

THE HUMAN GENOME PROJECT

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Genes and Genomes

Imagine knowing all of the ingredients that go into making the human body. This is the goal of the Human Genome Project, an international scientific effort to determine a complete list of all of these components. The instructions for making the different components are spelled out in the genes. Identification of the genes will tell us a great deal about how the body works and develops, and what can happen if everything does not go exactly right.

We should first go over some of the terms that are important in understanding genes and the genome. The genes are like a blueprint for how the body develops. Differences in genes can lead to differences in how a particular part of the body forms. They determine many physical characteristics of a person such as what color eyes or hair he/she might have. In addition, the genes play important roles in determining how other parts of the body form, such as the heart, and also contribute to how a child grows and learns. The genes are made up of a chemical called DNA (for deoxyribonucleic acid). Each gene contains the instructions for building a specific protein. The genome is all of the genetic material of a particular organism. Thus, the human genome is the complete information contained in the DNA in a person. DNA is thought to resemble a ladder with each rung being composed of a pair of chemicals termed bases. There are four types of bases: adenine (A), cytosine (C), guanine (G), and thymine (T). It is the particular order, or sequence, of these four bases that determines the “code” of what protein a given gene will make. It is the combination of these genes and proteins that determines whether the organism is a human, or a fly, frog, chicken, or mouse. The goal of the Human Genome Project is to determine the sequence of all of the bases, and thus identify all of the genes.

The Human Genome Project

How a person's body develops is very complicated, and, as you might guess, the information contained within the genes is extremely complex. In fact, it is estimated that there are approximately 3 billion bases and approximately 30,000 genes in the human genome. The Human Genome Project has recently announced that a draft of the entire genome has been completed. This extraordinary accomplishment is the result of a decade of work by many researchers throughout the world.

Knowing the complete sequence of the bases means that we can now identify all of the genes. By knowing all of the genes, we can begin to piece together what genes are important for the development of different parts of the body. For example, a change in one or more of these genes might lead to problems in formation of the heart, such as ventricular septal defect or coarctation of the aorta, two of the more common heart problems in children with Kabuki syndrome. Many medical conditions, such as cystic fibrosis or sickle cell anemia, are caused by an abnormality in a single gene. In fact, both conditions can be caused by a change in a single base out of the 3

billion bases that are in the genome. In other conditions, including cancers, high blood pressure, and diabetes, there are often contributions from several genes which influence if the disease will occur and how severe it might be.

Information from the Human Genome Project opens up the possibility of understanding what causes the variations that give each person his or her unique characteristics. As we begin to learn which genes are involved in forming the different organs, we can also understand what happens when there is a child is born with a medical problem. This information could lead to insights in developing new ways to diagnose, treat, and possibly even prevent many medical disorders. We will have a better understanding of genetic predispositions to disease. As we will discuss in the next section, while these benefits will arise in the future for many conditions, the practical application of much of the information from the genome will generally require a great deal more research over the coming years.

What is the Next Step for Learning About the Genome?

Although identifying all of the genes will be a very exciting accomplishment, in a certain sense it is just the beginning. There is a great deal more to be learned in order to understand what all the genes and proteins do and how they interact. Having a list of the genes will tell us what there is to work with, but it does not indicate which genes are important for forming the heart or what the function is of each gene or protein. Completing the sequence of the genome and identifying all of the genes is similar to having a complete list of 30,000 ingredients needed to prepare a feast. Knowing what the ingredients are is a start, but to make the dinner come out right, you need much more information. First, you would have to know which ingredients go into making the salad, which are for the soup, and which go into the main course, the dessert, or the beverages. Then, you would have to determine how much of each ingredient to add and in what order. You then have to know how to combine the ingredients to cook each dish.

This is similar to understanding what role all of the different genes play in the body. The Human Genome Project will tell us what genes are present. We then have to determine in which organ system (heart, brain, liver, etc.) the particular gene is active. For example, for a gene involved in heart development, we need to figure out how much of the protein of that gene needs to be made and during which steps in heart formation. We would have to learn in which specific regions of the heart the gene is active. And of course, in order to understand truly what the gene and protein do, we also need to determine how the protein operates and with what other factors it interacts.

Much of this information is not very well understood for most genes. So, knowing the genome will be the catalyst of a flood of new information that will give us a fuller understanding of how the different genes work during development.

What Does the Human Genome Project Mean for Kabuki Syndrome?

At the present time, we have very little information about what genes are important in Kabuki syndrome. On a very basic level, we still do not know if Kabuki syndrome is caused by a change in a single gene or in a group of genes. The Human Genome Project will provide a list of the genes, and this will help us to identify the gene by knowing what the options are. However, the

difficult part now is to determine which of the 30,000 genes are important in causing Kabuki syndrome. Thus, the genome information will provide a framework, but much more work will need to be done before the gene involved in Kabuki syndrome is known with certainty.

Once the gene (or genes) involved in Kabuki syndrome is identified, we can begin to grasp how the difference in the gene leads to the many features seen in the syndrome, such as congenital heart disease, cleft palate, or short stature. It will then be possible to determine for a given child how that gene differs from the normal gene. It may also provide a way of diagnosing Kabuki syndrome in children in whom the diagnosis is not clear. Knowing the gene could aid in recurrence risk estimates and potentially lead to prenatal detection of the gene change. Once the gene(s) involved in Kabuki syndrome have been identified, the genome project will also make it easier to learn about the function of the gene since information may be available regarding what other genes are affected by the changed gene in Kabuki syndrome.

Overall, this is a very exciting time for medical genetics as the explosion of information generated from the Human Genome Project will undoubtedly provide insight into both normal development and medical conditions. Although a great deal of work lies ahead in identifying and learning about the function of the gene(s) involved in Kabuki syndrome, the information from the genome project will provide tools for a better understanding of Kabuki syndrome.

About the Author

Jeffrey Ming, M.D., Ph.D. is an Assistant Professor of Pediatrics, Division of Human Genetics and Molecular Biology, at The Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine. He and his colleagues have seen approximately 12 children with Kabuki syndrome. He also has a very strong interest in learning more about what genes are involved in causing Kabuki syndrome.