

# Computational studies of the metal-binding site of the wild-type and the H46R mutant of the copper, zinc superoxide dismutase

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Impairment of the Zn(II)-binding site of the copper, zinc superoxide dismutase (CuZnSOD) protein is involved in a number of hypotheses and explanations for the still unknown toxic gain of function mutant varieties of CuZnSOD that are associated with familial forms of amyotrophic lateral sclerosis (ALS). In this work, computational chemistry methods have been used for studying models of the metal-binding site of the ALS-linked H46R mutant of CuZnSOD and of the wild-type variety of the enzyme. By comparing the energy and electronic structure of these models, a plausible explanation for the effect of the H46R mutation on the zinc site is obtained. The computational study clarifies the role of the D124 and D125 residues for keeping the structural integrity of the Zn(II)-binding site, which was known to exist but its mechanism has not been explained. Earlier results suggest that the explanation for the impairment of the Zn(II)-site proposed in this work may be useful for understanding the m