Title: Saethre-Chotzen Syndrome *GeneReview*: Animal Models
Author: Gallagher ER, Ratisoontorn C, Cunningham ML
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Animal models. Twist-related protein 1 and other bHLH transcription factors play central roles in specifying and maintaining cell identity. Twist-related protein 1 was initially characterized in Drosophila as being necessary during gastrulation for the establishment of the mesodermal germ layer, and embryos with *TWIST1* mutations fail to develop mesoderm [Thisse et al 1988]. During mouse development, Twist-related protein 1 is expressed in neural crest cells populating the cephalic region and branchial arches that differentiate into connective tissue, muscle, cartilage, and bone [Wolf et al 1991]. The migratory populations of cephalic neural crest cells were demonstrated to be the origin of the membranous bones of the skull (frontal, parietal, and squamosal), their intervening sutures, overlying dermis, and underlying dura mater [Morriss-Kay 2001, Jiang et al 2002], suggesting an early role in calvarial development.

One defined mechanism through which Twist-related protein 1 exerts its effects on transcription and cellular differentiation in the mouse is through interactions with histone acetyltransferase domains of acetyltransferases, p300 and p300/CBP-associated factor (PCAF), which inhibits acetyltransferase activity [Hamamori et al 1999]. These histone acetyltransferases play a critical role in transcriptional activity by relieving the repressive effects of tightly packed chromatin that hampers access of the transcriptional machinery. It remains to be clarified which downstream genes are regulated by Twist-related protein 1. Like other bHLH transcription factors, Twist1 is thought to play a central role in specifying and maintaining cell identity. Twist1 has been implicated in the inhibition of differentiation of multiple cell lineages, including muscle, bone, and neuronal cells. With regard to osteoblast development, Twist1 binds to the DNA-binding domain of Runx2, reversibly inhibiting its function [Bialek et al 2004]. Runx2 is a major bone regulatory transcription factor that increases the expression of osteocalcin through interaction with the vitamin D receptor [Sierra et al 2003, Paredes et al 2004a, Paredes et al 2004b]. It is presumed that the de-repression of RUNX2 in the presence of TWIST1 mutations is directly related to the pathogenesis of craniosynostosis. In addition to the two individuals described above with isolated single-suture craniosynostosis and mutations in the TWIST box, two individuals were recently described with duplications in a region encompassing RUNX2. These individuals were cousins who had metopic synostosis and hypodontia [Mefford et al 2010]. These findings further support the hypothesis that interruptions in the down-regulation of RUNX2 by TWIST1 result in RUNX2 overexpression, increased osteoblast differentiation, and craniosynostosis.

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