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Case Report

A novel *COMP* mutation in an Inuit patient with pseudoachondroplasia and severe short stature

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ABSTRACT. Pseudoachondroplasia (PSACH) is an autosomal dominant skeletal dysplasia, generally identified clinically at two years of age due to decreased linear growth and a waddling gait. Radiographic features include small and irregular epiphyses, with metaphyseal changes of the long bones and characteristic vertebral changes. Mutations in the *COMP* gene cause PSACH and some cases of multiple epiphyseal dysplasia. Mutations generally cluster in the calmodulin-like repeat regions of the gene. Mutations in exon 13 (encoding the seventh calmodulin-like repeat) have been associated with severe short stature (-6 SD) in PSACH. We examined an Inuit boy with PSACH and severe short stature. Height essentially remained at -1 SD on the PSACH growth curve (-7.5 SD on a normal growth curve at 10.5 years). Analysis of *COMP* in our patient revealed a previously undescribed heterozygous A>T substitution in exon 8, at nucleotide

812. This change in the sequence resulted in replacement of a highly conserved and negatively charged aspartic acid with an uncharged, hydrophobic valine at amino acid position 271. Both unaffected parents were negative for this genetic change. This exon encodes the first calmodulin-like repeat, which has not been previously implicated in severe short stature. We propose that this novel missense substitution is responsible for the phenotype of this patient.

Key words: Pseudoachondroplasia; *COMP*; Skeletal dysplasia; PSACH

