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MEDICAL GENETICS TO GENOMIC MEDICINE

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SUMMARY

The essay analyses the conceptual and methodological implication of genetics and genomics as applied to medicine. Genomic medicine calls attention to the genome as the ultimate source of life's continuity and variety; and indicates at the least the origin of disease in molecular and genetic variation, and at the most, the role of the genes in all variation, including disease. While the literature of medical genetics, genomics and proteomics is energized by a keen anticipation of discovery most physicians are still thinking to the genes as merely another proximate cause. To them the thought that functional genomics and genetics are at the heart of life, individuality and disease is still not relevant. A different context of thought is needed, based on a more evolutionary oriented views which recognize the individuality and heterogeneity of disease, the continuity of disease expression at the clinical level, and the multiplicity and integration of pathogenetic processes.

Once there was a time when medicine was essentially autonomous, closed and self-sufficient[1]. Basic scientists taught anatomy, physiology, biochemistry and the like to medical students. But when it came to research, medical investigators took from basic science only whatever seemed relevant to their work. For their part, the basic sciences developed rapidly posing for medicine an ever larger scope of "relevance", not only for researchers, but also for practitioners whose understanding was increasingly taxed, and for the public who came more and more to perceive their health as their problem no less than that of the

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doctor. And given the sweep, and sometimes invasiveness, of the new technology, all kinds of social and ethical questions presented themselves. So there was at all times a great deal of new information that had to be disseminated in appropriate form to individuals at many levels of readiness to grasp its meaning. One of the sciences that proliferated at an accelerating rate is genetics, and it is a description of the consequences of its movement into a central position in medicine that is the purpose of this paper.

Having adopted the title, "Medical Genetics to Genomic Medicine", I am obliged to define these alternatives. First of all, they are not alternatives, but sequential transitional states in a rapidly evolving field of both thought and practice.

Medical Genetics, Genetic Medicine, Genomic Medicine

Medical genetics took its origin in the 1950s from three roots. One was human biochemical genetics, itself an outcome of Beadle and Tatum's 1940s observation of the affinity of one gene for one protein, as well as the re-emergence of Archibald Garrod's concepts of the inborn error and chemical individuality[2]. It helped also that biochemistry was in a state of rapid development. The second root was human cytogenetics which originated in Tjio and Levan's accurate count of human chromosomes[3], and the third was clinical or phenotypic genetics, modeled closely on drosophila genetics, and which, having necessarily had a desultory existence in medicine[4], was much stimulated by the participation of geneticists from other fields[5,6]. It was these geneticists who, in 1947, founded the American Society of Human Genetics and its journal, with the express purpose of mutual education; medicine for non-medical geneticists and genetics for physicians[7]. By the 1960s, these three enterprises were woven into a seamless entity called Medical Genetics, which, as living organisms do, developed in: a) size (number of adherents); b) scope (clinics, divisions, and departments in medical schools and hospitals, and numerous journals); c) variety (clinical and biochemical genetics, cytogenetics, gene therapy, and genetic counseling); and d) presence (American Society of Human Genetics, American Board of Medical Genetics, American College of Medical Genetics). By the 1980s, Medical Genetics could be

perceived as fully accepted by, and integrated into, academic medicine in the USA and Europe.

But development, which we know to be a subtle process and often unnoticed until after the fact, was at work during all this time. Events led in a number of instances to a coalescence of independent ideas that enhanced the salience of genetics in medicine. One was the recognition by an originally reluctant molecular biology of its natural affinity for genetics, to form "molecular genetics" and later "molecular medicine"[8]. Another was a growing interest in disease on the part of biologists [9], certainly stimulated by the Human Genome Project whose premonitory rumblings were heard in the 1980s and '90s[10]. An outcome of that interest was recognition by biologists of the immense genetic and molecular variation to be seen in disease. Yet another such union of ideas resulted in the recognition of the continuity in disease exemplified in the demonstration that the inborn errors are no less multifactorial in their origin than what had come to be called "complex" diseases[11]. And a final and irrevocable wedding of medicine and genetics was attained in the suggestion of the gene and its products as the ultimate clues to pathogenesis and perhaps to diagnosis[12]. In the '90s, the diagnostic process that proceeded traditionally from phenotype to protein by way of history, physical signs, and physiological and biochemical expressions, began to be reversed so that the protein mediator of pathogenesis was discovered by way of the gene instead[13].

All of these developments raised the prospect of broader responsibilities for medical genetics than the inborn errors and congenital anomalies, chromosomal and otherwise, that had been its original preoccupation. All through the '90s, one heard allusions to the probability of genetic variation in all disease, and finally, to that end, a direct assault was begun, gene-by-gene, on some hitherto impregnable complex diseases, approached in the past only by statistics[14]. Then in the new century The Human Genome was presented, and one of its many implications is that genetic variation will participate in the origin of all disease: If all pathogenesis is mediated by proteins, and all proteins are specified variably by genes, how can the latter be omitted from the equation.

What about medical genetics, genetic medicine and genomic medicine? When was the latter introduced and how justified? One began to hear the term genetic medicine in the '90s, along with "Molecular Medicine" and, as the Human Genome neared its big moment, "Genomic Medicine". Genetic medicine is far from generally acknowledged. For me, it seemed that the word genetic should modify medicine to indicate that it is all of medicine that is modified by genetics rather than some part of genetics that is medical. The origin of Genomic Medicine, which is more popular today, is obvious.

Either way, medical genetics continues along its developmental trajectory, whether to become genetic medicine or genomic medicine or some vastly more inclusive medical genetics. But who can doubt that all of these modifiers are temporary usages needed only to advertise new ways to perceive disease and its impact on patients, families and societies. And who can doubt that all will be discarded when it is accepted by everyone that the genes and their products constitute the node whence principles of disease originate. After all, we never spoke of physiological medicine or of biochemical medicine, each a previous bottom level in the reductive descent from phenotype to gene. And the word "biomedicine", which became popular in the '60s, calling attention to our increasingly molecular analysis of disease, is already on the wane. Perhaps it is being replaced by genomic medicine, which calls attention to the genome as the ultimate source of life's continuity and variety but which will be replaced, in time, by something else. And that is what all of these usages intend; to indicate at the least the origin of disease in molecular and genetic variation, and at the most, the role of the genes in all variation, including disease.

Genomics

The advent of the genome has produced a flood of speculation about its meaning and impact. Only time will tell the reality, but it is clear that genomics will have a profound influence upon how we think about, understand and practice medicine.

Definitions

That influence is the point of this paper and why I begin with a definition of genomics. Our genome comprises the evolutionary

history of our species. It is a storehouse for genetic material, including genes, capable of being transmitted from one generation to the next, and by virtue of its code it specifies all of the proteins that mediate the functions of all cells, organs and individuals. So, genomics is the study of the history, structure, function and location of genes[15]. A similar study of protein gene products is proteomics, and since the two are interdependent, the amalgam has been dubbed functional genomics[16]. Genetics is the study of inherited variation; genes are subject to mutation and, in consequence, proteins are subject to variation in structure, amount, and the times at which they begin to function, which means that all of the processes of functional genomics are variable and that variability could be implicit in every use of that term. As it happens, usage has differentiated genomics and genetics, particularly in their methods of application. For example, genomic methods can, but need not always be, used for genetic purposes.

Only a variable species can survive, even if the variations are sometimes bad news for individuals. So, disease is a by-product of evolution. The variations are in and of both genome, and proteome, and are expressed clinically as outcomes of variations in the homeostatic devices of the organism. Thus it is *incongruence* between homeostatic device or devices and the conditions within which they function, whether within the organism or outside, that lead to disease.

What genomics does, then, is to give us the wherewithal of which humanity is made. Genetics individualizes it, but everything that follows, from the protein products on, derives, however indirectly from that origin, and everything in disease will have to be interpreted in that context. We have not previously had any such unifying basis for all disease. This, with all its implications, is, in my view, genomics' prime gift to medicine.

Two Levels of Functional Genomics and Genetics

Functional genomics and genetics can be perceived on two levels. The first defines their uses broadly, promoting the union of biology and medicine to offer the physician principles that give order and meaning to the facts. The aforementioned unifying role of functional genomics and genetics is one such principle. The sec-

ond level of perception distills narrowly the meaning of the principles of the first to apply them to diagnosis and treatment. Applications at the second level are possible without reference to the first, but are more informed when carried out in the latter's context. Of course we have always had some of such principles; rules of diagnosis, treatment and so on, and every disease has its own generalizations, but our lack of knowledge posed limits to their formulation. For example, no textbook of any medical subject ever begins with a definition of disease or a summary of general properties shared by all diseases. Nor do such books emphasize the variability and individuality of disease. I have searched innumerable indexes for these words, but always in vain.

But now, functional genomics and genetics are promoting a change in our thinking that is as sweeping as that begun with the recognition of infectious disease. Then, unitary causes led by unitary paths to unitary expressions of disease. In time, biochemistry and molecular biology enhanced the model with pathways, cascades, cycles and linear networks. Human biochemical genetics with its one gene-one enzyme slogan fit right in so that medical genetics was readily adapted to prevalent medical thinking.

This mentality has been changing to include multiple causes, acting in ways both multiple and complex to produce heterogeneous, even individual, results. Today, genetic and molecular analysis of complex diseases is a prominent goal. Our present method is to seek the genes involved and their proteins, and then to piece together their integration in pathogenesis, and there have been rewards both in the discovery of mendelizing disorders in complex phenotypes[17] and genes for familial but non-mendelizing forms[18]. But functional genomics and genetics is looking for ways that go beyond classical analysis to observe not only the genes and proteins of networks, but how these networks are integrated and work as units. That is, the analysis is at the level of integration, or systems[19].

Perceptions at the 1st Level

Where such an analysis will lead, we are all entitled to guess. One consequence we can hope for is the end to the distinction of Genetic or Environmental disease. Presumably the methods will

show that the outcome of any environmental stimulus will depend at the integrated level, upon the individual's genetic qualities while the outcome of the genetic qualities will depend upon those of the environmental contribution. A second change is likely to be that of nosology. Present classification is based on phenotypes at all levels. Functional genomics suggests a classification depending on the affected networks. We have seen a profound effect on classification of monogenic disease. In the book, "The Molecular and Metabolic Basis of Inherited Disease", phenotypes once classified as mental retardation, dwarfism, and the like are now assorted according to their molecular origins.

A third outcome is the application of functional genomics and genetics to the molecular analysis and evolution of development. These studies, mainly of insects, are the basis of a new vision of a lifetime continuity of development, maturation and aging, in which the daily dialectic between gene products and experiences of the environment is carried out[20]. So disease must be analyzed in three time scales at once; the phylogenetic, the ontogenetic and the present. A case in point is the elderly patient with osteoporosis whose peak bone mass was inadequate from the start possibly in consequence of, among other things, one of the polymorphic forms of vitamin D receptor, as well as smoking before peak bone mass is attained.

A fourth result is the opportunity to interrogate the proteome for generalizations about its role in disease. For example, Miller and Kumar concluded that disease-producing mutants are more likely to be conserved in evolution than polymorphisms and to include amino acid substitutions not commonly observed across species[21]. Goodstat and Ponting report that arginine and cystine are both more frequently substituted in disease mutations as well as more frequently substituting, suggesting something about the properties of these mutations in maintaining the stability of the proteins where they occur normally and the instability they introduce when in unnatural positions[22]. Jiminez et al examined the contributions of over 900 disease proteins in relation to age-at-onset of disease, mode of inheritance, severity and other properties and demonstrated differences in the proteins most frequently involved in disease at different ages[23]. And

Jeong et al used the deletion of single genes in yeast to show that while the organism showed a remarkable capacity to tolerate such deletions, there was a negative correlation between that tolerance and the degree of connectivity of the protein product of the deleted gene: deletion of proteins acting as nodes for connection of many proteins was lethal [24].

All such studies are necessarily preliminary and await the availability of more information to expand their observations, but it is clear that many new principles of disease will be exposed by just such means.

A fifth consequence, certainly the most salient, is a new emphasis on individuality. In medicine, although we see patients one at a time, we haven't had much interest in variation; we tend to compare the expression in the case at hand to that of a hypothetical classical case, and variation is perceived in relation to this standard. But 40 years ago we learned that there were one or more common variants at 30% of human loci so that individuals were heterozygotes at say 10%[25]. These variants were presumed at first to be harmless, but over the years more and more of them have cropped up as modifiers in many diseases, mostly of complex origin. Now, the same kind of variation, known today as single nucleotide polymorphisms or SNPS, have turned up in the millions, probably at all gene loci[26]. This means multilocus variation for all phenotypes, implying a genetically unique version of whatever disease we have, and when we add the variability of our lifetime experiences in the dialectic over the years through development, maturation and aging, our genetic uniqueness is compounded. So in future thinking about disease we will *begin* with the idea of variation and individuality and go on from there, rather than starting with a standard around which we observe variation. Which, and how much of the SNPs and other genetic variation is medically relevant is a knotty question, probably to be decided patient by patient.

So far I've emphasized proximate causes, but functional genomics and genetics perceive the origins of the proximate in remote causes, a relationship perceived and expounded by Mayr 40 years ago[27]. Biologists concentrate on proximate causes, asking questions preceded by how, as in how does this work. We in

medicine ask the how questions too, but we also ask some preceded by why, questions that are made more compelling by being urgently asked by the patients too. Why me the patient asks, and why this disease, and why now? These questions, based in the evolutionary viewpoint[28], emphasize the specificity of the patient, his origins and the experiences that have made him what he is. Surely functional genomics and genetics, in exposing the origins and extent of human variability, will compel us to ask these questions. For example, why this disease and why me have to do with the aggregation of genes in ethnic and geographic groups, in the biological randomness of mating and the variation in offspring. There is also variation in the social and cultural characteristics of populations whence patients are drawn. It is which of these factors and how they came together that characterize diseases in the particular patient. Indeed it is these elements that determine the specificity and individuality of the patient her/himself.

What about the genetic question of why now? All physicians have observed the concentration of familial disease in infancy and childhood, to which can be added a human fecundity of only 25% indicating an intra-uterine mayhem, mostly genetic. Physicians will also have observed that these early onset disorders exact a heavy toll of death and disability compared to those of adult life where only the early onset cases are both familial and more severely affected. Perhaps the point is made most succinctly by saying that concordance for disease between monozygotic twins declines as the age at onset rises. That is to be expected if natural selection winnows out the most disruptive genes before and early in reproduction, with the result of increasing prominence of the environmental contribution to the phenotypic variation of later life. This is the reason why the genes of non-familial complex disease are so exasperatingly problematic in prevention. So the answer to "why now", is that there is a gradient of selective effect that sends human populations into puberty and reproduction less burdened by undesirable genes. No doubt functional genomics and genetics will expose this variation for our use in diagnosis and prevention.

Perceptions at the 2nd level

It is to the practical level of application of functional genomics and genetics that the question of impact is usually directed, a question that might be rephrased to ask: how does this new viewpoint clarify pathogenesis? First it must be said that despite dazzling achievements, we are still wondering how the application of functional genomics to the solution of diseases will turn out. Now is a time of prologue. A first answer is that there are repositories from which the identity of genes and proteins can be provided on request. This is a tremendous leg up for the clinical investigator wrestling with some as yet undescribed or untreatable disease. But the functional genomicists want to do more. They want to measure everything at once.

We are accustomed to dealing with one protein at a time and designing treatment accordingly, and pursued in this way genes for complex diseases are coming to light, however slowly[29]. But functional genomics defines the protein, not only as enzyme or receptor, but as an element in an intricately interlocking and integrated network[30]. Some of these "all at once" studies are immense microarrays that reveal mRNA activity of thousands of genes and show their perturbations in response to stimuli[31]. Study of interactions also involve a search for "buffering genes"; that is, genes, once known as modifiers, that specify proteins that enhance, maintain or even suppress the activities of others, preserving thereby the purposeful action of the network[32]. A dramatic example was given by Rutherford who showed that the gene Hsp90, specifying a heat-shock protein was such a buffer in Drosophila[33]. Mutant Hsp90 loses this capacity, allowing the emergence of a variety of malformations.

One can imagine the virtues of these analyses of the cell at work. What we have called complex diseases are likely to be clarified as we learn which proteins interact with which, under what conditions and for what reasons, but we may be some way away from these insights. Prophecy has always exceeded performance and does so now. The study of disease is certainly biological, but disease, although a biological phenomenon, is different. Most of the new ideas of biology emanate from biologists who are not versed in the altered biology of disease, so there is the need in

both biology and medicine to find common ground and so to bring performance into consonance with prophecy.

Prevention

The logic of genetics is at its most cogent in promoting prevention. Although always present in medical thinking, until recently prevention has been more of a dream than an aim. But now epidemiologists extract from population studies risk factors in the form of individual habits, as well as products of the culture that although innocuous for the many may be inimical for the few. Geneticists, recognizing the prospect of individual genetic variation, ask for whom the risk factors are risky. Functional genomics is helpful here in exposing genes of susceptibility to disease, to be followed, presumably, by appropriate preventive measures[34]. Sounds good, and it is, but as the number of susceptibility genes increases we are faced with the paradox of simultaneous narrowing of populational probabilities and increasing individual uncertainty, both associated with the gradient of selective effect. When the gene effects are both salient and consistent in their phenotypes, as they are in inborn errors and early onset cases of complex diseases, we are on the safest grounds and prevention has the best chance. But for the non-familial cases of later onset, picking out those individuals who will have the disease is increasingly uncertain. Functional genomics and genetics will contribute many new genes that will increase predictability, but uncertainty will remain, even increase, as the number of genes multiplies. But what will happen when we direct our search for causes to *sets* of genes and their proteins, to networks, that is, to function at some integrated level? It's possible that predictability will be improved sometimes, sometimes not. Whichever way it goes, case by case, we will see the meaning at the genic level of the observation that every human being has his/her own version of each disease.

On the other hand, since in the diseases of mid to late life the prominence of genetic effect has declined, the identities of interest become the experiences of the environment that match the variations of the genes. The former can be manipulated, the latter cannot.

Treatment

Prospects for treatment are subject to the same provisos. Directing treatment to genetic variation is the generally expressed aim[35]. It is likely to work best in matching drugs to individual metabolic variations. In any case, there is much talk of drugs designed to fit the qualities of particular proteins[36]. But here too we shall have to await developments.

Conclusion

The literature of medical genetics, genomics and proteomics is energized by a keen anticipation of discovery, imminent and empowering. But also overwhelming to many in medicine to whom the genes are still merely another proximate cause. To them the thought that functional genomics and genetics are at the heart of life, individuality and disease is, if not exactly alien, perhaps not wholly relevant. It is a different context of thought and one that requires sweeping modification in their own. Indeed a new mentality is required (Table 1) in which there are shifts: a) from classes to individuals, from the concept of the person as a case of a disease to that of a person expressing individuality in a unique version of a disease; b) from discontinuity of expression as severe, mild or sub-clinical to continuity in which although such categories exist, all degrees make the expression continuous, as would be expected if every individual is unique; c) from the tacit acceptance of a fundamental likeness of all patients conforming to the name of the disease, to overt recognition that the disease has no essence, only individual heterogeneity and; d) from an imaginary uniformity and autonomy of the processes of pathogenesis to the multiplicity and integration of the processes of life that disease has altered.

This is a profound shift in thought, but necessary and not difficult once the transition is made from classes and types to the uniqueness of individuality expressed in disease. But such a new context raises a further question. Will knowledge of individuality of pathogenesis, clinical expression, response to treatment and approach to prevention promote a return to a long lost doctor-patient intimacy, or will the increase in knowledge of the details of the *case* only further a mechanized disposition? This

question is best answered by a re-invigorated medical education, an enterprise generally agreed to be in need of attention[37]. Like much else among the outcomes of applications of functional genomics and genetics in medicine, we shall see.

Table I. Changes in medical thinking likely to be stimulated by functional genomics and genetics

Changes in Thinking	
From	To
Types (classes)	Individuals
Conformity	Heterogeneity
Discontinuity	Continuity
Uniformity	Multiplicity
Autonomy	Integration

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