

CHAPTER

1

PAST, PRESENT, AND FUTURE OF PUBLIC HEALTH GENOMICS

LEARNING OBJECTIVES

- Learn about the history of human genetics
- Understand the history of public health genetics
- Realize the role of genetics in disease prevention
- Become familiar with the current status of clinical genetic testing
- Comprehend the future role of public health genomics

INTRODUCTION

To help readers achieve an understanding of how human genetics has evolved until now, this chapter begins by reviewing some of the major genetic discoveries of the past few centuries and how they have given rise to current concepts in genomics. Then the role genetics has come to play in clinical preventive medicine is introduced. The chapter concludes with a description of the future goals of genomics research and of how they are aimed at improving health promotion and disease prevention.

HISTORY OF HUMAN GENETICS

One of the earliest records of human genetic disorders appears in five-thousand-year-old Babylonian clay tablets that describe sixty birth defects (Majumdar, 2003). The Jewish Talmud, written about two thousand years ago, was the first document to accurately record the familial transmission pattern of hemophilia (a genetic blood-clotting disorder).

Khoury, Burke, and Thomson (2000) trace the more recent study of human genetics back to observations made by early philosophers, scientists, and laypeople, who noted similarities and dissimilarities among individuals, family members, tribes, and communities. These early observations have served as stepping stones to our modern-day multifaceted approach to genomics.

Laboratory genetics took its first step in the seventeenth century, when Anton van Leeuwenhoek, inventor of the microscope, discovered the existence of sperm. Although the existence of DNA was not known at the time, knowledge of sperm was a crucial prerequisite for that discovery. The concepts of family history and pedigree analysis (the study of disease transmission patterns in families) established their roots in the nineteenth century, when a physician named Joseph Adams wrote *A Treatise on the Supposed Hereditary Properties of Diseases*. He particularly noted that certain diseases appeared more frequently in the offspring of parents who were blood relatives (the practice of marriage between blood relatives is now known as *inbreeding*).

The beginnings of genetic epidemiology appeared soon after, with the work of Francis Galton. He published *Hereditary Talent and Character* in which he measured and statistically compared intelligence, height, and other quantitative traits in related individuals. At about the same time, Gregor Mendel performed the first, rudimentary experiment in genetic engineering—hybridizing pea plants and discovering the basic laws of human heredity. The foundation of metabolic genetics arose around the turn of the twentieth century, when Sir Archibald Garrod deduced that some hereditary diseases were caused by defects in enzymes and metabolism.

Modern molecular genetics was born when Alfred Day Hershey and Martha Chase proved that deoxyribonucleic acid (DNA) is the substance that transmits hereditary information in the cell. In 1953, a landmark year in genetics history, James Watson and Francis Crick, building on the work of Rosalind Franklin, discovered that the

structure of DNA is a double helix. A few years later, it was determined that the DNA in normal human body cells is contained in forty-six chromosomes. In the following decade, chromosome-staining techniques enabled the identification of distinct chromosomes and the production of karyotypes (chromosome spreads), used for diagnostic purposes.

In 1990, the U.S. Department of Energy (DOE) and the National Institutes of Health (NIH) initiated the Human Genome Project. Its purpose included identifying all the genes in human DNA and determining the sequence of the entire human genome. In 2001, a working copy of the human genome sequence was officially published, and the project was a boon to academia and the biotechnology industry. Scientists were able to build on this information to develop new medical applications. Over time, genetics gradually evolved from a basic science to an applied science with direct clinical uses. This development also gave rise to implications for public health.

HISTORY OF PUBLIC HEALTH GENETICS

Organized research in genetic epidemiology began in the mid-twentieth century in Europe and the United States, where state-mandated newborn screening programs also began testing for some of the same inborn errors of metabolism that Garrod had once investigated (Khoury, Burke, and Thomson, 2000). As a result of advances in cytogenetics, prenatal genetic diagnosis for chromosomal disorders such as Down syndrome emerged as well.

Applications to environmental health were also discovered. With the passage of the Occupational Safety and Health Act of 1970 and the Clean Air Act of the same year (and its subsequent amendments), officials sought to determine safety standards to protect people from harm due to toxic environmental exposures (Khoury, Burke, and Thomson, 2000). The standards were to be set so that even the most susceptible subgroups would be protected.

Realizing that genetic makeup can influence how one responds to toxic exposures, scientists soon embarked on the study of gene-environment interactions. Not only did they recognize that a person's genes could dictate his or her response to environmental toxins, but they also came to see that genetic makeup could play a role in the body's response to dietary intake (nutrigenomics) and to exposure to infectious diseases. Genetics and core public health concerns continued to intersect, and their shared territory continued to grow.

IMPACT OF GENETICS ON PRIMARY, SECONDARY, AND TERTIARY PREVENTION

Advances in genetics soon began to influence more than issues related to population health. Genetics also began playing a role in individualized practices aimed at disease

prevention. Approaches to disease prevention are usually divided into three levels: primary, secondary, and tertiary. Primary prevention entails modifying risk factors for disease in order to preclude the onset of illness. Secondary prevention has to do with early detection of disease to enable more effective treatment and/or cure. Tertiary prevention involves treatment of disease for the purpose of avoiding associated complications.

We can see how genetics can guide disease prevention by considering the example of type II diabetes mellitus (DM), a major public health problem. DM affects approximately twenty-one million Americans and is one of the leading causes of death in the United States (National Diabetes Information Clearinghouse, 2005). In people with the disease, blood sugar levels rise substantially because cells in the body become resistant to the action of insulin, a hormone that regulates sugar consumption by the cells.

Obesity and family history of type II diabetes are key risk factors for this disease. Therefore, losing weight is a means of primary prevention. Screening for type II diabetes is a form of secondary prevention. By detecting diabetes early and treating it, one can help prevent or delay its major complications (such as vascular, ophthalmologic, and renal disorders), which constitutes tertiary prevention.

How does genetics fit into this picture? As already mentioned, a strong family history of type II diabetes may indicate a genetic predisposition to the disease. Cognizant of this fact, genetic epidemiologists, by exploring families with type II diabetes, have begun to locate genes that appear to contribute to the development of the disorder (Singer, 2007). The ultimate goal of discovering such genes is to be able to determine whether a person possesses the genotype, or genetic makeup, that promotes the development of a diabetic phenotype (a phenotype is an expressed trait). That determination, once made, enables preventive measures to be tailored accordingly.

But doctors, even without performing genetic tests for diabetes predisposition, are now able to use family history information to help their patients prevent the disease. Physicians often document a patient's family history by drawing a pedigree, or family tree, which typically denotes the disorders that have appeared in the patient's relatives and the ages of onset of those disorders. Ideally, people who have parents or siblings with type II diabetes are encouraged to take a more vigorous approach toward maintaining an appropriate weight and are more closely monitored for evidence of this illness.

People already diagnosed with diabetes may be more responsive to certain therapies than to others, according to their genetic makeup. In this way, genetics can play a role in tertiary prevention as well. The study of how genetic makeup influences an individual's response to medication is called *pharmacogenetics*, or more broadly, *pharmacogenomics*. Pharmaceutical companies and academic institutions, among others, are actively researching this area right now.



GENOMICS, WARFARIN, AND PATIENT SAFETY

A concrete example of the application of pharmacogenetics to public health is seen in the guidelines offered by the American College of Medical Genetics on the use of genetic testing when prescribing the anticoagulant (anti-blood clotting) drug warfarin for the first time (Flockhart, O’Kane, Williams, and Watson, 2008). This drug, also known by the brand name Coumadin (among others), was prescribed to over thirty million people in the United States in 2004 and is used primarily to prevent a range of conditions:

- Deep venous thrombosis (blood clots arising from poor circulation in the legs)
- Pulmonary embolism (blood clots that lodge in the lungs)
- Blood clots resulting from a heart arrhythmia called *atrial fibrillation*
- Blood clots associated with artificial heart valve placement
- Repeat myocardial infarctions

Although the drug is generally effective in its intended use, determining the best dosage for each individual is a challenge because of interpersonal variations in drug metabolism, which raise the risks of toxicity and adverse effects, such as bleeding. People now taking warfarin are monitored with a blood test called the INR (the International Normalized Ratio, which reflects blood’s tendency to clot). Doctors titrate the patient’s warfarin dosage on the basis of this measure, aiming to maintain the INR within the target range believed to be associated with optimal safety and efficacy in clot prevention (Flockhart, O’Kane, Williams, and Watson, 2008). If the INR is found to be too high, this is taken to indicate a higher risk of bleeding, so the warfarin dosage will be adjusted downward to avoid this effect. If the INR is too low, this may indicate that the drug is not exerting enough of an anticoagulant effect, so the dosage will be adjusted upward to improve efficacy.

The goal of studying the pharmacogenetics of warfarin has been to improve our ability to determine correct dosages and thereby to further enhance therapy and patient safety. Studies have shown that variants in two genes account for about one-third to one-half of differences in warfarin metabolism in patients, and efforts have been made to translate this finding into a clinically useful genetic test (Flockhart, O’Kane, Williams, and Watson, 2008). So far, a study analyzing the analytical validity, clinical validity, clinical utility, and ethical, legal,

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and social implications of this form of genetic testing has been employed to evaluate its appropriateness for use in clinical settings. There is strong evidence for a correlation between certain gene variants and the appropriate warfarin dosages to be used in people who possess those variants, as well as evidence that this information is clinically useful in specific cases. However, there is still insufficient evidence to warrant a recommendation for or against routine genetic testing of this kind when warfarin is first prescribed (Flockhart, O’Kane, Williams, and Watson, 2008).

PHENOTYPIC VERSUS GENOTYPIC PREVENTION

What we have talked about so far, including our discussion of using genetic information to help prevent adverse drug events, is called *phenotypic prevention*. Phenotypic prevention is the process by which harmful interactions between environmental cofactors (such as poor diet, lack of exercise, or a potentially toxic exposure) and genetic predispositions (such as a family history of diabetes or possession of a particular gene variant) are interrupted by modification of risk factors that can be altered. This approach is currently the most common strategy used by public health programs that are designed to avert chronic diseases with a familial component—such as diabetes, cancer, and heart disease—typically seen in adults.

By contrast, *genotypic prevention*, defined as “interruption of genetic trait transmission from one generation to the next” (Khoury, Burke, and Thomson, 2000, p. 6), plays a more substantial role in the prevention of diseases that appear in the neonatal and pediatric periods. Genotypic prevention is typically accomplished through carrier screening, reproductive counseling, prenatal diagnosis, and termination of pregnancy. Examples of genotypically preventable diseases include Down syndrome, some inborn errors of metabolism, and other genetic disorders for which genetic testing is available.

As you might imagine, genotypic prevention in particular brings with it a flood of ethical, legal, social, and even religious concerns, some of which we will spend time on in subsequent chapters. To help address these issues, the designers of the Human Genome Project had the forethought to establish the Ethical, Legal, and Social Implications (ELSI) Working Group as part of the research initiative. As further genetic discoveries are made, one consequence will be expansion in the capabilities of genetic testing and more opportunities for clinical uses of genetic information. The ELSI Working Group will help ensure proper use of these new methods.

It is important to realize that genetic testing, by its very nature, cannot be done haphazardly. The blood tests used to check a person’s cholesterol level, for example, are simple, whereas learning about one’s genetic makeup entails profound psychosocial

consequences, not only for those being tested but for their relatives as well. Genetic testing can raise concerns about stigmatization in social settings, for example, which may be fueled by cultural attitudes toward genetic diseases. It may also create worries about discrimination in health insurance coverage. These and related concerns will be explored in more detail in Chapter Seven.

GENOMICS TODAY

Genetic testing is no longer hypothetical. We are now able not only to confirm genetic diagnoses by analyzing DNA but also to screen people to determine whether they carry gene mutations (alterations in the normal genetic code) that predispose them to diseases such as breast cancer or colon cancer. These tests are usually available through health care providers and are recommended primarily for high-risk individuals (U.S. Preventive Services Task Force, 2004). Screening for cancer gene mutations has direct medical benefits in that the information can be used to direct specific preventive measures.

Take the example of an Ashkenazic woman with two or more family members, in two or more generations, who have had early-onset breast cancer. She would be an especially good candidate for genetic testing, since breast cancer gene (BRCA) mutations are common in this ethnic group, and since her family history is strongly suggestive of a hereditary component (Kieran, Loescher, and Lim, 2007). When her Ashkenazic ancestry is considered together with her family history, a positive test for this woman could indicate a greater than 80 percent lifetime risk of developing breast and/or ovarian cancer (Lewis, 2007). She would therefore typically be counseled about such preventive measures as more frequent mammograms, prophylactic mastectomy (surgical removal of the breasts) and/or oophorectomy (surgical removal of the ovaries), and/or chemoprevention (medications).

Although testing for cancer gene mutations can be medically beneficial, preventive measures do not exist for all diseases. Therefore, as with any other kind of screening procedure, it is usually unacceptable to test for a disease-associated mutation when no preventive measures (either genotypic or phenotypic) will be available after test results come back. As opportunities expand for genetic testing, leaders in public health will need to play a role in ensuring that testing proceeds in an appropriate manner for individuals and populations as a whole, and they can do so by taking the following measures (Khoury, Burke, and Thomson, 2000):

- Monitoring the scientific evidence on genotypes, disease, and genetic test parameters
- Systematically reviewing the benefits, risks, and costs of genetic testing
- Shaping public policies regarding genetic testing
- Evaluating access to genetic testing
- Revising test recommendations as new knowledge emerges

Until now, one of the best examples of these processes at work has been seen in the genetic screening recommendations set forth by the U.S. Preventive Services Task Force (USPSTF). The USPSTF evaluates the costs and benefits of clinical preventive services and determines whether health care providers should incorporate them into practice. After extensive analysis, the USPSTF assigns recommendations that are graded according to the strength of the evidence available in the literature and the balance of health benefits versus harms likely to arise from the use of a particular preventive measure. A summary of each grade and what it signifies is given in Table 1.1.

TABLE 1.1. U.S. Preventive Services Task Force Recommendation Grades.

Grade	Definition	Guideline
A	Well-designed, well-conducted studies indicate that the preventive service provides health benefits and that these substantially exceed harms.	Clinicians should provide this preventive service to eligible patients.
B	Sufficiently designed but limited studies have found that the preventive service provides health benefits, and that these exceed harms.	Clinicians should provide this preventive service to eligible patients.
C	At least fair evidence has been found that the preventive service provides health benefits, but harms are too high to justify a general recommendation.	No recommendation is made for or against routine provision of this preventive service.
D	At least fair evidence has been found that the preventive service is ineffective, or that harms exceed benefits.	Clinicians are advised against the routine provision of this preventive service to asymptomatic individuals.
I	The evidence is insufficient in quality, quantity, or consistency to be able to determine a balance of benefits and harms.	Evidence is insufficient to recommend for or against provision of the preventive service.

Source: U.S. Preventive Services Task Force, 2004.



SCREENING FOR HEMOCHROMATOSIS

Only a small percentage of USPSTF recommendations involve genetic screening, but one that has received much attention is the one related to genetic screening for hemochromatosis, a disease that causes abnormally high levels of iron to be stored in the internal organs (such as the liver) and that can lead to severe tissue damage. Treatment for the disorder, which involves periodic phlebotomy (withdrawing of blood), is a relatively simple method of controlling the condition. In view of this fact, the USPSTF set out to determine whether the burden of suffering involved in hemochromatosis was great enough, and whether routine genetic screening for the disease was effective enough, to warrant a USPSTF recommendation in favor of screening (Whitlock, Garlitz, Harris, Bell, and Smith, 2006).

With regard to the burden of suffering, the task force looked at data on morbidity and mortality and found that the disease's prevalence and severity are relatively low in the general population (U.S. Preventive Services Task Force, 2006b). To determine whether to recommend for or against routine genetic screening for hemochromatosis, they investigated the degree to which testing positive predicted clinical expression of the disease, the degree to which morbidity and mortality due to the disease could be significantly reduced with early treatment, and the degree to which alternative approaches were available for estimating the risk of the disease (Whitlock, Garlitz, Harris, Bell, and Smith, 2006). The task force found that only a small percentage of those who tested positive actually developed clinical manifestations of the disease, and that there was no evidence showing any advantages of early treatment (U.S. Preventive Services Task Force, 2006b). They also discovered that testing positive could result in unnecessary harm to the patient, such as anxiety, stigmatization, and undue surveillance or treatment (U.S. Preventive Services Task Force, 2006b). The U.S. Preventive Services Task Force (2006a) ultimately recommended against routine genetic screening for hereditary hemochromatosis in asymptomatic individuals (a D recommendation) and encouraged further research into the development of targeted screening protocols that would combine genotyping with other indicators of high disease risk (Whitlock, Garlitz, Harris, Bell, and Smith, 2006). As this example shows, using genetic knowledge in mass efforts to prevent disease remains a challenge, but one that also entails great potential.

GENOMICS TOMORROW

In 2003, in a landmark paper, Francis S. Collins, director of the U.S. National Human Genome Research Institute, and his colleagues stated their vision for the future of genomics (Collins, Green, Guttmacher, and Guyer, 2003). Drawing on past successes, they described three major areas in which advances in genomics would be applied: biology, health, and society. In each of these areas they identified several “grand challenges” to be addressed via six avenues:

1. Increasing resources
2. Developing technology
3. Increasing the use of computational biology methods in generating hypotheses and analyzing data
4. Training more scientists in genomics
5. Continuing to explore ELSI issues
6. Educating health care professionals and the public about genomics and disease prevention

Table 1.2 offers a summary interpretation of their vision.

Khoury and others (2007) have also looked at how we can hasten the translation of discoveries in human genomics into practicable measures in public health and preventive medicine. They propose an organized framework that relies on evidence-based guidelines dictating progress through four stages of research:

- *Phase 1 translation (T1) research:* developing a genetic test or intervention based on a genomic discovery
- *Phase 2 translation (T2) research:* evaluating the test and developing evidence-based guidelines for its use
- *Phase 3 translation (T3) research:* implementing these guidelines within the health care system
- *Phase 4 translation (T4) research:* measuring real-world health outcomes of the test and guidelines

Similar to the clinical trial protocols that are used to evaluate newly developed medications, this systematic approach to applying genomic discoveries to public health offers an elegant foundation on which to proceed.

CHAPTER SUMMARY AND PREVIEW

This chapter has laid the groundwork for the rest of the text, by reviewing the history of genomics, its public health applications, and the ways in which it currently influences

TABLE 1.2. The Future of Genomics.

Area Related to Genomics	Grand Challenges
Biology	<p>Learn the structural and functional information encoded in the entire human genome, how genetic networks and protein pathways are organized, and how they influence phenotypes at cellular and organismal levels</p> <p>Understand genetic variation in humans and evolutionary variation across species</p> <p>Develop policies that foster the use of genomic information in clinical and research settings</p>
Health	<p>Create strategies for discovering genetic factors and/or genetic variants that influence health, disease, resistance to disease, and drug response</p> <p>Improve genomic approaches to predicting disease risk and drug response, detecting disorders early, and classifying disease states on a molecular level</p> <p>Use genomic knowledge to develop new therapies for diseases and new tools for health promotion/disease prevention</p> <p>Study the impact of communications about genetic risk and how genetic information affects health behaviors, outcomes, and costs</p>
Society	<p>Devise policies that guide the application of genomics to medical as well as nonmedical areas</p> <p>Comprehend the relationships among race, ethnicity, and genomics and understand the implications of these findings</p> <p>Comprehend the relationships among human traits, behaviors, and genomics and understand the implications of these findings</p> <p>Evaluate methods of developing ethical guidelines for use of genomics</p>

Source: Collins, Green, Guttmacher, and Guyer, 2003.

disease-prevention efforts. The chapter also has looked at the goals of key leaders who are dedicated to applying genomics to public health and preventive medicine in the future. The next chapter outlines the pivotal role that the government has played in putting public health genomics into practice.

KEY TERMS, NAMES, AND CONCEPTS

Alfred Day Hershey
Anton van Leeuwenhoek
Birth defects
Clean Air Act of 1970
Double helix
Ethical, Legal, and Social Implications (ELSI) Working Group
Family history
Francis Crick
Francis Galton
Francis S. Collins
Genotype
Genotypic prevention
“Grand challenges”
Gregor Mendel
Hemochromatosis
Hemophilia
Human Genome Project
Inbreeding
Insulin
James Watson
Joseph Adams
Karyotypes
Martha Chase
National Human Genome Research Institute (NHGRI)
National Institutes of Health (NIH)
Nutrigenomics
Obesity
Occupational Safety and Health Act of 1970
Patient safety
Pedigree analysis
Pharmacogenomics
Phenotype
Phenotypic prevention
Primary prevention
Secondary prevention
Sir Archibald Garrod
Tertiary prevention
Translation research
Type II diabetes mellitus
U.S. Department of Energy (DOE)
Warfarin

ANALYSIS, REVIEW, AND DISCUSSION

1. Draw a timeline of major genetic discoveries, starting from ancient times and continuing to the present.
2. Explain the difference between phenotypic and genotypic prevention. Discuss the ethical, legal, and social issues that may arise with each approach.