TBX1 and 22q11.2DS: Transcriptional mechanisms and phenotypic rescue.

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Some of the most typical findings of the 22q11.2 deletion syndrome (22q11.2DS) phenotype relate to developmental anomalies of the embryonic pharyngeal apparatus (PA). These include cardiac, thymic, craniofacial and other anomalies. The *TBX1* gene is located within the commonly deleted region of 22q11.2 and it encodes a T-box transcription factor required for the development of the PA. In addition, point mutations of the TBX1 gene, in the absence of a deletion, have been found in patients with a 22q11.2DS phenotype, demonstrating that this is a critical gene for the pathogenesis of 22q11.2DS, although the contribution of other genes cannot be excluded. Genetic studies have demonstrated that *Tbx1* is haploinsufficient in mice. Developmental biology studies in mice and other models have shown that TBX1 has critical roles in shaping the PA, including its typical segmentation, especially of its posterior aspect. In addition, these studies have also found brain phenotypes, some of which may be related to the neurobehavioral phenotype in patients. However, the mechanisms by which TBX1 regulates its target genes are not known in detail yet. In the last few years of our research, we have focused in trying to tease out how TBX1 works. In addition, we aim at exploiting functional mechanisms to devise approaches to counteract the consequences of Tbx1 gene mutation using the mouse model.
During the talk, I will summarize our recent findings concerning the interactions between Tbx1 and the transcriptional machinery, and our efforts to devise genetic and pharmacological rescue of the *Tbx1* mutant phenotype.