Title:	Dampening of cross-correlations in beta-strand of tip-link protein with aging induced hearing loss
Authors:	Garg, S. (/jspui/browse?type=author&value=Garg%2C+S.) Singaraju, G. (/jspui/browse?type=author&value=Singaraju%2C+G.) Rakshit, Sabyasachi (/jspui/browse?type=author&value=Rakshit%2C+Sabyasachi)
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Abstract:	Aging is an inevitable and involuntary process, associated with gradual deterioration of health. Age-related hearing loss (ARHL)is one of the most frequent sensory disabilities which advances with age. ARHL is a multifactorial aging disorder. These factors irreversibly and slowly damage the integrity of the auditory machinery present in the inner ear. Auditory machinery is com-posed of tiny hair cells along with the stereocilia which are pro-jected vertically in a stairway manner. The two consecutive stereo cilia are held together by the interaction of two proteins,proto cadherin-15 (Pcdh15) and cadherin-23 (Cdh23). Out of these two proteins, the Cdh23 is mapped with the ARHL pheno-type, and mutations in the Cdh23 are marked with congenital and progressive hearing loss (PHL). PHL is an accelerated state of ARHL that marks the early onset of hearing. The lack of any biophysical models is the major bottleneck in designing the precise therapeutic remedy for ARHL. Here, in search of molecular origins for ARHL, we dissect the conformational behavior of Cdh23 along with the PHL mutant (S47P) that progresses the hearing loss drastically. Using an array of ensemble and single-molecule experimental, and computational approaches, we high-light lower thermodynamic stability, significant weakening in the hydrogen-bond network, and loss of inter-residue correlations among beta-strands, due to mutation. This loss in correlated motions adverse the force adaptations from mechanical stimuli and slow down the folding in the mutant. As an antipode to the PHL mutant, we measured superior thermodynamic stability and correlated motions in another natural variant of tip-link protein,where serine is replaced by valine (S47V), found in vertebrates with a superior organ of corti and presumably no ARHL. Wethus 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 beta-strand-rich proteins.
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