Program

Thursday, October 14, 2010		Friday, October 15, 2010	
9:00 am	Welcome	8:30 am	Stephen Manuck, PhD
9:15 am	Steve Cole, PhD	9:15 am	Discussion
10:00 am	Ahmad Hariri, PhD	9:45 am	Coffee break
10:45 am	Discussion	10:15 am	Anne Wojcicki
11:30 am	Lunch (Provided)	11:00 am	James Fowler, PhD
12:30 pm	Jeanne Brooks-Gunn, PhD	11:45 am	Discussion
1:15 pm	Eric Turkheimer, PhD	12:30 pm	End
2:00 pm	Discussion		
2:45 pm	Coffee break		
3:15 pm	Marcus Feldman, PhD		All discussions are moderated by Gregory Gibson, PhD Georgia Institute of Technology
4:00 pm	David Goldstein, PhD		
4:45 pm	Discussion		
5:30 pm	End First Day		

Sponsor

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Organizers

Marcel Salathé, PhD, Center for Infectious Disease Dynamics (CIDD), Penn State University
George Slavich, PhD, Cousins Center for Psychoneuroimmunology, UCLA
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Genes & Environment: Finding the Missing Heritability of Complex Traits

Stanford University, October 14 & 15, 2010

Why is it that humans vary in their susceptibility to major diseases, such as cancer, depression, schizophrenia, and HIV/AIDS? What determines complex human traits? Is it genes, the environment, a combination of both, or something else? These questions lie at the heart of a debate that has been raging for decades, namely the nature vs. nurture debate.

Modern technology has allowed us to dig deep into the genetic variation in human populations and associate that variation with traits of interest. However, the results of these so-called genome wide association studies (GWAS) have been sobering: While some traits are clearly associated with particular genetic variants, most variation in traits cannot be explained by variation in genes. This poses a paradox: Many traits cluster in families, but genetic variation seems to explain little variation. Where does the missing heritability come from?

At this symposium, leading scientists from a wide range of fields will come together to present and discuss their findings and offer their perspective on this pressing question. Talks are followed by extensive moderated discussions with the speakers and the audience.

Steve Cole, PhD, UCLA | Relationships between genes and social behavior have historically been viewed as a one-way street, with genes in control. Recent functional genomics studies have begun to challenge this view by discovering broad alterations in the expression of human genes as a function of differing socio-environmental conditions. My talk summarizes the developing field of social genomics, and its efforts to identify the types of genes subject to social regulation, the biological signaling pathways mediating those effects, and the genetic polymorphisms that moderate socio-environmental influences on human gene expression. These studies provide a concrete molecular perspective on how external social conditions interact with DNA to shape the functional characteristics of our bodies, and alter our future biological and behavioral responses based on our personal transcriptional histories. The presentation concludes by describing some new opportunities for in silico prediction of DNA polymorphisms that interact with transcription control pathways carrying socio-environmental information.

Ahmad Hariri, PhD, Duke University | Two rapidly emerging and highly complementary strategies have accelerated progress into biological mechanisms mediating individual differences in behavior and related risk for psychopathology: imaging genetics and gene-environment interactions research. Through the systematic mapping of common genetic polymorphisms affecting brain chemistry onto variability in brain structure and function, imaging genetics has established multiple fundamental mechanisms through which individual differences in behavior emerge and bias responses to the environment. In parallel, gene-environment interactions research has demonstrated how such genetically mediated variability in behaviorally relevant brain function translates into individual risk for psychopathology upon exposure to environmental stress or adversity. In addition to reviewing findings at this research interface, I will illustrate how the application of a novel genetic profiling approach offers the opportunity to generate increasingly complete information regarding variability in behaviorally relevant brain function and related gene-environment interactions.

Jeanne Brooks-Gunn, PhD, Columbia University | Studies of human molecular genetics and social environment interactions on health have relied heavily on the classic diathesis-stress model that treats genetic variations and environments as being either risky or protective thereby diminishing the interactive space. We attempt to expand this space by 1) combining two polymorphisms (5-HTTLPR and STin2 VNTR) of the serotonin transporter gene (5-HTT) and 2) using a less truncated measure of the environment—socioeconomic status (SES). We find evidence of significant gene-environment interplay between the two 5-HTT polymorphisms and SES on depression in the first year after the birth of the child. More crucially, we find evidence that some people are genetically more or less reactive to the environment, resulting in a crossover of risks of PPD for the most reactive groups.

Eric Turkheimer, PhD, University of Virginia | I will argue that as we have known for a long time that all behavior is heritable, and are learning now that all behavior is related in complex way to genetic variation at the level of DNA, the old null model of no genetic association has become meaningless. A new null model states our expectation that behavior is related to DNA through the accumulation of small associations that cannot be individually specified, and that the multivariate structure of genetic relations does not differ from the multivariate structure of the phenotype. I explore this multivariate null model through a variety of research projects using both population and molecular genetic methods. One outcome of my analysis is that more complex models of genetic transmission at the DNA level are not likely to solve the missing heritability problem, at least when it comes to complex phenotypes in humans.

Marc Feldman, PhD, Stanford University | Genotype-environment interactions are still largely discussed in terms of Fisher's variance analysis. This leads to the phrasing of the apparent difference between the large number of SNPs with significant phenotypic risk and the low fraction of Fisherian genetic variance explained. Is this the way modern analysis of quantitative genetics should be carried out?

David Goldstein, PhD, Duke University | Genome wide association studies have proven successful in identifying regions of the genome that contain gene variants that influence both common diseases and drug responses. In most instances however, it has not been possible to track these associations down to the causal variants that are responsible, and this greatly reduces the utility of these findings in drug development and disease prediction.
Sequencing based strategies on the other hand offer the promise of identifying the precise mutations and the genes they influence that are responsible both for predisposition to common disease and drug responses. I outline how sequencing the entire genomes of patients is likely to change our understanding of human disease genetics over the next several years.

Stephen Manuck, PhD, University of Pittsburgh | Genetic effects on prominent behavioral phenotypes often vary by context, and such observations are frequently cited as instances of gene-environment interaction (GxE). According to one longstanding model of GxE in psychiatric genetics – termed diathesis-stress –some psychopathologies arise when individuals who carry certain genetic vulnerabilities (diathesis) encounter precipitating environmental adversities (stress). Several literatures framed within a diathesis-stress model have emerged recently, spawning mixed results and numerous narrative reviews, meta-analyses, and 'expert' commentaries. At the same time, others have faulted the diathesis-stress model for positing a truncated form of GxE that ignores "positive" environmental exposures – experiences that might analogously moderate genetic influences on psychological well-being and adjustment (referred to here as 'vantage sensitivity'). Finally, a third model proposes that the same genotypes promoting negative outcomes in adverse environments may, conversely, potentiate positive outcomes in salubrious environments ('differential susceptibility'), suggesting that the implicated genetic variation modulates behavioral or developmental plasticity under varying (good or bad) environmental circumstances. In my talk, I will summarize evidence for these several models and suggest a more general GxE framework, using as examples recent studies of context-dependent genetic associations involving pubertal timing, impulsive decision making, and adult antisocial and aggressive behaviors.

James Fowler, PhD, UCSD | It is well known that humans tend to associate with other humans who have similar characteristics, but it is unclear whether this tendency has consequences for the distribution of genotypes in a population. Although geneticists have shown that populations tend to stratify genetically, this process results from assortative mating and it is unknown whether genotypes may be correlated as a consequence of non-reproductive associations. Here, we study six available genotypes from the National Longitudinal Study of Adolescent Health to test for genetic similarity between friends. Maps of the friendship networks show clustering of genotypes, and, after we apply strict controls for population stratification the results, show that two genotypes are positively correlated (homophily) and one genotype is negatively correlated (heterophily). A replication study on an independent sample from the Framingham Heart Study verifies that DRD2 exhibits significant homophily and CYP2A6 exhibits significant heterophily. These novel results show that homophily and heterophily operate on a genetic (indeed, an allelic) level, which has implications for the study of population genetics and social behavior. In particular, they suggest that association tests should include friends' genes and that theories of evolution should take into account the fact that humans might, in some sense, be "metagenomic" with respect to the humans around them.

Anne Wojcicki, 23andMe | Anne Wojcicki, President and Co-Founder of 23andMe, a personal genetics company, will discuss how 23andMe is advancing disease research through a new kind of online research model that gives individuals the opportunity to actively participate in research that is meaningful to them. She will also address the company's long-term vision to help usher in personalized medicine.