Published in final edited form as:
Med Hypotheses. 2013 September ; 81(3): 443–447. doi:10.1016/j.mehy.2013.06.005.

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

John W. Petersen, MD and
Division of Cardiology, Department of Medicine, College of Medicine, University of Florida, 1600 SW Archer Road, Gainesville, FL 32610-0277

J. Yellowlees Douglas, PhD[*]
Clinical and Translational Science Institute, PO Box 117150, University of Florida, Gainesville, FL 32611-7150 USA

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 previous 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 sheer stress in adverse cardiovascular events.

[*]Corresponding author contact: Jane.douglas@warrington.ufl.edu, Telephone: +1 (352) 273-3215, Fax: +1 (352) 392-1043.

Conflicts of Interest Statement
None declared.

Introduction

Ehlers-Danlos syndrome (EDS) is the most common form of hereditary connective tissue diseases (HCTD). Once divided into eleven different types that delineated different clinical manifestations, inheritance patterns, and genetic loci, EDS now falls into six types, with three types receiving the most attention in both research and clinical practice: classical type (formerly types I and II), hypermobility type (formerly type III) and vascular (formerly type IV)(1, 2). While the classical and vascular types are relatively rare, have dramatic and distinctive clinical manifestations, and specific genetic loci, the hypermobility type is distinct from all other types in its frequency range of clinical manifestations, and, to date, a lack of a genetic locus(3). As the prevalence of EDS-hypermobility type (EDS-HT) is estimated to range from 1:5,000 to 1:20,000, researchers estimate a far greater incidence rate based on the clinical variability in its presentation and difficulty in diagnosis (4). Moreover, considerable debate exists over whether what some researchers have dubbed “benign joint hypermobility syndrome” (BJHS) is, in fact, either a feature of youthful flexibility, an adaptation to the demands paced on joints in careers that include dance and sports, or actually EDS-HT(5).

However, researchers over the past decade have discovered a genetic locus for what some believe to be a recessive form of EDS-HT, in contrast to the usual autosomal dominant pattern of inheritance for EDS-HT. In this subtype of EDS-HT, individuals may have either haploinsufficiency or a complete deficiency of *TNXB*, the gene responsible for tenascin-X(6). Tenascin-X regulates the structure and stability of elastic fibers within the ECM (7), and the TNXB genetic locus may account for both the range of symptom severity notable in EDS-HT and also in BJHS (8). More important, understanding the underlying genetic cause of EDS-HT has significant implications for its diagnosis—formerly measured solely by clinical signs according to the Beighton Scale—and for current standards of care for patients with EDS-HT.

Because of the severity of symptoms of EDS vascular type, and patients’ risk factors for arterial dissection, aortic and cerebral aneurysms (9), established guidelines frequently recommended that EDS-HT patients undergo a substantial cardiovascular workup, including baseline imaging of patients’ aortic root for signs of dilation(10) and annual echocardiography for children and adolescents every two to three years until approximately age twenty-five, even in the absence of aortic root dilation(3). However, the role of tenascin-X in the composition of the extracellular matrix (ECM) suggests the reason for the range of clinical manifestations of EDS-HT, from sinus and gastric dysmotility (11) to cardiac arrhythmias and orthostatic hypotension (12).

Hypothesis

Most strikingly, perhaps, insufficiency or deficiency of tenascin-X may actually provide some measure of protection against adverse cardiovascular events. Few patients with either EDS-HT or BJHS have had their serum TNX levels tested to measure haploinsufficiency or deficiency of *TNXB*. Moreover, researchers first identified haploinsufficiency or deficiency of *TNXB* less than a decade ago and have only studied levels of TNX in a few hundred patients world-wide, which may make TNXB the genetic locus of joint hypermobility syndrome, not a recessive and rare form of the most common form of joint hypermobility disorder. Our hypothesis, therefore, is two-fold, as well as both novel and unexpected. First, *TNXB* haploinsufficiency or deficiency causes EDS-HT and BJHS. Second, rather than placing patients at greater risk of adverse cardiovascular events, joint hypermobility syndrome and deficient or even insufficient levels of TNX may protect patients against heart attack and stroke.

Evidence

EDS-HT and BJHS may be the same phenomenon

In terms of its clinical manifestations, researchers and medical practitioners generally consider EDS-HT to be the least severe type of EDS. However, significant complications can include subluxations and dislocations, which occur spontaneously or with only minimal trauma (13). Other complications include gastroparesis, hiatal hernia, and pan-GI dysmotility (11), as well as orthostatic hypotension, positional orthostatic tachycardia, and orthostatic intolerance (12). Notably, all these clinical manifestations of EDS-HT have in common laxity or hypotonic tissues, consistent with some of the earliest studies of epidermis tissue samples from EDS-HT patients that found the epidermis to be both thicker and more extensible in EDS-HT patients, which pioneering researchers attributed to an abnormal disposition of collagen fibrils (14). The similarities between clinical manifestations of BJHS and EDS-HT led early researchers to class BJHS as a form of EDS-HT (9). In fact, the 1998 revised Brighton criteria for BJHS (15) and the 1997 revised Villefranche nosology for EDS (1) display considerable overlap, and many researchers consider the two conditions to represent the same disorder (16).

Providing a genetic locus and basis for the spectrum ofseverity of clinical manifestations of EDS-HT

Two other major puzzles have challenged researchers examining EDS-HT: the spectrum of severity of its clinical manifestations and its lack of a genetic locus, both of which differentiated this type of EDS from the other types. Other types of EDS have genetic loci, including C0L5A1 and C0L5A2 for classical type, C0L3A1 for vascular type, and C0L1A1, C0L1A2 for arthrochalasia type (17). Both C0L5A1 and C0L5A2 produce different components of type V collagen, present in the skin, bones, ligaments, tendons, muscles, and the ECM (17). C0L3A1, responsible for the production of type III collagen, is prevalent in the skin, intestinal walls, lungs, and blood vessels (18). C0L1A1 and C0L1A2 both produce components of type I collagen, the most prevalent form of collagen found in the body (19). Moreover, clinical manifestations for all other types of EDS were both consistent and observable in all patients exhibiting defects to the specific genes for each type of EDS, leading researchers to conclude that all forms of EDS resulted from a disorder of fibrillar collagen metabolism (17).

This common causation for both EDS-HT and BJHS was borne out in studies over the past decade that identified compound heterozygous or homozygous mutation or deletion of the gene *TNXB* in some patients diagnosed with EDS-HT, using the Beighton scale (2, 20). One of the earliest studies of TNX deficiency linked this deficiency with the skin and joint hyperextensibility and connective tissue findings typical of EDS-HT (21). This linkage both provides a genetic locus for EDS-HT and, as subsequent studies have focused on the effects of haploinsufficiency versus total deficiency of *TNXB*, also accounts for the spectrum of severity of clinical manifestations of EDS-HT, which may range from trivial to severe (6, 22).

Tenascin-X and the ECM

While not as well studied as the genes responsible for the production and organization of collagens, the *TNXB* gene provides instructions for the creation of the protein tenascin-X. Found in the ECM, tenascin-X appears to play a central role in organizing and maintaining the structure of tissue supporting muscles, joints, organs, and skin, specifically by determining the formation of collagen fibrils in the ECM. Tenascin-X may also regulate the structure and stability of elastic fibers within the ECM (7).

Unsurprisingly haploinsufficiency of the *TNXB* gene prevent one copy of the gene from creating functional protein, thus reducing the total levels of tenascin-X in the body. These reduced levels disrupt both the organization of collagen and of elastic fibers throughout the body. Studies of patients identified as having BJHS discovered patients with similarly reduced levels of tenascin-X serum levels (22). In ultrastructural examination of tissue samples from patients with TNX deficiency, Bristow et al. also found collagen fibrils of relatively normal size and shape but of a significantly reduced density in the dermis, which lead to a 30% reduction in the collagen content in skin (22). In contrast, in TNX-null samples, fibroblasts also had near-normal collagen synthesis but significant deficits in the amount of collagen in the ECM. From these studies, researchers hypothesized that TNX-deficiency is responsible for the clinical manifestations of EDS-HT, which also accounts for the same symptoms in patients with BJHS, through a mechanism different from the causative factors of other forms of EDS—not by interfering with collagen synthesis itself but by poorly regulating the organization of fibriis in the ECM via dermal fibroblasts. As dermal fibroblasts regulate the deposition of collagen, the impact of TNX haploinsufficiency or deficiency can have profound effects on the ECM (22-24).

The impact of the organization of collagen fibrils is far-reaching. In normal skin, fibrils align in tissue-specific patterns. In skin, for example, bundles of fibrils orient in different directions to resist forces from multiple axes. In contrast, in TNX-deficient patients and in TNX-null mice, fibrils are less densely organized and not as well aligned to neighboring fibrils (6). This lowered density and disorganization of fibrils could account for some of the most common clinical manifestations of hypermobility in both EDS-HT and BJHS populations: easy bruising, skin fragility, and joint laxity (25). Subsequently, researchers conducted studies of both *TNXB*-deficient mice (23, 26) and of human populations diagnosed with EDS-HT who displayed serum levels of TNX 50% below those of healthy patients (6, 27). In both murine and human models of TNX-deficiency, despite collagen fibrils appearing to be morphologically normal, their density and disorganization impairs the integrity of the collagenous matrix and has a significant impact on the structural integrity of the ECM (28). Given the ubiquity of both collagen and the ECM throughout the body TNX-haploinsufficiency or -deficiency accounts for the range of clinical manifestations of hypermobility disorders, impacting the cornea, lungs, gut, and blood vessels (29).

Moreover, tenascin-X deficient humans also display dramatic differences to elastic fibers, a component of the ECM that provides resilience and elasticity to all connective tissues, complementing the collagen fibrils that provide cells with tensile strength (20). Some researchers have hypothesized that TNX could be involved in the development of elastic fibers (30), a hypothesis confirmed in a subsequent study of TNX-deficient individuals whose skin has abnormal elastic fibers. At the light microscopic level, fibers displayed both substantial reductions in length, as well as disruptions in the typical branching structures at the dermal-epidermal junction. In the same study, ultrastructural examination of the dermis also showed abnormalities in both microfibrillar and the elastin component of TNX-deficient patients diagnosed with EDS-HT (5,16). Unsurprisingly TNXB haploinsufficiency resulted in mild-to-moderate neuromuscular effects from EDS-HT, while a complete absence of TNX resulted in more severe neuromuscular symptoms, including muscle rupture, musculoskeletal pain, and, significanty, muscle hypotonia (10, 31).

Cardiovascular effects of joint hypermobility syndromes

Most studies occurring during the first decades of research on all types of EDS have focused extensively on systemic manifestations in three areas: skin, joints, cardiac valves and major vessels. The earliest focus on skin and joint hypermobility likely resulted from the ease with which early observations of skin and join abnormalities could be both visualized and documented (2,14). In addition, this focus most likely also stemmed from the relatively non-

invasive nature with which tissue samples could be acquired from the epidermis and dermis. Other studies focused on serious and potentially fatal cardiovascular manifestations of joint hypermobility syndromes, particularly EDS-vascular type, largely due to their severity, relative rarity, and the links provided between collagen formation and large vessels (10,19). Moreover, testing for the genetic defect that causes EDS-vascular type is simpler, more sensitive, and less expensive than the testing for mutations in, for example, *COL3A1*, a large gene which can have many mutations and one in which relatively few alleles have received any form of study (18).

However, researchers have documented significant cardiovascular effects of joint hypermobility in both EDS-HT and BJHS. Patients with joint hypermobility frequently display orthostatic hypotension, orthostatic intolerance, and postural orthostatic tachycardia (32). Some studies have found distinct correlations between joint hypermobility and hypotension (12), with one study finding some form of orthostatic hypotension in 78% of patients with joint hypermobility versus only 10% of controls (33). These clinical manifestations are consistent with the same laxity seen in tissue of the skin and joints. And, when coupled with the gastrointestinal dysmotility associated with joint hypermobility (11) this pooling of blood in the lower limbs suggests a straightforward cause. Blood pools in the lower limbs, providing poor vascular return, because the vessels themselves display the same laxity or hypotonic state as other tissues affected by joint hypermobility (33). With the linking of tenascin-X insufficiency or deficiency with joint hypermobility in at least the small sets of patients previously studied, these hypotonic vessels are dearly associated with changes to the ECM caused by the impact of *TNXB* haploinsufficiency or deficiency.

TNXB, the ECM, and impacts on vessels

Prior to its association with joint hypermobility syndrome, tenascin-X lacked any clear evidence of a clinically relevant function. However, TNX may play several key roles that significantly impact the ECM and, with it, the structure of vessels. First, as ultrastructural analysis of the dermis of TNX-deficient patients revealed, elastin fibers were immature and contained few or no microfibrils. On staining, elastin showed fragmentation or reduced branching of fine elastic fibers. As no other forms of EDS show similar elastin abnormalities, these changes to elastin seem to be the direct result of TNX-deficiency and not a result of the impact of TNX-deficiency on altered collagen metabolism (20, 34).

As modular proteins, tenascins fold into small modules, and, of the three forms of tenascin described by Erickson in 1993, TNX appears in the smooth muscle, particularly in the gut, heart, and vessels, and is potentially highly flexible (35). Moreover, some researchers believe that TNX oligomers bind to a component of collagen fibrils, providing flexible links within the ECM (6, 36). A loss of TNX could lead to weakened links within the ECM. Moreover, all three components—collagen, elastin, and the ECM—constitute the basis of the subendothelium, which itself provides mechanical strength and elasticity to all blood vessels, while also enabling vessels to maintain their structural integrity, even in the face of the considerable stress exerted by the circulation of blood through them (37). As a result, vessels in TNX-deficient patients tend toward the hypotonic, rather than the elastic. As has been documented in patients with joint hypermobility, these hypotonic vessels have deleterious effects on patients' orthostatic hypotension and can result in syncope, tachycardia, and other effects (12, 32, 38). However, this same laxity in the responsiveness of the subendothelium of vessels in responding to gravity and to mechanical stresses may also provide an unexpected benefit to patients with joint hypermobility: lowered risk factors for adverse cardiovascular events.

Cardiovascular impacts of tenascin-X deficiency

EDS has been associated with adverse cardiovascular events, such as orthostatic hypotension and even vascular rupture in patients with EDS IV. However, these same insufficient levels of tenascin-X in patients with EDS-HT and BJHS may have beneficial cardiovascular effects. Hypotonic blood vessels may protect against high blood pressure, prevent against abnormal pressure wave propagation, and accommodate accrued atherosclerotic plaques.

The elastic central arteries, such as the aorta, are required to be distensible and compliant to accommodate the recurrent pulsatile flow generated by the left ventricle. Compliant vessels accept the blood ejected from the left ventricle without significant increases in systolic blood pressure. Further, compliant vessels prevent inappropriately quick travel time of the pressure wave that occurs after each heart beat. With each heartbeat, blood ejected from the left ventricle creates a pressure wave that travels forward through the aorta and toward the peripheral blood vessels. The pressure wave reflects off the peripheral arteries and returns toward the heart. In patients with stiff arteries, the round-trip travel time of the pressure wave is short, with the pressure wave returning toward the heart while the left ventricle is stiil attempting to eject blood in to the aorta. This premature return of the pressure wave can create central aortic hypertension and place increased demand on the heart with associated left ventricular dysfunction (39). Patients with low levels of tenascin-X may not develop abnormal arterial stiffness that is common with aging and therefore may be protected from the impact of abnormally quick round-trip travel time of the pressure wave. In fact, blood pressure and pulse pressure have been shown to be lower with increased joint mobility and skin extensibility (12). Small studies evaluating the mechanical properties of arteries in patients with EDS have demonstrated conflicting results as to the dispensability of the arteries of patients with EDS (40).

Another advantage of low tenascin-X levels may relate to the ability of hypotonic blood vessels to accommodate accrued atherosclerosis. Atherosclerosis accumulates in the intimal layer of the wall of the coronary artery. Examination of left main coronary arteries at autopsy demonstrated that the internal elastic lamina within the wall of the coronary artery expanded with the accumulation of atherosclerotic plaques so that the luminal area of the coronary did not change until significant atherosclerotic plaques had accrued (41).Because tenascin-X deficiency leads to disruption of the normal ECM within the wall of blood vessels, patients with tenascin-X deficiency may be able to have more substantial expansion of the internal elastic lamina with accommodation of larger atherosclerotic plaques until coronary luminal area is compromised.

In addition to preventing coronary luminal obstruction, tenascin-X deficiency may improve the rate of progression and stability of coronary atherosclerotic plaques by augmenting endothelial shear stress. Atherosclerotic plaques are known to develop at sites of low endothelial shear stress (42). Low endothelial shear stress initiates an intracellular signaling cascade that leads to up regulation of pro-atherogentic genes (43). In some areas of atherosclerotic plaque formation, the expansive remodeling of the internal elastic lamina allows for normalization of endothelial shear stress and stabilization of the atherosclerotic plaque. Tenascin-X haploinsufficiency or deficiency may lead to this protective expansive remodeling. However, in some instances expansive remodeling is known to be excessive with further pathologic decreases in endothelial shear stress and plaque progression and an increased risk of plaque rupture. Whether tenascin-X deficiency is more likely to promote protective or deleterious expansive remodeling remains unclear and warrants future study.

Conclusions

Clearly, tenascin-X haploinsufficiency and deficiency play a significant role in the broad range of clinical manifestations in patients with both EDS-HT and BJHS, which further research should definitively establish as the same syndrome, based on serum TNX levels from a large population of patients diagnosed with EDS-HT or BJHS. Moreover, the roles played by tenascin-X haploinsufficiency or deficiency in reducing risk factors for adverse cardiovascular events merits more intensive investigation. In particular, future studies should focus on the severity of clinical manifestations that differentiate haploinsufficiency from deficiency of TNXB. In particular, future studies should focus on the severity of clinical manifestations that differentiate haploinsufficiency from total deficiency of TNX, and aim to determine if certain TNX level thresholds predict adverse and protective cardiovascular effects.

References

[1]. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup R. Ehlers-Danlos Syndromes: Revised nosology, Villefranche, 1997. Am J Med Genet. 1998; 77:31–37. [PubMed: 9557891]

[2]. Beighton P. Ehlers-Danlos syndrome. Ann Rheum Dis. 1970; 29:332–333. [PubMed: 5432600]

[3]. Levy H. Ehlers-Danlos Syndrome, Hypermobility Type. Gene Rev. 2004

[4]. Hakim A, MacGregor A, Spector T. Joint hypermobility in the general population is common and strongly genetically determined: results of a study of female twins from a national sample. Arthritis Rheum. 2003; 48:S682.

[5]. Zweers M, Bristow J, Steijlen P, et al. Haploinsufficiency of TNXB Is associated with hypermobility type of Ehlers-Danlos syndrome. Am J Hum Genet. 2003; 73:214–217. [PubMed: 12865992]

[6]. Schalkwijk J, Zweers M, Steijlen P, et al. A recessive form of the Ehlers-Danlos Syndrome caused by tenascin-X deficiency. N Engl J Med. 2001; 345:1167–1175. [PubMed: 11642233]

[7]. Bornstein P, Sage E. Matricellular proteins: Extracellular modulators of cell function. Curr Opin Cell Biol. 2002; 14:608–616. [PubMed: 12231357]

[8]. Grahame R. Joint hypermobility and genetic collagen disorders: Are they related? Arch Dis Child. 1999; 80:188–191. [PubMed: 10325741]

[9]. Beighton P, Price A, Lord J, Dickson E. Variants of the Ehlers-Danlos Syndrome: Clinical, biochemical, haematological and chromosomal features of 100 patients. Ann Rheum Dis. 1969; 28:228–245. [PubMed: 5772518]

[10]. Wenstrup R, Meyer R, Lyle J, et al. Prevalence of aortic root dilation in the Ehlers-Danlos syndrome. Genet Med. 2002; 4:112–117. [PubMed: 12180144]

[11]. Solomon J, Abrams L, Lichtenstein G. GI manifestations of Ehlers-Danlos Syndrome. Am J Gastro. 1996; 91:2282–2288.

[12]. Uiterwaal C, Grobbee D, Sakkers R, Helders P, Bank R, Engelbert R. A relation between blood pressure and stiffness of joints and skin. Epidemiol. 2003; 14:223–227.

[13]. Byers P. Ehlers-Danlos Syndrome: Recent advances in current understanding of the clinical and genetic heterogenity. J Invest Dermatol. 1994; 103:47S–52S. [PubMed: 7963684]

[14]. Grahame R, Beighton P. Physical properties of the skin in the Ehlers-Danlos Syndrome. Ann Rheum Dis. 1969; 28:246–251. [PubMed: 5772519]

[15]. Grahame R, Bird H, Child A. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *J* Rheumatol. 2000; 27:1777–1779. [PubMed: 10914867]

[16]. Zweers M, Hakin A, Grahame R, Schalkwijk J. Joint hypermobility syndromes: The pathophysiologic role of tenascin-X gene defects. Arthritis & Rheumatism. 2004; 50:2742–2749. [PubMed: 15457441]

[17]. Mao J-R, Bristow J. The Ehlers-Danlos syndrome: on beyond collagens. *J* Clin Invest. 2001; 107:1063–1069. [PubMed: 11342567]

[18]. Pepin M, Schwarze U, Superti-Furga A, Byers P. Clinical and genetic features of Ehlers-Danlos Syndrome type IV, the vascular type. N Engl J Med. 2000; 342:673–680. [PubMed: 10706896]

[19]. Malfait F, Symoens S, Coucke P, Nunes L, De Almeida S, De Paepe A. Total absence of the alpha2(I) chain of collagen type I causes a rare form of Ehlers-Danlos syndrome with hypermobility and propensity to cardiac valvular problems. J Med Genet. 2006; 43:e36. [PubMed: 16816023]

[20]. Zweers M, van Vlijmen-Willems I, van Kuppevelt T, et al. Deficiency of tenascin-x causes abnormalities in dermal elastic fiber morphology. J Invest Dermatol. 2004; 122:885–891. [PubMed: 15102077]

[21]. Burch G, Gong Y, Liu W, et al. Tenascin-X deficiency is associated with Ehlers-Danlos Syndrome. Nature Genet. 1997; 17:104–108. [PubMed: 9288108]

[22]. Bristow J, Carey W, Egging D, Schalkwijk J. Tenascin-X, collagen, elastin, and the Ehlers-Danlos syndrome. Am J Med Genet Part C. 2005'; 139C:24–30. [PubMed: 16278880]

[23]. Erickson H. A tenascin knockout with a phenotype. Nature Genet. 1997; 17:5–7. [PubMed: 9288085]

[24]. Minamitani T, Ariga H, Matsumoto K. Deficiency of tenascin-X causes a decrease in the level of expression of type VI collagen. Exp Cell Res. 2004; 297:49–60. [PubMed: 15194424]

[25]. Pyertiz R. Ehlers-Danlos Syndrome. N Engl J Med. 2000; 342:730–732. [PubMed: 10706904]

[26]. Mao J-R, Taylor G, Dean W, et al. Tenascin-X deficiency mimics Ehlers-Danlos Syndrome in mice through alteration of collagen deposition. Nature Genet. 2002; 30:421–425. [PubMed: 11925569]

[27]. Zweers M, Bristow J, Steven P, et al. Haploinsufficiency of TNXB is associated with hypermobility type of Ehlers-Danlos syndrome. Am J Hum Genet. 2003; 73:214–217. [PubMed: 12865992]

[28]. Kadler K. Matrix loading: Assembly of extracellular matrix collagen fibrils during embyrogenesis. Birth Defects Res: Part C. 2004; 72:1–11.

[29]. Uitto J, Ringpfeil F. Ehlers-Danlos Syndrome—Molecular genetics beyond the collagens. J Invest Dermatol. 2004; 122:xii–xiii. [PubMed: 15102105]

[30]. Burch G, Bedolli M, McDonough S, Rosenthal S, Bristow J. Embryonic expression of Tenascin-X suggests a role in limb, muscle and heart development. Dev Dynam. 1995; 203:491–504.

[31]. Voermans N, Bönnemann N, Huijingb P, et al. Clinical and molecular overlap between myopathies and inherited connective tissue diseases. Neuromuscular Disorders. 2008; 18:843–856. [PubMed: 18818079]

[32]. Rowe P, Barron D, Calkins H, Maumenee I, Tong P, Geraghty M. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. J Peds. 1999; 135:494–499.

[33]. Gazit Y, Nahir A, Grahame R, Jacob G. Dysautonomia in the joint hypermobility syndrome. Am J Med. 2003; 115:33–40. [PubMed: 12867232]

[34]. Hausser I, Anton-Lamprecht I. Differential ultrastructural aberrations of collagen fibrils in Ehlers-Danlos Syndrome types I-IV as a means of diagnostics and classification. Hum Genet. 1994; 3:394–407. [PubMed: 8168810]

[35]. Erickson H. Tenascin-C, tenascin-R and tenascin-X: a family of talented proteins in search of functions. Curr Opin Cell Biol. 1993; 5:869–876. [PubMed: 7694605]

[36]. Egging D, van den Berkmortel F, Taylor G, Bristow J, Schalkwijk J. Interactions of human teanscin-X domains with dermal extracellular matrix molecules. Arch Dermatol Res. 2007; 298:389–396. [PubMed: 17033827]

[37]. Raghow, R.; Seyer, J.; Kang, A. Connective tissues of the subendothelium. In: D.V. Creager, MA.; Loscalzo, J., editors. Vascular medicine: A companion to Braunwald's heart disease. Saunders-Elsevier; Philadelphia, PA: 2006. p. 31-60.

[38]. Voermans N, van Alfen N, Pillen S, et al. Neuromuscular involvement in various types of Ehlers-Danlos syndrome. Annal Neurol. 2009; 65:687–679. [PubMed: 19557868]

[39]. Denardo S, Nandyala R, Freeman G, Pierce G, Nichols W. Pulse Wave Analysis of the Aortic Pressure Waveform in Severe Left Ventricular Systolic Dysfunction. Circulation: Heart Failure. 2010; 3:149–156. [PubMed: 19903930]

[40]. Sonesson B, Hansen F, Länne T. The mechanical properties of elastic arteries in Ehlers-Danlos Syndrome. Eur J Vasc Endovasc Surg. 1997; 14:258–264. [PubMed: 9366789]

[41]. Glagov S, Weisenberg E, Zarins C, Stankunavicius R, Kolettis G. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987; 316:1371–1375. [PubMed: 3574413]

[42]. Chatzizisis Y, Coskun A, Jonas M, Edelman E, Feldman C, Stone P. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: Molecular, cellular, and vascular behavior. J Am Coll Cardiol. 2007; 49:2379–2393. [PubMed: 17599600]

[43]. Resnick N, Yahav H, A S-S. Fluid shear stress and the vascular endothelium: for better and for worse. Prog Biophys Mol Biol. 2003; 81:177–199. [PubMed: 12732261]