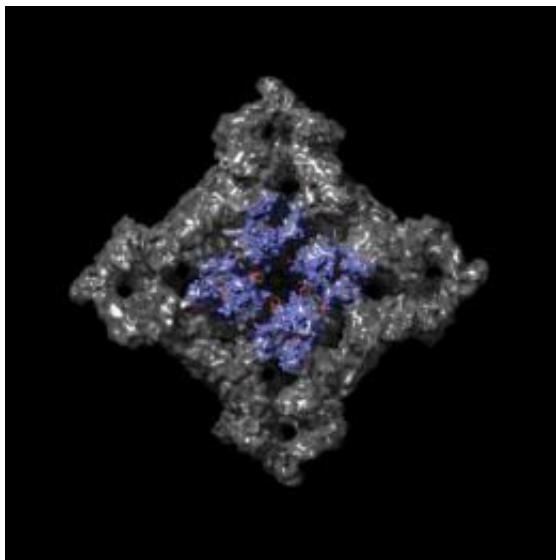


X-rays offer first detailed look at hotspots for calcium-related disease

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High-resolution images of the ryanodine receptor, a protein associated with calcium-related disease, reveal in unprecedented detail the locations of more than 50 mutations that cluster in disease "hotspots" along the receptor. The images were made with beams of intense X-rays at the Stanford Synchrotron Radiation Lightsource, located at the Department of Energy's SLAC National Accelerator Laboratory, and at the Canadian Light Source. The gray portion of the above image represents low-resolution information about the entire receptor. The high-resolution structure is shown in blue, where each sphere represents a single atom. Mutations identified in individual amino acids are colored red.

Credit: Image courtesy of Filip Van Petegem/University of British Columbia.

Calcium regulates many critical processes within the body, including

muscle contraction, the heartbeat, and the release of hormones. But too much calcium can be a bad thing. In excess, it can lead to a host of diseases, such as severe muscle weakness, a fatal reaction to anesthesia or sudden cardiac death.

Now, using intense X-rays from the Stanford Synchrotron Radiation Lightsource (SSRL) at the Department of Energy's SLAC National Accelerator Laboratory, researchers have determined the detailed structure of a key part of the ryanodine receptor, a protein associated with calcium-related disease. Their results, which combine data from SSRL and the Canadian Light Source, pinpoint the locations of more than 50 mutations that cluster in disease "hotspots" along the receptor.

"Until now, no one could tell where these disease mutations were located or what they were doing," said principal investigator Filip Van Petegem of the University of British Columbia in Vancouver.

The ryanodine receptor controls the release of [calcium ions](#) from a storehouse within skeletal-muscle and heart-muscle cells as needed to perform critical functions. Previous studies at lower resolution indicated that mutations cluster in three regions along the receptor, but without more detailed information it remained unclear exactly how they contributed to disease.

In a study published this week in *Nature*, Van Petegem and his group describe the structure of one of these hotspots in extremely fine detail and predict how the mutations might cause the receptor to malfunction and release calcium too soon.

The receptor is made up of more than 20,000 molecules called [amino acids](#). Van Petegem's group studied a string of about 560 amino acids, where they found 57 mutations. In 56 cases, the mutations involved a change in a single amino acid, while the last one involved a deletion of

35 amino acids from the string.

"These mutations most likely cause the same disease effects, but a severe mutation leads to stronger symptoms, and doesn't require as big of a stimulus to induce disease," Van Petegem said.

In the heart, the receptor is stimulated to open about once a second when the body is at rest, sending regular pulses of calcium into the rest of the cell. In skeletal muscles, the timing of the pulses is determined by how often the muscles contract. Each time the receptor opens, certain amino acids rearrange themselves to facilitate the calcium release. Mutations can disrupt this process by causing the receptor to open either earlier or more easily than it should.

This premature release of calcium produces extra electrical signals within the cells. In skeletal muscle, this can lead to fatal rises in body temperature under certain anesthetics, or the failure of major muscles. In cardiac muscle it can trigger an arrhythmia, resulting in [sudden cardiac death](#). While it is difficult to determine the exact number of people with these mutations, it is estimated that as many as one in 10,000 may be at risk for disease.

"Thanks to the technological capabilities at SSRL, we were able to rapidly screen hundreds of crystallized samples of this receptor protein to find ones with the best quality, giving the best structure. This study is a good first step toward designing new molecules that could be used as a drug," Van Petegem said. "These mutations could be a very promising therapeutic target for treating heart disease."

Future studies at SSRL and other synchrotron facilities will map out other receptor hotspots where these disease mutations cluster and use the detailed information to better understand the complex functions of the protein.

"It is very exciting to see the significant impact of our advanced structural biology technologies in helping users address difficult projects," said SSRL staff scientist Michael Soltis.

Provided by SLAC National Accelerator Laboratory

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