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A strategic approach to genetic model selection in association studies: A practical guide

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Genetic association studies, particularly in the post-genomic era, are widely used to evaluate potential links between genetic polymorphisms in candidate genes and the risk of complex multifactorial diseases. The case-control design is the most common approach in these studies. Naturally, after several studies on a topic have been published, a meta-analysis is often conducted. In such analyses, statistical comparisons are performed based on genetic models. The purpose of this guide is to clarify when each genetic model should be applied.

Consider a single-nucleotide polymorphism on an autosome chromosome involving an A to G transition. This gives us two alleles: the ancestral allele A (with a higher frequency) and the variant allele G (with a lower frequency). This polymorphism results in three possible genotypes: AA, AG, and GG. In genetic association studies, the strength of an association is expressed by calculating the odds ratio (OR). Most researchers use all four genetic models in their statistical analyses, which are:

1. Co-dominant model: The OR for the AG and GG genotypes is calculated separately, with the AA genotype as the reference.

2. Dominant model for the variant allele G: This model assumes that the AG and GG genotypes confer a similar change in disease risk. A single OR is calculated for the combined AG + GG group compared to the AA genotype.

3. Recessive model for the variant allele G: This model assumes that only the GG genotype is associated with an altered disease risk, while the AG genotype is considered to have the same risk as AA. A single OR is calculated for the GG genotype compared to the combined AA + AG group.

4. Allelic model: The number of alleles is compared between cases and controls, and an OR is calculated for the allele G compare to the allele A.

Many researchers feel obligated to perform all these comparisons. However, this is not only unnecessary but can also complicate the interpretation of results. Furthermore, increasing the number of comparisons requires the use of adjusted *p*-values to control for multiple testing, a key point that is often overlooked by researchers.

The recommended first step is to perform the statistical analysis under the co-dominant model. As mentioned, this yields two ORs for the GG and AG genotypes. The statistical significance of these ORs determines the subsequent analytical path. The decision process which is summarized in Figure 1, is as follows:

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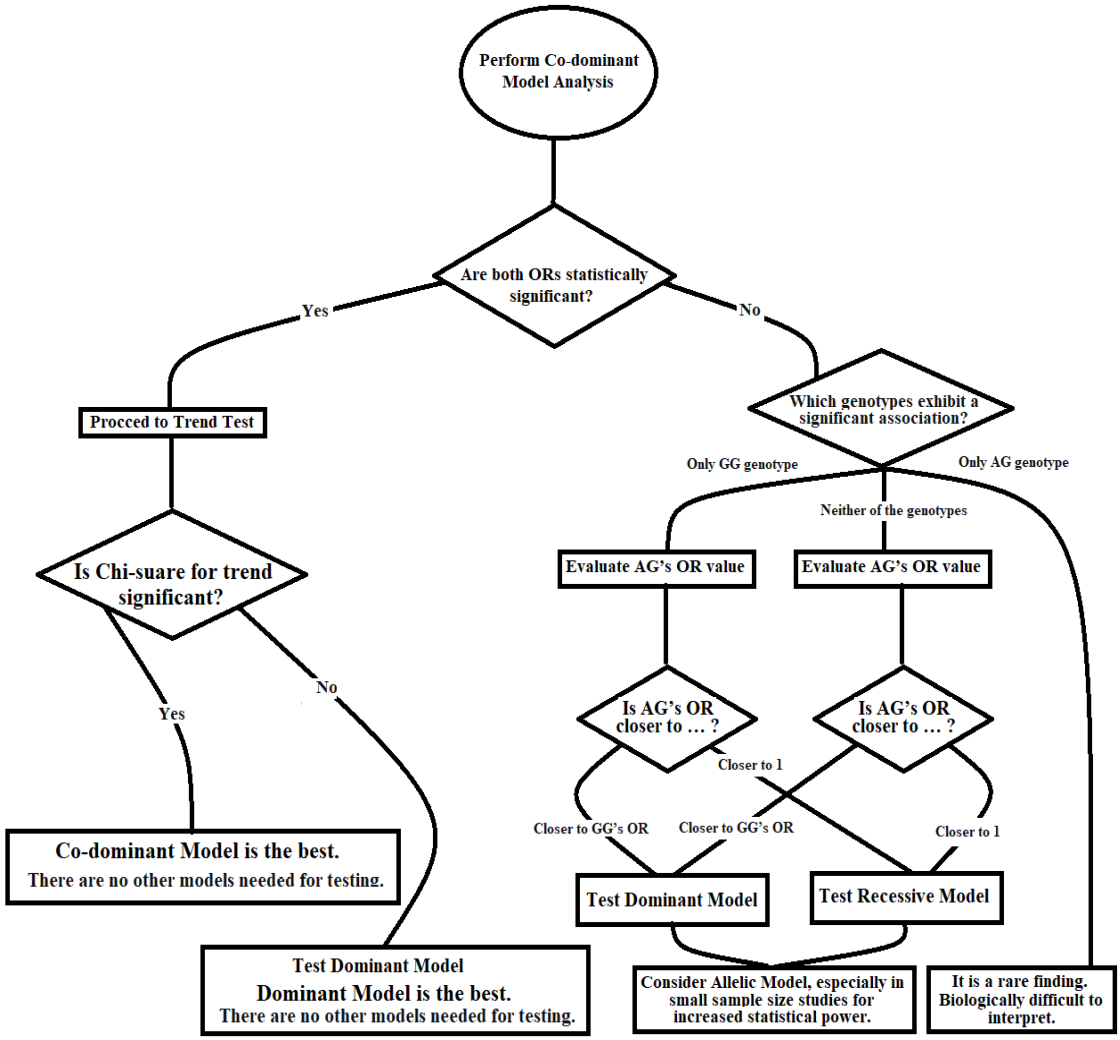

Figure 1: Workflow for Genetic Model Selection Based on Odds Ratios in Association Studies

If both ORs are significant: We know that genotypes AA, AG, and GG have 0, 1, and 2 the variant G alleles, respectively. The association between the number of the G alleles and the OR values of the genotypes is examined using a chi-square test for trend. If the trend is significant, the relationship follows a co-dominant model, meaning disease risk depends on the number of G alleles. No other models need to be tested. If the trend is not significant, it indicates that the ORs for the AG and GG genotypes statistically are similar, suggesting the G allele may act in a dominant manner, therefore, the dominant model (comparing AG + GG vs. AA) should be used. Since the individual ORs were significant, the OR from this model will also be significant, and no further models are needed.

If only the GG genotype OR is significant: The value of the AG genotype's OR must be examined. If this is closer to the GG OR, a dominant model is suggested and the comparison of AG + GG vs. AA should be performed. If the AG OR is closer to 1 (the risk of AA reference genotype), a recessive model is indicated and the comparison of GG vs. AA + AG should be done.

If neither OR is significant: The value of the AG genotype's OR must again be examined. If it is closer to the GG OR or closer to 1, a dominant or a recessive model is suggested, respectively.

Using the allelic model is not necessary when a clear co-dominant model is established. However, it can be useful in the other scenarios. This model is particularly recommended in studies with small sample sizes because the number of alleles (twice the sample size) provides greater statistical power, potentially revealing a significant association that was not detected in the genotype-based models.

Finally, it should be noted that in some studies, the heterozygote (AG) genotype shows a significant association while the GG genotype does not. Besides being a rare finding, this result is biologically difficult to interpret and requires careful consideration.

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