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Autor(en) des Beitrags: Klopocki, E; Lohan, S; Doelken, SC; Stricker, S; Ockeloen, CW; Soares Thiele de Aguiar, R; Lezirovitz, K; Mingroni Netto, RC; Jamsheer, A; Shah, H; Kurth, I; Habenicht, R; Warman, M; Devriendt, K; Kordass, U; Hempel, M; Rajab, A; Mäkitie, O; Naveed, M; Radhakrishna, U; Antonarakis, SE; Horn, D; Mundlos, S

Titel des Beitrags: Duplications of BHLHA9 are associated with ectrodactyly and tibia hemimelia inherited in non-Mendelian fashion.

Abstract: Split-hand/foot malformation (SHFM)-also known as ectrodactyly-is a congenital disorder characterised by severe malformations of the distal limbs affecting the central rays of hands and/or feet. A distinct entity termed SHFLD presents with SHFM and long bone deficiency. Mouse models suggest that a defect of the central apical ectodermal ridge leads to the phenotype. Although six different loci/mutations (SHFM1-6) have been associated with SHFM, the underlying cause in a large number of cases is still unresolved. High resolution array comparative genomic hybridisation (CGH) was performed in patients with SHFLD to detect copy number changes. Candidate genes were further evaluated for expression and function during limb development by whole mount in situ hybridisation and morpholino knock-down experiments. Array CGH showed microduplications on chromosome 17p13.3, a locus previously associated with SHFLD. Detailed analysis of 17 families revealed that this copy number variation serves as a susceptibility factor for a highly variable phenotype with reduced penetrance, particularly in females. Compared to other known causes for
SHFLD 17p duplications appear to be the most frequent cause of SHFLD. A ~11.8 kb minimal critical region was identified encompassing a single gene, BHLHA9, a putative basic loop helix transcription factor. Whole mount in situ hybridisation showed expression restricted to the limb bud mesenchyme underlying the apical ectodermal ridge in mouse and zebrafish embryos. Knock down of bhlha9 in zebrafish resulted in shortening of the pectoral fins. Genomic duplications encompassing BHLHA9 are associated with SHFLD and non-Mendelian inheritance characterised by a high degree of non-penetrance with sex bias. Knock-down of bhlha9 in zebrafish causes severe reduction defects of the pectoral fin, indicating a role for this gene in limb development.