

Researchers shine light on congenital heart disease 'hot spots'

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Using the Canadian Light Source synchrotron and the Stanford Synchrotron Radiation Lightsource, a team of researchers from the University of British Columbia has shed light on the ryanodine receptor, a structure within muscle cells that has been linked to life-threatening congenital heart conditions.

The findings were published online today in the journal *Nature*.

"The ryanodine receptor is a complex molecular machine within muscle cells," says Filip Van Petegem, an assistant professor in UBC's Department of Biochemistry and Molecular Biology and lead author of the study.

"We've known that it plays an important role in certain congenital heart conditions but due to its size and complexity, there has never been a good, detailed model of its structure or where many of the mutations that can lead to diseases are located."

Muscle cells contract in response to the release of [calcium](#) through ryanodine [receptors](#), which are made up of interlocking parts, or domains. Mutations of ryanodine receptors result in ill-fitted domains and cause calcium leakage.

"It's like having gears in a clock with missing or broken teeth – the domains slip," explains Van Petegem. "The leaking calcium causes [muscle cells](#) to 'misfire' and result in premature and jerky contractions."

In heart muscle, this can lead to fatal rapid or irregular heartbeats in response to cardiovascular stress. The same kind of irregular, rapid contractions in skeletal muscles can lead to dangerous spikes in body temperature – called malignant hyperthermia – that can be brought on by certain forms of general anaesthetics in people with a genetic mutation that causes leaky receptors.

The researchers shone super bright beams of X-rays generated at both synchrotrons onto crystallized receptor proteins and measured how the X-rays diffracted as they passed through the crystal. The resulting patterns were then used to build a high-resolution model of specific regions of the receptors prone to disease-causing mutations, or "hot spots."

"Now that we understand how these [mutations](#) affect how the channel works, we can come up with a strategy for developing new drug treatments to help prevent calcium leakage," says Van Petegem.

Provided by University of British Columbia

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