Authors’ response to a refinement to ‘how many genes underlie the occurrence of common complex diseases in the population?’ by Ramal Moonesinghe

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We appreciate Dr Ramal Moonesinghe’s derivation of a closed form to estimate the number of genes needed to achieve a particular population attributable fraction (PAF) assuming that the genotype frequency (\( G \)) and associated risk for disease (\( R_g \)) are constant. Dr Moonesinghe informed us of his result while our paper was in press. We tried to include this calculation in the paper with him as a co-author, but we were told that it was too late to do so.

Under the assumption of constant \( G \) and \( R_g \), an unlikely scenario in the real world, our results are consistent with that of the closed form for both additive and multiplicative models. However, the closed formula provides an exact point estimate of the number of genes needed for a PAF, while our approach provides a whole number estimate. For example, for \( G = 0.1 \), \( R_g = 1.2 \) to achieve a PAF of 30% under additive model, the closed form gives number of genes needed = 21.43, and our algorithm gives 22. Our algorithm will always give the whole number that is just above the desired PAF because we increase the number of genes one at a time during calculation. For the above example, our algorithm calculates the PAF produced by 21 genes, finds that it corresponds to a PAF just <30%, then increases to 22 genes. For 22 genes, the algorithm calculates the corresponding PAF, finds that it is just over 30%, and stops, reporting 22 as the number found.

Dr Moonesinghe’s closed form calculation applies when both \( G \) and \( R_g \) are constant. Our algorithm can be modified to estimate the number of genes needed for a PAF with varying \( G \) and/or \( R_g \); a closed form has not been identified for this situation.

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