# Angiogenin loss-of-function mutations in amyotrophic lateral sclerosis

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## Technology description

## Summary

MARKETS ADDRESSED:
Further efforts are under way at Harvard to determine the role of Angiogenin (ANG) in motor neuron function, to characterize the involvement of ANG deficiency in amyotrophic lateral sclerosis (ALS) pathogenesis, and to optimize the therapeutic activity of ANG in ALS. The hypothesis is that ANG plays a role in motor neuron function and that systemic treatment with ANG protein will improve the motor muscular function of ALS patients and extend their survival. Additionally, the laboratory is testing engineered mutants of the ANG protein, as well as - through a collaboration with a third party - several ANG naturally-occurring splice variants.
Mouse angiogenin (Ang) protein is strongly expressed in the central nervous system (CNS) during development. Human angiogenin (ANG) protein is strongly expressed in both endothelial cells and motor neurons of normal human fetal and adult spinal cords. ANG has also been shown to stimulate neurite outgrowth and pathfinding of cultured motor neurons and protect stress-induced motor neuron degeneration, whereas the ALS-associated mutant ANG proteins lack these activities.
Preliminary studies carried out in the laboratory of Dr. Guo-fu Hu at Harvard Medical School show that both ANG protein and mRNA are diminished in the spinal cord of human ALS patients and in that of SOD1G93A mice that develop ALS-like symptoms. Systemically injected ANG protein crosses the blood spinal cord barrier and reaches at the spinal cords of both WT and SOD1G93A mice. Intraperitoneal administration of WT ANG protein enhances the motor muscular function of SOD1G93A mice and prolongs their survival by four weeks. However, the P112L mutant ANG protein (occurred in ALS patients) does not have this activity in SOD1G93A mice. Taken together, these results suggest that ANG dysfunction is relevant to ALS pathogenesis.

## Advantages

ANG, encoding a 14 kDa angiogenic ribonuclease, is the first loss-of-function gene identified in ALS. Since original discovery of ANG as an ALS candidate gene, a total of 15 missense mutations in the

coding region of ANG have been identified in 37 of the 4,193 ALS patients. Among them, 10 have been characterized in detail and shown to be loss-of-function mutations.

## Institution

Harvard University