Human Genetics--Biol 102
Refining The Concept Of "Genetic Diseases"

I) Single-Gene Disorders Versus Multifactorial Disorders

A) Single-Gene Disorders Often Have More Dramatic Effects On The Individual's Health

If someone was to ask you to think of a situation in which a genetic factor caused someone to have a disease, you would probably think of a child who was born with some type of genetic birth defect, or who had some recognized genetic syndrome (ex. cystic fibrosis). When we think of genes and disease, we often think of these life-long disorders, many of which have dramatic effects on the development and function of several of the individual's body systems. A person with cystic fibrosis, for example, has problems with his/her respiratory system that begin in early childhood. This leads to frequent, even life threatening, lung infections. Many also have problems with the function of their pancreas. When the pancreas does not function properly, you cannot digest your food properly. Many cystic fibrosis patients experience a failure to thrive, because they cannot get the proper nutrition out of their food.

Many of the diseases we think of when we think of "genetic diseases" are **single-gene disorders** like cystic fibrosis. As the name implies, these diseases are caused by mutations in a single gene (ex. cystic fibrosis caused by mutations in the CFTR gene). Many of these disorders affect the individual throughout his/her entire life, and these disorders represent dramatic and memorable examples of the influence our genes have on our health.

B) Multifactorial Disorders Are Far More Common, And Represent A Larger Burden On Human Health

There is another, much more common, group of diseases, however--the **multifactorial disorders**. Many of our most common diseases (cancer, heart disease, asthma, diabetes, Alzheimer disease, depression, alcoholism and many more) are examples of multifactorial disorders. Many of the more common multifactorial disorders do not appear until later in life, even though a person may be born with an increased risk of developing that disorder. In addition, many of them (ex. asthma, diabetes) have less dramatic medical effects on the individual than the single gene disorders usually do. However, these are the kinds of chronic diseases that touch almost everyone's family, and often reduce the quality of a significant portion of the individual's life. Multifactorial disorders are far more common than the single-gene disorders. Consequently, they affect many more people, and place a much larger collective burden on human health than the single-gene and chromosomal disorders do (Figure 1.1).

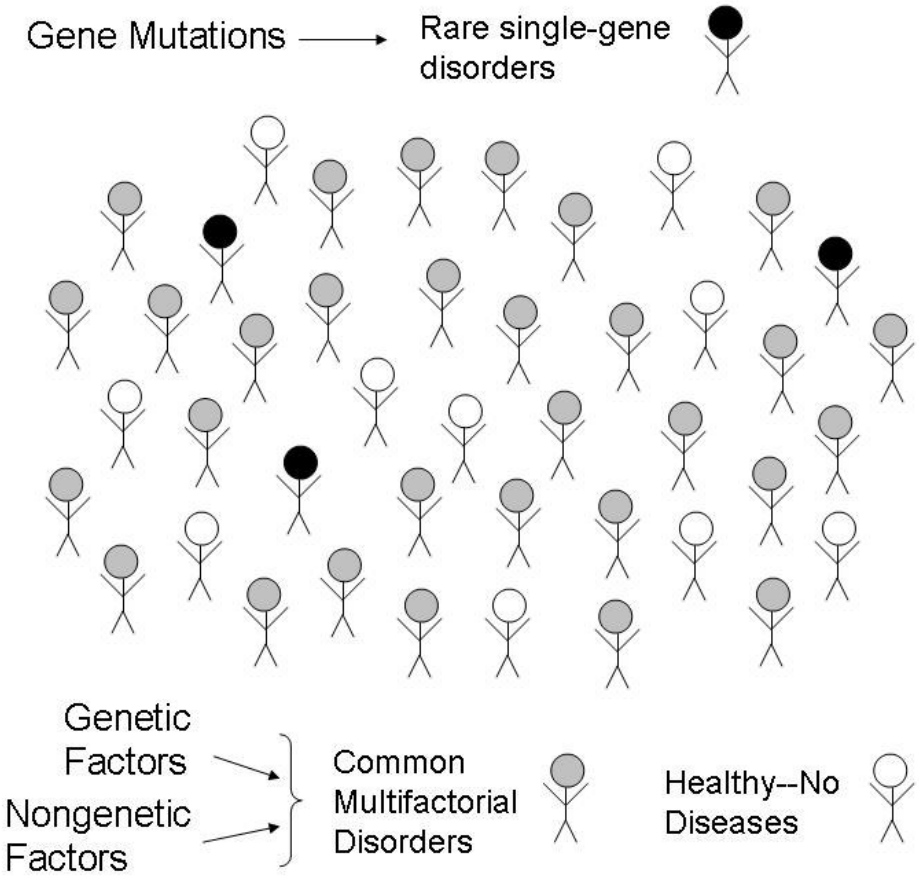

Figure 1.1 In a typical population, many more people are at risk for one of the multifactorial disorders than the single-gene disorders. (Note: the proportion of unshaded, grey and black-headed figures is not intended to accurately portray the proportion of the population who are or are not affected with these types of disorders. To do this accurately, one would need to specify the age, ethnicity and other characteristics of the population.)

II) Genetic And Nongenetic Factors Interact To Influence The Overall Risk For A Disease

A) Genetic Factors—Different Gene Alleles Produce Forms Of The Protein That Have Different Levels Of Activity

The biological processes that provide the foundation for personalized medicine are extremely complicated. Fortunately, you don't need to understand the details of these processes to understand how your genes influence your health. Much of the action centers around your proteins. Your proteins do most of the jobs that must be done in order to keep you healthy. They break down your food and deliver the nutrients to your body, they battle against the disease-causing bacteria and viruses you encounter in your environment, and they repair the damage that environmental factors such as the ultraviolet (UV) rays of the sun do to your body, or the damage that you do to your body through lifestyle choices such as smoking.

The most important fact to remember is that there are many different versions (alleles) of a gene's sequence in the population, and different alleles of the gene make different forms of the protein, which have different levels of activity. Therefore, different people have different levels of

activity in their proteins. This is what causes some people to be more susceptible to a certain disease than others, or causes one person to benefit from a drug, while another person will not.

B) Nongenetic Factors Come From Your Diet, Environment And Lifestyle

People often characterize the factors that influence our development and health as "genetics and environment." When we think of environment, we usually think of the environment outside our bodies. The term "nongenetic factors" is a better term than "environment," though, because it includes the things we expose ourselves through by our choices of diet, environment and lifestyle. Nongenetic factors include exercise, fat level in our diet, sun exposure, and a host of other factors.

C) Genetic And Nongenetic Factors Interact To Influence Your Overall Risk For A Multifactorial Disease Or An Adverse reaction To A Drug

As the name implies, a multifactorial disorder is caused by multiple factors acting together. A multifactorial disorder is said to result from a combination of genetic factors (level of activity in your proteins) and nongenetic factors (from your diet, environment and lifestyle).

There are some aspects of the way your genes influence your health that you can understand as just another version of the classic battle between good and evil that you've seen play out in so many books, movies and TV shows. There are a number of situations in which your everyday activities bring you into contact with something that has the potential to make you sick, but some of the proteins you have in your body either battle against the disease-causing agent, or repair the damage it causes.

For example, consider the fact that being outdoors on a sunny day exposes you to ultraviolet (UV) rays from the sun, which can damage your DNA. This is dangerous, because the damage the sun's UV rays do to your DNA can cause you to get skin cancer. You have a family of proteins that can repair the damage that the sun's UV rays do to your DNA, however, and keep you from getting skin cancer. Someone who has a high level of activity in these proteins will be less likely to get skin cancer than someone who has a low level of activity in these proteins will be. On the other hand, someone who has a low level of activity in these proteins will be more likely to get skin cancer than someone who has a high level of activity in these proteins will be

It's not quite as simple as that, of course. There are other types of situations in which your proteins actually create the disease-causing agent. For example, your body breaks down the fats in the food you eat, or the fat that your body has stored, to provide you with the energy you need to do the things you do. In the process, it creates chemicals know as "reactive oxygen species," or "superoxide radicals." These superoxide radicals can damage the lining of your arteries. This can ultimately cause the buildup of deposits that clog your arteries, and cause you to have atherosclerosis, or hardening of the arteries. This is one reason why people are encouraged to eat a diet that is rich in antioxidants; antioxidants can break down the superoxide radicals before they can damage your tissues.

In this situation, the proteins your body uses to harvest the energy from your fats create the superoxide radicals. Because your proteins create the disease-causing agent, someone who has a high level of activity in these proteins will be more likely to have atherosclerosis than someone who has a low level of activity in these proteins will be. On the other hand, someone who has a low level of activity in these proteins will be less likely to have atherosclerosis than someone who has a high level of activity in these proteins will be.

The level of activity in key proteins also affects the way your body responds to prescription drugs. Some of the proteins in your body break down the drugs you take, and carry them out of the

body. Someone who has an especially high level of activity in these proteins may not benefit from the typical dose of the drug, because he/she does not build up enough of a concentration of the drug for the drug to have the effect he/she needs it to have. On the other hand, someone who has an especially low level of activity in those proteins may build up a dangerously high concentration of the drug in his/her body after a typical dose, and suffer a toxic side effect as a result.

Most of the time, your doctor has no way of knowing how fast you'll clear a drug out of your system, and therefore prescribes everyone with your disease the typical dose of his/her favorite first-line drug. The fact that individual metabolic factors are not taken into account is one reason why 40-50% of the people who get prescribed a drug/dose do not respond to it. This is also one reason why adverse drug responses account for approximately 10-15% of emergency room admissions.

III) Almost All Disease Are Genetic Diseases

As we learn more about the way in which our genes work, it is becoming apparent that we need to change our concept of "genetic diseases." We need to understand that almost all diseases are genetic diseases to some extent, because our genes play an important role in determining how susceptible we are to most diseases. Nearly every family gets touched by one of these multifactorial disorders sooner or later.

Another concept we need to revise is to come to a better understanding of the fact that we can sometimes reduce our risk for developing a multifactorial disease later in life by making health-conscious choices about our diet, environment and lifestyle while we are young. Many people accept declining health as an inevitable part of getting older. While some decline is truly inevitable, some of the disease and decline we accept as inevitable really isn't.

We are entering an age in which genetic testing will allow your doctor to determine whether you have genetic factors that predispose you to one multifactorial disease or another. In order to keep this information in perspective, people must avoid falling into that logical fallacy we call **genetic determinism**. Genetic determinism involves someone thinking that their genetic status is the sole determinant of their health, and that, if he/she has a "bad gene," he/she will definitely develop the corresponding disease. It is true that, if you have enough of the genetic factors that cause a disease, there may be little you can do through diet, environment and lifestyle to avoid getting the disease. In most cases, however, when someone possesses a risk-increasing gene allele, that genetic factor will only increase his/her risk for the disease by a small amount. There is often plenty of room for the person to influence his/her risk for disease by controlling his/her diet, environment and lifestyle factors.

Study Questions—Refining The Concept Of "Genetic Disease"

1. Please explain the difference between a single-gene disorder and a multifactorial disorder. Which of the two do you have more control over in terms of whether you develop the disease or not? Explain your answer briefly.

2. What does it mean when we say that genetic factors influence what dose of a drug will be safest and most effective for you?

3. What does it mean when we say that nongenetic factors influence your risk for a multifactorial disease?

4. What is "genetic determinism," and should we avoid it or embrace it? Why?