Functional and cellular localization diversity associated with Fukutin-related protein patient genetic variants.

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Abstract
Genetic variants in Fukutin-related protein (FKRP), an essential enzyme of the glycosylation pathway of α-dystroglycan, can lead to pathologies with different severities affecting the eye, brain, and muscle tissues. Here, we generate an in vitro cellular system to characterize the cellular localization as well as the functional potential of the most common FKRP patient missense mutations. We observe a differential retention in the endoplasmic reticulum (ER), the indication of misfolded proteins. We find data supporting that mutant protein able to overcome this ER-retention through overexpression present functional levels comparable to the wild-type. We also identify a specific region in FKRP protein localized between residues 300 and 321 in which genetic variants found in patients lead to correctly localized proteins but which are nevertheless functionally impaired or catalytically dead in our model, indicating that this particular region might be important for the enzymatic activity of FKRP within the Golgi. Our system thus allows the functional testing of patient-specific mutant proteins and the identification of candidate mutants to be further explored with the aim of finding pharmacological treatments targeting the protein quality control system.

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