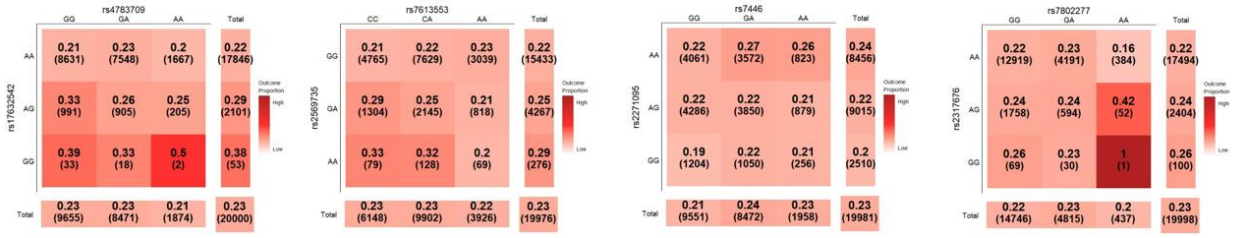
Supplementary Method Section

Simulation process for the 12 “causal” pairs in Part 1

1. **Templates of 4 significant SNP-SNP interaction pairs:** Use a template of the 4 SNP-SNP interaction pairs associated with a binary outcome based on our published paper to generate 12 causal pairs.



Footnote: Selected SNP-SNP interactions associated with prostate cancer aggressiveness. The 1st number in the cell is the prevalence of prostate cancer aggressiveness, and the 2nd value inside the paraphrasis is the sample size in the genotype combination. The darker the color indicates the higher risk of prostate cancer aggressiveness.

2. **Assign each subject a genotype combination of an SNP pair:** The samples per each of the 9 genotype combinations were generated using a multinomial distribution based on the sample distribution from the 3*3 table for a real pair.

3. **Generate the outcome for each subject:** For each SNP pair, there were 9 genotype combinations (such as AA-GG, AA-GA, and AA-AA). Using a logistic model with an SNP pair with 9 genotype combinations, we obtained 8 model coefficients, excluding an intercept based on real data. Then, we calculated the predicted probability of the outcome (such as Y=1 as a disease) based on this logistic model for the subjects in each genotype combination. Next, the outcome status for each subject was decided using a binomial distribution based on the predicted probability for each genotype.

4. **Test 3 various significance levels for each interaction pattern:** For each of the 4 interaction patterns, 3 various significance levels (low significance (L), medium significance (M), and high significance (H)) were tested. For generating pairs with various significance levels under a similar interaction pattern, we generated the predicted probabilities of the outcome based on the logistic models with and without adding a random variable from a normal distribution with a mean of 0 and standard deviation of 1 and 2 [N(0, 1) and N(0, 2)].

5. Other settings: Based on Steps 1-3, 12 causal pairs were generated. Each was tested under 3 sample sizes (n=5,000, 10,000, and 20,000).

Supplementary Table S1. Simulation setting of the 4 sets of causal pairs with a total of 12 causal pairs under 3 sample sizes in Part 1

Set	SNP1 Min<Maj (MAF)[2]	SNP2 Min<Maj (MAF)[2]	Pair[1]	Sample size	SNP-SNP p-pair[3]	SNP1 p-Main[3]	SNP2 p-Main[3]
C1-C2	G<A (0.055)	A<G (0.306)	$C1_H$-$C2_H$	20,000	$4.5X10^{-18}$	$1.2X10^{-15}$	0.022
			$C1_M$-$C2_M$		$9.1X10^{-14}$	$6.1X10^{-12}$	0.036
			$C1_L$-$C2_L$		$1.6X10^{-08}$	$2.2X10^{-7}$	0.090
			$C1_H$-$C2_H$	10,000	$7.5X10^{-10}$	$1.4X10^{-8}$	0.093
			$C1_M$-$C2_M$		$9.6X10^{-8}$	$8.4X10^{-7}$	0.122
			$C1_L$-$C2_L$		$3.8X10^{-5}$	$1.9X10^{-4}$	0.179
			$C1_H$-$C2_H$	5,000	$9.0X10^{-6}$	$6.6X10^{-5}$	0.159
			$C1_M$-$C2_M$		$1.5X10^{-4}$	$6.1X10^{-4}$	0.189
			$C1_L$-$C2_L$		$2.7X10^{-3}$	$8.2X10^{-3}$	0.227
C3-C4	A<G (0.121)	A<C (0.444)	$C3_H$-$C4_H$	20,000	$3.9X10^{-13}$	$5.3X10^{-9}$	0.244
			$C3_M$-$C4_M$		$2.1X10^{-10}$	$2.9X10^{-7}$	0.259
			$C3_L$-$C4_L$		$1.1X10^{-6}$	$9.3X10^{-5}$	0.277
			$C3_H$-$C4_H$	10,000	$2.1X10^{-7}$	$3.5X10^{-5}$	0.277
			$C3_M$-$C4_M$		$5.0X10^{-6}$	$2.5X10^{-4}$	0.261
			$C3_L$-$C4_L$		$4.1X10^{-4}$	$4.4X10^{-3}$	0.297
			$C3_H$-$C4_H$	5,000	$1.8X10^{-4}$	$3.4X10^{-3}$	0.294
			$C3_M$-$C4_M$		$6.8X10^{-4}$	$7.0X10^{-3}$	0.276
			$C3_L$-$C4_L$		$5.7X10^{-3}$	$3.4X10^{-2}$	0.290
C5-C6	G<A (0.351)	A<G (0.310)	$C5_H$-$C6_H$	20,000	$2.1X10^{-12}$	$9.2X10^{-7}$	$1.6X10^{-5}$
			$C5_M$-$C6_M$		$8.4X10^{-10}$	$1.4X10^{-5}$	$2.0X10^{-4}$
			$C5_L$-$C6_L$		$1.5X10^{-6}$	$9.0X10^{-4}$	0.003
			$C5_H$-$C6_H$	10,000	$4.9X10^{-7}$	$3.5X10^{-4}$	0.002
			$C5_M$-$C6_M$		$8.8X10^{-6}$	0.001	0.007
			$C5_L$-$C6_L$		$3.7X10^{-4}$	0.012	0.039
			$C5_H$-$C6_H$	5,000	$3.0X10^{-4}$	0.011	0.033
			$C5_M$-$C6_M$		$9.0X10^{-4}$	0.018	0.050
			$C5_L$-$C6_L$		$6.2X10^{-3}$	0.051	0.132
C7-C8	G<A (0.065)	A<G (0.142)	$C7_H$-$C8_H$	20,000	$6.7X10^{-5}$	0.019	0.070
			$C7_M$-$C8_M$		$5.6X10^{-4}$	0.042	0.071
			$C7_L$-$C8_L$		$4.5X10^{-3}$	0.106	0.120
			$C7_H$-$C8_H$	10,000	$3.1X10^{-3}$	0.077	0.134
			$C7_M$-$C8_M$		$6.0X10^{-3}$	0.123	0.163
			$C7_L$-$C8_L$		0.016	0.163	0.183
			$C7_H$-$C8_H$	5,000	0.017	0.163	0.207
			$C7_M$-$C8_M$		0.024	0.176	0.195
			$C7_L$-$C8_L$		0.046	0.240	0.241

[1] Significance level of an interaction pair: H (high significance), M (medium significance), L (low significance)

[2] Min: minor allele, Maj: major allele, MAF: minor allele frequency

[3] p-main median of the p-value of SNP main effect; p-pair: median p-value of SNP-SNP interaction pair based on 1000 simulation runs.

Supplementary Table S2. Summary of the selected causal-null (C-N) SNP-SNP interaction pairs associated with a binary outcome for 8 real SNPs

SNP pair SNP1-SNP2	SNP1 Min<Maj (MAF)[1]	SNP2 Min<Maj (MAF)[1]	SNP1 p-value (p-main)[2]	SNP2 p-value (p-main)[2]	SNP-SNP Interaction p-value (p-pair)[2]
rs17632542-N0	G<A (0.06)	A<G (0.05)	**2.2×10^{-15}**	0.365	**1.1×10^{-15}**
rs17632542-N1	G<A (0.06)	A<G (0.10)	**2.2×10^{-15}**	0.305	**1.3×10^{-15}**
rs17632542-N2	G<A (0.06)	A<G (0.20)	**2.2×10^{-15}**	0.746	4.3×10^{-14}
rs17632542-N3	G<A (0.06)	A<G (0.30)	**2.2×10^{-15}**	0.615	7.7×10^{-14}
rs17632542-N4	G<A (0.06)	A<G (0.40)	**2.2×10^{-15}**	0.690	0.354
rs17632542-N5	G<A (0.06)	A<G (0.50)	**2.2×10^{-15}**	0.212	0.455
rs2569735-N0	A<G (0.12)	A<G (0.05)	**5.5×10^{-9}**	0.365	**3.4×10^{-9}**
rs2569735-N1	A<G (0.12)	A<G (0.10)	**5.5×10^{-9}**	0.305	1.0×10^{-8}
rs2569735-N2	A<G (0.12)	A<G (0.20)	**5.5×10^{-9}**	0.746	3.0×10^{-7}
rs2569735-N3	A<G (0.12)	A<G (0.30)	**5.5×10^{-9}**	0.615	1.6×10^{-7}
rs2569735-N4	A<G (0.12)	A<G (0.40)	**5.5×10^{-9}**	0.690	1.5×10^{-7}
rs2569735-N5	A<G (0.12)	A<G (0.50)	**5.5×10^{-9}**	0.212	2.6×10^{-8}
rs1058205-N0	G<A (0.15)	A<G (0.05)	**9.5×10^{-8}**	0.365	**8.1×10^{-8}**
rs1058205-N1	G<A (0.15)	A<G (0.10)	**9.5×10^{-8}**	0.305	3.3×10^{-7}
rs1058205-N2	G<A (0.15)	A<G (0.20)	**9.5×10^{-8}**	0.746	1.6×10^{-6}
rs1058205-N3	G<A (0.15)	A<G (0.30)	**9.5×10^{-8}**	0.615	2.6×10^{-6}
rs1058205-N4	G<A (0.15)	A<G (0.40)	**9.5×10^{-8}**	0.690	2.4×10^{-6}
rs1058205-N5	G<A (0.15)	A<G (0.50)	**9.5×10^{-8}**	0.212	1.1×10^{-6}
rs4802755-N0	A<G (0.46)	A<G (0.05)	**1.8×10^{-7}**	0.365	**1.2×10^{-7}**
rs4802755-N1	A<G (0.46)	A<G (0.10)	**1.8×10^{-7}**	0.305	**1.6×10^{-7}**
rs4802755-N2	A<G (0.46)	A<G (0.20)	**1.8×10^{-7}**	0.746	1.4×10^{-2}
rs4802755-N3	A<G (0.46)	A<G (0.30)	**1.8×10^{-7}**	0.615	6.0×10^{-7}
rs4802755-N4	A<G (0.46)	A<G (0.40)	**1.8×10^{-7}**	0.690	3.7×10^{-7}
rs4802755-N5	A<G (0.46)	A<G (0.50)	**1.8×10^{-7}**	0.212	2.3×10^{-6}
rs174776-N0	A<G (0.11)	A<G (0.05)	**7.9×10^{-7}**	0.365	1.8×10^{-6}
rs174776-N1	A<G (0.11)	A<G (0.10)	**7.9×10^{-7}**	0.305	3.6×10^{-6}
rs174776-N2	A<G (0.11)	A<G (0.20)	**7.9×10^{-7}**	0.746	1.1×10^{-6}
rs174776-N3	A<G (0.11)	A<G (0.30)	**7.9×10^{-7}**	0.615	3.2×10^{-6}
rs174776-N4	A<G (0.11)	A<G (0.40)	**7.9×10^{-7}**	0.690	3.1×10^{-6}
rs174776-N5	A<G (0.11)	A<G (0.50)	**7.9×10^{-7}**	0.212	1.9×10^{-5}
rs2271095-N0	G<A (0.35)	A<G (0.05)	**2.0×10^{-6}**	0.365	3.6×10^{-6}
rs2271095-N1	G<A (0.35)	A<G (0.10)	**2.0×10^{-6}**	0.305	2.5×10^{-6}
rs2271095-N2	G<A (0.35)	A<G (0.20)	**2.0×10^{-6}**	0.746	3.4×10^{-5}
rs2271095-N3	G<A (0.35)	A<G (0.30)	**2.0×10^{-6}**	0.615	5.9×10^{-6}
rs2271095-N4	G<A (0.35)	A<G (0.40)	**2.0×10^{-6}**	0.690	4.1×10^{-5}
rs2271095-N5	G<A (0.35)	A<G (0.50)	**2.0×10^{-6}**	0.212	2.8×10^{-5}
rs7446-N0	A<G (0.31)	A<G (0.05)	**2.0×10^{-5}**	0.365	2.9×10^{-5}
rs7446-N1	A<G (0.31)	A<G (0.10)	**2.0×10^{-5}**	0.305	1.1×10^{-5}
rs7446-N2	A<G (0.31)	A<G (0.20)	**2.0×10^{-5}**	0.746	2.4×10^{-5}
rs7446-N3	A<G (0.31)	A<G (0.30)	**2.0×10^{-5}**	0.615	1.2×10^{-4}
rs7446-N4	A<G (0.31)	A<G (0.40)	**2.0×10^{-5}**	0.690	7.0×10^{-4}
rs7446-N5	A<G (0.31)	A<G (0.50)	**2.0×10^{-5}**	0.212	1.0×10^{-4}
rs266876-N0	G<A (0.24)	A<G (0.05)	**3.2×10^{-6}**	0.365	2.2×10^{-6}
rs266876-N1	G<A (0.24)	A<G (0.10)	**3.2×10^{-6}**	0.305	1.4×10^{-5}
rs266876-N2	G<A (0.24)	A<G (0.20)	**3.2×10^{-6}**	0.746	1.4×10^{-4}
rs266876-N3	G<A (0.24)	A<G (0.30)	**3.2×10^{-6}**	0.615	2.2×10^{-5}
rs266876-N4	G<A (0.24)	A<G (0.40)	**3.2×10^{-6}**	0.690	4.2×10^{-4}
rs266876-N5	G<A (0.24)	A<G (0.50)	**3.2×10^{-6}**	0.212	3.5×10^{-5}

[1] Min: minor allele, Maj: major allele, MAF: minor allele frequency

[2] Bold for significant results based on the Bonferroni criteria. p-main< 8.1×10^{-5} (=0.05/614), and p-pair< 2.7×10^{-7} (= $0.05/{}^{614}C_2$)

Supplementary Table S3. Summary of the selected null-null (N-N) SNP-SNP interaction pairs associated with a binary outcome

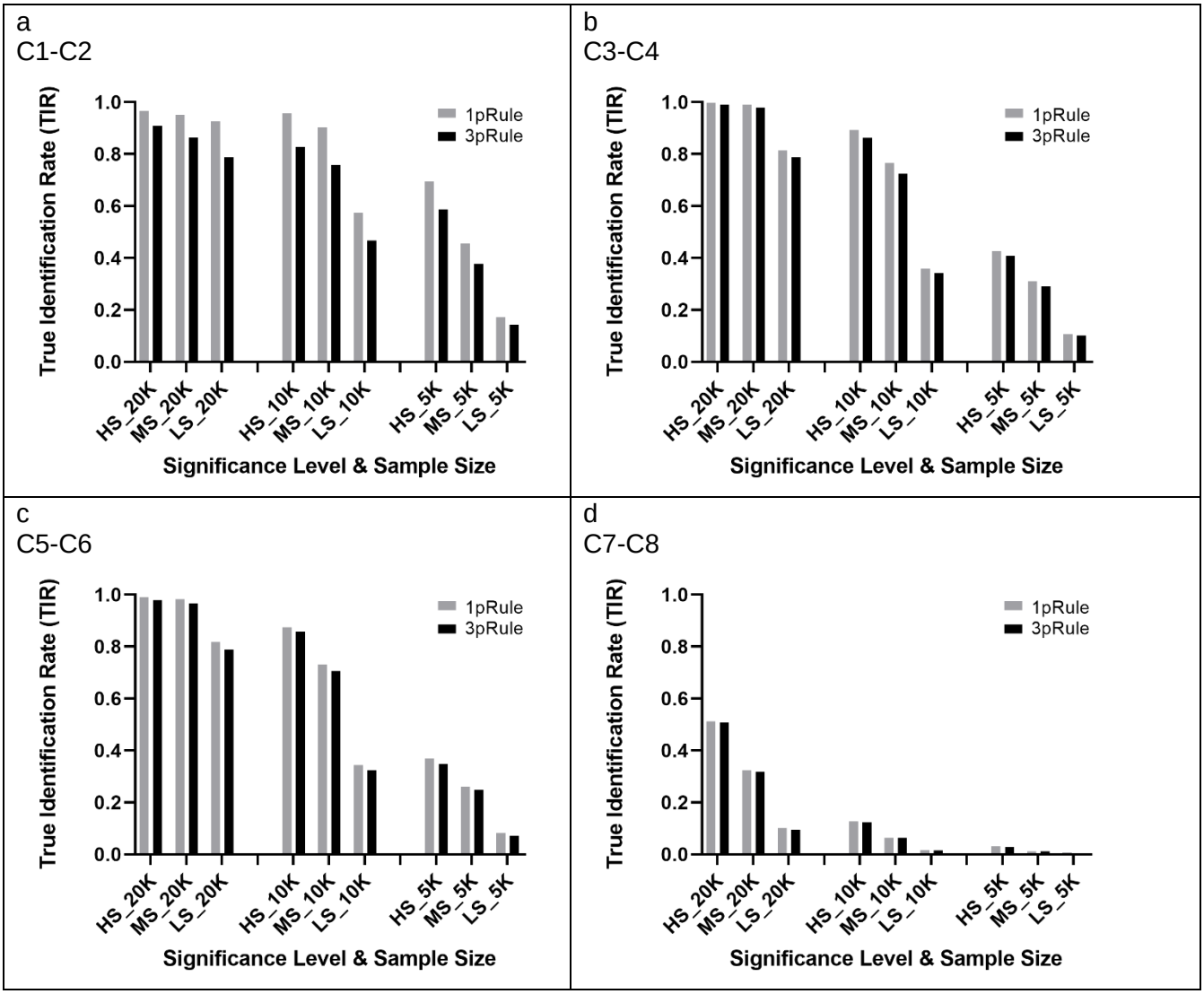
SNP pair SNP1-SNP2	SNP1 Min<Maj (MAF)[1]	SNP2 Min<Maj (MAF)[1]	SNP1 p-value (p-main)	SNP2 p-value (p-main)	SNP-SNP Interaction p-value (p-pair)
N0-N1	A<G (0.05)	A<G (0.10)	0.365	0.305	0.180
N0-N2	A<G (0.05)	A<G (0.20)	0.365	0.746	0.928
N0-N3	A<G (0.05)	A<G (0.30)	0.365	0.615	0.168
N0-N4	A<G (0.05)	A<G (0.40)	0.365	0.690	0.205
N0-N5	A<G (0.05)	A<G (0.50)	0.365	0.212	6.0×10^{-3}
N1-N2	A<G (0.10)	A<G (0.20)	0.305	0.746	0.092
N1-N3	A<G (0.10)	A<G (0.30)	0.305	0.615	0.014
N1-N4	A<G (0.10)	A<G (0.40)	0.305	0.690	0.013
N1-N5	A<G (0.10)	A<G (0.50)	0.305	0.212	9.0×10^{-3}
N2-N3	A<G (0.20)	A<G (0.30)	0.746	0.615	0.041
N2-N4	A<G (0.20)	A<G (0.40)	0.746	0.690	0.643
N2-N5	A<G (0.20)	A<G (0.50)	0.746	0.212	0.161
N3-N4	A<G (0.30)	A<G (0.40)	0.615	0.690	0.330
N3-N5	A<G (0.30)	A<G (0.50)	0.615	0.212	0.294
N4-N5	A<G (0.40)	A<G (0.50)	0.690	0.212	0.237

[1] Min: minor allele, Maj: major allele, MAF: minor allele frequency

Supplementary Table S4. Linkage disequilibrium (LD) among the null SNPs in a cluster

Cluster (bold: hub SNP)	No. of pairwise LD tests (No. Null SNPs)	Average LD	Min LD	Max LD
rs17632542-rs4783709	4005 (90)	0.00005	0	0.0009
rs2569735-rs7613553	6555 (115)	0.00005	0	0.0007
rs1058205-rs2274545	6105 (111)	0.00005	0	0.0006
rs4802755-rs4473378	26796 (232)	0.00005	0	0.001

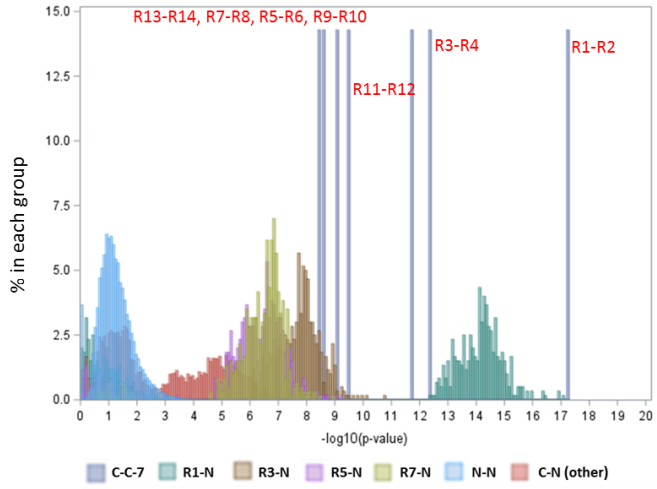
Supplementary Figure S1. True identification rates (TIR_{s1k}) for 4 sets of causal SNP pairs based on 1000 runs



Note: Each set had 3 clusters with a causal pair with various significance levels, such as HS, MS, and LS, for a high, medium, and low significance level, respectively. Sample size: 20K (n=20000), 10K (n=10000), and 5K (n=5000). Significance rules: 1pRule: p-pair < 2.7×10^{-7} ; 3pRule: p-pair< 2.7×10^{-7} and p-pair < p-main for SNP1, and p-pair< p-main for SNP2.

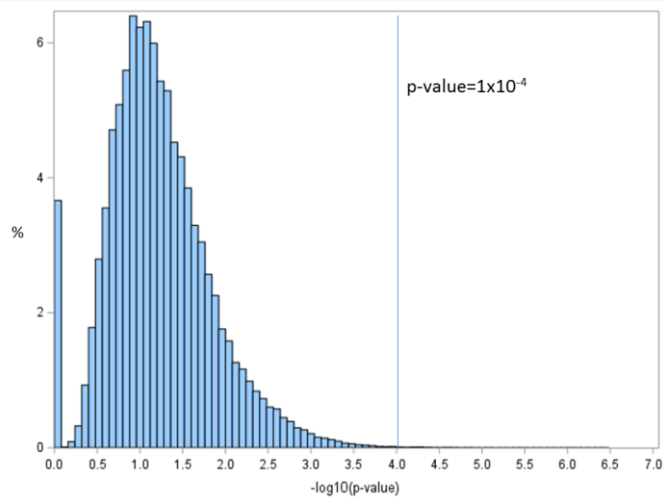
Supplementary Figure S2. Distribution of significance of SNP-SNP interactions by pair types

a



Causal (C-C-7) pairs	SNP pair SNP1-SNP2	SNP1 p-main	SNP2 p-main	p-pair
R1-R2	rs17632542-rs4783709	$2.2x10^{-15}$	0.027	$5.7x10^{-18}$
R3-R4	rs2569735-rs7613553	$5.5x10^{-9}$	0.551	$4.4x10^{-13}$
R5-R6	rs1058205-rs2274545	$9.5x10^{-8}$	0.065	$8.5x10^{-10}$
R7-R8	rs4802755-rs4473378	$1.8x10^{-7}$	0.728	$2.3x10^{-9}$
R9-R10	rs174776-rs1250240	$7.9x10^{-7}$	0.279	$3.5x10^{-10}$
R11-R12	rs2271095-rs7446	$2.0x10^{-6}$	$2.0x10^{-5}$	$1.7x10^{-12}$
R13-R14	rs266876-rs9521694	$3.2x10^{-6}$	0.001	$3.4x10^{-9}$

b



Note: a: 7 causal pairs and types of null pairs (C-N and N-N), and b: null pairs (N-N pairs). Note: ”C” represents a SNP from an observed causal pair; “N” represents a simulated null SNP; Results are based on 7 causal (C-C) pairs, 8400 causal-null (C-N) pairs, and 179700 null-null (N-N) pairs. The percentages were calculated based on the number of pairs in each group.

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