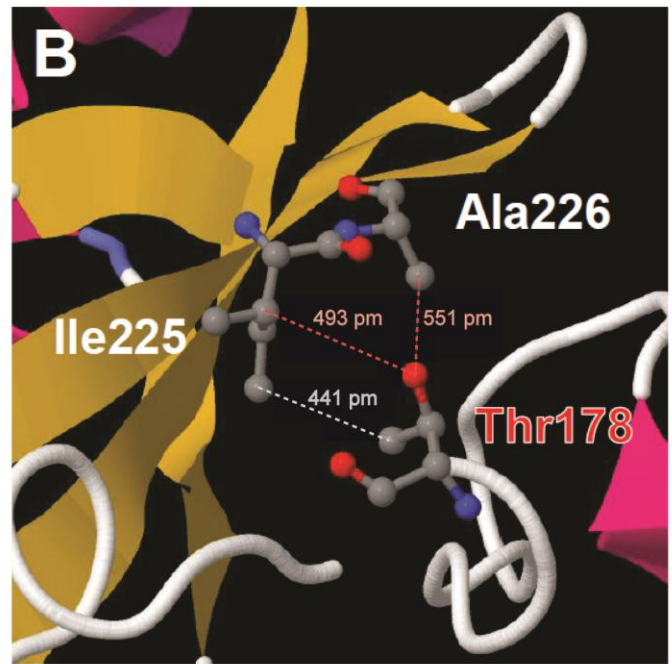


wildtype



mutation

Supplementary Figure S2: The hs. *ATP6V1C2* mutation *c.503T>C*, p.Ile168Thr affects a hydrophobic pocket in ATP6V1C2.

The hs. *ATP6V1C2* mutation was modeled on the cryo-EM structure of yeast V-ATPase (Zhao J , Nature 2015; 521:241-5).¹⁵ Ile178 in yeast *vma5* corresponds to Ile168 in hs. *ATP6V1C2*, and forms a hydrophobic pocket together with yeast Ile225 and Ala226. The human mutation p.Ile168Thr (yeast p.Ile178Thr) introduces a polar, hydrophilic amino acid, changes the distance of the hydrophobic bonds between yeast *vma5* Thr178 and Ala226 (539pm → 551pm) and between Thr178 and Ile 225 (483pm → 493pm) and therefore, may modify and interfere with the hydrophobic pocket.