Understanding the molecular pathogenesis of *SOX9 Y440X* campomelic dysplasia

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Human *SOX9* mutations cause the skeletal malformation syndrome campomelic dysplasia (CD). Complete inactivation of the *Sox9* gene in mice results in failure of cartilage formation. Studies in zebrafish and *Xenopus* suggest that *Sox9* may be crucial for specification of the otic placode. In mice, loss of Sox9 results in failure of otic placode invagination. Heterozygous mutations in human *SOX9* result in conductive and sensorineural deafness in some CD patients, implying a later morphogenetic role but phenotypic details are limited. *Sox9*$^{-/-}$ null mice die before morphogenesis of the inner ear is complete, precluding investigation of the role of *Sox9* later in ear development. Because all the *SOX9* mutations are heterozygous and appear to cause loss of function, the CD phenotype has been attributed to haploinsufficency of SOX9. However SOX9 proteins containing an intact HMG box and a truncated activation domain may act dominant negatively by competition with the wild-type for binding to target genes and interfere with interaction with partner factors via the transactivation domain. To assess whether such mutations in *SOX9* may act via a dominant interference mechanism we generated transgenic and conditional knock'in mice expressing a mouse equivalent of a CD mutation, a Y440X nonsense mutation causing premature termination within the trans-activation domain of SOX9 (*Sox9*^{Y440X}). We compared the phenotypic impact of the *Sox9*^{Y440X} mutation with a *Sox9* null mutation. These studies point to an essential role for Sox9 in inner ear and intervertebral disc development and context dependent mechanisms for the Y440X nonsense mutation.