By Richard Robinson

The recent discovery of the C9orf72 gene has provided a genetic explanation for up to 40 percent of familial ALS cases and up to 6 percent of sporadic cases. Mutations in the C9orf72 gene also account for a large fraction of cases of a second neurodegenerative disease, frontotemporal dementia (FTD). In a recent webinar, Clotilde Lagier-Tourenne, M.D., Ph.D., of Massachusetts General Hospital and Harvard Medical School in Boston, discussed the evidence regarding the gene mutation, how it causes disease and the important progress that is being made in development of new treatments against it.

Both ALS and FTD are neurodegenerative diseases. ALS causes progressive paralysis due to loss of motor neurons in the brain and spinal cord, while FTD causes language and behavioral dysfunction due to loss of neurons in the frontal and temporal lobes of the brain. But in families with mutations in the C9orf72 gene, some individuals may develop ALS, while others develop FTD, and individuals carrying the mutation may develop symptoms of both disorders. They are not separate diseases, Dr. Lagier-Tourenne said. Instead, they exist on a spectrum.

At the cellular level, both are characterized by the appearance of protein aggregates within dying neurons. These aggregates contain the protein TDP-43, which is normally found mainly in the cell nucleus, but in ALS and FTD caused by C9orf72 mutation, the protein aggregates outside the nucleus in the cell’s cytoplasm. The consequence of this is not entirely clear, but it is likely to contribute to the disease process. TDP-43 aggregates are also found in most other types of ALS, strengthening the case that they contribute to disease.

The discovery of the gene mutation was followed quickly by the discovery of three different pathological consequences of the mutation in neurons. The gene encodes a protein of unknown function, and the mutation prevents the production of the normal amount of this protein. Second, the mutation causes the accumulation of large amounts of the cellular messenger molecule RNA, which clumps together to form “foci” that can be seen under a microscope. Third, the extra RNA leads to the production of unusual proteins each composed of only two types of amino acids (most proteins are made of up to 20 types), called “dipeptide repeat” proteins or DPRs. Much of the current research is exploring the contribution to disease of each of these three pathological hallmarks.

Recent work in multiple disease models has demonstrated that while reduction in the normal levels of the C9orf72 protein are harmful, they do not cause neurodegeneration. In contrast, introducing the human mutation into mice (which retain functional copies of their own version
of the gene) does lead to neurodegeneration, indicating it is a toxic gain of function, not loss of function, that contributes the most to the disease.

Those findings argue for a therapy that can reduce the amount of toxic RNA, or disable the DPR proteins or both. The first strategy is the goal of antisense therapy, while the second is the goal of immunotherapy.

Immunotherapy uses an antibody, a type of immune protein, to bind to and disable DPR proteins. Antibodies have become powerful therapeutic tools in many fields of medicine, including cancer and rheumatology. Dr. Lagier-Tourenne is working to develop such a tool for C9orf72 ALS and FTD, in collaboration with the biotechnology company Neurimmune. Once the antibody binds to the DPR, it is degraded and removed from the cell.

Antisense therapy administers a short piece of an RNA-like molecule that binds to and disables the long RNA made from the C9orf72 gene. Antisense treatment is being developed for both C9orf72 and SOD1, the second most common genetic cause of ALS. Work in C9orf72 mice shows that antisense treatment reduces both the RNA foci and the DPR proteins. Treatment improves cognitive ability of mice, indicating the potential of the treatment to have a beneficial clinical effect. Dr. Lagier-Tourenne is collaborating with Ionis Pharmaceuticals (formerly Isis) to develop antisense therapy for C9orf72 ALS and FTD.

“We are making important strides in therapy development against the C9orf72 mutation,” commented ALS Association Chief Scientist Lucie Bruijn, Ph.D., M.B.A. “Dr. Lagier-Tourenne’s work, especially in developing the mouse model of this challenging mutation, has been instrumental in moving the field forward.”