Characterization of the function of disease associated mutations in Inositol 1,4,5-trisphosphate receptors

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The inositol 1,4,5-trisphosphate (IP3) receptors (IP3R) form tetrameric channels which play pivotal roles in governing the spatiotemporal patterns of intracellular calcium signals. Mutations in IP3Rs have been increasingly associated with many debilitating human diseases such as ataxia, Gillespie syndrome and generalized anhidrosis. These mutations, which occur throughout the three IP3R genes, include nonsense, missense, insertions, deletions, and splice mutations. How mutations affect IP3R function, and how the perturbation of the calcium signals contribute to the pathogenesis and severity of these diseases remains largely uncharacterized. Moreover, many of these diseases occur as the result of autosomal dominant inheritance and thus, it is expected that wild type and mutant subunits associate in heterotetrameric channels. How the incorporation of varying numbers of mutant subunits within the tetrameric channels affects its activities and results in different disease phenotypes is unclear. We have investigated a number of disease-associated missense mutations to determine their effects on IP3R channel activity. Our findings generated using channels assembled both from monomers or concatenated dimers suggest that the effect of mutations on channel function may depend on the location of the mutation as well as on the stoichiometry of mutant subunits assembled within the tetrameric channel. These studies provide insight into the cellular mechanism of these devastating human diseases and further demonstrate the utility of concatenated constructs in exploring IP3R role in pathophysiology.