Review

Achondroplasia: From genotype to phenotype

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Abstract

This review focuses on the rheumatological features of achondroplasia, which is the most common skeletal dysplasia and the most frequent cause of short-limbed dwarfism. It is inherited in an autosomal dominant manner but results in the majority of cases of de novo mutations. The disease is related to a mutation in the fibroblast growth factor receptor-3 (*FGFR3*) gene encoding one member of the FGFR subfamily of tyrosine kinase receptors, which results in constitutive activation of the receptor. Biochemical studies of FGFR3 combined with experiments in knock-out mice have demonstrated that FGFR3 is a negative regulator of chondrocytes proliferation and differentiation in growth plate. This mutation induces a disturbance of endochondral bone formation. The diagnosis of achondroplasia is based on typical clinical and radiological features including short stature, macrocephaly with frontal bossing, midface hypoplasia and rhizomelic shortening of the limbs. The most common rheumatological complications of achondroplasia are medullar and radicular compressions due to spinal stenosis and deformities of the lower limbs. Current treatment and future therapies are discussed.
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1. Introduction

Achondroplasia is the most common hereditary form of dwarfism with an incidence rate between 1/15,000 and 1/40,000 live births. It is a fully penetrant autosomal dominant disorder and the majority of cases are the result of a de novo mutation [1]. The phenotype of achondroplasia is related to a disturbance in endochondral bone formation, due to a mutation in the fibroblast growth factor receptor-3 (FGFR3). Consequently, affected individuals exhibit short stature and often present with neurological and skeletal complications, which can be encountered in rheumatological practice. Most individuals with achondroplasia have normal intelligence. Although serious problems may arise during infancy, they affect only 5–10% of infants with achondroplasia [2].

Unexpected death occurs in approximately 2–5% of all infants with achondroplasia [3]. Children affected with achondroplasia commonly have otitis media and bowing of the lower legs. Less commonly, infants and children may have serious health consequences related to hydrocephalus, craniocervical junction compression, upper-airway obstruction, or thoracolumbar kyphosis [2]. The most common complication occurring in adulthood is related to lumbosacral spinal stenosis with compression of the spinal cord or nerve roots. This review focuses on the rheumatological aspects of this skeletal genetic disease [2].

2. Genetics of achondroplasia

The gene for achondroplasia was assigned in 1994 by linkage analysis to 4p16.3 [4]. Within few months, causative mutations in the fibroblast growth factor receptor-3 (FGFR3) were identified by the candidate gene approach independently by Shiang et al. and by Rousseau et al. [5,6]. The four FGFs

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receptors (FGFRs1−4) are members of the tyrosine kinase receptor family. They bind with variable affinity a polypeptide family that is composed of at least 18 members: the fibroblast growth factors (FGFs). These extramembraneous proteins are implicated in different cellular mechanisms such as angiogenesis, spatial patterning, apoptosis, growth and differentiation of various cells from mesenchymal and neuroectodermal origin [1,7−9]. The 4.4-kb cDNA of the *FGFR3* gene contains an open reading frame of 2520 nucleotides and consists of 19 exons and 18 introns. It encodes for a protein containing three domains: a large glycosylated extracellular ligand-binding domain consisting of three immunoglobulin subdomains, a single hydrophobic trans-membrane region and a split intracellular tyrosine kinase catalytic domain (Fig. 1).

Binding of the FGF ligands to the FGFR3 leads to activation and dimerization of the receptor that in turn, alters its conformation and activates its tyrosine kinase activity. This activation leads to autophosphorylation of selected tyrosine residues in the cytoplasmic domain of the receptor. The phosphorylated tyrosine residues stimulate MAP (microtubule associated protein kinases) cascade, which finally activates different intranuclear transcriptional factors [10].

In most cases of achondroplasia, the genetic abnormality is due to a mutation located within a critical region of the tyrosine kinase domain activation loop of FGFR3. In at least 98% of patients with achondroplasia, the mutation results in the substitution of arginine for a glycine residue at position 380 (Gly380Arg). Bellus et al. found that 150 of 154 unrelated achondroplasts had the G−A transition and only three had a G−C transversion at nucleotide 1138 of the *FGFR3* gene [11]. Nucleotide 1138 of the *FGFR3* gene is considered as the most sensitive point for germline mutation in the entire human genome [7]. Recently, Santos et al. have reported on a mother and daughter with hypochondroplasia caused by a new heterozygous double mutation at the same codon 380, but encoding a lysine instead of the usual arginine. These patients displayed a milder phenotype than the one encountered during achondroplasia [12]. Previous functional assays of these codon 380 amino acid substitutions demonstrated a lesser activation of receptor signaling by lysine compared

to arginine. At this date, other mutations (Gly375Cys, Gly346-Glu and Ser279Cyst) have been exceptionally reported [1,13] and interpreted as resulting from positive selection of spermatogonial cells owing to gain-of-function in the encoded protein [12]. As suggested by an increased paternal age at the time of conception, it has been demonstrated that the mutated allele is always from a paternal origin [7,14,15]. Interestingly, several diseases other than skeletal dysplasias are also associated with mutations in FRGR3. Indeed, it has been reported that seborrheic keratoses, epidermal nevi and urothelial carcinomas were also due to somatic FGFR3 mutations [16].

3. Effects of FGFR3 mutations on endochondral bone formation

The phenotype observed in achondroplasia is the consequence of severe disturbances in endochondral bone growth induced by abnormal activity of FGFR3.

3.1. Endochondral bone formation

Endochondral ossification, in which bone replaces pre-existing cartilage, is the predominant form of bone formation. In sharp contrast with the adult articular cartilage, the growth plate cartilage is characterized by an intensive mitotic activity and an important matrix proteins synthesis. Growth plate cartilage is arranged in four successive zones from epiphysis to metaphysis: (1) the reserve zone containing quiescent chondrocytes in small clusters of two or three cells, (2) the proliferative zone where chondrocytes undergo clonal expansion and divide rapidly to form organized longitudinal columns, (3) the hypertrophic zone where the cells enlarge and finally, (4) the mineralization zone (Fig. 2). During the late hypertrophic stage, the chondrocytes undergo apoptotic cell death. The cartilage matrix left behind provides a scaffold for osteoblasts that invade the cartilage mould along with local recruitment of blood vessels. This endochondral ossification leads to the progressive replacement of cartilage by bone
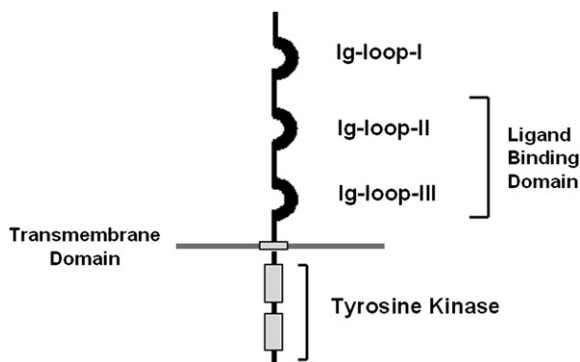

Fig. 1. The FGFR3 receptor is composed of an external part that consists of three immunoglobulin-like domains, and a trans-membrane element that extends to a cytoplasmic tyrosine kinase. The two membrane proximal immunoglobulin-like domains (loops 2 and 3) comprise the ligand-binding domain.
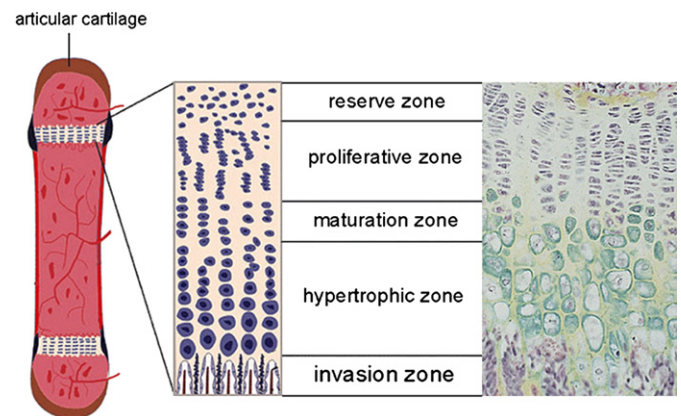

Fig. 2. During endochondral ossification, the chondrocytes progress through a complex differentiation process. Once fully differentiated, hypertrophic chondrocytes undergo cell death and participate in the mineralization of the cartilaginous matrix that is progressively replaced by bone.