Molecular Dynamics Simulations of Cx26-Wt and deafness related mutants M34A, A40G and V37I.

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Abstract

Gap junctions are specialized regions of the cellular membrane in which protein oligomers form channels for intercellular communication that allow the exchange of nutrients, metabolites, ions and small molecules up to ~1KDa. Gap junction channels are formed by the end-to-end docking of the extracellular portion of connexins, a family of transmembrane proteins that forms hexameric arrays on the plasma membrane. Mutations in at least three human connexin genes, Cx26, Cx30 and Cx31, widely expressed throughout the cochlea, are the leading causes of syndromic and nonsyndromic hereditary hearing loss. To date, the only available 3D structure of this protein family corresponds to the Cx26 hemi-channel. Taking this structure as a starting point we have developed fully-atomistic models of Cx26-Wt and three deafness-associated mutants: M34A, V37I and A40G. These models have been used to perform molecular dynamics simulations aimed to characterize and compare their dynamic behavior in order to get insights about the structure-function relationships coded into the molecular architecture of Cx26. Our results show that the studied mutations modify the position of the constriction zone in the hemmi-channel, change the diameter of the pore and produce rearrangements on the electrostatic potential inside the channel. These changes are related to an increase on the freedom of movement of the N-terminal helix and transmembrane helix 1 (TM1) of each sub-unit. These results provide relevant clues and insights about the effect of these mutations over the hemi-channel perm-selectivity and conductance.

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