Genetic Research 101: How genetic research works

The goal of medical and clinical research is to make life better for the individuals and families living with health conditions and diseases. Genetic research helps meet this goal by finding and studying genes that cause or contribute to a particular condition or disease. Once a specific gene is associated with a particular disease, researchers learn about what that gene does in the body and how the “normal” gene acts differently from the “mutated” or changed gene. When we learn what the gene does in the body and how the mutated gene causes the disease symptoms, research moves forward to develop new ways to diagnose, treat or manage the disease.

Step One

Like medicine, genetic research begins with people (see figure). In the case of dystonia research, it begins with people with any type of dystonia or a related movement disorder. When a doctor sees many people who have the same health problems and other characteristics (especially if the people are family members), the doctor begins to ask questions about the condition and begins to wonder if something genetic is causing the similar health problems.

Step Two

In genetic research, we must first carefully describe and measure the symptoms that people have. This is referred to as “description of phenotype” in the figure. Doctors and researchers developed (and continue to improve) systems to classify and organize different types of dystonia. They also created scales to rate symptoms of dystonia so that one person’s symptoms can be compared to another person’s symptoms. These classification and rating systems make it easier to put people with similar types of dystonia and symptoms (also called similar phenotypes) into a group. It is easier to find a single cause or gene for a problem that creates the exact same symptoms each time than it is to find a single cause for a problem that creates different symptoms each time (even if the symptoms are related).

Example – Dr. Sharma asks her research participants about their medical history, family history and does a thorough examination. Then, Dr. Sharma separates the participants into groups based on their symptoms and type of dystonia. People with cervical dystonia go into one group, people with generalized dystonia go into another group, etc. She also keeps track of which people in the groups have family members with dystonia and which people do not.

Step Three

With clear classification systems and people with dystonia divided into groups based on their symptoms, we begin to look for genes that may be associated with each group. First, we need DNA from individuals with dystonia and their family members (we get DNA from blood samples given by people who take part in research studies).
Dystonia-Related Gene Update: Working on step three

Past successes

Under the direction of Xandra O. Breakefield, Ph.D., researchers at Massachusetts General Hospital identified the DYT1 gene in 1997. A mutation, or change, in the DYT1 gene is associated with early-onset generalized dystonia. The DYT1 gene makes a previously unknown protein named torsinA. Since 1997, a handful of other genes associated with different types of dystonia have been found.

Recent findings

Within the DYT1 gene there are actually four places where changes have been found. The change that we know the most about is called deltaGAG, and it is the change or mutation that is associated with dominantly inherited early-onset generalized dystonia. Another change within the DYT1 gene, called D216H, is more common than the deltaGAG change (so D216H is called a polymorphism rather than a mutation). We wanted to find out if D216H has any influence on the torsinA protein or the deltaGAG mutation. For example, we know that only 30-40% of people with deltaGAG develop symptoms of dystonia. So we wondered if D216H could give us more information about who develops symptoms and who does not.

The TorsinA Protein: The foundation of step four

When we found the DYT1 gene that is associated with early onset torsion dystonia, we found a new protein, which we named torsinA. Thus our search for the gene led to another search - figuring out what the torsinA protein does and how a specific mutation in the protein causes dystonia.

The first clue about what the torsinA protein does came from studying the order of the building blocks (amino acids) that make up the protein. (The order of a protein’s building blocks is determined by the gene for that protein. If there is a mutation in a gene, there will be a mutation in the protein made from that gene.) The order of the torsinA protein’s building blocks puts it in a family of proteins that are involved in physical manipulation of other proteins – something like a hand resetting a clock or molding a pot.

We know that torsinA is found in brain cells that control body movement. In these cells, the mutant form of the protein changes the position of membranes within the cell, so the cell takes on an unexpected shape. The effect of having mutant torsinA in brain cells is similar to having a room in your home remodeled, but by a bad contractor.

TorsinA is found in brain cells throughout our lifetime. However, the highest levels of torsinA are found in the brain just after birth. During this time, brain cells undergo major structural changes that alter their size and shape.

It appears that in people who are carriers of the torsinA mutation (meaning they have both the normal form of torsinA protein and mutant form), the mutant form of the protein suppresses, but does not completely eliminate the activity of the normal form. Thus, people with the torsinA mutation have a reduced level of normal torsinA activity. This reduced level of torsinA activity is enough for most bodily and mental functions, including good physical health and high intelligence. However, in a small number of brain cells this reduced activity may lead to changes in their size and shape that affects their ability to communicate properly with other brain cells. Miscommunication between brain cells can result in miscommunication between the brain and muscle, resulting in dystonia.

Research on this intriguing protein has gained momentum. Future results should provide insights into how the brain controls movement in general, as well as information about how the mutant torsinA protein causes dystonia.
Mouse Model of Dystonia: More on step four

Since the discovery of the DYTI mutation in Dr. Breakefield’s laboratory in 1997, we put a large effort into developing an animal model of DYTI-associated dystonia. The goal in developing an animal model of DYTI-associated dystonia is to study the effects of dystonia on the brain, as a whole organ. If experiments are only done in cells that are grown in Petri dishes, it is not possible to study all the effects of the DYTI mutation or to fully understand how the brain is affected by the mutation. The advantage of using mice to model DYTI-associated dystonia, as opposed to other animals, is that a lot is already known about how the mouse brain functions and large numbers of mice can be bred relatively quickly.

We developed a transgenic mouse model of DYTI dystonia. A transgenic mouse is a mouse in which a gene that it does not normally have is inserted by artificial means (see figure). We made and are now studying mice that express the human DYTI gene mutation. We found that these transgenic mice have some difficulty learning motor skills. This finding is exciting because humans who have the DYTI mutation have difficulty learning motor skills. This means that the DYTI transgenic mice we created are similar to humans with the DYTI mutation. Thus, the DYTI transgenic mice are worth studying in greater detail, because they show problems that are similar to people. Most importantly, this means that these DYTI transgenic mice can be used to screen potential medications for dystonia. A compound that makes it easier for the mice to perform motor skills may help people with DYTI dystonia as well.

Questions and Answers

Question:
Do I need genetic testing now that I know genes associated with dystonia have been found?

Answer:
Most likely the answer is no. Genetic testing is only available for a small number of people with dystonia. If you are offered genetic testing, you should talk with your doctor or a genetic counselor about what the test may mean for you and your family before the test is done. (Just because genetic testing is available does not mean that you need or should want it done.) Right now, we only offer clinical genetic testing to three groups of people with dystonia.

Group 1 – People with early onset generalized dystonia or people with another type of dystonia who have a family member with early onset generalized dystonia. People in this group are offered testing of the DYTI gene.

Group 2 – People with early onset dystonia that improves when they take dopamine (L-dopa or Sinemet), which is also called dopa-responsive dystonia. People in this group are offered testing of the GTP-cyclohydrolase1 gene and sometimes the tyrosine hydroxylase gene.

Group 3 – People with myoclonus-dystonia. Myoclonus-dystonia is a rare condition where people can have symptoms of dystonia in addition to symptoms of myoclonus, which is a related movement disorder. People with myoclonus-dystonia are offered testing of the epsilon sarcoglycan gene.

If you have a question that you would like to appear in the Dystonia Research Newsletter, please contact Trisha at tmulthaupt@partners.org.

More on - Dystonia Defined

Dystonia is a neurological movement disorder. The medical discipline that manages people with conditions beginning in the brain is neurology. Dystonia falls under the category of neurology because the cells that control muscle movement are located in the brain. Movement disorders are a special category within neurology. Movement disorders include conditions like Parkinson’s disease, tics, tremors and ataxia, in addition to dystonia.

Learn more at: http://www.dystonia-foundation.org/defined/
Learn more at:

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When we have a way to tell the two forms of the gene apart, we can create experiments to see what happens to cells when we increase or decrease the amount of one or both forms of the gene.

The next big challenge is to uncover the problem causing DYT1-associated dystonia. It could be that the mutant (changed) form of the DYT1 gene protein (torsinA) interferes with normal function, which is called a dominant negative effect. Or the problem could be because only half of the wildtype (normal) protein is not enough to keep cells functioning correctly. When we figure this out, we will have a much better idea about how to treat dystonia at the level of the cell."

Q: What are you working on now?

“We are learning about what torsinA (the DYT1 gene protein) does in the body, how it responds to different conditions, and what other cell structures torsinA interacts with. We put cells under different types of stress using chemicals and we see how torsinA reacts.

We are also working with a company, Alnylam, on RNA interference (RNAi). We can use RNAi to “silence” genes. So if it turns out that dystonia occurs because the mutant (changed) form of torsinA interferes with normal function, we could “silence” the mutant form of the DYT1 gene with RNAi. This silencing would hopefully prevent symptoms of dystonia.

Q: What keeps you going after 15 years?

“Dystonia is curable. (Jeffrey speaks very sincerely and excitedly.) With dystonia, unlike Parkinsons Disease, the neurons in the brain are not dead. All we need to do is figure out where the gap in the cells’ communication goes wrong and fix that gap. Plus, I love science. I would still be working on this even if I were a millionaire. And on the personal side, I would never want my kids to be affected with dystonia and feel powerless to help them.”

It is clear that Jeffrey Hewett has a true passion and commitment for science and a deep understanding of dystonia research history and its future. Without a doubt, he is a wonderful asset to the dystonia community.

- Trisha Multhaupt-Buell is a research coordinator and genetic counselor in the MGH dystonia group.

At the Bench
An interview with Jeffrey W. Hewett

Jeffrey Hewett is a lab manager and senior research technologist in Xandra O. Breakefield’s Dystonia lab at Massachusetts General Hospital. Jeffrey attended Bridgewater State College where he received his bachelor’s degree in Biology and Chemistry.

Impressively, Jeffrey has worked in research for 17 years, and he has spent 15 of those years working on dystonia research.

Q: How did you get started in Dystonia research?

“My general interest in science began in 7th grade. I had a captivating chemistry and biology teacher, Mr. White. After college, I took a job working for a company that does research. After a couple years, I wanted to go into academic research and a position in Dr. Breakefield’s lab was open. I took it, and I am still here.”

Q: What are the biggest challenges in your work?

“The first big challenge is to figure out a way to tell the difference between the wildtype (normal) DYT1 gene and the mutant (changed) DYT1 gene in cells. Once we have a way to tell the two forms of the gene apart, we can create experiments to see what happens to cells when we increase or decrease the amount of one or both forms of the gene.

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More on - Linkage

For every trait, such as eye color, we have at least one gene. For every gene, we have two alleles (although there can be more than two alleles for any one gene/trait). For example, gene “eye color” has alleles “A” (brown) and “a” (blue) that occur with a frequency of 90% and 10%, and gene “hair color” has alleles “B” (brown) and “b” (blonde) that occur with frequencies 70% and 30%. Then, the frequency of individuals in a population who have combination AB (brown eyes and brown hair) would be 63% (multiply the frequency of “A” by the frequency of “B”).

However, if a mutation in allele “B” causes a disease (green hair), and it almost always occurs with a particular allele of gene eye color (for example “aB”) then genes alpha and beta are assumed to be close together on the same chromosome (i.e. they are linked).

In research, we use regularly spaced markers to tell us where we are in the genome and what part of the genome we are looking at. When we look for linkage, we are hoping that a gene that causes dystonia is linked to one of the markers. We can tell if a dystonia gene is linked to a marker when we see the marker more often in the genome of people with symptoms of dystonia that we would expect by chance (more than 10% of the time in the above example).

Learn more at: http://en.wikipedia.org/wiki/Genetic_map

Clinical Corner

Partners Dystonia Center

The Partners Dystonia Center, which operates at Massachusetts General Hospital and The Brigham and Women’s Hospital, is a collaborative clinic in which the goal is to provide both adults and children with dystonia with the best possible medical, emotional and social support. The collaborative approach of the center allows individuals with dystonia to receive coordinated, comprehensive care in one clinic. The Dystonia Center is staffed by a team of skilled health professionals, dedicated to the care of dystonia patients. Dr. Nutan Sharma is director of the center. Dr. Sharma works closely with Lisa R. Paul N.P., a nurse practitioner specializing in dystonia, Trisha Multhaupt-Buell, M.S., a genetic counselor who also serves as research coordinator, Janet Callahan, P.T., a physical therapist who evaluates and develops exercise programs, and Caitlin Barrett, who coordinates all appointments.

The Center serves as a clearing-house for information about dystonia. This includes information about the latest treatments as well as the latest clinical research opportunities. The Center also trains physicians and other health care professions in the diagnosis and treatment of dystonia. To learn more, visit the Dystonia Clinic at MGH website at http://neuro-www.mgh.harvard.edu/%7Edystonia/
(continued from p. 1) Then, we find genes associated with dystonia in one of two ways: 1) linkage/association or 2) candidate genes.

In linkage and association studies, we take the DNA from everyone in one dystonia group, and we look at the DNA for an area that is the same among people with symptoms but different from people without symptoms. If we find this to be the case, we assume that there might be a gene in that area that is associated with the dystonia (see linkage side bar p. 4). When several members of the same family have the same type of dystonia (a strong family history), we can use fewer DNA samples. When people are or appear to be the only person in their family with dystonia, we use more samples (from unrelated individuals).

The second way to locate genes is by testing candidate genes that we already know (from the human genome project and other research) are related to the brain and movement. If we think that a certain gene might be related to dystonia, we can look for mutations in that gene that correlate with symptoms of dystonia.

Once a gene is found to be associated with a condition, clinical genetic testing usually becomes available. Clinical genetic testing is typically the first benefit of genetic research. People and families with dystonia can use clinical genetic testing in diagnosis and family planning.

Step Four:
The next step in genetic research is to learn about what the gene associated with dystonia does in our bodies. In this stage, we want to figure out how a mutation in this particular gene ends up causing or increasing the risk of symptoms of dystonia. In general, we start by learning about what protein the gene makes, and what type of protein it is. Then we try to figure out the difference between what the protein does when it is normal and what the protein does when it is mutated. We learn more about what genes and proteins do through experiments with cells and animals in a research laboratory.

When we learn what the protein does when it is mutated, it gives us information on the underlying cause of the condition. If we better understand the cause of a condition, we can move on to the next step in the process.

Example – After finding the DYT1 gene, we learned that it makes a protein called, TorsinA. TorsinA is the type of protein that makes sure that other proteins are in the right shape and in the right place. Researchers are currently doing experiments that will tell us about the difference in what TorsinA and the proteins that it works with do depending on whether or not TorsinA is mutated.

Step Five:
Now that we understand how the gene and its protein cause or increase the risk of developing a disease, we can find new ways to treat, manage and possibly cure the disease. We use what we learn to develop treatments that target the specific cause of the disease. That could mean using gene therapy to make more of the normal protein (to overcome the lack of work done by the mutated protein) or to decrease the amount of the mutated protein (to make sure that the mutated protein can’t interfere with the normal protein). Or it could mean developing a drug that acts on the cell process or cell cycle that is affected by the mutated protein.

In Appreciation

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Inside learn more about:
Ongoing dystonia research projects
The answers to your questions
The people behind dystonia research

Massachusetts General Hospital

Dystonia Update

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