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Comments on 'Delta-Centralization Fails to Control for Population Stratification in Genetic Association Studies'

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Dadd et al. [1] raise concerns about the simulation methods we employed in our two previous publications [2, 3], concerning our delta-centralization (DC) method of dealing with population stratification (PS). They conclude that the DC method should 'be dropped from the list of valid methods for the correction of PS in association studies.' Our aim in this short communiqué is two-fold: (i) to clarify why we used the particular simulations we did in Gorroochurn et al. 2006 and 2007 [2, 3]; (ii) to suggest how DC can be adjusted to work properly under the Balding-Nichols (BN) simulation model used by Dadd et al. [1].

Our previous simulation methods assumed pre-specified subpopulation allele frequencies at the candidate loci so as to be able to fix different values of our PS parameter, δ , and then be able to compare the performance of DC and genomic control (GC) under different levels of PS. Such a comparison would not have been pos-

sible under the BN simulation model, where subpopulation allele frequencies are generated according to a beta distribution.

DC depends on choosing 'null' loci whose allele frequencies in the controls match that at the candidate locus. Under the BN model, extra variability is allowed in the allele frequencies at the null loci. It is then possible for the allele frequencies at several null loci to match that at the candidate locus and yet some null loci will have a δ -estimate opposite in sign to that at the candidate locus. In this case, the overall δ will be under-estimated, yielding high type I error rates, as shown by Dadd et al. [1]. Our preliminary simulations under the BN model show that when null loci that match are all assigned the 'correct' sign, DC maintains proper type I error rates. We are in the process of fully investigating the power of such a procedure, and a full paper describing this adjustment and its ramifications will be forthcoming.

References

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