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Identification and characterization of TGFβ-dependent and -independent *cis*-regulatory modules in the *C4ST-1*/*CHST11* locus

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ABSTRACT. Chondroitin-4-sulfotransferase-1(C4ST-1)/carbohydrate sulfotransferase 11 (CHST11) is a Golgi-bound enzyme involved in the biosynthesis of the glycosaminoglycan chondroitin sulfate. The sulfation pattern of chondroitin is tightly regulated during development, injury and disease, with the temporal and spatial expression of chondroitin sulfotransferase genes believed to be a crucial determinant of the fine balance of chondroitin sulfation. We have previously identified mouse *C4st-1* as a target gene of ligands of the TGFβ superfamily of growth factors, which could positively regulate *C4st-1* expression in a number of cell types. We have also shown that a gene trap loss-of-function mutation in *C4st-1* leads to severe skeletal abnormalities during mouse embryogenesis. In addition, we described a highly specific temporal and spatial expression pattern of *C4st-1* during mouse embryogenesis. However, the transcriptional regulatory mechanisms that control *C4st-1* gene expression remain unexplored. In order to gain knowledge on the transcriptional regulation of *C4ST-1*, we used a bioinformatical approach to identify conserved putative long-range *cis*-regulatory modules in a region of

120 kb spanning the 5' end of the *C4ST-1* gene. Luciferase reporter assays in human HEK293T and mouse NmuMG cells identified a functional *C4ST-1* promoter, as well as a number of *cis*-regulatory modules able to positively and negatively regulate *C4ST-1* expression. Moreover, we identified TGFβ-responsive regulatory modules that can function in a cell type-specific fashion. Taken together, our results identify TGFβ-dependent and -independent *cis*-regulatory modules of the *C4ST-1* gene.

Key words: C4ST-1; CHST11; Chondroitin sulfate; Gene expression; TGFβ; *cis*-regulatory modules