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Genetics, Individuality, and Medicine in the 21st Century*

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Introduction

These are exciting times! I say this fully recognizing that, by their very nature, scientists think "their time" is exceptional. For example, consider this comment: "We live in a revolutionary age. Our science has caught the spirit of the times, and more improvements have been made in all its branches in the last 20 years than have been made in a century before," made by Benjamin Rush in 1791! Or this one by our own L. C. Dunn, who opened his presidential address to the members of the ASHG in 1961 with the observation that "There is, I believe, general agreement that interest and activity in human genetics has today reached a peak never before attained." (Dunn 1962, p. 1).

So let me defend my assertion. In this year, 2003, we celebrate only the 59th anniversary of the demonstration by Avery, McCloud, and McCarty that DNA is the stuff that genes are made of (Avery et al. 1944). We also celebrate the 50th anniversary of the discovery of the double helical, antiparallel, complementary nature of DNA structure by James Watson and Francis Crick (Watson and Crick 1953). The chemical consequences of the complementary structure of DNA underlie much that we do today in molecular biology and genomics. And, finally, in 2003, we marked the completion of the "finished sequence" of the human genome. A draft sequence of our genome was published in 2001 in papers that were monumental in both content and length (International Human Genome Sequencing Consortium 2001; Venter et al. 2001). Now, we have a finished copy that is being published chromosome by chromosome, with the most recent, chromosome 6, appearing just two weeks ago, in *Nature,* by Jane Rodgers and her colleagues from The Sanger Institute (Mungall et al. 2003).

In addition to these landmark achievements in genomics, human geneticists have been busy developing molecular and other resources that are changing the way we do clinical genetics. The list of disease genes continues to increase at a dizzying pace. Currently, OMIM lists ~1,500 identified disease genes, and GeneTests lists just over 1,000 diseases for which there are molecular tests, 650 of which are clinically available. Not to be outdone, the diagnostic precision and sensitivity of cytogenetics is improving rapidly with increasing use of molecular probes and related resources (The BAC Resource Consortium 2001; Albertson and Pinkel 2003; Albertson et al. 2003). In the clinic, rather than making diagnoses by goodness of fit of phenotypic features to a mythical classic case, we increasingly rely on precise

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molecular assays. As a consequence, we provide our patients and their families more accurate diagnosis and prognosis, together with more informed and effective management. Importantly, human geneticists are also deeply engaged in the thorny problems of how best to acquire and utilize genetic information in ways that maximize the benefits and minimize the potential for misuse (Foster and Sharp 2000; Clayton 2003).

These amazing accomplishments in genomics and genetics and the vista of opportunities they make available justify my assertion that our time is truly revolutionary. We are all privileged to be participants.

The Challenge

But with opportunity comes challenge, as emphasized in a recent paper by Susan Haga and her colleagues concerning "Genomic Profiling" (Haga et al. 2003). The authors define genomic profiling as the concurrent detection of multiple gene variants associated with greater risk for or predisposition to disease, for the purpose of recommending specific risk-reducing actions appropriate for the at-risk individual. This sounds like what we all hope to achieve, but there are problems in applying this approach at our current level of knowledge. In addition to the epidemiological concerns of poor test validation and lack of rigorous outcome evaluation, Haga et al. emphasize a fundamental biological problem: "the vastness of the genome and high degree of individual variability…creates substantial challenges to identifying which gene or set of genes combines with nongenetic experiences to produce a disease phenotype" (Haga et al. 2003, p. 349).

I would restate this simply by saying that we do not know enough about *individuality.* In this context, I define "individuality" as the biological qualities that distinguish one person from another. These include variations in bodily or cellular structure or function and in homeostasis and adaptation. These are all properties mediated by proteins, which themselves express the individuality of the genes that specify them. Thus, the root of individuality expressed in these terms is genetic.*

One exciting consequence of the progress in our field is that we are beginning to be able to identify the genetic differences contributing to individuality. As an extreme example, consider the olfactory system. Earlier this year, Menashe and colleagues at the Weizmann Institute sequenced 26 human olfactory receptor genes chosen from a subset of the total of ~500 such functional genes in our genome because they were polymorphic for inactivating mutations. Among 189 individuals sequenced, they found 178 (94%) with unique functional combinations (Menashe et al. 2003). The take-home message from genotyping even this small subset of olfactory receptors is that no two people perceive the environment of odorants in the same way. Less extreme but equally polymorphic variation has been described at the molecular level for taste (Dulac 2000; Kim et al. 2003) and vision (Nathans 1994). This high level of inherited variation in the proteins we use to sample our environment plays out in a constellation of experiences also unique for each individual, confirming what law enforcement agents and lawyers who deal with "eye witnesses" have learned: perception of the world around us is highly individual.

Why Individuality?

Aside from its being the "spice of life," why are we interested in individual variation (table 1)?

First is a biologic reason: individual variation and selection are at the center of evolution, and, as Dobzhansky famously told us, "Nothing in biology makes sense except in the light of evolution" (Dobzhansky 1973, p. 125). So, if we want to understand where we came from and how evolutionary forces continue to shape our species, we must understand the origins and consequences of individuality.

Second, at the level of genetics, any casual student of the human phenotype sees that all of us are different. This is apparent from the appearance of our face or how we grow or how we respond to environmental experiences. As geneticists, we want to understand these differences—what accounts for them and why.

Third, as physicians, we encounter the outliers—our patients are those whose individuality results in the inability to develop normally and/or maintain physiologic homeostasis in response to their particular set of environmental experiences. As we become more sophisticated observers, we recognize that each patient has a *personal phenotype* that reflects his or her genetic and experiential individuality (Scriver 2002).

Finally, there is the desirability and challenge of applying genetics and genomics to preventive medicine, as we saw in the paper on genomic profiling (Haga et al. 2003) and as many others have emphasized (Collins 1999; Emery and Hayflick 2001; Collins et al. 2003).

For all these reasons, I will now consider what we know about individuality: the history of the development of our

Table 1

Individuality: Levels of Interest

Biologic—variation, selection, and evolution
Genetic—phenotypic differences
Medical—outliers comprise our patients
Clinical/Epidemiological—prevention

* This definition grew out of a graduate-level seminar course in Human Genetics taught by Barton Childs and me.

ideas, the extant explanatory evidence, and some areas that seem likely to provide additional, as-yet-unappreciated, reservoirs of human variation.

Historical Context

To provide historical context for our understanding of individuality, I start, of course, with Sir Archibald E. Garrod (fig. 1), who started his medical career at Great Ormond Street Hospital for Sick Children and eventually (1920) became the Regius Professor of Medicine at Oxford. Garrod wrote two books; most of us know the first, published in 1909, in which he originated the concept of "inborn errors," giving this class of disorders the name we still use today (Garrod 1909). His ideas developed from astute observations of patients with a handful of disorders, most notably alkaptonuria. Imagine working on the crowded hospital wards in Garrod's time, surrounded by patients with infectious disease, malnutrition, and the like, and developing an interest in alkaptonuria, a disorder with a frequency of ~1/100,000 (LaDu 2001)! Garrod was deeply interested in chemistry, especially as applied to medicine, and this may explain, in part, his fascination with inborn errors (Bearn 1993). He came by this interest honestly; his father, Alfred, was a rheumatologist and was also interested in the interface between chemistry and medicine (Garrod 1848). What set the younger Garrod apart, however, was not so much his recognition and characterization of these rare disorders but rather his ability to generalize what he learned from them to all medicine. In his classic 1902 paper in *Lancet,* he concluded that alkaptonuria and similar disorders were "merely extreme examples of variations of chemical behavior which are probably everywhere present in minor degrees and that just as no two individuals of a species are absolutely identical in bodily structure neither are their chemical processes carried out in exactly the same lines" (Garrod 1902, p. 1620). In his second book, *Inborn Factors in Disease,* published in 1931, Garrod revealed how his thinking on these ideas had matured, speaking of "chemical individuality" or the genetically determined, biochemical characteristics and capabilities that confer "our predisposition to and immunities from the various mishaps which are spoken of as diseases" (Garrod 1931, p. 157; Childs 1970). Imagine how Garrod would have appreciated the flood of evidence for the genetic basis of individuality to which we are privy today.

So why did it take so long for Garrod's ideas to have an appreciable effect on medical and genetic thinking? At the same time Garrod was developing his ideas, genetics was undergoing impressive growth. In an intellectual tour de force, T. H. Morgan and his *Drosophila* geneticists in the fly room at Columbia were formulating genetic principles that are still in use today (Kohler 1994). And yet, for them, the gene was an operational concept, a unit of mutation, recombination, and function with no basis in chemistry (Childs 1999). The "wild type" was monolithic, with little consideration of or means to in-

Figure 1 Archibald Garrod on rounds, early in the 20th century (courtesy Alec Bearn)

vestigate normal variation. Later, in the early '40s, Beadle and Tatum, in their Nobel Prize–winning work on the "one gene, one enzyme" concept that provided our current context for understanding how the information in the genes relates to the proteins that do the work, gave little consideration to the idea of individuality (Beadle and Tatum 1941; Beadle 1959).

Genetics finally began to appreciate the variation necessary to explain Garrod's "chemical individuality" with the recognition and enumeration of polymorphic enzyme variants—simultaneously by Harry Harris in humans and by Richard Lewontin in flies—in the late 1960s (Lewontin 1974; Harris 1976). With their work and the advances in genomics and genetics that we are celebrating at this meeting, our understanding of the genetic basis of individuality has increased rapidly.

Extant Evidence for Variation

We now appreciate several kinds of mutations or heritable changes in the DNA sequence that vary over a wide range of frequency. In addition to a potentially limitless number of rare variants, there are several categories of common mutations or polymorphisms (frequency ≥ 0.01) contributing to the 0.1% of our sequence that varies from one individual to the next (International Human Genome Sequencing Consortium 2001; Venter et al. 2001). Chief among these are the single nucleotide polymorphisms or SNPs, which number ~5 million in our genome (dbSNP Home Page), with other kinds of changes (insertion/deletion and length polymorphisms) making up a much smaller fraction of the variation. Recombination serves to shuffle the sequence variants in limitless combinations from one generation to the next.

So, given this amount of sequence variation, how different are we are at the level of our genes? Although the answer to this question is still not known across the entire genome and in people from all around the globe, the HapMap project currently under way should go a long way toward answering these questions (The International HapMap Consortium 2003). Until these data are available, useful estimates come from the work of Halushka et al. (1999) and Cargill et al. (1999). Both groups performed extensive resequencing of a large number of genes (76 involved in blood pressure homeostasis in the former and 106 involved in cardiovascular disease, endocrinology, and neuropsychiatry in the latter). The studies yielded similar results. Table 2 presents the results of Halushka et al. (1999). Note that the amount of variation is such that >75% of the proteins were polymorphic at the level of amino acid sequence; Harry Harris would certainly have approved.

Table 2

Estimates of Measures of Genetic Individuality from Halushka et al. (1999)

~3 × 10^6-bp differences, or ~1 cSNP/kb
~80%–85% polymorphism at the protein level
~17% average heterozygosity

Potential New Sources of Variation

But is this amount of protein sequence variation sufficient to explain the major extent of genetic individuality? And, if not, what are other sources of variation in our genome? The answers to these questions are nearly in hand, but I am willing, at this point, to speculate that there are sources of substantial genetic variation that are yet relatively underappreciated. In what follows, I will briefly consider three possible such sources: allelic variation in gene expression, alternative splicing and its variations, and epigenetics.

Although there are many reports of promoter mutations altering expression of particular genes to produce genetic disease (e.g., see Weatherall et al. [2001]), the first systematic survey of allelic variation in expression of human genes that I am aware of was a short paper by Kinzler, Vogelstein, and their colleagues (Yan et al. 2002). These investigators used SNPs in the transcripts of interest to compare the levels of expression of two "normal alleles" of the same gene in heterozygous individuals. Among 13 genes studied, roughly half showed allelic variation in expression, ranging from 1.3- to 4.3-fold. These expression differences followed Mendelian segregation in informative CEPH families, indicating that the responsible variation was *cis*-acting. A subsequent study of 603 genes also found that about half showed significant allelic variation in expression ranging from two to more than fourfold (Lo et al. 2003). Sequence variation accounting for some of these differences (long-range enhancers) detected by a combination of comparative genomics and transgenic assays may be hundreds of kilobases away from the regulated gene (Nobrega et al. 2003). Additional work on the extent, mechanisms, and consequences of this variation is required, but it could have substantial effects on our understanding of Mendelian disease, complex traits, and normal variation. Some of these consequences are reviewed by Cheung and Spielman (2002).

A second potential major source of variation contributing to individuality involves the factors that perform and regulate alternative splicing. Current evidence suggests that 30%–50% or more of our genes undergo alternative splicing, greatly multiplying the protein repertoire of our genome (Black 2003). The molecular apparatus for this process includes *cis*-acting enhancer and repressor sequences, SR proteins and others that bind to

these sequences, small ribonuclear proteins that catalyze the splicing, and others (Black 2003; Jurica and Moore 2003). The extent and consequences of variation in this complex system are unknown, but the potential for contribution to genetic individuality is large. We do know that variation in splice enhancer sequences has been found to contribute to genetic disease (Cartegni and Krainer 2002; Cartegni et al. 2002; Nurtdinov et al. 2003), and a Web site is available to assist in identifying these sequences (ESEfinder) (Cartegni et al. 2003).

The last of the three possible sources of additional genetic individuality has to do with epigenetics, or stable alterations in gene-expression potential that arise during development and cellular proliferation (Jaenisch and Bird 2003). Imprinting results from differential epigenetic modifications that differ depending on the parent of origin. The molecular mechanisms underlying epigenetics include DNA methylation and histone modifications and have been the subject of several recent reviews (Jones and Takai 2001; Feinberg et al. 2002; Jaenisch and Bird 2003; Murphy and Jirtle 2003). The picture that is emerging is a dynamic one, with layers of regulation affecting the state of chromatin and gene expression (Jaenisch and Bird 2003).

Increasingly, we are learning how environmental variables influence epigenetic regulation. Using coat-color alleles at the *agouti* locus, Wolff and his colleagues have shown than maternal nutritional variables during pregnancy (e.g., methyl donors) can have effects over the lifetime of her pups (Wolff et al. 1998). Moreover, some of these epigenetic modifications are not completely erased during oogenesis and influence epigenetic regulation in the next generation (Cooney et al. 2002). Thus, environmental experiences can have profound effects on epigenetics and contribute to long-term individual variation in gene expression. We know much less, however, on the effects and extent of inherited variation on epigenetic mechanisms. Sapienza and his colleagues have recently described familial clustering of methylation ratios at certain imprinted loci and have reviewed the evidence for individual variation in imprinting (Sandovici et al. 2003). What is clear is that inherited variation in genes encoding proteins that perform or regulate epigenetic mechanisms could have profound effects on genetic individuality. This area is likely to be a fruitful one for understanding normal and disease-producing variation (Beaudet 2002).

Variation and Systems

Enumeration of the sources and extent of genetic variation at each individual locus is only the first part of the story. In the intact organism, proteins are integrated into complex biological systems ("modules") that are themselves organized into still larger systems (Hartwell et al. 1999; Ravasz et al. 2002). In his book *The Logic of Life,* François Jacob called these systems "integrons," saying that organisms are built by a series of integrations—"a hierarchy of integrons" (Jacob 1976, p. 302). To appreciate individuality, we must understand the consequences of the variation in our genome on the behavior of these systems; that is, we must understand the structure, dynamics, control mechanisms, and design of the myriad protein modules or integrons required for normal development and physiological homeostasis. This challenge, covered broadly under the heading of "systems biology" (Kitano 2002*a*, 2002*b*), was something geneticists could hardly envision until the tremendous progress catalyzed by the Human Genome Project. Whole-genome sequence essentially provides a complete parts list for all the systems in an organism, and new technologies—such as the yeast two-hybrid assay, tandem affinity purification, expression profiling, and tandem mass spectrometry—provide tools to enumerate the interactions (protein-protein, protein-DNA, and protein-metabolite) characteristic of each system (Uetz et al. 2000; Ideker et al. 2001; Ito et al. 2001; Gavin et al. 2002; Ho et al. 2002). Using these resources, we have already made considerable progress in understanding the structure of biological systems. Barabási, Oltvai, and their colleagues have found that most biological systems form highly inhomogeneous, scale-free networks in which the components, or "nodes," have widely different connectivities (Albert et al. 2000; Jeong et al. 2000, 2001). Most nodes in such networks have only a few links to others, whereas a few are highly connected "hubs" (Barabási 2002). Networks constructed in this fashion are inherently tolerant to variation, buffering perturbations in ways that allow the system to maintain acceptable function (Wagner 2000; Hartman et al. 2001; Jeong et al. 2001). This ability to buffer variation confers a robust response to errors, enabling such systems to degrade gracefully rather than catastrophically (Kitano 2002*b*). The behavior of biological systems is highly relevant to our understanding of the consequences of accumulating "normal" variation and of the pathophysiological mechanisms at work in complex traits and monogenic disease. One challenge for training geneticists of the future is to entice computationally talented individuals to study the behavior of biological systems.

Summary

We are fortunate participants in a biomedical revolution; even better, we are at the edge of the wedge of knowledge that is driving this revolution. Understanding individuality in terms of its genetic basis, evolutionary origin, effect on phenotype, and consequences for health is a central challenge that looms before us. Ultimately, we must learn how to evaluate and incorporate individuality into an effective, prospective form of medicine that relies heavily on prevention.

The way forward will require interdisciplinary basic research by investigators with expertise in genetics and genomics, as well as many other fields, including computational biology, evolutionary biology, and systems engineering. To bring the advances in basic research to bear on medical problems, we will need clinical research both on individuals and on populations. Perhaps these new opportunities for clinical research will help invigorate an area of research that we desperately need but that is currently understaffed (Goldstein and Brown 1997).

Education of our students, our colleagues, and our patients will continue to be a catalyst for these activities. For this reason and others, I emphasize the educational opportunities at hand. You will not be able to walk away from this meeting without realizing that genetics is a dynamic, vibrant, and rapidly evolving subject. What we have to say is relevant to all of biology and medicine—to quote Vogel and Motulsky, "genetics…[is] the leading basic science of medicine" (Vogel and Motulsky 1997, p. vii). Understanding individuality and applying this understanding to basic and clinical research as well as to the practice of medicine promises to be highly challenging and rewarding.

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Electronic-Database Information

The URLs for data presented herein are as follows:

ESEfinder, http://exon.cshl.edu/ESE/
Gene Tests, http://www.genetests.org/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlmnih.gov/Omim/
dbSNP Home Page, http://www.ncbi.nlm.nih.gov/SNP/

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