iScience, Volume *26*

Supplemental information

Genetic influences on human blood metabolites in the Japanese population

Takeshi Iwasaki, Yoichiro Kamatani, Kazuhiro Sonomura, Shuji Kawaguchi, Takahisa Kawaguchi, Meiko Takahashi, Koichiro Ohmura, Taka-Aki Sato, and Fumihiko Matsuda

Figure S1. Regional association plots of identified loci in the current study, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase 3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

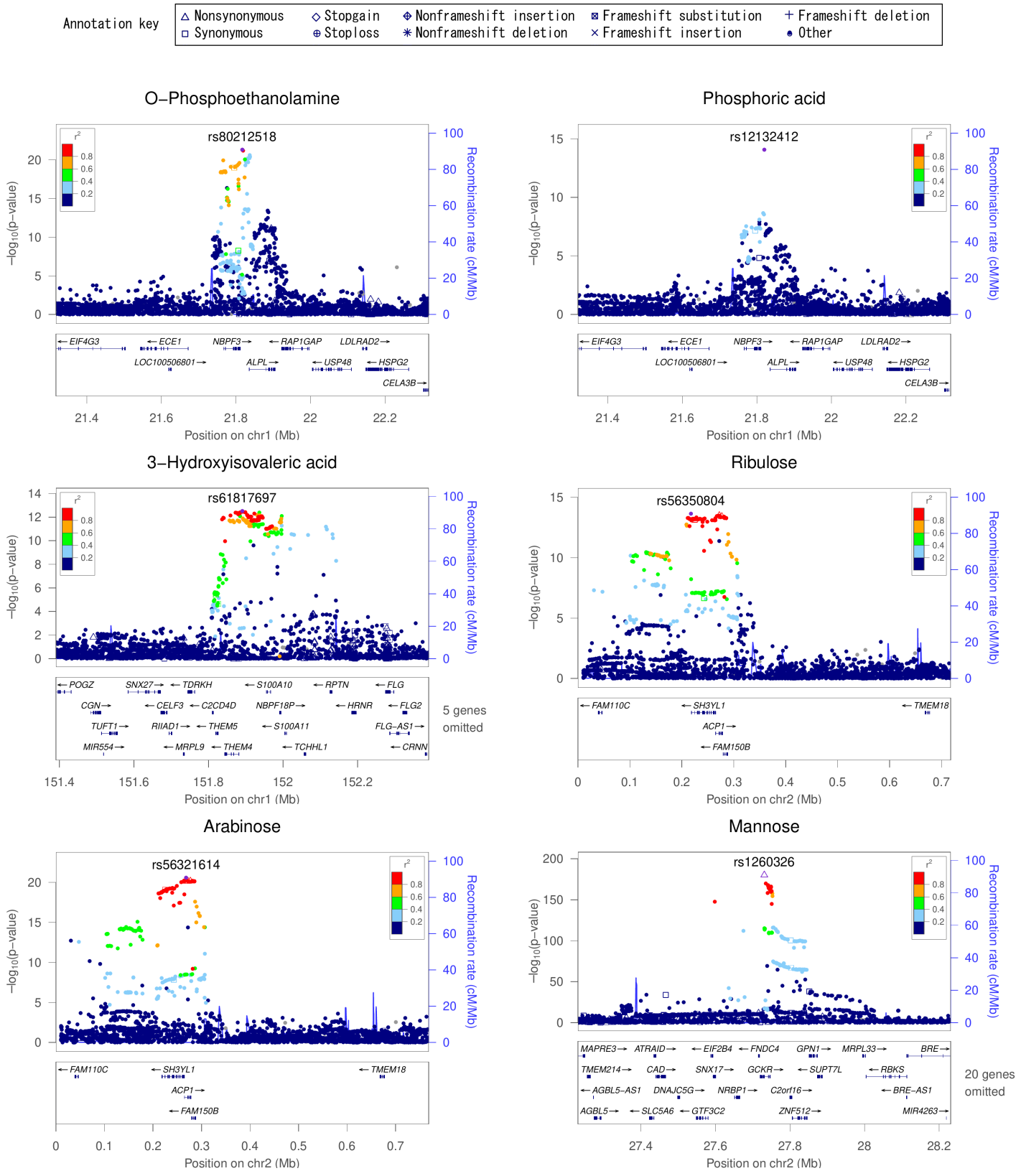


Figure S2. Regional association plots of identified loci in the current study, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase 3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

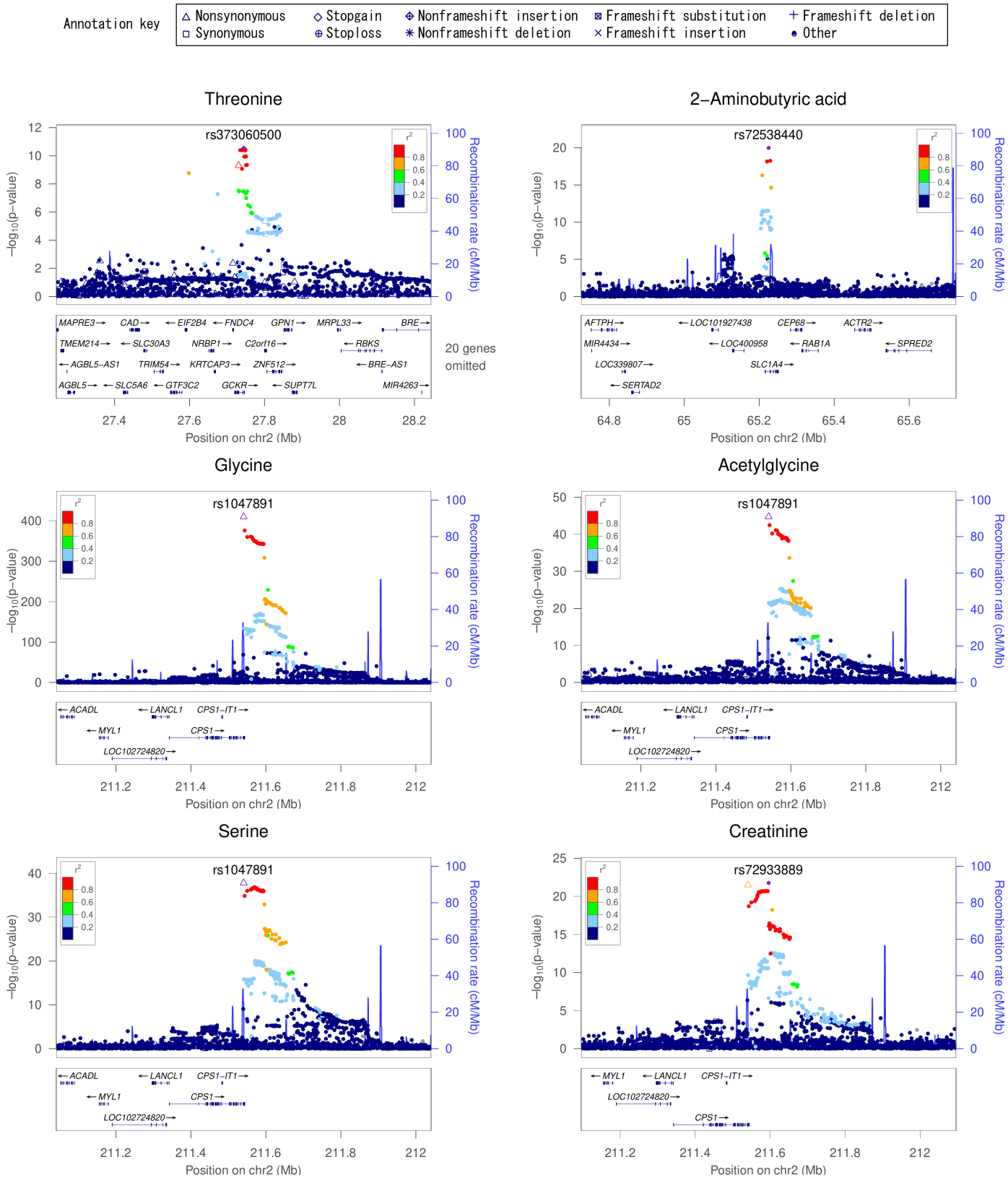


Figure S3. Regional association plots of identified loci in the current study, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase 3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

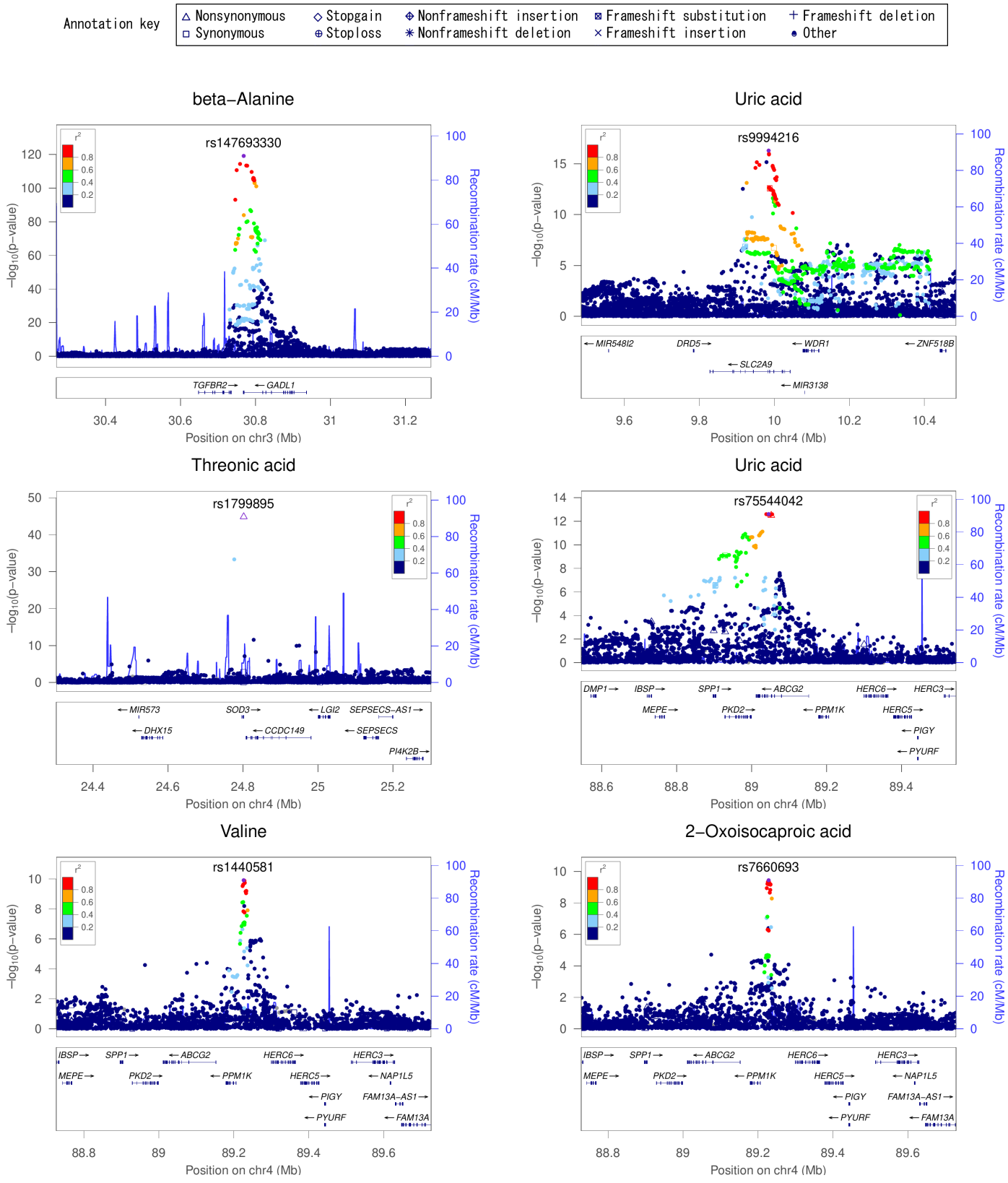


Figure S4. Regional association plots of identified loci in the current study, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase 3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

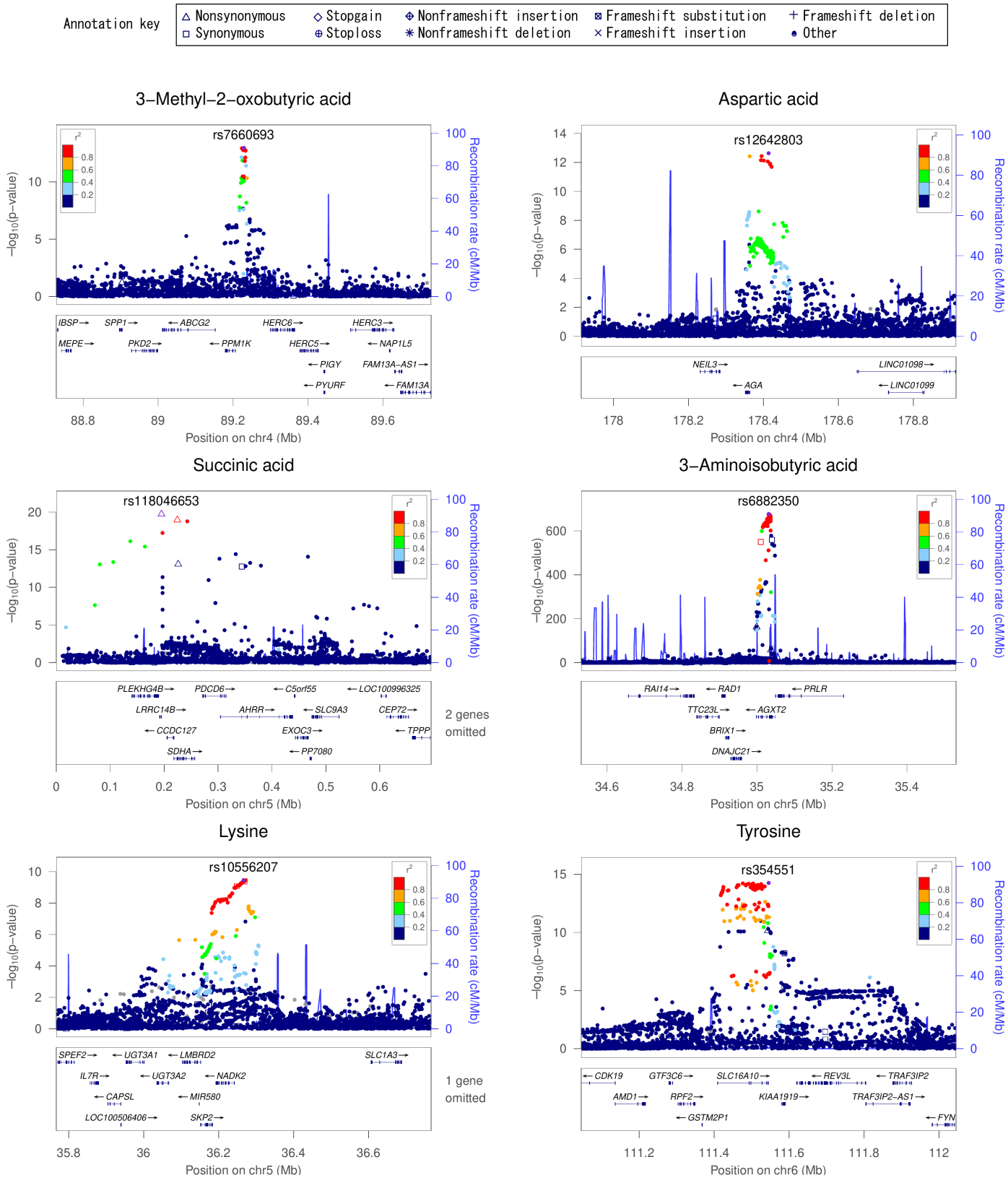


Figure S5. Regional association plots of identified loci in the current study, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase 3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

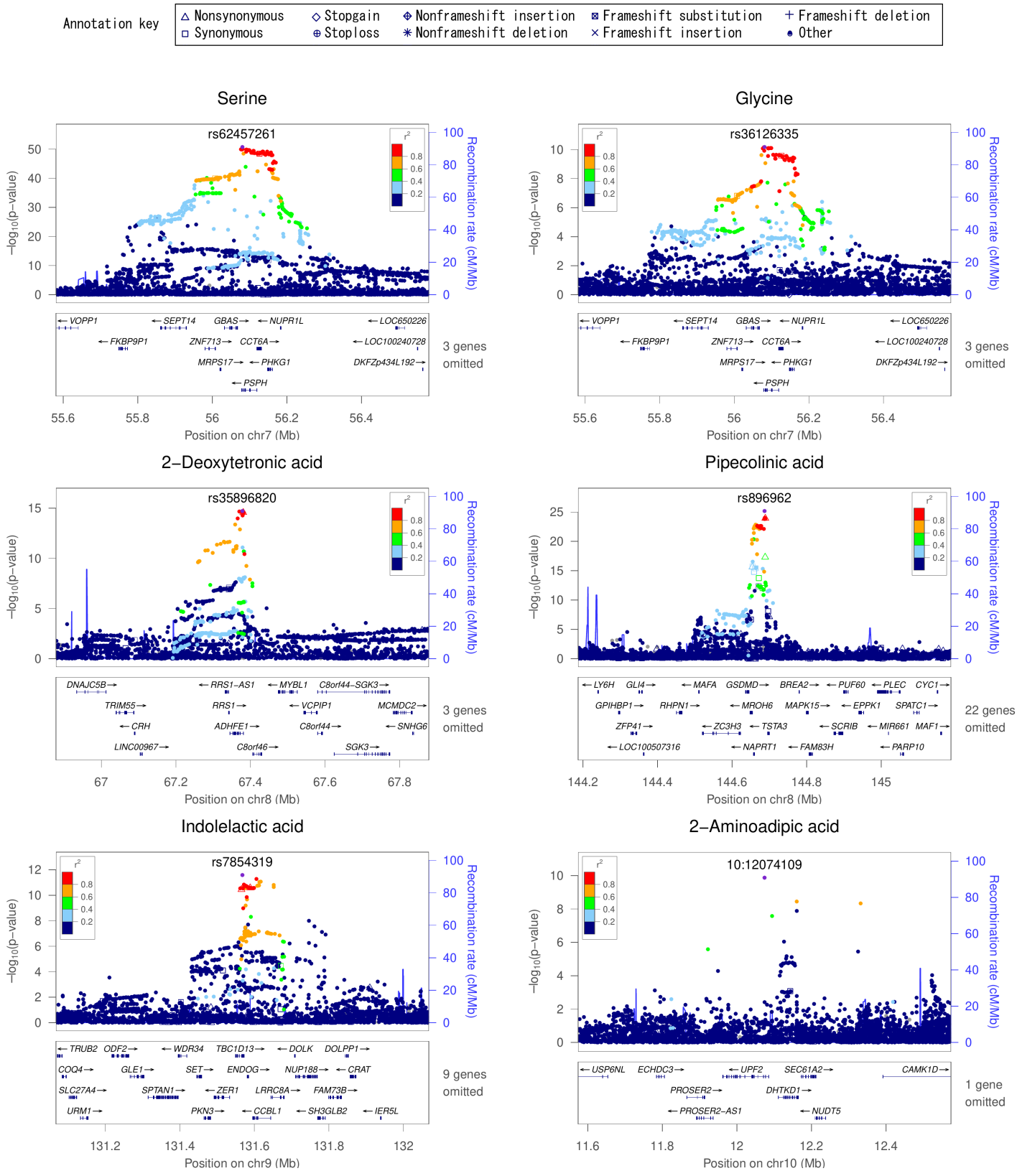


Figure S6. Regional association plots of identified loci in the current study, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase 3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

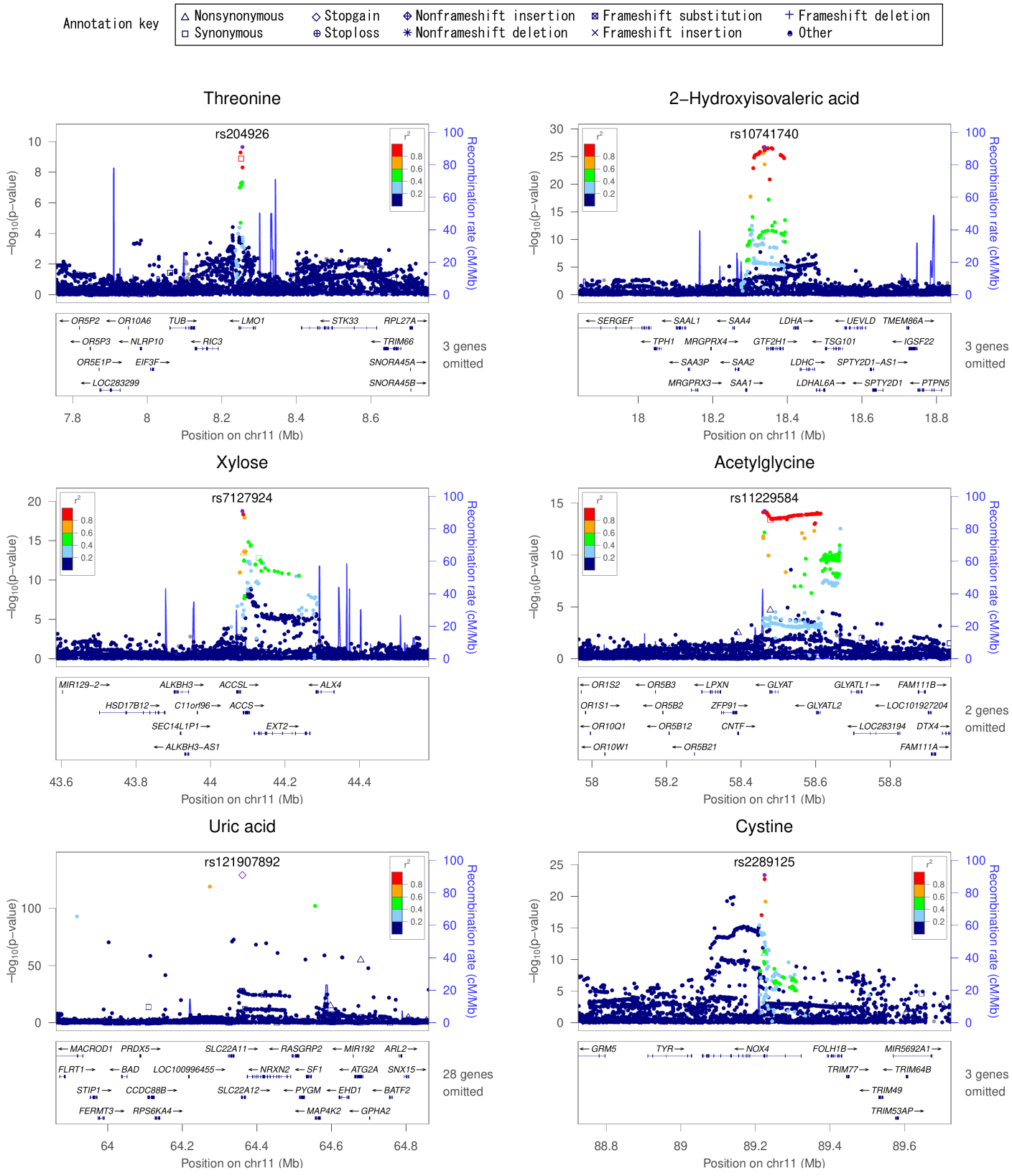


Figure S7. Regional association plots of identified loci in the current study, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase 3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

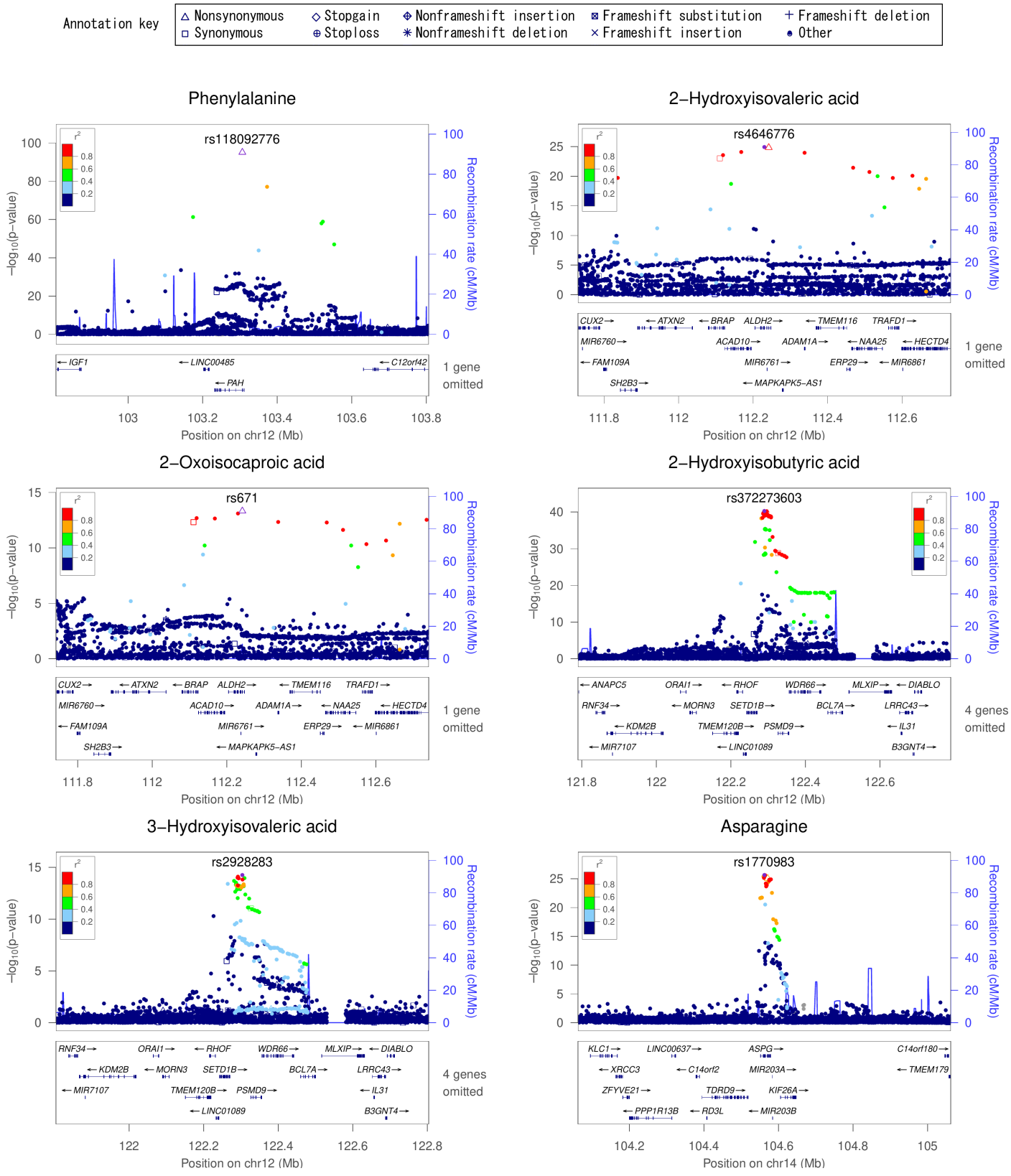


Figure S8. Regional association plots of identified loci in the current study, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase 3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

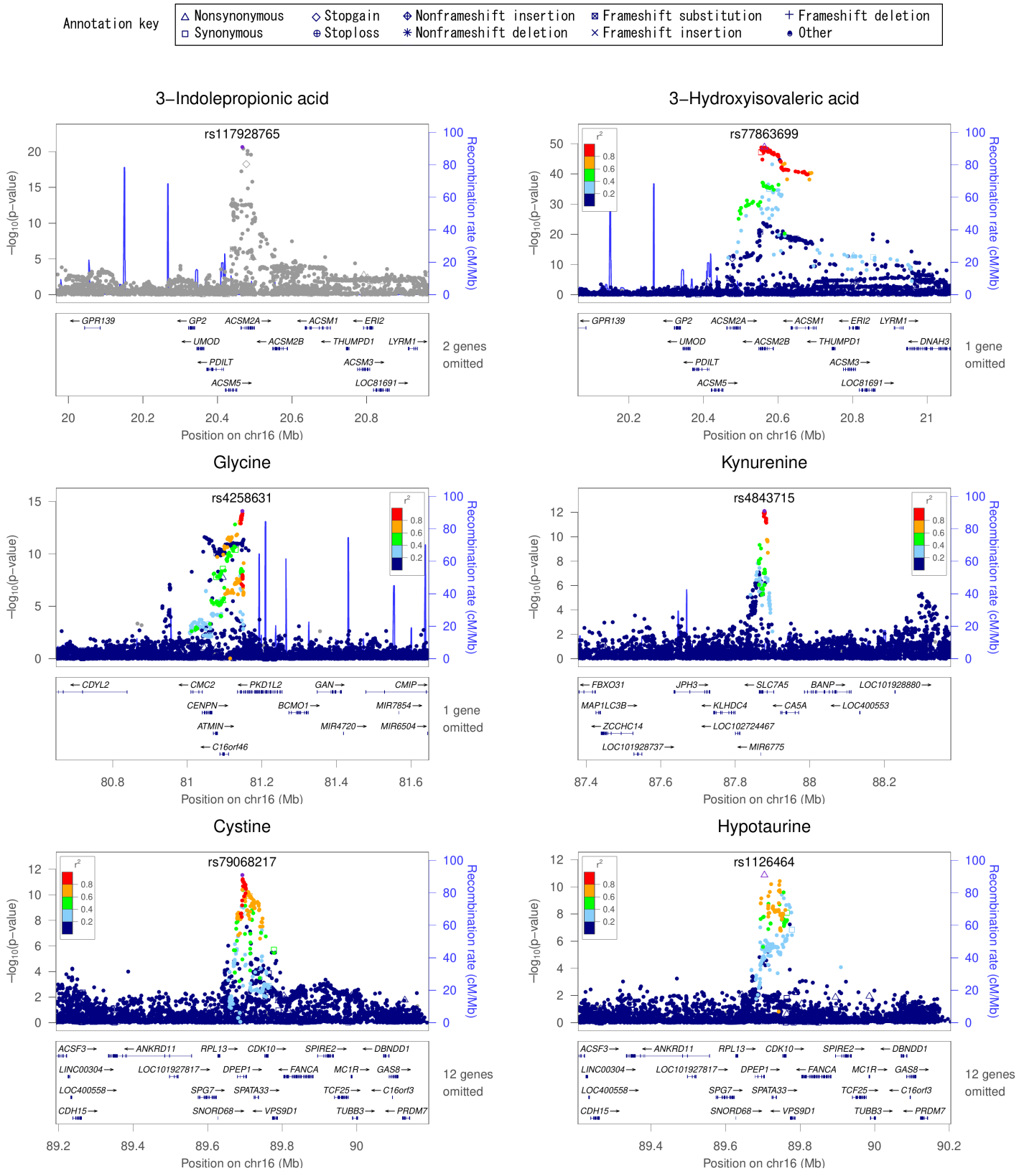


Figure S9. Regional association plots of identified loci in the current study, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase 3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

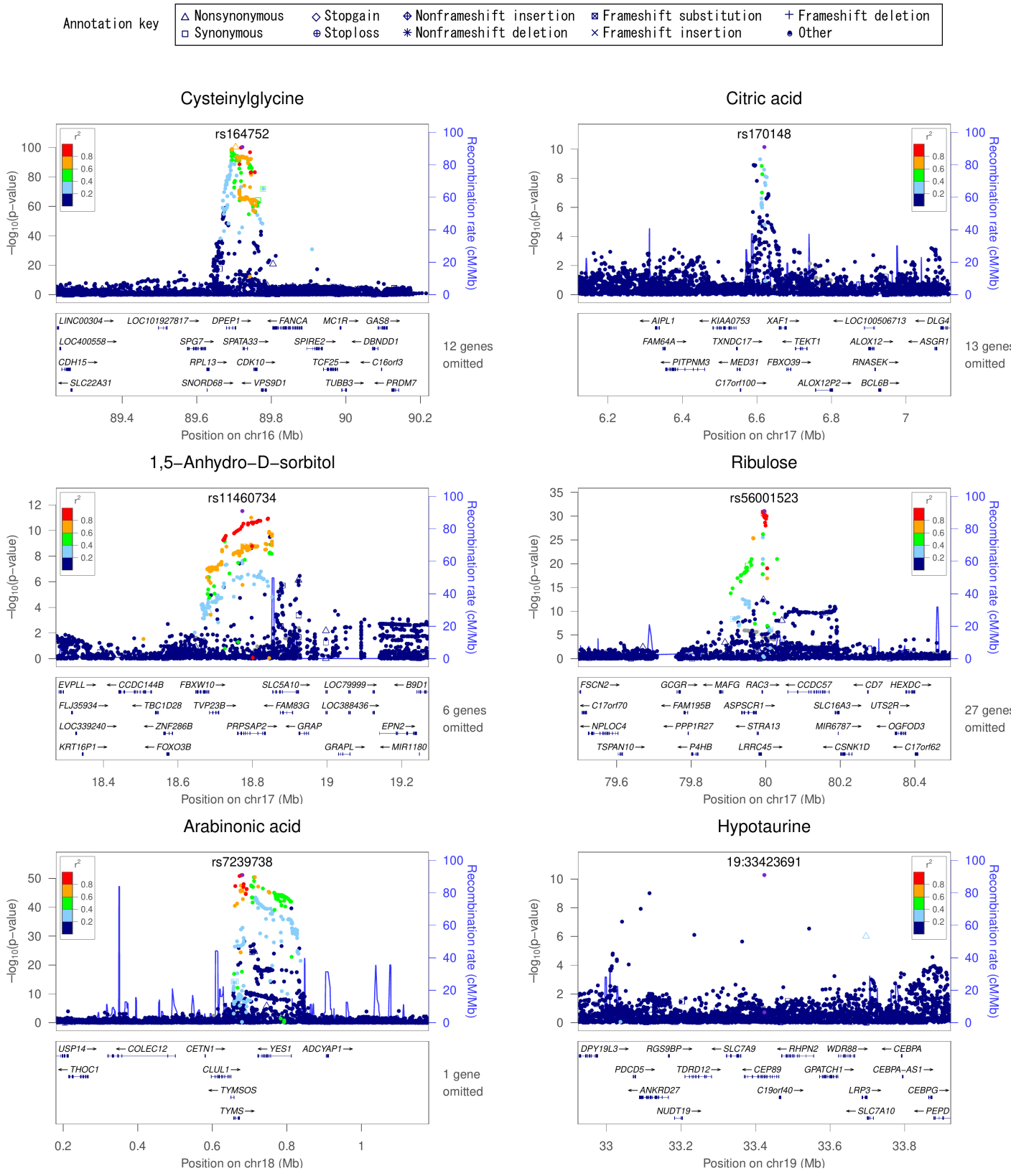


Figure S10. Regional association plots of identified loci in the current study, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase 3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

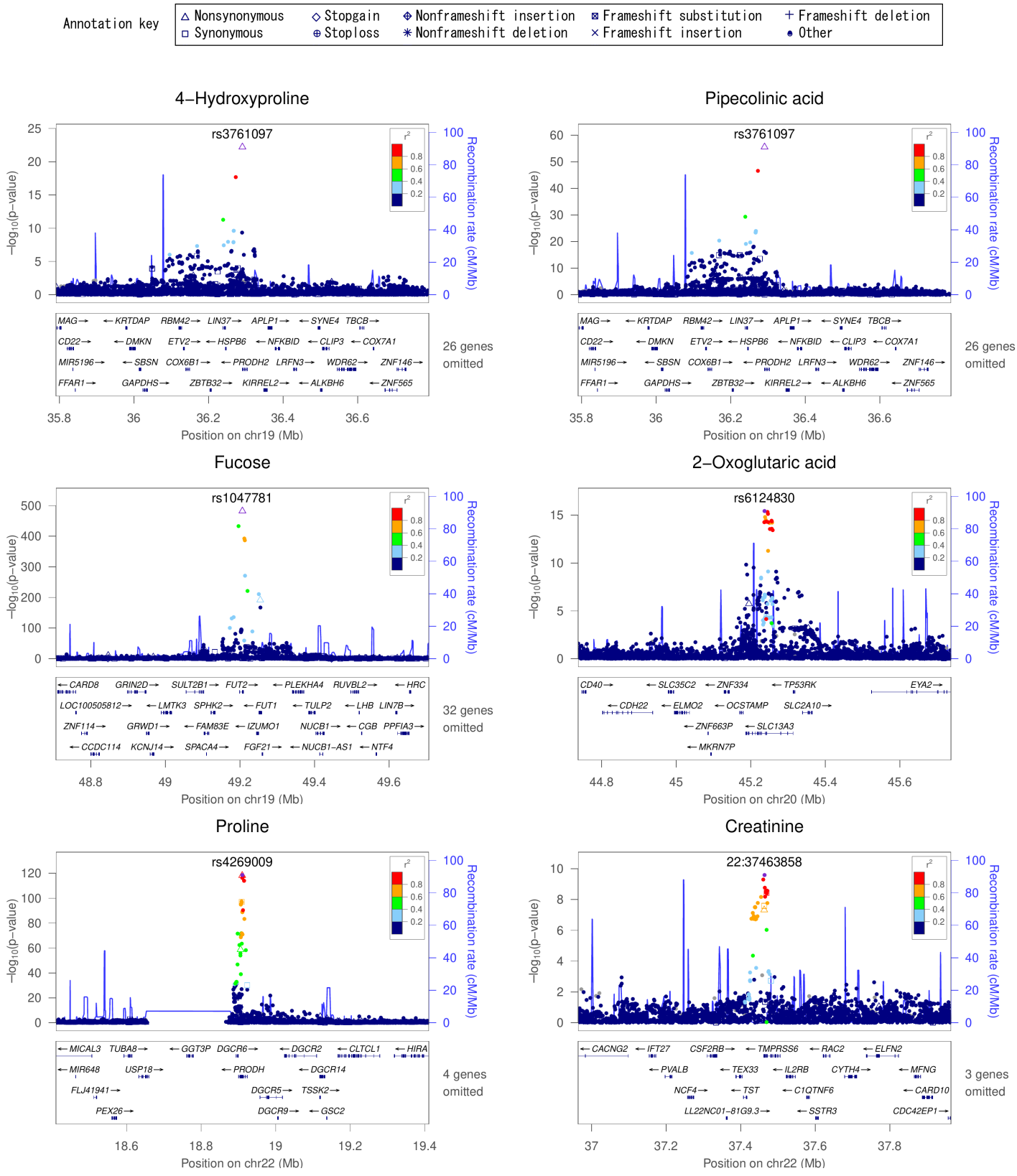
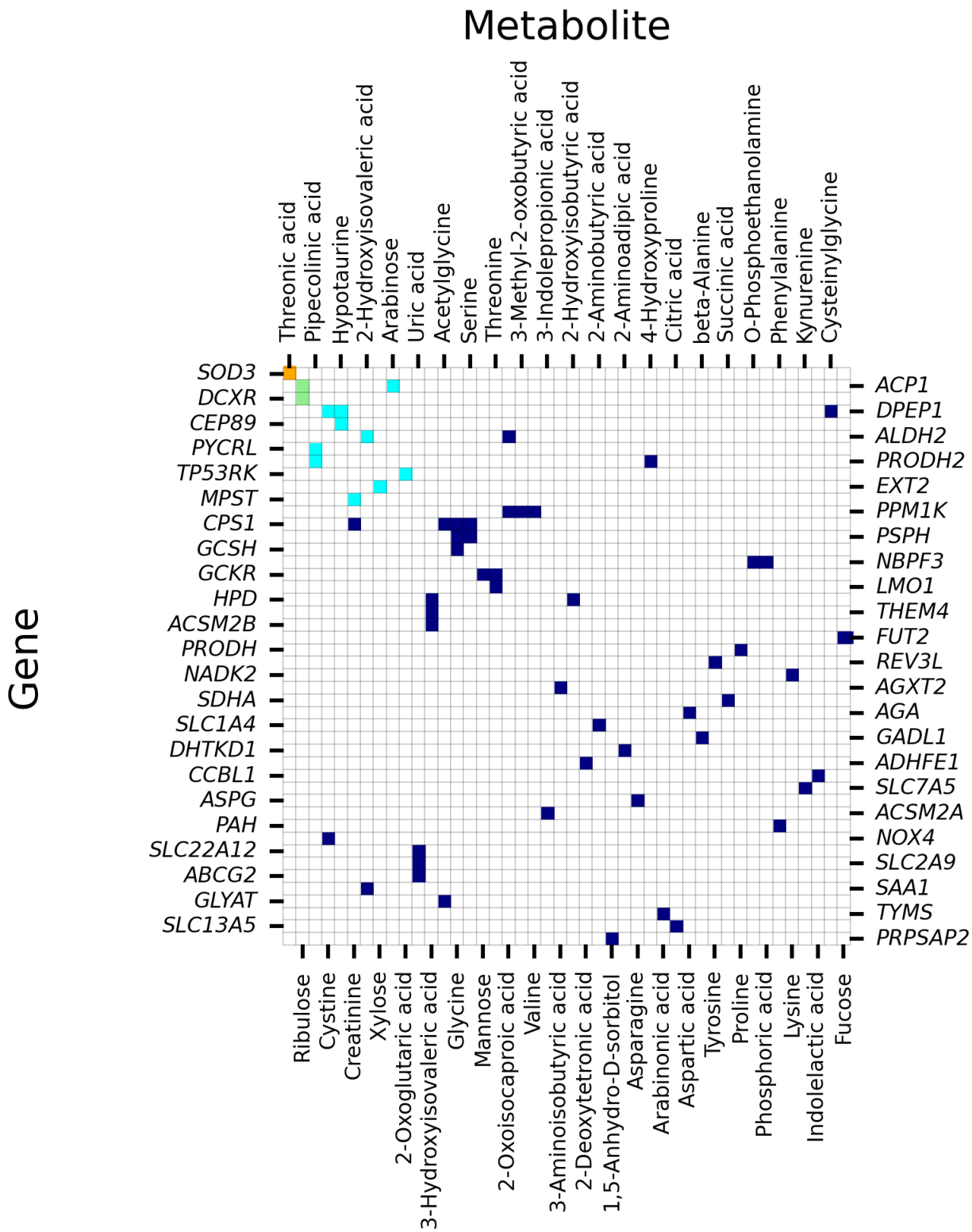


Figure S11. Matrix of metabolites and genes found to be associated, Related to Table 1



Here, an "association" refers to a genome-wide significant association between a human metabolite and a gene.
Orange: Other associations have been reported for this metabolite, and no association has been reported for this gene.
Green: No association has been reported for this metabolite, and other associations have been reported for this gene.
Cyan: Other associations have also been reported for this metabolite, and other associations have been reported for this gene, but as a pair it is novel.
Navy: This association between metabolites and genes has been previously reported.

Figure S12. Result of conditional analysis, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

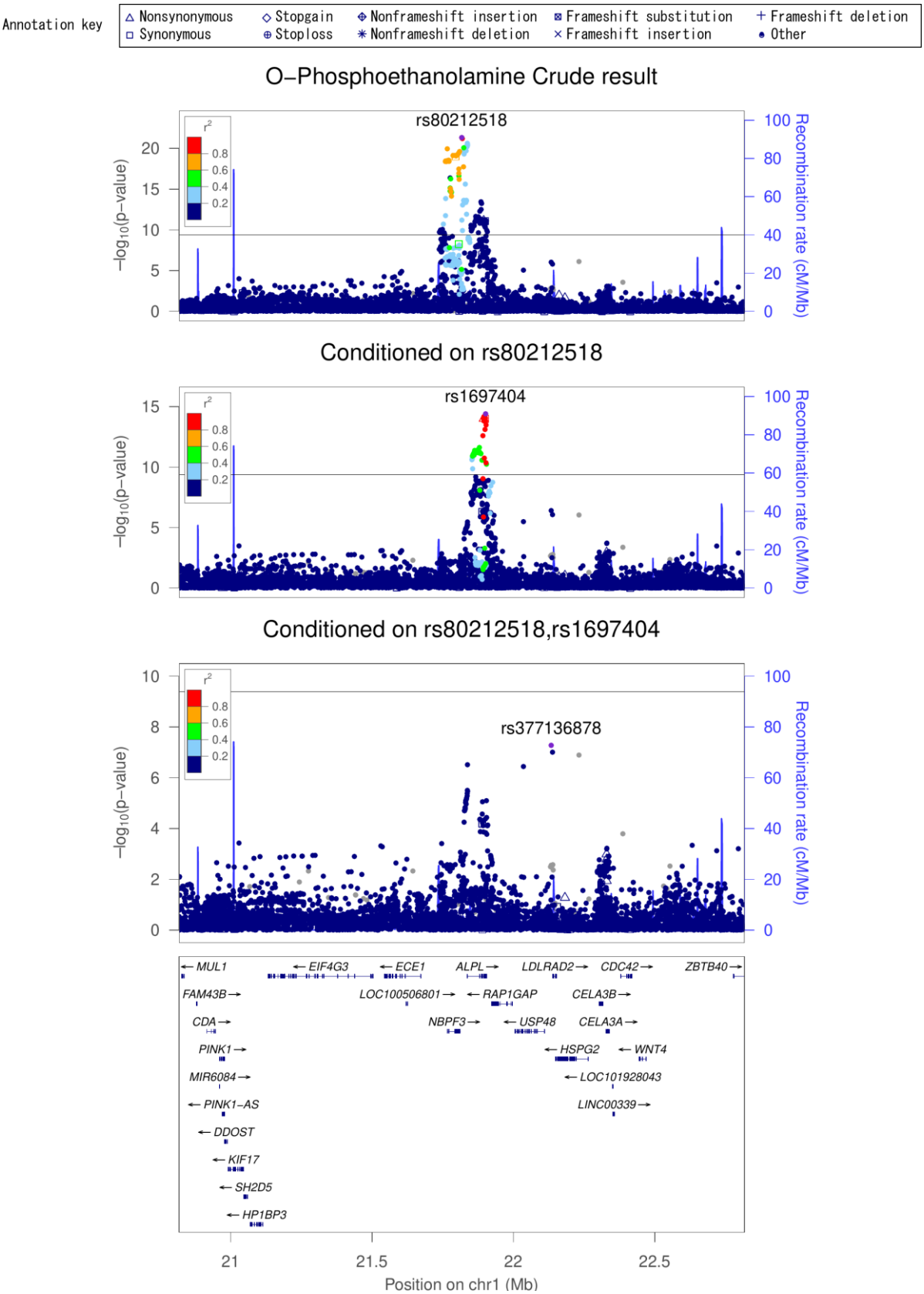


Figure S13. Result of conditional analysis, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

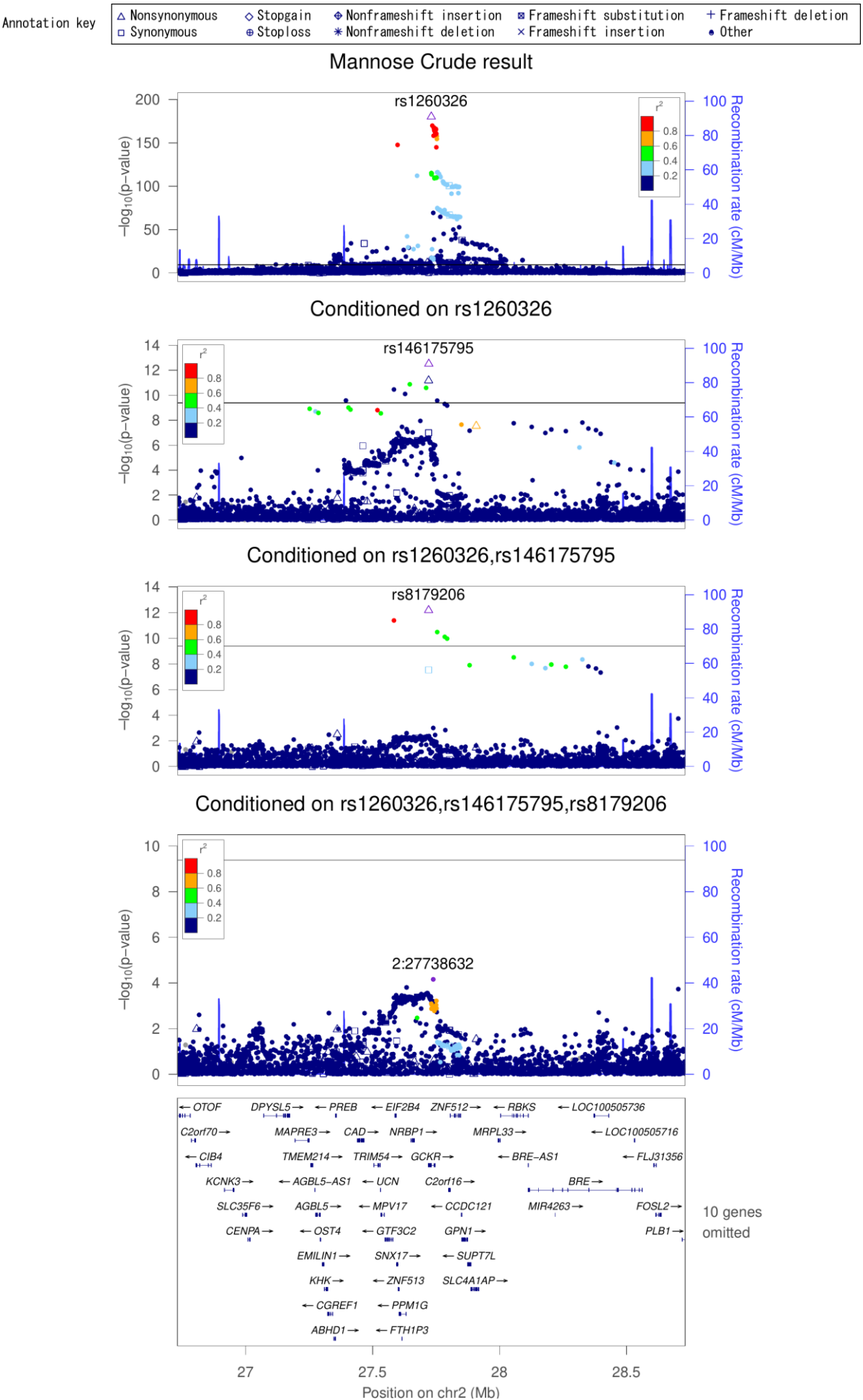


Figure S14. Result of conditional analysis, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

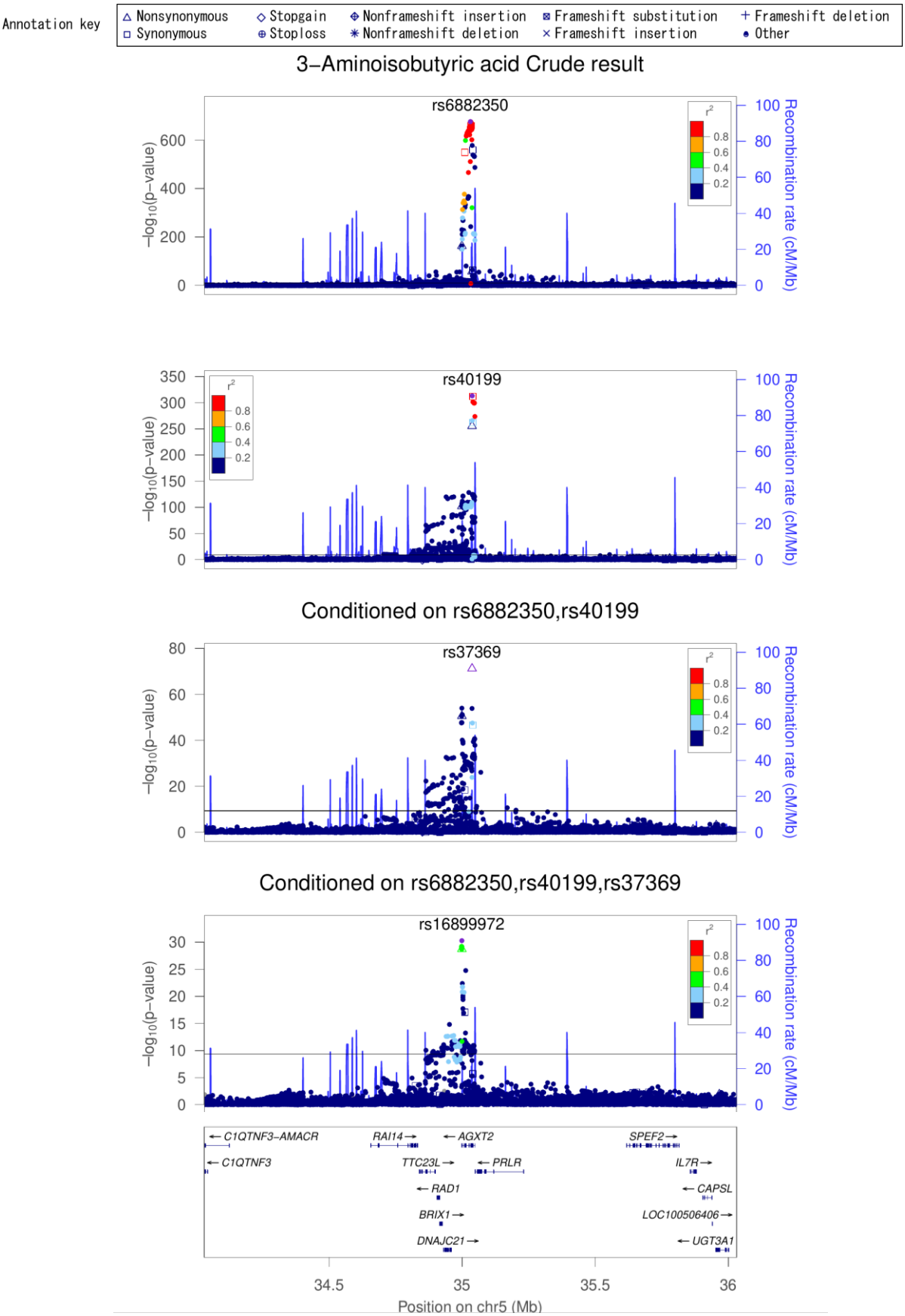


Figure S15. Result of conditional analysis, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

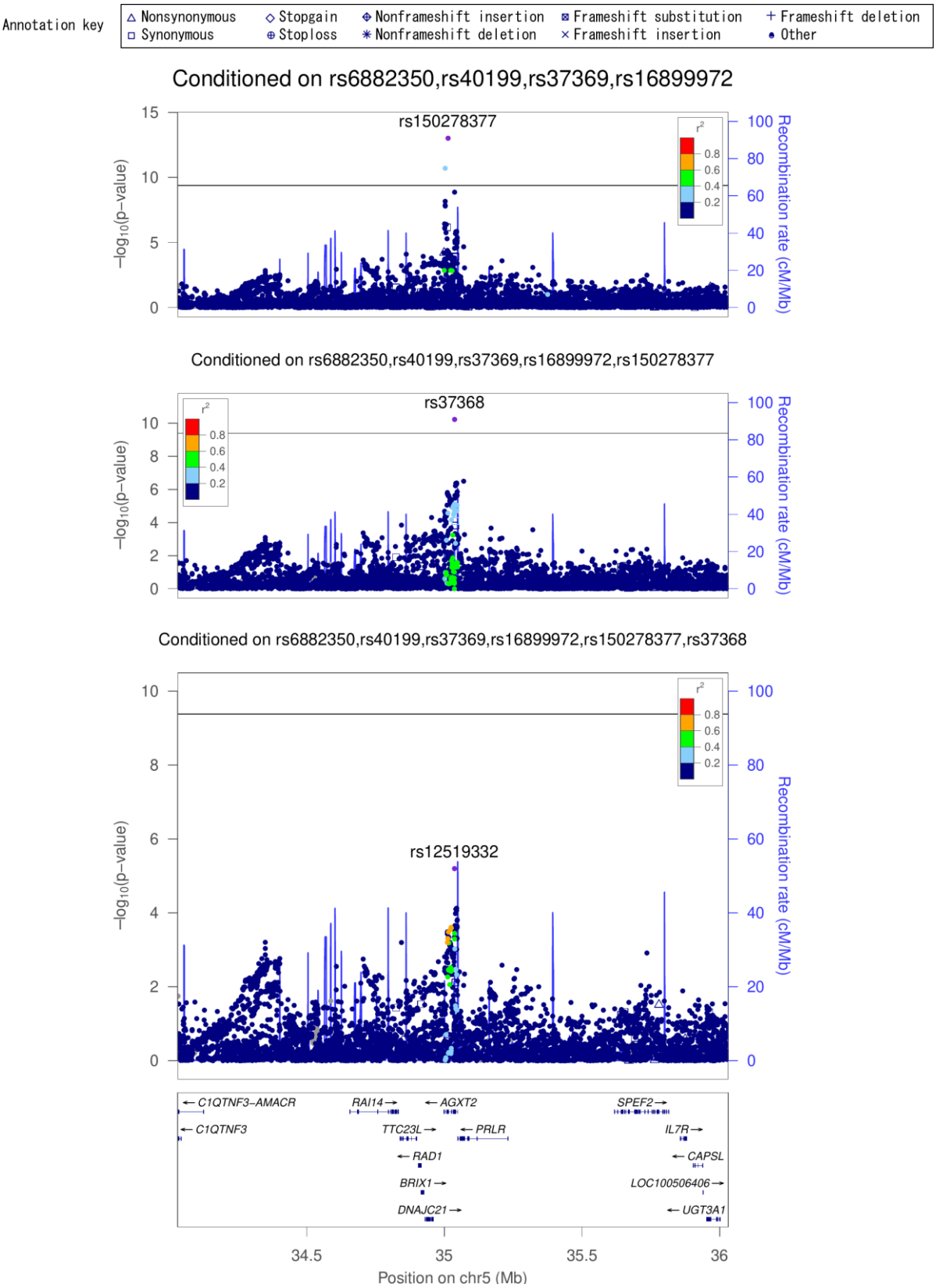


Figure S16. Result of conditional analysis, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

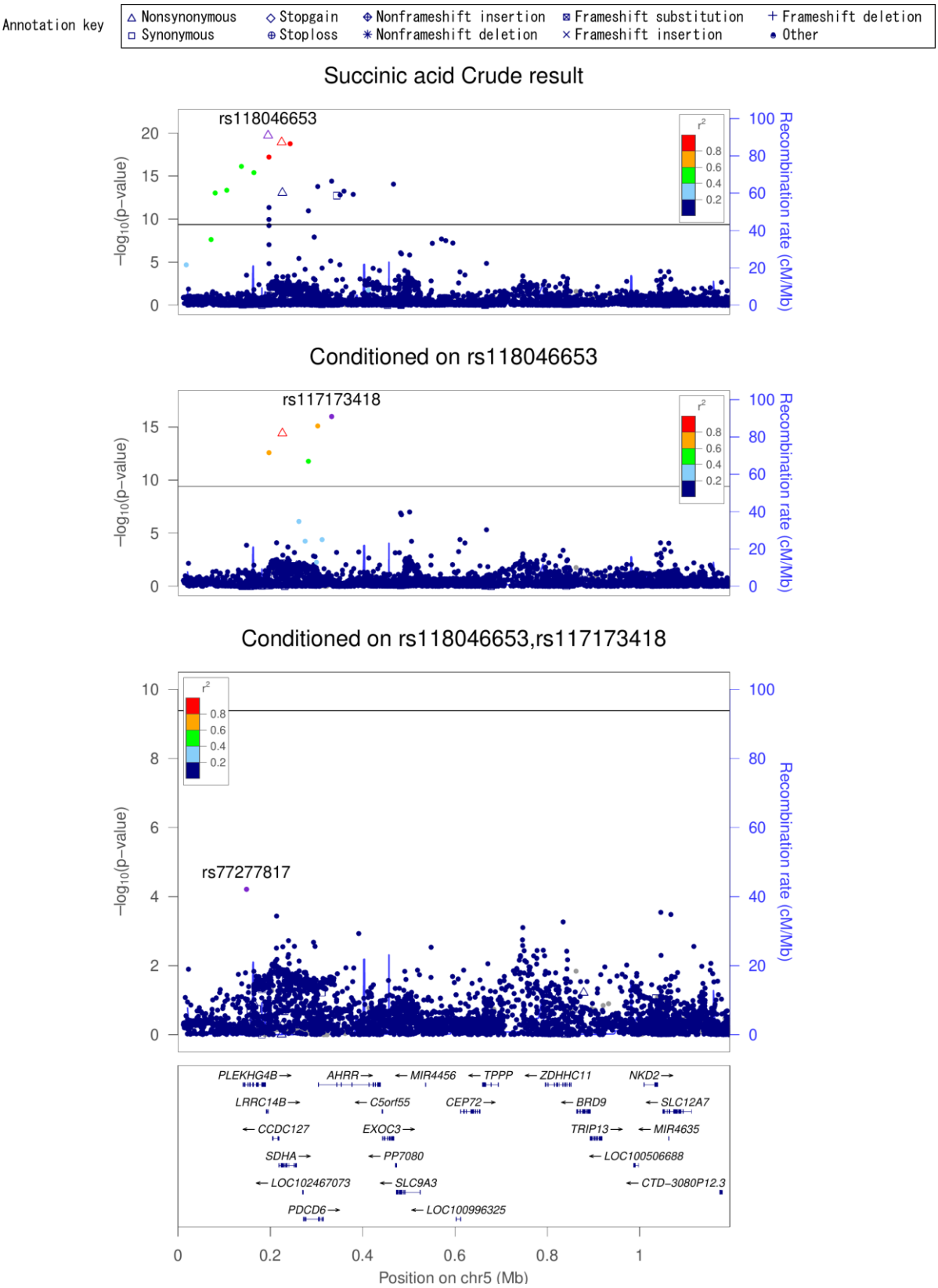


Figure S17. Result of conditional analysis, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

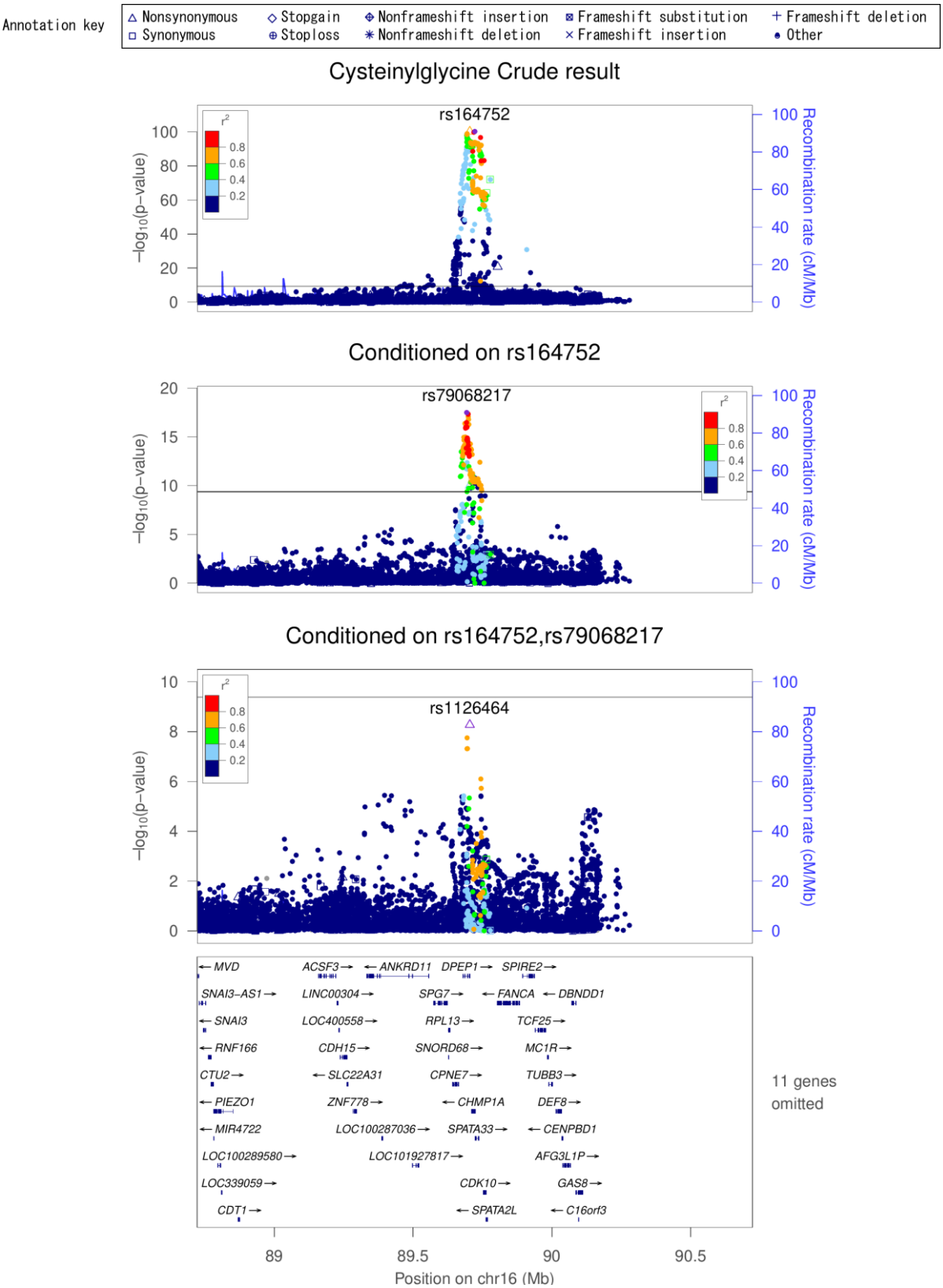


Figure S18. Result of conditional analysis, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

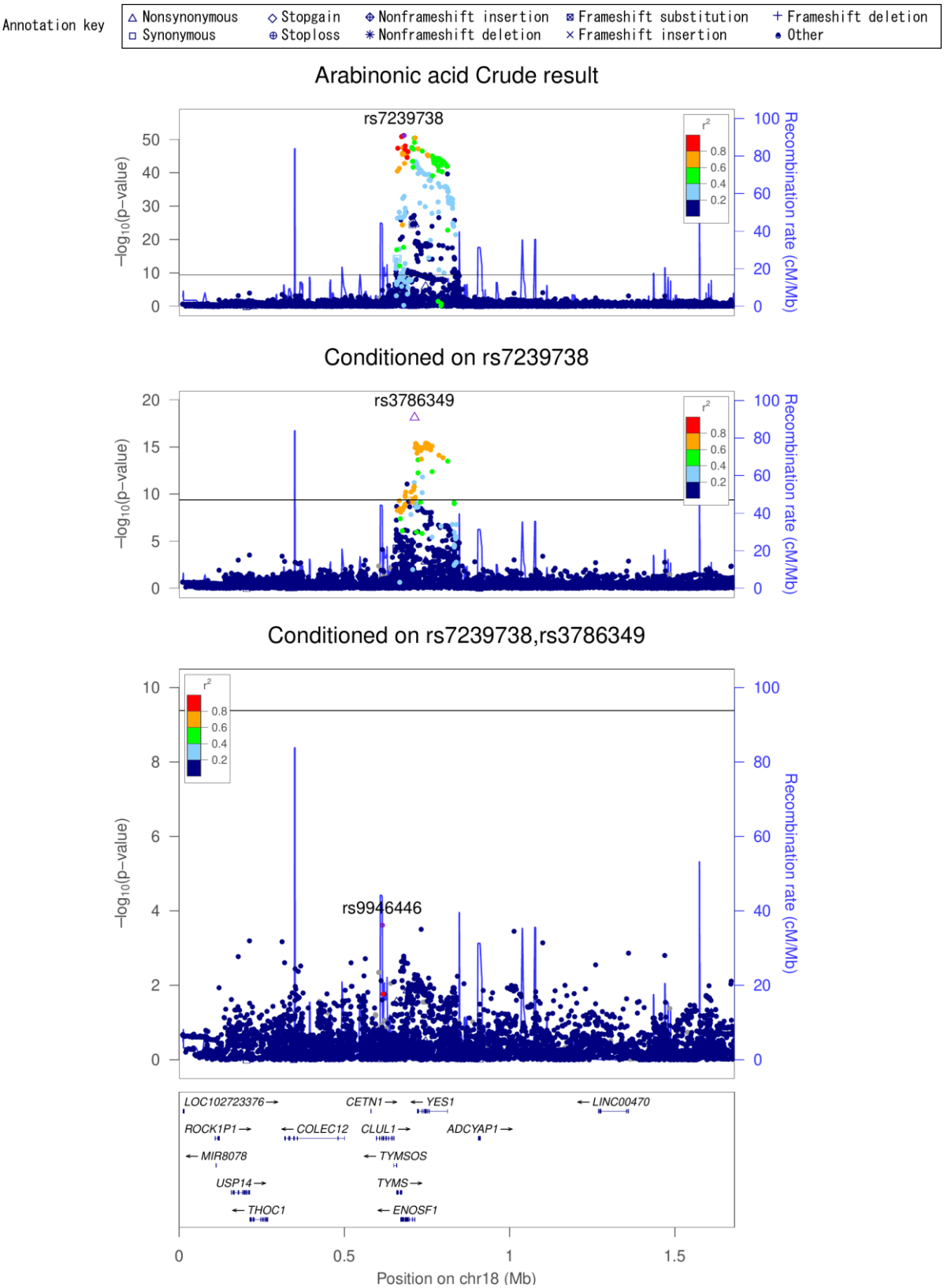


Figure S19. Result of conditional analysis, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

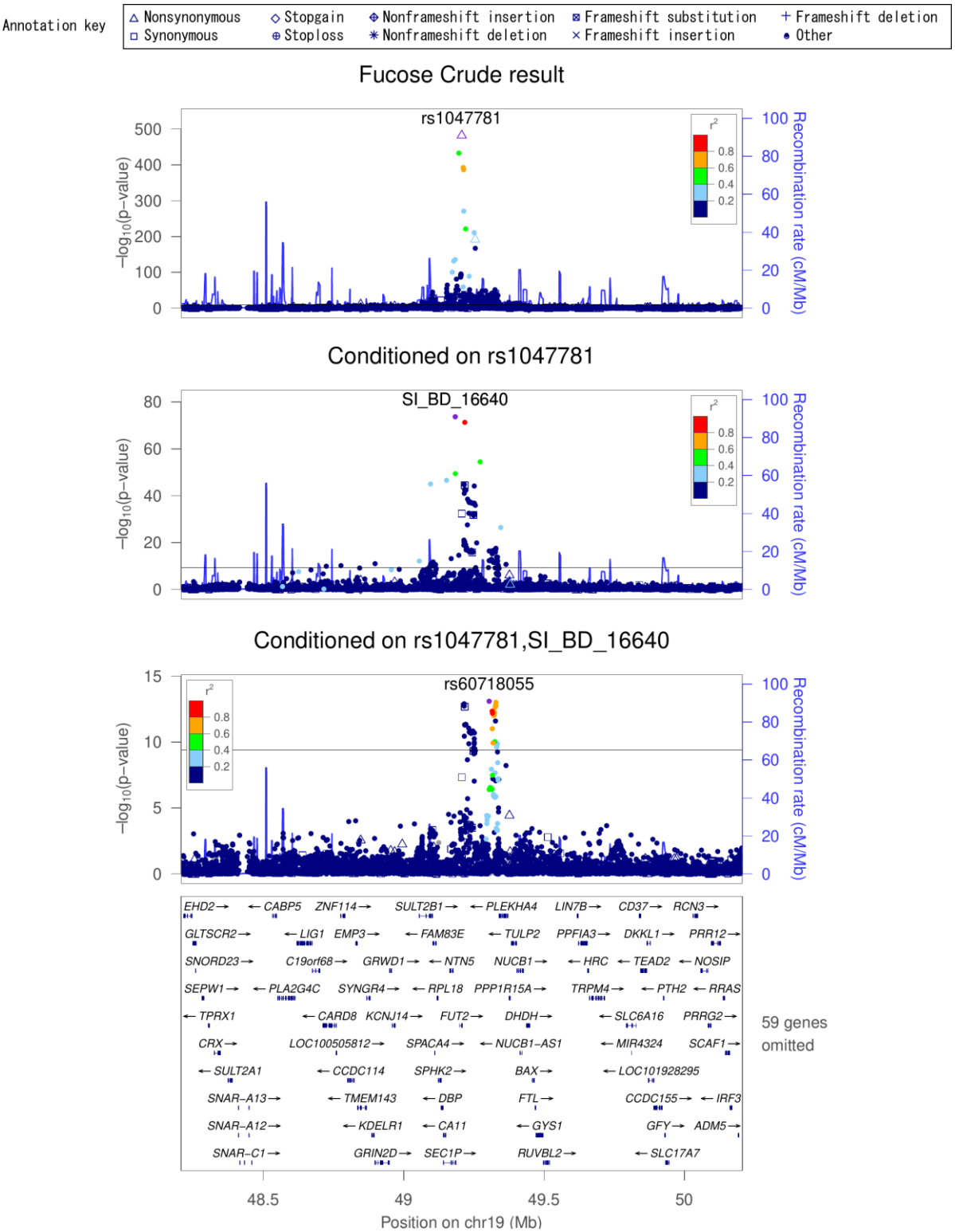


Figure S20. Result of conditional analysis, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

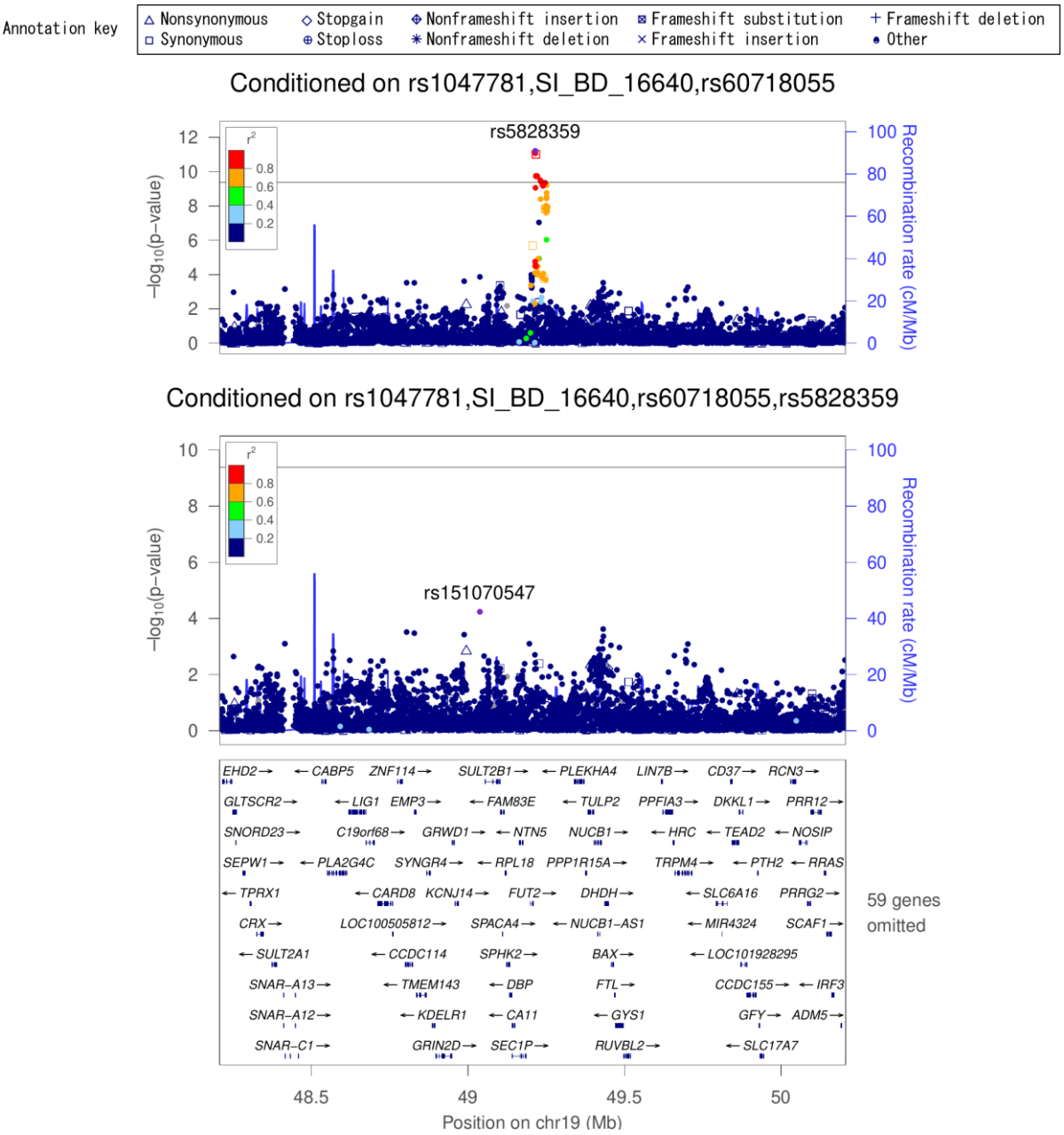


Figure S21. Result of conditional analysis, Related to Table 1

The calculated r^2 with the lead SNP in the 1KG Phase3 East Asian (EAS) population are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

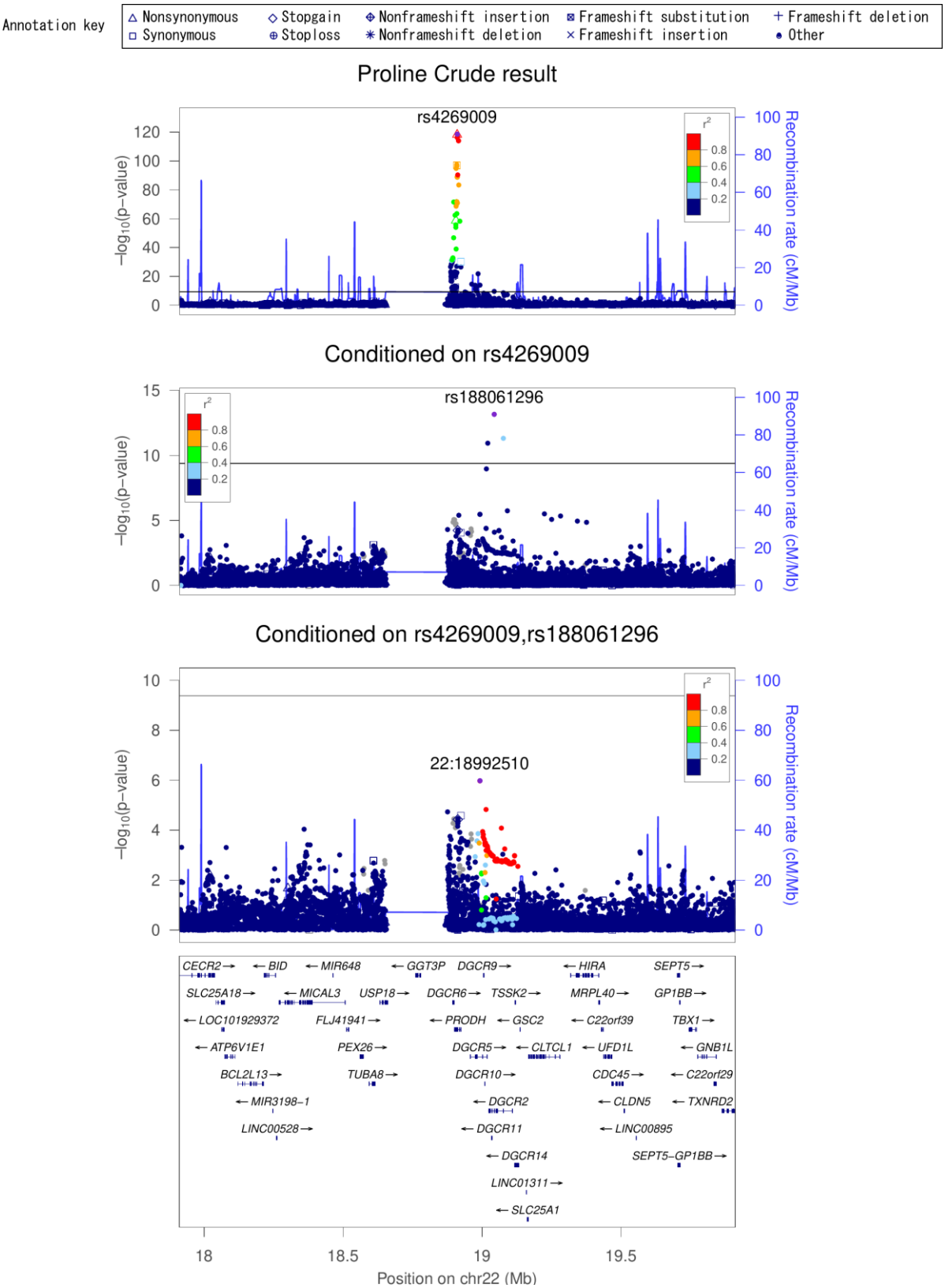
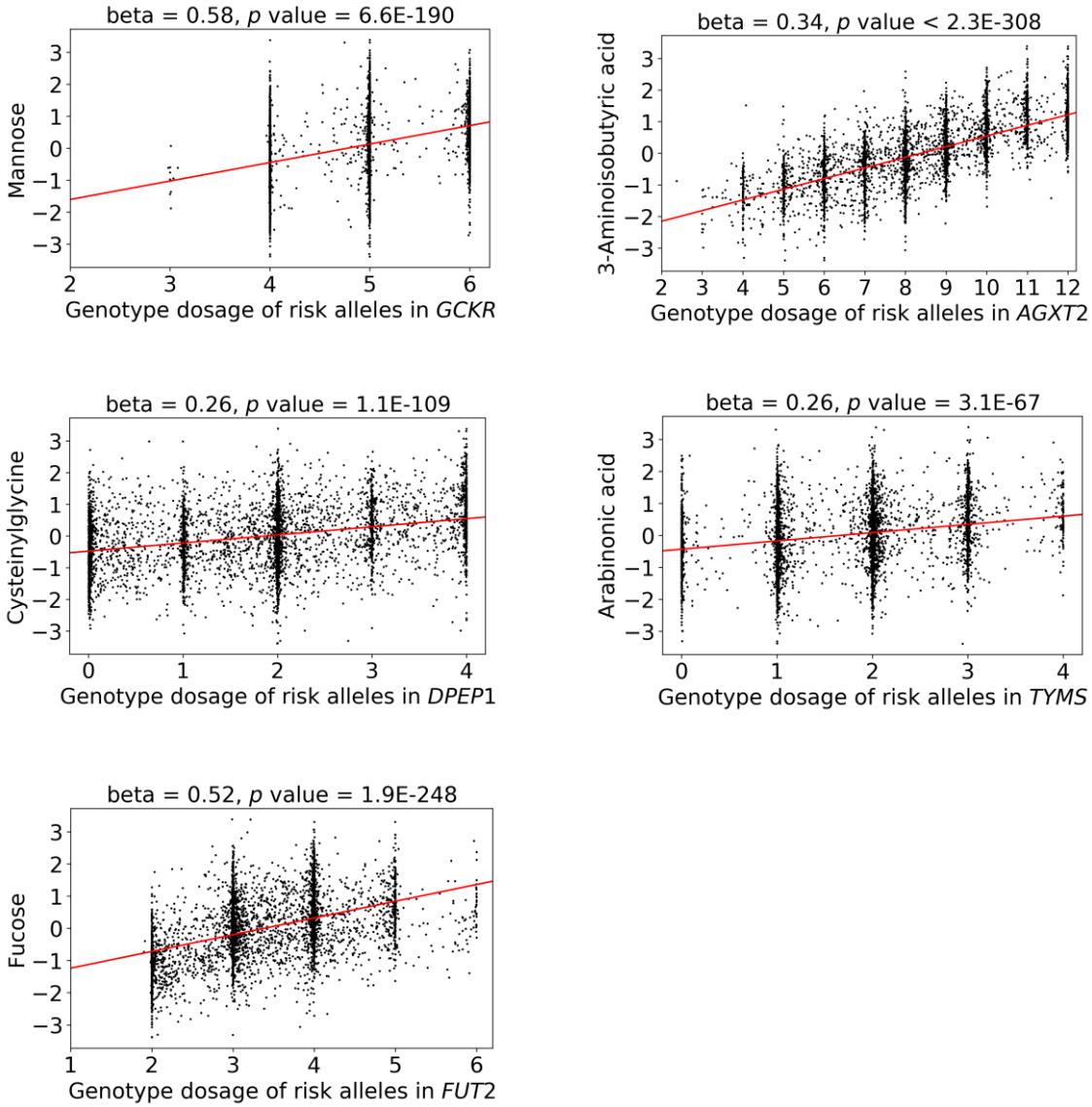


Figure S22. Association between blood metabolite levels and the sum of genotype dosage of the lead and additional SNPs in the same gene, Related to Table 1



Association test was conducted by the least-squares regression.

Figure S23. The region plots of identified loci in the meta-analysis with Tohoku Medical Megabank Organization (ToMMo), Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

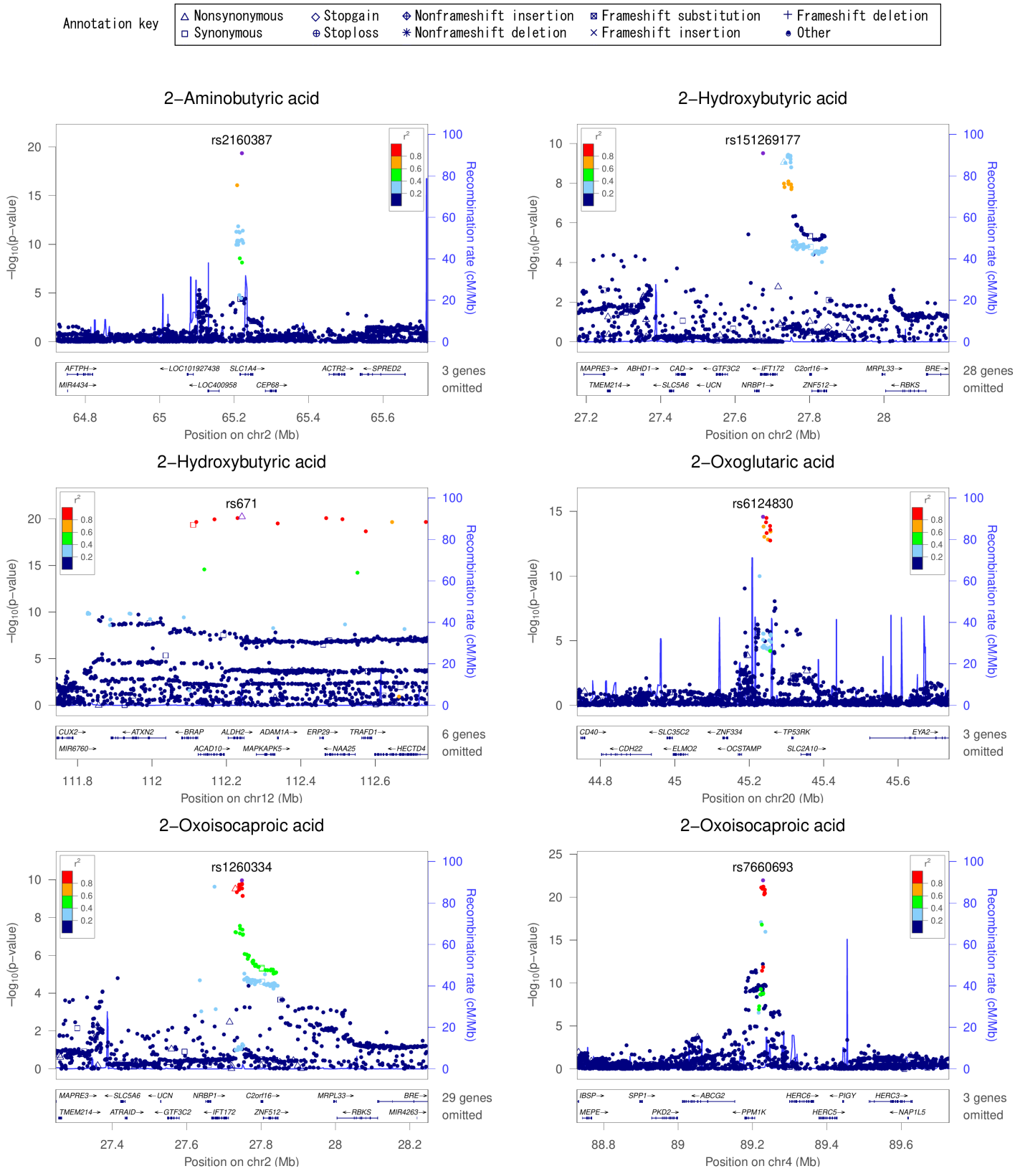


Figure S24. The region plots of identified loci in the meta-analysis with Tohoku Medical Megabank Organization (ToMMo), Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

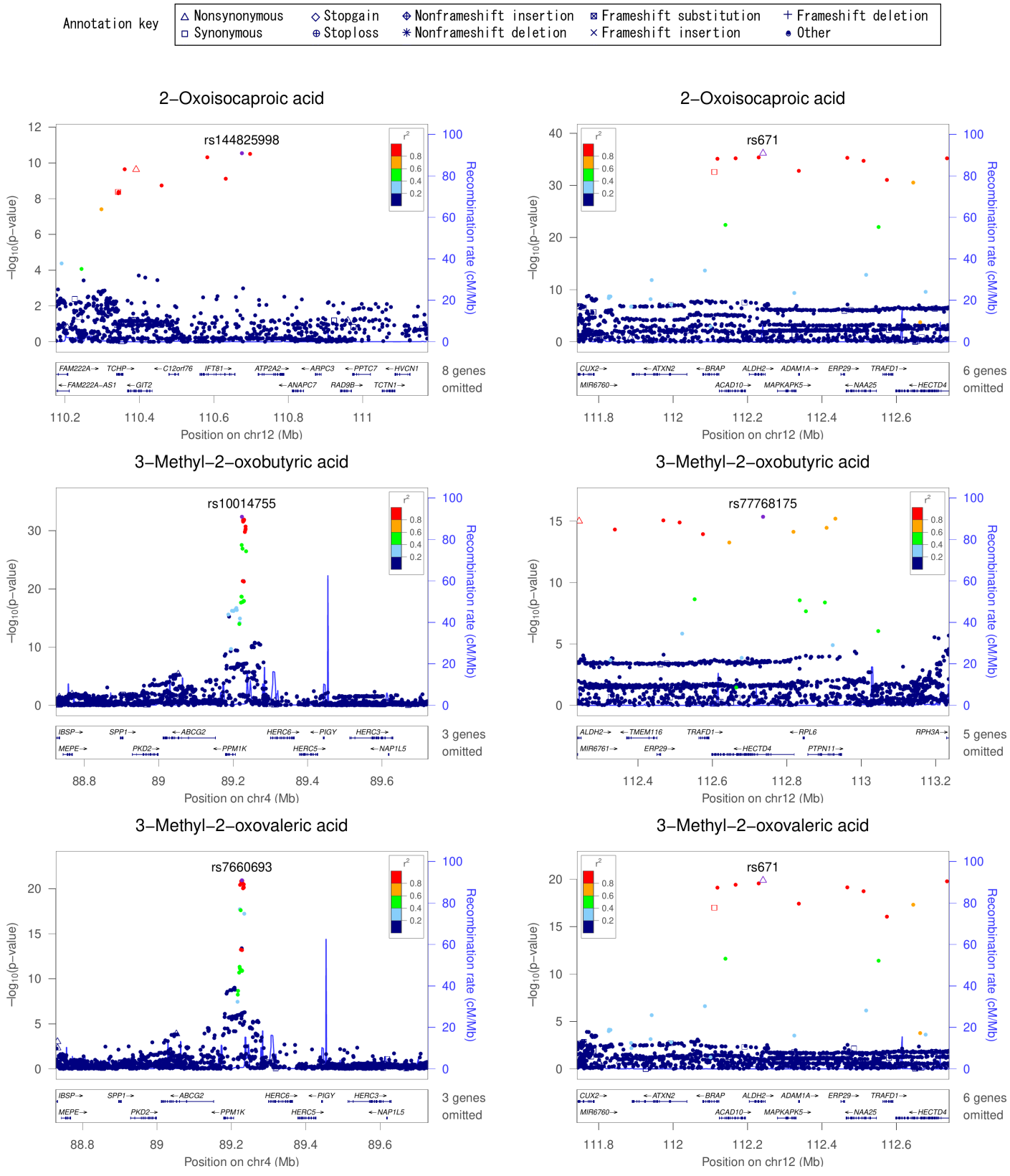


Figure S25. The region plots of identified loci in the meta-analysis with Tohoku Medical Megabank Organization (ToMMo), Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

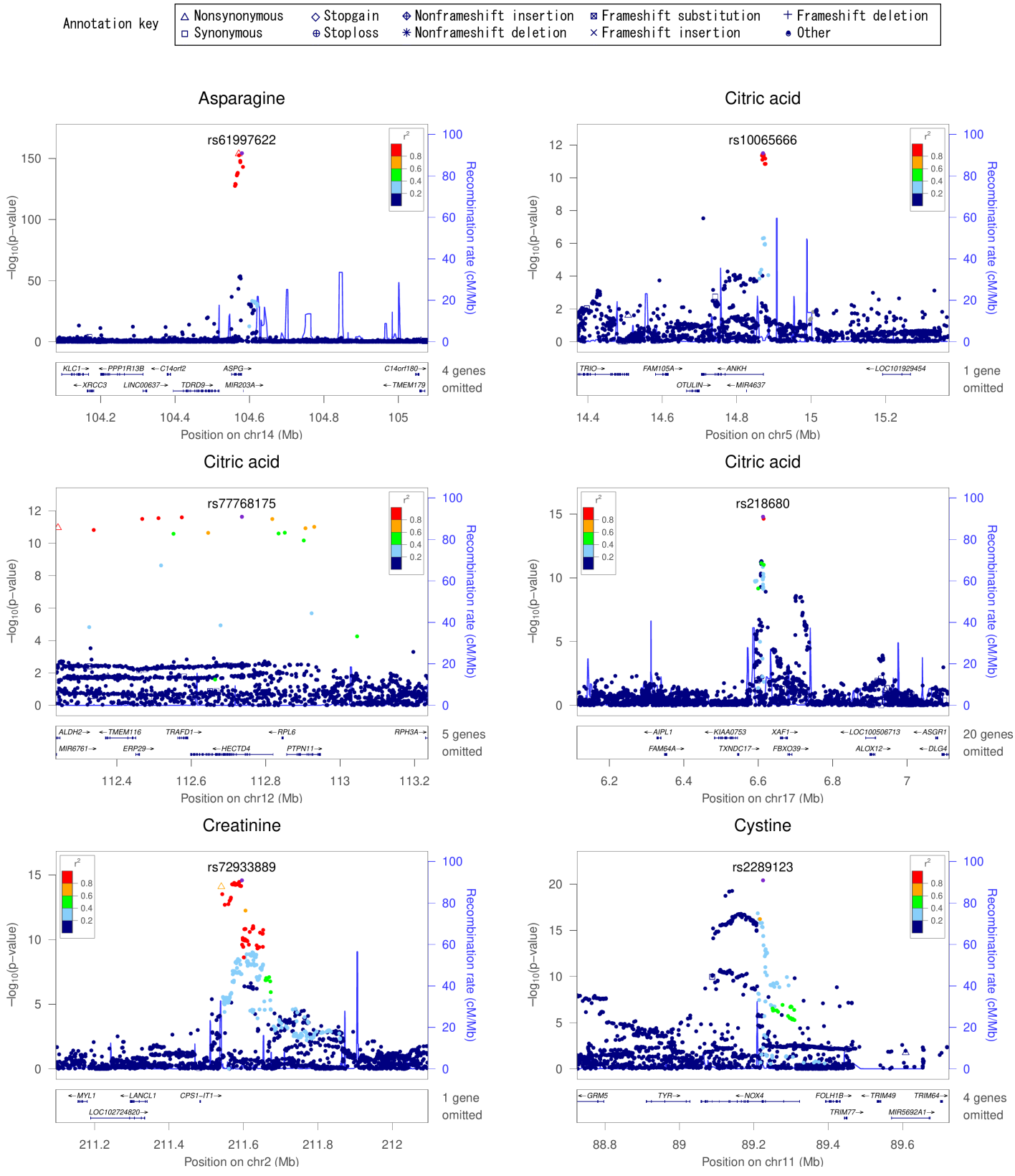


Figure S26. The region plots of identified loci in the meta-analysis with Tohoku Medical Megabank Organization (ToMMo), Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

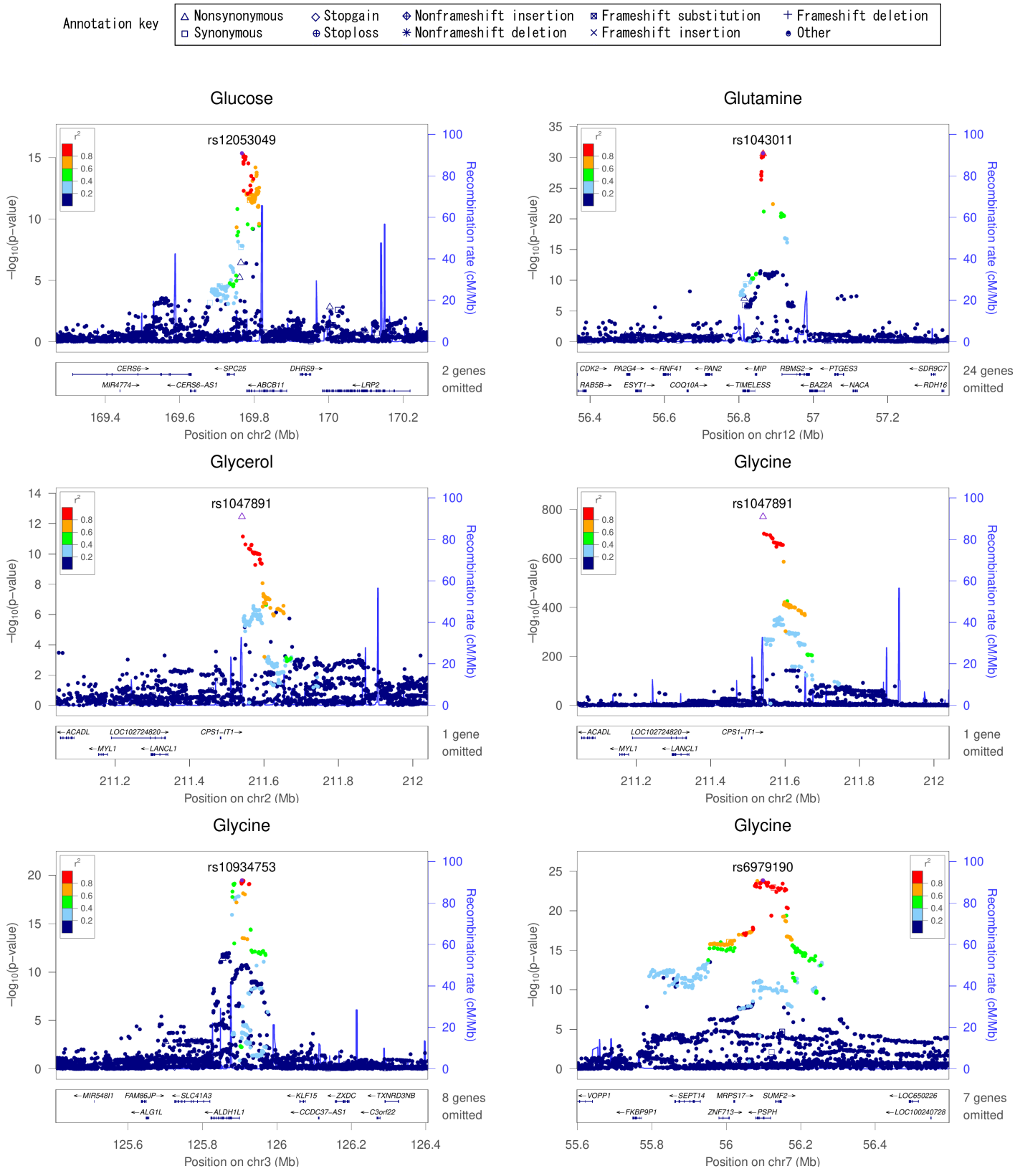


Figure S27. The region plots of identified loci in the meta-analysis with Tohoku Medical Megabank Organization (ToMMo), Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

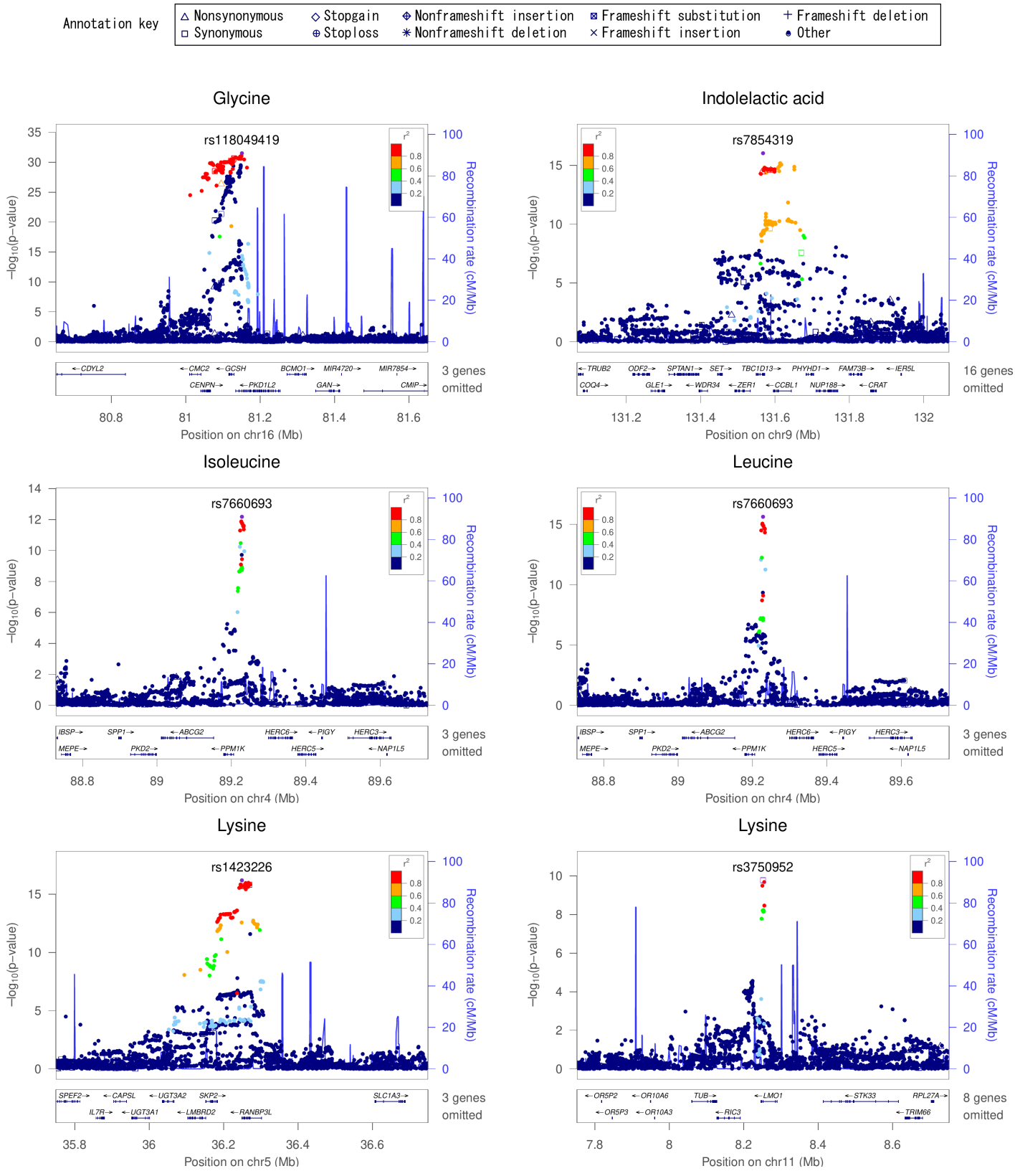


Figure S28. The region plots of identified loci in the meta-analysis with Tohoku Medical Megabank Organization (ToMMo), Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

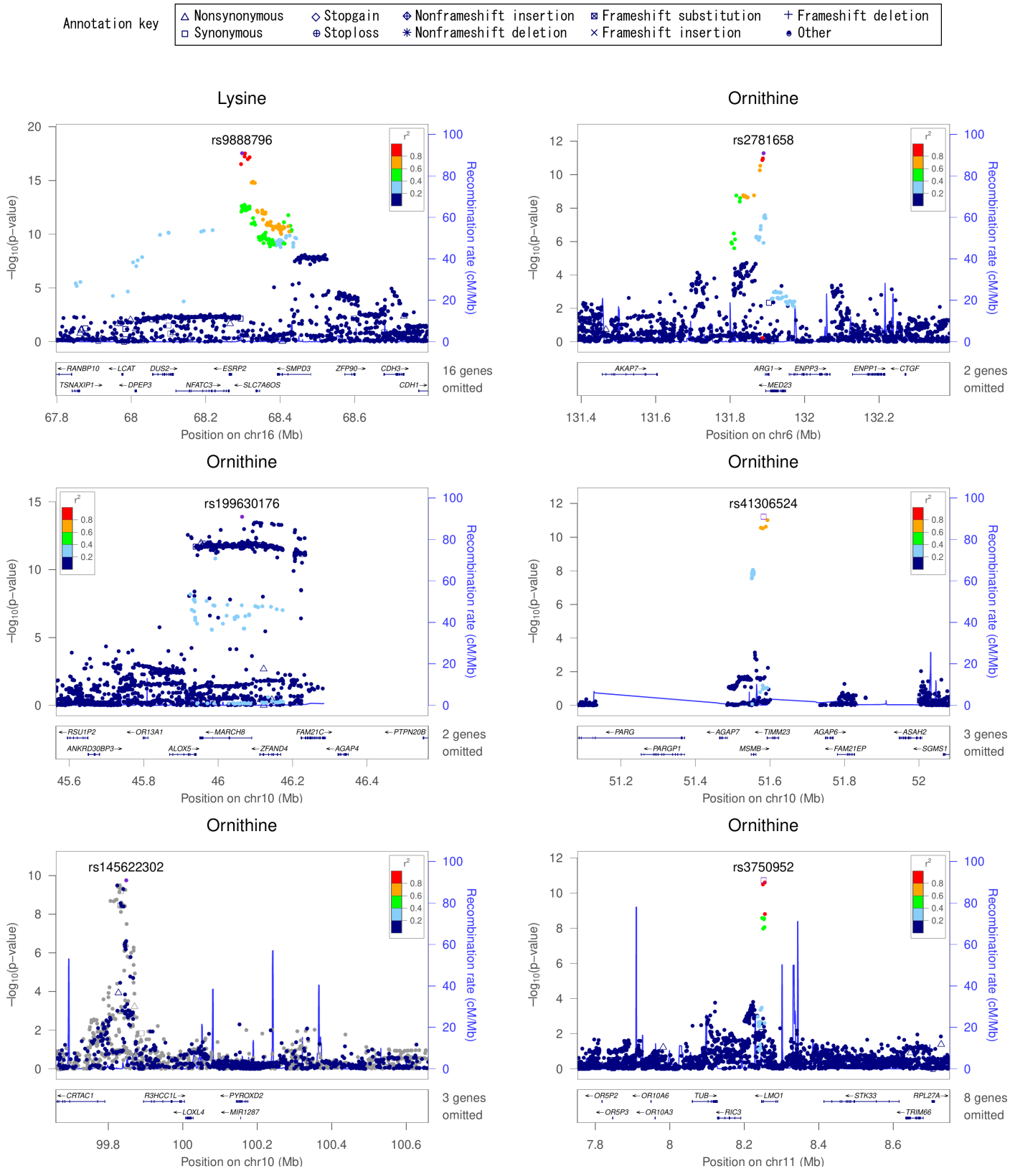


Figure S29. The region plots of identified loci in the meta-analysis with Tohoku Medical Megabank Organization (ToMMo), Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

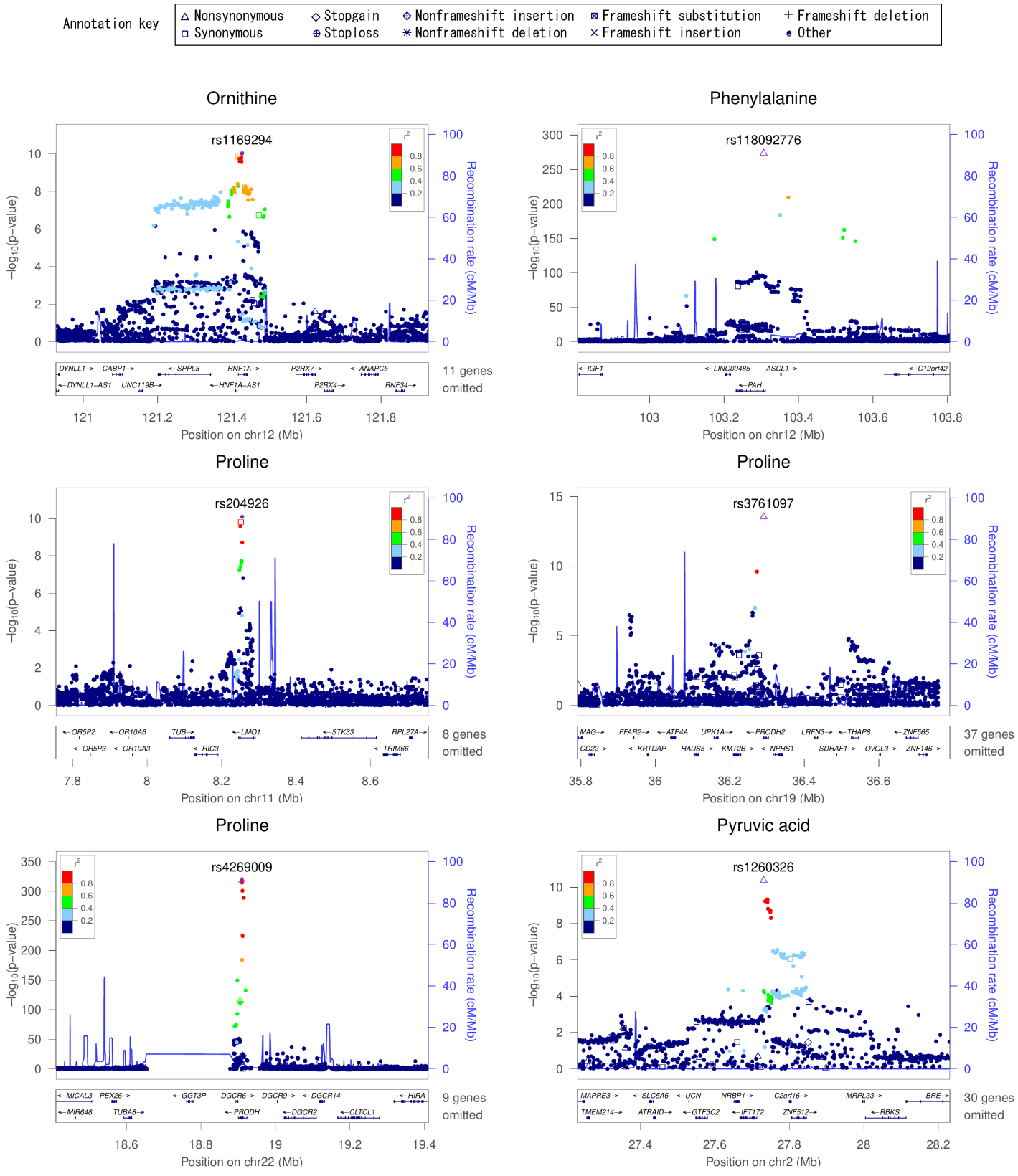


Figure S30. The region plots of identified loci in the meta-analysis with Tohoku Medical Megabank Organization (ToMMo), Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

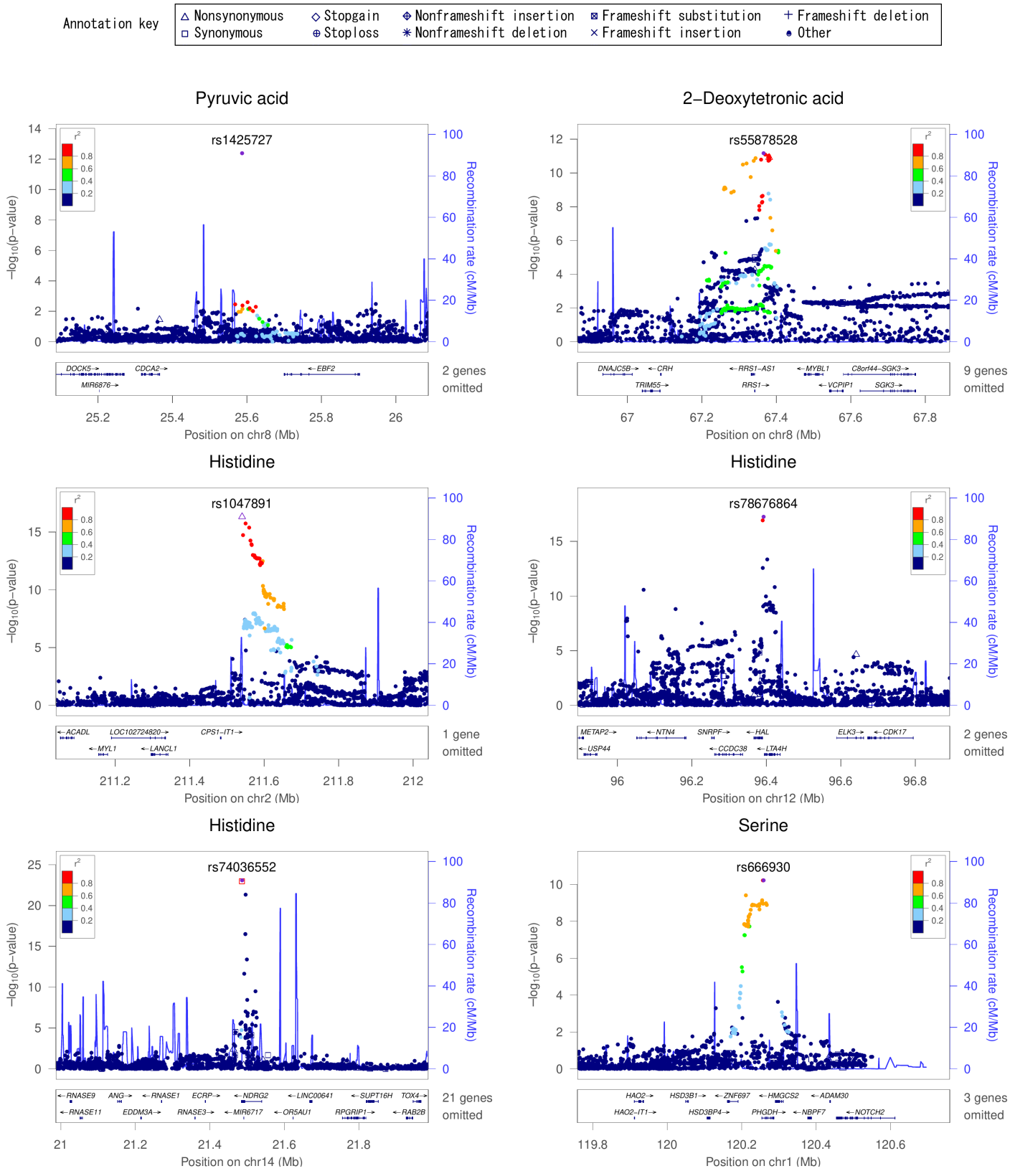


Figure S31. The region plots of identified loci in the meta-analysis with Tohoku Medical Megabank Organization (ToMMo), Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

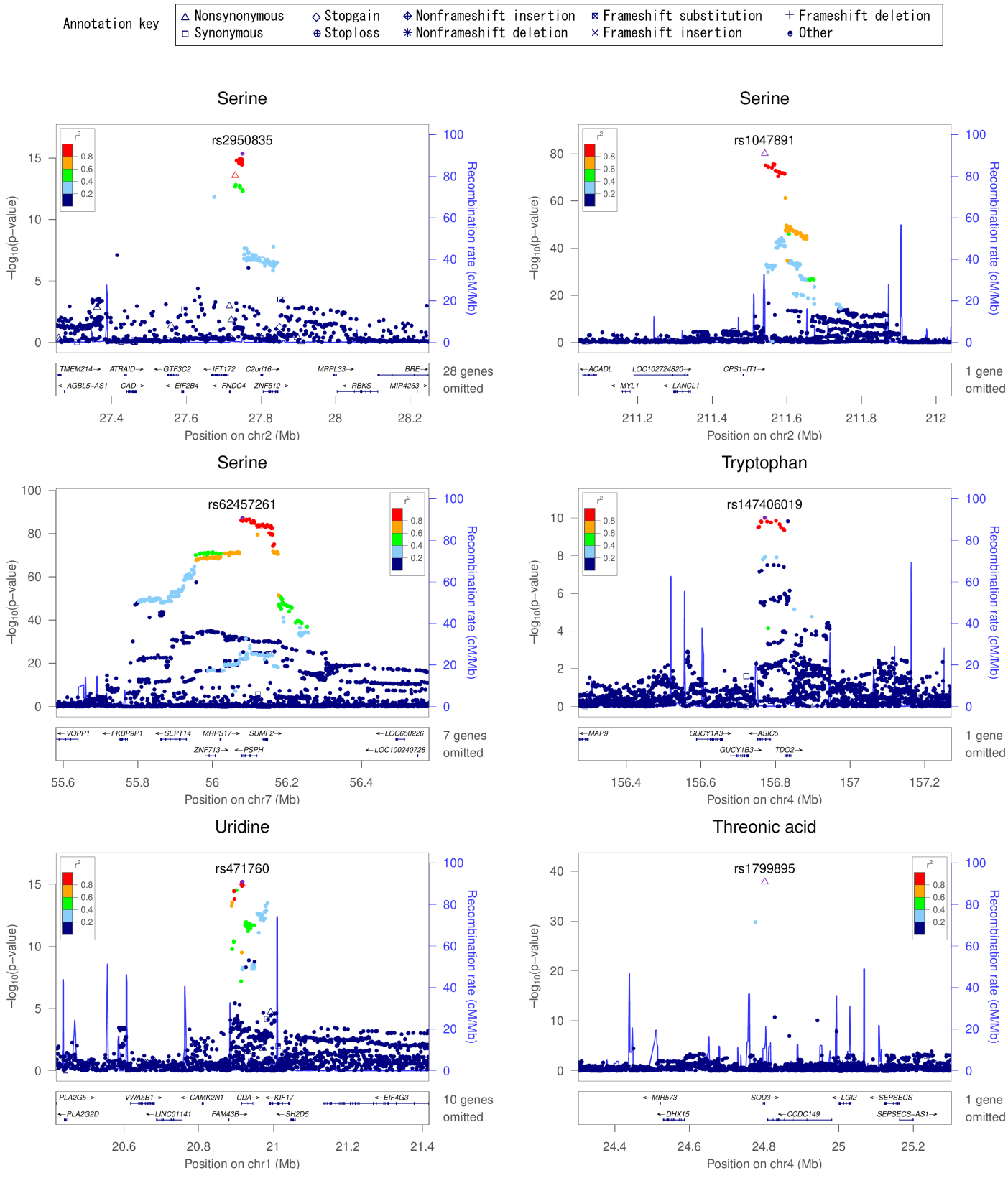


Figure S32. The region plots of identified loci in the meta-analysis with Tohoku Medical Megabank Organization (ToMMo), Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

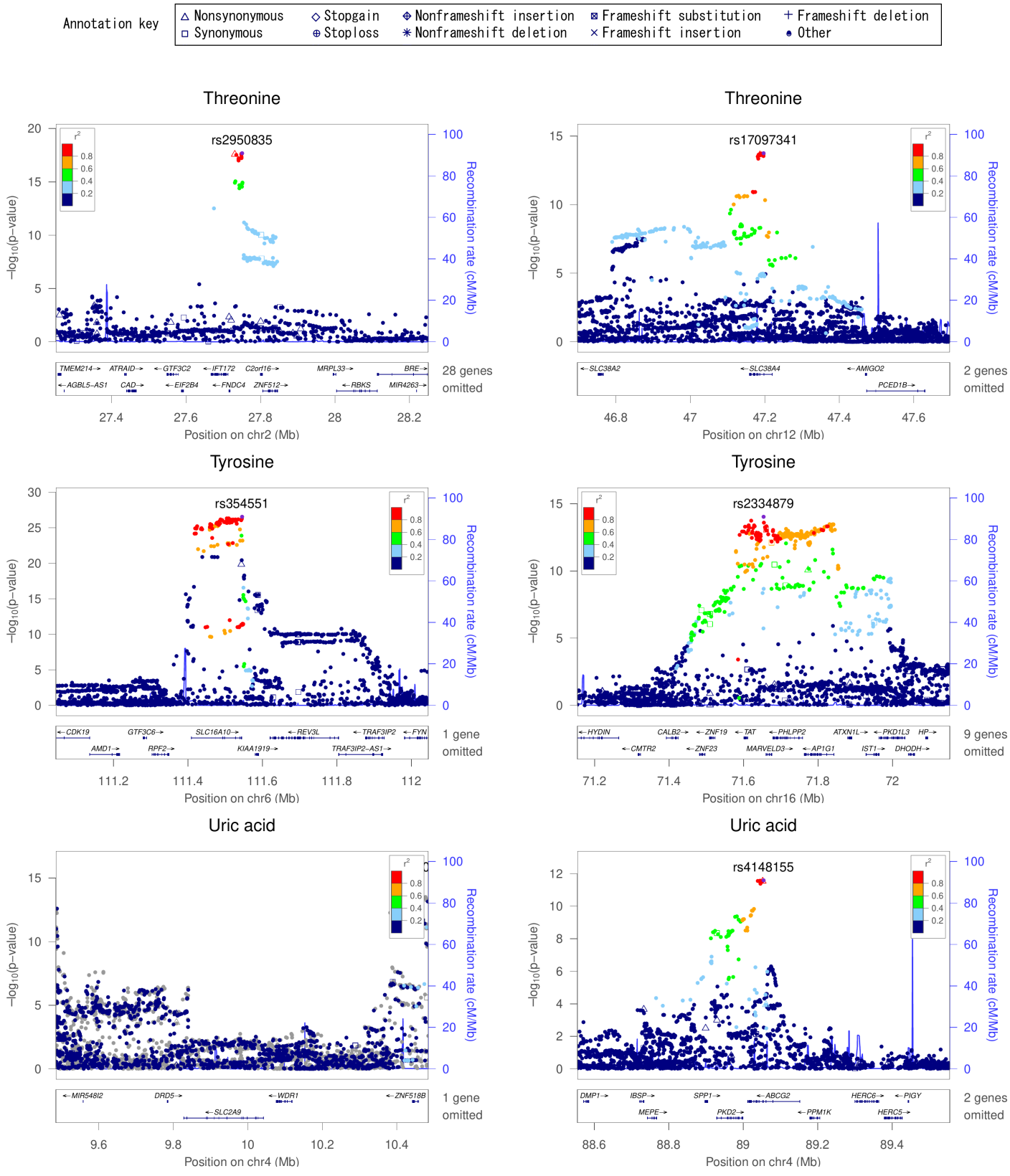


Figure S33. The region plots of identified loci in the meta-analysis with Tohoku Medical Megabank Organization (ToMMo), Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

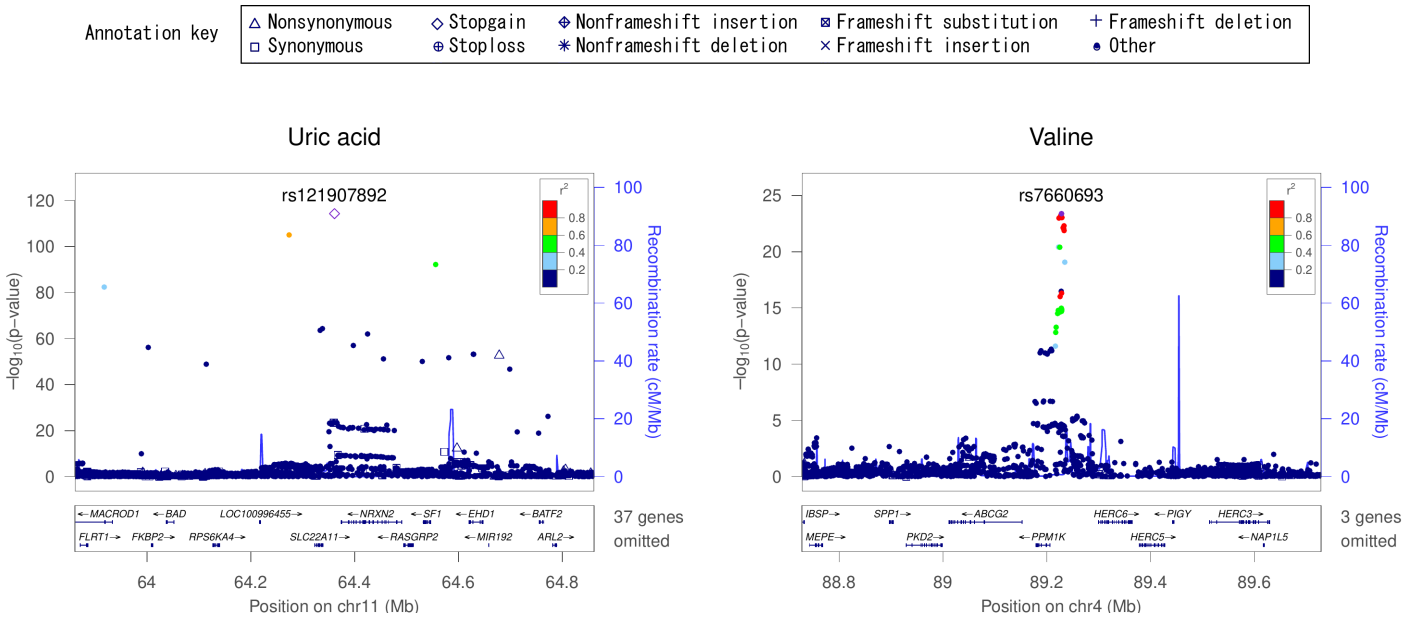


Figure S34. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

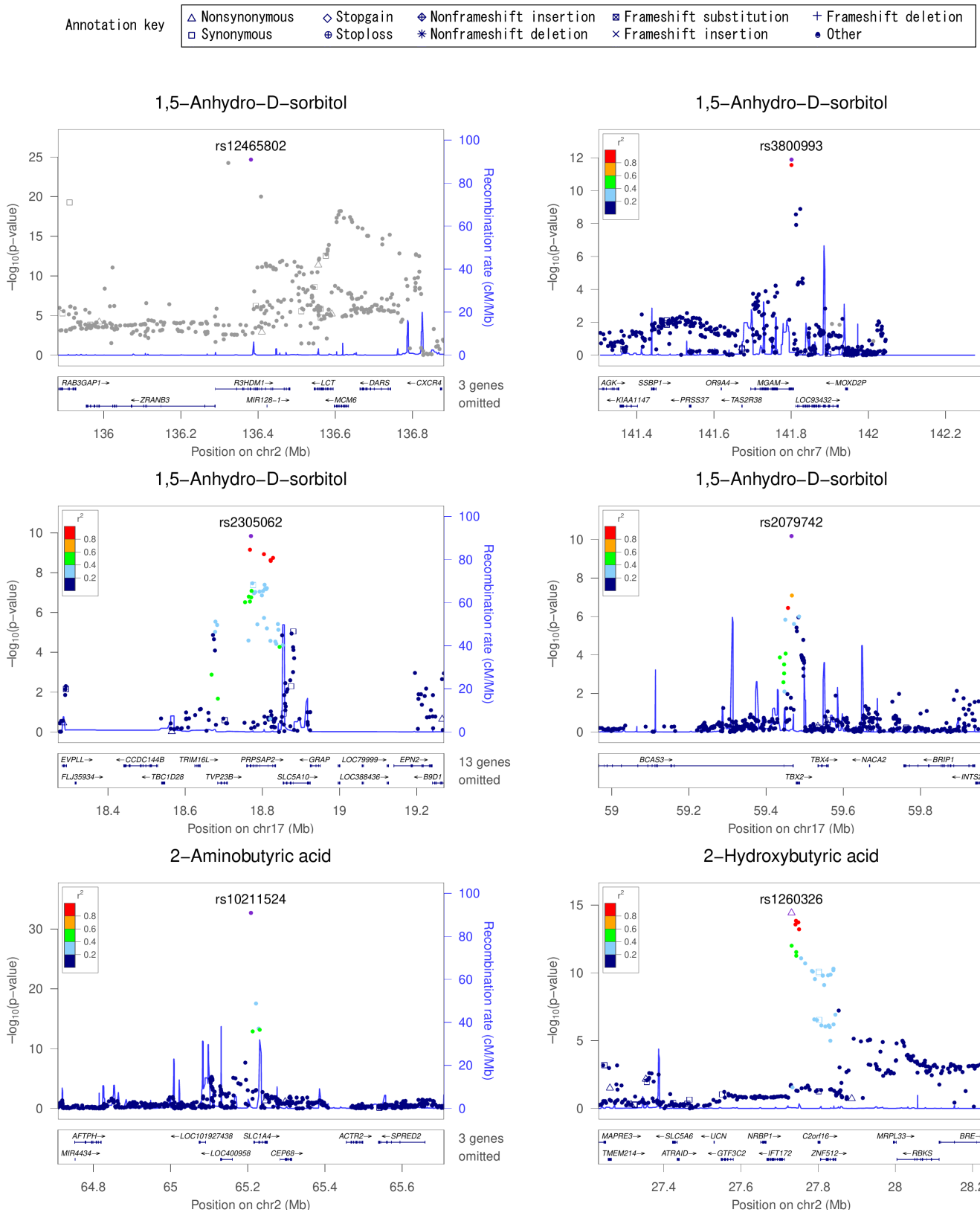


Figure S35. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

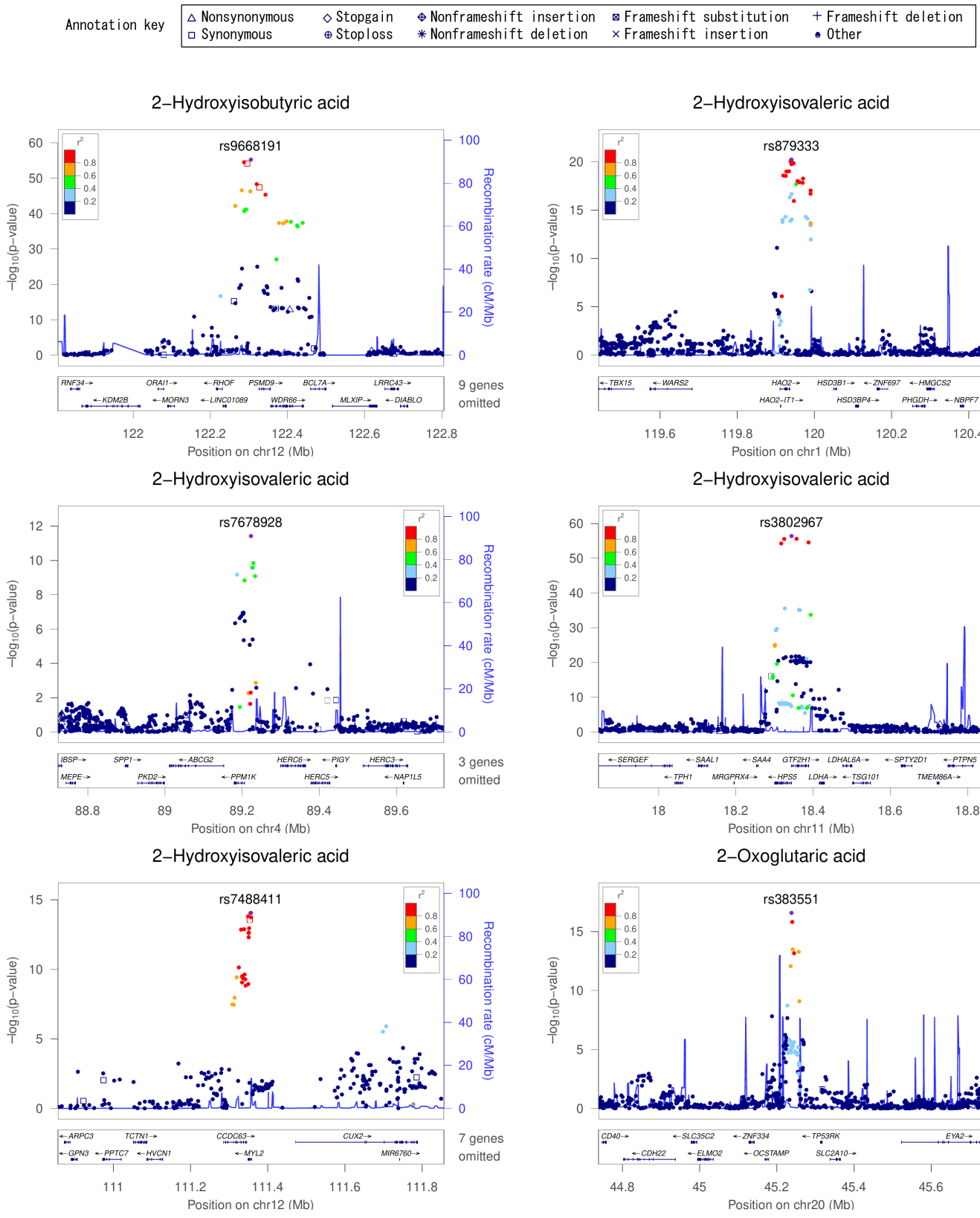
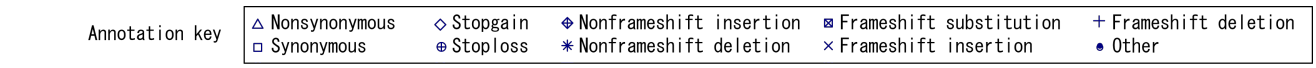
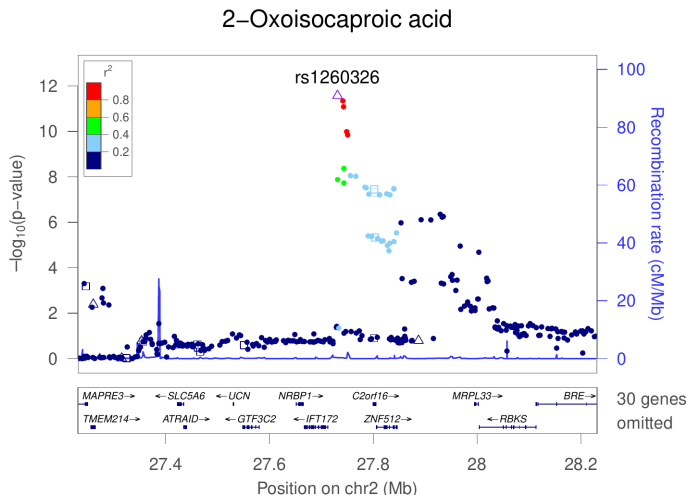
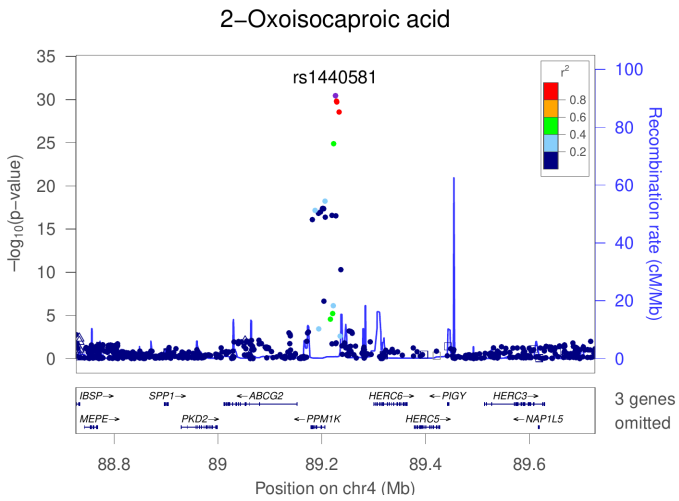


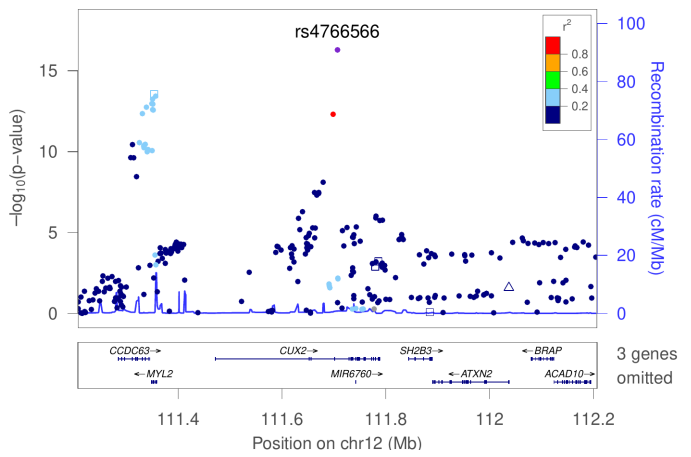
Figure S36. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

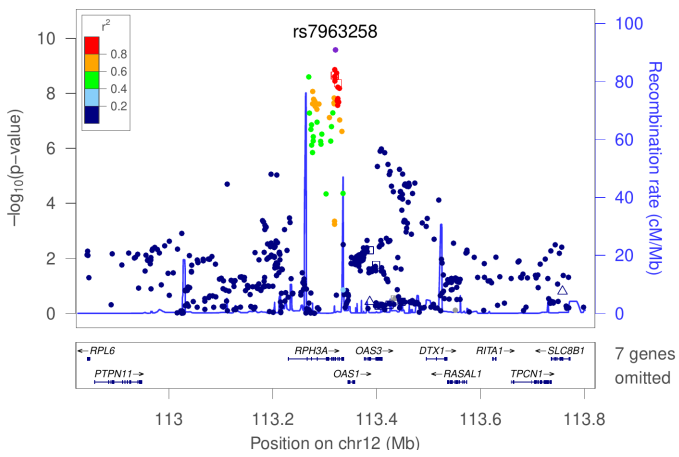
The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

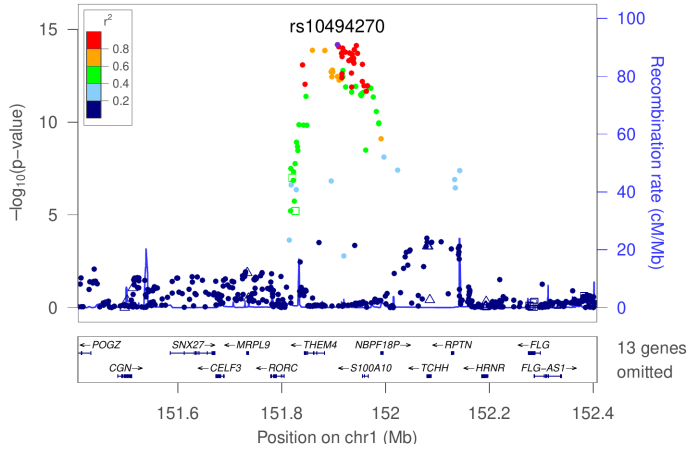












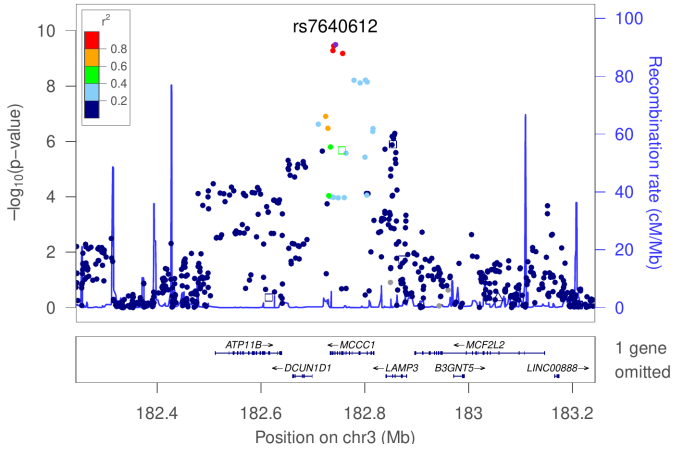


Figure S37. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

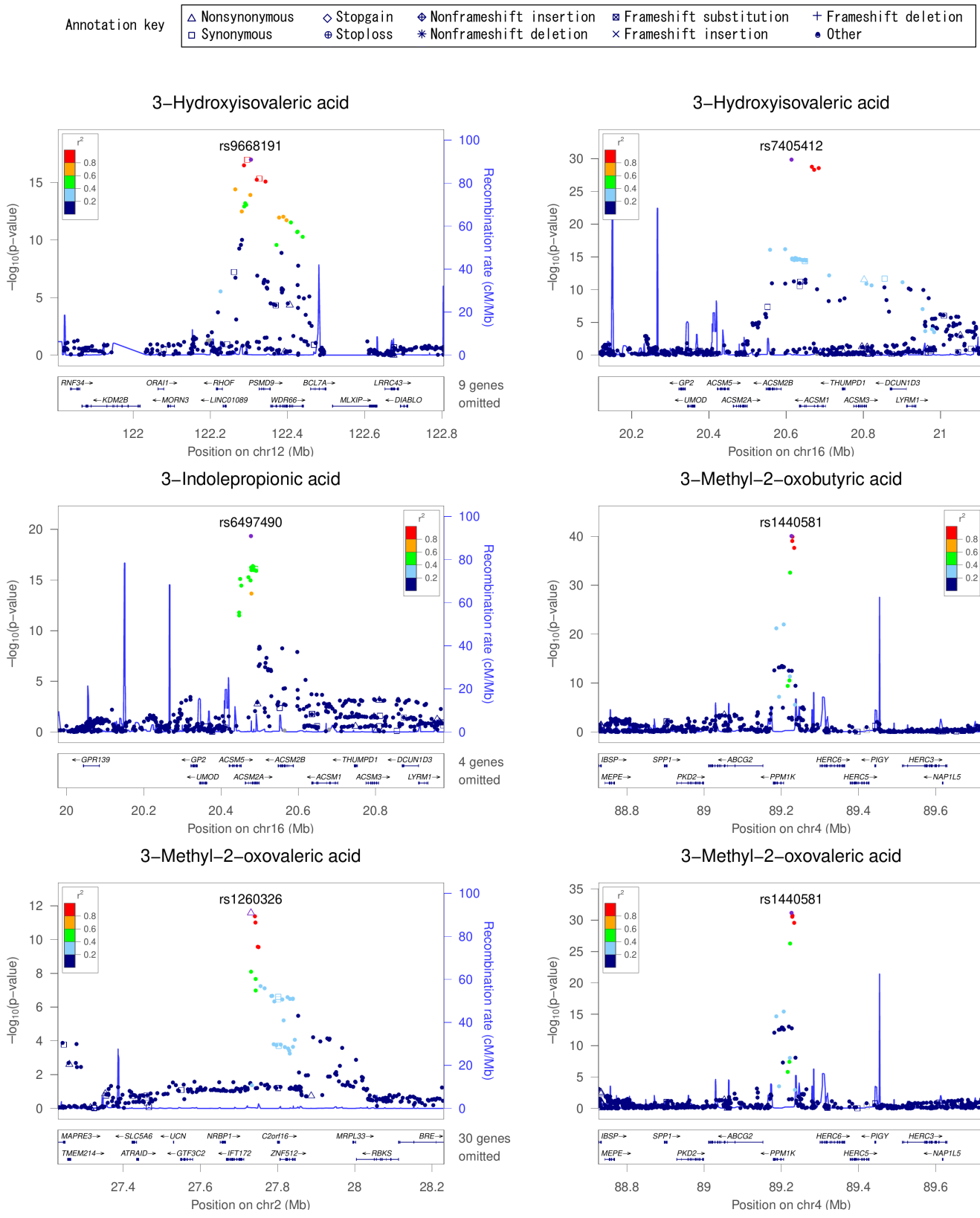


Figure S38. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

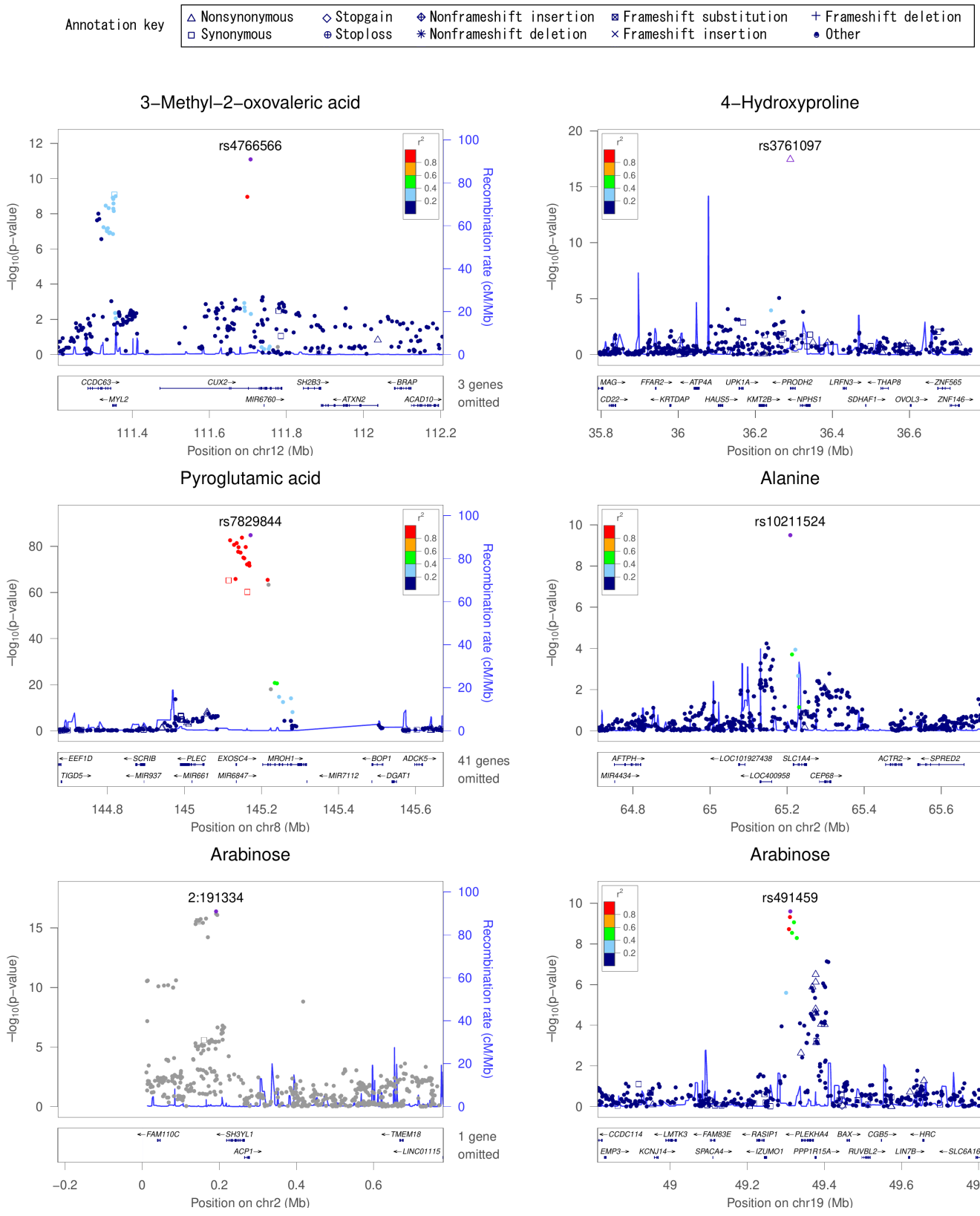
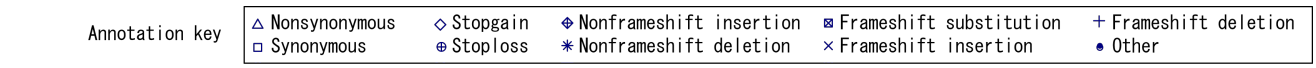
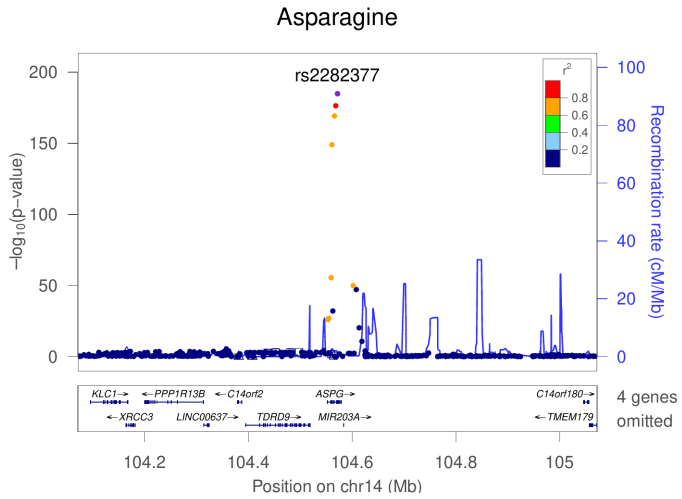
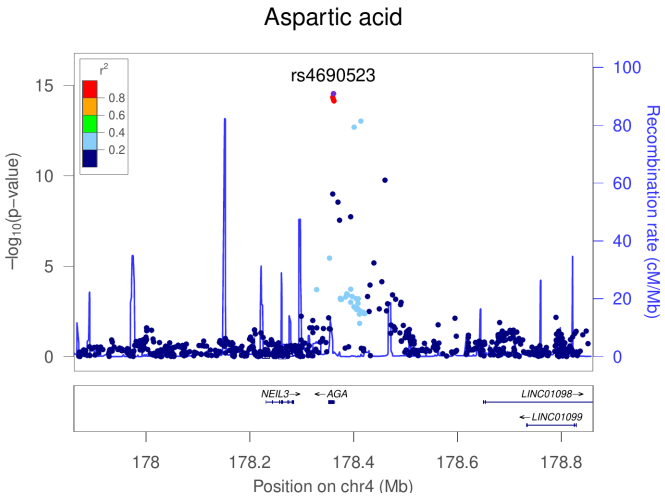


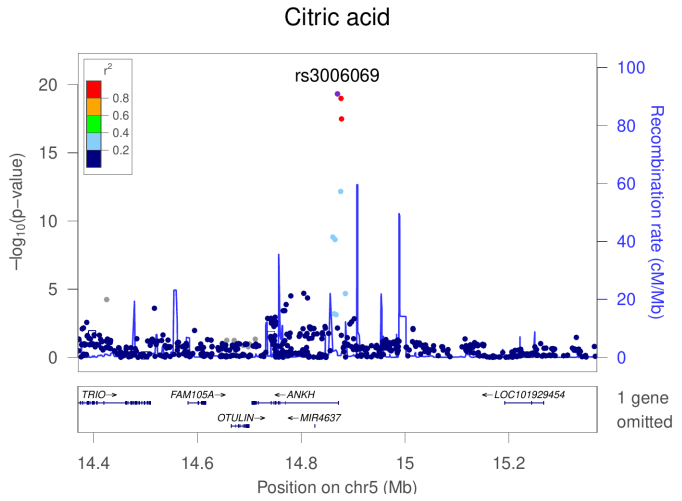
Figure S39. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

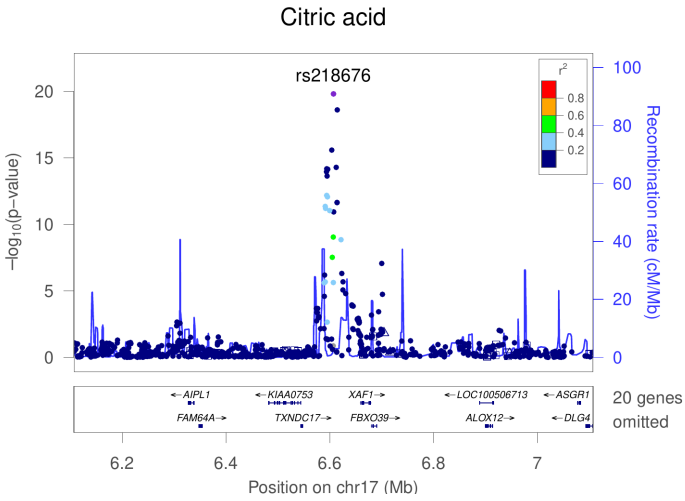
The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

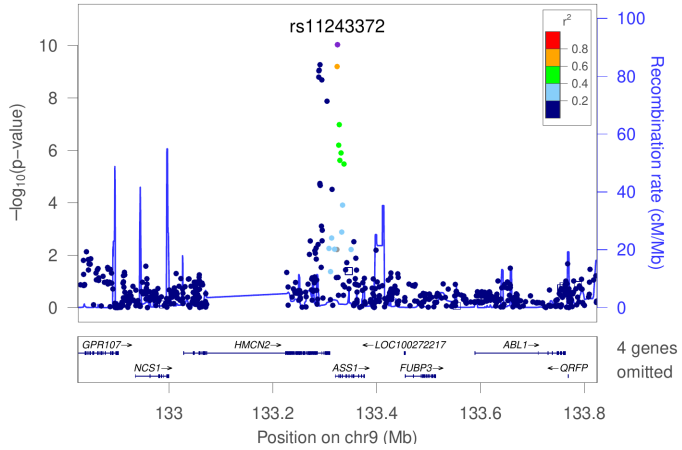












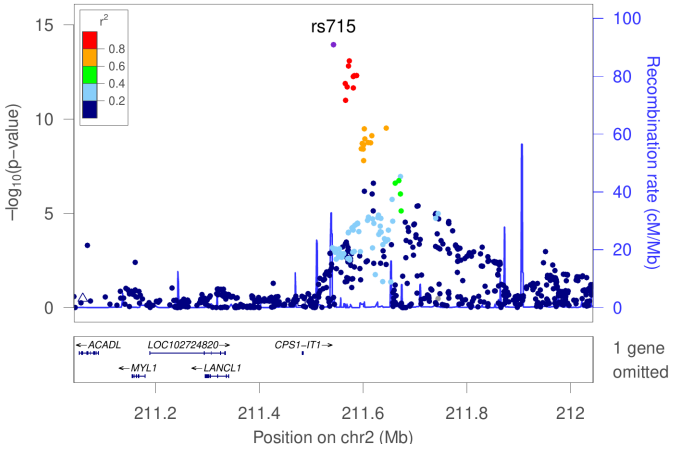
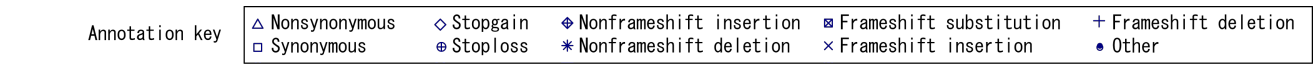
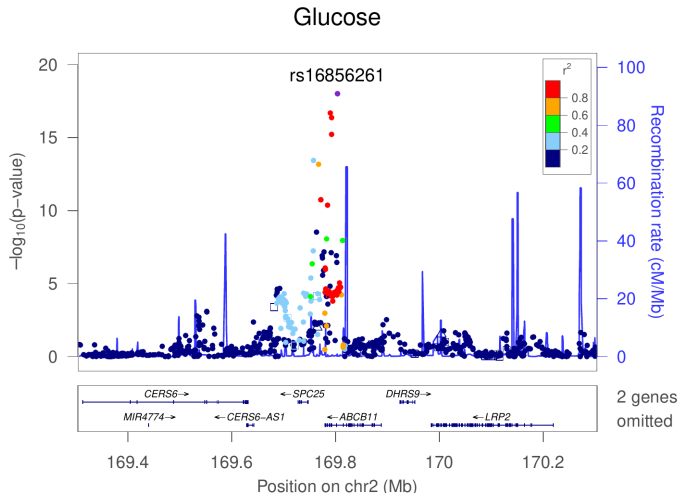
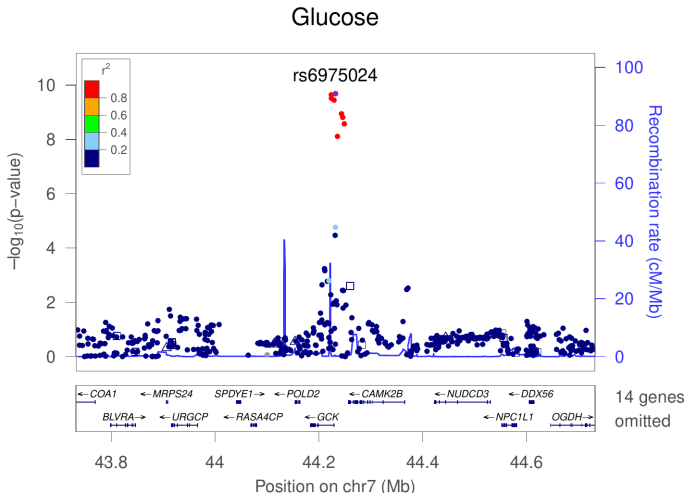


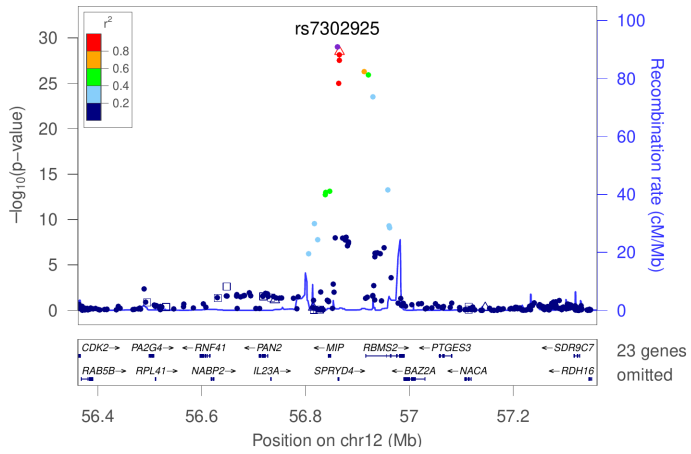
Figure S40. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

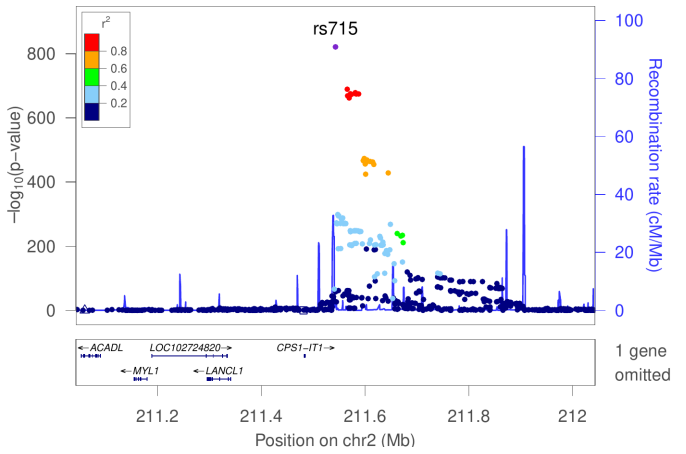
The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

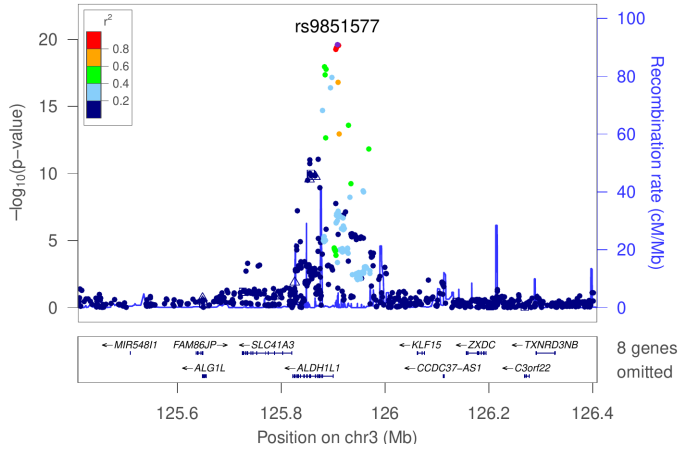












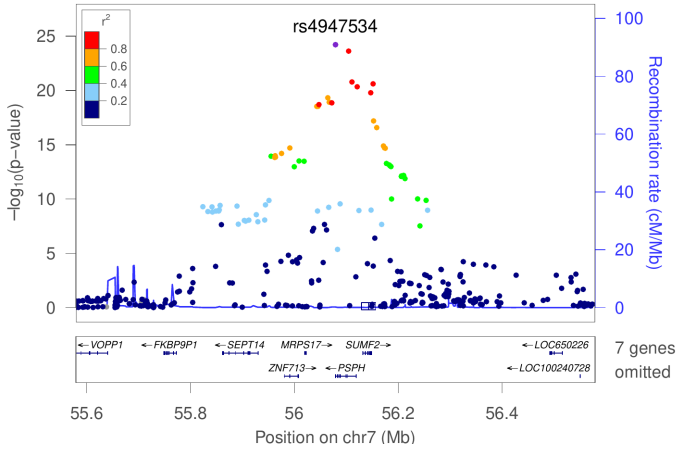


Figure S41. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

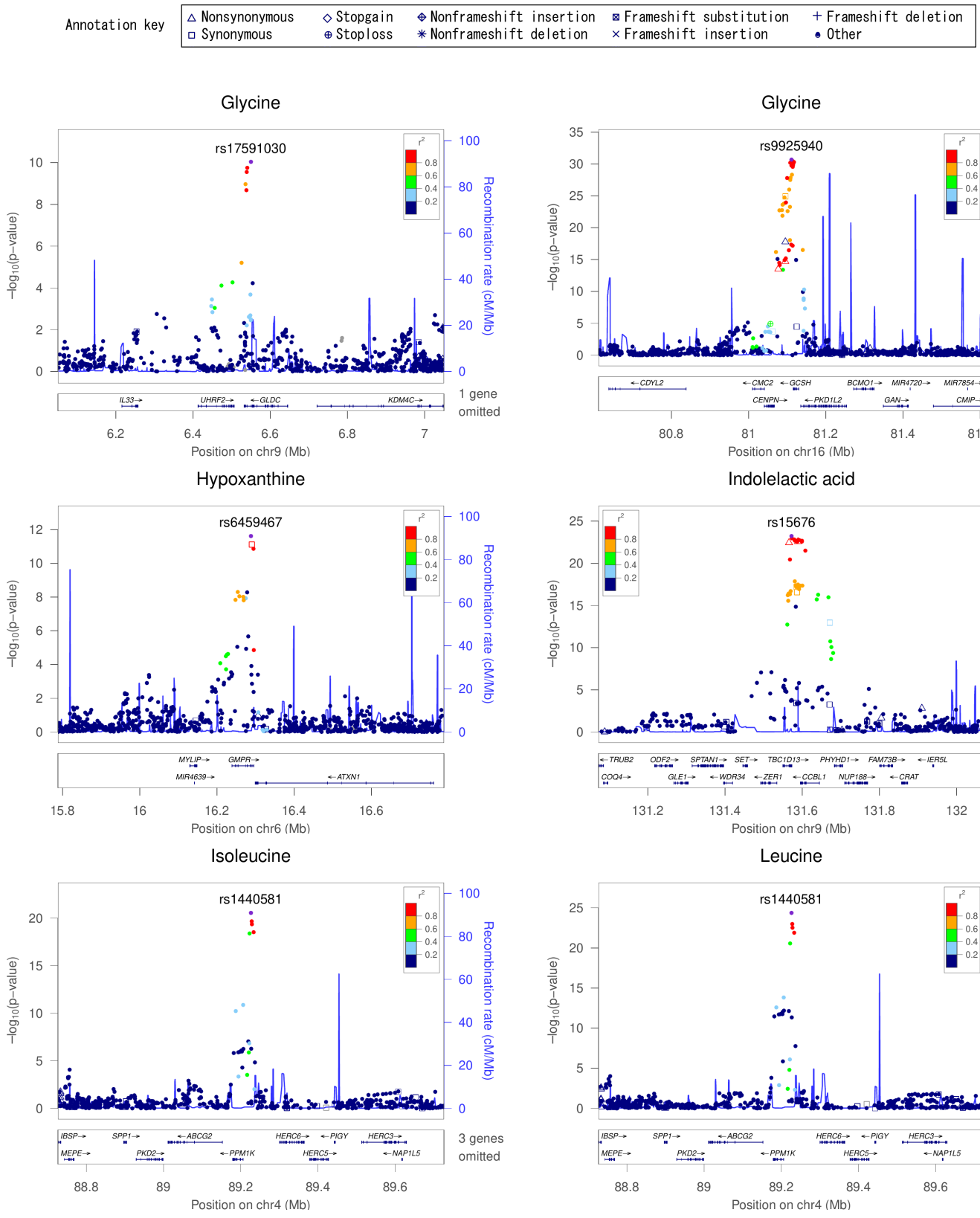


Figure S42. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

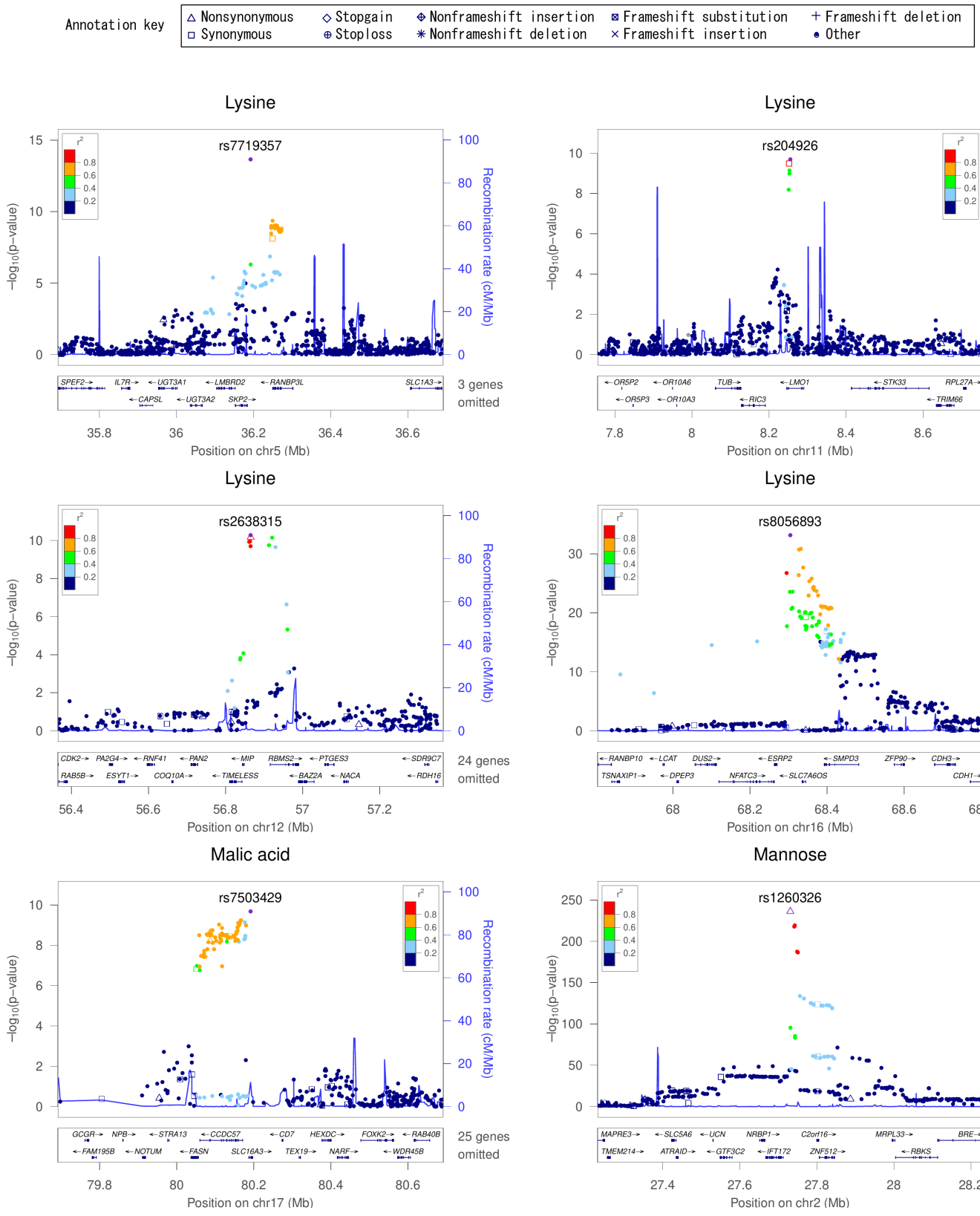


Figure S43. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

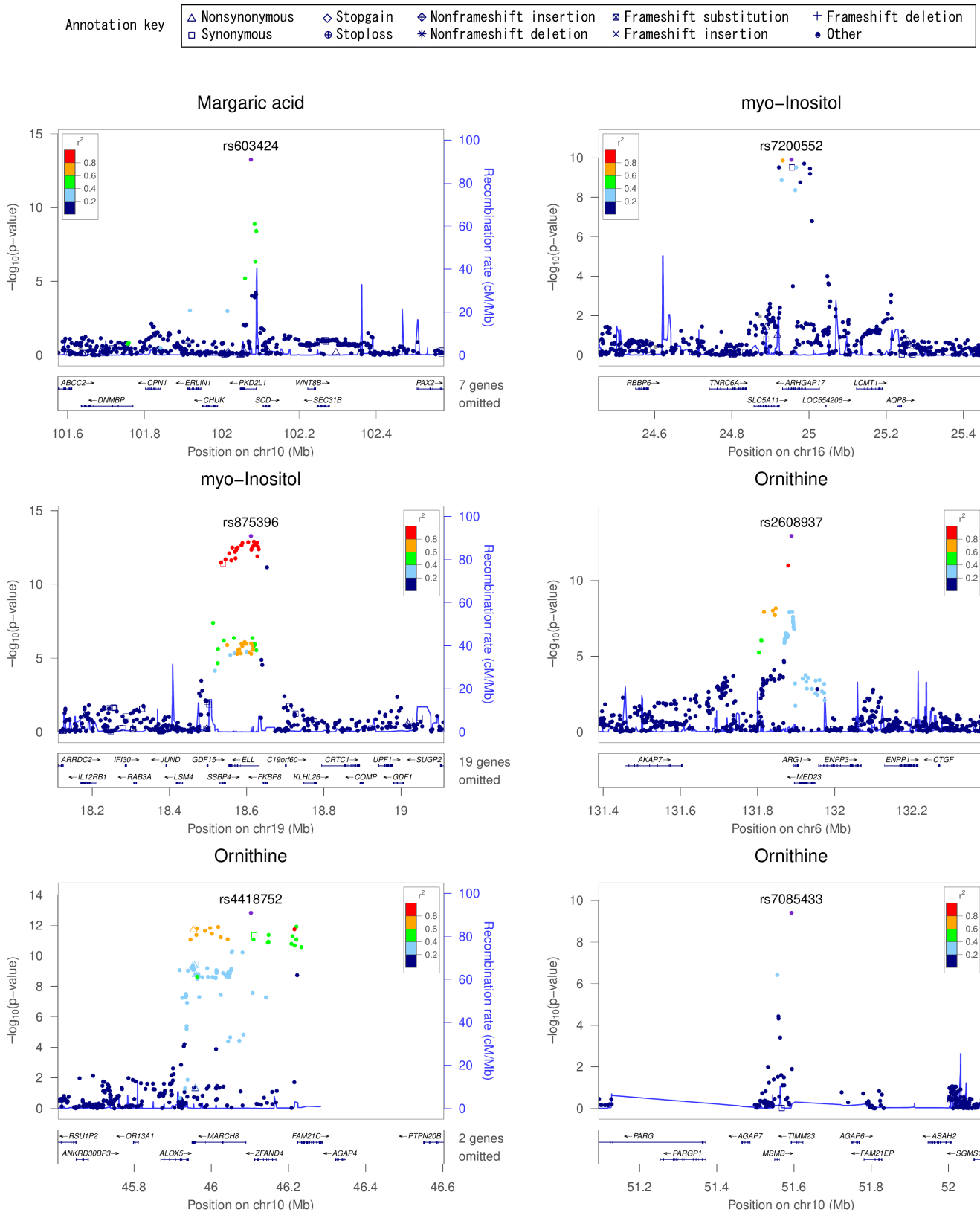


Figure S44. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

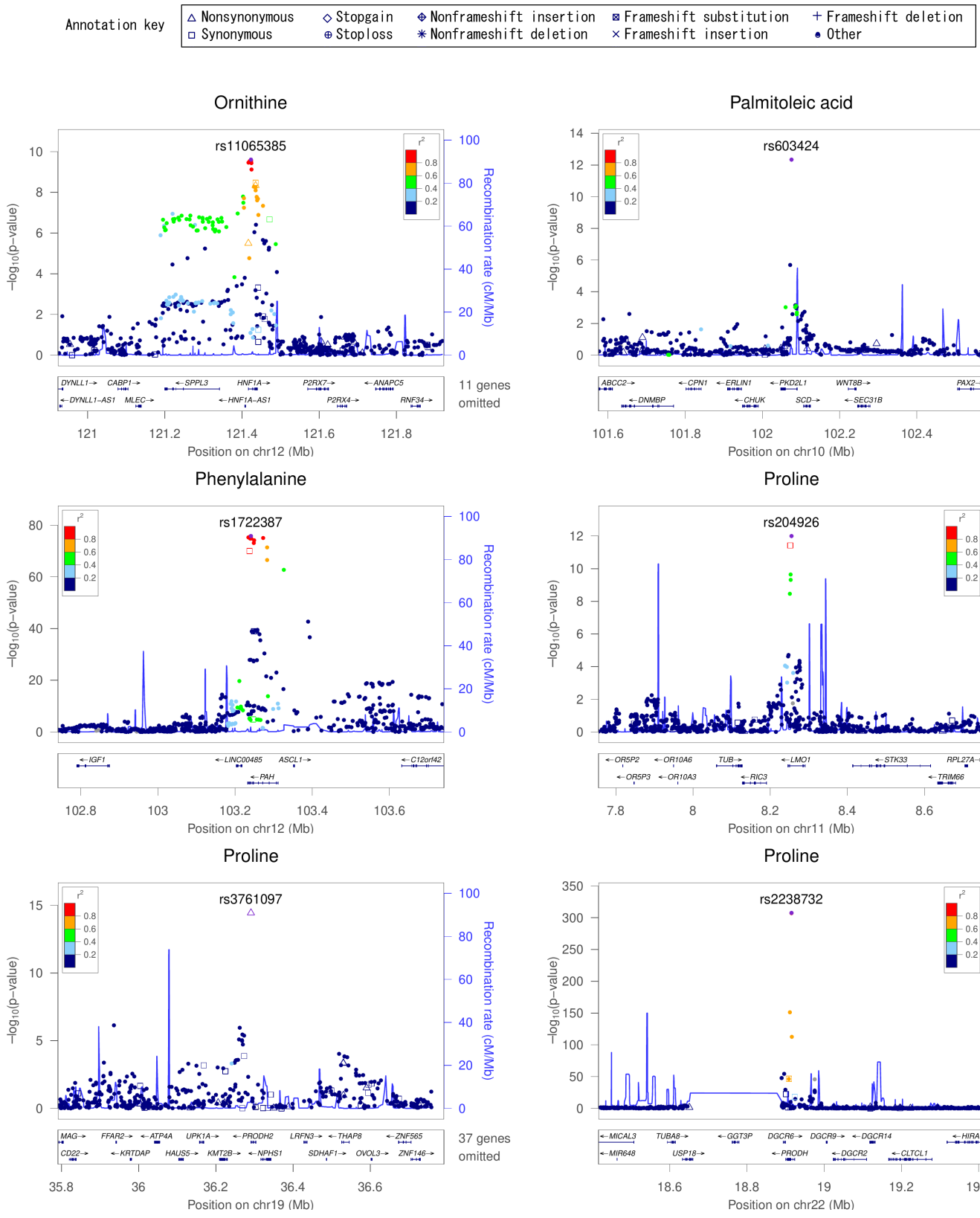
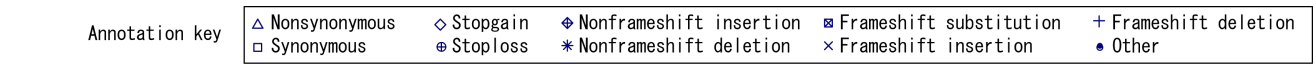
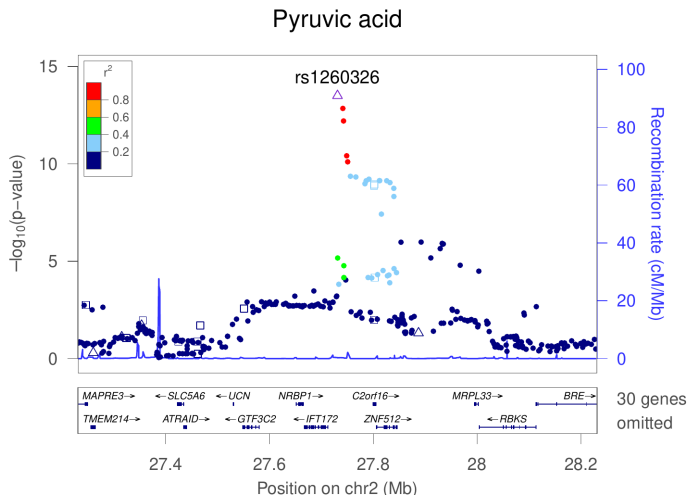
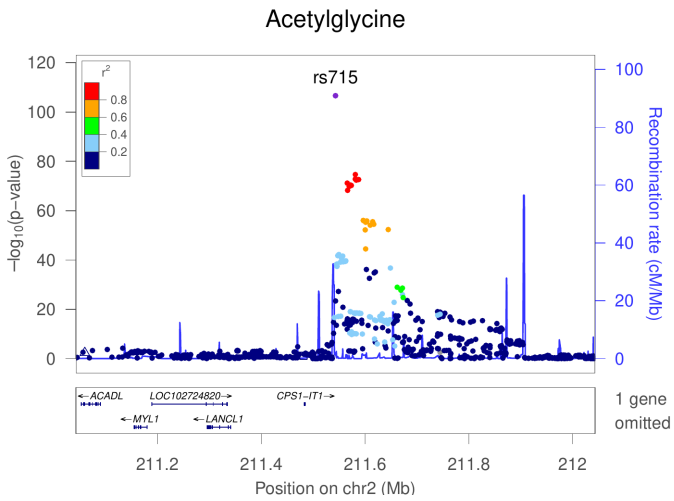


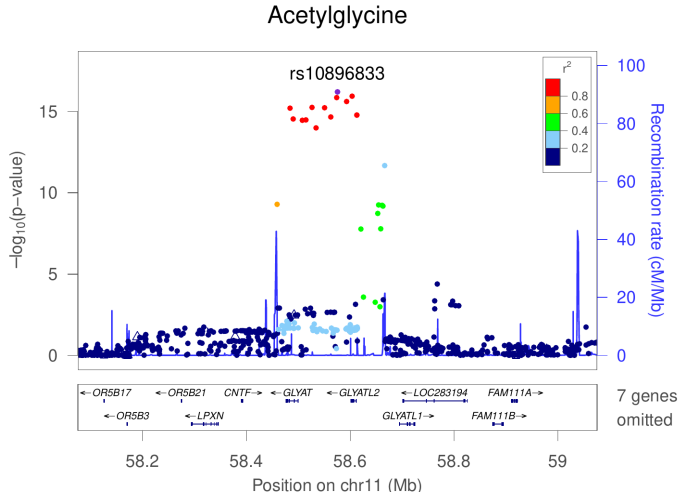
Figure S45. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

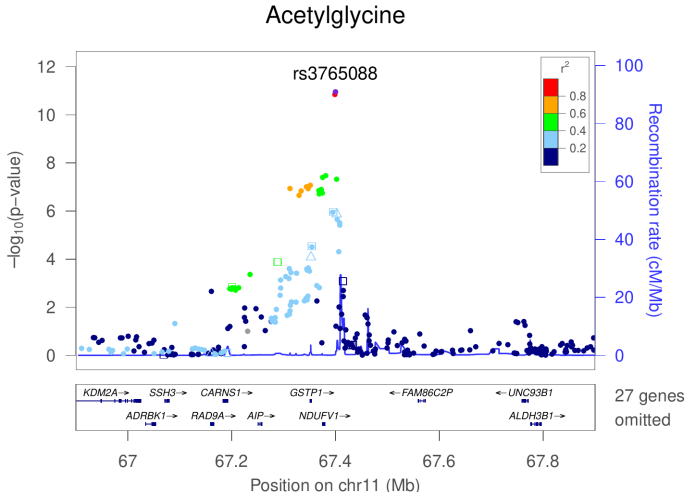
The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

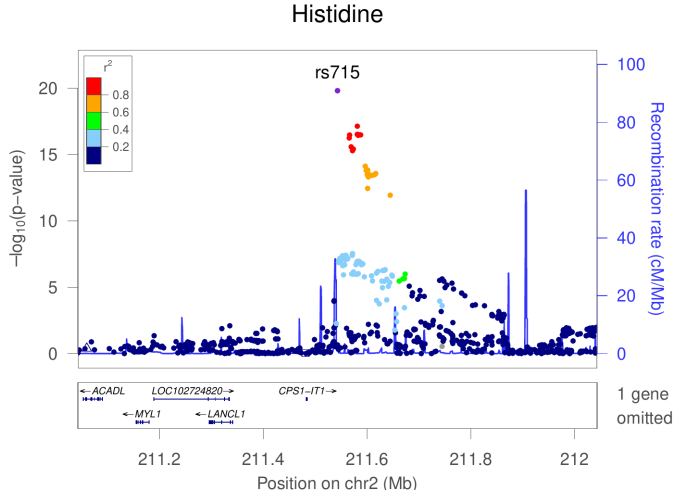












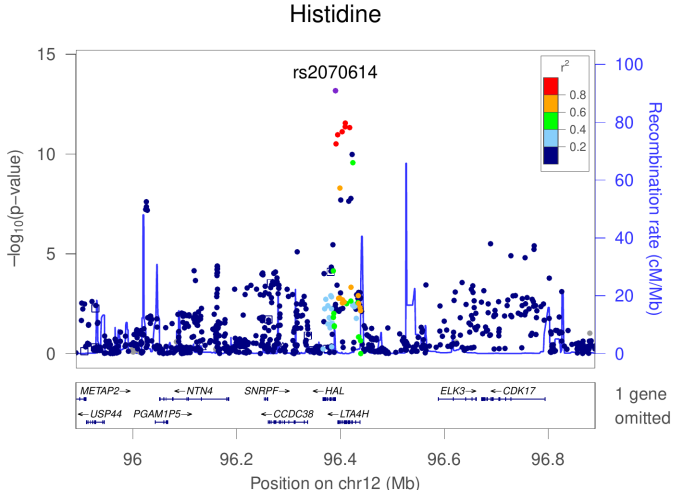
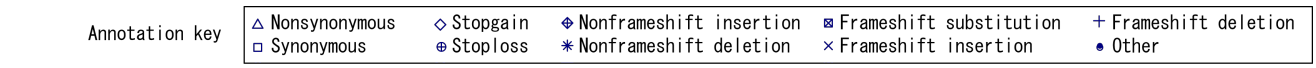
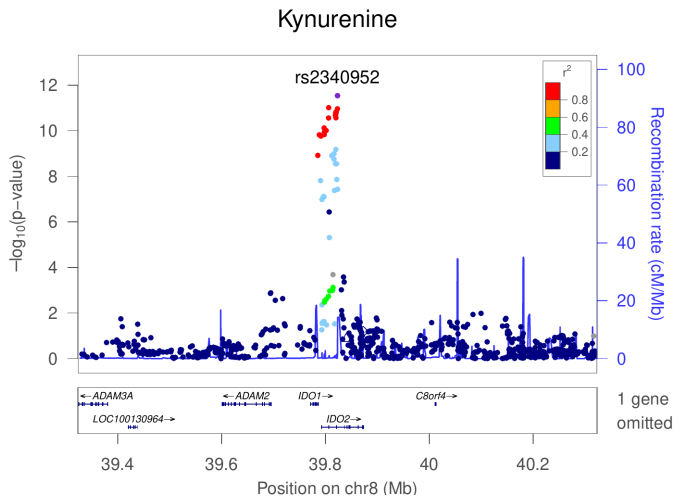
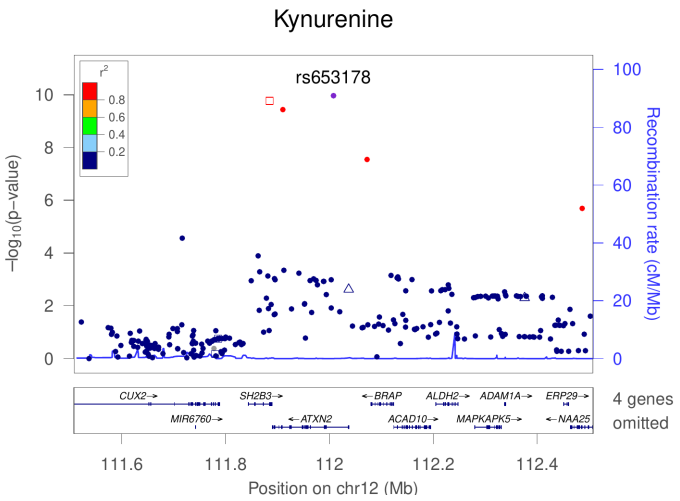


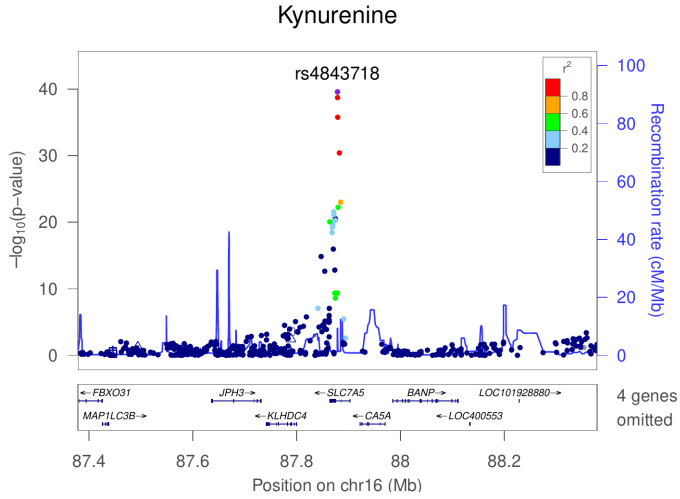
Figure S46. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

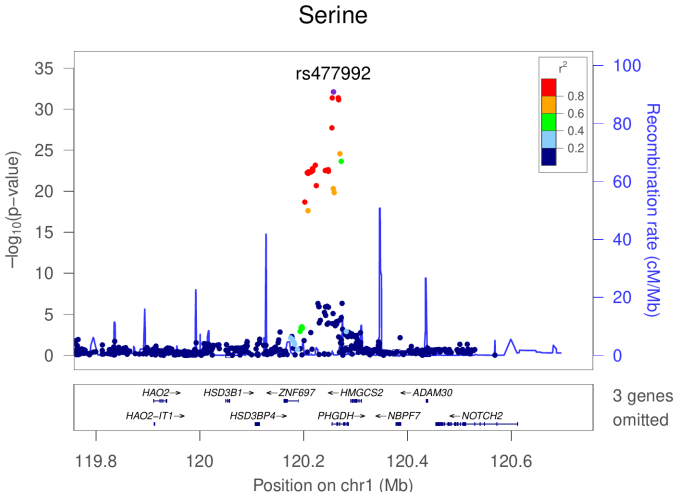
The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

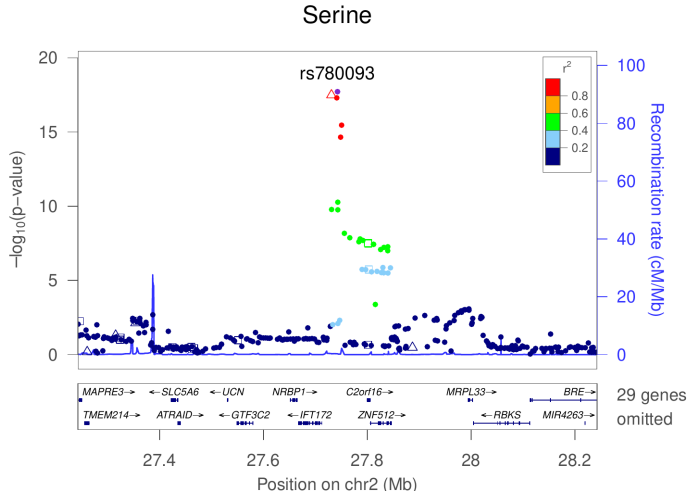












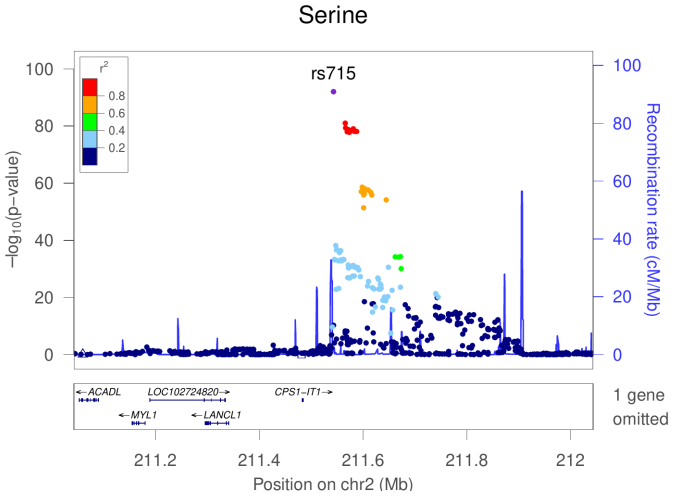


Figure S47. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

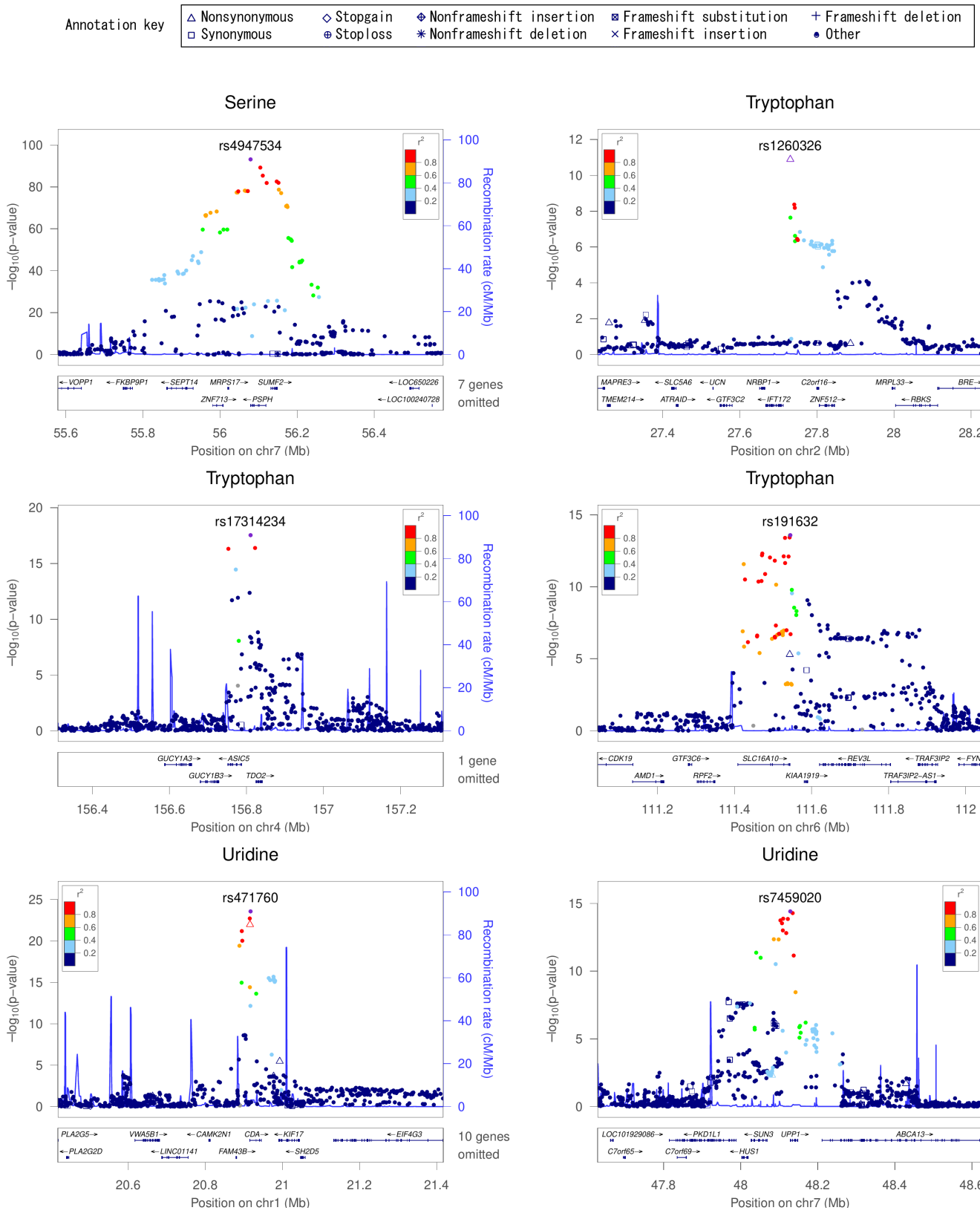
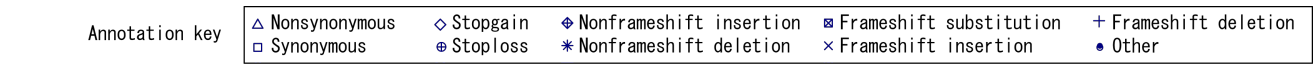
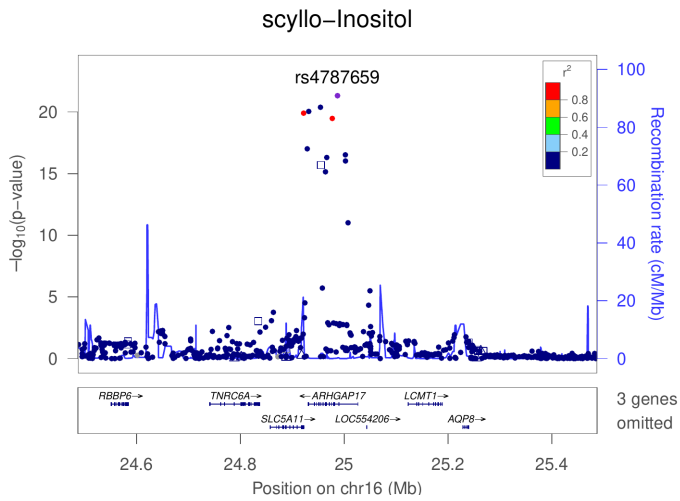
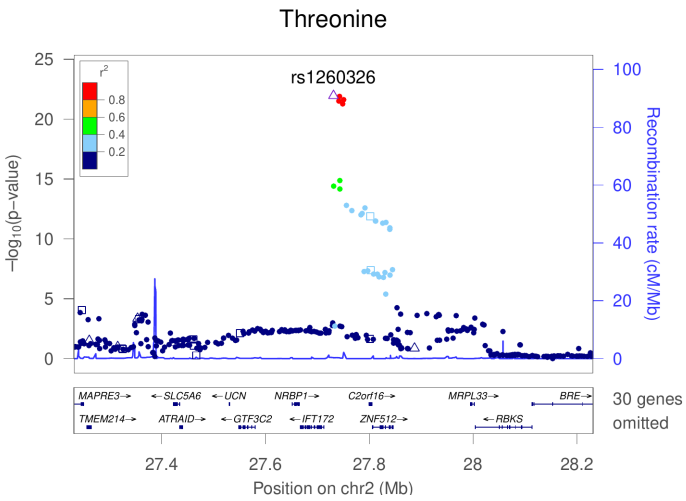


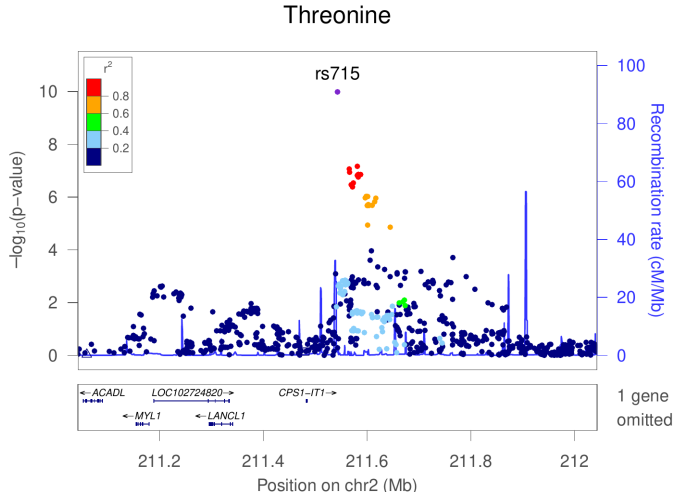
Figure S48. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

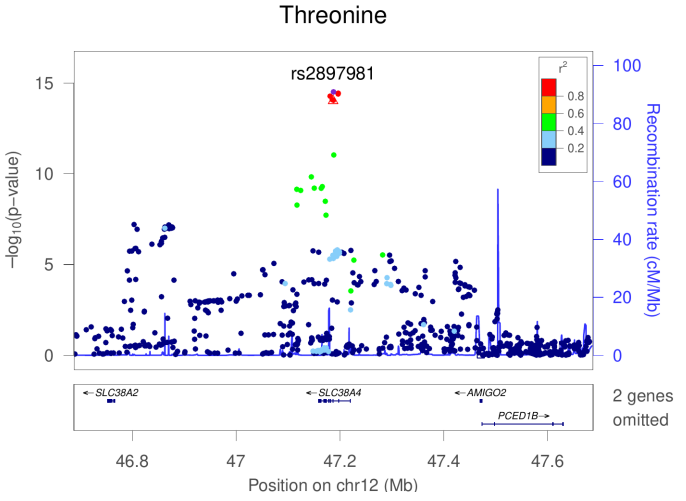
The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

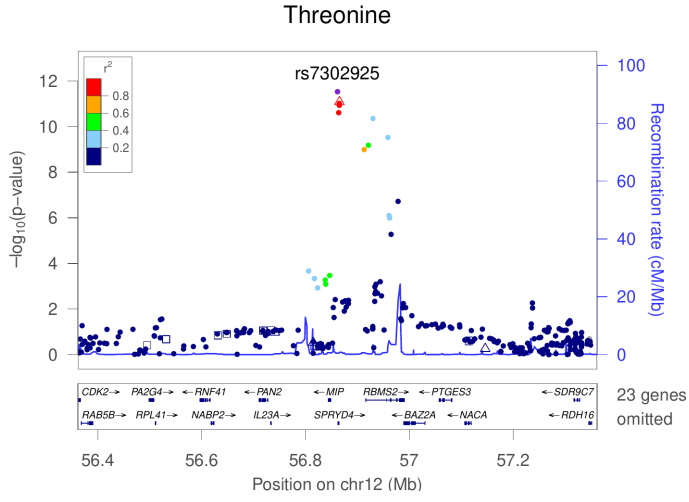












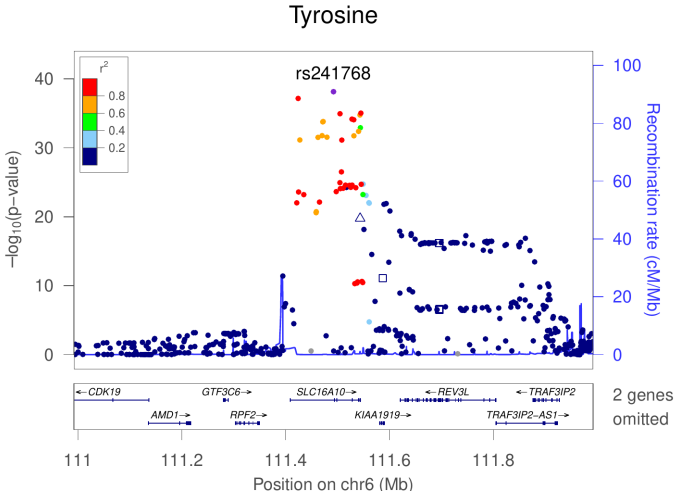


Figure S49. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

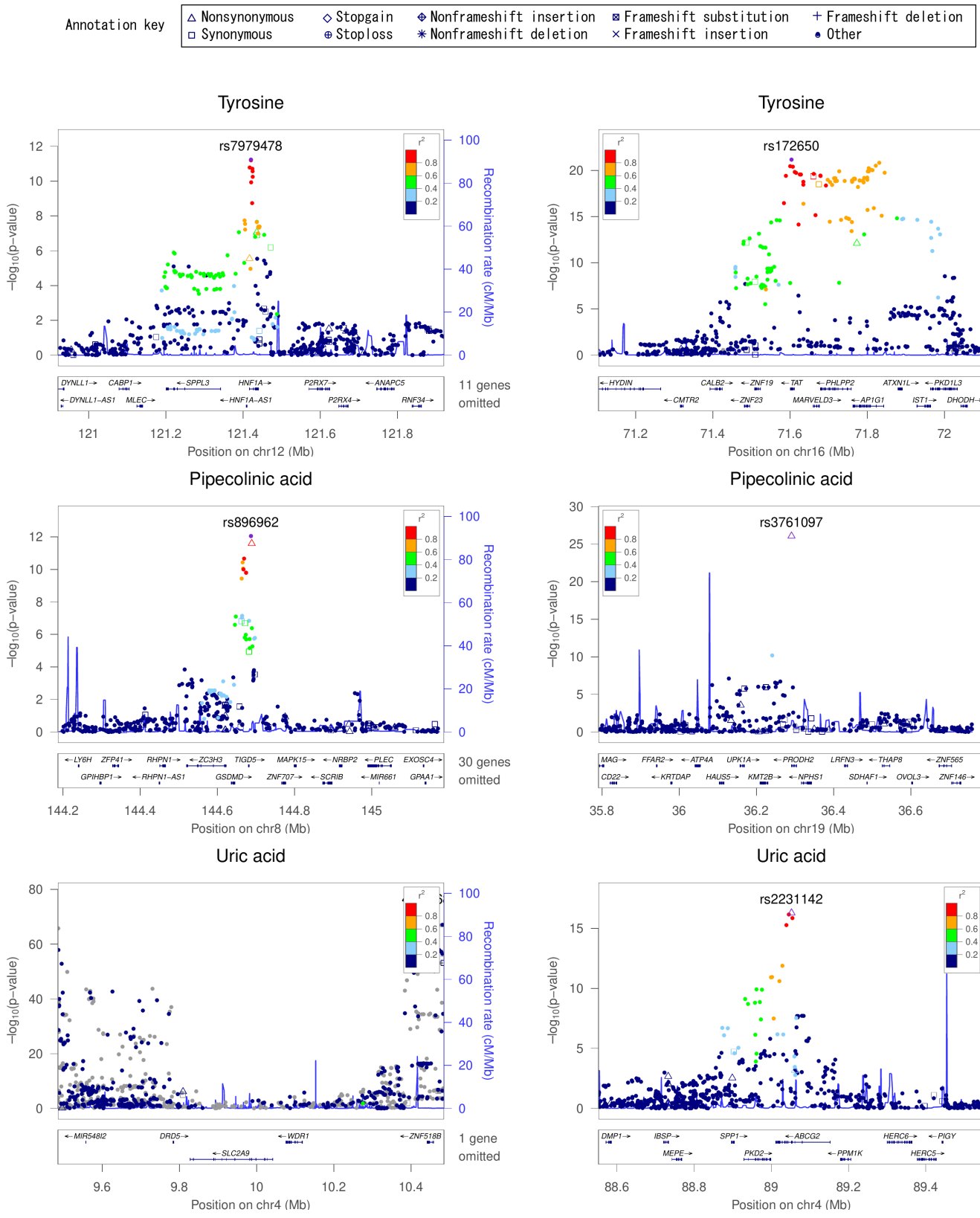


Figure S50. The region plots of identified loci in the multi-population meta-analysis, Related to Table 1

The calculated r^2 with the lead SNP in the East Asian (EAS) population (1KG Phase3) are shown in color. The gray plots indicate the lead SNP or the corresponding SNP was a monomorphic variant.

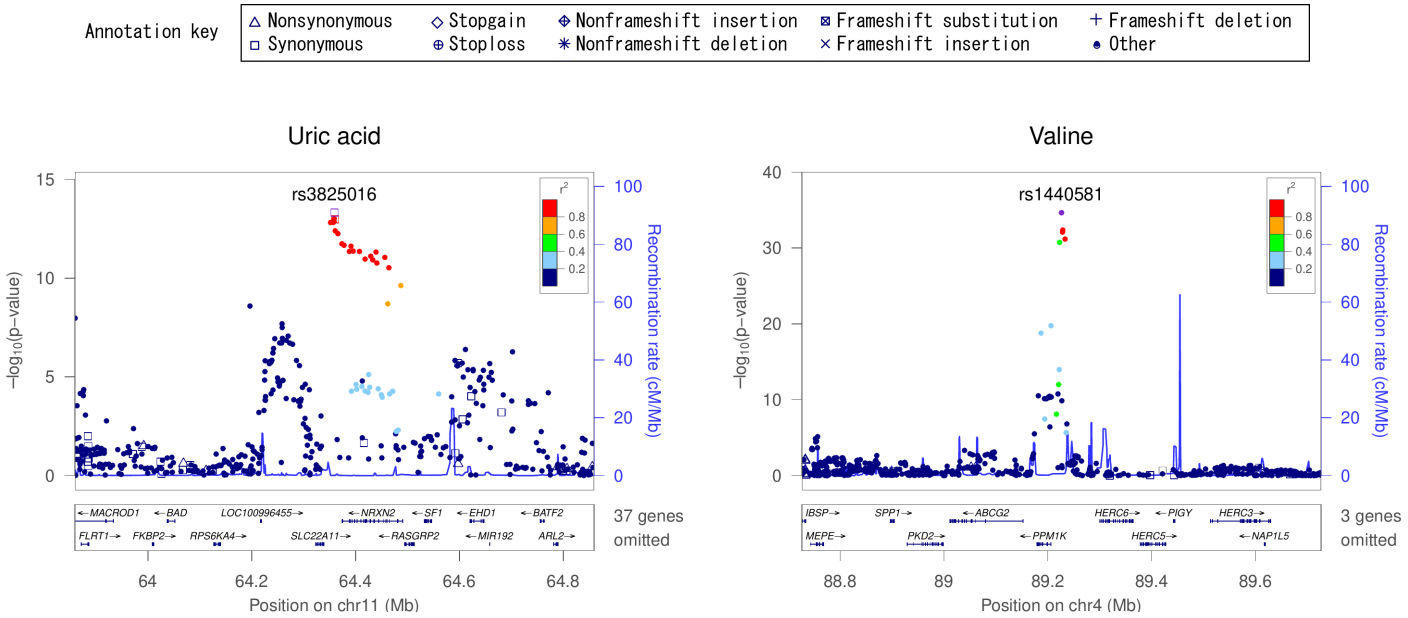
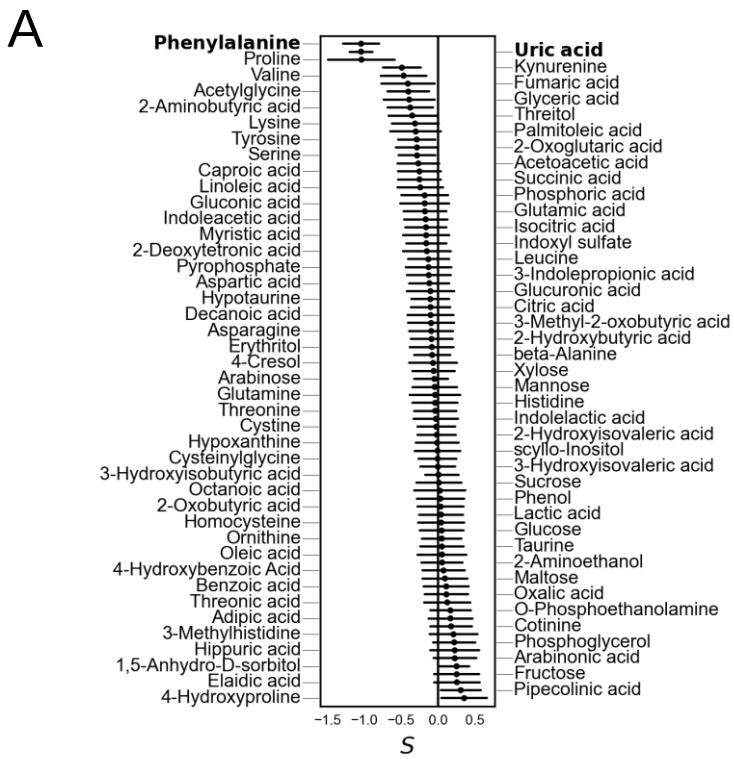
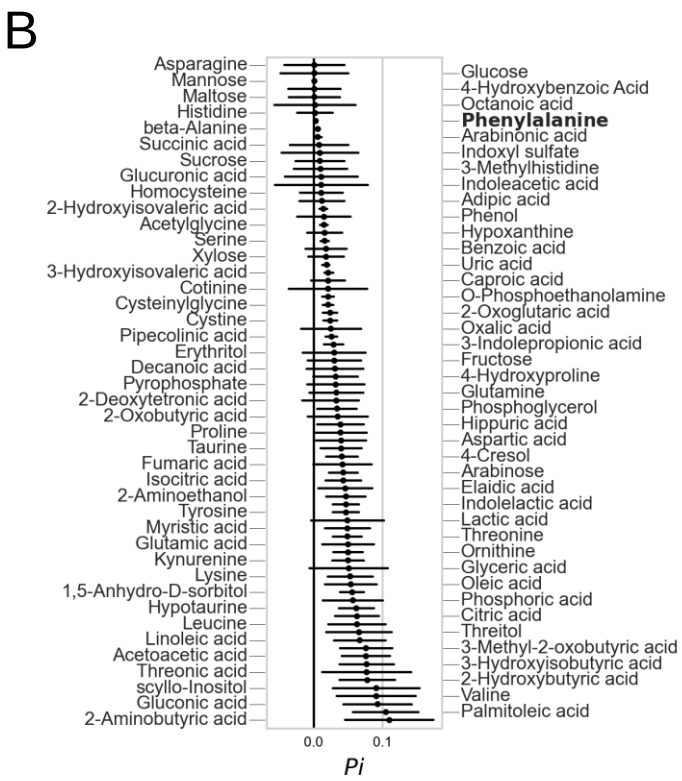
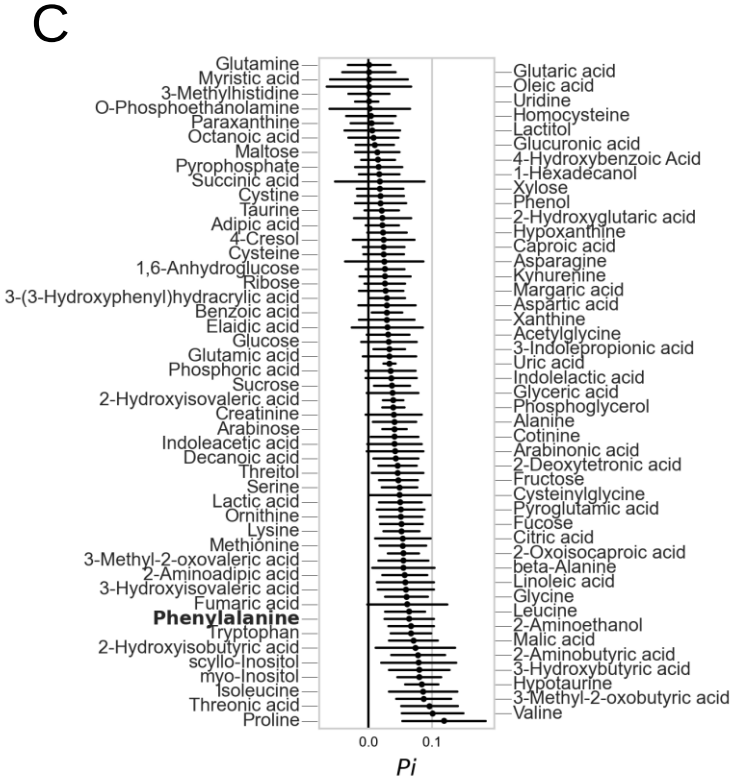


Figure S51. Selection signature and polygenicity for each metabolite estimated by BayesS model using genome-wide SNPs, Related to Figure 5







A. Selection signature for each metabolite estimated by BayesS model using genome-wide SNPs. The metabolite in bold font showed significant selection signature.
B. Polygenicity for each metabolite estimated by BayesS model using genome-wide SNPs.
C. Polygenicity for each metabolite estimated by BayesS model using genome-wide SNPs excluding the corresponding metabolites' QTL and regions with pleiotrophic effect on multiple metabolites.

Figure S52. Validation of metabolite measurement, Related to STAR Methods

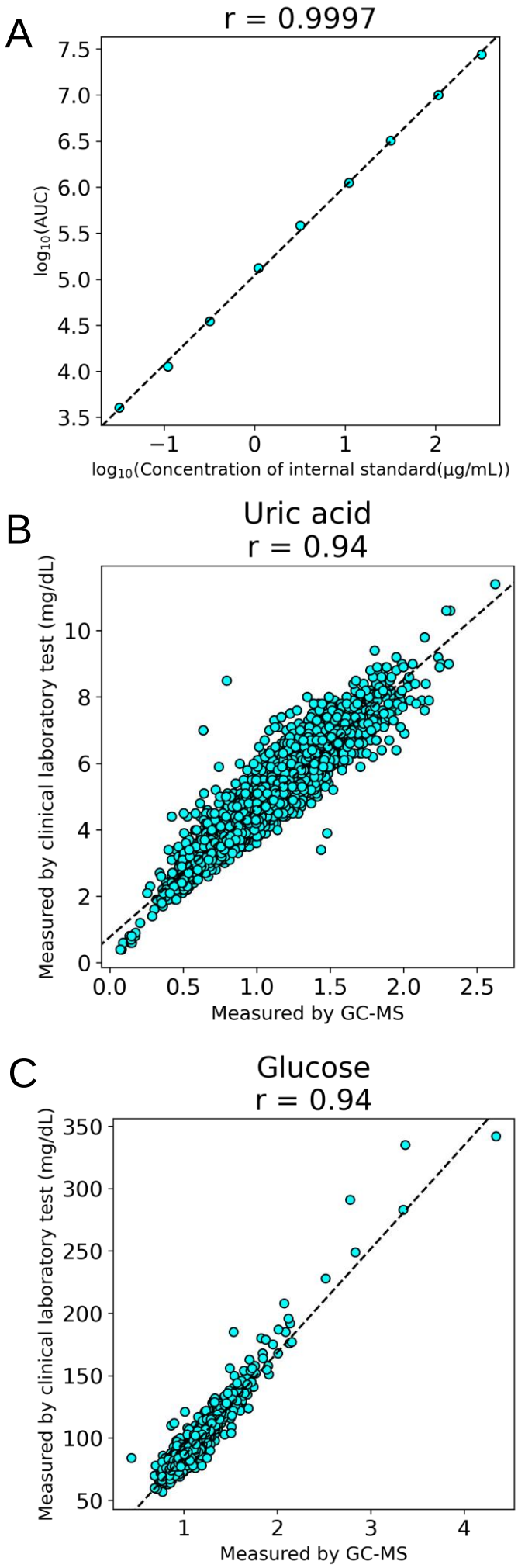
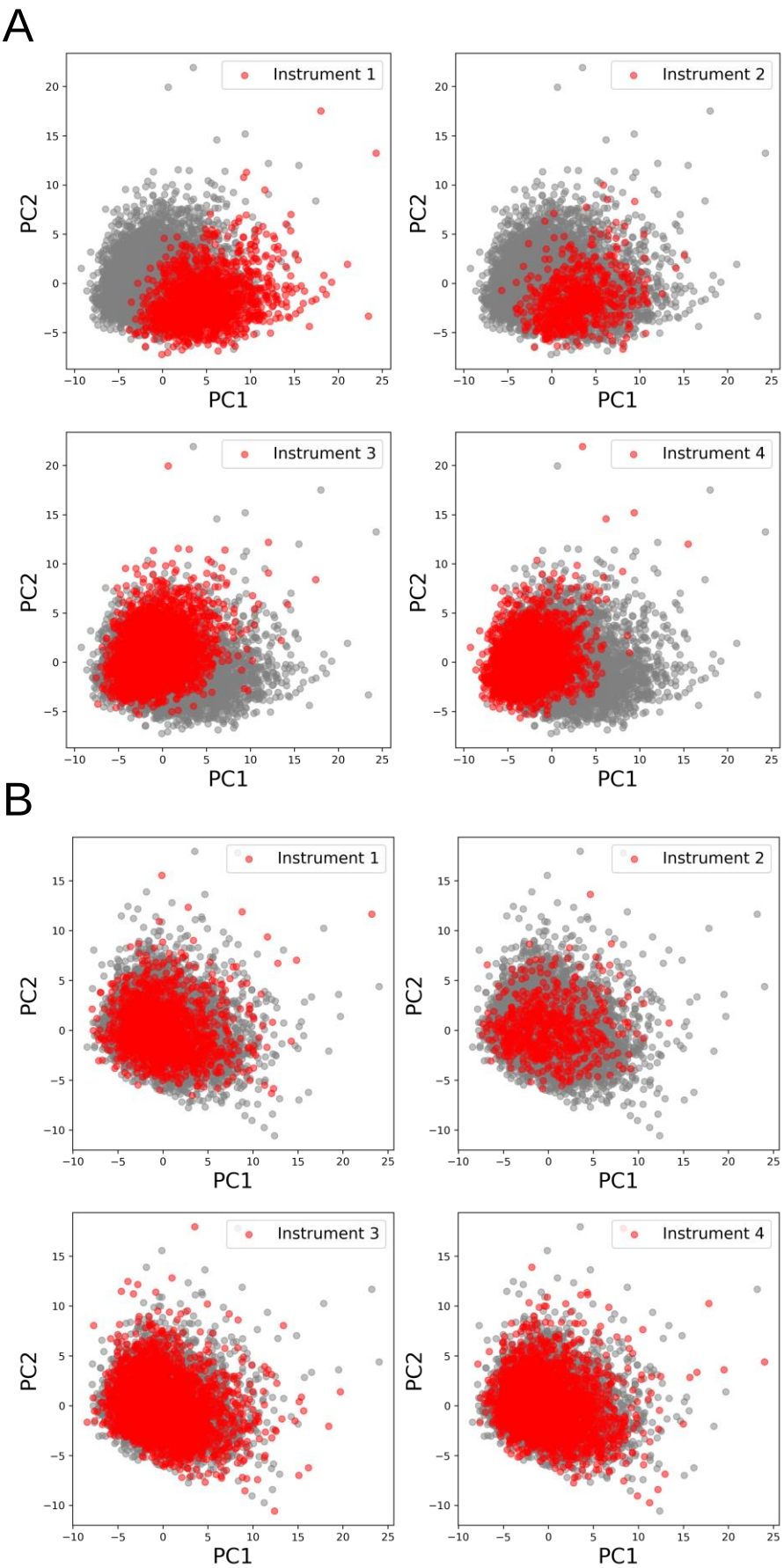
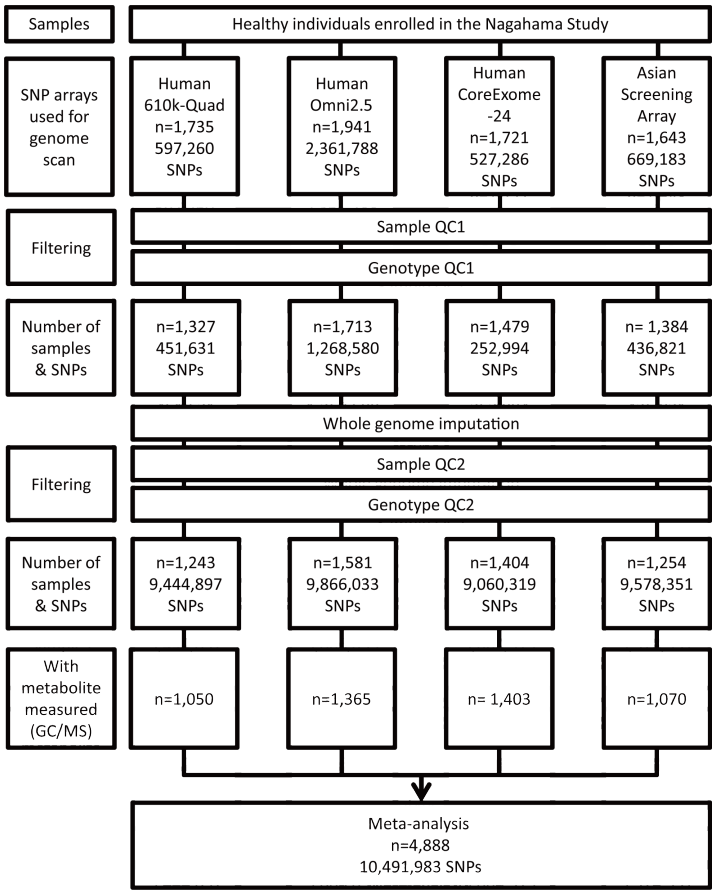


Figure S53. The PCA plots of metabolome data, Related to STAR Methods



The PCA plots before (A) and after (B) normalization using 121 metabolite concentration data from 8,270 samples. For each instrument, the sample measured with it is indicated in red.

Figure S54. The flow of quality control of samples and SNPs, Related to STAR Methods



Sample QC 1 : Exclude samples showing one of the following criteria.

1. Having PI_HAT in PLINK software (ver1.9b, Purcell et al., 2007) greater than 0.1 with any other sample.
2. Outliers from the EAS population (1KG Phase 3) in the principal components of joint samples by the Nagahama and 1KG populations.
3. Success rate of SNPs is less than 95% in Human 610k-Quad (610k), Omni2.5, Asian Screening Array (ASA), less than 98% in Human CoreExome-24.

Genotype QC 1 : Exclude variants showing one of the following criteria

1. The MAF is less than 0.01 in 610k , ASA, less than 0.005 in Omni 2.5, HumanCoreExome-24
2. Hardy-Weinberg equilibrium (HWE) p-value is less than 1.0 $\times$ 10^{-6}
3. Success rate of variant is less than 98%

Sample QC2 : Exclude samples showing the following criteria.

One of the top ten principal component scores of SNPs is out of range (–3 $\times$ IQR below the 25th percentile or 3 $\times$ IQR above the 75th percentile)

Genotype QC2 : We excluded variants showing one of the following criteria.

1. MAF is less than 0.005.
2. r^2 is less than 0.3.

Figure S55. The flow of quality control of studies and SNPs included in the summary of 40 metbolite GWAS, Related to STAR Methods

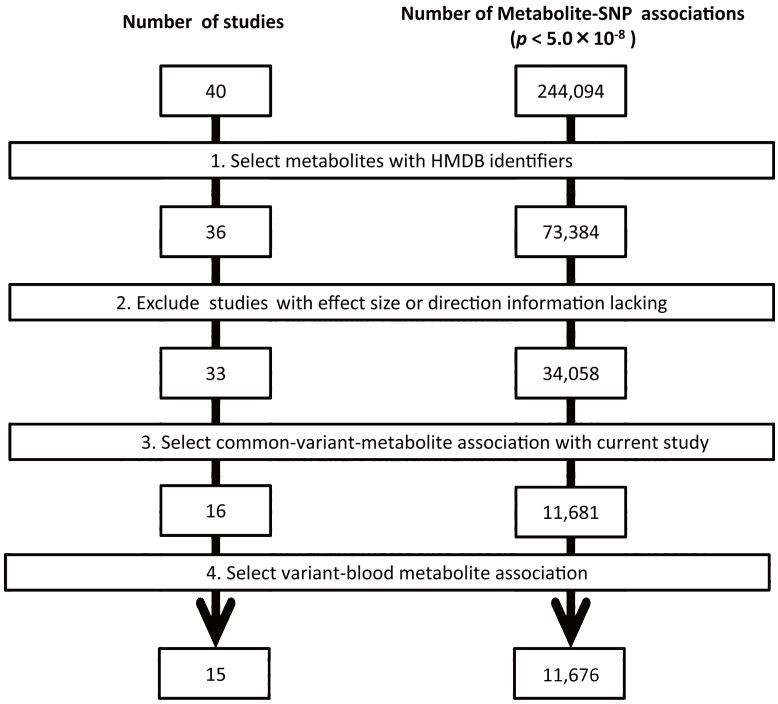
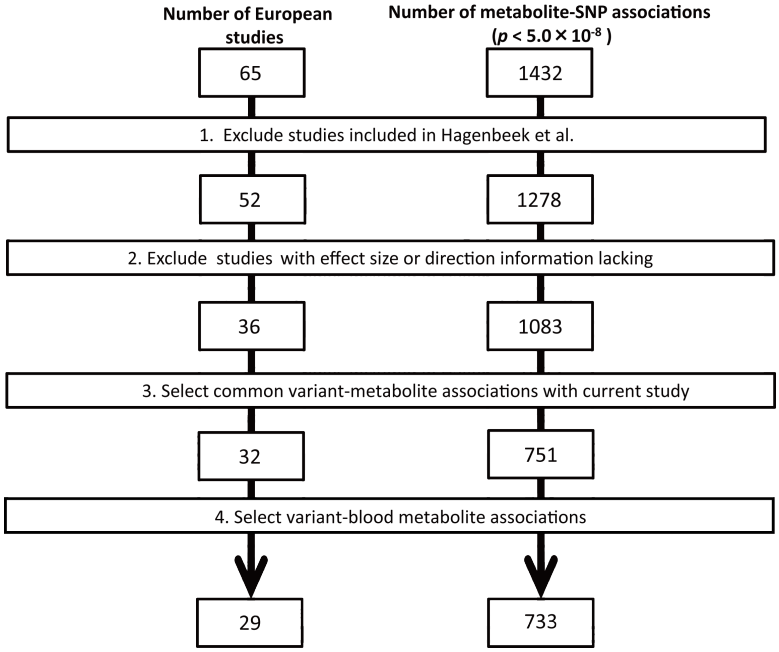


Figure S56. The flow of quality control of studies and SNPs included in the GWAS Catalog, Related to STAR Methods



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