S2-3
A new categorized COL3A1 mutation detected by genome scanning with vascular Ehlers-Danlos syndrome (vEDS)
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Keywords: vascular Ehlers-Danlos syndrome, COL3A1

Objective: Vascular type of Ehlers-Danlos syndrome (vEDS), also known as EDS type IV (NIM#130050) is a life-threatening autosomal dominant inherited disorder of connective tissue, caused by mutations of the COL3A1 gene. Vascular EDS causes severe fragility of connective tissues with arterial and intestinal ruptures and complications associated with both surgical and radiological treatment. The genetic testing of COL3A1 is important to diagnose vEDS. After making a positive diagnosis of COL3A1, the establishment of a network among medical specialists to perform a long-term follow-up for vEDS may help to improve the management of vascular and visceral complications.

Case: We describe a 20-year-old Japanese male with both pneumothorax and cervical artery dissections. His brother suffered sudden death at of 25 years of age due to an aortic rupture.

Results: The sequencing of cDNA containing the triple-helical domain of COL3A1 from cultured skin fibroblasts obtained from the patient showed no nucleotide abnormalities. However, a DNA analysis of the COL3A1 gene revealed a nonsense mutation (c.2491C>T; Gln831Stop). A possible reason for this discrepancy may be due to nonsense-mediated mRNA decay and needs to be discussed.

Conclusion: This is a first report with a nonsense COL3A1 mutation in individuals who exhibited symptoms of vEDS. We would therefore like to stress that a genomic DNA analysis of COL3A1 should be performed in all patients when there is a strong suspicion of vEDS despite negative findings in a cDNA analysis of COL3A1.

REFERENCES

Symposium III
S3-1
Insights into Aggrecan and Collagen Degradation using Knockin Mice
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Accelerated catabolism of aggrecan and type II collagen is a feature of cartilage destruction in arthritis. ADAMTS-5 is the major aggrecanase in mouse cartilage and MMP-13 is the major cartilage collagensases in several species including humans. One approach to studying the activity of these enzymes is to mutate the aggrecan and collagen II substrates, rendering them resistant to aggrecanases or collagenases, respectively. We have generated the Bailey mouse which is resistant to aggrecanase cleavage in the triple helical region of type II collagen, and the Jaffa mouse which is resistant to ADAMTS cleavage in the aggrecan interglobular domain. Degradation of fibrillar collagens is initiated by collagenase cleavage at a highly conserved site in the triple helix. We mutated the mouse col2a1 gene to change amino acids PQG 775LAG to PPC 775L776MG in collagen II. Bailey collagen II is resistant to all collagenases. The Jaffa mouse whose aggrecan is resistant to ADAMTS cleavage was made by mutating the agec1 gene to change amino acids EGE 734L736ALG to EGE 734L736NVY. Aggrecanases do not recognise this sequence as a cleavage site.

The enzyme-resistant Jaffa and Bailey mice offer distinct advantages over the ADAMTS-5 and MMP-13 null mice for studying aggrecanalysis and collagenolysis, because the consequences of targeted mutations in the aggrecan or collagen substrates are not confounded by the effects of null mutations in enzymes, on other substrates, or compensation by other enzymes. We have compared the extent of aggrecan loss and cartilage erosion in inflammatory arthritis, between Jaffa and Bailey mice. This study will identify the contributions of aggrecanases and collagenases to key phases of arthritic disease by determining whether ablation of one or both activities can modulate disease initiation and/or disease progression. These results will identify whether single or combination therapies are required for the management of arthritic disease.