Alterations in the ankyrin domain of TRPV4 cause congenital distal SMA, scapuloperoneal SMA and HMSN2C

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Spinal muscular atrophies (SMA, also known as hereditary motor neuropathies = HMN) and hereditary motor and sensory neuropathies (HMSN) are clinically and genetically heterogeneous disorders of the peripheral nervous system. Here we report that mutations in the thermo- and osmosensitive transient receptor potential vanilloid 4 receptor (*TRPV4)* gene cause congenital distal SMA, scapuloperoneal HMN (SPHMN), and HMSN 2C. We have identified three missense mutations (R269H, R315W, and R316C) within the intracellular N-terminal ankyrin domain of the *TRPV4* gene in five families. While mature *tetrameric* wild-type TRPV4 channel complexes preferentially localize to the plasma membrane to exert their physiological function, mutant TRPV4 proteins show granular accumulation in the cytoplasm and reduced Ca^{2+} gating activation upon induction by hypoosmotic solution in vitro. Co-transfected HeLa cells display cytoplasmic aggregates formed by both wild-type and mutant TRPV4 proteins. Basal Ca^{2+} levels and channel activation upon stimulation by hypoosmotic solution in co-transfected cells were not changed compared to cells transfected with the wild-type TRPV4 alone, in vitro. In summary, we describe a new channelopathy elicited by mutations in *TRPV4* that disturb proper channel assembly indicated by accumulation of TRPV4 proteins in the cytoplasm and reduced surface expression of functional TRPV4 channels.