described as the combination of (i) a method for performing variable selection on the SNPs used to estimate genetic similarity and (ii) the removal of test SNPs and those nearby from the estimation of genetic similarity (performed[6] efficiently for each test SNP in turn).

When reanalyzing the simulated data of Mathieson and McVean, we selected only those rare SNPs that were likely to predict the sharp, spatial non-genetic causes (and any causal SNPs) to estimate genetic similarity. In contrast, use of all available SNPs to estimate genetic similarity, as in the comparison included in Mathieson and McVean[1], leads to increased variance in the parameter estimates, diluting the ability of the LMM to correct well for confounding[7]. Note that, if the causal variants were spatially structured (following the population structure), a model such as ours that controls the type I error would also lose power to detect the causal variants because they would appear as confounders. In contrast, a model that maintains power to detect these causal variants, such as linear regression, would not control the type I error. We see no way to maintain both power and control of type I error in such a setting.

Although we have here applied FaST-LMM-Select only to real-valued phenotypes, we have previously applied it to both real and synthetic case-control studies for common variants with great success[6]. Additionally, others have provided theoretical arguments for the use of linear models for case-control data[4,10].

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Mathieson and McVean reply:

Listgarten and colleagues demonstrate that their recently reported FaST-LMM-Select method for controlling for population structure in association studies[1] can correct the inflation in test statistics for rare variants described in our study of structured populations[2] while still retaining power to detect causal variants that are not spatially clustered. However, as they note, their method will inevitably lose power to detect rare causal variants that are spatially clustered (as most rare variants are likely to be), and the problem of how to reliably detect such associations remains open. Simple association studies are fundamentally limited in this way, and we believe that different study designs may be required to reliably detect rare causal variants. Family based studies can correct for population structure and retain power when effect sizes are large, but, for more modest effects, perhaps the most promising approach comes from large studies in isolated populations. Many of these populations have extended pedigree information, and transmission-style tests using these pedigrees or local genomic relatedness information (for example, regions of shared identity by descent, IBD) may be able to combine the robustness of family based tests with the sample sizes and consequent power of association studies.

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