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The first reported case of the DRAGON gene deletion in human. A case with a de-novo interstitial deletion of chromosome 5q15-21.1

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Chondrodysplasia punctata (CDP) is an etiologically heterogenous condition caused by single gene disorders, chromosome abnormalities, maternal diseases or exposures to teratogens. We report a male fetus with rhizomelic CDP associated with deletion at 5q15-5q21.1. This segment contains the DRAGON gene, a bone morphogenetic factor co-receptor, also known as RGMb (repulsive guidance molecule b). It is postulated that its haplo-insufficiency is associated with the phenotype in this fetus. The mother (30yo, G2P0SA1L0) was referred at 19.3 weeks for abnormal antenatal ultrasound findings of short limbs, short splayed digits, brachycephaly, small cistern magna, hypoplastic inferior cerebellar vermis, micrognathia, multiple intracardiac echogenic foci and 2-vessel umbilical cord. There was no history of maternal disease/ exposures. The pregnancy was terminated at 21 weeks. Autopsy confirmed the ultrasound findings and in addition showed brain hypomyelination with ventriculomegaly. Biochemical studies revealed normal plasmalogen and cholesterol biosynthetic function. Radiograph showed numerous abnormal calcific stipplings and prematurely calcified ossification centers. There was rhizomelic shortening of proximal long bones, abnormal calcification/ossification in the cervical, thoracic and sacral spine and poorly formed with platyspondyly of the cervical and thoracic spine with thin ribs. The findings were in keeping with rhizomelic CPD. The Agilent 105K array (Signature Genomics) shows a de novo 3.4Mb deletion at 5q15-5q21.1. The region does not contain any OMIM disease genes and has not been reported in the DECIPHER Initiative. It contains 3 genes including the DRAGON (RGMB) gene, which is of interest as its encoding protein is a bone morphogenetic protein (BMP) co-receptor. BMPs induce ectopic bone and cartilage formation in experimental animals. They are important for skeletal patterning and are involved in the development of many tissues including bones, craniofacial structures and nervous system. As a co-receptor for BMPs, DRAGON is important in neural and neural crest patterning early in development. DRAGON is also found to be expressed in brachial arches, somites and the tail bud of developing mouse and Xenopus but its function in skeletal patterning is not well

described. Since a copy of the DRAGON gene is deleted in our patient, we postulate that haplo-insufficiency of this gene is related to the pathogenesis of the CDP phenotype.