NTR and NESDA Cohorts Create Roadmap for Gene Expression

Researchers at the Netherlands Twin Register (NTR) and the Netherlands Study of Depression and Anxiety (NESDA) have taken the first steps toward creating a roadmap that may help scientists narrow down the genetic cause of numerous diseases. Their work also sheds new light on how heredity and environment can affect gene expression.

Pinpointing the genetic causes of common diseases and complex traits is not easy, as multiple genes may be involved. Moreover, disease-causing variants in DNA often do not act directly, but by activating nearby genes. To add to the complexity, genetic activation is not like a simple on/off switch on a light, but behaves more like a “dimmer switch” – some people may have a particular gene turned all the way up, while others have it only turned halfway on, completely off, or somewhere in between. And different factors, like DNA or the environment, play a role in the dimmer switch’s setting.

The new study analyzed blood sample data from 2,752 adult twins (both identical and fraternal) from the Netherlands Twin Register and an additional 1,895 participants from the Netherlands Study of Depression and Anxiety. In all participant, for all 20,000 individual genes, researchers determined whether those genes were heritable – the DNA “dimmer switch” – or largely affected by environment.

The Netherlands Twin Register has followed twin pairs for over 25 years and in close collaboration with the longitudinal Netherlands Study of Depression and Anxiety established a resource for genetic and expression studies. Professor Dorret Boomsma, who started the twin register, says, “in addition to the fundamental insights into genetic regulation and disease, the results provide valuable information on causal pathways. The study shows that the twin design remains a key tool for genetic discovery.” “Everyone has the same set of genes. Unless data are collected in twins, it’s difficult to determine which genes are heritable, or controlled by your DNA, versus those that may be affected by the environment. Teasing out the difference between heredity and environment is key to narrowing the field when you’re looking for a genetic relationship to a particular disease.”

“Identical twins have identical DNA,” Fred Wright, co-first author of the study explains, “so if a gene is heritable, its expression will be more similar in identical twins than in fraternal twins. This process allowed us to create a database of heritable genes, which we could then compare with genes that have been implicated in disease risk. We saw that heritable genes are more likely to be associated with disease – something that can help other researchers determine which genes to focus on in future studies.”

“This is by far the largest twin study of gene expression ever published, enabling us to make a roadmap of genes versus environment,” co-first author Sullivan adds, noting that the new study measures relationships with disease more precisely than had been previously possible, and uncovers important connections to recent human evolution and genetic influence in disease.

The study appears online April 13 in Nature Genetics and was done in close collaboration with researchers at the North Carolina State University, UNC-Chapel Hill, and Rutgers University Cell and DNA Repository (RUCDR). Funding for the study included grants
from the National Institute of Mental Health and other NIH Institutes, the Gillings Innovation Lab, the Netherlands Organization for Scientific Research, the Center for Medical Systems Biology, Biobanking and Biomolecular Resources Research Infrastructure, the European Science Foundation and European Research Council.

Note to editors: Abstract of the paper follows.

“Heritability and genomics of gene expression in peripheral blood”

doi:10.1038/ng.2951

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Published: Online April 13, 2014 in Nature Genetics

Abstract: We assessed gene expression profiles in 2,752 twins, using a classic twin design to quantify expression heritability and quantitative trait loci (eQTLs) in peripheral blood. The most highly heritable genes (~777) were grouped into distinct expression clusters, enriched in gene-poor regions, associated with specific gene function or ontology classes, and strongly associated with disease designation. The design enabled a comparison of twin-based heritability to estimates based on dizygotic identity-by-descent sharing and distant genetic relatedness. Consideration of sampling variation suggests that previous heritability estimates have been upwardly biased. Genotyping of 2,494 twins enabled powerful identification of eQTLs, which we further examined in a replication set of 1,895 unrelated subjects. A large number of local eQTLs (6,988) met replication criteria, whereas a relatively small number of distant eQTLs (165) met quality control and replication standards. Our results provide a new resource toward understanding the genetic control of transcription.