

## **Genetic testing for inherited arrhythmia conditions**

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Genetic research in arrhythmias has made tremendous advances in recent years and we are starting to see genetic testing impact the clinical care and evaluation of patients with arrhythmias. Genes, the basic unit of heredity, are the DNA sequences that code for proteins. Alterations in some genes are quite common and lead to the diverse physical characteristics of individuals. When alterations occur in genes that make proteins that are important in regulating the heart rhythm, such alterations may predispose to the development of dangerous heart rhythms. These alterations are called mutations, and everyone has mutations and proteins that do not function properly. Genetic research aims to identify which gene or genes are altered, and how this may cause a condition. For example, research on Long QT syndrome in the 1990s led to the discovery of several genes that are crucial to normal heart rhythms. This research took many years and involved hundreds of families affected with Long QT syndrome.

The discovery of the Long QT genes in turn led to more research and discoveries of other genes involved with arrhythmias. There are genetic mutations known to cause catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy (ARVC) and some other types of cardiomyopathies. However, genetic testing does not detect a mutation in every person with these conditions. This could be for two reasons. First, it is likely that there are other genes, yet to be discovered, that cause these conditions. Secondly, there are likely some types of genetic alterations that are not detected with the current methods used in genetic testing. Thus, researchers continue to study individuals and families with inherited arrhythmia conditions, but in the meantime, some genetic testing is now available clinically.

### **When is genetic testing helpful?**

Genetic research has led to clinical laboratories offering genetic tests and there are several situations where this is helpful for patients, for their family members and for the physicians. Genetic testing can be used in conjunction with standard cardiac testing such as ECGs and treadmill tests to determine if someone has an arrhythmia condition. There are two situations where genetic testing might be a useful addition. The first is if there is uncertainty about the exact diagnosis. For example, a patient could have a history of fainting spells, but does not quite meet the diagnostic criteria for Long QT syndrome (LQTS) based on the family history and cardiac tests. Genetic testing of 5 genes that are known to cause LQTS can be performed. If a gene alteration known to cause LQTS is found, that would make the diagnosis of LQTS syndrome in this patient much more likely. However, if no gene alterations are found, the genetic tests do not 'rule out' LQTS, since the tests do not find a mutation in 100% of people definitely affected with LQTS. In fact only 70% of people who are definitely affected by LQTS are found to have a gene alteration, using the current testing methods.

In cases of autopsy-negative sudden cardiac death, there is often uncertainty about the diagnosis. Genetic testing can be performed if DNA samples are saved from an autopsy, even if the samples are many years old. Determining the exact diagnosis in a case of sudden cardiac death can be helpful in providing an answer for why the death occurred, providing closure to the family and community. In addition, the diagnosis can help determine the risk of arrhythmias in the surviving family members. Recently, we have worked with several families where a sudden death occurred many years ago, before genetic testing was possible. Now, by testing the autopsy tissue, we can look for gene alterations associated with arrhythmias, and then test other family members to see if they inherited the same gene alteration.

Genetic testing may also be useful when there is a definite clinical diagnosis in one person, and there are family members at risk of inheriting the condition. Currently, the standard of care would be to have all the family members go for cardiac testing on a regular basis. The exact list of cardiac tests would vary depending on the condition, but usually there are several tests needed every couple of years. The repeated testing is time consuming for family members and can be costly over a period of many years. For most of the arrhythmia conditions, close family members have a 1 in 2 or 50% risk of carrying the same genetic alteration. Conversely, this means that half of the family members are not carrying the gene, not at increased risk for arrhythmias, and do not need regular cardiac testing. The genetic testing strategy in this case would be to test the individual who definitely has the arrhythmia condition in order to determine the causative gene. If the gene alteration is found, the genetic test could be offered to family members. The family members who are found to have the gene alteration are at higher risk of developing the arrhythmia condition and would need cardiac follow up. However, the family members who do not have the gene alteration are at lower risk, and could be followed less often.

Researchers and physicians continue to collect the data to try to correlate clinical findings to specific genetic findings. Currently the genetic tests do not help predict what age someone will develop arrhythmias or if beta blockers will adequately prevent arrhythmias. In fact, through genetic testing and research, we now know that it is not uncommon for a family member to carry a gene alteration that causes LQTS but have no symptoms at all.

Thus, genetic testing will not provide all the answers for families with known or suspected inherited arrhythmia conditions. Genetic counselling is an integral part of all genetic testing and a time when individuals can decide if the genetic testing is going to be helpful, or if the information might be burdensome or difficult to cope with. Some people would prefer to have regular cardiac testing, rather than a genetic test that could show they are in fact at increased risk for an arrhythmia.

The tests performed in the clinical laboratories are expensive because they take a great deal of time and expertise. Provincial health plans usually cover the cost of the tests and the genetic counseling. Genetic testing is usually requested by a cardiologist or geneticist and they take into account the medical and family history, in order to decide which laboratory to use and which genes to test, in order to maximize the chances of getting useful results. As well, some research facilities will perform

genetic testing under research protocols, which is particularly useful when the clinical testing is unable to detect a gene alteration.

The hope is that in the future, we will be able to not only say that a patient has a genetic arrhythmia caused by a certain gene, but also to use that information to guide the treatment with medications or give personalized advice on how to avoid an arrhythmia. Those of us in medical research look forward to the day when we can offer a personalized prescription rather than a "one size fits all" approach to treating inherited arrhythmias.

**Want more information on genetic testing for arrhythmia conditions?**

If you would like to find out if genetic testing might be useful for you or your family members, talk to your family doctor or your arrhythmia specialist. There are a growing number of academic medical centers where cardiology and genetics teams have established collaborations to help evaluate individuals and families. In addition, every province has a network of genetic services. Usually the first step is for a genetics counselor or a genetics nurse to review your family and medical history and determine what testing would be best for your situation. Finally, there is a list of genetics centres available on the website of the Canadian Association of Genetic Counsellors at [www.cagc-accg.ca](http://www.cagc-accg.ca).

Updated December 2006