# Scientists identify more powerful approach to analyze melanoma's genetic causes

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There may be a better way to analyze the genetic causes of cutaneous melanoma (CM) according to a study published in *Human Genetics* conducted by researchers Yale and Dartmouth. A statistical analysis using the natural and orthogonal interaction (NOIA) model showed increased power over existing approaches for detecting genetic effects and interactions when applied to the genome-wide melanoma dataset.

The gene-gene interactions underlying CM had not been fully explored. The usual functional model uses substitution of alleles for estimating genetic effects but the estimators are confounded. The NOIA model estimates population effects of alleles and the resulting estimators are orthogonal and no longer confounded. In simulation studies, the NOIA model had higher power for finding interactions and main effects than the usual model.

"We confirmed the previously identified significant associated genes HERC2, MC1R, and CDKN2A using a NOIA one-locus statistical model," said Christopher I. Amos, PhD, associate director for Population Sciences, Norris Cotton Cancer Center, Geisel School of Medicine at Dartmouth, a corresponding author of the study. "When compared to the usual one-locus model we found that the HERC2 signal was detected more clearly by the NOIA model" The NOIA model also identified an additional potential interaction between the rs1129038 of HERC2 gene and a region at chromosome 5. The SNPs that interact with HERC2 to increase melanoma risk are located in the IL31RA gene, which is involved in STAT3 signaling and upregulated in activated monocytes.

The first author Feifei Xiao, a postdoctoral associate of Yale University, concluded that the power of the NOIA model was better for detecting genetic effects when interactions are tested. When main and interaction effects between two loci were modeled, the usual functional model was less powerful.

CM is highly aggressive and accounts for the majority of deaths from skin cancer. Prior genome-wide association studies have identified multiple genetic factors for the illness, including MC1R, HERC2, and CDKN2A. This study provides new insights for understanding the influence of gene-gene interactions on melanoma risk.

The NOIA framework was developed for modeling gene-gene interactions in the analysis of quantitative traits, to allow for reduced genetic models, dichotomous traits, and gene-environment interactions. The NOIA statistical model can be used for additive, dominant, and recessive genetic models as well as for a binary environmental exposures. It is an easily implemented approach that improves estimation of genetic effects that include interactions.

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