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The Effect of Metal Deficiency on the Structure of Human Copper-Zinc Superoxide Dismutase and Implications for FALS. Lisa J Whitson, Peter A Doucette, Sylvester Siller, Joan S Valentine, P John Hart, Dept. of Biochemistry and the X-ray Crystallography Core Laboratory, Univ. of Texas, Health Science Center at San Antonio, San Antonio, TX.

Familial amyotrophic lateral sclerosis (FALS) is a fatal neurodegenerative disorder involving the motor neurons of the brain and spinal cord. The pathogenesis of FALS remains elusive; however, approximately 20% of cases are linked to mutations within the gene encoding copper-zinc superoxide dismutase (SOD1). Based on recent experimental evidence and similarity to other neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, aggregation of mutant SOD1 is likely involved in motor neuron dysfunction. FALS-associated SOD1 structures of S134N and H46R have metal deficiency and pack in an amyloid-like filamentous arrangement, serving as models for SOD1 aggregation. To further investigate the role of metal deficiency on filament formation, we solved the structures of two pathogenic SOD1 proteins, E133Δ and H80R. Comparison of metal bound and free structures of E133Δ support the hypothesis that metal deficiency results in the filamentous packing previously characterized. Furthermore, structural studies of H80R, a zinc ligand substitution, highlight that zinc deficiency is the minimum requirement for filament formation.