CReATing a Deeper Understanding of ALS

A major goal of the CReATe (Clinical Research in ALS and Related Disorders for Therapeutic Development) Consortium is to give a deep clinical context to the burgeoning genetic understanding of ALS and related disorders.

"In recent years, there has been an explosion of genetic information in ALS, fueled by advances in sequencing technology," notes CReATe principal investigator, Michael Benatar, MD, PhD, of the University of Miami Miller School of Medicine in Florida.

But the intense scrutiny of genes, exomes and genomes in ALS has not been accompanied by any detailed understanding of the clinical phenotype of the subjects being studied. In many analyses, the clinical data has been limited to whether or not the subject has ALS. "That is an incredibly superficial view of the disease," Dr. Benatar says, since it ignores major differences between individuals with ALS. "ALS is a complex disease, constituted by multiple overlapping endophenotypes, or phenotypes within the broader clinical syndrome we call ALS."

There are differences in the age of onset, the rate of disease progression, the presence or absence of frontotemporal dysfunction, predominance of bulbar versus limb involvement, and upper versus lower motor neuron pathology. And it is possible, and perhaps likely, that there are significant genetic underpinnings to each of these clinical elements, Dr. Benatar says, "and so a large part of what the CReATe consortium is predicated upon is that need to pair up the deep genotypic data with deep phenotypic data."

Understanding the nuanced relationship between genotype and phenotype will enlighten disease biology, and could give clinicians the ability to offer patients and families more insight into disease prognosis. For those with familial forms of the disease, they may also help predict disease onset in asymptomatic gene carriers. "We have almost no ability to predict when a person at genetic risk for ALS will develop disease," he points out. "That's a huge impediment in the field." Finally, and perhaps most excitingly, this information could lead to future treatments. "Imagine we find a genetic polymorphism that causes dramatically delayed disease onset, or slower progression" says Richard Bedlack M.D., Ph.D., of Duke University, CReATe's director of patient advocacy and outreach. "If we can then understand what that polymorphism does, we might be able to develop drugs that drive the system in that direction, thereby modifying disease in a clinically meaningful way."

A major initiative of the CReATe consortium is to prospectively and systematically study a cohort of 700 ALS patients longitudinally, to collect the kind of deep phenotypic information needed to inform genetic studies on these same individuals. The cohort will include approximately 200 individuals with familial ALS, and 500 individuals with sporadic ALS, who are enrolled at half a dozen large clinical centers in the United States and Europe. Biological fluids will also be collected, to permit both discovery of new biomarkers and to validate lead biomarker candidates that have already been identified.

Collecting information on sporadic disease is just as important as familial disease, Dr. Benatar says. Multiple and varied genetic causes of sporadic ALS are increasingly being discovered, and the clinical data are likely to prove invaluable in understanding the genotype-phenotype correlations among such cases. “You can’t begin to do that without good clinical information,” Dr. Benatar says, and it must be collected prospectively, not after a new genetic finding emerges. “Our goal is to explain the full picture of ALS, and we won’t know what we will find in these studies until we look.”

“Every week in clinic I see all this phenotypic variability and think Mother Nature is trying to give us clues to better understand these diseases” says Dr. Bedlack. “Our CReATe Consortium will bring patients, clinicians and geneticists together in an unprecedented effort to decipher these clues.”