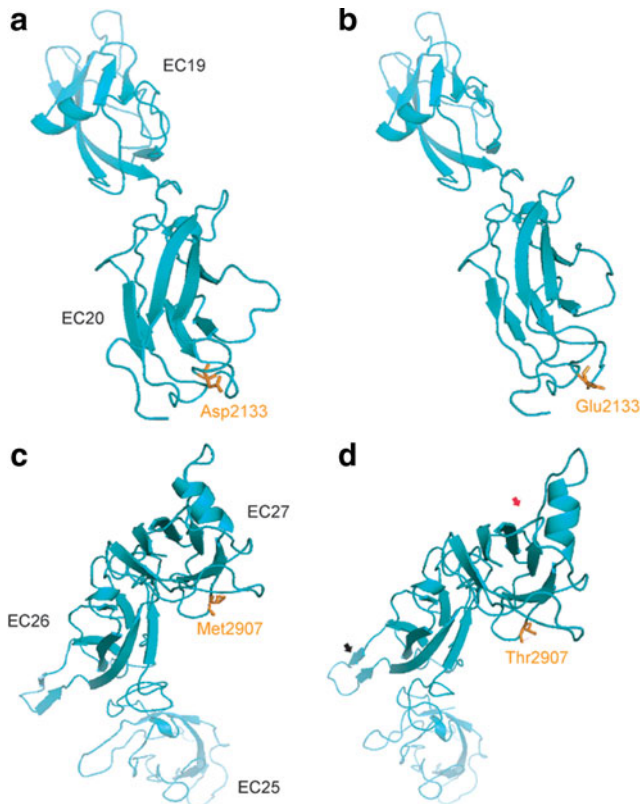


Supplementary Data



SUPPLEMENTARY FIG. S1. Molecular modeling of CDH23 p.Asp2133Glu and p.Met2907Thr. **(a)** Using CDH23 extracellular cadherin repeat domains EC1-2 as template, the Asp2133 residue occurs at a putative Ca^{++} binding site that is highly conserved between β strands E' and F' within EC20. **(b)** The additional methylene group in glutamic acid compared to aspartic acid confers higher affinity for calcium, which would likely affect stiffness of stereociliary tip links that are formed by CDH23 (i.e., increased rigidity), degree of unfolding when exposed to stretching forces, and the *trans*-binding strength between EC20-21 within the same CDH23 protein. **(c)** Based on CDH8 structure, the Met2907 residue is predicted to lie within EC25 of CDH23. **(d)** The p.Met2907Thr variant is predicted to affect H-bond formation, resulting in the gain of a β -sheet within the linker region between EC26-27 (*black arrow*) and a more open configuration for EC27 (*red arrow*) that is linked to the transmembrane region of the CDH23 protein.