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Knowing genetic makeup may not significantly improve disease risk prediction

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Harvard School of Public Health (HSPH) researchers have found that detailed knowledge about your genetic makeup—the interplay between genetic variants and other genetic variants, or between genetic variants and environmental risk factors—may only change your estimated disease prediction risk for three common diseases by a few percentage points, which is typically not enough to make a difference in prevention or treatment plans. It is the first study to revisit claims in previous research that including such information in risk models would eventually help doctors either prevent or treat diseases.

"While identifying a synergistic effect between even a single genetic variant and another risk factor is known to be extremely challenging and requires studies with a very large number of individuals, the benefit of such discovery for risk prediction purpose might be very limited," said lead author Hugues Aschard, research fellow in the Department of Epidemiology.

The study appears online May 24, 2012 and will appear in the June 8, 2012 print issue of The *American Journal of Human Genetics*.

Scientists have long hoped that using genetic information gleaned from the Human Genome Project and other genetic research could improve disease risk prediction enough to help aid in prevention and treatment. Others have been skeptical that such "personalized medicine" will be of clinical benefit. Still others have argued that there will be benefits in the future, but that current risk prediction algorithms underperform because

they don't allow for potential synergistic effects—the interplay of multiple genetic risk markers and environmental factors—instead focusing only on individual genetic markers.

Aschard and his co-authors, including senior author Peter Kraft, HSPH associate professor of epidemiology, examined whether disease risk prediction would improve for breast cancer, type 2 diabetes, and rheumatoid arthritis if they included the effect of synergy in their statistical models. But they found no significant effect by doing so. "Statistical models of synergy among genetic markers are not 'game changers' in terms of risk prediction in the general population," said Aschard.

The researchers conducted a simulation study by generating a broad range of possible statistical interactions among common environmental exposures and common genetic risk markers related to each of the three diseases. Then they estimated whether such interactions would significantly boost disease prediction risk when compared with models that didn't include these interactions since, to date, using individual genetic markers in such predictions has provided only modest improvements.

For breast cancer, the researchers considered 15 common genetic variations associated with disease risk and environmental factors such as age of first menstruation, age at first birth, and number of close relatives who developed breast cancer. For type 2 diabetes, they looked at 31 genetic variations along with factors such as obesity, smoking status, physical activity, and family history of the disease. For rheumatoid arthritis, they also included 31 genetic variations, as well as two environmental factors: smoking and breastfeeding.

But, for each of these disease models, researchers calculated that the increase in risk prediction sensitivity—when considering the potential

interplay between various genetic and environmental factors—would only be between 1% and 3% at best.

"Overall, our findings suggest that the potential complexity of genetic and environmental factors related to disease will have to be understood on a much larger scale than initially expected to be useful for risk prediction. The road to efficient genetic risk prediction, if it exists, is likely to be long," said Aschard.

"For most people, your doctor's advice before seeing your genetic test for a particular disease will be exactly the same as after seeing your tests," added Kraft.

Still, Aschard and his co-authors recommend further study of gene-gene and gene-environmental interactions because it can provide important clues, if not about disease risk, at least about disease causes—which could in turn lead to improved treatment and prevention strategies.

Marilyn Cornelis, research associate in the Department of Nutrition at HSPH, was also a co-author on the study.

More information: "Inclusion of Gene-Gene and Gene-Environment Interactions Unlikely to Dramatically Improve Risk Prediction for Complex Diseases," Hugues Aschard, Jinbo Chen, Marilyn C. Cornelis, Lori B. Chibnik, Elizabeth W. Karlson, Peter Kraft, *The American Journal of Human Genetics*, online May 24, 2012

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