

Three New Primary Dystonia Genes Identified by Next-Generation Sequencing

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The month of December 2012 was a banner month for the genetics of primary dystonia with the identification of three different primary dystonia genes doubling the total number of primary dystonia genes that have been found since the first one (DYT1) was identified in 1997. You ask, what made this possible? Beyond the obvious answers such as hard work and enough research funding to perform the work, are the major innovations that have occurred in the field of human genetics.

First, we need a few definitions. DNA is the hereditary material found in our cells that is responsible for encoding all of the instructions needed to make an organism, including making all the molecules that perform different functions within our cells called proteins. DNA is made up of four main types or bases, commonly referred to as G, A, T and C. The order of the bases is called the sequence and when we decipher this order, we are sequencing the DNA. Over a 13 year period from 1990-2003, the Human Genome Project deciphered all the bases (3 billion) that make up our DNA (our genome) at a cost of \$3 billion. It turns out, that all of us are 99.9% identical, meaning any two people differ at about 3 million locations where single base pair changes occur called single nucleotide polymorphisms (SNPs).

The Human Genome Project has been a bonanza for genetic research not only producing the first sequence but also allowing us to identify the 20-30,000 genes that encode all of our proteins. In the last several years, a new way of sequencing called next-generation sequencing has made it possible to sequence the entire genome of a person in about 2 weeks for around \$5,000. In this method, the DNA is sequenced in small pieces of only 100-200 base pairs and then reassembled by comparing it to the original genome sequence. Although the time and cost of producing the DNA sequence is significantly reduced our ability to reassembly all of the smaller pieces into meaningful sequence and identify all the variants in a person's genome takes time.

This new technology, next-generation sequencing, was used to identify all three of the new dystonia genes but rather than sequencing the entire genome, only the regions coding for proteins, called the exome, was sequenced as this is the region most likely to have a mutation that leads to an inherited disease. One gene, ANO3, was discovered in families with cranio-cervical dystonia by Professors Nick Wood and Kailash Bhatia from University College Hospital in London. The ANO3 gene encodes a calcium channel that is found in the striatum, a brain region involved in control of movement. Another gene, GNAL was found by myself and Dr.

Tania Fuchs at Mount Sinai working with Dr. Susan Bressman at Beth Israel Medical Center and other clinicians located in the US and Canada. We identified GNAL mutations in 8 families with mainly focal segmental dystonia involving the neck. This gene is part of the dopamine signal transduction system that transmits chemical signals (dopamine) from the outside of the cell to the inside setting off a cascade of reactions. The third gene, TUBB4A, was identified by two independent teams of researchers led by Professors Christine Klein at the University of Lubeck, Germany and Henry Houlden at the Institute of Neurology Queen Square, London. The two groups were studying the same DYT4 dystonia family. Affected individuals in this family have severe dysphonia as well as progressive limb and cervical dystonia. TUBB4A is expressed in neurons and is a component of the cytoskeleton or cellular scaffolding necessary for cellular division as well as for transport within the cell.

The immediate impact of the discovery of these disease genes will be the development of genetic tests to confirm diagnosis, identify unaffected adult carriers, and allow patients and their families to make informed reproductive choices. These new genes also point to novel pathways involved in dystonia and should contribute to our understanding of disease mechanism as well as provide a basis for developing new therapies. Next generation sequencing is a powerful tool that will continue to accelerate the pace of dystonia gene discovery in the coming months and years. Finally, I think I can speak for all of the researchers and clinicians involved in these studies when I send a big thank you to the patients and families involved in this work as these genetic discoveries are only possible with the generous cooperation and participation of families.

Citations:

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