EDITORIAL

Gene–environment interplay

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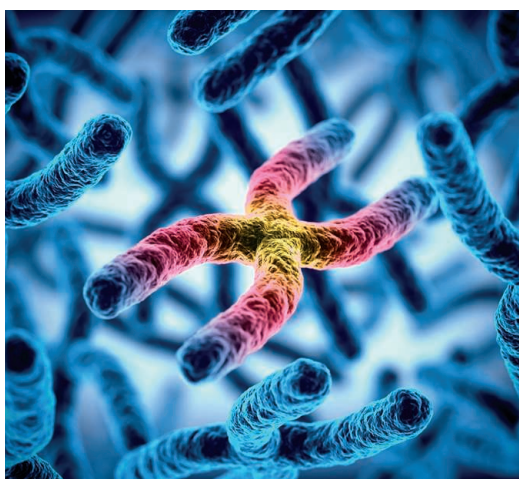
Science *Journals*

The advent of increasingly powerful and inexpensive DNA sequencing methods is changing many aspects of genetics research. In particular, human genome sequencing is transforming our understanding of many aspects of human biology and medicine. However, we must be careful to remember that genes alone do not determine our futures—environmental factors and chance also play important roles.

I recall a discussion with Nobel laureate Michael Brown at a scientific meeting some years ago when he described his opening lecture for a medical school human genetics course. He asked the class, "How would you produce a new genetic disease in the state of Texas?" After listening to answers almost invariably based on inducing mutations, Dr. Brown described his preferred answer—he would change the building codes so that no doorway could be taller than 6 feet. This would produce a "bruised forehead syndrome" that would be sex-linked (more common in males) and would also have other predisposing genetic factors for which variations are associated with tall stature. His answer captures an essential aspect of the interplay between genes and environment. Genetic variants that have evolved in one set of circumstances to be beneficial or neutral can be quite detrimental in other conditions. For example, many aspects of our metabolism evolved under conditions where calories were hard to come by. Now, in the environments of rich nations where calories are all too easy to acquire, these genetic factors contribute to obesity and other detrimental health effects.



"...genes alone do not determine our futures..."

Among the oldest and most powerful methods for examining the genetic contributions to different traits is the study of twins. In these studies, populations of monozygotic ("identical") and fraternal twins are examined for the likelihood that twins share particular traits. For example, height is highly heritable, and most monozygotic twin pairs differ in height by less than an inch. Nonetheless, a small percentage of such twins show larger height differences, and these have been associated with the occurrence and timing of early childhood illnesses—chance events related to environmental factors. Other traits show much lower concordance in twin studies. For example, if one member of a monozygotic twin pair has developed the autoimmune disease rheumatoid arthritis, then the probability that the other member will develop it is estimated to be 15%. This is substantially higher than the risk in fraternal twin pairs, supporting the presence of important genetic risk factors; indeed, some important genes have been identified. Clearly, however, other, environmental and chance factors are also important, although these remain largely elusive at present.

Even if traits are largely determined by genetics, predicting these traits from genome sequence information can be extremely challenging. For example, in a recent large study, variations in more than 400 genes were associated with differences in adult stature that together account for less than half of the observed distribution in height. This result is humbling, but it should not be surprising considering all of the cell-cell interactions, growth factor expression cascades, and other events that occur between fertilization and maturity.

In addition to elucidating genetic makeup, powerful genetic analysis tools should enable progress in understanding environmental effects on health and other important traits. Investigators can stratify populations according to genetic makeup and inferred genetic risk as a prelude to examining environmental factors, just as has been done with monozygotic twins. Without tools for such stratification, the effects of genetic and environmental factors are entangled in ways that greatly obscure insight. This is particularly important because precise and accurate measurement of environmental exposures, including diet, materials in our surroundings, and stress, is a great challenge. New technologies such as wearable devices that monitor personal characteristics and, perhaps, environmental exposures may help in this regard, but only time will tell.

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10.1126/science.aal0219

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Science **354** (6308), 15.
DOI: 10.1126/science.aal0219