



Understanding Genes Is the Key to Developing Treatments

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Host: ALS Association Chief Scientist Lucie Bruijn, Ph.D.

Guest Speaker: Chris Shaw, Ph.D., 2012 Sheila Essey Award Winner

Within the past several years, understanding of the genetic basis of ALS has progressed rapidly with new genes leading to new animal models and new theories of disease. “Only when we understand the genetics will we be able to develop the tools to attack this disease,” said Christopher Shaw, Ph.D., of Kings College in London. Dr. Shaw is the 2012 recipient of the Sheila Essey Award for his outstanding contributions to research in ALS. He outlined the important implications of the newest gene discoveries in a recent ALS Association webinar.

“Dr. Shaw has made many important contributions to the field of ALS research, especially in genetics,” said ALS Association Chief Scientist Lucie Bruijn, Ph.D., who hosted the webinar. Among other accomplishments, he was the first to discover that mutations in the TDP-43 gene can cause ALS, which has begun to reshape ideas about how gene mutations cause the death of motor neurons. Those ideas have been honed even further by the discovery of the C9ORF72 gene.

While TDP-43 mutations themselves can cause ALS, they are very rare. Despite that rarity, what has led researchers to focus so intently on TDP-43 is that TDP-43 protein accumulates in the cell body of motor neurons in 95% of all people with ALS. The protein normally resides in the nucleus, but in ALS, it becomes mis-localized to the cytoplasm, the material surrounding the nucleus, where it forms aggregates. TDP-43 aggregates are also found in about 60% of people with another neurodegenerative disease called frontotemporal dementia (FTD). “This shows that these two diseases can be linked and gives us a common target,” Dr. Shaw said.

The mutant TDP-43 gene has been very useful in developing disease models, and the gene has now been introduced into flies, fish, mice, and cell cultures to look for its effects on motor neurons and to aid in drug discovery.

Potentially even more significant is the discovery of the C9ORF72 gene, which studies throughout the world have now shown accounts for between 20% and 40% of all familial ALS as well as up to 6% of cases of sporadic disease, those not thought to be due to any known cause. “This gene is a huge step forward,” Dr. Shaw said, “and is perhaps one of the most significant shifts in the ALS field.” Its normal function is still unknown, a fact reflected in its name, which simply describes its position on chromosome 9. “As soon as we know what it does, we’ll give it a better name,” he said.

The C9ORF72 gene also provides a strong link between ALS and FTD since the same gene mutation can cause both diseases. The normal gene contains a small number of GGGGCC repeat units, while the mutated gene may contain hundreds to thousands of them. The nature

of the mutation makes it a challenge to work with the gene because the molecular tools researchers use have trouble coping with the vast amount of extra genetic material.

The same problem may underlie the disease-causing activity of the mutation in motor neurons. The mutation in the DNA, when copied into RNA, leads to accumulation of large amounts of RNA within the nucleus. It is possible that the RNA aggregates bind and inactivate many proteins that normally regulate functions within the nucleus.

Among those carrying the C9ORF72 mutations, males and females are affected equally. Compared to people with ALS not due to this gene, those with the mutation are more likely to have onset in the bulbar (speech and swallowing) muscles and to have problems with behavior, language and cognition (thinking). Some people with the mutation will have only ALS, while others will have only FTD, and others will have symptoms of both disorders. Age at onset and survival do not seem to be different compared to those who do not carry the mutation.

Dr. Shaw noted that some people with the mutation may develop symptoms quite late in life, and some may never develop symptoms, a phenomenon known as “incomplete penetrance.” “Not everybody who carries the gene variant is going to get the disease, and it may come on quite late. That’s an important fact to mention when counseling families,” he said.

With the growing understanding of the C9ORF72 gene, it is not too soon to contemplate treatments based on preventing the accumulation of RNA it causes. Dr. Shaw noted that a recent paper by Don Cleveland and colleagues showed that in another neurodegenerative disease, Huntington’s disease, “antisense” nucleotides could be delivered to mice to cause brain cells to destroy the RNA made from the gene. That may be one strategy to attack the C9ORF72 mutation.

“My belief is that ALS is not incurable,” Dr. Shaw concluded. “With greater effort, smarter experiments, and more funding, we will discover what causes ALS. Only then can we develop treatments that can really cure this disease. We are making extraordinary progress.”

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