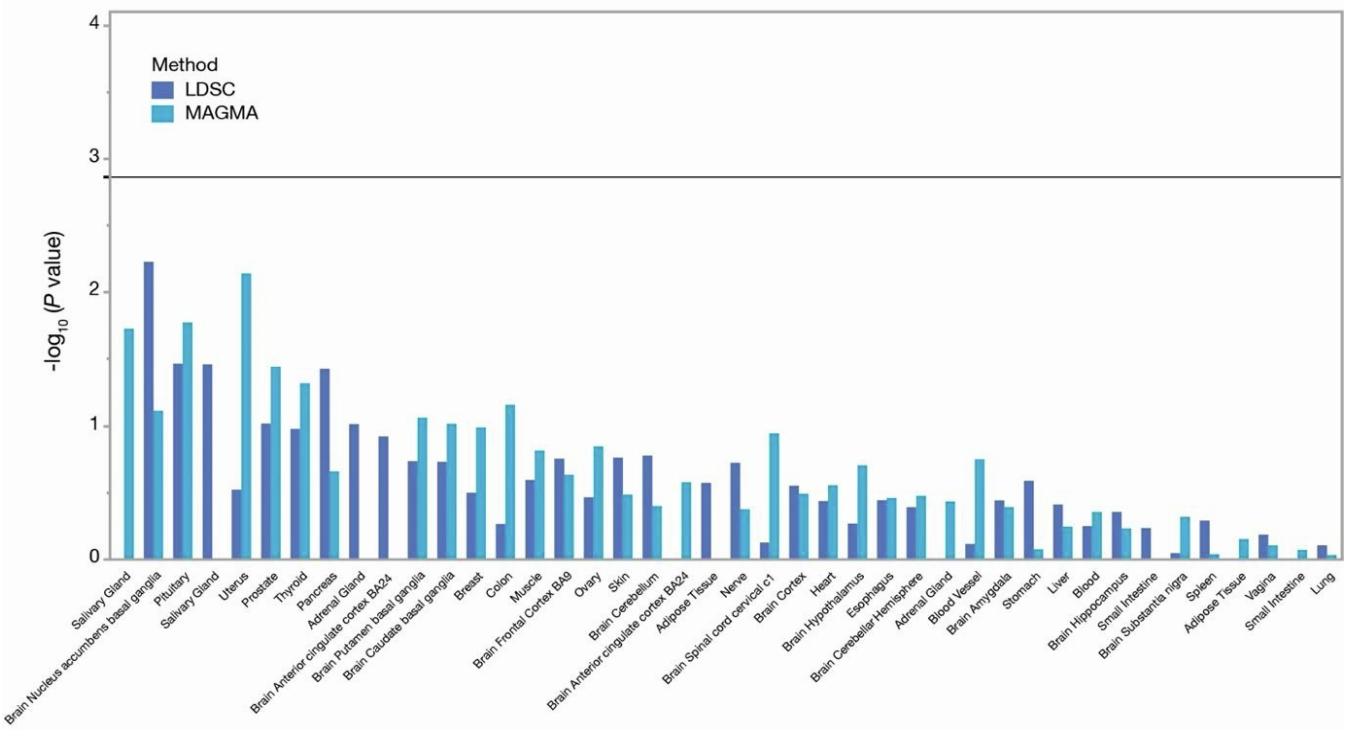
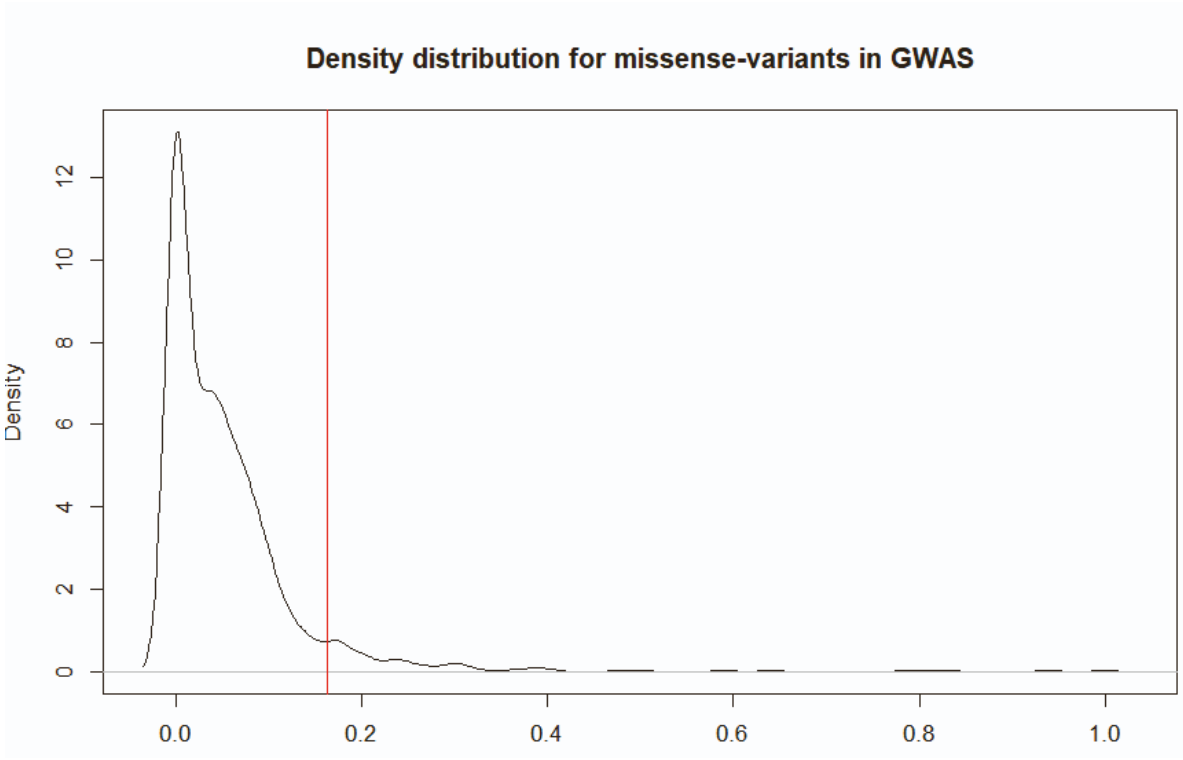
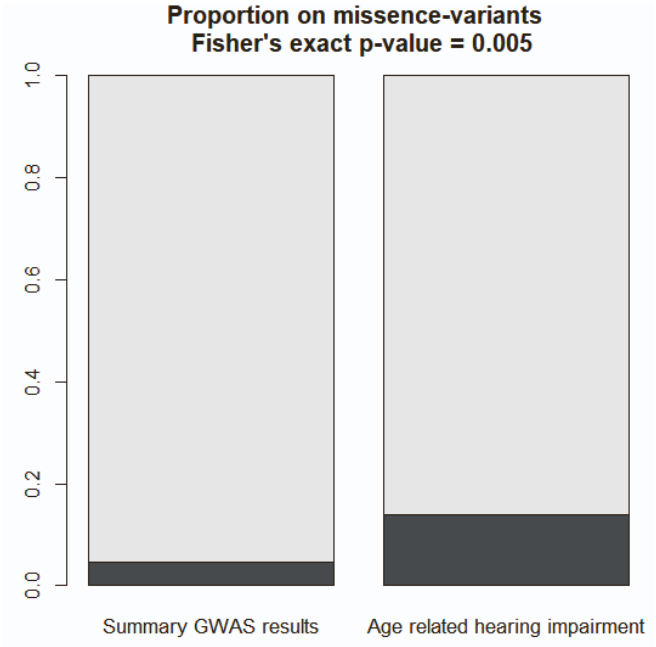


Figure S9. Density plot and b) bar plot demonstrating the proportion of missense variants in GWAS studies with more than 10 significant loci obtained from GWAS catalog. Fisher exact test p-values = 0.005

a)



b)



Supplementary Methods

Study Descriptions

Age, Gene/Environment Susceptibility Reykjavik Study: AGES-Reykjavik Study

The Reykjavik Study cohort originally comprised a random sample of 30,795 men and women born in 1907-1935 and living in Reykjavik in 1967[17]. A total of 19,381 people 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.

The Danish Twin Registry

The Danish Twin Registry (DTR) sample included 1,314 individuals collected as part of the study of Middle Age Danish Twins (MADT, N=1,055) and the Longitudinal Study of Aging Danish Twins (LSADT, N=259)[18]. MADT was initiated in 1998 and includes 4,314 twins randomly chosen from the birth years 1931-1952. Surviving participants were revisited from 2008 to 2011, where the blood samples used in the present study were collected. The survey data used in the present study was obtained from the Omnibus 2 survey undertaken in 2002[18]. LSADT was initiated in 1995 and includes twins aged 70 years and older. Follow-up assessments were conducted every second year through 2005. The individuals included here all participated in the 1997 assessment, where blood samples were collected from same sex twin pairs, and in the 2001 assessment where the survey data used in the present study was collected[18].

Written informed consents were obtained from all participants. Collection and use of biological material, and survey and registry information were approved by the Regional Scientific Ethical Committees for Southern Denmark (MADT: S-VF-19980072, LSADT: S-VF-20040241). The study *is registered in SDU's internal list (notification no. 10.903) and complies with the rules in the General Data Protection Regulation.*

EGCUT

EstBB is a population-based cohort of 200,000 participants with a rich variety of phenotypic and health-related information collected for each individual[19]. At recruitment, participants have signed a consent to allow follow-up linkage of their electronic health records (EHR), thereby providing a longitudinal collection of phenotypic information. EstBB allows access to the records of the national Health Insurance Fund Treatment Bills (from 2004), Tartu University Hospital (from 2008) and North Estonia Medical Center (from 2005). For every participant there is information on diagnoses in ICD-10 coding and drug dispensing data, including drug ATC codes, prescription status and purchase date (if available).

At the time of this study 155,772 genotyped samples from the Estonian Biobank were available and genotyping was done at the Genotyping Core Facility of the Institute of Genomics, University of Tartu, using the Global Screening Array (GSAv1.0, GSAv2.0, and GSAv2.0_EST) from Illumina. Altogether 155,772 samples were genotyped and PLINK format files were exported using GenomeStudio v2.0.4. During the quality control all individuals with call-rate < 95% or mismatching sex that was defined based on the heterozygosity of X chromosome and sex in the phenotype data, were excluded from the analysis. Variants were filtered by call-rate < 95% and HWE p-value < 1e-4 (autosomal variants only). Variant positions were updated to Genome Reference Consortium Human Build 37 and all variants were changed to be from TOP strand using reference information

provided by Dr. Will Rayner from the University of Oxford (https://www.well.ox.ac.uk/~wrayner/strand/). Before imputation variants with MAF<1% and Indels were removed. Prephasing was done using the Eagle v2.3 software[20] (number of conditioning haplotypes Eagle2 uses when phasing each sample was set to: --Kpbwt=20000) and imputation was carried out using Beagle v.28Sep18.793[21,22] with an effective population size ne=20,000. As a reference, Estonian population specific imputation reference of 2,297 WGS samples was used[23]. For the current study, we determined 5,717 cases of hearing loss based on the participants EHRs as individuals with the ICD10 codes H90.3 or H91.1 and included only subjects of 45 years of age and above. We excluded among cases individuals with additional records of any of the following ICD10 diagnosis: H80, H81.0, H83, H90.4, H91.0, H91.2, H91.3, H93.0, H93.3, H94*, H95. Controls (n=49,806) were individuals 45 years of age and above and defined as undiagnosed participants. Individuals with records of H65, H66, H67, H68, H69, H70, H71, H72, H73, H74,H75,H80, H81.0, H83, H90, H91, H92, H93, H95, Q16, Z45.3,Z46.1,Z96.2,Z97.4 were removed among controls. We conducted the GWASes using the SAIGE software[24] adjusting for the first ten principal components of the genotype matrix, as well as for age and sex.

FinnGen

The FinnGen research project (www.finngen.fi) was launched in 2017 with an aim to improve human health through genetic research. The project combines genome information with digital health care data from national registries: the genotype data are linked to national hospital discharge, death, cancer, and medication reimbursement registries using the national personal identification numbers. The FinnGen study will combine approximately 200,000 existing samples from Finnish biobanks with approximately 300,000 samples from ongoing collections. Once final, the data resource will cover roughly 10% of the Finnish population. The present study comprised data of 212,544 Finnish adults (15,952 cases; 196,592 controls) from FinnGen Preparatory Phase Data Freeze 5.

Patients and control subjects in FinnGen provided informed consent for biobank research, based on the Finnish Biobank Act. Alternatively, separate research cohorts, collected prior the Finnish Biobank Act came into effect (in September 2013) and start of FinnGen (August 2017), were collected based on study-specific consents and later transferred to the Finnish biobanks after approval by Fimea, the National Supervisory Authority for Welfare and Health. Recruitment protocols followed the biobank protocols approved by Fimea. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) approved the FinnGen study protocol Nr HUS/990/2017.

The FinnGen study is approved by Finnish Institute for Health and Welfare (THL), approval number THL/2031/6.02.00/2017, amendments THL/1101/5.05.00/2017, THL/341/6.02.00/2018, THL/2222/6.02.00/2018, THL/283/6.02.00/2019, THL/1721/5.05.00/2019, Digital and population data service agency VRK43431/2017-3, VRK/6909/2018-3, VRK/4415/2019-3 the Social Insurance Institution (KELA) KELA 58/522/2017, KELA 131/522/2018, KELA 70/522/2019, KELA 98/522/2019, and Statistics Finland TK-53-1041-17.

The Biobank Access Decisions for FinnGen samples and data utilized in FinnGen Data Freeze 5 include: THL Biobank BB2017_55, BB2017_111, BB2018_19, BB_2018_34, BB_2018_67, BB2018_71, BB2019_7, BB2019_8, BB2019_26, Finnish Red Cross Blood Service Biobank 7.12.2017, Helsinki Biobank HUS/359/2017, Auria Biobank AB17-5154, Biobank Borealis of Northern Finland_2017_1013, Biobank of Eastern Finland 1186/2018, Finnish Clinical Biobank Tampere MH0004, Central Finland Biobank 1-2017, and Terveystalo Biobank STB 2018001.

Framingham Heart Study

The Framingham Heart Study is a prospective longitudinal investigation of the development of atherosclerosis and its clinical sequelae. Study participants were recruited at three time periods. The study was initiated in 1948-50 with the recruitment of 5209 individuals ages 28-62 (including some spouse pairs, parent-offspring pairs and siblings) for the purpose of investigating the multiple factors involved in the development of cardiovascular disease[25]. This group, known as the Original Cohort, has been examined every two years with a total of thirty-two examinations to date. In 1971-1975, offspring of the Original Cohort and the offspring spouses were recruited to examine among other goals the familial components of cardiovascular disease and its risk factors[26]. In 2002-2005, the third generation (children of the Offspring and grandchildren of the Original Cohort) was recruited[27]. The Offspring Cohort totalled 5124 and the Third Generation totalled 4095 at recruitment and have been examined every 4 to 8 years. The Offspring Cohort now has 9 examinations completed and the Third Generation has 2 examinations completed.
Between 1973 and 1975, hearing examinations were conducted on 2293 members of the original cohort, and between 1995 and 1999, identical examinations were conducted on 2262 members of the offspring cohort. Standard pure-tone audiograms were obtained on all participants using environments and meeting American National Standards Institute standards.

G-EAR

Within the International consortium called G-EAR, we used, in this study, individuals coming from two isolated cohorts: **Friuli Venezia Giulia (FVG)** Genetic Park and the **Salus in Apulia Study** (formerly known as Great Age Study).
The FVG cohort is a collection of samples coming from six small villages (Clauzetto, Erto, Illegio, Resia, San Martino del Carso and Sauris) located in north-eastern Italy, in the Friuli Venezia Giulia region[28]. The FVG Genetic Park is part of the INGI project, a collaboration between research institutions in Italy aimed at reconstructing the molecular bases of complex traits by investigating genetically isolated Italian populations. Studies were conducted referring to a common operational protocol. In each population, genotype samples were collected, alongside a detailed anamnesis, more than 120 biochemical parameters and 400 phenotypes, including anthropometric measures, lifestyle habits, diseases and pure-tone audiometry[29].
The “Salus in Apulia Study” is an ongoing population-based prospective cohort comprising 2,472 individuals aged >= 65 years and residents in Castellana Grotte, a town located near Bari, Puglia, in the Southeast of Italy. It focused on the sequence of lifestyle including diet, frailty, and other age-related impairments and age-related disease outcomes. In detail, Salus is a public health initiative funded by the Italian Ministry of Health and Apulia Regional Government and carried on at IRCCS “S. De Bellis” that combines data from two previous populations: the baseline data (MICOL3, M3) were recorded from 2003 to 2005 and the follow-up data from 2013 to 2015 (GreatAGE Study - MICOL4, M4). The GreatAGE-M4 study has been described elsewhere[30]. The invitation included also subjects of the MICOL studies that were in the respective age range above 64 years. In the GreatAge-M4 examination, in addition to the assessment of clinical and lifestyle aspects, sensory-related outcomes have been also evaluated together with neuropsychological features and genetic components. The study adhered to the “Standards for Reporting Diagnostic Accuracy Studies” (STARD) guidelines (http://www.stard-statement.org/), the “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) guidelines (https://www.strobe-statement.org/).

Health, Aging, and Body Composition (HABC) Study

The HABC Study is a NIA-sponsored cohort study of the factors that contribute to incident disability and the decline in function of healthier older persons, with a particular emphasis on changes in body composition in old age. Between March 1997 and July 1998, 3075 70-79 year-old community-dwelling adults (41% African-American) were recruited to participate in the Health ABC Study.

Medicare beneficiary listings were used to recruit in metropolitan areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee. Eligibility criteria included having no difficulty walking one-quarter of a mile, climbing 10 steps, or performing activities of daily living (transferring, bathing, dressing, and eating); no history of active treatment for cancer in the prior 3 years; and no plans to move from the area within 3 years.

The Rotterdam Study

The Rotterdam study is a prospective, population-based cohort study among inhabitants of Ommoord, a district of Rotterdam, The Netherlands[31]. As of 2008, 14,926 subjects aged 45 years or over comprise the cohort. Since 2016, it is being expanded by persons aged 40 years and over. The Rotterdam study targets cardiovascular, endocrine, hepatic, neurological, ophthalmic, psychiatric, dermatological, otolaryngological, locomotor, and respiratory diseases. The participants were all examined in some detail at baseline. They were interviewed at home (2 h) and then had an extensive set of examinations (a total of 5 h) in a specially built research facility in the center of the district. Written informed consent was obtained from all participants and the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, approved the study.

The Swedish Twin Registry

The Swedish Twin Registry (STR) sample included in this study was recruited among Swedish born twins participating in two main national ascertainments; 1) the Screening Across the Lifespan Twin Study (SALT), which was a telephone interview study conducted in 1998-2002, covering twins born before 1959 and 2) Study of Twin Adults: Genes and Environment (STAGE), an online questionnaire study conducted 2005-2006, covering twins born 1959-1985[32]. Phenotypic information about hearing was collected though self-reports in these studies. Additional phenotypic information was available from a paper questionnaire (called SALTY) administered during 2009 to SALT participants born 1944-1985. DNA was collected from blood or saliva, and extracted by standard procedures. All genotyping was performed by SNP&SEQ genotyping facility in Uppsala, in three waves using three different Illumina chip arrays, OmniExpress for the blood DNA, Psychchip and Global screening array for the saliva DNA samples. Written informed consents were obtained from all participants.

TwinsUK

TwinsUK is the only adult twin registry in the UK, comprising of over 12,000 healthy twin volunteers aged 16-98[33]. Collection of data and biologic materials commenced in 1992 and is ongoing. Twins have completed detailed health and lifestyle questionnaires, and attended clinical evaluations. The pure tone audiometry data was collected on a subset of the cohort (N=1242) between April 2010 and November 2012. Participants were recruited with an aim to study aging in females. An air-conduction pure-tone audiogram was conducted by trained personnel using a Madsen XETA audiometer including TDH39 headphones. All research was conducted according to the ethical standards as defined by the Helsinki declaration. Ethical approval for this study was obtained from the National Research Ethics service London-Westminster (REC reference number: 07/H0802/84). Written informed consent was obtained from all participants prior to study conduction. Participants were excluded from analysis based on missing data, male, age <45. There were 819 female participants aged >45 remaining for analysis.

Women's Genome Health Study (WGHS)

WGHS is a prospective cohort of female North American health care professionals representing participants in the Women's Health Study (WHS) trial who provided a blood sample at baseline and consent for blood-based analyses[34]. Participants in the WHS were 45 years or older at enrollment and free of cardiovascular disease, cancer or other major chronic illness. The current data are derived from 23,294 WGHS participants for whom whole genome genotype information was available at the time of analysis and for whom self-reported European ancestry could be confirmed

by multidimensional scaling analysis of 1,443 ancestry informative markers in PLINK v. 1.06. At baseline, BP and lifestyle habits related to smoking, consumption of alcohol, and physical activity as well as other general clinical information were ascertained by a self-reported questionnaire, an approach which has been validated in the WGHS demographic, namely female health care professionals.

Information on hearing loss in the WHS (the WGHS parent cohort) was collected by self-report on the fourth observational questionnaire in 2008. Participants were asked: "As you age, do you have more trouble hearing in a crowded room?" with choices of "yes" or "no" as a response, encoded as 1 or 0, respectively.

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