

Table I. Evaluation of Candidate Gene Case-control Association Studies

ISSUE	KEY QUESTIONS	POSSIBLE SOLUTIONS
1. Selection of Cases and Controls	<ul style="list-style-type: none"> a. How was selection of cases and controls done? b. Do the case subjects meet appropriate criteria for disease status? a. Are control subjects free of disease and potential confounders? b. Are cases and controls similar for demographic and environmental factors? 	<ul style="list-style-type: none"> a. Population-based selection b. Family-based association design
2. Sample Size	<ul style="list-style-type: none"> a. Are there adequate no. of cases and controls? 	<ul style="list-style-type: none"> a. Minimum number of cases and controls included
3. Population Stratification	<ul style="list-style-type: none"> a. Are cases and controls matched? 	<ul style="list-style-type: none"> a. Matching on ethnicity b. Family-based association designs c. Negative results with multiple unlinked markers
4. Selection of Candidate Gene Polymorphism	<ul style="list-style-type: none"> a. Biologically reasonable? b. Positional candidate? c. All variants identified? 	<ul style="list-style-type: none"> a. Demonstration of biologically functional effect b. Within linked region in human or syntenic from animal model c. Complete sequencing of the gene
5. Observation Bias	<ul style="list-style-type: none"> a. How was the phenotyping and genotyping done? 	<ul style="list-style-type: none"> a. Blind assessment of genotype and phenotype
6. Linkage Disequilibrium	<ul style="list-style-type: none"> a. Are there other genes? b. Are there other polymorphisms in this gene? 	<ul style="list-style-type: none"> a. Haplotypes b. Family-based association
7. Allele or Genotype-Based Analysis	<ul style="list-style-type: none"> a. How are the heterozygotes treated in analysis? 	<ul style="list-style-type: none"> a. Use appropriate genetic model
8. Multivariate Analysis	<ul style="list-style-type: none"> a. Are relevant covariates identified? 	<ul style="list-style-type: none"> a. Use appropriate genetic model
9. Gene by Environment Interaction	<ul style="list-style-type: none"> a. Is sample size large enough to detect a gene environment 	<ul style="list-style-type: none"> a. Stratification by environmental exposure b. Multivariate analysis interaction
10. Multiple Comparisons	<ul style="list-style-type: none"> a. How many alleles were tested? 	<ul style="list-style-type: none"> a. Bonferroni correction

b How many phenotypes were tested?

b. Estimation of empirical p
values

c. How many genetic loci were tested?

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