A New Method Founds Evidence of Genetic Heterogeneity in Nicotine Dependence

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Aim: To study the genetic heterogeneity of complex diseases, we develop a non-parametric method for association analysis of high-dimensional genetic data, and use it to study the genetic heterogeneity of Nicotine Dependence (ND).

Methods: In this work, we propose a heterogeneity weighted U (HWU) method for association analysis that takes genetic heterogeneity into account. HWU can be applied to various types of phenotypes (e.g., binary and continuous) and is computationally efficient for high-dimensional genetic data. Through simulations and a genome-wide association analysis of ND, we compared HWU with a non-heterogeneity weighted U (NHWU) method and the conventional generalized linear model (GLM).

Results: The results showed that HWU attained higher power than NHWU and GLM when the underlying genetic etiology of a disease is heterogeneous. In the absence of heterogeneity, HWU attained similar performance to NHWU and GLM. Using HWU, we conducted a genome-wide analysis of ND. The genome-wide analysis of nearly one million genetic markers from the Study of Addiction: Genetics and Environments dataset took 7 hours, identifying heterogeneous effects of two new loci on nicotine dependence.

Conclusions: Converging evidence from previous study suggests that complex human diseases undergo substantial genetic heterogeneity. The development of new statistical methods with the ability to model genetic heterogeneity could facilitate the gene discovery process, as well as improve our knowledge of the complex mechanisms underlying human diseases. By applying the new method to a large-scale ND genetic dataset, we found no evidence of genetic heterogeneity due to ethnic or genetic background. However, our results suggested that the genetic causes of ND may differ in males and females.

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