GENE-ENVIRONMENT INTERACTIONS IN THE DEVELOPMENT OF COMPLEX PHENOTYPES

A Distinguished Lecture

By

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Abstract: The lack of knowledge that we have about the earliest events in disease development is largely due to the multi-factorial nature of disease risk. This information gap is primarily the consequence of the lack of appreciation of the fact that most diseases arise from the complex interactions between genes and the environment as a function of the age or stage of development of the individual. The relationship between genes and the environment is best captured by the quotation: “genetics loads the gun, but the environment pulls the trigger.” A loaded gun by itself causes no harm. It is only when the trigger is pulled that the potential for harm is released or initiated. Likewise, one can inherit a predisposition for a devastating disease, yet never develop the disease unless exposed to the environmental trigger(s). That is, diseases result from an unfavorable combination of genetic variations and environmental exposures. Whether an environmental exposure causes illness or not is dependent on the efficiency of the so-called “environmental response machinery” (i.e., the complex of metabolic pathways that can modulate response to environmental perturbations) that one has inherited. Thus, elucidating the causes of most chronic diseases will require an understanding of both the genetic and environmental contribution to their etiology. Unfortunately, the exploration of the relationship between genes and the environment has been hampered in the past by the limited knowledge of the human genome, and by the inclination of scientists to study disease development using exposure to a single environmental agent. Rarely in the past were interactions between multiple genes or between genes and environmental agents considered in studies on the causes of human illness. The phrase gene-environment interaction means that the direction and magnitude of the effect that a genetic variant has on the phenotype can vary as the environment changes, or the converse. Genetic risk is modifiable in an environment-specific manner. That is, whether a particular variant allele is expressed, the degree to which it is expressed, and when it is expressed can be influenced by the environment. However, since the genotype evolves or changes very slowly over hundreds of years, one can assume that most of the increase in disease burden in industrialized nations is the result of a variable environment interacting with a relatively constant genetic substrate.