The relationship between fibrillin and Marfan's syndrome

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Fibrillin is a 350kDa calcium-binding glycoprotein that is vital for the formation of elastic and non-eleastic fibers in connective tissue. It is secreted into the extracellular matrix by fibroblasts and becomes incorporated into insoluble microfibrils, which provide a scaffold for deposition of elastin. Mutations in fibrillin are associated with several different connective tissue diseases, especially Marfan's syndrome (MFS). The initial hypothesis has been that mutations in fibrillin result in defective microfibrils. However, fibrillin-1 also interacts with latent transforming growth factor-β binding proteins and controls TGF-β bioavailability; dysregulation of TGF-β activation and signalling has been demonstrated in the diseased tissues of an MFS-affected mouse model. Therefore, one or both mechanisms of dysfunction may result in the MFS phenotype. The human FBN gene consists of repeating EGF (epidermal growth factor) domains and TB (transforming growth factor β-binding protein) domains. The majority of EGF domains contain a Ca^{2+} binding consensus sequence and are known as cbEGF domains (43/47 cbEGF domains in FBN1 and FBN2; 42/44 cbEGF domains in FBN3). Ca^{2+} confers structural rigidity to the fragment, producing a rod-like conformation by structural and dynamic studies of tandem repeats of cbEGF domains. TB domains exist uniquely in the microfibril protein family, locating in extracellular matrix fibrils; the major function is involved in extracellular matrix construction and storage of latent TGF-β. All TGF-β isotypes are over expressed in MFS. We have examined the locations of over 600 mutations in fibrillin-1 that cause MFS, then correlated and classified the mutations in terms of their structural and functional consequences. We have shown that in some case Ca^{2+}-binding is impaired (EGF domain structural defect) and in other cases storage of latent TGF-β is predicted to be altered due to TB domain structural perturbations.