FUNCTIONAL REDUNDANCY BETWEEN HUMAN SHOX AND MOUSE SHOX2 IN THE REGULATION OF SINOTRIAL NODE FORMATION.

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The SHOX gene (short stature homeobox gene) was initially identified to be associated with idiopathic growth retardation, Turner syndrome, and Leri-Weill dyschondrosteosis in humans, while the other member of SHOX family, SHOX2, has not yet been linked to any known syndrome so far. We have previously shown by gene targeting that Shox2 is essential for the development of multiple organs in mice, including the heart, limbs, palate, and TMJ. Shox2 null mutation results in embryonic lethality due to severely hypoplastic sinoatrial node and sinus valves. Since the mouse only has Shox2 but not the SHOX ortholog in the genome, the presence of two closely related SHOX genes in the human, which exhibit overlapping and distinct expression patterns, implicates a functional redundancy between these two genes during embryogenesis. Since the mouse Shox2 shares 99% identity at the amino acid with its human counterpart and the expression pattern of Shox2 during mouse embryogenesis is very similar to that of human SHOX2, creation of a SHOX/Shox2 knock-in mouse line (replacement of mouse Shox2 with human SHOX, referred as Shox2KI/KI) would provide an excellent model for the studies on functional relationship between human SHOX and SHOX2. We report here that mice carrying Shox2KI/KI alleles survive embryonic lethality. Histological and molecular analyses demonstrate a fully developed sinoatrial node and sinus valves. Our results indicate the functional redundancy between the SHOX and mouse Shox2 in the regulation of sinotrial node formation. (Supported by NIH R01 DE17792 and American Heart Association Established Investigator Award 0340166N)