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The Future of Genetic Testing Is Now

by Wayne Heidenreich, M.D.



Wayne F. Heidenreich, M.D., joined Northwestern Mutual as a medical director in 1993. Since 1997, he has been responsible for medical standards for Northwestern Long Term Care Company's long-term care insurance product and for issues of medical risk stratification in underwriting, requirements, claims and product development for the long-term care product. He can be reached at wayneheidenreich@northwesternmutual.com.

The world of medicine was transformed by the study of pathology under the microscope in the late 1800s, again with the growing science of biochemistry in the early 1900s, and imaging in the 1980s and 1990s. Medicine is now inextricably linked with genomics, and within the clinical community the call is out for frontline physicians to become familiar with genetic science. As an editorial in the *New England Journal of Medicine* states, “Both genetic and non-genetic information is important; the more we know about a patient—genes and physiology, character and context—the better we will be as physicians.”¹ Genomics is moving out of the research academic centers and the pharmaceutical labs into primary care offices. Today, it is part of many individuals’ care. *A little history: How did we get here?*

INHERITANCE PATTERNS

Mankind has recognized the results of good breeding since before cities were built. Animal husbandry and horticulture have been important elements to establish civilization. Going into the 18th century, people recognized the inheritance of features in their royal families and in their own families. The science of breeding assumed that only one trait is inherited between two mating individuals. In 1865, Gregor Mendel, an Austrian monk, presented his studies of the inheritance patterns of pea plants to the scientific community. He had observed that when two differently colored plants were crossed with one another, neither a blended color nor a single coloring resulted from his crossings. Instead, he observed different proportions of plants resulting from different colored plants. With meticulous observation of generations of plants, Mendel formulated his concept of dominant and recessive traits without any knowledge of paired chromosomes or DNA.

Mendel’s work forms the basis of modern genetics, or *Mendelian genetics*. In the 20th century the “traits” were found to be located on autosomal chromosomes that are inherited as pairs, one each from each parent. But one does not need to know what

chromosome or gene is involved to understand the inheritance pattern. An understanding of a simplified example of Mendelian inheritance patterns will help explain how two parents with brown hair color can have a child with blond hair. Brown or dark hair is a dominant trait over the recessive trait of light or blond hair. If both parents carry a recessive trait for blond hair, they have a one-in-four chance of producing an offspring with blond hair. This offspring receives only the recessive trait from each parent and can only manifest blond hair color. When both a brown trait and blond trait is present, the brown trait is dominant and manifests while the recessive trait is “unexpressed.” Probability dictates that three in four will have brown hair, a trait that is dominant over the recessive blond hair trait for expression (See Figure 1 on page 23).

When generations are studied, it becomes evident that some individuals are carriers of a recessive trait with the dominant trait manifesting. Other individuals inherit a dominant trait from each parent. These individuals will always have offspring with the dominant trait because that is all they have to contribute to their offspring.

Family trees of manifest or “expressed” traits or disorders could help predict the risk of inherited traits many decades before chromosomes were seen under the microscope or before DNA was described by Watson and Crick in 1952. Detailed family trees actually helped define some diseases as genetic when they produced a pattern consistent with Mendelian inheritance.

Sex-linked inheritance patterns were described when females rarely have the trait or disorder but half of male offspring have the trait. This pattern of inheritance can be documented without knowing that the trait is carried on the female X-chromosome while the male Y-chromosome always functions as a recessive contribution.

The discussion of inheritance has been limited to the concept of “traits” to reinforce the familial pat-

terns of inheritance. But the unit of inheritance is the gene that ultimately produces proteins. Both autosomal and sex-linked inheritance represents types of single gene inheritance. Much of clinical genetics is based upon the knowledge of single gene mutations and their effect on individuals and risk for passing to the next generation. This discussion is very basic, and the function of genes in inheritance is influenced by many modifications. Nevertheless, Tables 1 through 3 on page 23 list some disorders that manifest Mendelian inheritance and are referred to as monogenic disorders. Traits or disorders that are recessive do not manifest in the offspring unless both parents contribute the recessive trait.

Polygenic inheritance is now recognized as the basis for inheritance of many normal traits and many common disorders. As the knowledge of biochemistry grew in the second half of the 20th century, it became clear that many disorders were the result of multifactorial interactions. A predisposition to develop a disorder can be inherited with the development of the disorder, for example coronary artery disease, being the culmination of multiple factors interacting. Multiple genes influence or modify a biological activity resulting in the expression of health or disease.

Hypertension, hyperlipidemia and diabetes contribute to the development of coronary artery disease. But some individuals have accelerated atherosclerosis beyond what could be predicted by their risk factors. There are other factors, both inherited and environmental, that affect the development of coronary artery disease. There are still factors unaccounted for.

Today, medical and public health initiatives emphasize how individuals can affect their likelihood of developing a disorder by lifestyle and nutritional interventions. *Epigenetics* describes how environmental forces can alter the genes and their function. In many ways we are able to influence the traits we have inherited, for better and for worse.

MOLECULAR GENETICS AND GENETIC TESTING

To emphasize the importance of the pattern of inheritance, this discussion has purposefully saved the



discussion of deoxyribonucleic acid (DNA) to after the description of Mendelian inheritance at the core of classical genetics. This science was established before the growth of molecular genetics and long before the Human Genome Project began. It is a science built on observing the phenotype or expression of inherited traits and the pattern of transmission of these traits within families.

A brief primer of the foundation of molecular genetics is now in order. Life is built on proteins that form the structure of the body and direct the chemical reactions that energize and maintain it. We now know there are between 25,000 and 30,000 human proteins. The blueprint instructions for all of these proteins are sequences of four different nucleotides—adenine, guanine, cytosine and thymine. A person's *entire* DNA is referred to as their genome, and it consists of 3.3 billion nucleotides in chains paired with a mirrored copy of itself and organized into coiled double-helix chains. The genome is organized into segments as chromosomes, of which there 23 pairs, one chromosome of each pair from each parent. A gene is a segment of the DNA strand that codes for one protein.

Insulin was the first protein to have its sequence of amino acid building blocks sequenced in 1958. In 1965, when Dr. Victor McKusick first published

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CONTINUED ON PAGE 20

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his landmark *The Mendelian Inheritance in Man*, he had catalogued over 1,500 inherited disorders. It was not until the late 1970s that the protein structure of insulin was mapped to its DNA sequence on chromosome 11. By that time there were over 3,000 entries; and, by the start of the Human Genome Project in 1990, there were approximately 5,000. The entries were summaries of the studies of families manifesting the disorder, discovery of abnormal proteins responsible for the disorders, and finally mapping of the genetic sequences and where on the chromosomes they were located.²

Every person shares about 99 percent of identical nucleotide sequences. One percent of the genome may vary from one individual to another, which means there are 12 million potential variations.³ Triplets of nucleotides code for individual amino acids that are the building blocks of protein chains. Even a single substitution of one nucleotide for another, a *single nucleotide polymorphism (SNP)*, can potentially code for an abnormal protein sequence that may result in structurally abnormal protein. A single substitution of a nucleotide accounts for the abnormal hemoglobin protein of sickle cell anemia.

A gene is a sequence of DNA with a specific location on a chromosome, which codes for one protein. A variation of a gene that is found in a population less than 1 percent of the time is called a mutation. Mutations are relatively rare and variations are more common in a population. Each mutation or variation of a gene is called an allele. The terms mutation, variation and allele all refer to differences in the DNA sequence of a gene.

When there is reference to an abnormal BRCA1 gene, there are many different mutations possible, or many different alleles. Many of these variant alleles are catalogued; some are not yet discovered. Some alleles result in an abnormal BRCA1 protein that is dysfunctional and contributes to an increased risk for cancers, especially breast and ovarian.

GENETIC TESTS CURRENTLY USED IN CLINICAL MEDICINE

Cytogenetic tests visualizing the chromosomes have been used since the 1950s. These tests rely

on chemical stains of cells and imaging of tissue to determine if abnormalities in the chromosomes are visible. During reproductive formation of the sperm and ovum, damage can occur with the result of missing chromosomes or duplications of a chromosome. Fragments can be missing or moved from the normal location on one chromosome to another, and sections of a gene can be repeated. Down syndrome observed and described since 1880 as a morphologic abnormality was first seen under the microscope in 1952 as trisomy-21, or three copies of the chromosome 21.

Probes for individual alleles can be performed. These tests search for specific sequences of a single gene. The complexity of testing can be seen with the cystic fibrosis gene for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. A recessive disorder by Mendelian inheritance, abnormal alleles of the CFTR gene can be tested for in prenatal carrier screens. A database is available that lists 1,300 different identified alleles.⁴ The most common variant allele accounts for 70 percent of cystic fibrosis in Caucasians in the United States. Three nucleotides are missing out of 250,000 in the gene, resulting in an abnormal CFTR protein. In the Ashkenazi Jewish population, five different mutations account for 97 percent of cystic fibrosis. In screening for carrier status, a panel of common mutations is used. Negative results will generate an analysis of what the remaining probability is for the presence of an abnormal cystic fibrosis allele to be present. Since all mutations are not tested for, it will not be 0 percent.

Linkage analysis is used in situations where a disorder is evident throughout a family but the specific alleles have not been identified. Sometimes even the location or identity of the abnormal causative gene has not been identified. In linkage analysis, multiple family members are tested and individuals with the disorder may have a discrete section of a chromosome that is matched by DNA probes but not found in family members without the disorder or trait. These sections of DNA become candidates for the location and identity of potentially newly discovered genes.

Genome-wide sequencing (GWS) and genome-wide association (GWA) studies identify single varia-

tions of nucleotides between genomes at precise locations in the genome. These are called single nucleotide polymorphisms or SNPs. These studies are one of the triumphs of the Human Genome Project. They identify the gene where the SNP is located and the impact the variation has on coding for that gene's protein. Sometimes the SNP is not associated with any identifiable gene and has to be statistically analyzed to determine its significance in relation to the populations studied.

Ten years after the Human Genome Project's completion of the first complete genome, there was discussion in the scientific community and media of whether the hope of medical progress had been met. The hope had been that there would be many discoveries that could be translated into new treatments to cure common diseases. But work in the last decade keeps revealing the increasingly polygenic nature of disorders. While a GWA study may identify SNPs shared by a study group with a disorder, we are sometimes unable to identify the effect the polymorphism has on the gene and how the protein gene product contributes to the disorder.

During the decade of the 1990s, many labs were part of the Human Genome Project and were contributing to open-access cataloguing, a library of millions of SNPs. Technology allows known identified molecular probes to be used. A person's genetic material is run against the known reference sequences, and their genome can be identified in days instead of the decade it took the first genome to be described in the Human Genome Project.

While not being encountered in clinical medical care records, GWA studies are common front-page news. They identify associations of SNPs and clusters of SNPs that differ between individuals with and without studied traits or diseases. In some cases they do not identify the protein gene product or even the gene itself that differentiates the genomes. In this way, some GWA studies may not answer the question of what causes the studied trait or disease and exactly how the gene causes it.

Not all studies identify disease. In 2011, Scripps Lab announced collaboration with Dr. Eric Topol in studying the genome of 1,000 individuals who

had reached 80 years of age without chronic or major illness.⁵ The first step will be to generate in GWA studies the single nucleotide polymorphisms that differentiate these healthy individuals from the group with chronic diseases. It is not only the absence of *dysfunctional* genes that determine health. Healthy traits may positively influence and modify the same inherited risk for disease between the two groups. The next step is determining how these identified differences work and what we can do to intervene. We have moved to the age of the "\$10,000 test" (whole genome sequencing may cost \$1,000 in the near future) and the "million-dollar data analysis." The Human Genome Project developed phenomenal technology to analyze the entire genome of an individual in a fraction of the time and cost that the initial complete genome sequence required. As greater understanding of the pattern of SNPs is gained, more panels for health and for disease will become part of primary care. The next decade will see increasing data analysis of whole genomes from groups of people with a trait or disorder and comparing their markers to control groups. While mapping the human genome has moved from costing billions of dollars to near \$10,000, we will still need the "million-dollar" analysis.

THE USE OF GENETIC TESTING TODAY

The path from DNA code to protein structure and function will be further delineated in the decades of the future. But there are many genetic tests commonly seen in clinical records today. Some of their uses today include:

- Newborn testing. All newborns in the United States are screened for the inherited inborn metabolic disorders of phenylketonuria and galactosemia. Both are treated with dietary restrictions. They are actually tests for the metabolic manifestation of the recessive disorder. Many states require more testing of newborns that includes genetic tests. The American College of Medical Genetics recommended a panel with 29 genetic and metabolic screening tests, and 21 states have adopted this recommendation.
- Prenatal carrier testing. Panels of tests should be used in conjunction with counseling as targeted

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CONTINUED ON PAGE 22

carrier status is checked. If each parent carries a recessive mutation, there is a chance the child will have the disease if the child inherits the carrier gene from each parent. Technologic advances now allow many genes and gene sequences to be tested on a single “microchip.” One company announced a chip that could screen 448 severe recessive childhood diseases.⁶ This is “disruptive technology.” While the science is exquisite, it calls for significant consideration for counseling of parents.

- Screening for cause. Family history of risk or suggestive symptoms. These tests are becoming routine in many situations. A family history of familial adenomatous polyposis is associated with a high risk for colon cancer with a recommendation for preventive complete colectomy. It is inherited as a dominant disorder. Screening the adult children of an affected parent can help plan surveillance and preventive surgery.
- Diagnostic criteria. There are many presentations where genetic testing will be used to confirm or rule out a diagnosis. For instance, with multiple cysts in the kidney, testing for the polycystic kidney disease mutations can confirm the diagnosis.

- Pharmacogenetics. New pharmaceutical agents are being rolled out with genetic tests that assess for adverse reactions to the medication or help with dosing for optimal response. Individuals are now being tested to determine how they may respond to a medication based on the type of allele they have in a gene that processes the drug.
- Personal interest with direct-to-consumer (DTC) tests. A Web search for DTC genetic test kits will turn up multiple companies that will test for markers of significant disease along with healthy traits. The tests can be obtained without a physician’s order. The FDA is concerned over the validity of these tests and consumers’ understanding of the results. These tests are not diagnostic, but the results give increased probability of having the trait or disorder. In an online survey, 64 percent of over a thousand respondents said they would eventually try a test.⁷ The respondents were in their 30s, college-educated, and 75 percent female. While 80 percent would try a test out of general curiosity, 40 percent said they wanted to learn about their genetic makeup without going through a doctor. Genetics have become a household name.



GENETIC MEDICAL SCIENCE IS HERE TO STAY

Genetic medical science has been with us for many decades. Recent technological developments allow us to get the nucleotide sequences that are behind the inheritance patterns we observe and the metabolic abnormalities associated with them. Just as biochemistry has been part of medical workups for decades, so will medical genetics come into the primary care office. The medical literature is now exhorting clinicians to study and learn this science as they will need to know its place in screening, diagnosis, counseling and treatment. But we are just beginning to grasp the multifactorial influences on disease and how to move from genome-wide studies into clear opportunities for prevention and treatment. ■

Table 1. Autosomal Dominant Inherited Disorders

Table 1	
Autosomal Dominant	Significant Manifestation
Marfan's	Connective tissue aneurysms
Huntington's Chorea	Neurodegenerative dementia
Miltoic Dystrophy	Chronic degenerative sympathy
Adult Polycystic Kidney Disease	Renal failure
Von Hipper Landau	CNS vascular tumors
Familial Adenomatous Polyposis	Colon cancer and others
Von Recklinghausen's Disease	Neurofibromatosis
Retinoblastoma	Childhood retinal cancer
Hypertrophic Cardiomyopathy	Heart failure and sudden death
Spinocerebellar Ataxia	Movement disorder




Table 2. Autosomal Recessive Inherited Disorders

Table 2	
Factor Leiden Deficiency	Blood clots
Alpha-1 Antitrypsin Deficiency	Premature COPD
Sickle Cell Anemia	RBC abnormality with anemia
Alport's Syndrome	Renal failure
Wilson's Disease	Cirrhosis
Cystic fibrosis	Lung disease
Phenylketonuria	Intellectual disability
Gaucher Disease	Lysosome storage disorder in soft tissues and bone marrow
Tay Sachs	Degenerative motor disease
Familial Dysautonomia	Progressive sensorimotor autonomic neuropathy

Table 3. Sex-Linked Inherited Disorders

Table 3	
Hemophilia VIII	Bleeding disorder
Color Blindness	Visual restriction
Agammaglobulinemia	Immune deficiency due to immunoglobulin deficiency
X-linked Spinobulbar Atrophy	Progressive limb and bulbar muscle weakness
Duchenne's Muscular Dystrophy	Progressive diffuse skeletal muscle atrophy

Figure 1. Example of Dominant Mendelian Inheritance

 = brown hair as dominantly inherited trait.
  = blond hair as recessively inherited trait. Manifestation of blond hair is only possible if both parents transmit the recessive  trait.

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