Case-Control Data

Sample	SNP1	SNP2	···	SNP1000	Status
1	0	1		2	Control
⋮					⋮
200	⋮	⋮	···	⋮	Control
201					Case
⋮					⋮
400					Case

Two-Locus Analysis (SNP1,SNP2)

Status	Genotype			
	AABB	*AaBB*	···	*aabb*
Control	63	35	···	0
Case	0	0	···	3

$\longrightarrow$ $p_0^{(1,2)}$ (Bonferroni-Corrected Chi-Square's *p*-value)

Permutation Test (Ensemble 3)

Data Set	Two-Locus Analysis			Fisher's Statistic
	(SNP1,SNP2)	(SNP2,SNP3)	(SNP1,SNP3)	
Original	$p_0^{(1,2)}$	$p_0^{(2,3)}$	$p_0^{(1,3)}$	T_0^3
Replicate 1	$p_1^{(1,2)}$	$p_1^{(2,3)}$	$p_1^{(1,3)}$	T_1^3
⋮	⋮	⋮	⋮	⋮
Replicate 10,000	$p_{10000}^{(1,2)}$	$p_{10000}^{(2,3)}$	$p_{10000}^{(1,3)}$	T_{10000}^3

$\longrightarrow$ p_0^3 (Raw *p*-value)

$$p_0^e = \left|\left\{i : 1 \le i \le 10000, T_i^e \ge T_0^e\right\}\right| / 10000$$

Global *p*-value Determination (4 Hypotheses)

Data Set	Ensemble 1		···	Ensemble 4	
	Fisher's Statistic	Unadjusted/ Raw *p*-value		Fisher's Statistic	Unadjusted/ Raw *p*-value
Original	T_0^1	p_0^1		T_0^4	p_0^4
Replicate 1	T_1^1	p_1^1		T_1^4	p_1^4
⋮	⋮	⋮	···	⋮	⋮
Replicate 10,000	T_{10000}^1	p_{10000}^1		T_{10000}^4	p_{10000}^4

$$p_i^e = \left|\left\{j : 0 \le j \le 10000, j \ne i, T_j^e \ge T_i^e\right\}\right| / 10000 \qquad p_i^{\min} = \min_e p_i^e \qquad p_0^{\min} = \min_e p_0^e$$

$$p_{\text{global}} = \left|\left\{i : 1 \le i \le 10000, p_i^{\min} \le p_0^{\min}\right\}\right| / 10000$$

Progressive Search

Iteration	Ensemble	Raw *p*-value (p_0^e)	Global *p*-value	Termination
1	{(SNP1,SNP2)}	0.0000	0.0000 (1 hypothesis)	No
2	{(SNP1,SNP2),(SNP2,SNP3)}	0.0000	0.0000 (2 hypotheses)	No
3	{(SNP1,SNP2),(SNP2,SNP3), (SNP1,SNP3)}	0.0000	0.0000 (3 hypotheses)	No
4	{(SNP1,SNP2),(SNP2,SNP3), (SNP1,SNP3),(SNP4,SNP5)}	0.0600	0.0000 (4 hypotheses)	Yes