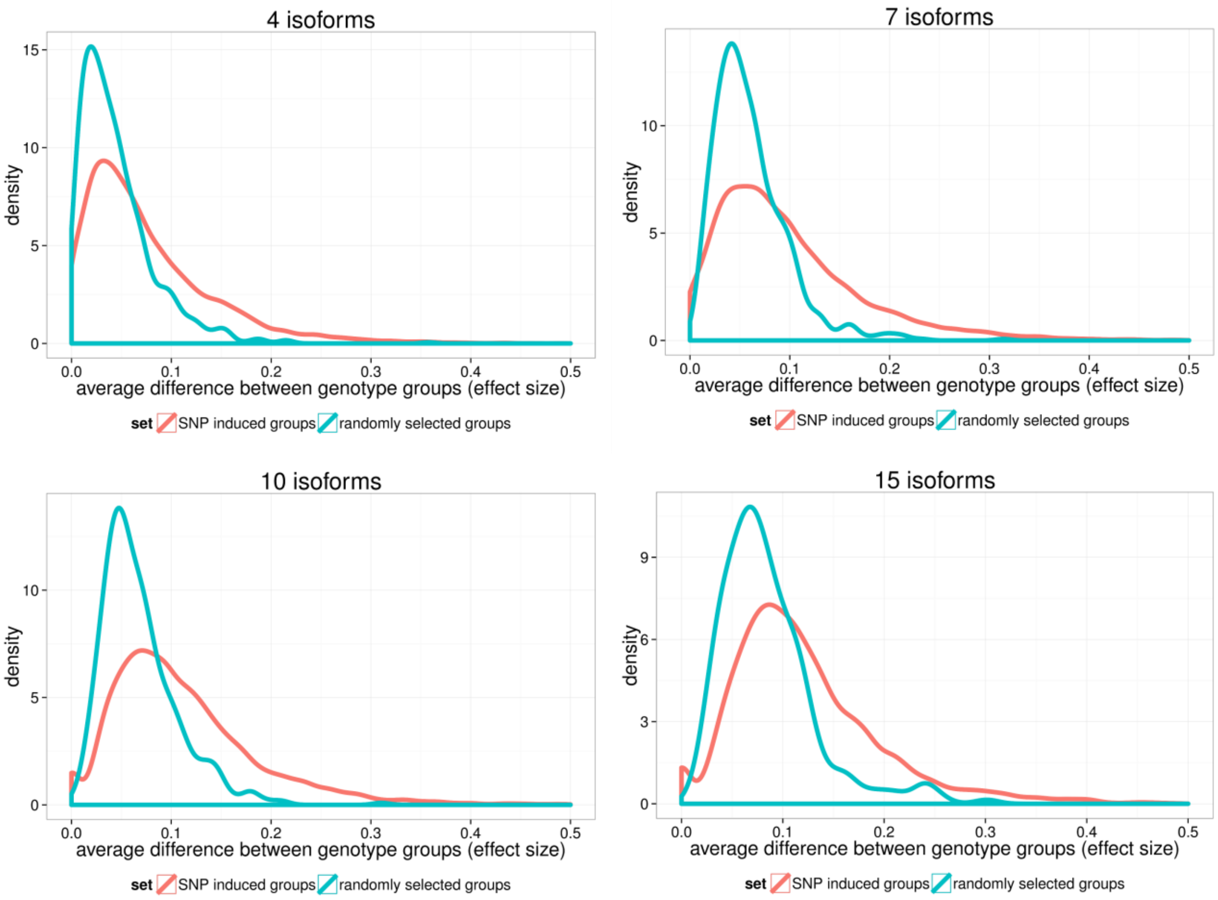
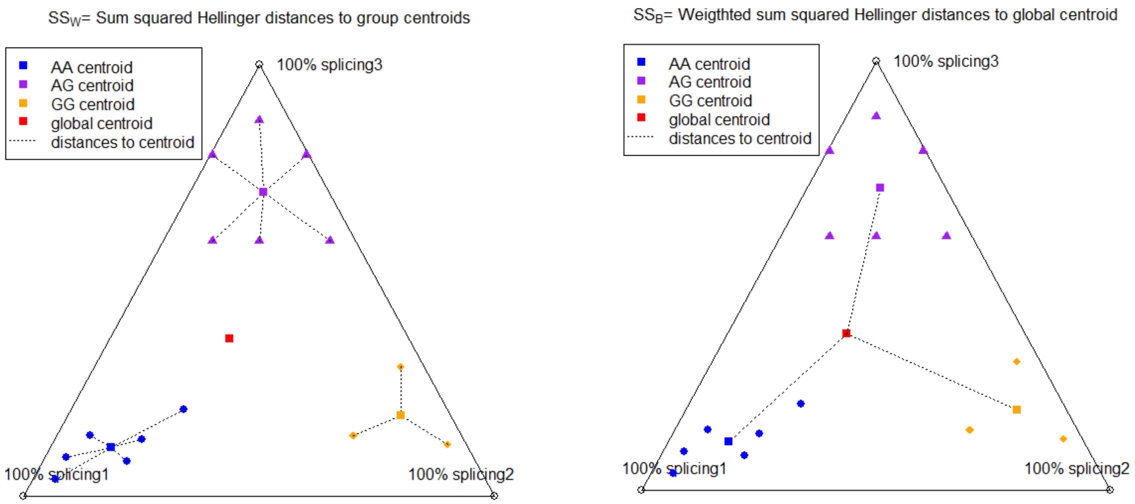


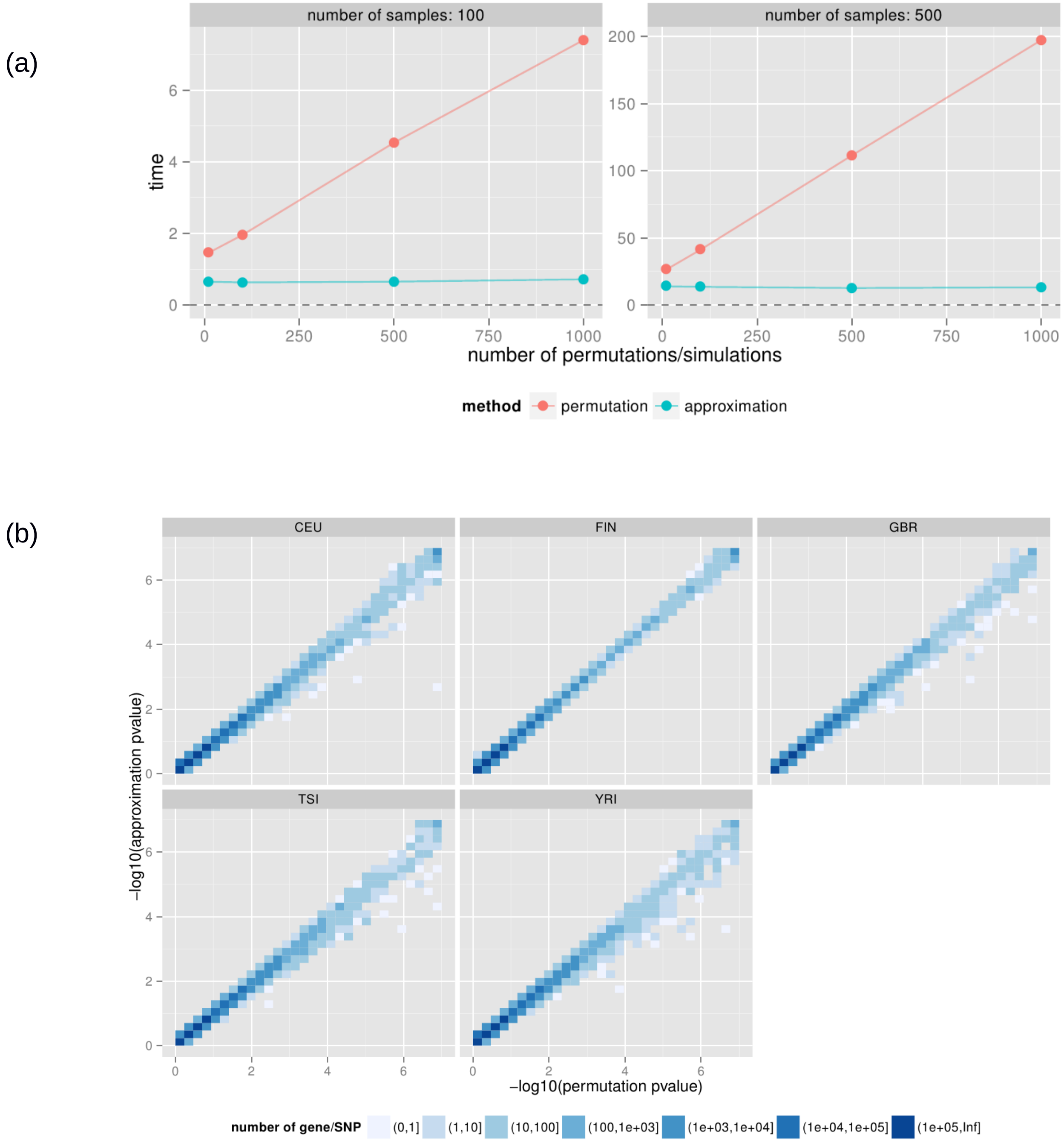
Supplementary Figure 1: Distribution of effect sizes in real and simulated SNPs. The effect size is measured as the sum of the absolute differences in average splicing ratios between two groups, divided by two. In red, effect sizes when comparing groups according to SNPs tested on the CEU population. In blue, effect sizes computed comparing two randomly created groups from the CEU population. Partitions of the CEU population induced by SNPs are more likely to generate biologically relevant groups than random partitions.



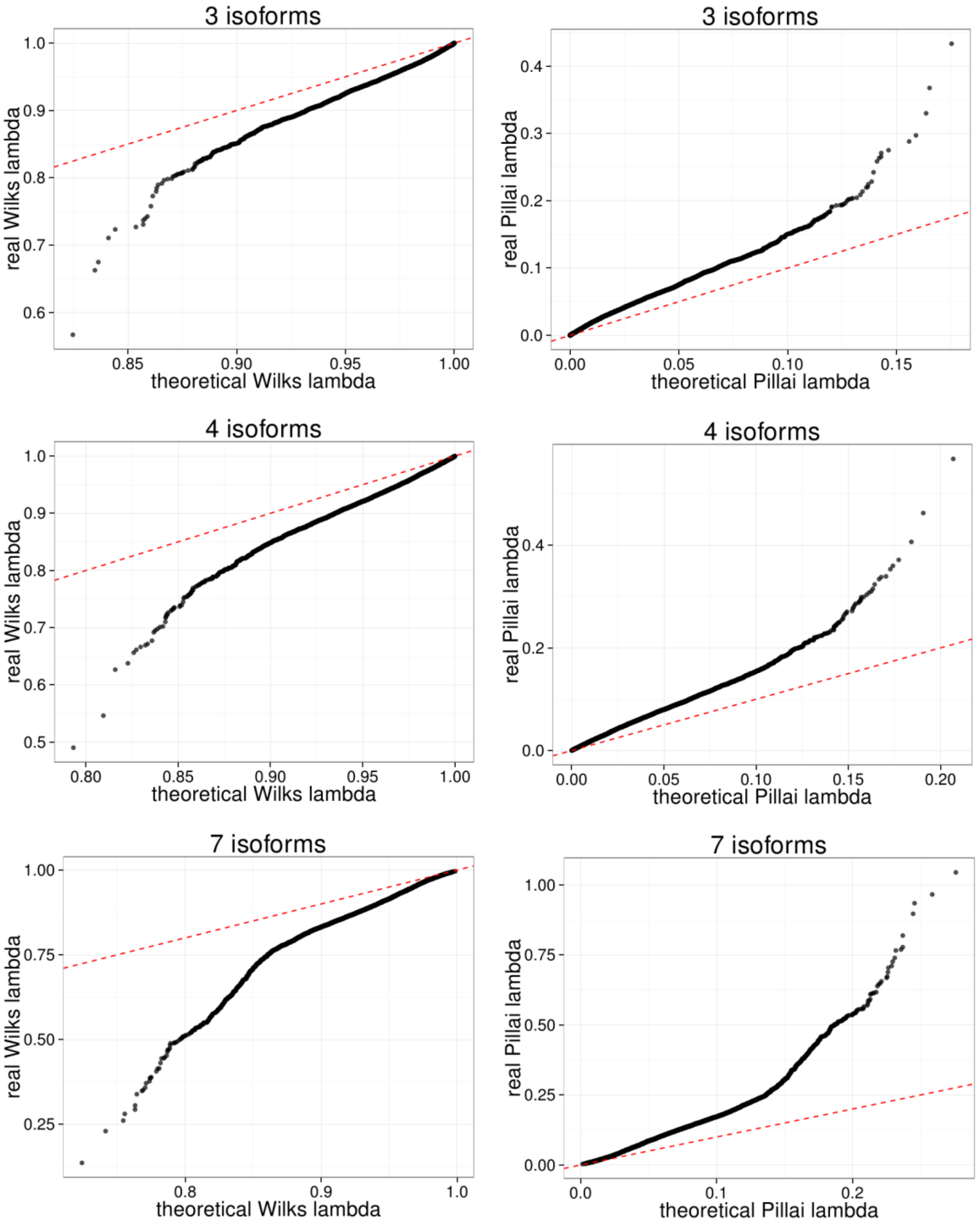
SS_W= Sum squared Hellinger distances to group centroids

SS_B= Weigthted sum squared Hellinger distances to global centroid

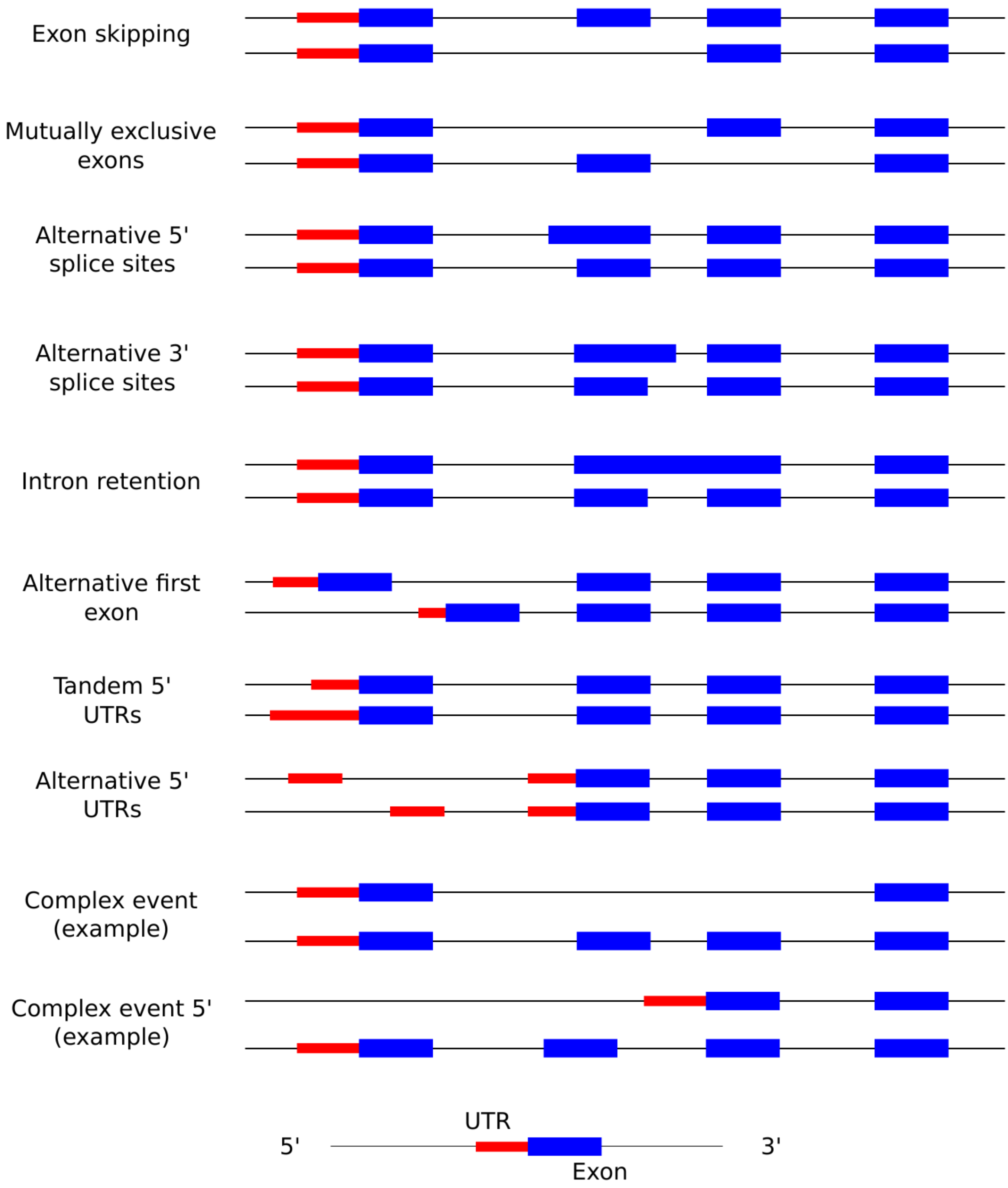
Supplementary Figure 2 : Within group SSW and between group SSB variability in the case of a gene with three isoforms (2-simplex space). Each color corresponds to a genotype and each triangle to a given observation (that is the proportion of the three isoforms in an individual). In the figure, individuals express predominantly an isoform depending on the genotype: isoform 1 for individuals with the AA genotype, isoform 2 for GG genotypes and isoform 3 for AG genotypes. Squares correspond to the centroids within each population and the red square to the global centroid. **Left:** the dotted lines represent the distance of the points corresponding to each genotype to the genotype centroid, that is the variability of the splicing ratios within genotypes. **Right:** the dotted lines represent the distance of the group centroids to the global centroid. sQTLseekeR relies on the comparison of these two variabilities.



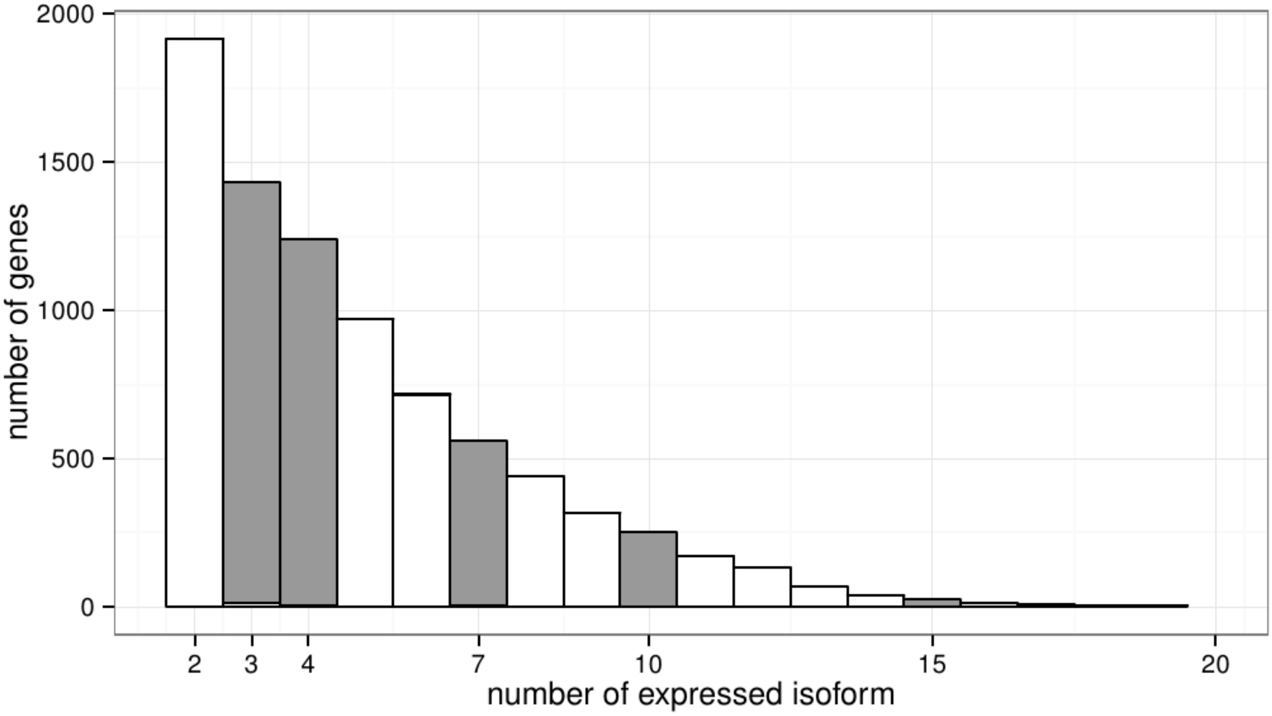
Supplementary Figure 3 : Permutation versus the approximation approach for the estimation of the significance of the associations. a) Number of permutations/simulations as a function of the number of samples analyzed. b) P-values estimated via permutations compared to P-values estimated via simulations in the Geuvadis population investigated.



Supplementary Figure 4 : Theoretical and real distribution of MANOVA statistics. Quantile-Quantile plots of Wilk's lambda (left) and Pillai's trace (right) of the distributions simulated under a model of multivariate normality (theoretical) and computed from the real data by randomly permuting the labels of the groups (real). Distributions were computed on the CEU population for genes expressing 3, 4 and 7 isoforms.



Supplementary Figure 5 : Splicing events denition. Summary of the splicing events definition used in the event classification Figure 4.



Supplementary Figure 6 : Number of genes (among the tested ones) expressing a given number of isoforms. The bar show the average across the ve populations. The shaded bars correspond to the number of isoforms of the genes simulated in our study**.**

	CEU	FIN	GBR	TSI	YRI
Samples	91	95	94	93	89
Associations tested within the gene					
Tested SNPs	1,258,255	1,293,086	1,266,258	1,252,401	1,895,204
Tested genes	9,997	10,029	10,006	10,043	9,983
Associated SNPs	2,517	2,422	1,694	1,701	1,433
Associated genes	69	77	85	86	83
Associations tested with a randomly selected gene					
Tested SNPs	1,158,299	1,195,389	1,131,122	1,117,988	1,754,599
Tested genes	9,335	9,25	8,971	8,879	9,345
Associated SNPs	13	21	12	5	38
Associated genes	5	5	6	4	17

Supplementary Table 1 : sQTLs in Geuvadis populations. Number of tested and associated variants and genes at 1% FDR.

Gene	**GO terms**
ATXN3	transcription, DNA-dependent; regulation of transcription, DNA-dependent
BAZ2B	transcription, DNA-dependent; regulation of transcription, DNA-dependent
CARD11	positive regulation of NF-kappaB transcription factor activity
CORO2A	transcriptional repressor complex
EFTUD2	RNA splicing; nuclear mRNA splicing, via spliceosome
ESRRG	transcription, DNA-dependent; positive regulation of transcription, DNA-dependent; transcription initiation from RNA polymerase II promoter; sequence-specific DNA binding transcription factor activity
FER	positive regulation of NF-kappaB transcription factor activity
GPS2	negative regulation of transcription from RNA polymerase II promoter; transcriptional repressor complex; transcription corepressor activity
ITGA6	positive regulation of transcription from RNA polymerase II promoter
JUP	positive regulation of sequence-specific DNA binding transcription factor activity; transcription coactivator activity
LEF1	negative regulation of transcription from RNA polymerase II promoter; positive regulation of transcription, DNA-dependent; negative regulation of transcription, DNA-dependent; positive regulation of transcription from RNA polymerase II promoter; positive regulation by host of viral transcription; regulation of transcription from RNA polymerase II promoter; transcription factor complex; sequence-specific DNA binding transcription factor activity; RNA polymerase II distal enhancer sequence-specific DNA binding transcription factor activity; transcription factor binding; transcription regulatory region DNA binding
OR7D2	regulation of transcription, DNA-dependent
PARP1	regulation of transcription, DNA-dependent; transcription from RNA polymerase II promoter; transcription factor complex; transcription factor binding
POLR2J	transcription initiation from RNA polymerase II promoter; RNA splicingtranscription from RNA polymerase II promoter; nuclear mRNA splicing, via spliceosometranscription elongation from RNA polymerase II promoter; RNA splicingtranscription-coupled nucleotide-excision repair; nuclear mRNA splicing, via spliceosomepositive regulation of viral transcription; RNA splicing
PTPRK	negative regulation of transcription, DNA-dependent
RNF4	positive regulation of transcription from RNA polymerase II promoter; transcription factor binding; transcription, DNA-dependent; positive regulation of transcription, DNA-dependent; regulation of transcription, DNA-dependent; sequence-specific DNA binding transcription factor activity; transcription coactivator activity
RORA	positive regulation of transcription from RNA polymerase II promoter; transcription initiation from RNA polymerase II promoter; sequence-specific DNA binding transcription factor activity; ligand-activated sequence-specific DNA binding RNA polymerase II transcription factor activity; regulation of transcription, DNA-dependent; transcription, DNA-dependent
SKIL	negative regulation of transcription from RNA polymerase II promoter; transcription corepressor activity
SNURF	RNA splicing
TCF12	transcription, DNA-dependent; positive regulation of transcription, DNA-dependent; regulation of transcription, DNA-dependent; regulation of transcription from RNA polymerase II promoter; transcription factor complex; sequence-specific DNA binding transcription factor activity; transcription regulatory region DNA binding

ZNF280D	transcription, DNA-dependent; regulation of transcription, DNA-dependent
ZNF438	transcription, DNA-dependent; negative regulation of transcription, DNA-dependent; nucleic acid binding transcription factor activity
ZNF583	regulation of transcription, DNA-dependent; transcription, DNA-dependent
ZNF621	transcription, DNA-dependent; regulation of transcription, DNA-dependent
ZNF721	regulation of transcription, DNA-dependent; transcription, DNA-dependent

Supplementary Table 2 : Genes with trans-sQTLs and RNA transcription or processing activity.