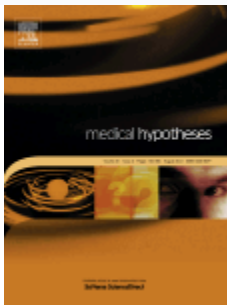







## Medical Hypotheses

Available online 3 July 2013



### Tenascin-X, collagen, and Ehlers–Danlos syndrome: Tenascin-X gene defects can protect against adverse cardiovascular events

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#### Abstract

Long thought to be two separate syndromes, Ehlers–Danlos syndrome hypermobility type (EDS-HT) and benign joint hypermobility syndrome (BJHS) appear on close examination to represent the same syndrome, with virtually identical clinical manifestations. While both EDS-HT and BJHS were long thought to lack the genetic loci of other connective tissue disorders, including all other types of EDS, researchers have discovered a genetic locus that accounts for manifestations of both EDS-HT and BJHS in a small population of patients. However, given the modest sample size of these studies and the strong correlation between

serum levels of tenascin-X with clinical symptoms of both EDS-HT and BJHS, strong evidence exists for the origins of both types of hypermobility originating in haploinsufficiency or deficiency of the gene *TNXB*, responsible for tenascin-X.

Tenascin-X regulates both the structure and stability of elastic fibers and organizes collagen fibrils in the extra-cellular matrix (ECM), impacting the rigidity or elasticity of virtually every cell in the body. While the impacts of tenascin-X insufficiency or deficiency on the skin and joints have received some attention, its potential cardiovascular impacts remain relatively unexplored. Here we set forth two novel hypotheses. First, *TNXB* haploinsufficiency or deficiency causes the range of clinical manifestations long identified with both EDS-HT and BJHS. And, second, that haploinsufficiency or deficiency of *TNXB* may provide some benefits against adverse cardiovascular events, including heart attack and stroke, by lowering levels of arterial stiffness associated with aging, as well as by enhancing accommodation of accrued atherosclerotic plaques. This two-fold hypothesis provides insights into the mechanisms underlying the syndromes previously identified with joint hypermobility, at the same time the hypothesis also sheds light on the role of the composition of the extracellular matrix and its impacts on endothelial shear stress in adverse cardiovascular events.