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4-phenylbutyrate therapy restores the calcification inhibition potential of ABCC6 missense mutations

ABCC6, a plasma membrane transporter protein primarily expressed in the liver, facilitates the release of ATP. Inside the liver, the ATP is rapidly converted into pyrophosphate (PPi), which inhibits ectopic calcification. Since ABCC6 mutations hinder ATP release, mutations lead to decreased PPi levels and are responsible for diseases such as pseudoxanthoma elasticum (PXE) and cases of generalized arterial calcification of infancy (GACI), which both exhibit soft tissue calcification symptoms. Many ABCC6 mutations are missense and still have transport activity, but are retained intracellularly. The chemical chaperone, 4-phenylbutyrate (4-PBA), allows ABCC6 mutants to reach the plasma membrane, and we investigated whether 4-PBA treatments could restore soft tissue calcification inhibition of certain ABCC6 mutants. Using the dystrophic cardiac calcification (DCC) phenotype of *Abcc6-/-* mice as an indicator of ABCC6 function, we were able to quantify the effect of 4-PBA on human ABCC6 mutants expressed in the liver. 4-PBA administrations restored the cellular localization and calcification inhibition potential of some ABCC6 mutants. Because 4-PBA is an FDA approved drug, it can potentially be used to treat PXE and GACI patients.