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Title:	Weakening of interaction networks with aging in tip-link protein induces hearing loss
Authors:	Garg, Surbhi (/jspui/browse?type=author&value=Garg%2C+Surbhi) Sagar, Amin (/jspui/browse?type=author&value=Sagar%2C+Amin) Singaraju, Gayathri S (/jspui/browse?type=author&value=Singaraju%2C+Gayathri+S) Dani, Rahul (/jspui/browse?type=author&value=Dani%2C+Rahul) Bari, Naimat K (/jspui/browse?type=author&value=Bari%2C+Naimat+K) Naganathan, Athi N (/jspui/browse?type=author&value=Naganathan%2C+Athi+N) Rakshit, Sabyasachi (/jspui/browse?type=author&value=Rakshit%2C+Sabyasachi)
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Abstract:	Age-related hearing loss (ARHL) is a common condition in humans marking the gradual decrease in hearing with age. Perturbations in the tip-link protein cadherin-23 that absorbs the mechanical tension from sound and maintains the integrity of hearing is associated with ARHL. Here, in search of molecular origins for ARHL, we dissect the conformational behavior of cadherin-23 along with the mutant S47P that progresses the hearing loss drastically. Using an array of experimental and computational approaches, we highlight a lower thermodynamic stability, significant weakening in the hydrogen-bond network and inter-residue correlations among $\beta$ -strands, due to the S47P mutation. The loss in correlated motions translates to not only a remarkable two orders of magnitude slower folding in the mutant but also to a proportionately complex unfolding mechanism. We thus propose that loss in correlated motions within cadherin-23 with aging may trigger ARHL, a molecular feature that likely holds true for other disease-mutations in $\beta$ -strand-rich proteins.
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