

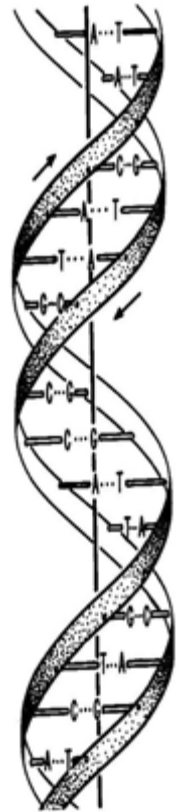
What is ET?

An estimated 5-10 million people in the US have essential tremor, the most common movement disorder in humans. It affects males and females equally. ET differs from Parkinson's disease, another common movement disorder, characterized by resting tremor, muscle stiffness (rigidity), and a generalized slowness of movement (bradykinesia). With ET, hand tremor is present with voluntary movement and is absent when the hands are at rest. Also, ET does not cause slowness of movement or muscle stiffness. While hand tremor is the most common form of ET, essential tremor may involve the head, voice, arms, and less frequently, the legs.

ET is a slowly progressive, chronic condition. The symptoms of essential tremor may begin at any age; however, onset is rare in childhood, and the incidence of ET increases with advancing age. The average age of onset is about 45 years. Symptoms of essential tremor often involve both kinetic and postural tremors. Kinetic tremor occurs when a person attempts any voluntary, coordinated movement. These tremors may interfere with fine motor skills such as writing, eating, or drinking from a cup. Postural tremor arises while voluntarily holding a body part in a fixed position against gravity. Within and among families, the tremors can range from being mild and a minor annoyance in one individual to severe and disabling in another family member.

Although ET is not life threatening, it can have a tremendous impact on the quality of daily life. Medical as well as surgical treatments are available for ET; even so, the cause of ET remains unknown. Further research to identify the genes that cause ET is the most promising way to more fully understand the disorder and develop new, more effective treatments.

Essential tremor is common yet relatively unknown. Outside of individuals and families with essential tremor, the public at large is not familiar with this movement disorder or misjudges the symptom of tremor as being Parkinson's disease. You probably know a neighbor, a coworker, a service club member, or a faith member who has essential tremor. If not, you may know some of the following famous people with essential tremor: Samuel Adams, legislator of Massachusetts and signer of the Declaration of Independence; Magnus Berg, famous Norwegian painter and ivory-cutter; Robert C. Byrd, US Senator; Oliver Cromwell, Member of Parliament and Lieutenant General in the British Army; Katharine Hepburn, actress; Sandra Day O'Connor, Supreme Court Justice; and Eugene O'Neill, American playwright.



The Genetics of ET

ET may occur sporadically or be inherited. In the familial cases, each child of a parent who has ET has a 50% risk of inheriting the gene that causes ET and eventually developing the disease. Past research studies have reported that the percentage of individuals who reported having other members of their family with ET has ranged from 17-70%.

As you may recall from biology class each cell in the body contains 23 pairs of chromosomes. They are numbered from 1-22 and the 23rd pair, the so-called sex chromosomes, are designated as X or Y. In any genetic disorder in which there are several genes known to cause it, the genes are numbered in the order in which they are identified. Previous research has shown that one gene that causes ET is located on chromosome 3 (called Essential Tremor 1 or ETM1) and a second one is located on chromosome 2 (called ETM2). The ETM2 gene was recently identified as "HS1binding protein 3" (HS1-BP3) by the scientists who originally localized the gene to chromosome 2. Two unrelated ET families were observed to carry the same mutation in this gene. While this is a very important finding, we also know there are more than two genes that cause ET because there are numerous families who have been tested who do not have either the ETM1 or ETM2 gene.

An Introduction to Human Genetics

What is a gene?

Genes are very small structures inside almost every cell of the body. Genes are the instructions, or blueprints, that tell our body how to grow and develop and build necessary proteins. Genes determine an individual's characteristics, such as eye color and blood type. It is estimated that there are about 30,000 genes, each of which is an instruction that the cells of the body need to grow and survive. Genes come in pairs and are made of strands of genetic material called deoxyribonucleic acid, or DNA. They line up similar to beads on a string to form larger structures called chromosomes. Genetic disorders are caused when the instruction coded by a particular gene is changed and the gene can no longer perform its proper function.

What is a chromosome?

Just as genes come in pairs, chromosomes also come in pairs. Each cell in our body has 23 pairs of chromosomes (for a total of 46); one member of each pair is inherited from the mother and the other from the father. The first 22 pairs (numbered 1 through 22) are called autosomes and they determine most of our features. The last pair is called the sex chromosomes and they determine if we are male or female. Females have two X chromosomes and males have one X chromosome and one Y chromosome.

How do scientists search for genes?

Scientists use maps of the chromosomes (similar to a road map) to look for genes. However, these maps are still somewhat incomplete. Thus, looking for a gene is a difficult task and often takes years to accomplish. Searching for genes that cause a specific disorder is somewhat like trying to find a specific street on a city map that lists the city's major landmarks, but not the streets.

What do scientists use as genetic "landmarks"?

Just as gas stations or restaurants can be used as landmarks when locating a friend's house, scientists use markers to find a gene. The instructions encoded in genes are written in a special genetic alphabet consisting of four letters---A, T, C, and G (called nucleotide bases). These bases are the critical chemicals from which DNA is made. Markers are areas of DNA along the chromosomes that have differences in the string of genetic letters so that the "message" on each member of a chromosome pair is slightly different. These differences (called polymorphisms) do not usually affect a person's health; they act as "flags" that can be tested in individuals. Scientists can track which marker came from a person's mother and which came from a person's father.

Scientists have maps of the markers on each chromosome, just like people have maps that tell them where streets are. These maps have been developed by scientists all over the world. One of the major goals of the Human Genome Project, which is funded, in part, by the U.S. Department of Energy and the National Institutes of Health, is to develop a detailed map of markers evenly spread throughout the entire human genome, or the whole human DNA (like a landmark found on every other street block). Each year this map gets better, providing researchers with more markers to test when looking for genes that cause disorders. In fact, there are so many markers on the genetic map that the scientists' ability to find genes responsible for disorders has progressed rapidly.

CHG Publications and Presentations on ET

The following posters were presented at the 8th International Congress of Parkinson's Disease and Movement Disorders in Rome, Italy, in June 2004:

A genomic screen for a novel essential tremor locus

A.E. Ashley-Koch, L. Zhang, J.M. Stajich, S. West, M.A. Pericak-Vance, J.R. Gilbert

One of the largest of our research families was analyzed to try to identify the gene causing ET in their family. The family had previously been screened and ruled out for association with the identified gene on chromosomes 2 and 3. We identified regions on two other chromosomes, 5 and 15, which looked promising for containing a third ET gene.

Prevalence of tandem gait and intention tremor in familial essential tremor

J.M. Stajich, S. Knauer, B. Scott, J.M. Vance, A.E. Ashley-Koch, J.R. Gilbert

It has been reported in the medical literature that as many as 50% of individuals who have ET also have abnormalities when trying to perform tandem gait (heel-to-toe walking). We analyzed physical examination data from 24 of our research families and found a lower prevalence of tandem gait abnormalities (TGA). Additionally, in those individuals who had TGA, there was also a significant percentage of

individuals who had a tremor when performing finger-to-nose movements (IT). The inability to perform tandem gait and finger-to-nose movements strongly suggests involvement of the cerebellum or "little brain" which is located behind the main part of the brain (the cerebrum). The cerebellum controls a person's ability to perform coordinated actions. Previous reports in medical literature had shown that individuals with ET have both TGA and IT and the observations in our families supported those findings.

Prevalence and severity of tremor in familial essential tremor

J.R. Gilbert, J.M. Stajich, S. Knauer, B. Scott, J.M. Vance, A.E. Ashley-Koch

Again, by analyzing physical examination data from 24 of our research families, we found that the prevalence of different kinds of tremor (hand, head, voice, and trunk) was not different from other reports in the medical literature. We also found that there were fewer individuals with postural tremor (tremor of the hands when holding the arms extended) than those with kinetic tremor (tremor when performing finger-to-nose movements). Historically, ET has been described as causing individuals to primarily develop a postural tremor. Our findings, along with another report in the medical literature, suggest this assumption is not entirely correct. The following poster was

presented in October 2004, at the annual meeting of the American Society of Human Genetics in Toronto, Canada. It was also presented in March, 2005 at 9th International Congress of Parkinson's Disease and Movement Disorders in New Orleans, LA.

SNP Genomic Screening Provides Further Evidence for Genetic Heterogeneity in Essential Tremor

J.R. Gilbert, L. Zhang, S. Knauer, C. Haynes, C. Salzman, M. Menold, S. West, J. Stajich, B. Scott, A.E. Ashley-Koch

Using 3 large research families, our group again conducted an analysis to identify the gene(s) causing ET. A number of regions on chromosomes 1, 3, 4, 5, 9, 15, 17, and 20 looked promising. The region on chromosome 3 is different from the region that has already been reported for 1st ET gene identified, ETM1. While we have not yet identified these genes, two of our families clearly have genes on different chromosomes, supporting the idea that there is more than one ET gene remaining to be identified. When different families have different genes that contribute to their genetic disorder, this is called *genetic heterogeneity*. We are currently performing additional analyses to move closer and closer to identifying these new ET genes.

Questions and Answers

We speak to many families about participating in research studies. Here are some frequently asked questions:

Q: What is involved in study participation?

A: The first step in joining a genetic research study is to talk with one of the researchers about the family history. Family history information is obtained during a telephone interview. From this information, we can determine which family members are needed in order for the family to be used in research studies. We will request permission to review the medical records of at least one family member who has been diagnosed ET.

Q: How will you obtain a blood sample from my family?

A: In almost all cases Jeffrey Stajich, a physician assistant from our team from the Center for Human Genetics (CHG), travels to an individual's home or other suitable location to enroll family participants and obtain blood samples. Families and individuals also have the option of traveling to the CHG. Lastly, for family members who live in rural, distant locations from the CHG and where no other research participants are located, we will provide a mailer kit so that blood samples can be sent to the CHG

Q: How long will the study take?

A: Genetic research studies take many years to complete because we must gather information and blood samples on many different families in many locations, run a series of tests in the laboratory, and then analyze the results. Once a gene is found, it may require many more years to understand its function and/or to develop any treatment based on that understanding. Through our newsletters, we will keep you updated on our progress.

Q: Will my family get results from the study?

A: If we identify the gene responsible for ET in your family, we will inform all participating family members by mail. As a research lab, we are unable to provide specific results to family members. For example, if we knew that the gene for Family A was located on chromosome 2, we cannot tell Family A member John Smith who currently has no signs or symptoms of ET whether he carries the gene on chromosome 2 or not. That specific type of information would be available to John Smith if a commercial laboratory was willing to provide formal DNA testing and he wished to pursue this. This type of testing, of course, would not be free. Until such breakthroughs occur, this newsletter will provide you and your family with updates on research progress.

Q: Is there any cost to my family to participate in the study?

A: No, we do not charge families for participating in our study. Any costs associated with having blood drawn or sent to our laboratory are paid for by the research study.

Q: Will my family's medical history and any other information that is collected be kept confidential?

A: All personal and family information that is shared with our research team is kept strictly confidential. Families and the family members who participate in our research are assigned unique numbers in order to protect their identities. Records associated with the research are kept separate from the medical records at Duke University Medical Center. Only authorized researchers directly involved in the ET study can access the research records and family medical histories.