

Supplemental Methods**Statistical Tests***Allelic χ^2 Test and Fisher's Exact Test*

Consider the 2×2 contingency table of allele counts by disease state, for a given SNP with alleles $A = \{A, a\}$. The standard χ^2 statistic is calculated

	A	a	
cases	A_{cas}	a_{cas}	$2N_{cas}$
controls	A_{con}	a_{con}	$2N_{con}$
	A_{total}	a_{total}	$2N$

as

$$\chi^2 = \frac{N(A_{cas}a_{con} - a_{cas}A_{con})^2}{2N_{cas}N_{con}A_{total}a_{total}}$$

Fisher's Exact test is calculated from the corresponding hypergeometric distribution,

$$p = \frac{(2N_{cas})!(2N_{con})!(A_{total})!(a_{total})!}{(A_{cas})!(a_{cas})!(A_{con})!(a_{con})!(2N)!}$$

Cochran-Armitage Trend Test

For a given SNP, consider the 2×3 contingency table of genotype count by disease state, with genotype classes $G = \{g_0, g_1, g_2\}$ corresponding to carriers of zero, one, or two copies of the minor allele.

We calculate the test-statistic as

	<i>AA</i>	<i>Aa</i>	<i>aa</i>	Total
cases	AA_{cas}	Aa_{cas}	aa_{cas}	$2N_{cas}$
controls	AA_{con}	Aa_{con}	aa_{con}	$2N_{con}$
Total	AA_{total}	Aa_{total}	aa_{total}	$2N$

$$T = \frac{\sum_{i=0}^2 w_i \cdot (N_{con} \cdot g_{i|con} - N_{cas} \cdot g_{i|cas})}{Var(T)}$$

where $w = \{w_0, w_1, w_2\}$ is the set of weights to be applied to the k genotype categories. Under an additive model, in which each additional copy of a disease-associated allele increases liability to illness, we apply weights $w = \{0, 1, 2\}$. For large N , the approximation of T_{catt} is a normally distributed ($N_{(0,1)}$), *1d.f.* random variable and a more powerful test of association than a genotypic χ^2 test.

Wald Test

Using logistic regression, we modeled the predicative value of genotype $X = X_1, \dots, X_N$ for disease state $Y = Y_1, \dots, Y_N$ as

$$Y_i \sim \beta_0 + \beta_1 \cdot X_i$$

where β_1 is the SNP regression coefficient. The Wald Test statistic, Z , is calculated as $\frac{\beta_1}{se(\beta_1)}$, where $se(\beta_1)$ is the estimated standard error. By comparing the value of Z to the normal distribution, we obtain the corresponding p -value.