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Case of Skeletal Dysplasia in Post-Menarchal Pediatric Patient due to Novel Mutation of CSGALNACT1

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We report the case of a 14 year old Yemenite female diagnosed with autosomal recessive skeletal dysplasia secondary to a novel mutation of CSGALNACT1. She was initially referred to pediatric endocrine for poor linear growth at the age of 11 year 7 months. At that time, her height was well below the growth curve with z-score of -3.51. She had no reported history of intellectual disability. She had a normal MRI of the brain as well as normal growth factors, growth hormone stimulation test, thyroid function, IgA celiac antibodies, and a normal karyotype (46,XX). SHOX and microarray were negative. Her bone age was slightly delayed at 10-11 years with a chronological age of 11y8m. On initial evaluation by genetics, she was normocephalic with no dysmorphic facial features. She had proportionate limbs but was noted to have mild lumbar lordosis, increased joint laxity, and flattened feet with fifth toe clinodactyly. Notably there was a family history of consanguinity (parents are first cousins once removed). A skeletal dysplasia gene panel was not thought to be indicated, and she was referred back to endocrine. She was lost to follow up with endocrine but returned to clinic after 1 year when she was post-menarchal. She continued to have poor linear growth. Upon reevaluation, she was noted to additionally have a high-arched palate and shortened hallux. A panel for skeletal dysplasia was sent which detected a novel homozygous mutation of CSGALNACT1 with autosomal recessive inheritance. CSGALNACT1 encodes chondroitin sulfate N-acetylgalactosaminyl transferase which is crucial for chondroitin sulfate chain biosynthesis and glycosaminoglycan synthesis. Congenital disorders of glycosylation are genetically inherited conditions due to abnormal glycan biosynthesis. Glycosaminoglycans (GAGs) are vital in normal development of cartilage and the brain. We performed a PubMed search and saw four reported cases of individuals with mutations of CSGALNACT1. Clinically these individuals had relative macrocephaly, rhizomelia, hyperlordosis, joint laxity, and mild neurodevelopmental delay. Reported radiographic findings of affected individuals include advanced bone ages, flattened acetabular roofs, and vertebral anomalies. Our patient in contrast did not have overt dysmorphic features on exam nor reported intellectual disability to prompt a more immediate workup for skeletal dysplasia. There have been only a handful of cases with CSGALNACT1 mutations and skeletal dysplasia. These individuals more typically have findings of dysmorphia on exam including macrocephaly, lordosis, and joint laxity. Our patient lacked these typical features that are more normally associated with skeletal dysplasia yet was revealed to have a novel mutation of CSGALNACT1. Based on her initial genetic evaluation, her clinical findings were subtle and did not indicate a workup for skeletal dysplasia. Her case however shows that even in the absence of dysmorphic features, skeletal dysplasia should be considered in individuals with severe short stature.

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