Jordan University of Science and Technology

COL6A5 variants in familial neuropathic chronic itch.

Authors: Martinelli-Boneschi F, Colombi M, Castori M, Devigili G, Eleopra R, Malik RA, Ritelli M, Zoppi N, Dordoni C, Sorosina M, Grammatico P, Fadavi H, Gerrits MM, **Almomani R**, Faber CG, Merkies IS, Toniolo D; INGI

Abstract: tch is thought to represent the peculiar response to stimuli conveyed by somatosensory pathways shared with pain through the activation of specific neurons and receptors. It can occur in association with dermatological, systemic and neurological diseases, or be the side effect of certain drugs. However, some patients suffer from chronic idiopathic itch that is frequently ascribed to psychological distress and for which no biomarker is available to date. We investigated three multigenerational families, one of which diagnosed with joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type (JHS/EDS-HT), characterized by idiopathic chronic itch with predominantly proximal distribution. Skin biopsy was performed in all eight affected members and revealed in six of them reduced intraepidermal nerve fibre density consistent with small fibre neuropathy. Whole exome sequencing identified two COL6A5 rare variants co-segregating with chronic itch in eight affected members and absent in non-affected members, and in one unrelated sporadic patient with type 1 painless diabetic neuropathy and chronic itch. Two families and the diabetic patient carried the nonsense c.6814G>T (p.Glu2272*) variant and another family carried the missense c.6486G>C (p.Arg2162Ser) variant. Both variants were predicted as likely pathogenic by in silico analyses. The two variants were rare (minor allele frequency < 0.1%) in 6271 healthy controls and absent in 77 small fibre neuropathy and 167 JHS/EDS-HT patients without itch. Null-allele test on cDNA from patients' fibroblasts of both families carrying the nonsense variant demonstrated functional haploinsufficiency due to activation of nonsense mediated RNA decay. Immunofluorescence microscopy and western blotting revealed marked disorganization and reduced COL6A5 synthesis, respectively. Indirect immunofluorescence showed reduced COL6A5 expression in the skin of patients carrying the nonsense variant. Treatment with gabapentinoids provided s