Title:	Broken force dispersal network in tip-links by the mutations at the Ca2+-binding residues induces hearing-loss
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Abstract:	Tip-link as force-sensor in hearing conveys the mechanical force originating from sound to ion-channels while maintaining the integrity of the entire sensory assembly in the inner ear. This delicate balance between structure and function of tip-links is regulated by Ca2+-ions present in endolymph. Mutations at the Ca2+-binding sites of tip-links often lead to congenital deafness, sometimes syndromic defects impairing vision along with hearing. Although such mutations are already identified, it is still not clear how the mutants alter the structure-function properties of the force-sensors associated with diseases. With an aim to decipher the differences in force-conveying properties of the force-sensors in molecular details, we identified the conformational variability of mutant and wild-type tip-links at the single-molecule level using FRET at the endolymphatic Ca2+ concentrations and subsequently measured the force-responsive behavior using single-molecule force spectroscopy with an Atomic Force Microscope (AFM). AFM allowed us to mimic the high and wide range of force ramps (103–106 pN s−1) as experienced in the inner ear. We performed in silico network analysis to learn that alterations in the conformations of the mutants interrupt the natural force-propagation paths through the sensors and make the mutant tip-links vulnerable to input forces from sound stimuli. We also demonstrated that a Ca2+ rich environment can restore the force-response of the mutant tip-links which may eventually facilitate the designing of better therapeutic strategies to the hearing loss.
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