

# *Family Participation in Genetic Research*

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A little more than ten years ago, studies on the genetic basis of the inherited long QT-Interval syndrome began to appear in the medical literature. The early studies became the foundation for a more general explosion of research into the genetic basis for life-threatening heart rhythm disturbances. The earliest investigations into the genetics of long QT-Interval syndrome were designed to seek single gene variations that were reasoned to control the length of the QT-interval. These studies, indeed, identified a number of mutations that affected electrical properties of the heart and were associated with QT-interval lengthening.

## **The Complexity of Long QT Genetics**

At the time of the first studies, it rapidly became apparent that the story was much more complex than a single mutation causing a predictable disorder in an individual patient. Scientists working on this problem came to recognize that the presence of a specific mutation among members of a single family did not predict life-threatening events in all of those individuals. In fact, not only did the presence or absence of heart rhythm problems vary among the genetically affected people in a given family, but even lengthening of the QT-interval was not consistent among everyone carrying the mutation. There are several possible explanations for lack of uniform expression of a genetic defect, one of which is the concept of “modifier genes.” These are variations in other genes that are thought to interact with the primary genetic defect, determining whether an individual carrying the primary genetic abnormality will actually have the disorder. Identification of modifier gene locations and roles is far more complex than identification of a primary “candidate” gene, which would be predicted to have an effect on the QT-interval. Another complexity is the recognition that patients with genetic defects that cause only minor changes in the electrical activity of the heart might be susceptible to a dangerous electrical problem during a naturally occurring disease process, or exposure to certain drugs. This notion forms the basis for cautions about the use of drugs that can be harmful to individuals carrying the mutation, and of the development of the field of genetic epidemiology of arrhythmias. The latter seeks strategies for measuring cardiac arrest risk based upon genetic profiles. The concept of genetic epidemiology has more important population implications than does study of a few rare arrhythmia disorders, looked at in isolation.

## **Importance of the Extended Family**

For both of the forgoing reasons, the role of family members in discerning complex patterns of genetics serves as a key for the future success of these endeavors. When two or more variations in the genetic profile are present in a single family, studies of only the first-degree relatives may be insufficient for identifying the complex genetic interactions between multiple genes that influence the electrical activity of the heart.

Before the development of technologically sophisticated systems to study the structure of multiple genes simultaneously, the technique called “linkage analysis” was used to identify genetic associations suggesting the location of a gene responsible for a particular disorder. With the evolution of new technology, finding genetic variations in individuals and a manageably small number of family members, has become feasible. However, a new role for extended family members now has come on the scene because of the recognition of the concept of interactions among the products of multiple genes in the expression of a specific disorder. Thus, for research to continue to go forward and to gain further applicability to affected family members, the research must include studies of large kindreds in order to work out multi-genic complexities.

### **Incentives for Broader Profiling of the Family Constellation**

Unfortunately, cooperation of non-affected or remote family members in genetic studies is often disappointing. Concerns about loss of insurability and anxiety over the knowledge of a defect in a healthy individual are two of the commonly stated reasons for reticence. This results in a barrier to the scope of potentially fruitful research that may contribute to understanding not only the dynamics of individual families being studied, but to the population more generally. A number of research centers have noted that cooperation of members in the primary family unit is usually reasonably good, but the valuable addition of remote family members is much more difficult to achieve. Physicians and genetic counselors can help by educating the primary and remote family members, but it is likely that greater cooperation can be achieved by active recruiting of other family members by affected members of the family. The scope of new information will serve to enhance our ability to predict outcomes in single individuals among a family constellation, as we gain more knowledge about the complexities of genetics and genetic prediction. To the extent that we are able to do this, physicians and genetic counselors will be able to provide more reliable guidance and appropriate therapy to their patients, and de-label others in regard to potential risk. Viewed globally, this is a mission in which medical scientists, practicing physicians, paramedical personnel, and the public can all work together toward a common good.