An atomic-level investigation of the disease-causing A629P mutant of the Menkes protein, ATP7A

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Menkes disease is a fatal disease that can be induced by various mutations in the ATP7A gene, leading to unpaired uptake of dietary copper. The ATP7A gene encodes a copper(I)-translocating ATPase. In this work the disease-causing A629P mutation was investigated, which occurs in the last of the six copper(I)-binding soluble domains of the ATPase (hereafter MNK6). The solution structures and dynamics on various time scales of wild-type and A629P-MNK6 were determined both in the apo- and copper(I)-loaded forms. Mutation A629P is located in the middle of the last β-strand. Experimental data of hydrogen/deuterium exchanging rates shows that the last and the first β-strands of the mutant open easier than those of the wild type. The interaction in vitro with the physiological ATP7A copper(I)-donor (HAH1) was additionally studied. A small reduction of the affinity for copper(I) is also observed. Therefore, it can be proposed that the mechanism by which the A629P mutation causes Menkes disease in humans can be linked to two factors. The first one is a slightly decreased metal-binding ability of the soluble sixth domain, within which the mutation is located, possibly leading to decreased efficiency in transporting copper(I) across the membrane. The second is that the increased readiness of the sixth domain to undergo partial unfolding may increase the turn-over rate of the protein, ultimately leading to a decreased “effective” concentration on the membrane surface.