Supporting Information

Lo *et al.* 10.1073/pnas.0805242105
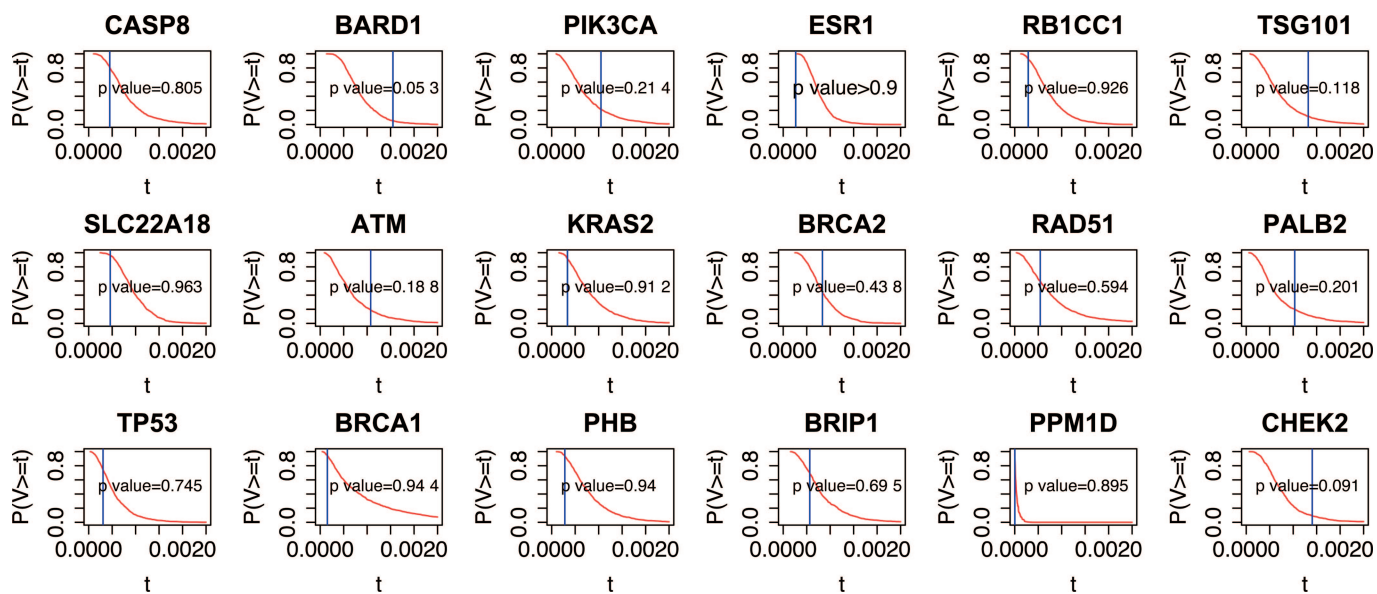

Fig. S1. $P(V \geq t)$ under the null estimated by permutations and the P values of the observed marginal effects.
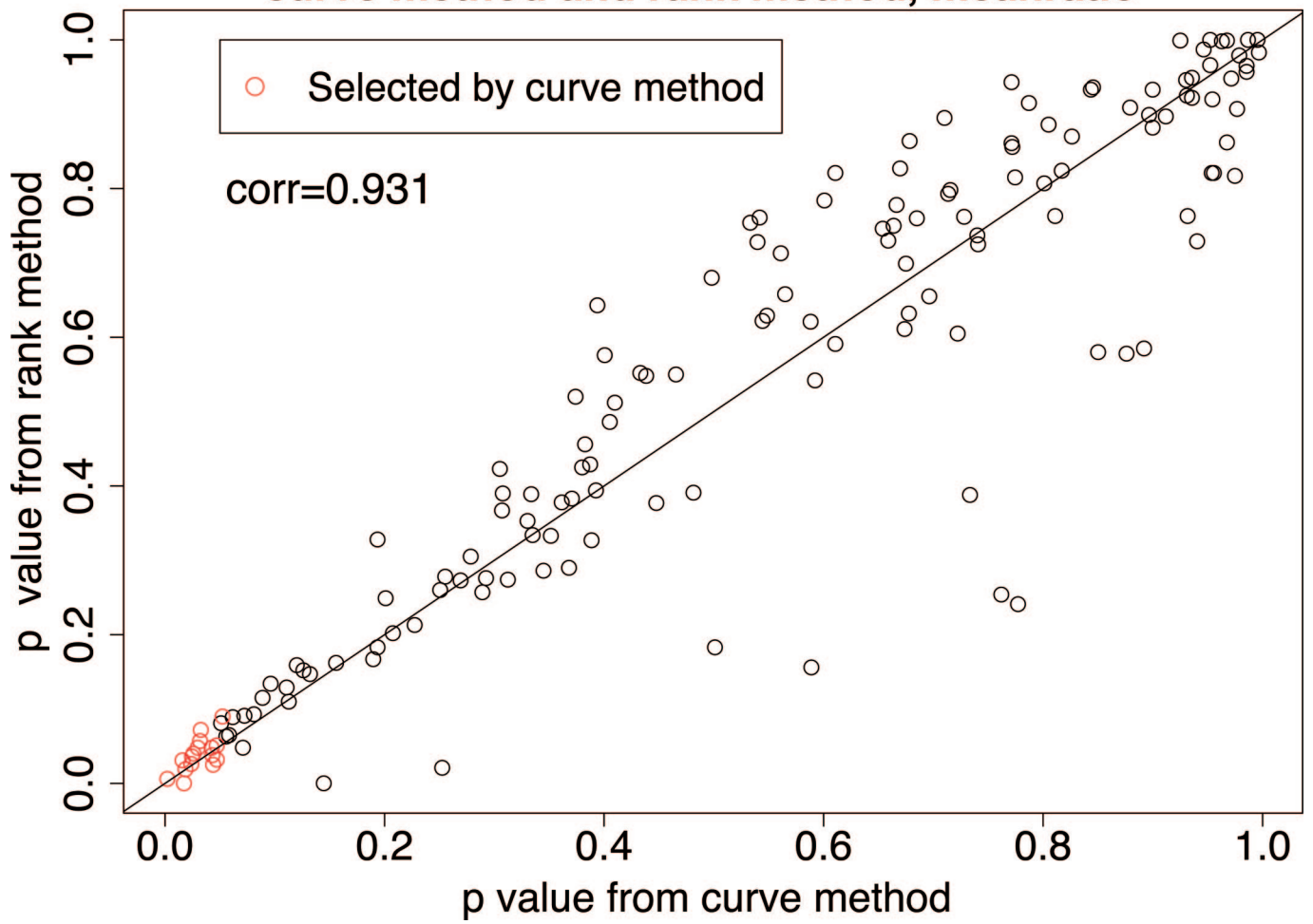
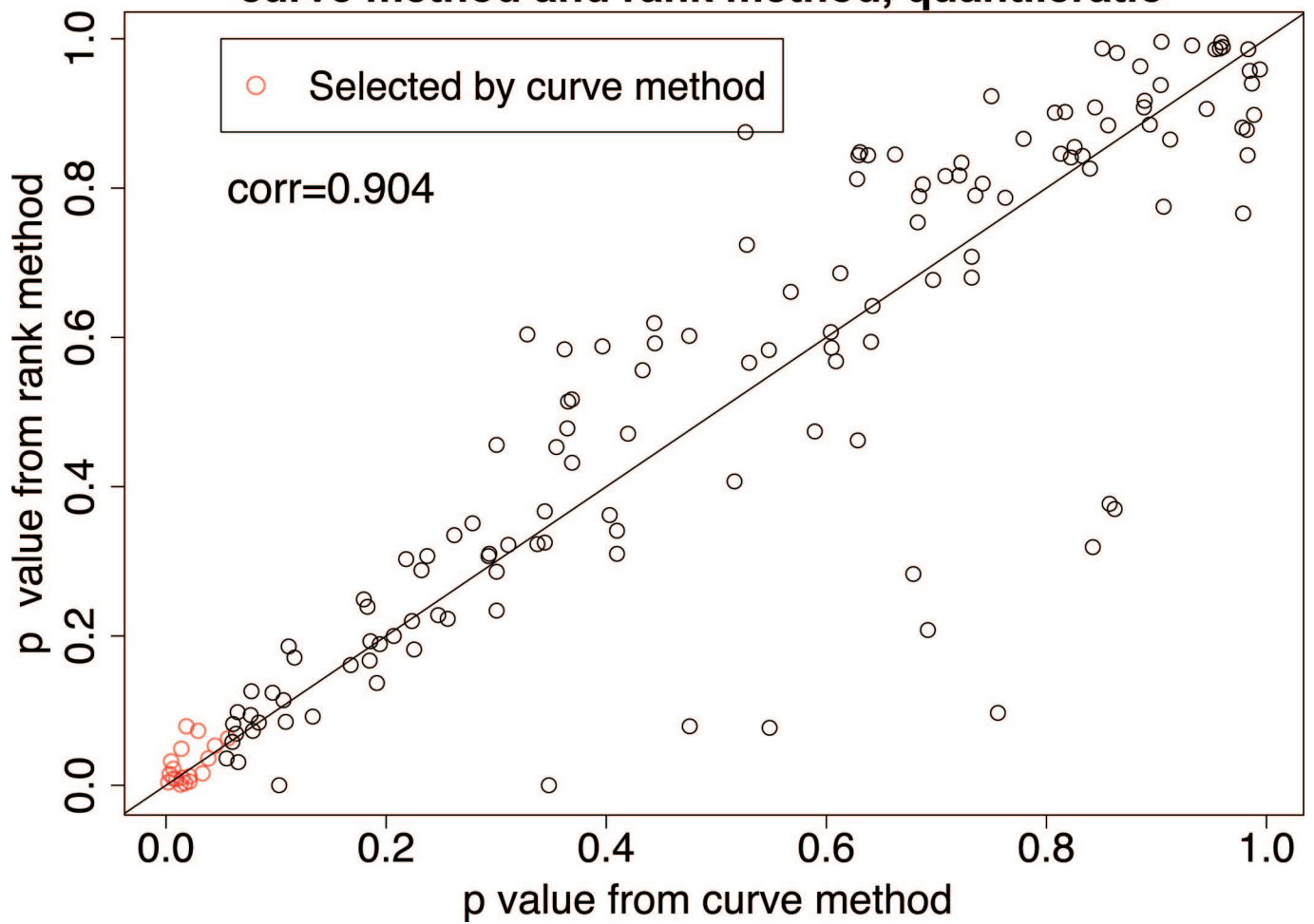**Fig. S2.** Correlation between *P* values from the Curve and Rank methods, for Mean-ratio statistics.

Fig. S3. Correlation between *P* values from the Curve and Rank methods, for Quantile-ratio statistics.
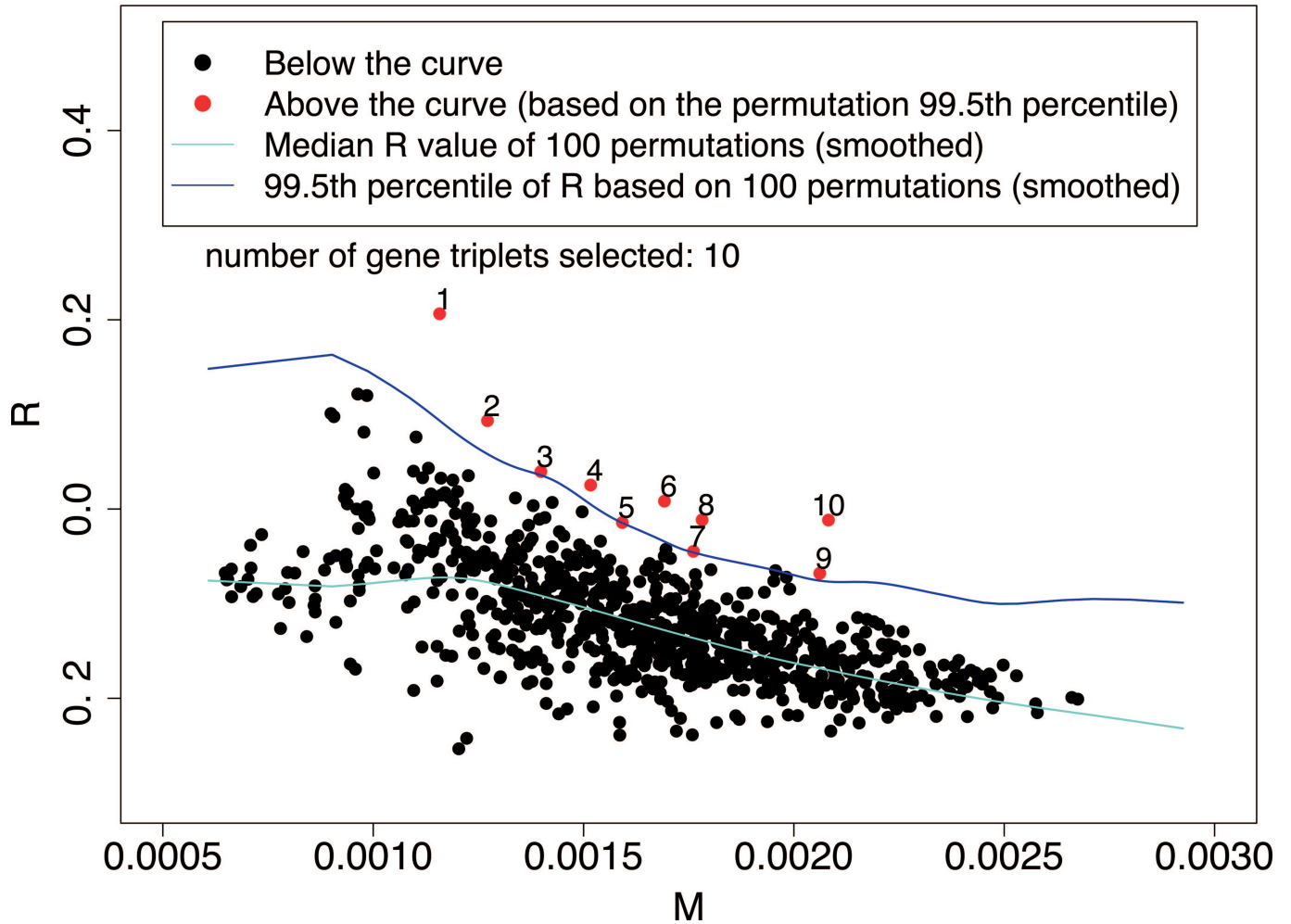
(M,R)plane, 3way Interaction

Fig. S4. (*M, R*) plane: observed data and permutation quantiles, three-way interactions. 1, *RAD51 TP53 BRCA1*; 2, *SLC22A18 RAD51 BRCA1*; 3, *RB1CC1 BRCA1 PHB*; 4, *KRAS2 BRCA1 PPM1D*; 5, *RB1CC1 PALB2 BRCA1*; 6, *ESR1 KRAS2 BRCA1*; 7, *KRAS2 BRCA1 BRIP1*; 8, *PALB2 BRCA1 PHB*; 9, *BARD1 BRCA1 PHB*; 10, *KRAS2 BRCA1 CHEK2*.
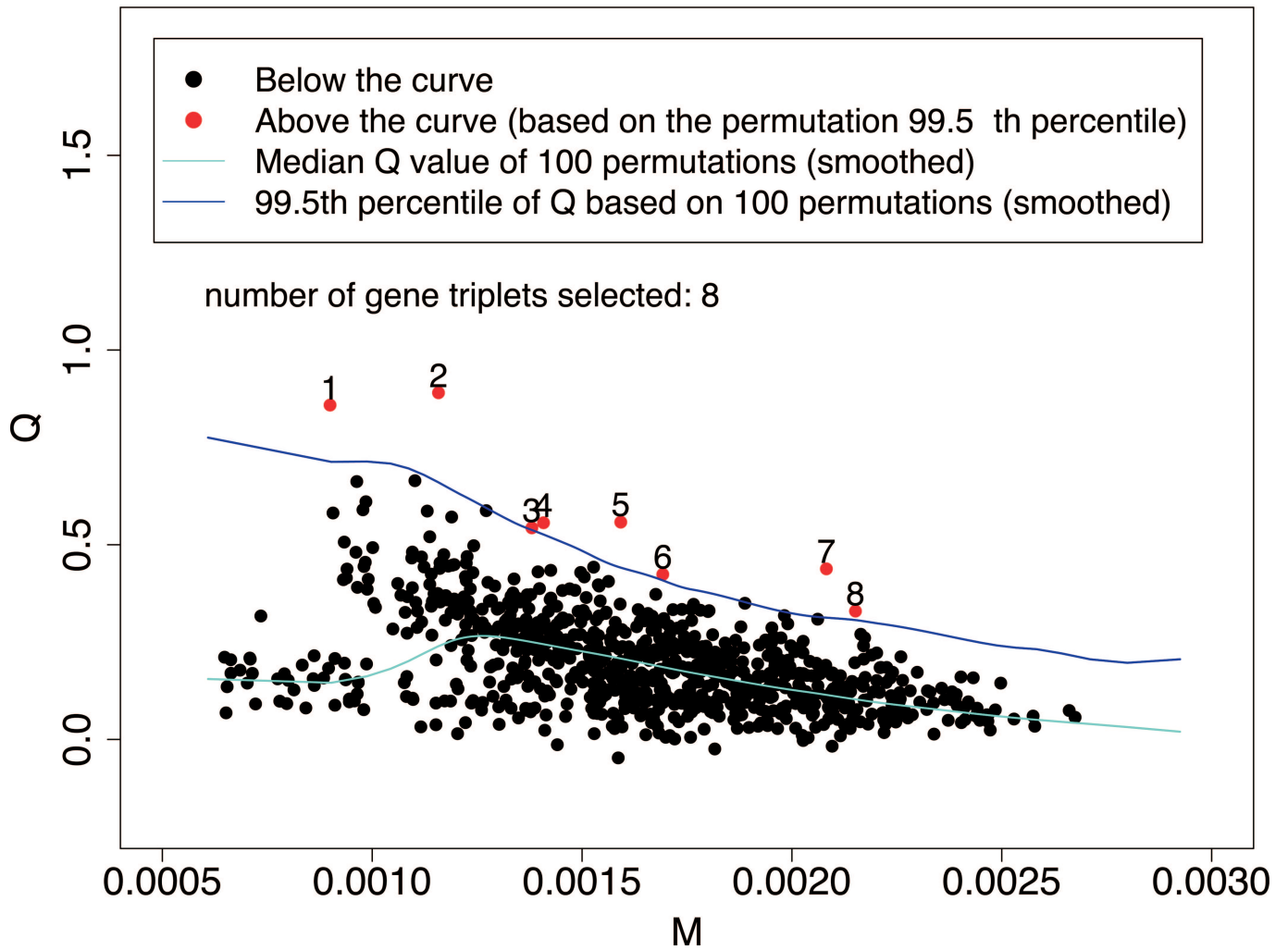
(M,Q)plane, 3way Interaction

Fig. S5. (*M, Q*) plane: observed data and permutation quantiles, three-way interactions. 1, *CASP8 TP53 BRCA1*; 2, *RAD51 TP53 BRCA1*; 3, *CASP8 PALB2 BRCA1*; 4, *RAD51 PALB2 BRCA1*; 5, *RB1CC1 PALB2 BRCA1*; 6, *ESR1 KRAS2 BRCA1*; 7, *KRAS2 BRCA1 CHEK2*; 8, *BARD1 TSG101 BRCA1*.
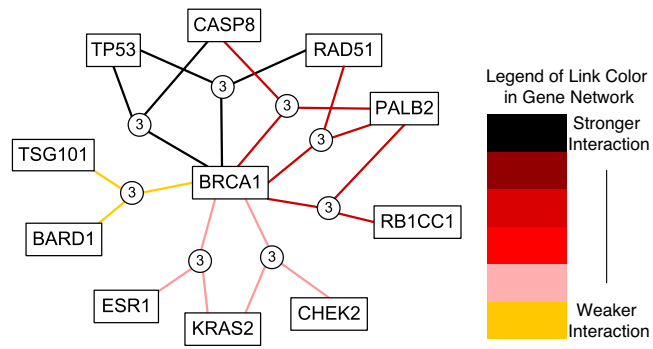
Fig. S6. Three-way interaction network based on 10 genes identified by Mean-ratio method.

Fig. S7. Three-way interaction network based on eight genes identified by quantile-ratio method.