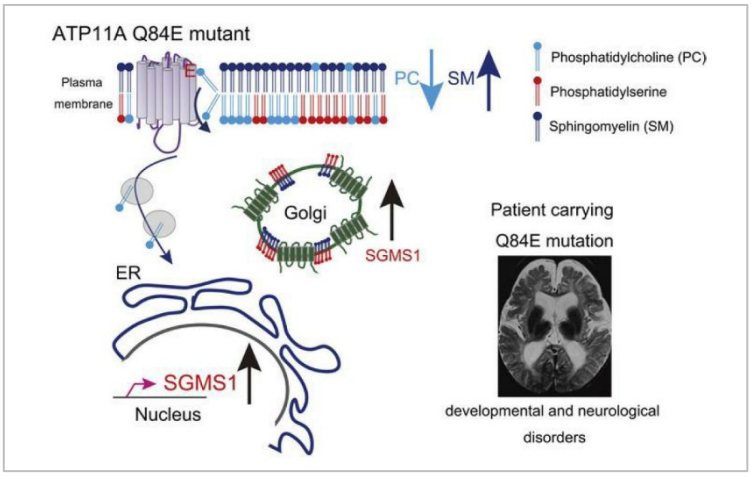
A sublethal ATP11A mutation associated with neurological deterioration causes aberrant phosphatidylcholine flipping in plasma membranes.

ATP11A translocates phosphatidylserine (PtdSer), but not phosphatidylcholine (PtdCho), from the outer to inner leaflet of plasma membranes, thereby maintaining the asymmetric distribution of PtdSer.

Shigekazu Nagata (Biochemistry & Immunology, IFReC), Katsumori Segawa (present: TMDU) and the research group detected a de novo heterozygous point mutation in ATP11A in a patient with developmental delays and neurological deterioration. Mice carrying the corresponding mutation died perinatally or soon after birth with signs of neurological disorders. This mutation caused an amino acid substitution (Q84E) in the first transmembrane segment of ATP11A, and mutant ATP11A flipped PtdCho. Molecular dynamic simulations revealed that the mutation allowed PtdCho binding at the substrate entry site. Aberrant PtdCho flipping markedly decreased the concentration of PtdCho in the outer leaflet of plasma membranes, whereas sphingomyelin (SM) concentrations in the outer leaflet increased. This change in the distribution of phospholipids altered cell characteristics, including cell growth, cholesterol homeostasis, and sensitivity to sphingomyelinase. MALDI-imaging mass-spectrometry showed a marked increase of SM levels in the brains of Q84E knock-in mouse embryos.

These results provide insights into the physiological importance of the substrate specificity of plasma membrane flippases for the proper distribution of PtdCho and SM.



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