Modeling the Structures of Disease-Causing ACVR1 Mutants Using Ab Initio Methods

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Mutations in the human ACVR1 receptor protein have been proven to cause the degenerative disease Fibrodysplasia Ossificans Progressiva (FOP). To date, in vivo methods of small-molecule drug discovery have been utilized, but an effective treatment for FOP has not been found. To accelerate the process of drug discovery and to support further research of the ACVR1 protein, novel in silico models of the kinase domain of the unmutated wild-type receptor and the six most common FOP-causing mutations were generated in complex with the FKBP12 inhibitor. An incomplete, experimentally-derived structure was used as the basis for the models, and missing residue loops were generated with Prime. A unique mutation was applied to six of the models. All seven models were docked with an inhibitor using the ClusPro and ROSIE servers. The models were energy-minimized using YASARA, and their structural qualities were validated with PROCHECK. Molecular dynamics simulations were run with GROMACS, and information relating to stability and behavior was analyzed. Five of the six mutant models had less stable structures than the wild-type, and each had a translated binding site. The behavior of the R206H-mutant differed the most from the wild-type, whereas the behavior of the L196P-mutant differed the least. This data offers insight into the effects of each mutation on kinase domain function. These novel in silico models enhance the understanding of FOP-causing mutations, and they can be used to accelerate the rate of small-molecule drug discovery by reducing the time, cost, and resources inherent to traditional in vivo methods.

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