Does Population Structure Affect Murine Genome-Wide Association Study (GWAS) Results?

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Since population structure (PS) increases the number of false positive associations in human GWAS, PS correction has become a routine step for human GWAS analysis. While it has been assumed that PS correction should also be routinely used for inbred strain GWAS, murine and human GWAS have two major differences. (i) Murine GWAS analyze <40 inbred mouse strains, while 10³ to 10⁵ subjects are examined in human GWAS. (ii) Human subjects are an interbreeding natural population with a heterozygous genome, and environmental variables are poorly controlled; while the inbred strains are non-interbreeding, their genome is homozygous, and environmental variables are strictly controlled. Consequently, human GWAS identify multiple genetic factors, each with a small genetic effect size; while murine GWAS identify a small number of genetic factors, each with a large genetic effect size. To assess the impact of PS on murine GWAS, we examined the strains and identified genetic factors from analysis of 8300 datasets that measure biomedical responses in inbred strain panels. Surprisingly, when responses in ≤30 strains were characterized, PS had a very minimal impact on murine GWAS results. Also, PS correction could lead to rejection of an experimentally confirmed true causative genetic factor, which is catastrophic for a murine GWAS. In summary, our analysis reveals that PS has a much smaller effect than expected for murine GWAS, and that other methods should be used to eliminate false positive associations.