Published in final edited form as:

Arch Dermatol. 2008 March ; 144(3): 389–391. doi:10.1001/archderm.144.3.389.

Dermatology in the Postgenomic Era:

Harnessing Human Variation for Personalized Medicine

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In 2001, *JAMA* and its related journals published a special genomics issue at a time when the sequencing of the human genome was finishing.¹ This issue of the *Archives* on clinically relevant genetics and genomics comes a mere 7 years later and heralds the rapid progress in deciphering the human genome and the genetic basis of disease. This issue showcases a few of the latest advances in clinical genetics of the skin. While scientific progress opens opportunities for medical breakthroughs, it also engenders additional challenges that need to be addressed in the years to come.

HOW FAR HAVE WE COME?

Since the 2001 issue, several major advances in genomics have revolutionized our understanding of human genetics. First, both genetic and archeological data suggest that all modern humans have descended from a common ancestor who came out of Africa approximately 100 000 years ago. These studies suggest that modern humans share a common ancestral genome and are much more alike than we previously imagined.² The similarity has been reiterated by the completion of the sequence of the euchromatic genomes of *Homo sapiens*. Bioinformatic and functional studies currently place the number of protein coding genes at 24 000, 2 to 5 times less than once predicted. Moreover, even within the 3 million total base pairs, all humans share 99% identity, leaving only 1% of the sequence that is different. To put it another way, the genetic differences that encompass *all* variation seen within humans, whether normal or diseased, can be ascribed to changes in an extremely small fraction of the genome.

Efforts to quantify the small variation into definable markers have come to fruition with the publication of the human haplotype (HapMapII) database. Launched in 2002,³ the international HapMap project has identified small contiguous blocks of these nucleotide differences, or haplotypes, that are remarkably similar across population groups. The development of easily assayable markers for these haplotypes allows geneticists excellent statistical power to track disease-causing mutations that have occurred within the block. The high-density array of haplotypes in the HapMapII database is expected to make it easier, faster, and cheaper to find variations in human genes that influence an individual's susceptibilities to common diseases such as cancer, diabetes, and heart disease.⁴ For the first time in history, we know all the genes that compose the human genome and have the ability to quantify much of the genetic variation that defines our species in terms of a defined set of haplotypes. This monumental breakthrough was recently awarded the scientific "Breakthrough of the Year" for 2007 by *Science* magazine.⁵

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Financial Disclosure: None reported.

OPPORTUNITIES

Annotation, Annotation, Annotation

The progress made in understanding the basic variation present in humans brings a number of exciting opportunities and challenges to better understand and treat dermatologic disorders. First, we have the ability to thoroughly annotate the normal relationships between genes. Because we have a finite number of genes, no more and no less, we have the opportunity to understand fully how each gene functions in the human genome to effect skin function in a wide variety of populations. The database of gene function will be invaluable for the dermatology research community to understand how one gene affects other genes in the genome. For example, in this issue Harting et al⁶ report in detail the role of *ALOX12B* in nonbullous congenital ichthyosiform erythroderma, and Drenth et al⁷ demonstrate that erythromelalgia is more complex than mutations in sodium channels *SCN9A*, *SCN10A*, and *SCN11A*. These reports demonstrate novel functions for *ALOX12B* and identify the need to find additional genes responsible for erythromelalgia. Ultimately, the understanding of how each of the 24 000 or so genes contributes to cutaneous development and maintenance would provide an invaluable resource on which the research community could create or test hypotheses.

Understanding the Genetic Basis of Human Variation

The availability of a haplotype map brings the opportunity to correlate genetic changes at particular portions of the genome with medically important variations across all populations. The genetic basis of diseases that are caused by single gene defects that have a high penetrance such as epidermolysis bullosa (EB) have been systematically identified over the past 2 decades. However, the more common but polygenic diseases such as psoriasis,⁸ atopic dermatitis,⁹ or alopecia areata¹⁰ remain challenging to analyze. The publication of a high-density map of common human haplotypes in the past few months means that there is a higher resolution of markers now available for study. Besides uncovering genetic factors underlying common polygenic diseases, an understanding of the genetic basis of response to environmental factors will also be dramatically improved by recent genetic advances. These include the burgeoning field of pharmacogenomics, where the genetic variation in a patient's response to particular drugs is defined prior to drug administration.¹¹

Toward Personalized Genetic Therapy

The goal of a complete annotation of gene function and the affect of gene variants on phenotypes brings the opportunity for a more personalized and efficient set of therapies. Currently, most diagnosis and therapy relies on surprisingly little personalized information; patient histories are presented as "Mrs Jones is a 65-year-old Hispanic female." With the identification of all the genes in the genome and much of the variation that exists, a very futuristic presentation might be: "Mrs Jones is a 65-year-old *PTPN22*^{R620W}, *CD226*^{S307G}, *IL7-R*^{T244I}," where the particular allelic variation for each of up to 24 000 genes is identified.¹² If the response to a given therapy for a particular set of human variations was understood, the efficiency of therapy would be greater and the cost of treating the condition would be reduced.

Physicians could then focus on the many types of postgenomic, personalized "gene" therapy. Traditional gene therapy focuses on replacing the ability of a cell to express a single gene and is making great progress in recent years for diseases such as junctional EB.¹³ However, personalized "gene"-based therapies based on our understanding of how genes interact and compensate for the function of others could also be envisioned. An illustrative recent example comes from the study of another type of EB, EB simplex, that is caused by a mutation in basal keratins such as keratin 14 (*K14*).¹⁴ Studies of mouse models of *K14*

mutations suggested that another keratin, keratin 17 (*K17*) could functionally compensate for *K14* if present. Kerns et al¹⁴ found that a natural product, sulforaphane, could induce *K17*. Because of the compensatory relationship between *K14* and *K17*, they were able to demonstrate that sulforaphane corrected much of the blistering phenotype. This type of therapy holds great promise for patients with EB simplex.

In addition, personalized gene therapy could tailor therapies based on particular haplotypes. This concept is not new, as pharmacogenomic medicine has been in use with several drugs for many years. For example, when starting azathioprine therapy, many clinicians ascertain the levels of a key metabolizing enzyme, thiopurine methyltransferase (TPMT), whose activity varies with several gene alleles. Studies show that the TPMT activity levels inversely correlate with toxic metabolite levels and bone marrow suppression.^{15,16} Pretreatment knowledge of the patient's *TPMT* genotype guides clinician dosing, with the 10% of patients with low or intermediate TPMT activity receiving consideration for dosage adjustment. Similar tests are currently being used to test for P450 enzymes such as CYP2C9 with warfarin or CYP2D6 for tamoxifen because these enzymes can reduce the time to achieve proper therapeutic levels and reduce toxic effects.¹⁷ While tailored therapies are not a new idea, the extent to which they might affect patient care is sure to increase. One could imagine the use of similar tests in any setting in which genetic variation can effect the therapeutic outcome, including susceptibility to emerging infections, response to humanized antibody therapy, or even efficacy of cosmetic procedures.

CHALLENGES

How to Bring Genomic Advances to Individual Patients

While both the human genome sequence and a high-density haplotype map are available publicly, the real challenge (and where dermatologists may be most helpful) will be to translate these tools into clinically useful and economically viable tools for the clinician. The first hurdle is how to economically obtain a patient's genomic data. One approach could be to sequence the entire genome and include it in the patient's electronic medical record. A decade ago the thought would be absurd, but the technology development efforts of the Human Genome Project have brought the cost of sequencing plummeting from \$2 per base to less than \$0.09 per base.¹⁸ The reduced cost has led several prominent geneticists to begin the era of personalized genomics by having their genomes sequenced and put into the public domain.¹⁹ However, the cost is still estimated to be about \$100 000 per genome, and additional technological break-throughs are needed to make the genome sequencing available to the general population. The advances are likely to come in the next decade, as considerable research effort is being spurred on through the efforts of the Human Genome Project, industry, and even by foundations (the Archon X Prize²⁰). Similar engineering is being done to reduce the cost of human haplotyping strategies as well.

Associated with the challenge in obtaining a patient's genetic data would be the development of appropriate guidelines to use the potentially new patient-sequencing data or haplotype. Several companies are developing diagnostic tests that will be used for assessing the status of an individual's predisposition to drug toxicity. However, the widespread appeal has been difficult to assess even with TPMT or warfarin. While there are clear data that a small fraction of individuals will have severe bone marrow toxic effects if given azathioprine, the Food and Drug Administration still does not mandate the test prior to administration of the drug.²¹ The cost (\$100-\$300) to the patient and the hassle to the physician must be weighed against the benefit from potentially optimizing therapy. Tests for P450 enzyme variants are particularly tricky because while the genome predisposes the patient to particular metabolic state, other drugs or environmental causes can modify

enzyme levels or activity, confounding the genetic test. Clearly, additional outcomes studies must be done in the future to compare the utility of these new genetic tests with their cost.

How to Best Administer Ethical Genetic Testing

Equally challenging will be developing guidelines for the ethical use of an individual's genomic information, given the issues of informed consent, privacy, and insurability. To obtain informed consent from a patient to obtain genomic information, the provider must explain the known risks and benefits to the patients at the time the test is administered. Several aspects of genetic testing make it more complex than a standard blood test. First, because genetic tests affect families as well as individuals, decisions made by the patient may have ramifications for a wide variety of others. Second, because we know that environmental factors can strongly modify the phenotypic expression of a particular genotype, precisely knowing the risk or benefit for any patient can be extremely difficult. Third, presymptomatic testing for conditions in which no effective treatment options exist can cause severe psychological, social, and financial sequelae. While assaying for *TPMT* alleles appears straightforward, assaying for genomic variants associated with cancer or psychiatric predisposition would likely require much greater care. This is particularly challenging with the rapidly changing understanding of human haplotypes, wherein the significance of a particular allelic variation in the context of other alleles and environments can change overnight.

A likely scenario will be that genetic testing will need to be performed in the context of a qualified counselor who can clearly explain the particular risks and benefits to an individual. Such counseling will become increasingly important because of the rapidly changing meaning of many of the tests. Moreover, medical economics has spawned a growing industry of direct-to-consumer genetic testing services on the Internet.²²⁻²⁴ These latter tests allow individuals to directly send DNA samples (cheek swabs) to a company in exchange for a test result sent to them. While potentially a valuable service to the consumer, several medical societies have released statements warning the public about the possible risks of these tests and the potentially misleading or oversimplified explanations of the results.^{25,26}

We are at a nexus in medical history where we have acquired a large repository of information about our species and are just now learning how to use it to change the course of disease management for our patients. There are unprecedented opportunities and great pitfalls that must be overcome to efficiently and ethically use the information. In 7 short years since the last genomics issue was published, the genetics and genomics world has changed dramatically. By the time the next issue is published, the pace of change will undoubtedly also bring equally dramatic changes to medical therapy.

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