

In genetic association studies, different complex phenotypes are often associated with the same marker. Such associations can be indicative of common genetic causes, but can also be solely attributable to non-genetic/environmental links between the traits. The presence of multiple associations disguises the causative association and aggravates its identification. To identify the phenotypes with the inducing genetic association, statistical methodology is needed to distinguish between the different origins of the associations. Here, we propose a simple, general adjustment principle that can be incorporated into any genetic association test which is then able to infer whether a SNP has a direct biological influence on a given trait other than through the SNP's influence on another correlated phenotype. The proposed adjustment is straightforward to compute and is robust against population admixture. It is particularly relevant for genome-wide association studies, pathway analysis, and association studies with an integrative genomic component. Using simulation studies, we show that, in the presence of a non-marker related link between phenotypes, standard association tests without the proposed adjustment can be biased. The simulations confirm our theoretical derivations that the proposed methodology is unbiased in such situations. The adjusted tests have sufficient power to infer causal genetic effects for realistic sample sizes. An application of the principle to three genome-wide association studies illustrates its practical importance.