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Mutations in KCNH1 and ATP6V1B2 cause Zimmermann-Laband syndrome
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ABSTRACT: Zimmermann-Laband syndrome (ZLS) is a developmental disorder characterized by facial dys-morphism with gingival enlargement, intellectual disability, hypoplasia or aplasia of nails and terminal phalanges, and hypertrichosis. We report that heterozygous missense mutations in KCNH1 account for a considerable proportion of ZLS. KCNH1 encodes the voltage-gated K+ channel Eag1 (Kv10.1). Patch-clamp recordings showed strong negative shifts in voltage-dependent activation for all but one KCNH1 channel mutant (Gly469Arg). Coexpression of Gly469Arg with wild-type KCNH1 resulted in heterotetrameric channels with reduced conductance at positive potentials but pronounced conduct-ance at negative potentials. These data support a gain-of-function effect for all ZLS-associated KCNH1 mutants. We also identified a recurrent de novo missense change in ATP6V1B2, encoding the B2 subunit of the multimeric vacuolar H+ ATPase, in two individuals with ZLS. Structural analysis pre-dicts a perturbing effect of the mutation on complex assembly. Our findings demonstrate that KCNH1 mutations cause ZLS and document genetic heterogeneity for this disorder.

STATEMENT: *By applying next-generation sequencing, we identified dominant missense mutations in the KCNH1 or ATP6V1B2 gene in individuals with Zimmermann-Laband syndrome (ZLS) and unraveled the molecular basis of this developmental disorder. We provided genetic, structural and functional evidence supporting the dysregulation of the potassium channel KCNH1 (Eag1) in the pathogenesis of ZLS. We also show that a distinct amino acid alteration in the V-ATPase B2 subunit account for a small proportion of ZLS.*
This was an interdisciplinary work between the Institute of Human Genetics, the Department of Cellular and Integrative Physiology, the Bioinformatics Service Facility, all at the UKE, and the group of Prof. Dr. Marco Tartaglia from Rome, Italy. By using the next-generation sequencing platform at the Heinrich-Pette Institute (Prof. Dr. Adam Grundhoff) this work also shows the successful collaboration between the UKE and the HPI.

BACKGROUND: This work was performed in the groups of Kerstin Kutsche (Institute of Hu-man Genetics) and Christiane K. Bauer (Department of Cellular and Integrative Physiology). Fanny Kortüm has her own DFG-funded position. The teams of Kerstin Kutsche and Fanny Kortüm have strong research interests in uncovering the genetic basis of rare human diseases and understanding their underlying pathophysiological mechanisms. Christiane K. Bauer has joined the project as electrophysiologist with special interest in the function and pathophysiology of K+ channels. This study was supported by the DFG (KO 4576/1-1 and KU 1240/5-1).