The Meaning of the Human Genome Project for Neuropsychiatric Disorders

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The past 3 years have witnessed a series of replicable, credible, and increasingly useful genetic discoveries in autism, schizophrenia, and bipolar disorder. I cannot emphasize enough the significance of this progress. Neuropsychiatric disorders are outsized contributors to global disease burden, yet treatment development has reached a near standstill. The problem is that the brain, with its myriad cell types and complex circuitry, represents such a difficult scientific frontier. Because genes play powerful roles in neuropsychiatric disorders, identification of causal variation could provide invaluable clues to their pathogenesis. Sadly, the genetic architecture of neuropsychiatric disorders is fiendishly complex, but unlike other areas of medicine wrestling with genetic complexity, psychiatry lacks objective phenotypic markers.

When I became director of the National Institute of Mental Health (NIMH), NIH, in 1996, I did not foresee quite how complex the genetics would prove, but did recognize that the contemporary technologies were overmatched. (I ruefully joked that I had the only institute with no low-hanging Mendelian fruit to pluck.) With expert advice, I decided that the only rational approach was to amass large collections of patient DNAs, but for most, that day has long passed. I am pleased that some investigators resisted sharing extensive phenotype information. Some investigators resisted sharing samples, but for most, that day has long passed. I am pleased that these NIMH collections have proven useful, albeit as only a small fraction of the needed sample sizes.

It was not, of course, the first human sequence per se that turned the tide for neuropsychiatric disorders. As for much of medicine, the associated technologies and analytic approaches (above all, the availability of ever cheaper and more accurate DNA sequencing) are proving decisive. These advances have given investigators, clinicians, and patients hope that genetics will finally yield tools that neurobiologists have dreamt of to study the brain in health and in illness.

A Healthy Son

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Gutenberg must have felt like this: the sense of endless possibilities, of infinite applications exploiting the new technology, of the world having changed forever. It seems audacious, but is, I think, correct, to compare his time to ours. I offer a single case study to explain.

K is the youngest of eight siblings. Three of her fi ve brothers were severely developmentally delayed, with cognitive impairment and intractable behavioral disorders. No one else in their large extended family was affected. The most likely explanation for her brothers’ condition was X-linked inheritance following a new mutation in their mother. Fragile X was excluded, and the critical gene had eluded detection. The region of the X-chromosome shared by the three affected brothers was 40 megabases, too long to enable prenatal diagnosis.

K despaired of having a healthy son. Then early last spring, targeted X-exome sequencing of constitutional DNA from the affected brothers revealed a nonsense mutation in a gene known to be implicated in mental retardation. The mutation had not been detectable by conventional technologies but was transparent to massively parallel sequencing. K carried the mutant allele. Armed with knowledge of the mutation, K and her husband undertook pregestational diagnosis (PGD), which involves in vitro fertilization of their egg and sperm, then genotyping of embryos via the polar bodies, and implanting a normal embryo in the mother’s uterus. In experienced hands, PGD works very well.

K and her husband have a healthy newborn son.

Genetics is a way of thinking. Genomics is a set of tools. If we think rigorously about genetics and use these tools well, the resolution of inherited disorders on behalf of our patients will be bounded only by our imaginations. One healthy infant at a time is not a bad way to begin.

Socializing Genetic Diseases

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The sequencing of the human genome has been a major scientific adventure of the late 20th and early 21st centuries. It has played a decisive role in the development of biomedicine and has led to numerous partnerships between researchers, clinicians, and the pharmaceutical and biotech industries.

Patient organizations have also been involved in these partnerships from the very beginning. In France, for instance, the French muscular dystrophy organization, the AFM (Association Française Contre les Myopathies), is a classic example. To step up the struggle against neuromus-
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Science 331 (6020), 1026.
DOI: 10.1126/science.1204088

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