Appendix S1. Descriptions of genes.

The growth differentiation factor 5 (GDF5) gene, also known as cartilage-derived morphogenetic protein-1 (CDMP-1), encodes a 501 amino acid protein and is a member of the bone morphogenetic protein (BMP) family and the TGF-beta superfamily. This family includes regulators of cell growth and differentiation in both embryonic and adult tissues. Mutations in the GDF5 gene are associated with Hunter-Thompson acromesomelic dysplasia, brachydactyly type C and chondrodysplasia type Grebe in humans, and all result in disruption of skeletal development. The human GDF5 gene consists of two exons spanning 4879 bp.

FRZB encodes secreted frizzled-related protein 3 (sFRP3), which is an antagonist of the wingless (wnt) signaling pathway. The wnt pathway is a complex network of proteins, critical in skeletal and joint patterning in embryogenesis. A reduced ability of mutated variant sFRP3 to antagonize wnt signaling may predispose females to hip osteoarthritis. The human FRZB gene contains six exons spanning 32762 bp.

The Pax1 protein belongs to the Paired box (Pax) family of tissue specific transcription factors and contributes to the development of vertebral column in mice and humans. Based on studies of PAX1 mutations in mice with vertebral column abnormalities, PAX1 has been identified as a candidate gene in vertebral malformations and congenital scoliosis in humans. The human PAX1 gene contains five exons spanning 10257 bp.

Sonic hedgehog homolog (SHH) is one of three proteins in the mammalian hedgehog family and plays a role in regulating vertebrate organogenesis. SHH is a morphogen involved in patterning, including limb and midline structures in the brain and spinal cord. Mutations in the human SHH gene cause holoprosencephaly type 3 (HPE3) because of the loss of the ventral midline of the brain. The human sonic hedgehog homolog gene consists of three exons spanning 9410 bp.

Twist1 is transcription factor which may affect the transcription of fibroblast growth factor receptors that are involved in the modulation of craniofacial and limb development in humans. Mutations in the human TWIST1 gene have been associated with Saethre-Chotzen, Crouzon and Pfeiffer syndromes, which result in cranial abnormalities and defects of appendicular skeleton. The human TWIST1 gene includes single exon and spans 2205 bp.

REFERENCES