**Biallelic gene disrupting variants in *PKDCC* cause a skeletal disorder characterized by rhizomelic shortening of extremities and distinctive facial features.**

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## ABSTRACT

**Introduction:** *Protein kinase domain containing, cytoplasmic*, or *PKDCC* (also known as *VLK*), codes for a protein demonstrated to be the first known secreted tyrosine kinase [Bordoli MR, et al. (2014) Cell 158(5):1033-1044]. During mouse development it is expressed in several tissues including the ventral part of the mid-brain, with especially strong signals seen in branchial arches and limb buds. Homozygous *Pkdcc* knockout mice have shortened long bones as the most obvious morphological abnormality due to delayed endochondral ossification which results in reduced long bone mineralization as well as craniofacial abnormalities including small and shortened nasal capsule and maxilla. In mice, the *Pkdcc* gene product affects bone development through hedgehog (HH) signaling by interacting with the products of *Gli3* and *Ihh* genes [Probst S, et al. (2013) Differentiation 85(4-5):121-130]. Homozygous knockout mice for the latter two genes also display skeletal abnormalities comprising of short limbs and craniofacial abnormalities [St-Jacques B, et al. (1999) Genes Dev 13(16):2072-2086; Mo R, et al. (1997) Development 124(1):113-123]. Finally, compromised function of the *IHH* (OMIM #600726) and *GLI* (OMIM #165240) genes in humans cause skeletal disorders involving short stature and shortened limbs. These observations make *PKDCC* a candidate gene for human skeletal dysplasia. We report two unrelated patients with skeletal abnormalities comprising of rhizomelic shortening of limbs and distinctive facial features with homozygous, gene disrupting variants in *PKDCC* identified by trio clinical diagnostic exome sequencing (DES).

**Methods:** DES and candidate gene analysis were carried out as described previously [Farwell Hagman KD, *et al*. (2017) *Genet Med* 19(2): 224-235].

**Results:** The first patient was a 17-year-old girl who had radiographic findings consistent with omodysplasia that was first noted at the age of 2 months. Her skeletal findings included rhizomelic and milder mesomelic shortening of the upper and lower extremities, short thumbs, and bilateral short 5th fingers. Hyperextensible fingers, limited range of motion at shoulder joints, chronic joint pain and bilateral patellofemoral joint dislocation were also reported. Dysmorphic facial features included a prominent forehead, down slanting palpebral fissures, broad nasal bridge, and long philtrum. She was found to be homozygous for the prematurely truncating nonsense variant p.Y217* (NM_138370 c.651C>A) in the second exon of *PKDCC* expected to result in nonsense mediated decay of the mutant transcripts.

The second patient was a 23-month-old boy whose skeletal survey at the age of 4 months indicated a flattening of the dorsal aspect of the skull compatible with plagiocephaly and rhizomelic short stature most evident in his upper extremities. He was hypotonic, had joint laxity and prominent fingertip pads. He was noted to have craniofacial dysmorphic features including macrocephaly, short neck, micrognathia, mild proptosis, depressed nasal bridge, and a long

smooth philtrum. He was found to be homozygous for the c.639+1G>T variant at the canonical splice donor site in the first intron of *PKDCC* predicted to abolish the splice donor site by three in-silico splice prediction algorithms.

**Conclusions:** This is the first report of biallelic gene disrupting variants in *PKDCC* causing skeletal defects in humans including rhizomelic shortening of limbs and distinctive facial features.