

NAAR and NLM Family Foundation Support International Autism Genetics Collaboration

By Eric London, M.D., Vice President-Medical Affairs

In March 2001, NAAR and the NLM Family Foundation co-sponsored, for the second consecutive year, an autism genetics retreat for an international consortium of prominent autism genetics researchers. Referred to as the "Callaway Gardens Collaboration" for the remote retreat site in Georgia where the meetings have been held, the participating genetics research teams are breaking new ground for collaborative efforts. This "collaboration of collaborations" is comprised of six groups of autism genetics research teams:

- (i) Duke University and their collaborators at the University of South Carolina,
- (ii) the Collaborative Linkage Study of Autism which includes Tufts/New England Medical Center, Vanderbilt University, the University of Iowa, and the University of North Carolina,
- (iii) the Mount Sinai School of Medicine,
- (iv) a Canadian collaboration among McMaster University, The Hospital for Sick Children in Toronto, and McGill University,
- (v) a Paris-based collaboration which also includes collaborators from Scandinavia and Israel, and
- (vi) Stanford University.

Together, these research teams have the genetics data of between 800 and 1000 "multiplex" families--i.e. families with more than one affected family member. While each of these recognized autism genetics groups receive funding for their own research from the NIH or other governmental agencies, they had no government funding to explore the possibility of establishing a "collaboration among collaborations". NAAR and NLM Family Foundation, NAAR's largest donor, determined to support this critically important endeavor.

Why is Genetics Research Vital to Autism Research?

Autism is frequently cited in the medical literature as the most highly heritable of all complex genetic disorders involving the brain. As a result, there is now

considerable interest and enthusiasm in the genetics community to study autism spectrum disorders. Over the past few years, an increasing number of genetics research teams have been attracted to autism research and we are fortunate to now have some of the world's leading geneticists studying this problem.

Why does this scientific enthusiasm exist? Research studies to date have demonstrated an intriguing fact: in identical twins the concordance rate for autism spectrum disorders is about 90% while in fraternal twins it is about 10%. "Concordance rate" refers to the probability that if one of the twins has the disorder then the other twin will have it too. While born at the same time and subject to the same fetal environment in the mother's womb, the major difference between identical and fraternal twins is their genes. Identical twins have exactly the same genes while fraternal twins have no more likelihood of having genes in common than any set of siblings would. The significant concordance for autism in identical twins, as opposed to fraternal twins, provides strong support for a genetic component as a cause of autism spectrum disorders.

As a result, many genetics research teams around the world are investigating autism and, for the same reason, the National Institutes of Health and non-U.S. government agencies have invested heavily in genetics research. In light of this, the question of how much progress has been made is surely relevant. There have now been several full genome screens and, thus far, no obvious genes have emerged as a major contributor to the cause of autism. Although some areas of interest have proven to be significant or almost significant, the genome scans are not consistent in their results with respect to which areas are most promising, although there are some regions that overlap with each other across studies. The reason why is that autism, like most of the psychiatrically classified brain disorders, is a complex genetic disease with several genes working together to cause the disorder.

About two years ago, as the first of the full genome scans were being reported in the scientific literature, it became apparent that the identification of one or more "autism genes" would not be as simple as

Continued on page 13

Continued from page 12

investigators (and parents) hoped. Each of these genome scans involved about 100 sibling pairs with autism. This led the geneticists to the realization that collaboration would be advantageous if not essential to this effort.

Informal meetings were held among various researchers. From these early efforts, Dr. Susan Folstein of Tufts University assumed the rather onerous task of formalizing the developing network. Several groups began to talk regularly on conference calls but it soon became clear that a significant time period was needed for face-to-face discussions. There being no available governmental funding for such an effort, NAAR and the NLM Foundation agreed to underwrite the meetings.

The aim of the retreats was to explore the possibility of a large collaboration among the individual collaborations and to begin to work out the very complex, technical issues involved

with respect to combining genetics data. To participate in the retreat, the only requirement was that all attendees be willing to present their unpublished data and agree to maintain the confidentiality of the shared information. By the end of the first meeting it was decided that the collaboration would be formalized and a grant to the NIH would be submitted to support the collaborative efforts.

The Potential of the Callaway Collaboration

The participating research groups in the Callaway Collaboration are among the most experienced in the world in exploring the genetics of autism. One important strength of these researchers is that their 800 sib-pairs and other non-sibpair multiplex families (i.e. cousin pairs; parent-child) have been diagnosed using the highest research standards and have been fully "worked up" by experienced clinical teams. Their combined data would enable the largest sib-pair analysis ever accomplished.

However, it is not just that a genome screen could be accomplished with nearly a thousand multiplex families. There is also a strong belief that for the autism genes to be identified, there will need to be adequate analysis of autism "subtypes." Subtypes are when research subjects have not only a diagnosis of autism but at least one feature which may make them different from the remaining population of individuals with autism as a whole. Examples of this could include the extent of language impairment, dysmorphic facial features, or a host of other criteria. The Callaway Collaboration is trying to analyze their combined genetics data by categorizing their patients by clinical findings and agreed upon subtypes.



Callaway Gardens Collaboration - March 2001

The sharing of preliminary, unpublished data is another advantage gained by this large collaboration. When new findings emerge, other research groups within the collaboration can attempt to replicate and validate them and this can be done very rapidly

with such a large voluntary collaboration.

From the Perspective of the Parent Advocate

As a parent of a child with autism and a committed research advocate, I can testify that the Callaway Collaboration represents the best in the autism research world. Scientists, as a rule, choose a research profession because they love the science. It is not an easy life. The financial remuneration is not great. In fact, scientists can often make far much more money in private industry (and many do choose that route). For those who are dedicated to an academic research career, there is a constant need to secure funding by submitting competitively reviewed grants to granting agencies such as the NIH and NAAR. Even scientists of great merit and noted success spend months writing grants that do not secure funding. A scientist's likelihood of receiving funding and, generally, his or her professional reputation and standing is largely based on his or her research publications. In other

Continued on page 14