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A hidden architecture: Researchers use novel methods to uncover gene mutations for common diseases

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Human geneticists have long debated whether the genetic risk of the most common medical conditions derive from many rare mutations, each conferring a high degree of risk in different people, or common differences throughout the genome that modestly influence risk.

A new study by Brigham and Women's Hospital (BWH) researchers has harnessed data and new analysis tools to address this question in four common diseases: rheumatoid arthritis; celiac disease; coronary artery disease and myocardial infarction (heart attack); and type 2 diabetes.

The study will be electronically published on March 25, 2012 in Nature Genetics.

The researchers developed a new statistical method built upon "polygenic risk score analysis" to estimate the heritable component of these diseases that is explained by common differences throughout the genome.

Their method takes advantage of data from previously published genome-wide association studies, or GWAS, an approach used to scan DNA samples for common genetic markers seen throughout the population—called SNPs (single nucleotide polymorphisms).

According to senior author Robert Plenge, MD, PhD, BWH director of

Genetics and Genomics in the Division of Rheumatology, Immunology and Allergy, "We used GWAS data and a Bayesian statistical framework to demonstrate that a substantial amount of risk to these four common diseases is due to hundreds of loci that harbor common causal variants with small effect, as well as a smaller number of loci that harbor rare causal variants."

Using data on rheumatoid arthritis, they estimated that variation in hundreds of locations throughout the genome might explain 20 percent of rheumatoid arthritis risk, after excluding all of the known rheumatoid arthritis genetic risk factors.

They used computer simulations to demonstrate that the underlying genetic risk in rheumatoid arthritis is largely explained by many common alleles rather than rare mutations.

They observed similar results for celiac disease (43 percent), myocardial infarction (48 percent) and type 2 diabetes (49 percent).

"What is remarkable is that our statistical model was broadly applicable to several common diseases, not just rheumatoid arthritis," said Plenge, who is also an assistant professor at Harvard Medical School and an associate member of the Broad Institute of MIT and Harvard. "Our study provides a clear strategy for discovering additional risk alleles for these and likely many other common diseases."

According to the researchers, these methods can be applied to other genome-wide datasets (e.g., GWAS or whole genome sequencing) to estimate the degree to which there is a genetic component.

One exciting possibility is assessing the genetic basis of individual response to drugs.

"Our method may be particularly useful for diseases and related traits that cannot be easily studied in families," said Eli Stahl, PhD, lead study author, BWH research associate and member of the National Institutes of Health-funded Pharmacogenomic Research Network (PGRN). "For traits such as treatment efficacy or toxicity, we often assume there is a genetic basis to the clinical variability observed among patients. Now, we have the statistical tools to quantify the extent to which this is the case directly."

"Our study reinforces a common thread in the literature, that many subtle differences throughout the genome explain much of the differences in risk for individuals for all kinds of diseases—this has powerful implications for the genetic architecture of disease, for risk prediction and prognosis, as well as for basic biology and developing new drug targets," said co-senior author Soumya Raychaudhuri, MD, PhD, BWH Division of Immunology, Allergy and Rheumatology, assistant professor of medicine at Harvard Medical School.

Provided by Brigham and Women's Hospital