The effect of somatic mutations in the voltage-gated proton channel hH_V1 from molecular simulations

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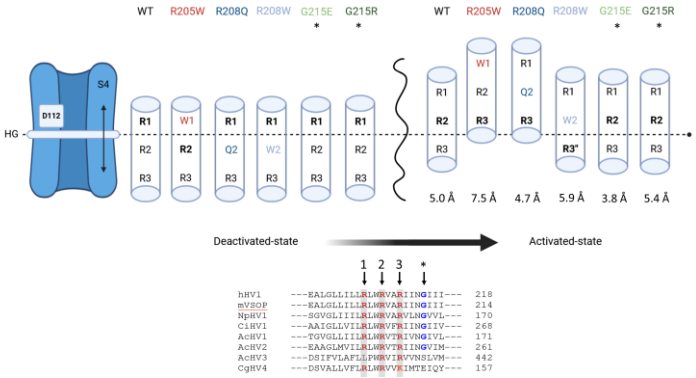

Somatic mutations are common in cancer, with only a few driving progression of the disease, while most are silent passengers. Some mutations may hinder or even reverse cancer progression. The voltage-gated proton channel (H_V1) plays a key role in cellular pH homeostasis and shows increased expression in several malignancies. Inhibiting H_V1 in cancer cells reduces invasion, migration, proton extrusion, and pH recovery, impacting tumor progression. Focusing on HVCN1, the gene coding for human H_V1 (hH_V1), we identified 197 mutations essentially clustered in two hotspots: the central region of the N-terminus and the region coding for the S4 transmembrane domain, which contains the channel's voltage sensor. We selected five mutations within the S4 segment (R205W, R208W, R208Q, G215E, and G215R) for electrophysiological analysis and MD simulations. Our findings reveal that while all mutants remain proton-selective, they all exhibit reduced effective charge displacement and proton conduction. The mutations differentially affect hH_V1 kinetics, with the most pronounced effects observed in the two Arg-to-Trp substitutions. Mutation of the first voltage-sensing arginine (R1) to tryptophan (R205W) causes proton leakage in the closed state, accelerates channel activation, and diminishes the voltage dependence of gating. Except for R205W, the mutations promote the deactivated channel configuration. Altogether, our findings are consistent with impairment of hH_V1's function by mutations in the S4 transmembrane segment, potentially affecting pH homeostasis of tumor cells. This work has been published recently [1].

[1] C. Jardin, C. Derst, A. Franzen, I, Mahorivska, T.E. DeCoursey, B. Musset and G. Chaves, *Biomolecules*, **2025**., 15, 156. doi: 10.3390/biom15020156.