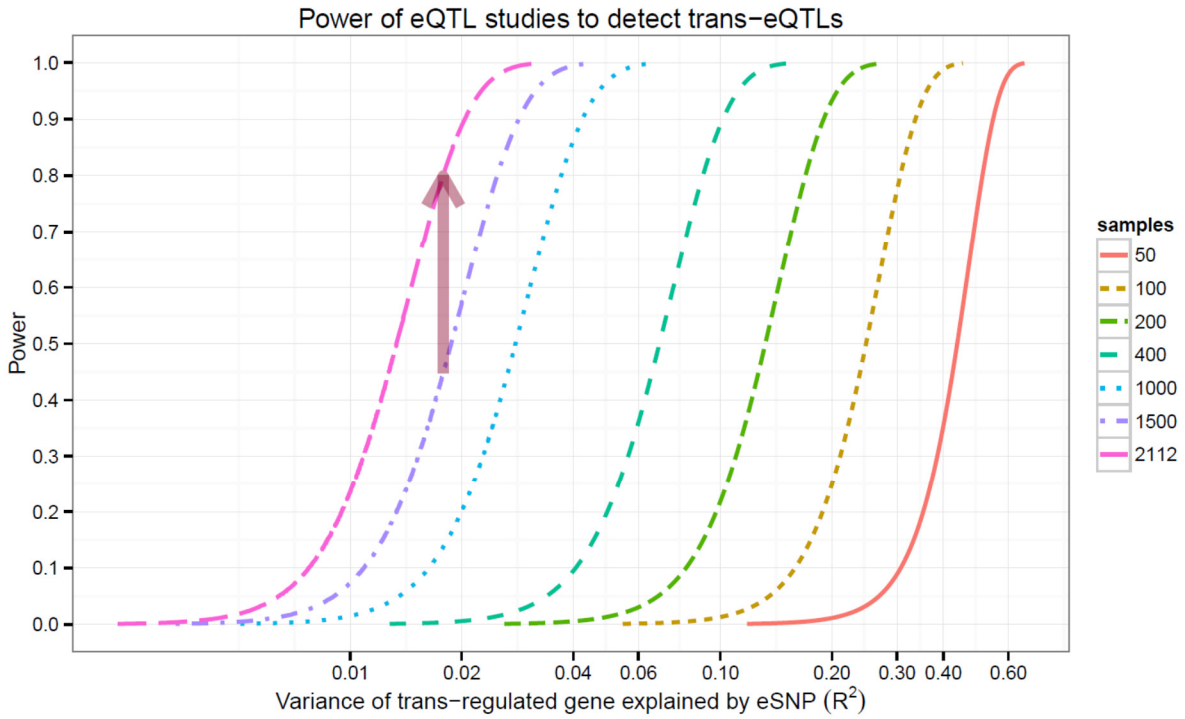
Supplementary figures

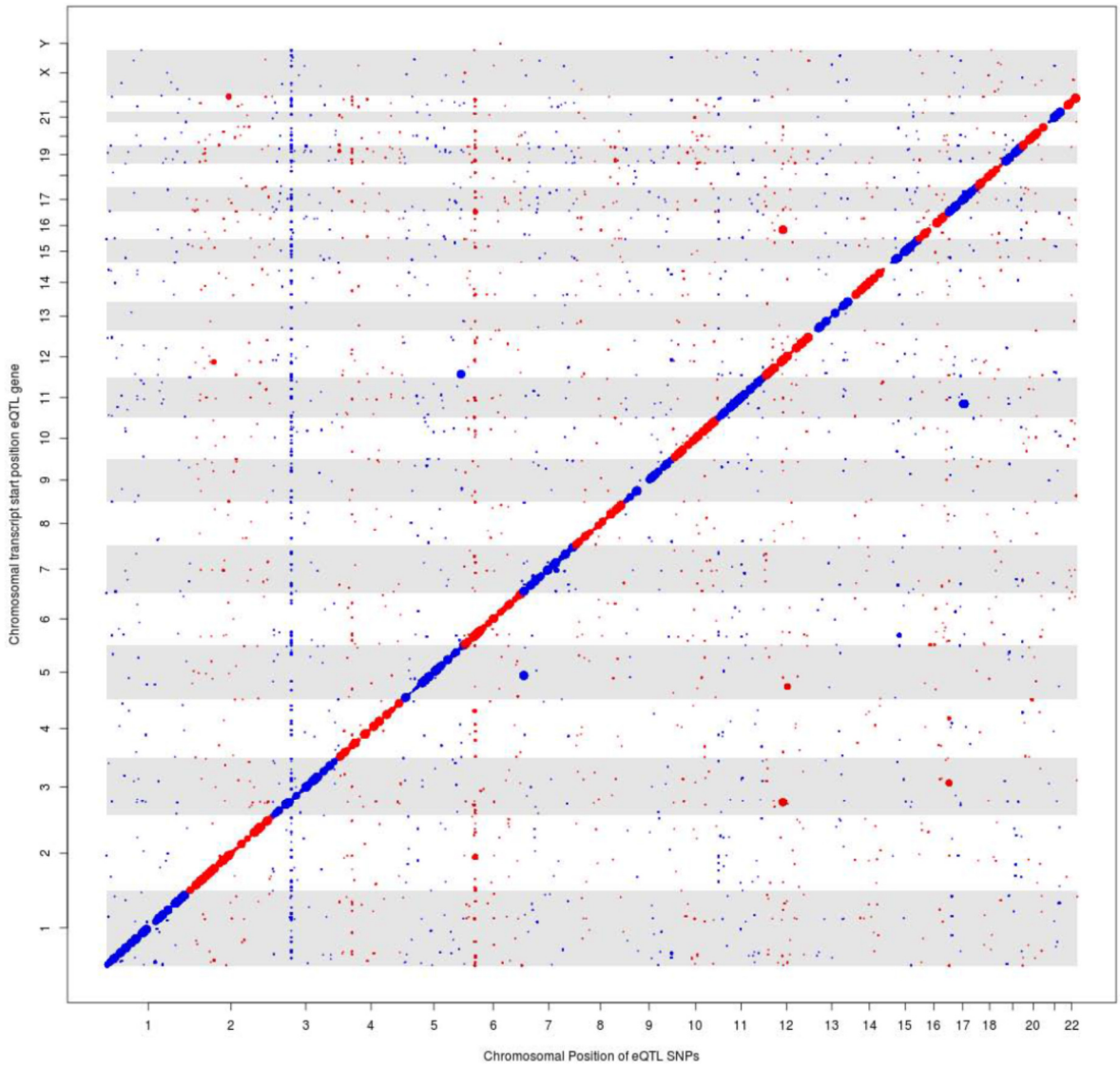
Supplementary Figure 1: Power analysis of eQTL studies

Power calculation to detect a certain effect sizes was based on a p-value cut-off corresponding to our study-wide significance to detect trans-eQTLs at 5% FDR ($p \leq 1.02 \times 10^{-7}$). The arrow indicates that compared to a study of 1500 individuals we had a power of 80% instead of 44.8% to detect an eQTL explaining 1.8% of the variance of a trans-regulated transcript's expression level.



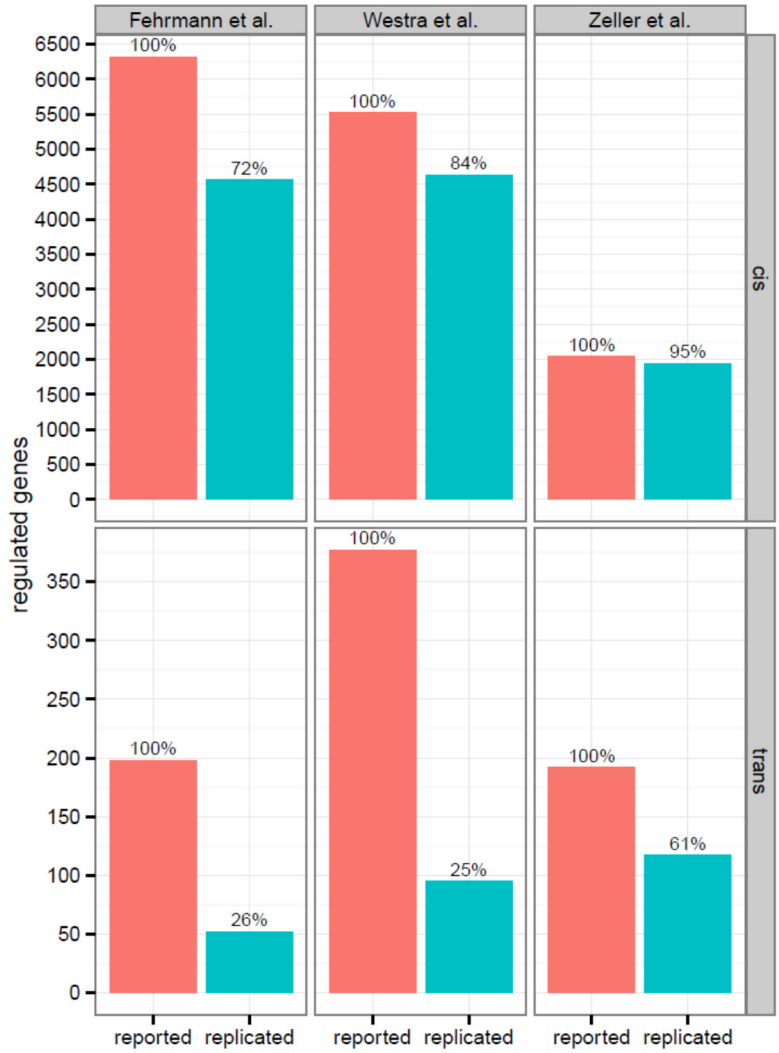
Supplementary Figure 2: Genome-wide plot of genomic locations of all identified eQTLs

Numbers refer to chromosome numbers. Increased point size indicates higher significance of the eQTL.



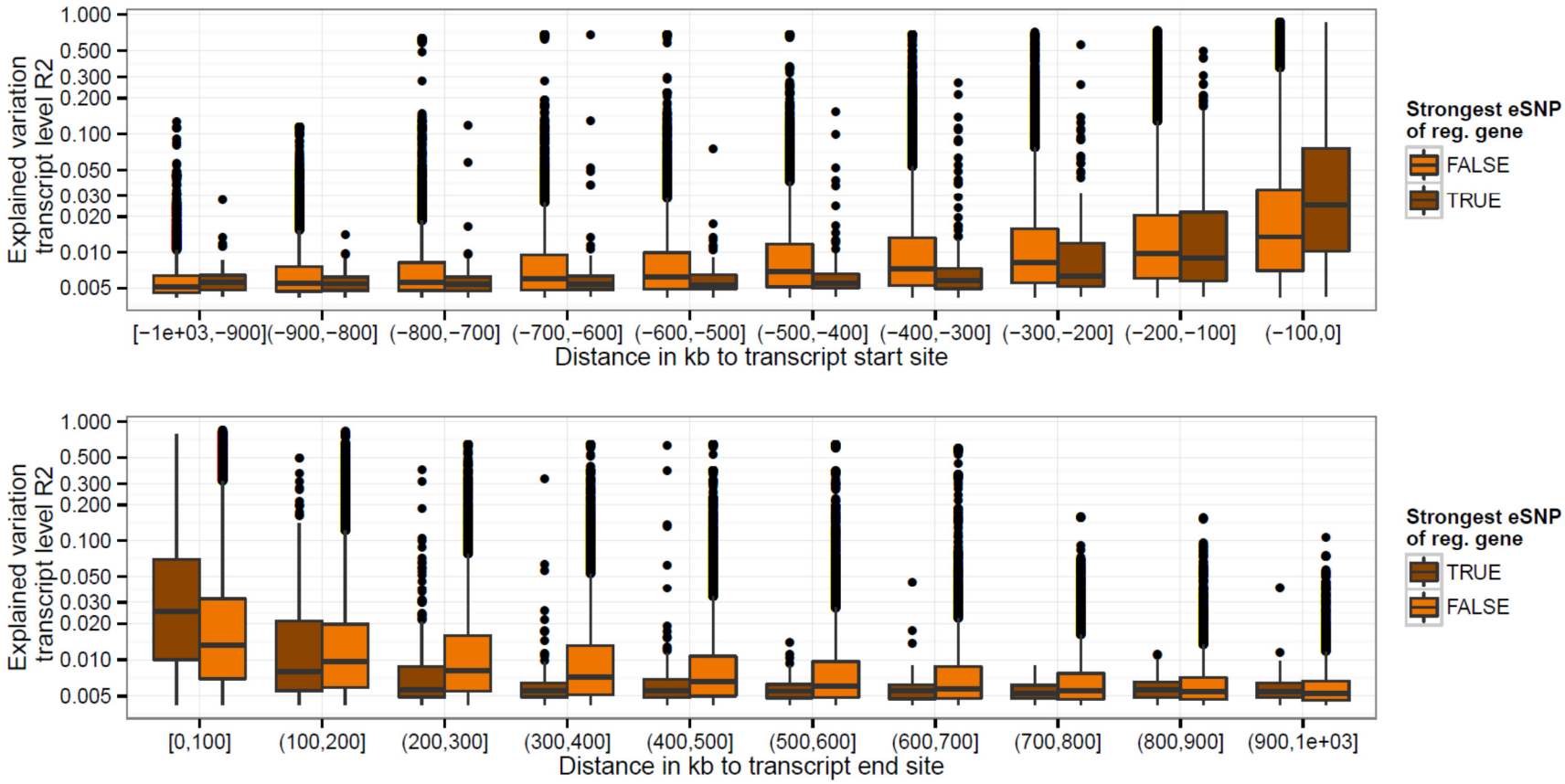
Supplementary Figure 3: Replication analysis of reported eQTLs

Replication rates of regulated genes reported by Zeller et al., Fehrmann et al., and Westra et al. (1-3) in our data.



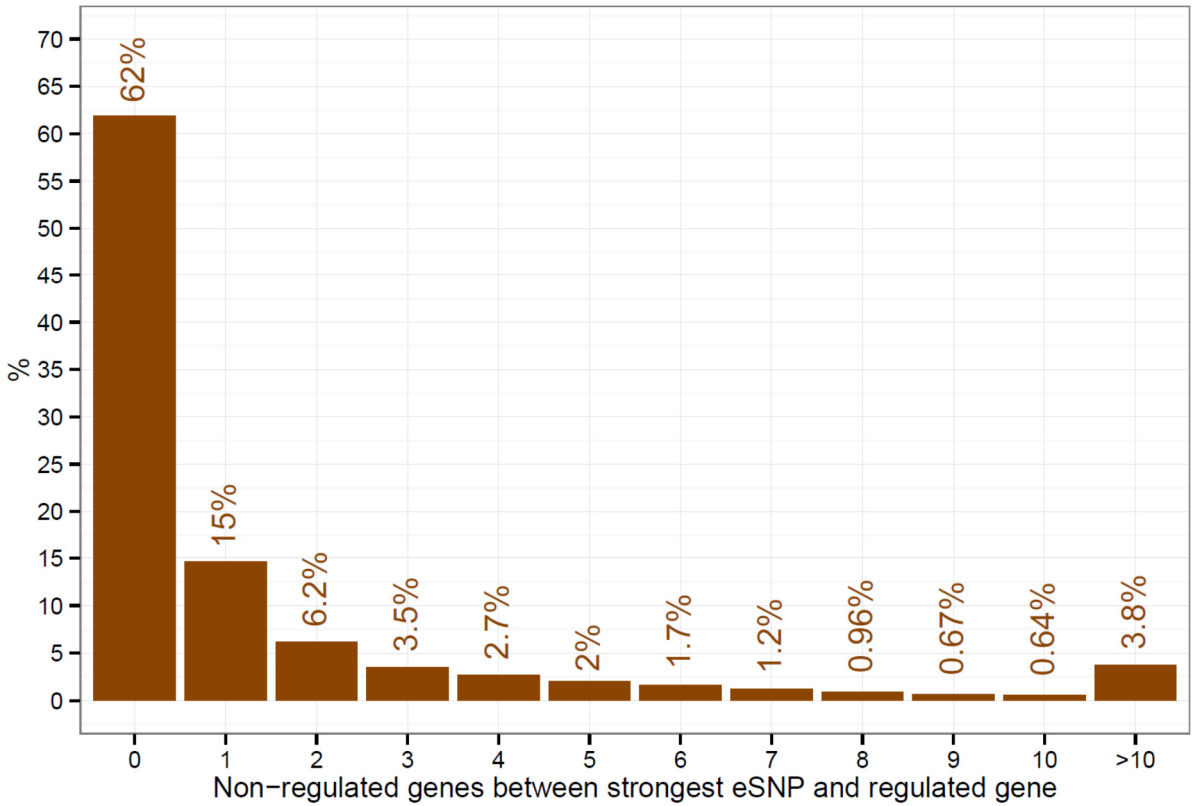
Supplementary Figure 4: Effect size of eQTL decreases as distance to regulated genes increases

Distribution of explained variance of transcription levels of regulated genes in dependence on distance to transcript start site and transcript end site. A trend towards smaller effect size with increasing distance can be observed, especially for the strongest eSNP per regulated gene (shown in dark).



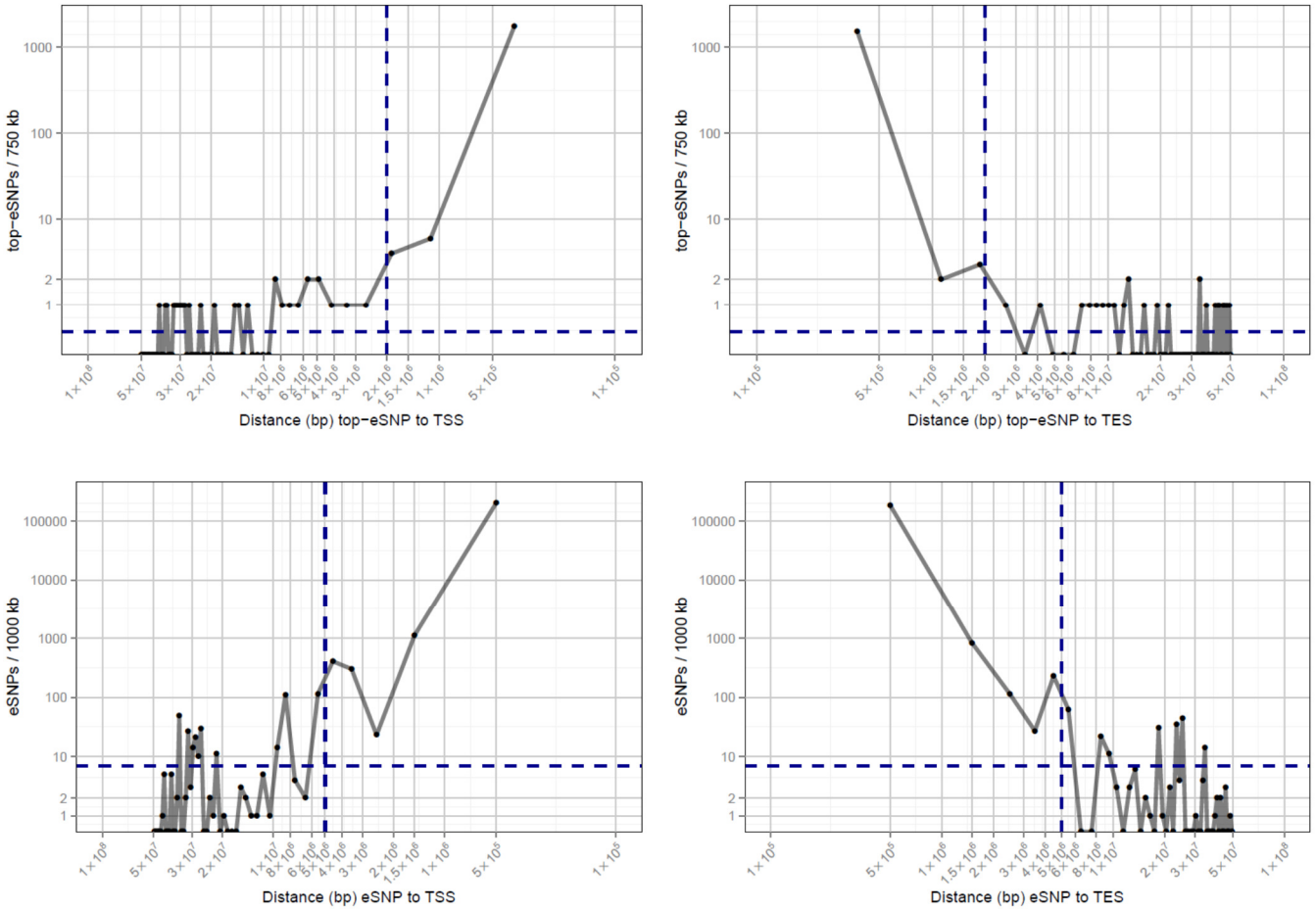
Supplementary Figure 5: Non-regulated genes found between top-eSNPs and corresponding regulated genes

Shown is the number of genes that are 'bridged', i.e. how many genes are found between the top-eSNP and the corresponding cis-regulated gene. Only bridged genes not regulated by the considered eSNP are counted. Exemplarily, for 6.2% of all strongest eSNPs per gene, two additional genes were located in-between the top-eSNP and the transcription start site of the regulated gene located on the same chromosome.



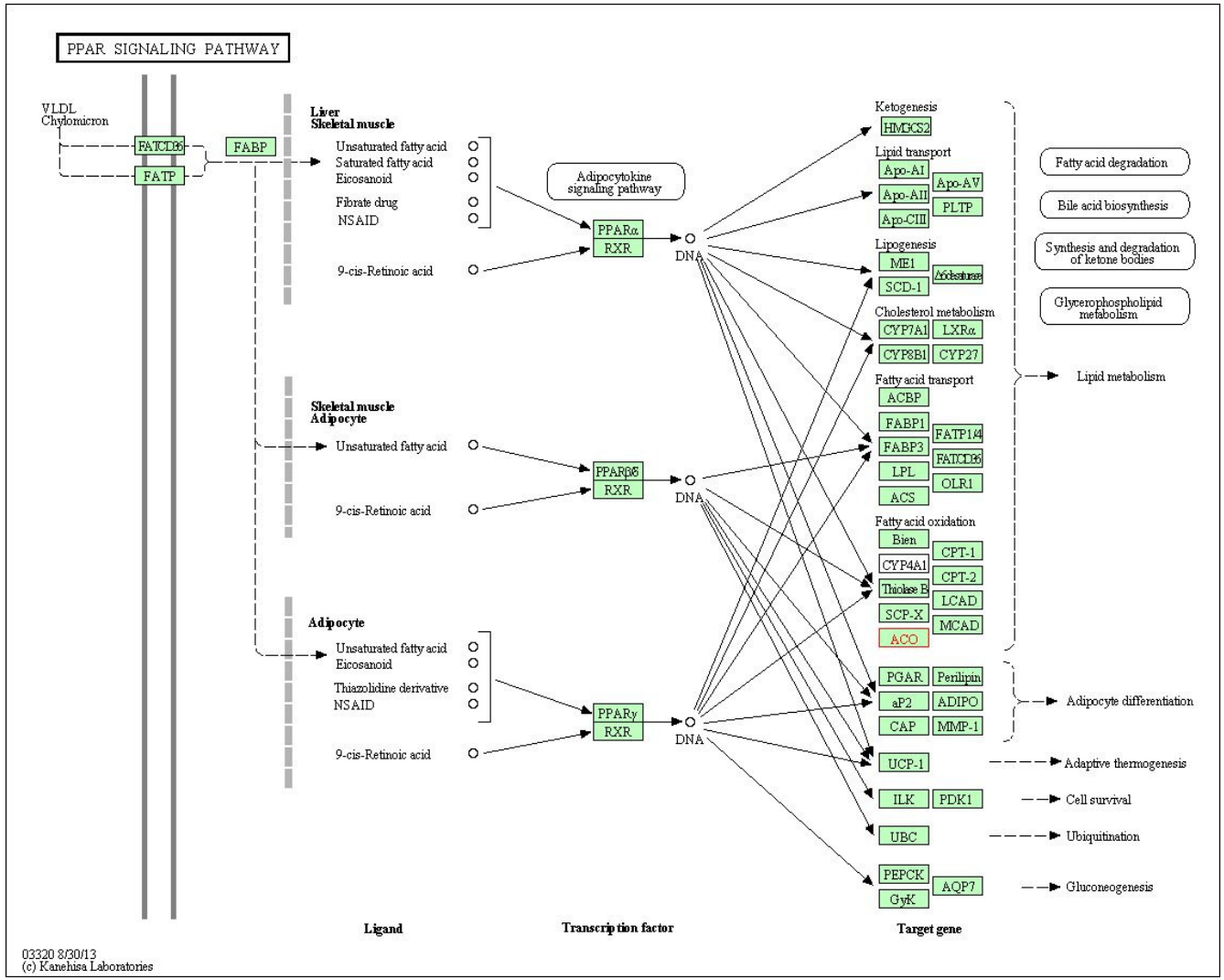
Supplementary Figure 6: Density of intra-chromosomal eQTLs in dependence to the distance between eSNP and transcript start site (TSS) and transcript end site (TES) of the regulated gene

Shown is the number of eQTLs found at certain distances to the TSS and TES. If a certain eSNP was associated with multiple probes of the same gene, the corresponding eQTL gene distance was counted only once per gene.
Upper panel: Density of the top-eSNP per regulated gene. Here, points represent averages in bins of 0.75 Mb. The horizontal line represents the average rate of top inter-chromosomal trans-eQTLs (0.6 top-eQTLs/Mb). The vertical line represents 2 Mb, up to this distance enrichment is clearly observable.
Lower panel: Density of the all eSNP per regulated gene. Here, points represent averages in bins of 1 Mb. The horizontal line represents the average rate of inter-chromosomal trans-eQTLs (6.9 eQTLs/Mb). The vertical line represents 5 Mb, up to this distance enrichment is clearly observable.



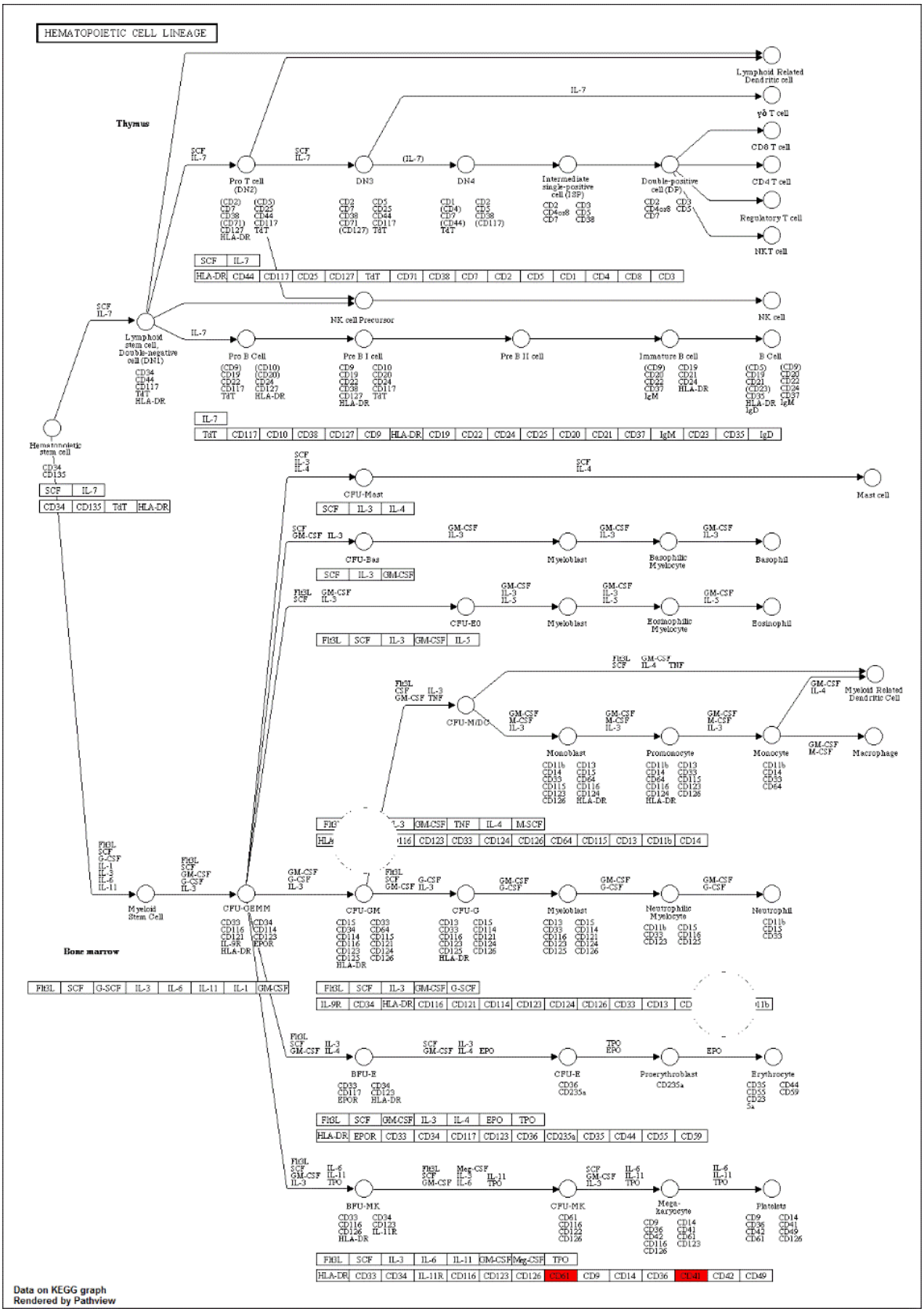
Supplementary Figure 7: Enrichment of KEGG-term 03320 'PPAR signaling pathway' within trans-regulated genes of the trans-cluster regulated by rs34856868

RS34856868 was reported in a GWAS of obesity-related traits (4) and regulates a trans-cluster. The novel trans-regulated gene *ACOX2* (marked in red) is found in KEGG-term 'PPAR signaling pathway' thereby corroborating mechanistic relevance of this trans effect.



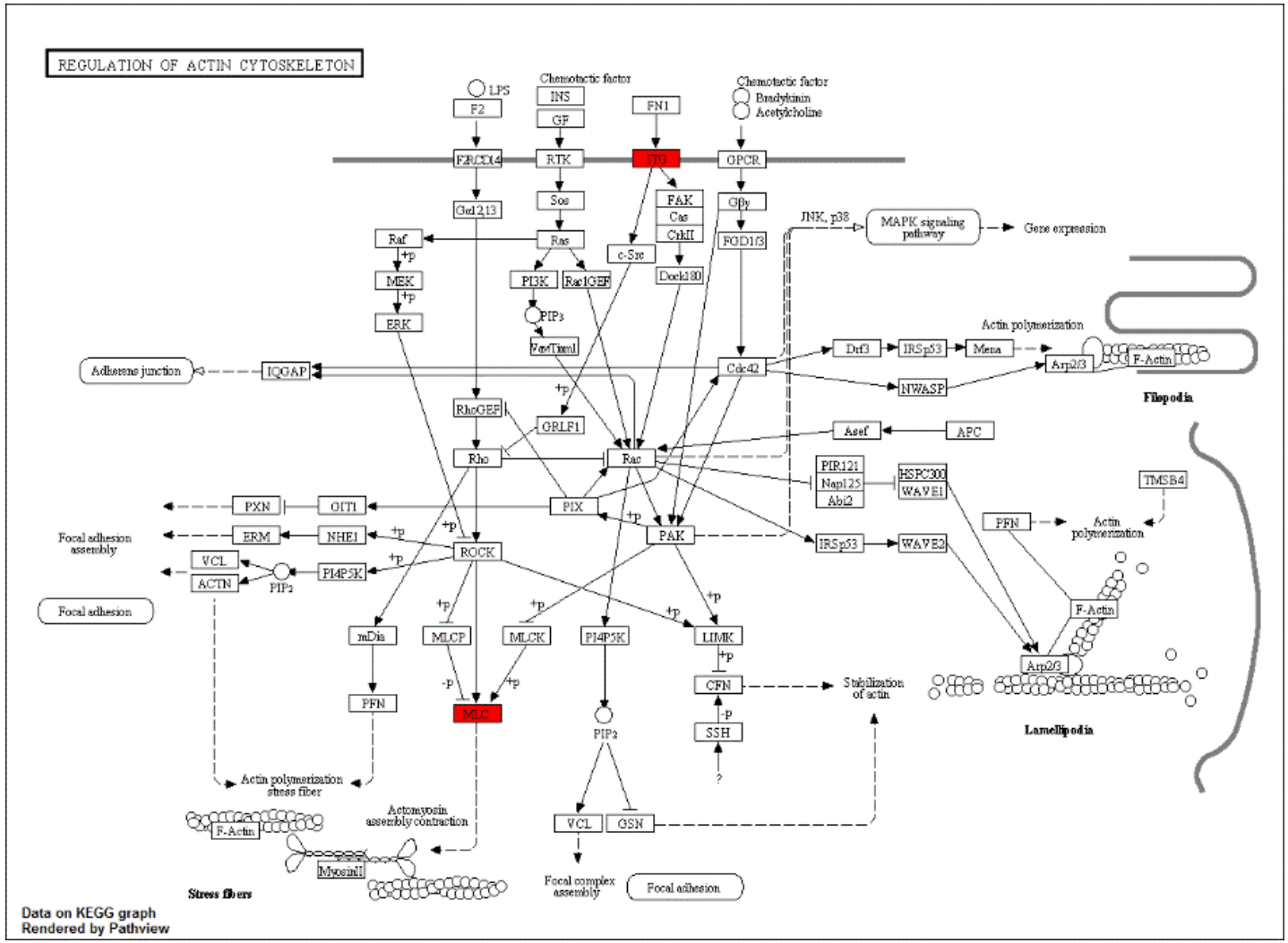
Supplementary Figure 8: Enrichment of KEGG-term 04640 'Hematopoietic cell lineage' within trans-regulated genes of the trans-cluster regulated by rs10512472

RS10512472 and SNPs in LD were reported in GWAS of platelet count and mean platelet volume (5) and regulates a trans-cluster. The novel trans-regulated genes *ITGA2B* and *ITGB3* (also known as *CD41*/*CD61,* marked in red) result in enrichment of KEGG-term 'Hematopoietic cell lineage' thereby corroborating mechanistic relevance of identified trans-regulated genes



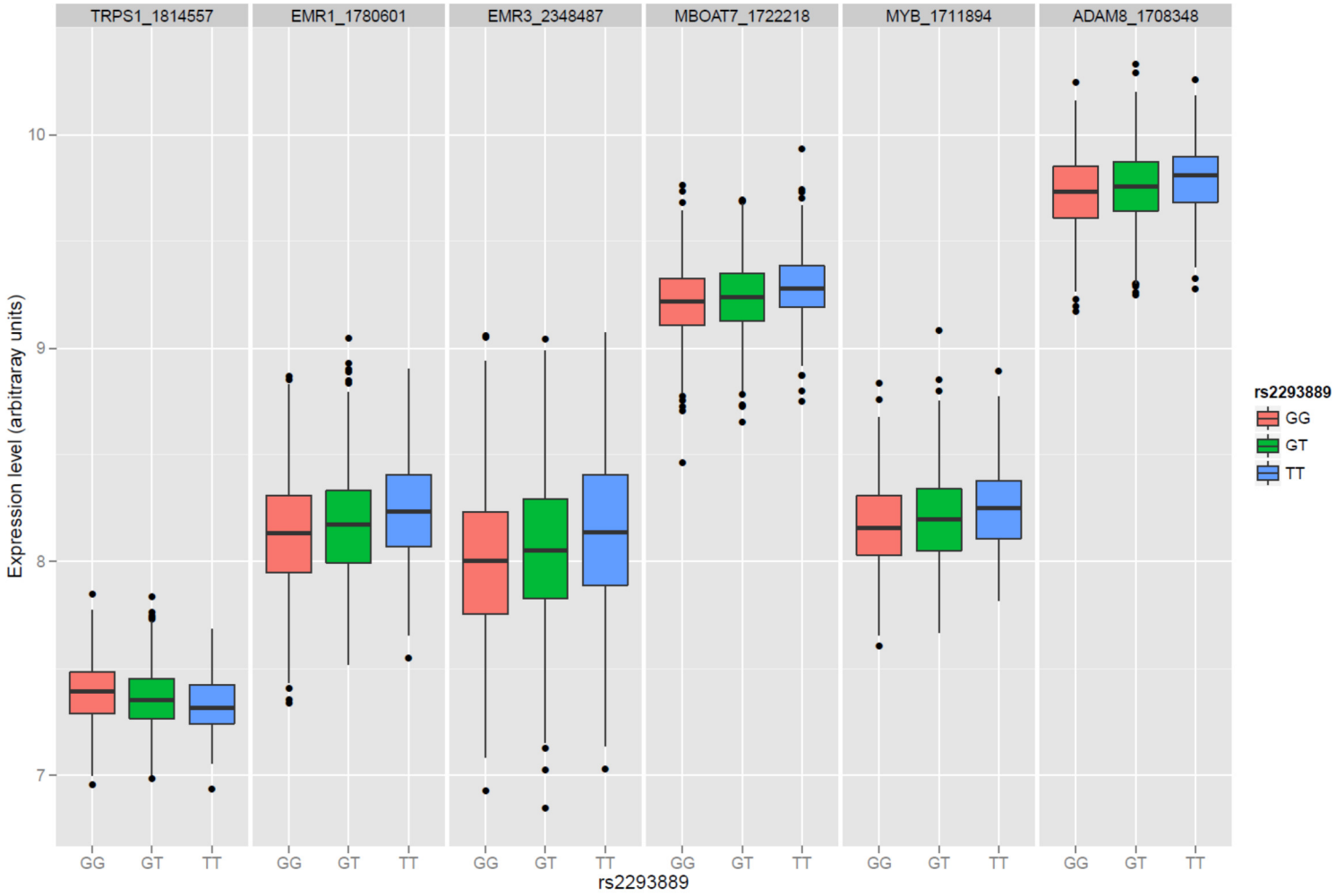
Supplementary Figure 9: Enrichment of include KEGG-term 04810 'Regulation of actin cytoskeleton' within trans-regulated genes of trans-cluster rs10512472

Trans-cluster rs10512472 comprehends of a SNP related to a GWAS of platelet count and mean platelet volume. Novel trans-regulated genes *ITGA2B* / *ITGB3* (here named *ITG)* and *MYL9* (shown is the corresponding protein MLC) are marked in red. As these processes lead to actomyosin assembly contraction, a mechanistic implication of these novel trans-regulated genes in regulation of the GWAS-related phenotype mean platelet volume is plausible.



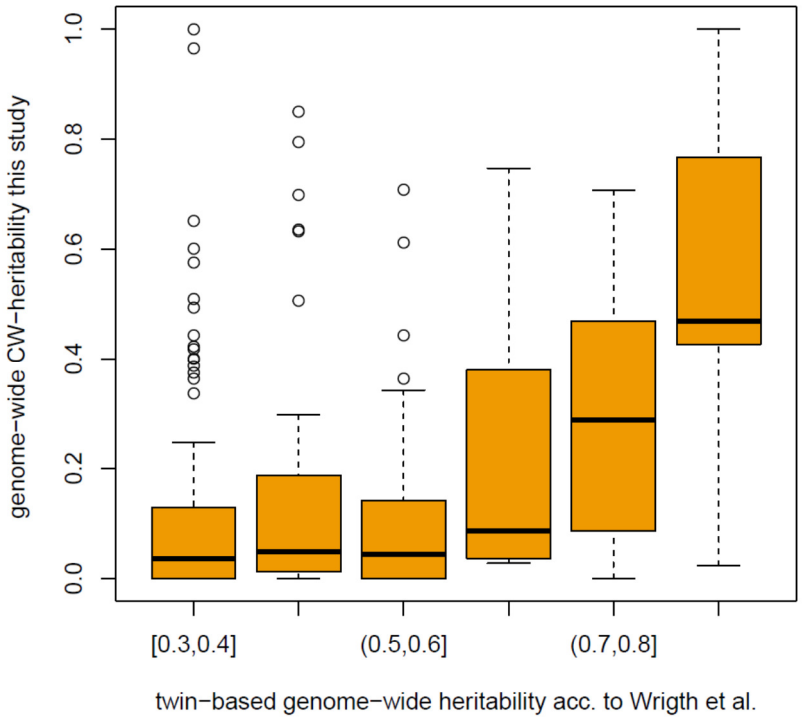
Supplementary Figure 10: Expression values of cis vs. trans-regulated genes of trans-cluster regulated by rs2293889 related to HDL-levels

Individuals were grouped according to genotypes of rs2293889. Note that allele rs2293889-T was reported to be associated with decreased HDL concentrations (6). Expression levels are shown for cis-regulated gene *TRPS1*, a transcriptional repressor for GATA-regulated genes, and the five trans-regulated genes. We observe that along genotypes GG, GT, and TT expression levels of the trans-regulated genes increase, whereas for the same genotypes expression levels of *TRPS1* decrease. This is in line with a GATA-mediated control of the trans-regulated genes. Numbers following the gene name indicate Illumina's probe IDs.



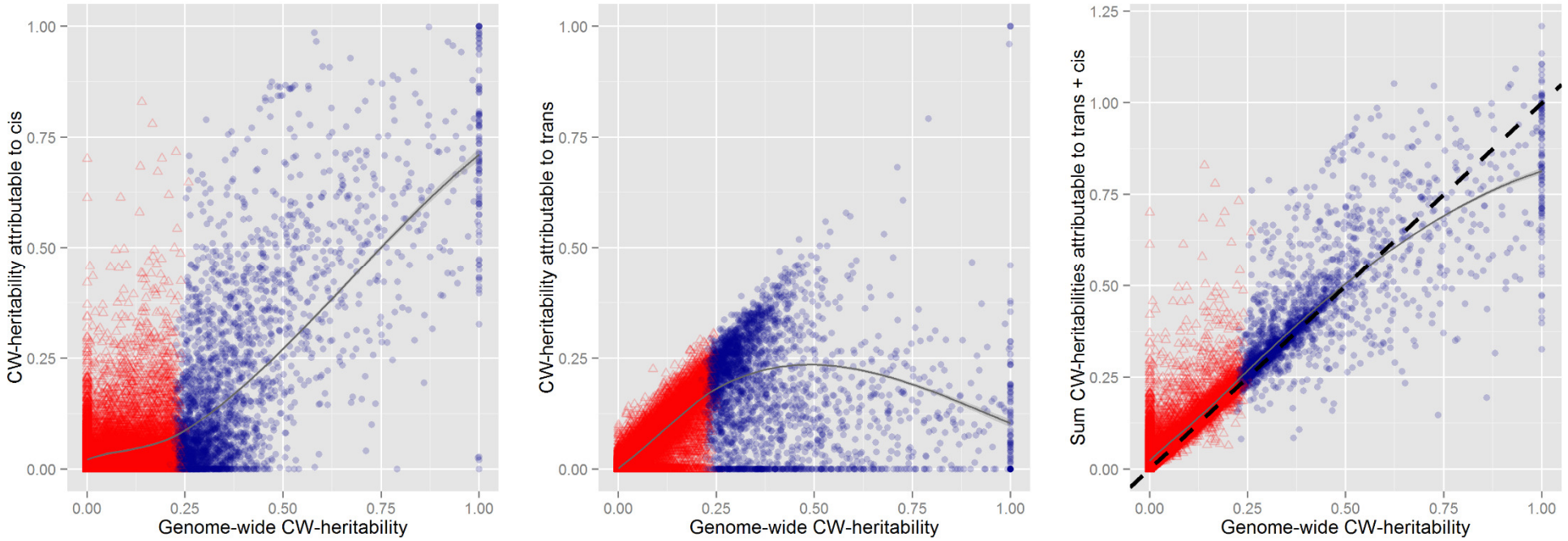
Supplementary Figure 11: Relationship of twin-based heritabilities reported by Wright et al. with genome-wide CW-heritabilities from our study

For genes with reported twin-based heritability ≥ 0.5 we observed a significant correlation (p = 0.004, r = 0.39, 95%CI: 0.13-0.60). Data from Wright et al. (7) represents results of 228 of 269 genes that could be matched to our data.



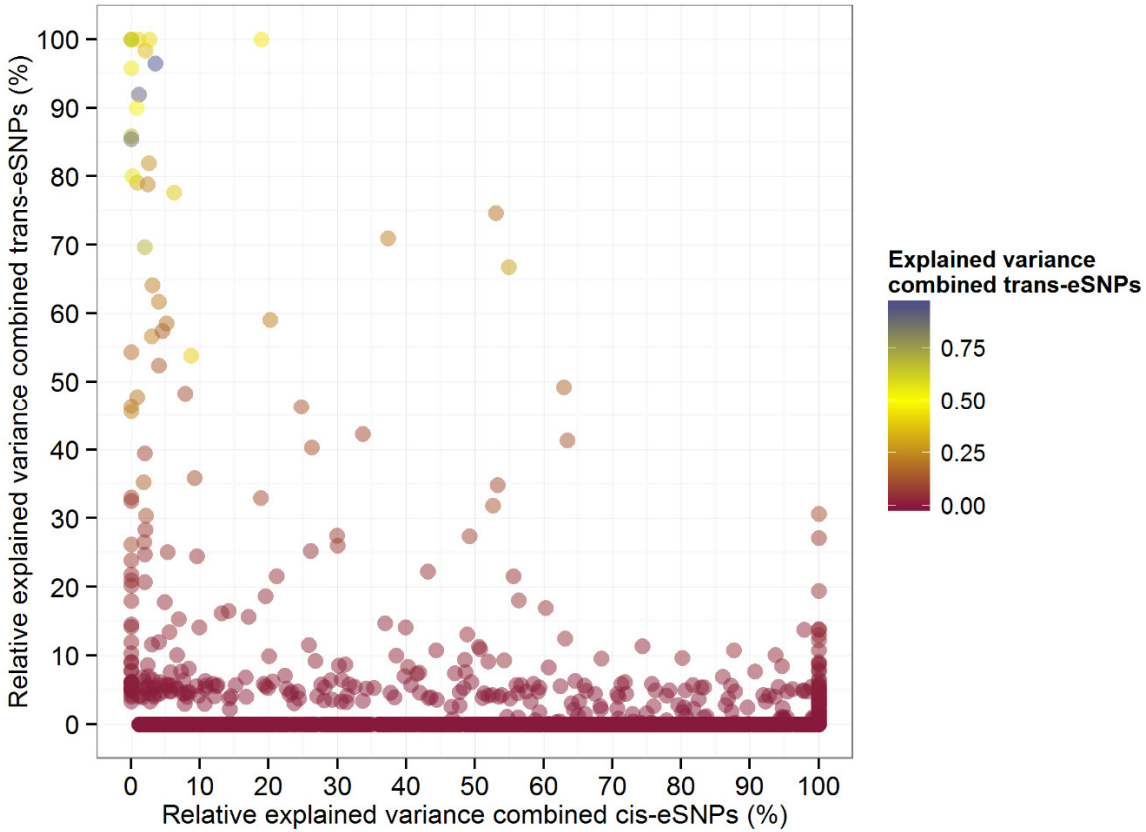
Supplementary Figure 12: Cis- and Trans-CW heritability versus genome-wide CW-heritability

Left: Comparison of CW-heritability attributable to cis, i.e. heritability resulting from all SNPs found on the chromosome where the regulated gene is located vs. genome-wide CW-heritability. Middle: Comparison of CW-heritability attributable to trans vs. genome-wide CW-heritability. Right: Agreement between separately estimated cis- and trans-attributable CW heritability and genome-wide CW heritability. Blue circles indicate transcripts with a significant genome-wide CW-heritability ($p \leq 0.05$). For each graph, a loess-estimator including confidence bounds is shown, the dashed line in the right graphs indicates the diagonal.



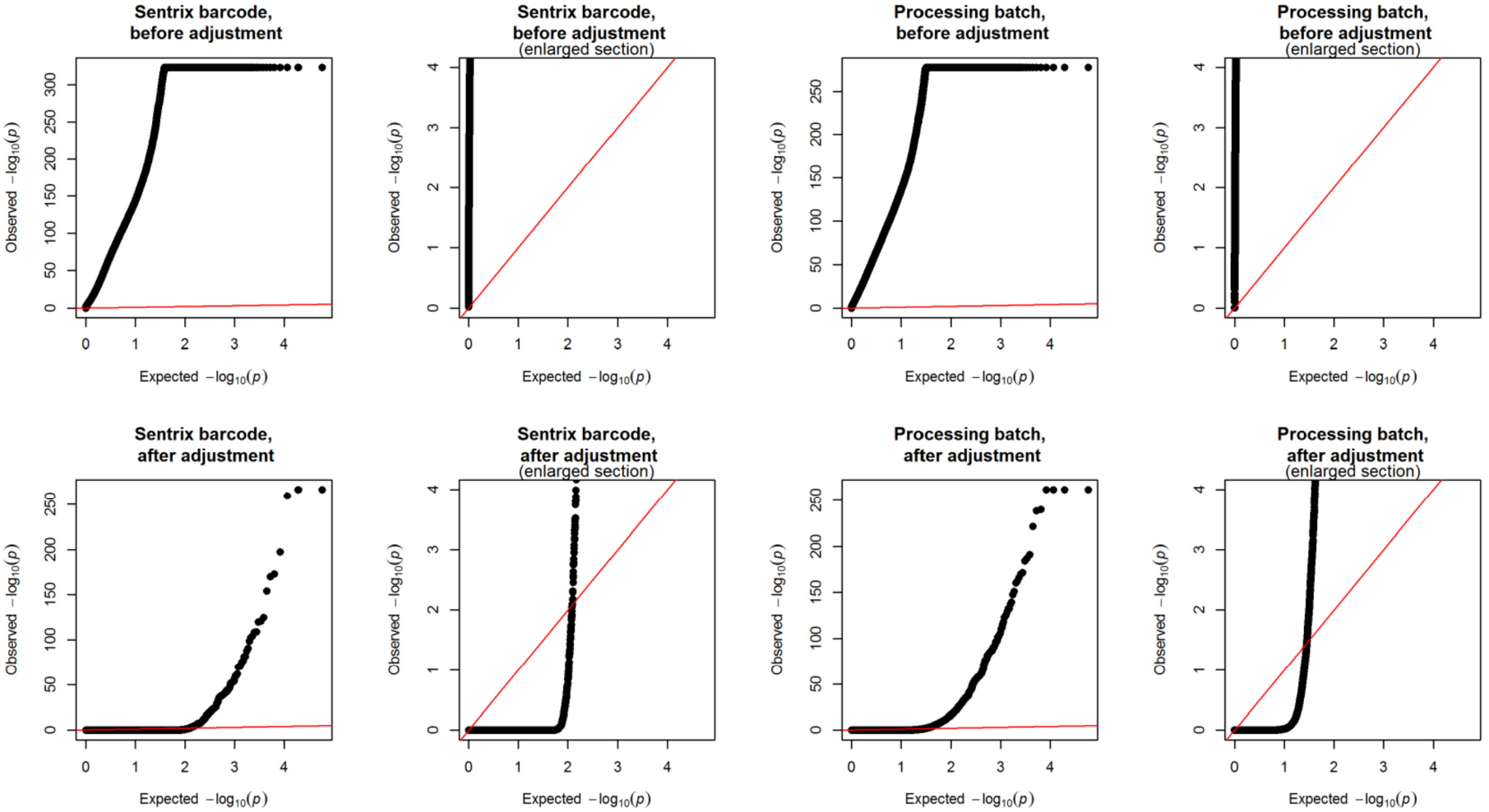
Supplementary Figure 13: Comparison of the identified cis- vs. trans-regulated genetic component

For each transcript, we compared the variance of transcript expression levels explained by all cis- vs. all trans-eSNPs identified in this study (thereby accounting for linkage disequilibrium between eSNPs). The cis- and the trans-component are shown in relation to the total genetic variance as estimated by the CW-heritability. Only transcripts with a significant genome-wide CW-heritability ($p \leq 0.05$) are included in this analysis. Colours show absolute values of the explained variance of combined trans-eSNPs.



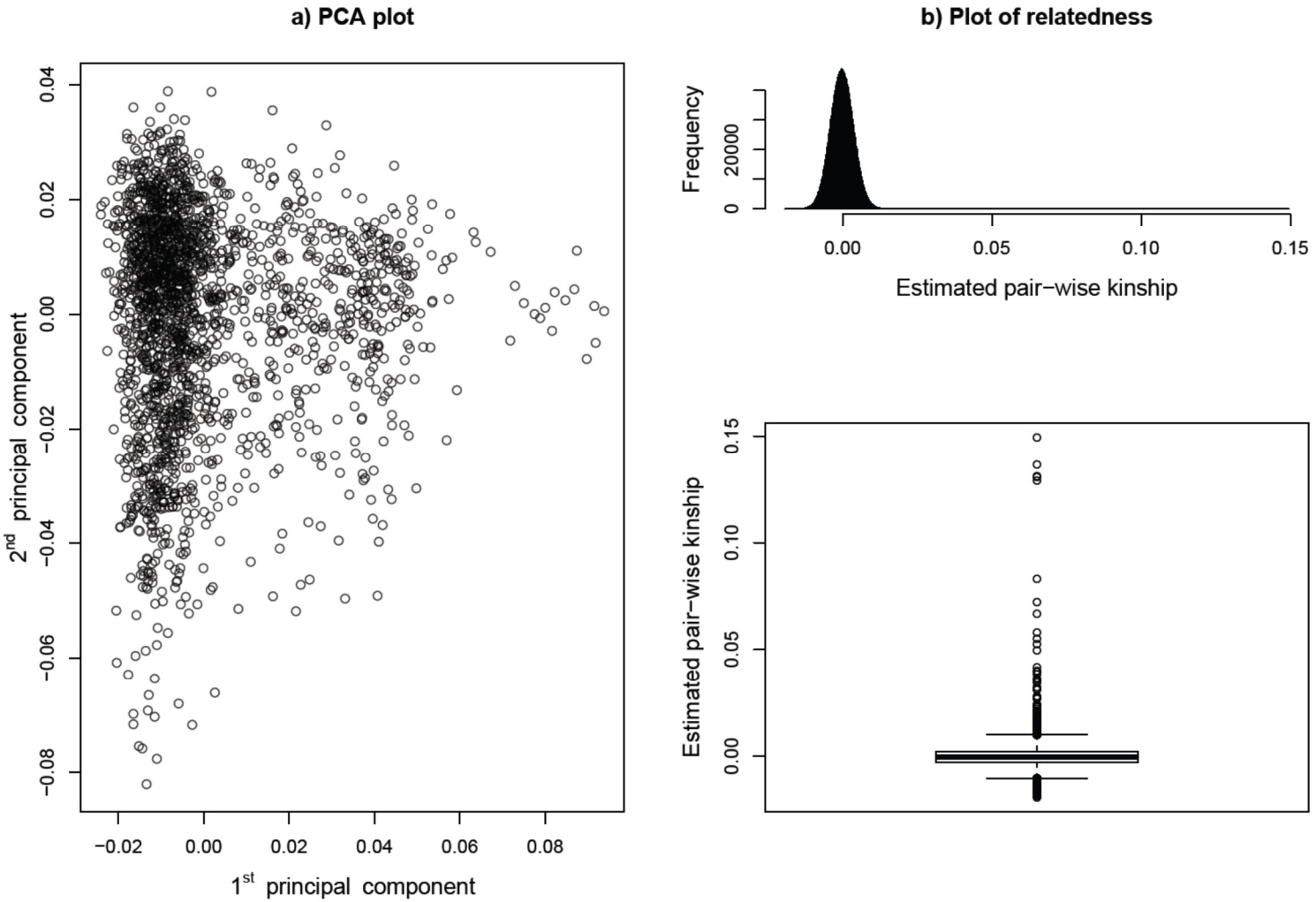
Supplementary Figure 14: Correction of technical batch effects (Sentrix barcode ID)

Before and after adjustment (8) of transcript levels for known batches of Sentrix barcode (i.e. expression chip-ID) we performed an ANOVA for both, the Sentrix barcode as well as the processing batch which included disjoint groups of Sentrix barcodes. Only few probes (2.2%) were over-inflated following adjustment demonstrating efficacy of this method. Over-inflated probes were removed for final analysis.



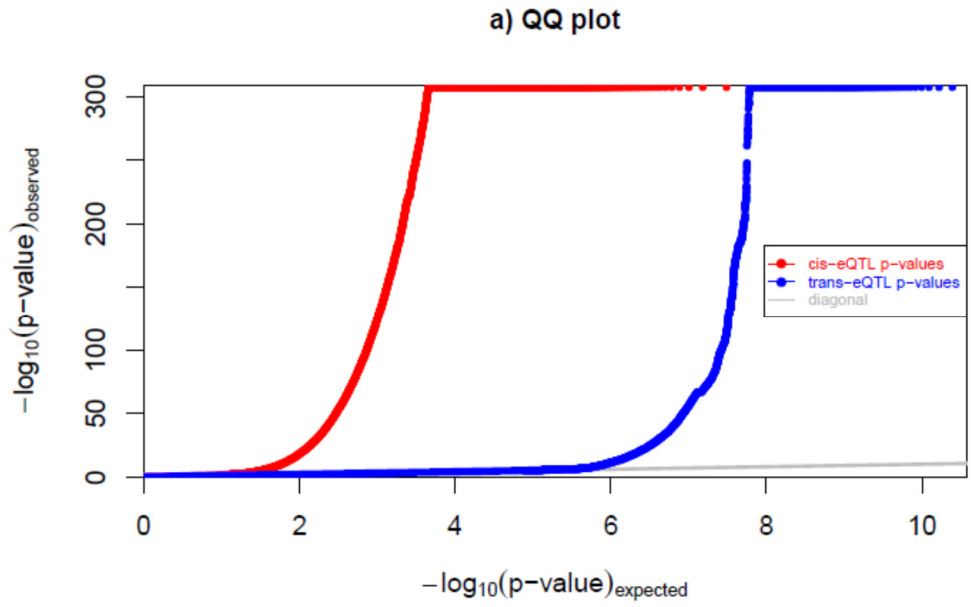
Supplementary Figure 15: Plot of population stratification and estimated relatedness

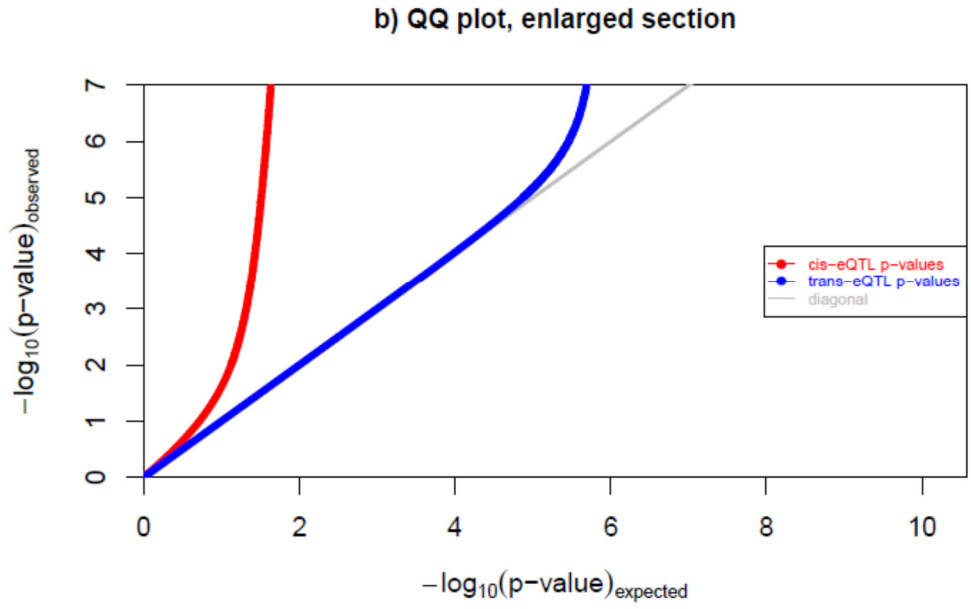
For all included 2,112 individuals, we show the first two principal components (a) and estimated relatedness quantified as pair-wise kinship (b).



Supplementary Figure 16: QQ-plot of all association tests

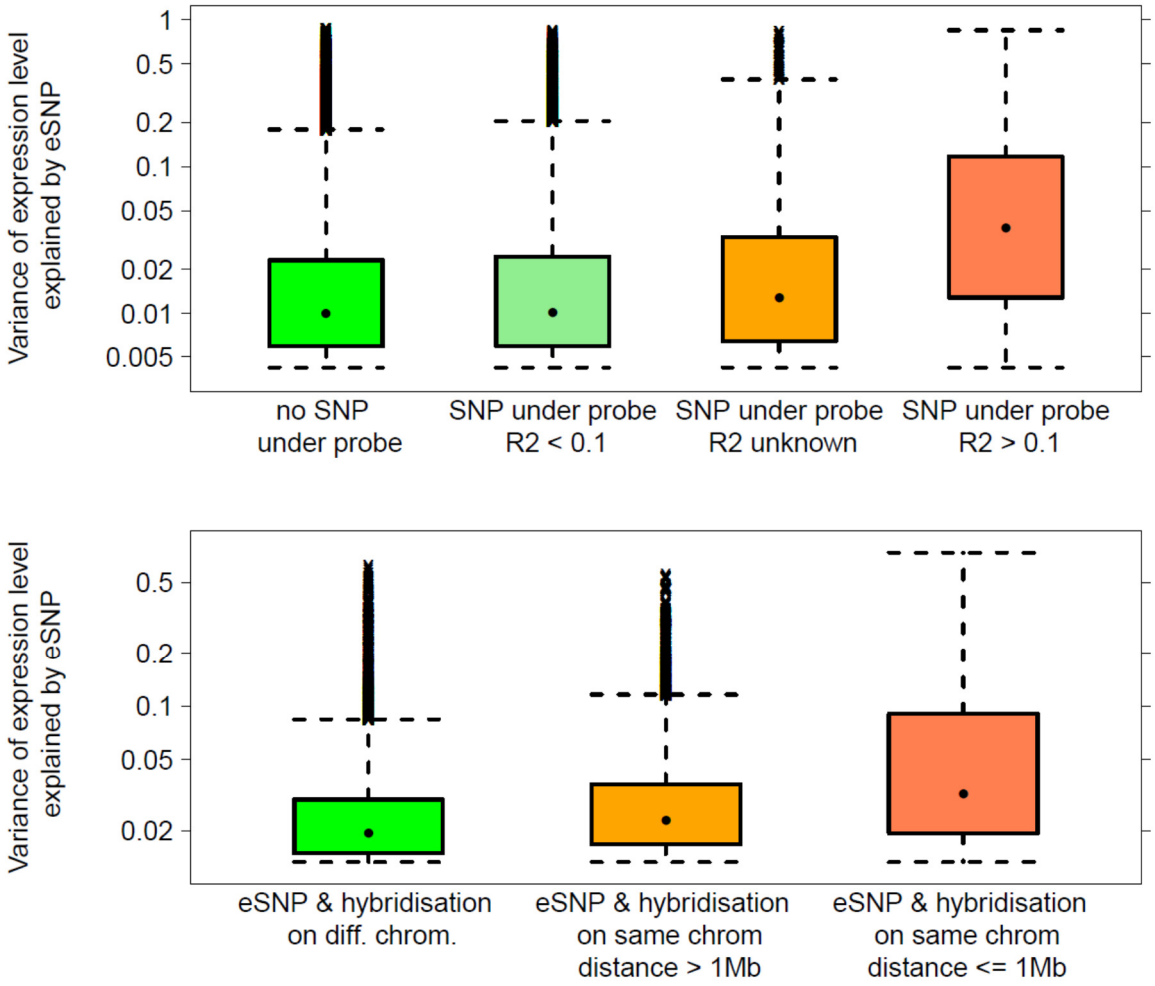
Genome- and transcriptome-wide QQ – plot of all tests showing expected test statistics versus observed test statistics.





Supplementary Figure 17: Effect sizes of eQTLs potentially being false positive

Distribution of R^2 (variance of the transcription levels explained by eSNPs) within (a) potentially false-positive cis-eQTLs and (b) potentially false positive trans-eQTLs. Categories including potential false positive eQTLs (marked in orange or red) partly show increased R^2 values since false positives typically become apparent by relatively large effect sizes.



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