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Review

Genetics of human isolated acromesomelic dysplasia

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ABSTRACT

Acromesomelic dysplasia is a type of skeletal malformation affecting distal and middle segments of the extremities. It occurs in both isolated (non-syndromic) and syndromic forms. In later case, it shows association with cardiac, respiratory, neurological and genital abnormalities. Acromesomelic dysplasia segregates in autosomal recessive mode. Mutations in three genes (*GDF5*, *NPR2*, *BMPR1B*) have been reported to cause different forms of acromesomelic dysplasia.

In the present review, we have discussed clinical spectrum, genetics and signalopathies of isolated acromesomelic dysplasias.

Contents

1. Introduction

Acromesomelic dysplasia (AMD) is a group of autosomal recessive form of skeletal disorders characterized by dwarfism associated with anomalies of middle and distal segments of the extremities. AMD occurs both in isolated (non-syndromic) and syndromic forms. In the syndromic form, it is associated with respiratory, genital, cardiac and neurological abnormalities (Haliloglu et al., 1999; Demirhan et al., 2005; Kurt et al., 2013).

Based on clinical and radiographic investigations of the condition observed in a number of patients, isolated form of AMD is further divided into various types; Acromesomelic Dysplasia Grebe-type (AMDG), Acromesomelic Dysplasia Hunter–Thompson type (AMDH) and Acromesomelic Dysplasia Maroteaux type (AMDM). Acromesomelic dysplasia, Osebold–Remondini type (MIM 112910) with dominant inheritance mode has been reported.

AMDG is characterized by severe dwarfism at birth, severe shortening and abnormalities of limbs and long bones. It was localized to chromosome 20q11.22 (Thomas et al., 1996) and

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subsequently small mutations in the growth and differentiation factor-5 (*GDF5*) gene were detected in several families (Thomas et al., 1996). Recently, point mutations in bone morphogenetic protein receptor IB (*BMPR1B*) gene have been identified in families segregating AMDG (Graul-Neumann et al., 2014). Similarly, AMDH is characterized by severe dwarfism, lower limbs more affected than upper limbes and large joint dislocations. It was also mapped to chromosome 20q11.22 and large duplications in the coding segment of *GDF5* gene were detected in AMDH patients as well (Thomas et al., 1997). As, GDF5 is a ligand for BMPR1B, therefore, we classify AMDG and AMDH under GDF5-BMPR1B signalopathies.

The third type is AMDM, characterized by severe dwarfism, limbs and vertebral shortening, results from mutations in the gene natriuretic peptide receptor-2 (*NPR2*) (Kant et al., 1998). Similarly animal model studies show similar phenotypic presentation, if CNP is lacking. CNP is a ligand for NPR2 and therefore, we will discuss AMDM under heading of CNP-NPR2 signalopathy (Chusho et al., 2001). Vertebral abnormalities are observed in AMDM in contrast to AMDG and AMDH where vertebral bones are normal.

Among the syndromic forms of acromesomelic dysplasias, gene is known only for the AMDG associated with genital anomalies. It is also caused by mutations in *BMPR1B* gene located on human chromosome 4q22.3 (Demirhan et al., 2005).

2. GDF5-BMPR1B signalopathy

AMDG (MIM 200700) is a chondrodysplasia, characterized by severe acromesomelia, dwarfism, severe micromelia with increasing severity in a proximo-distal gradient and deformation of upper and lower limbs (Grebe, 1952). Radiologically, it is marked by extremely short limbs with legs being more severely affected than arms. The hands are extremely short with toe-like fingers, and feet show valgus deformity (Thomas et al., 1997). In addition, short femoral neck, tibial absence and fibular diaphysis, hypoplasia of the ulna, malformed radial head, fusion of carpals and metacarpals, fusion of tarsals and metatarsals, absence of proximal and middle phalanges have been reported in the patients (Table 1) (Costa et al., 1998; Faivre et al., 2000). Facial, intelligence and vertebral abnormalities have not been observed in any patient with AMDG.

AMDH (MIM 201250) is characterized by abnormalities of limbs, especially the lower limbs. Middle and distal segments of the limbs are most affected. Hands are less severely affected with abnormally short metacarpals and phalanges. Phalanges are almost square in shape. Short humerus, curved radius with dislocated head and ulna, short femur, tibia and fibula along with dislocated ankle are the hall marks of AMDH. Feet are short and averted with globular toes (Hunter and Thompson, 1976; Langer et al., 1989). The craniofacial and axial skeleton is normal (Table 1).

The two different types of acromesomelic dysplasia, including AMDG and AMDH are caused due to pathogenic sequence variations in the genes involved in GDF5-BMPR1B signalopathy.

Cartilage derived bone morphogenetic protein-1 (CDMP1) also known as growth and differentiation factor 5 (GDF5) encodes a gene *GDF5* is located on chromosome 20q11.22. It comprises of only two coding exons (Hötten et al., 1994). It expresses predominantly in cartilaginous tissues of the developing long bones and in more distal elements of the appendicular skeleton that develop from the budding limb (Storm and Kingsley, 1999). GDF5, a secreted protein, is a member of the bone morphogenetic protein (BMP) family and the transforming growth factor-β (TGF-β) superfamily (Storm and Kingsley, 1999; Luyten, 1997; Chang et al., 1994). The GDF5 precursor polypeptide contains 501 amino acids with Arg-X-X-Arg polybasic proteolytic processing site at amino acid 377–381 and seven highly conserved cysteine motifs at its C-terminus. Both are critical for the proper folding, homo- and hetero dimerization (Thomas et al., 1997; Luyten, 1997; Chang et al., 1994; Storm et al., 1994; Massagué and Wotton, 2000). All, but one of the highly conserved cysteine are involved in the formation of intrachain disulfide bonds, while the other cysteine forms a disulfide bond with another monomer forming a homo- or hetero-dimer (Massagué, 1990). Subsequent cleavage of the prodomains by subtilisin-like proteases forms the mature active GDF5 dimer that is secreted from the cell (Schreuder et al., 2005). The GDF5 is a ligand of BMP receptors (Type 1 and 2), results in activation of BMPR1B by trans-

Table 1
Phenotypic comparison of Grebe, Hunter–Thompson and Maroteux type of Acromesmelic Dysplasia.

Acromesomelic dysplasia type		Clinical presentation	Radiological findings	Gene involved
GREBE	**Adult Height**	Average adult size is 100 cm		*GDF5 & BMPR1B*
	Distal bones of the limbs:	Extremely short hands with toe-like fingers, occasionally polydactylous and absent joints, valgus deformity of feet	Fusion of carpals and metacarpals, fusion of tarsals and metatarsals, absence of several metacarpal and metatarsal bones, absence of proximal and middle phalanges	
	Proximal bones of the limbs:	Legs more severely affected than arms, Severe shortening and deformed femoral and tibial bones	Short femoral neck, absent tibial and fibular diaphyses, hypoplasia of the ulna, malformed radial head	
	Axial Skeleton:	Normal		
HUNTER–THOMPSON	**Adult Height**	Average adult size is 100–130 cm		*GDF5*
	Distal bones of the limbs:	Hands are less severely affected than feet. Feet are short and averted with globular toes. Normal distal phalanges.	Abnormally short metacarpals and phalanges, with phalanges almost square in shape, Single phalangeal bone in digit 5, abnormally shaped carpal bones	
	Proximal bones of the limbs:	Joint dislocations, Proximal to distal shortening	Short humerus, Hypoplastic femoral condyles, Curved radius with dislocated head and ulna, short femur, tibia and fibula along with dislocated ankle	
	Axial Skeleton:	Normal		
MAROTEUX	**Adult Height**	Average adult size is 120 cm		*NPR2*
	Distal bones of the limbs:	Short and broad fingers without fusions	Short and broad phalanges, metacarpal and metatarsal bones	
	Proximal bones of the limbs:	Shortening of middle and distal segments of proximal bones	Ulna shorter than radius, bowing of the radius	
	Axial Skeleton:		wedging of vertebral bodies with the dorsal margins being shorter than the ventral margins	