Kyphoscoliotic Type EDS Caused By Compound Heterozygous Mutations In Fkbp14 Including A Novel P.lys190del Mutation

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Kyphoscoliotic Type EDS Caused by Compound Heterozygous Mutations in FKBP14 Including a Novel p.Lys190del MutationFKBP14-related Kyphoscoliotic type EDS was first described in 2012. The major clinical features for this syndrome, as established in the 2017 revised Ehlers-Danlos syndrome (EDS) nosology, are congenital muscular hypotonia, congenital or early onset kyphoscoliosis, and generalized joint hypermobility. Gene-specific minor features, distinguishing FKBP14-related disease from PLOD1-related Kyphoscoliotic type EDS, are early onset sensorineural, conductive or mixed hearing impairment, muscle atrophy, follicular hyperkeratosis, and bladder diverticula. Other minor findings include a marfanoid habitus, pectus deformity, talipes equinovarus, skin hyperextensibility, easily bruisable skin, umbilical or inguinal hernias, rupture/aneurysm of a medium-sized artery, blue sclerae, osteopenia, osteoporosis, and myopia or hypermetropia. The GeneReviews for this syndrome, created in May 2019, states that there are 30 patients described to date, with three mutations known to be pathogenic at this time (c.362dupC, p.Glu122ArgfsTer7; c.573_575del, p.Glu191del; and c.143T>A, p.Met48Lys). The c.362dupC variant accounts for approximately 70% of disease alleles reported at this time. We describe a proband with clinical features consistent with Kyphoscoliotic type EDS and biallelic mutations in FKBP14, c.362dupC and a novel mutation of c.568_570del, p.Lys190del).Our proband is a 15 year old Caucasian male who was born at 38 weeks gestation by SVD to a 39-year-old G4P2 mother weighing 7 lb 8 oz and 19 inches in length. He did not have significant feeding difficulties, but had some global developmental delays in the first few months of life prompting the need for physical, occupational, and speech therapy for the first 3-5 years. He walked at 18 months, but did not ride a bike until 9 years of age. He does have some challenges at school, but does not require special education accommodations in class or in physical education activities. He was diagnosed with scoliosis at 14 years of age, with 36 degree lumbar and 20 degree thoracic curves. Due to scoliosis and pectus excavatum, he was referred to cardiology, where he was found to have trivial tricuspid regurgitation on ECHO and a borderline increased aortic diameter with a Z-score of 1.9. His cardiologist recommended a genetics evaluation for possible Marfan syndrome. He has a history of myopia with a -3 diopter correction and has significant hypermobility with a Beighton score of 8/9 and a Marfan systemic score of 9, with hind foot deformity, flat feet, and a positive thumb and wrist sign. Genetic testing was sent for connective tissue disorders and the patient was found to have the known pathogenic c.362dupC variant and a novel c.568_570delAAA, p.Lys190del variant of unknown significance in the FKBP14 gene. He also has a PLOD1 variant of unknown significance, c.1321 C>T, p.Arg441Trp, but no second variant in PLOD1 was found on sequencing or deletion/duplication testing. Because of concerns for kyphoscoliotic type EDS, he was sent for hearing testing and was found to have moderate high frequency sensorineural hearing loss.We report a new mutation in FKBP14, c.568_570delAAA, p.Lys190del, which, in conjunction with the known pathogenic mutation, c.362dupC, causes kyphoscliotic EDS. We have anecdotal reports from the performing laboratory of homozygous c.568_570delAAA mutations causing no apparent disease. We postulate, therefore, that this novel mutation causes decreased protein function, but the amount is sufficient in homozygosity. In compound heterozygous presentations with the loss of function c.362dupC mutation, however, the residual function of c.568_570delAAA is insufficient and, therefore, disease-causing. More studies will be needed to confirm this suspicion.

Comments (un-moderated)

FKBP14: variant 1 is the (well-)known c.362dupC, and variant 2 is a novel 3-bp inframe deletion c.568_570delAAA, p.Lys190del. This is very interesting:
"... anecdotal reports ... homozygous c.568_570delAAA mutations causing no apparent disease." and the hypothesis is
homozygous variant 2 -> decreased but sufficient protein function
compound heterozygous (variant 1 & 2) -> insufficient function and disease-causing
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