FURTHER INSIGHTS IN THE RARE KYPHOSCOLIOTIC EHLERS-DANLOS SYNDROME: REPORT OF 3 UNRELATED INDIVIDUALS AND 2 NEW PATHOGENIC VARIANTS

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The Ehlers-Danlos syndromes (EDS) are an umbrella term for a clinically and genetic heterogeneous group of heritable connective tissue disorders. The kyphoscoliotic subtype of EDS is a rare autosomal recessive EDS type with typical presence of severe kyphoscoliosis, muscle hypotonia and joint hypermobility. It results from deficiency of either the post-translational modifying enzyme lysyl hydroxylase (LH1 encoded by PLOD1) or the peptidyl-prolyl cis-trans isomerase family FK506-binding protein 22kDa (FKBP22 encoded by FKBP14), two proteins participating in collagen crosslinking and folding. FKBP22 is one of the proteins of the molecular ensemble for collagen biosynthesis as it acts as a molecular chaperone involved in the folding and quality control of certain types of collagen. This study brings the clinical manifestations of 3 non-related individuals in whom homozygous pathogenic variants were found: patient 1 (c.587A>G; p.(Asp196Gly)); patient 2 with (c.362dupC; p.(Glu122Argfs*7)) and patient 3 (c.2T>G; p.(Met1?)) variant; with experimental data of the variants found in patient 1 and 2. We show that both variants cause complete loss of the FKBP22 protein. In addition, we found intracellular accumulation of type III and type IV collagen with immunocytochemistry and impaired fibroblast migration with a scratch assay. Investigation of ER-stress related proteins (CHOP, LC3B, xBP1, ATF6, (p)eIF2aplha, BIP) with immunoblotti ng and RT-qPCR did not reveal any significant upregulation. Conclusion: This study broadens the clinical and molecular spectrum of FKBP14-related kyphoscoliotic Ehlers-Danlos syndrome with 2 new pathogenic variants and 3 non-related individuals. We bring the first evidence of a homozygous pathogenic missense variant with experimental data.