Mutations in polycystin-1 and transient receptor potential polycystin 2 (TRPP2) account for almost all clinically identified cases of autosomal dominant polycystic kidney disease (ADPKD), one of the most common human genetic diseases. TRPP2 functions as a cation channel in its homomeric complex and in the TRPP2/ polycystin-1 receptor/ion channel complex. The activation mechanism of TRPP2 is unknown, which significantly limits the study of its function and regulation. Here, we generated a constitutively active gain-of-function (GOF) mutant of TRPP2 by applying a mutagenesis scan on the S4–S5 linker and the S5 transmembrane domain, and studied functional properties of the GOF TRPP2 channel. We found that extracellular divalent ions, including Ca\textsuperscript{2+}, inhibit the permeation of monovalent ions by directly blocking the TRPP2 channel pore. We also found that D643, a negatively charged amino acid in the pore, is crucial for channel permeability. By introducing single- point ADPKD pathogenic mutations into the GOF TRPP2, we showed that different mutations could have completely different effects on channel activity. The in vivo function of the GOF TRPP2 was investigated in zebrafish embryos. The results indicate that, compared with wild-type (WT), GOF TRPP2 more efficiently rescued morphological abnormalities, including curly tail and cyst formation in the pronephric kidney, caused by down-regulation of endogenous TRPP2 expression. Thus, we established a GOF TRPP2 channel that can serve as a powerful tool for studying the function and regulation of TRPP2. The GOF channel may also have potential application for developing new therapeutic strategies for ADPKD.