How do ALS-associated mutations in superoxide dismutase 1 promote aggregation of the protein?

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More than 100 different mutations in the gene encoding copper-zinc superoxide dismutase (SOD1) cause familial forms of amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease in which aggregation of the SOD1 protein is considered to be the primary mode of pathogenesis. Recent results show that these mutations have remarkably diverse and unexpected effects on the structure, activity and native state stability of SOD1. Some of the mutations cause enormous changes in the structures, stabilities, and enzymatic activities of the enzyme. Intriguingly, by contrast, many mutations seem to have no measurable effect on its biophysical and biochemical properties, except for decreasing the net charge of the protein. Thus, it seems likely that different ALS-associated mutations promote SOD1 aggregation by fundamentally distinct mechanisms. Understanding this complexity has implications for prevention and treatment of this disease.