Substrate specificity controlled by the exit site of human P4-ATPases, revealed by de novo point mutations in neurological disorders

ATP11A is a flippase that specifically translocates phosphatidylserine from the outer to the inner leaflet of plasma membranes. The research group of Shigekazu Nagata previously reported that a point mutation at its exoplasmic site causes the aberrant translocation of phosphatidylcholine (PtdCho), leading to the up-regulation of sphingomyelin (SM) synthetase and the accumulation of SM in the outer leaflet of the plasma membrane.

In the report, the group identified three patients with a neuronal disorder, each carrying novel de novo point mutations near the substrate exit site of ATP11A. These mutations also resulted in the abnormal translocation of PtdCho to the intracellular region. Using Molecular Dynamics Simulation Analysis, they discovered that these mutants bind PtdCho tightly at the exit gate, which may induce conformational changes at the entry gate, altering substrate specificity. Equivalent point mutations in 12 other P4-ATPases are known to be associated with various brain diseases, including motor and sensory disorders, epileptic seizures, and memory issues. It would be intriguing to explore whether these mutations similarly alter substrate specificity as seen with ATP11A.

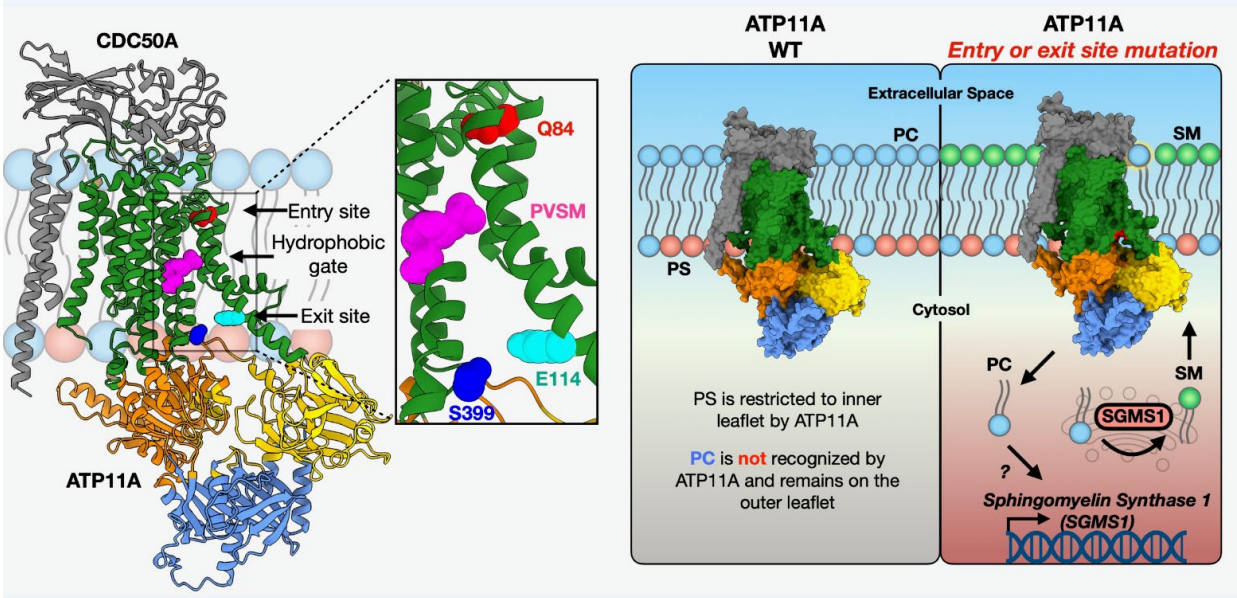

Figure: Gain-of-Function De Novo ATP11A Mutations Identified in Patients with Neurological Disorders

(Left): The AlphaFold3-predicted structure of the ATP11A-CDC50A complex reveals key features, including the substrate entry/exit sites and the hydrophobic gate. The zoomed-in view highlights the phospholipid channel, where the PVSM residues (magenta) form the hydrophobic gate. Gain-of-function mutations, Q84E, E114G, and S399L, were identified in patients with neurological disorders. Notably, the Q84 residue (red) is located at the entry site, while E114 (cyan) and

S399 (blue) are positioned at the exit site.
(Right): ATP11A typically translocates phosphatidylserine (PS) and phosphatidylethanolamine, maintaining their distribution to the inner membrane leaflet. However, mutations at Q84(E), E114(G), or S399(L) alter the enzyme's substrate specificity, enabling the translocation of phosphatidylcholine (PC) to the inner leaflet. This aberrant translocation results in the incorporation of PC and the upregulation of sphingomyelin synthase (SGMS1) gene expression, leading to the conversion of PC to sphingomyelin (SM) in the Golgi apparatus. The accumulation of SM on the outer leaflet may contribute to cellular fragility, providing insight into the molecular mechanisms underlying the associated neurological disorders.

Calianease et al.
Substrate specificity controlled by the exit site of human P4-ATPases, revealed by de novo point mutations in neurological disorders. *Proc Natl Acad Sci U S A.* 2024.

DOI:
10.1073/pnas.2415755121

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