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Study paves way for new therapies in fight against calcium disorders

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A study led by researchers at Georgia State University provides new insights into the molecular basis of human diseases resulting from mutations in the calcium-sensing receptor (CaSR), a protein found in cell membranes.

Their findings, published Friday (May 27) in the journal *Science Advances*, may assist in the development of novel receptor-based therapeutics for mutations that lead to certain types of hypocalcemia and neonatal hyperparathyroidism, in addition to Alzheimer's disease and some cancers.

Calcium is abundant in the human body and participates in nearly every vital process. CaSR plays a crucial role in maintaining calcium concentration in the human body. However, the molecular basis underlying how CaSR regulates such important cell function has been unclear.

"In this study, we reported the first crystal structure of the extracellular domain of the human CaSR, which enables us to visualize a large number of residues involved in disease-associated mutations," said Jenny Yang, lead author on the paper, Distinguished University Professor and associate director of the Center for Diagnostics and Therapeutics at Georgia State.

Nearly 200 mutations and 15 polymorphisms associated with a variety of human disorders have been found in CaSR. In this study, researchers

were able to map the mutations on the high-resolution CaSR structure. High-resolution structures of the CaSR are essential to gain a better understanding of the underlying mechanism in its regulated physiological functions as well as pathological activities.

"Further uncovering of the structural and functional mysteries of the calcium-sensing receptor could aid in the the development of novel receptor-based therapeutics for use in the treatment of many different diseases," Yang said.

"It is quite interesting that an unexpected small molecule occupies the native ligand binding site and functions as a high-affinity co-activator, which suggests that it may serve as a lead compound for CaSR regulators," said Jian Hu, paper co-author and assistant professor at Michigan State University.

The researchers' discoveries lay the groundwork for the development of agonists and antagonists as potential therapies for human diseases related to the CaSR.

More information: C. Zhang et al. Structural basis for regulation of human calcium-sensing receptor by magnesium ions and an unexpected tryptophan derivative co-agonist, *Science Advances* (2016). DOI: 10.1126/sciadv.1600241

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