

CHAPTER 25

What Does It Mean to have a Gene?

by Walter Allan, M.D.



More than a year after we had sent the blood samples on Kara, Guerin, Tom and Maryann to Dr. Mark Keating's lab in Salt Lake City we still did not have the results. This is not a problem with Dr. Keating's lab, but rather is a problem with DNA testing in general. Because the Keating lab is in the process of discovering the mutations associated with Long QT syndrome and working out how these mutations produce their effects, they can only test the most informative samples. In order to identify the DNA link with a disease the blood samples of at least eight affected and eight unaffected family members are needed. Thus, larger family groups than the Anglims would be screened first.

This problem is not unique to Long QT syndrome. Although new gene mutations that are responsible for inherited diseases are being discovered at a tremendous rate, tests for these mutations do not easily become available in the day-to-day practice of medicine. Partly this is because these tests are still in the research phase when they are announced and the full ramifications of having a specific mutation have not been worked out. And partly it is in the nature of genetic tests in general. This brings up the question of how could knowing the results of DNA tests be of help to the Anglims?

Our hypothesis was that Kara and Maryann had one of the previously discovered mutations (or perhaps, a unique mutation) in one of the ion channel genes. Testing could have confirmed that. Testing could also have excluded Tom as the originator of the gene in Kara. And, finally, it would have been good news for the Anglims if the testing had shown that Guerin did not have the gene. Until Dr. Keating's lab found a mutation accounting for Kara's Long QT syndrome which

could be excluded in Guerin, Guerin would have to be considered at risk for sudden death. This was true even though Guerin had a normal QT interval on her ECG, because a small percentage of people with a Long QT syndrome gene will have a normal QT interval. Guerin is on a swimming scholarship at Providence College and since the provocative event that produces ventricular fibrillation in individuals with Long QT Syndrome is often high-level exercise, Maryann and Tom could not help but worry about her fifty percent risk of having the gene. So, as with other autosomal dominant conditions, we think we know what it means to NOT have the gene. That is, the person is NOT at increased risk of the family's inherited condition. But what if Guerin had the gene? And what does it mean that Maryann has the gene?

A germ line (or inherited) mutation in a cardiac ion channel gene alters cells in every person who has that mutation. However, not every person with this alteration suffers the consequences of having abnormal cardiac repolarization to the degree that Kara did. Maryann, for instance, has had only a single fainting episode that she can recall, but that occurred under emotional circumstances. Since a single fainting episode is quite frequent in people in general, and has many benign causes, that single episode for Maryann may not have been a result of the characteristic ventricular tachycardia that occurs in Long QT syndrome. However, knowing with the certainty of DNA testing that Maryann has the gene, and that this gene had the terrible consequences that it did for Kara, it makes sense to protect Maryann. A daily dose of a beta-blocker—a drug that prevents a rapid heartbeat by blocking the sympathetic nervous system input to the heart—is very effective protection. Mike Vincent told me he has never had a patient die who was adequately beta-blocked. Maryann decided to go on a beta-blocker when we recognized she had a prolonged QT interval, so the gene test would not have altered what we did for Maryann. If Guerin had the gene, I would have advocated she also take a beta-blocker. But, since she had never had an episode, Guerin may have objected to the treatment. What then? What risk would Guerin be facing?

This is where our scientific knowledge begins to show its weakness, the same weakness we hoped would be remedied by finding the genetic basis of Long QT syndrome. That is, having the gene does not mean the affected person will suffer a cardiac arrest, or even faint. This is called variability of expression and is common in autosomal domi-

nant disorders. Why that is, is not known. It may be because other altered genes are needed for the problem to be as serious as it was in Kara. Or it may have to do with something else about the person or their environment. For instance, the serum potassium can drop from a variety of causes and make the person with Long QT syndrome more susceptible to problems with cardiac ion channels. We had such a case this past summer. A child presented to our emergency room because of a faint or seizure. He was visiting Maine from Utah and had become dehydrated on a hot summer day. The serum potassium was low and the ECG showed a prolonged QT interval. Dick McFaul, the pediatric cardiologist who first evaluated Kara, saw the child and recognized this association since he had just read a paper about Long QT syndrome and low potassium. He wrote a letter to the child's physician in Utah and mentioned Dr. Vincent as a resource.

There could be other reasons that the gene expresses itself more dramatically as well. When Dick McFaul saw Kara at age eight, he pointed out that Kara had a will that exceeded her endurance when she did her treadmill test. Could that have had something to do with Kara's multiple episodes of what we thought were seizures? There has always been a theory that the nervous system plays a role in the events associated with the gene for Long QT syndrome. Why else would exercise, or being startled by an alarm clock, be associated with attacks. Could it be that if Kara had a different personality she would not have had a cardiac arrest? This same drive is what we love about her and is what is carrying her through and getting her better despite her cardiac arrest. So, should we have wished (for wishing is all we could have done about it) that Kara had a different personality? It reminds me of the comment Maryann made to me when I worried that I was reminding them of Kara's problem as we left the first pupil evaluation team meeting in fall 1995. "It is who we are," was what she said and I think she would say the same thing if I asked her that question about Kara's personality.

Convincing people that Long QT syndrome is a real threat can be difficult. It goes against our common sense notion of our own health. People with Long QT syndrome feel fine. It is not until someone in their family suffers a cardiac arrest that the terrible nature of this condition becomes evident. Some families with Long QT syndrome will have a low mortality rate per affected person per year and other families will have a high rate. But even a high risk of sudden death is on the order of

one percent per year. That sort of information would not be known for the Anglisms since they have just discovered this gene in their family and as far as they can trace the family tree, no one else has had sudden death. It may turn out that the different mutations in the more than four different genes for Long QT syndrome are associated with different risks of sudden death. That is information that we do not have at present but information that could be used to convince individuals of the gravity of the problem.

Because the diagnosis is still relatively unknown and difficult to make, it can be missed even when a sudden death occurs in successive generations. This story is all too common and our cardiologists recently referred a patient to our genetics group at the Foundation for Blood Research where I continue to work since doing my sabbatical. This patient, Mrs. Childs, had lost her brother, her daughter and then her granddaughter before Long QT syndrome was considered. Her story is instructive since it shows how insidious this condition can be and how having a test that can establish the diagnosis with certainty could be helpful.

Mrs. Childs's Story

In the winter of 1996 (about a year after Kara's arrest) our local newspaper had a story about a twelve year-old girl who died a sudden cardiac death while playing basketball on her middle school team in South Hiram, Maine. Brandy died in front of teammates, coaches and spectators. Sudden death in a young healthy person always causes a tremendous stir in a community. The report in the papers of the funeral at the school tells that story. All this publicity, however, would eventually serve this family well.

In the weeks following Brandy's death Mrs. Childs, her grandmother, kept calling the state coroner's office to find out what had caused her granddaughter to die. She was told there was no discernible cause. Brandy was cared for by her grandmother because Brandy's mother (Mrs. Childs's daughter) had dropped dead while standing in the kitchen having a cup of coffee years before. Brandy's mother had a history of drug abuse so her death had been attributed in some way to that. Mrs. Childs had never believed this since her daughter was not using drugs at the

time her death occurred. In addition, Mrs. Childs's brother had driven to work one day at age forty-four and was found dead at the wheel of his truck on the way to work. He had been in good health all his life.

A few weeks after Brandy's funeral, Mrs. Childs got a phone call from an older woman she remotely knew in a neighboring town. This woman asked Mrs. Childs if she had ever heard of Long QT syndrome and when Mrs. Childs said she had not, the woman told her the story of her family. Mrs. Childs's acquaintance had lost two sons to sudden cardiac death and only recently had doctors for her other two sons discovered that their family had Long QT syndrome. The woman advised Mrs. Childs to call Brandy's doctor and ask about it. She did and Dr. Neil Korsen (a family practitioner trained at Maine Medical Center) said he had never heard of it, but would find out more for her. He called Maribeth Hourihan. She told Dr. Korsen to have Mrs. Childs and her family get ECGs and to have Brandy's siblings come see her and Mrs. Childs's children see Joel Cutler.

As our cardiologists took the family history, it turned out Mrs. Childs had eleven siblings! She had four children herself and each of Mrs. Childs's brothers and sisters had children. Maribeth found prolonged QT intervals in two of Mrs. Childs's grandchildren who were Brandy's siblings and a suspicious QT in the other sibling. Joel found suspicious QTs in Brandy's uncles and aunts. They knew they had uncovered a very large kindred of Long QT syndrome and, perhaps, one hundred people could be at risk.

I became involved with this large family through my new position at the Foundation for Blood Research. As we took down the pedigree it was striking how many young adults had died of what was said to be a seizure. Mrs. Childs had a great aunt Tora who remembered her grandfather had died as a young man in a small fishing village in Denmark before her grandmother had immigrated to this country. As Mrs. Childs was in the process of rounding up information about her family tree, a friend called to tell her the *Reader's Digest* had an article about Long QT syndrome. This article discussed Mike Vincent's work with the large family of Danish descent in Utah named Christensen. That family had come to the United States about the same time Aunt Tora mentioned Mrs. Childs's ancestors had immigrated. After reading the *Reader's Digest* article Mrs. Childs asked Aunt Tora the name of her Danish grandfather who had died in a seizure and Tora said it was

Christensen. Mrs. Childs wondered if she could be related to the Long QT syndrome family Mike Vincent has helped. Interestingly, Mike Vincent told me there was a rumor that there was another Christensen brother, so it could be that Mrs. Childs's family is part of this very large Utah pedigree. We are currently trying to gather this large family in our area to screen them for the condition and place those who are affected on beta-blockers. When genetic testing on Mrs. Childs's blood sample is completed we will know whether or not her family is a branch of this large Danish family with Long QT syndrome.

The fact that a deadly condition like this can be in a family for generations without coming to light is what makes Long QT syndrome such a challenge. It is likely, as in Mrs. Childs's case, that public education does a better job than physician education at finding new cases and getting the correct treatment. The reason for this is that people with Long QT syndrome are largely healthy and do not see physicians. And if they do, the story of their faints might never come up. When someone dies, more common and less complex reasons are given as the cause of death unless someone knows about Long QT syndrome. But once you know about this condition, you worry that it is everywhere. Maryann cannot read a newspaper report of the sudden death of an athlete or a young person without thinking of Long QT syndrome. And every time I see someone in my office with a faint or an unexplained seizure, I see Kara sitting on my exam table telling me about seeing that blue light in March 1995. It is true for others in our community as well. Because of Kara and her story, our pediatric and adult cardiologists and neurologists are much more aware of this condition than they had been in the past.

The diagnosis is likely to remain a challenge for the near future. Gene testing is not available as a routine laboratory test at present, and new mutations are likely to be discovered which will make testing for the condition more difficult as time passes. But, these are technical problems that will eventually be worked out. More problematic is what to do when we have a technically good test and can uncover the genetic mutations in anyone tested. Who do we test? Everyone at birth? Will the mutations that cause Long QT syndrome be screened for along with multiple other mutations as part of a routine newborn infant blood test? And what other genes will also be screened?

The mutations that cause Long QT syndrome can be thought of as “susceptibility” genes. That is, they pass on to an affected person a susceptibility for the consequences of having a problem with cardiac muscle repolarization (fainting, secondary seizures or cardiac arrest). These consequences may never occur. Of course, if they do occur, and are benign, treatment could be instituted then. However, family stories of Long QT syndrome are full of examples where the first event in an affected individual is sudden death. So maybe we should decide to treat every affected individual with beta-blockers. This is not a bad solution for Long QT syndrome, since the treatment is relatively benign, although a lifetime treatment with any medicine is a problem. But what about the other “susceptibility” genes we were also going to screen? Knowing about a gene mutation where there is no treatment or the treatment is drastic is a major problem. An example is BRCA-1, the breast cancer susceptibility gene. Women who inherit a mutation in that gene face a lifetime risk of breast cancer of 85-90%. Since, statistically, breast cancer will not occur until age 30 or more, surveillance is all that is needed until that age. But then surgery to remove both breasts and ovaries may be recommended. Is this something someone wants to anticipate from birth? Hopefully, better surveillance or treatment will become available so that this drastic preventative treatment will not be necessary. But until it is, knowing about BRCA-1 is a mixed blessing.

I have learned over the past two years since Kara’s cardiac arrest that it is not easy to know what it means to have a susceptibility gene. And there is a lot to work out before we can give families information to help them decide how to face their risk when a susceptibility gene is discovered. Hopefully, in the near future we will be able to tell with certainty when Long QT syndrome is present and what degree of risk that mutation confers to an affected person. But there is still much for medical science to discover to really know what it means to have a Long QT syndrome gene.