

Multiplex epithelium dysfunction due to CLDN10 mutation: the HELIX syndrome

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PMID: 28771254 DOI: 10.1038/gim.2017.71

Abstract

PurposeWe aimed to identify the genetic cause to a clinical syndrome encompassing hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, and xerostomia (HELIX syndrome), and to comprehensively delineate the phenotype.**Methods**We performed homozygosity mapping, whole-genome sequencing, gene sequencing, expression studies, functional tests, protein bioinformatics, and histological characterization in two unrelated families with HELIX syndrome.**Results**We identified biallelic missense mutations (c.386C>T, p.S131L and c.2T>C, p.M1T) in CLDN10B in six patients from two unrelated families. CLDN10B encodes Claudin-10b, an integral tight junction (TJ) membrane-spanning protein expressed in the kidney, skin, and salivary glands. All patients had hypohidrosis, renal loss of NaCl with secondary hyperaldosteronism and hypokalemia, as well as hypolacrymia, ichthyosis, xerostomia, and severe enamel wear. Functional testing revealed that patients had a decreased NaCl absorption in the thick ascending limb of the loop of Henle and a severely decreased secretion of saliva. Both mutations resulted in reduced or absent Claudin-10 at the plasma membrane of epithelial cells.**Conclusion**CLDN10 mutations cause a dysfunction in TJs in several tissues and, subsequently, abnormalities in renal ion transport, ectodermal gland homeostasis, and epidermal integrity.