A new categorized COL3A1 mutation detected by genome scanning with vascular Ehlers-Danlos syndrome (vEDS)

Aitushi Watanabe, 1,2 Banyar Naing Tang, 2 Takashi Shimada 1

1Department of Molecular Genetics, Nippon Medical School, JAPAN; 2Division of Clinical Genetics, Nippon Medical School Hospital, JAPAN

Objective: Vascular type of Ehlers-Danlos syndrome (EDS), 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 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 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


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Insights into Aggrecan and Collagen Degradation using Knockin Mice

Amanda J Fosang1,*, Stephanie J Gauci1, Leonie M Kurth1, Christopher B Little1, Eunice R Lee3, and Natalie A Sims4, Liliana Tatarczuch1, Eleanor J Mackie5

1University of Melbourne Department of Paediatrics & Murdoch Childrens Research Institute, Royal Children’s Hospital, Parkville, Australia; 2University of Sydney at the Royal North Shore Hospital, St. Leonards, Australia; 3Shriners Hospital for Children, Division of Surgical Research, McGill University, Montreal, Canada; 4University of Melbourne Department of Medicine at St Vincents Hospital, Fitzroy, Australia; 5University of Melbourne School of Veterinary Science, Parkville, Australia.

*Contact author: amanda.fosang@mcri.edu.au

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 collagenases 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 collagenase 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 POG7731LAG to PPC7731778MPG 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 agg1 gene to change amino acids EGE7371738ALG to EGEN7371738NYV. 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 aggrecanolysis 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.