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CAPZB - a novel player in heart development

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Objectives:
Congenital heart defects (CHD) are the most common birth defects in humans with an incidence of 8 per 1000 live births. In 25% of the cases, the CHD is life-threatening and needs intervention directly after birth or in the first year of life. The aetiology of CHD is still poorly understood. Here we present a new candidate gene for CHD – CAPZB -, which was identified in a patient with hypoplastic left heart syndrome (HLHS). CAPZB encodes the beta subunit of the fast growing-end actin binding protein, which belongs to the F-actin capping protein family. It regulates the assembly and disassembly of actin filaments, modulates the cytoskeleton as well as tethers actin filaments to the Z-line of the sarcomere and is therefore essential for muscle development.

Methods:
Using exome sequencing, we identified CAPZB in a patient with HLHS. To understand the functional relevance of the mutation we used a mutant zebrafish. We performed cardiac output measurements on zebrafish larvae at different developmental stages. Additionally, to identify physiological and morphological defects, we performed immunofluorescence staining, electron microscopy and optical mapping. To determine differentially regulated genes influenced by CAPZB mutation we performed RNA-Seq on 48 hours (hpf) old zebrafish larvae.

Results:
Zebrafish larvae being homozygous for the mutation (capzb-/-) died after 100 hours hpf. Heterozygous zebrafish (capzb+/-) survived until adulthood and were used for husbandry. Mutant capzb-/- zebrafish larvae developed microcephaly, short stature, hypoplastic jaw and an elongated, unlooped heart at 96 hpf compared to their heterozygous capzb+/- and wildtype siblings. Cardiac output measurements showed an impaired contractility in capzb-/- compared to capzb+/- and wildtype larvae at 72 hpf, which was significantly reduced after 96 hpf. Moreover, capzb-/- larvae showed physiological and morphological defects after 72 hpf compared to capzb+/- and wildtype siblings. RNA-Seq revealed differentially expressed actin binding genes in capzb-/- larvae.

Conclusion:
Loss of CAPZB in zebrafish results in physiological and morphological defects, which phenocopy part of the observed human HLHS phenotype of the identified patient. These results highlight the importance of CAPZB as a new candidate gene for CHD and show its role during early cardiac development.