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The prelingual deafness DFNB9 is caused by a synaptopathy of inner hair cells

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The molecular mechanisms underlying the specific functional properties of the auditory hair cell ribbon synapse are largely unknown. Here we studied otoferlin, a predicted transmembrane protein containing six C2-domains, which is defective in a recessive form of human deafness. We show that otoferlin expression in the hair cells parallels their afferent synaptogenesis. Using immunogold electron microscopy, we localized otoferlin to ribbon-associated synaptic vesicles. Otoferlin displays Ca2+-dependent interactions with the SNARE proteins syntaxin1 and SNAP25, in vitro. Otoferlin null mice (Otof-/-) are profoundly deaf. Exocytosis of Otof-/- inner hair cells, as monitored by membrane capacitance measurements, was nearly completely abolished, despite normal ribbon synapse morphogenesis and Ca2+ current. Furthermore, these cells lacked the fast secretory component of the exocytic burst in Ca2+-uncaging experiments. Therefore, otoferlin is essential for a late step of synaptic vesicle exocytosis, probably by acting as the major Ca2+ sensor triggering fusion at the auditory hair cell ribbon synapse. We conclude that DFNB9 represents an auditory synaptopathy.