



## **Clinical Trials / Genetics**

### **Searching for Modifiers of CF – The US CF Twin and Sibling Study**

When the gene causing CF was identified in 1989, families sounded a sigh of relief. At last, the basis for developing a cure for CF! Yet, despite Herculean efforts over a number of years, a cure for the basic defect in the CFTR gene is still elusive. By late 2000, Garry Cutting, MD, a pediatrician and geneticist at Johns Hopkins Medicine in Baltimore, and others in the field, had worked through some of the biology of CFTR: how it functions, and the consequences of certain CFTR mutations. Yet, they puzzled about some of the CF families they had come to know so well. Why were there such stark differences in CF siblings' lung disease, and overall status, when they have the same parents, have the same genotype, live in the same home, and generally go to the same schools? As he began to ponder the problem and review the publications of other colleagues, he suspected that there must be other genes and environmental influences at work in CF disease. Dr. Cutting gathered a research team together to discuss the feasibility of hunting for those genes – other than CFTR - that alter the course of Cystic Fibrosis.

In 2001, approximately 100 twins with CF were living across the US. With the support of the CF Foundation, the original project goal was to recruit every twin pair with CF, gather information about their diagnosis, clinical course, growth, environment and pulmonary disease along with blood samples, to determine the “phenotype” (clinical picture) and the genotype (genetic code) of our patients. Collecting a significant amount of clinical information, in the framework of a family based study, could ensure that the identification of “phenotype” was done accurately, and when placed against the background of a person's genetic makeup might point to a gene or genes that caused or contributed to the “picture”. Information about the environment could inform the researchers about certain things like second hand smoke or access to care as influences in overall severity. In those earlier years, work on the Human Genome was incomplete. Many genes that contribute to disease hadn't been identified or weren't understood. Genes that were thought to contribute to CF lung disease (candidate genes) were proposed and studied based on how researchers knew or believed they worked. One gene for example, Mannose Binding Lectin, is involved in innate immunity thought to influence resistance or susceptibility to lung infections and survival. Another gene, TGF $\beta$  1, influences the development of fibrotic tissue. Could these genes – and others that might influence body mass or the development of diabetes, or liver disease- be critical influences on survival in CF? These were the questions that the CF Twin Study Team set out to answer.

In the interim, the research team began to recruit siblings with CF. There were far more siblings than twins in the US, which could mean a greater ability to find gene differences that occurred rarely or had smaller effects on illness. The same type of clinical and environmental data would be collected, along with the siblings' blood sample, but a new twist was added. The team would ask for the parents of CF siblings to participate with their children in the study by giving a blood sample as well. The transmission of parental genes to their children would be extremely informative as to what gene differences were “preferentially” passed on and why they affected their child's fight with CF.



As this project has progressed, so has our understanding of genetic influences on human disease. In parallel, the technology used to “hunt” for genes has exploded in capacity. What took researchers years to accomplish in the 1980s can be done in a few weeks in 2010. The detective work has been made easier with better tools, but more difficult with the rapidly expanding identification of disease causing gene variants and the beginning knowledge of environmental influences on genes and how they affect each other and disease. In order to maximize the hard work and investment in gene modifier research, the CF Twin and Sibling Study is collaborating with other CF Genetic Modifier Studies using a genome wide association approach to finding the genes that influence the course of CF. As always, the goal of this research is to find targets for treatment that will improve the quality and longevity of life in people with this disease.

Thanks to the efforts of CF Centers and Families across the US, Australia, and Great Britain, we now have 2800 parents, twins and siblings participating in this project. The CF Twin and Sibling Study is grateful for the sponsorship of the National Institutes of Health and the Cystic Fibrosis Foundation. This study began in 2001, and will continue through at least 2012. If you are interested in learning more about this unique project, please visit our website at [cftwinsibstudy.net](http://cftwinsibstudy.net) or email the study team at [knaught1@jhmi.edu](mailto:knaught1@jhmi.edu).