1. TITLE: Structural investigation of disease-associated mutations in the Ryanodine Receptor pore and EF hand region.

2. ABSTRACT

Central core disease (CCD) mutations are found throughout the sequence of the skeletal muscle Ryanodine Receptor (RyR1), but a large cluster is located within the pore-forming region. The pore-forming region encodes the minimal pathway through which Ca^{2+} ions can permeate a biological membrane. Although recent cryo-electron microscopy studies have visualized full-length rabbit RyR1 at resolutions near 3.8Å, this has been possible only with native protein material. As such, a direct comparison of 3D structures of disease mutant versions of the proteins using this approach is currently not possible. Here we propose to solve high-resolution crystal structures of the RyR1 pore-forming region in wild-type and disease-mutant forms. Preliminary crystals are already available. In addition, we will investigate the high-resolution structure of an EF-hand containing domain and the effect of disease-causing mutations on structure, stability, and the ability to interact with the transmembrane area. We expect these structures in wild-type and disease mutant forms to provide new insights into CCD and other RyR1-related disorders, and to serve as templates for the generation and optimization of novel compounds that can interfere with RyR1 function in disease states.

3. RYR-1 RESEARCH PRIORITY AREA: ***G. Cell and Molecular Mechanisms of RYR-1 Disease***