

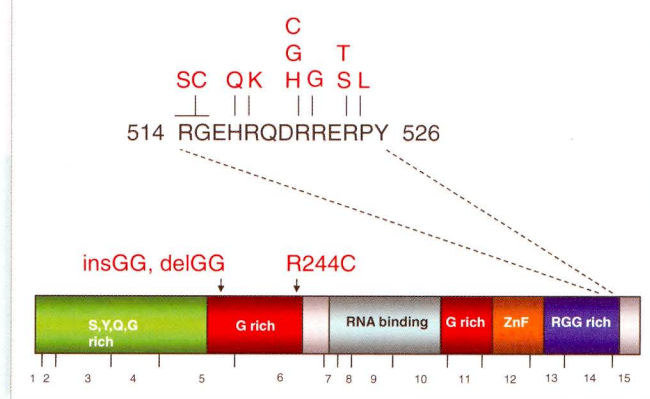
## New ALS Gene Discovery

Northwestern investigators in a collaborative study identified a new gene whose mutations cause 4 percent of inherited cases of ALS (amyotrophic lateral sclerosis). The study, reported in the February 27 issue of *Science*, points to a common cellular deficiency in the fatal neurological disorder, said Teepu Siddique, MD, Les Turner ALS Foundation/Herbert C. Wenske Foundation Professor in the Davee Department of Neurology and Clinical Neurological Sciences at the medical school. The new research is part of a national collaboration directed by Dr. Siddique, principal investigator for the “Genetics of ALS” project funded by the National Institutes of Health (NIH).

In earlier research Dr. Siddique and colleagues discovered the first and second ALS genes (the SOD1 gene in 1993 and the ALSIN gene in 2001) leading to familial, or inherited, ALS. They also identified ALS-related loci on chromosomes 9, 15, 16, and X.

The new study found mutations in the FUS/TLS gene in ALS families participating in the NIH-funded, multi-center project and included, among others, a large Italian family previously studied by Drs. Siddique and Pietro Cortelli of the University of Modena in Italy.

ALS causes the death of motor neurons in the central nervous system, which compromises the brain’s ability to send signals to the body’s muscles. This leads to loss of voluntary muscle movement, paralysis, and, eventually, death from respiratory failure. The cause of most cases of ALS is unknown.



This schematic drawing shows the positions of the FUS/TLS mutations superimposed on the exon and domain organization of the gene. FUS/TLS is encoded by 15 exons that span a genomic region of 11.6 kb. The S, Y, Q, G-rich region denotes a region rich in the amino acids serine, tyrosine, glutamine, and glycine. G-rich and RGG-rich regions are enriched in either glycine or the arginine-glycine-glycine motif, respectively.

“The purpose of this national study is to understand what causes the degeneration and death of motor neurons in order to find new cellular models of ALS, with the ultimate goal of advancing research that leads to a treatment,” explained Dr. Siddique. “Approximately 10 percent of ALS cases are inherited.”

The discovery of mutations in FUS/TLS shows a convergence of molecular pathway defects that damage motor neurons. FUS, like a previously identified familial ALS gene, TDP-43, is also a member of a class of proteins that bind RNA in neurons, according to Dr. Siddique.

The lead author on the *Science* paper was Robert H. Brown Jr., MD, of the University of Massachusetts, one of three institutions that collaborate with Dr. Siddique on the national study.