Chapter 3

Genetic Determinants of Short Stature

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Abstract

Growth in height is a multifactorial process in which 80–90% of the contributing factors are genetic. The genes that determine the appropriate morphology and function of the skeletal and endocrinal system are the most being involved. Short stature is a clinical sign noted in conditions that intrinsically affect the growth plate, such as skeletal dysplasia, or in genetic syndromes such as Turner's, Silver-Russell, Noonan's, Cornelia de Lange's, Rubinstein-Taybi and Prader-Willi syndrome. Also, some endocrine diseases or chronic disorders can lead to change growth in the plate physiology, leading to short stature; the endocrine disorders are often genetically determined. Another category is idiopathic short stature, which is the most important in terms of frequency, and even though in this case, the aetiology is not proven; it seems that the genetic factors have the main role. In this chapter, the genetic syndromes with primary effect on growth are presented and the principal aim is to highlight the main clinical signs associated with short stature, which can lead to an easier clinical diagnosis of a genetic disease that mainly influence growth, thus facilitating the selection of the genetic test needed for the etiologic diagnosis in short stature.

Keywords: short stature, skeletal dysplasia, genetic syndromes, genetic testing

1. Introduction

Growth is defined as elongation and maturation of the bones and is a multifactorial process; more than 80% of growth is contributed by coordination of genetic factors [1]. Genetic influence is argued by the height difference observed in different ethnic populations or in different families. An argument for the role of environmental factors is done by the secular trend of growth observed in the last 150 years and is usually correlated with a better socio-economic status [2].

In order to understand the effect of genes on processes of growth, it is important to know about 'major genes' and 'minor genes' [3]. 'The major genes' have a critical role on growth, and single mutations in them usually results in growth pathology (monogenic disorders) [3]. Mutations of 'the minor genes' only provide a susceptibility for growth abnormalities (multifactorial disorders) [3] whose effect being validated as a disease when multiple genetic and environmental factors act together.

A mutation of a 'major gene' (monogenic disease) is usually considered, when the short stature is severe, under -3DS or when the short stature is associated with malformative syndrome or/and dysmorphic features or/and intellectual disability or there is an evidence for skeletal dysplasia or microcephaly or small for gestational age (SGA) without catch-up growth or severe growth hormone (GH) deficiency or multiple pituitary hormones deficits [4]. The mutations of 'minor genes' are usually conducted to a growth phenotype that is only slightly affected (familial or constitutional short stature), this effect being multifactorial determined.

Concerning 'the minor genes', the genome-wide association studies (GWAS) demonstrated that there are more than 180 genetic variants correlated with growth, on autosomes, with independent, additional effect of 0.2–0.6 cm for every allele [5, 6]. Also, it was also observed that there are two types of genes: 'height genes', having the main role in adult height, and 'tempo genes' , important for the starting moment of the different processes of growth [6, 7]. Genetic factors act mainly through skeletal and endocrine systems.

Short stature represents a height under -2DS for the average of general population of the same age, sex and ethnicity. A useful classification of the aetiology in short stature divides it into primary, secondary and idiopathic short statures.

Primary short stature includes intrinsic conditions of the growth plate (15–20% of cases) [8], such as skeletal dysplasia, genetic syndromes (Turner, Down, DiGeorge, Silver-Russell, Noonan, Cornelia de Lange, Rubenstein-Taybi, Prader-Willi and neurofibromatosis type I) and SGA with failure of catch-up growth.

Secondary short stature refers to conditions that change growth plate physiology (30–35% of cases) [8], such as endocrine disorders, chronic disorders in different organ and systems, insufficient nutrient intake (malnutrition) and metabolic or psychosocial disorders.

Idiopathic short stature (50% of cases) [8] includes familial short stature, non-familial short stature and constitutional growth and puberty delay.

In every category, the genetic aetiology is obvious for a great number of disorders, especially in primary short stature and endocrine disorders. Even in idiopathic short stature, it was observed that in more than 20% of cases, there is a subtle skeletal dysplasia that is also genetically determined [9], 4% of them were demonstrated to have short stature homeobox (SHOX) gene deletion [10]. Also in familial idiopathic short stature, the genetic background is evident.

In this chapter, the disorders included in the category primary short stature, where genetic factors have a clearer contribution and where usually one major gene is implicated in the processes of abnormal growth, will be mainly presented. In the genetic evaluation of a child

with short stature, 'the major genes' are usually searched, the others, such as 'minor genes', give only a predisposition and are considered only after the exclusion of the major factors. An adequate genetic evaluation usually facilitates decisions about therapeutic intervention and gives clues about the prognosis.

2. Genetic disorders with primary effect on growth

2.1. Skeletal dysplasia

The specific clinical trait of the skeletal dysplasia is a disproportionate short stature, with associated signs such as shorter and bowed long bones, shorter ribs, polydactyly, impaired bone density and bone modelling, disorganized development of growth cartilage and ossification defects. Growth retardation is seen in some skeletal dysplasia beginning with intrauterine life or, for others, has a post-natal onset in the first year of life or even later in some cases. The diagnosis is usually established by clinical and radiological signs. Molecular analysis for confirmation is required particularly in the situation of genetic counselling in order to evaluate a future pregnancy by pre-natal diagnosis. Otherwise, sometimes a skeletal dysplasia can be diagnosed even for a patient with isolated short stature, apparently proportionate, whom only a radiological assessment may show the signs of dysplasia [9].

Skeletal dysplasia is a group of disorders, and is very heterogeneous; clinically and molecularly, more than 400 syndromes have been described, the more recent classification dividing them into 40 principal groups [11]. Skeletal dysplasia without identified molecular bases is also identified. In the following section, the most common and molecularly well-characterized skeletal dysplasia are presented.

2.1.1. The FGFR3-related chondrodysplasias

The *FGFR* gene (4p16.3) encodes for *fibroblast growth factor receptor 3* that has a main effect in the regulation of chondrocyte proliferation, differentiation and apoptosis [12, 13]. *FGFR3* regulates osteogenesis and post-natal bone mineralization by osteoblasts, the main role being in endochondral ossification [12, 13]. It has an extracellular region with three immunoglobulin-like domains, a transmembrane domain and an intracellular region with tyrosine kinase domains. Mutations in *FGFR3* gene lead to several syndromes with a phenotype more or less severe according to the affected region of the receptor, such as achondroplasia, hypochondroplasia, SADDAN syndrome (Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans) and thanatophoric dysplasia. The *FGFR3* mutations responsible for these syndromes are mutations with gain of function, inducing an activation of the receptor.

2.1.1.1. Achondroplasia

It is the most known form of disproportionate short stature and has a frequency of 1:25,000 births. In achondroplasia, *FGFR3* gene mutations affect the transmembrane region of the receptor [14]. Note that 98% of cases show G1138A mutation, an additional 1% of cases

presenting the G1138C mutation [15, 16]. Achondroplasia is an autosomal dominant disorder with complete penetrance. About 80% of cases occur as a result of *de novo* mutations, often produced in paternal gametes, usually in case of an advanced paternal age at procreation [17]. These mutations are activating ones and affect mainly the endochondral ossification, with impact on hypertrophic cellular compartment, chondrocyte proliferation in growth cartilages and cartilage formation [12, 13].

Disproportionate short stature is a characteristic of the disease, adult height usually not exceeding 125–130 cm. The clinical picture is represented by the specific skeletal features: short rhizomelic limbs, relative macrocephaly, frontal bossing with mid-face hypoplasia, trident hands and hyperlordosis. The patients had associated with hypotonia (at young age) and obesity (often in adults).

2.1.1.2. Hypochondroplasia

Hypochondroplasia is a pathology often produced by *FGFR3* mutations in the extracellular or intracellular region in the proximal tyrosine kinase domain [16]. In 70% of cases, *FGFR3* mutations are described [18]. Some authors have noticed, in some cases, the association of hypochondroplasia with *IGF1* mutations [19]. There are some cases for which genetic determinant is not yet identified. Thus, unlike the achondroplasia, the hypochondroplasia is characterised by genetic heterogeneity.

The clinical picture is that of a mild achondroplasia and is represented by disproportionate short stature with short limbs but without an obvious rhizomelia, brachydactyly affected spine by narrowing the interpediculate distance at the lumbar level [20]. Final height is not as severely affected as in achondroplasia and is usually in the range 130–165 cm.

2.1.1.3. SADDAN syndrome

SADDAN syndrome is a severe form of achondroplasia associated with developmental delay and *acanthosis nigricans*, the name of syndrome being an acronym of the main clinical signs. In these disorders, a *FGFR3* missense mutation Lys650Met was described, located at the distal tyrosine kinase domain [21]. This mutation is located in the same codon as the specific mutations that produce thanatophoric dysplasia.

Patients have bone dysplasia as described in achondroplasia, but more severe are important short stature, micromelia, macrocephaly, frontal bossing, wide anterior fontanelle, mid-face hypoplasia, bowed tibia and narrow thorax [22]. In addition, they also have progressive *acanthosis nigricans*, CNS abnormalities, epilepsy and severe developmental delay [21]. SADDAN syndrome clinically overlaps with thanatophoric dysplasia, but survival in the first one is beyond the neo-natal period, cases with this pathology are even reported in young adulthood.

2.1.1.4. Thanatophoric dysplasia

It is the most common lethal skeletal dysplasia in the neo-natal period. Two subtypes have been described: thanatophoric dysplasia type I, caused by mutations in the extracellular or

intracellular region of *FGFR3* gene, and thanatophoric dysplasia type II, which is produced by mutations at the distal tyrosine kinase domain [23, 24]. The most common mutation in type I is R248C, confirmed in about 50% of the patients [24]. In type II, the K650E mutation is the only one reported, which is present in more than 99% of the patients [23, 24].

The two forms of thanatophoric dysplasia were divided according to the clinical picture. In type I, the clinical characteristics are the short and bowed long bones with skull normal appearance [25, 26]. In type II, the traits are represented by the cloverleaf skull with short and straight long bones [25]. Other associated signs, common to the two types are: platyspondyly, narrow and short thorax, ventriculomegaly and polyhydramnios [25].

2.1.2. Disorders produced by abnormalities of collagen and other extracellular structural protein

2.1.2.1. Osteogenesis imperfecta

It occurs in 95% of cases due to *COL1A1* (17q21.33) and *COL1A2* (7q21.3) mutations, genes encoding α1 and α2 polypeptide chains of type I collagen [27]. Type I collagen is the most abundant collagen found in extracellular matrix protein and it is mainly present in cartilage, bone, ligaments, tegument, dentin and sclera [28, 29]. Its role is structural, which interacts with other matrix proteins (proteoglycans or fibronectins) and with the cells by anchoring them into the matrix. A functional role was also described in signalling receptors on surface cells to regulate cell growth, motility and differentiation [28–30].

The mutations of the chains of type I collagen lead to quantitative or qualitative impairment and the clinical picture will be represented by the signs of the organs more abundant in type I collagen: bones, articulations, dentin and sclera. These signs are multiple fractures arisen usually after minor traumatisms, bone deformities, short stature, osteoporosis, joint hyperlaxity, *dentinogenesis imperfecta*, blues sclera, deafness and wormian bones. The skeletal impairment is secondary to osseous fragility and osteopenia. Short stature is observed usually secondary to the pathologic bone and its deformities. There are several clinical forms of osteogenesis imperfecta, with different degree of severity. In 1979, Sillence and colleagues described the four classical types of osteogenesis [31]. The actual classification includes fifteen types, the first four being the known ones, produced by type I collagen mutations, the others being the result of different gene mutations. Type I is a mild non-deforming form of osteogenesis imperfecta, with a blue sclera and a little or absent effect on growth. Type II is the most severe form, lethal in the peri-natal period. The clinical picture is represented by an important osteopenia that leads to multiple fractures, secondary deformities and very short length from the intrauterine period. Type III has also a severe phenotype, but less than the type II, represented by very short stature, deformities, *dentinogenesis imperfecta* and blue sclera. Type IV has an intermediate severity with a mild short stature, moderate deformities after recurrent fractures, *dentinogenesis imperfecta* and normal sclera. If the chains of type I collagen are affected, the transmission is autosomal dominant. In 5% of cases, osteogenesis imperfecta is secondary to mutations of different genes, such as *SERPINF1* (17p13.3), *LEPRE1* (1p34.1), *CRTAP* (3p22), *PPIB* (15q21-q22), *SERPINH1* (11q13.5), *FKBP10* (17q21.2), *SP7* (12q13.13), *BMP1* (8p21.3),

TMEM38B (9q31.2) and WNT1 (12q13.12); these disorders having an autosomal recessive transmission, usually with a severe clinical phenotype [27].

2.1.2.2. Skeletal dysplasia in type II collagen abnormalities

Type II collagen is mostly found in cartilage, intervertebral disc and eye, and various mutations lead to a group of diseases that have in common the abnormalities of epiphysis, spine and eyes, which can easily be recognized by the signs in these structures [32]. The disorders of this group of pathologies are specifically produced by different mutations of the same gene *COL2A1* (12q13.11) that encodes for α1 chain of type II collagen [32]. The majority of *COL2A1* mutations were observed in the triple-helical region of alpha 1 chain [33]. These disorders have an autosomal dominant transmission. However, they are often produced by *de novo* mutations and show a great variability of clinical expression.

2.1.2.2.1. Achondrogenesis

Achondrogenesis is one of the most severe skeletal dysplasia, with an important lethality, in foetal life or in the neo-natal period. There are two forms that differ by the type of transmission (type I, recessive, and type II, dominant) and by the length and structure of long bones. The clinical picture is characterized by very small length, extreme micromelia, very short trunk, vertebral, skull and pelvis ossification defects, cupping metaphysis, cystic hygroma and polyhydramnios [34]. Type II is secondary to neo-mutations in type II collagen and is less severe than achondrogenesis type I that is produced by *TRIP11* or *DTDST* mutations. Achondrogenesis type II is the most severe pathology of type II collagen group of disorders. Hypochondrogenesis represents a mild form of achondrogenesis type II and is also produced by mutations in type II collagen [35].

2.1.2.2.2. Spondyloepiphyseal dysplasia congenita

It is characterized by poor somatic growth since intrauterine life. An important associated sign is vertebral dysplasia, usually seen as platyspondyly. Other abnormalities often seen in this disorder are cleft palate, ophthalmologic abnormalities (myopia, nystagmus, cataracts and retinal detachment) and deafness. Short stature is also an important sign in the post-natal period, the height not exceeding 130 cm, other signs of skeletal dysplasia being deformation of femoral head with a secondary *coxa vara*, scoliosis and impaired cervical spine [36]. There is a significant clinical variability, the clinical spectrum including various forms of severity. The responsible mutations that occur are missense mutations that substitute bulky amino acids for glycine residues in the triple-helical region of α1 chain of type II collagen [33].

2.1.2.2.3. Kniest dysplasia

Kniest dysplasia is characterized by extreme short stature, prominent joints, especially in knee, and mid-face hypoplasia. It is also associated with myopia, deafness or cleft palate. At vertebral region, platyspondyly can be seen with vertical clefts, kyphoscoliosis or hyperlordosis [37]. Epiphysis is generally large, especially in the knee. The femoral head is often absent due to a

developmental defect of the femoral epiphysis and the iliac bones are characteristically shaped [37]. In Kniest dysplasia, the α1 chain of type II collagen is modified by exon skipping due to splice-site mutations in the region encoding the triple-helical region [33].

2.1.2.2.4. Stickler dysplasia type I

Stickler dysplasia is characterized by genetic heterogeneity, the mutations in type II collagen or type XI collagen being responsible for this pathology. The abnormalities of type II collagen lead to Stickler dysplasia type I. The haploinsufficiency of truncation mutations that occur in the triple-helical region of α1 chain of type II collagen is responsible for the phenotype [33]. This syndrome also presents a clinical variability. The main clinical signs are represented by skeletal and ophthalmologic disorders (high myopia and retinal detachment), auditory abnormalities (deafness) and craniofacial dysmorphia (mid-face hypoplasia, micrognathia, midline cleft of the face and Pierre Robin sequence) [38, 39]. The patients usually present a short stature associated with a moderate spondyloepiphyseal dysplasia [39]. Radiologic signs are often minor, such as discreet flattening and irregularities at the epiphyseal region or a minimum platyspondyly, especially in the dorsal region. Patients associate widening joints, especially in the knee, and osteoarthritis with early onset [39].

2.1.2.3. Skeletal dysplasia in type IX collagen, cartilage oligomeric matrix protein (COMP) and matrilin 3 (MATN3) abnormalities

Type IX collagen, *cartilage oligomeric matrix protein* and *matrilin 3* are components of the cartilage extracellular matrix that strongly interacts to maintain cartilage assembly and integrity [40, 41]. A mutation of one of these components modifies the secretion of the others and the common pathology produced for each gene mutation is multiple epiphyseal dysplasia (MED) [41]. The pathogenesis is represented by the impairment of endochondral ossification due to cartilage abnormalities.

There are six types of MED produced by mutations of *COMP* (19p13.1) (MED type I), *COL9A2* (1p32.2–33) (MED type II), *COL9A3* (20q13.3) (MED type III), *DTDST* (5q32–33) (MED type IV), *MATN3* (2p23–24) (MED type V) and *COL9A1* (6q13) (MED type VI) [11]. With the exception of MED type IV, all these disorders are transmitted in autosomal dominant manner. All these types share a common clinical picture; some particularities being observed in each type. The most specific signs of these disorders are short stature and precocious osteoarthritis. Characteristically, the patients present pain and precocious fatigability when a physical activity is initiated. The phenotypic signs are observed only post-natally, after an apparently normal initial development. Even if the skeletal impairment is generalized, the bones of inferior limbs are more frequently involved, being often observed an angular deformation at this level, such as *coxa vara*, *genu varum*, *genu valgum* and *valgum* deformities at the distal tibia.

The mutations of α1, α2 or α3 chain of type IX collagen (*COL9A1, COL9A2, COL9A3*) are associated with a preponderant impairment of the knee [42].

In *COMP* mutations, the impairment of proximal femur and acetabulum is particularly observed [43].

In *MATN3* mutations, the clinical picture is similar with that observed in *COMP* mutations, but less severe [44].

2.1.2.4. Skeletal dysplasia in type X collagen abnormalities

Type X collagen also has an important role in endochondral ossification, influencing the compartmentations of different matrix components and also the regulation of the mineralization [45].

2.1.2.4.1. Metaphyseal chondrodysplasia, Schmid type

It is produced by mutations of α1 chain of type X of collagen gene (*COL1A10*) (6q21–22.3), and the transmission of the disorder is autosomal dominant. It is characterized by moderately short stature with post-natal onset, the size at birth being within normal limits. Radiography showed irregularities in the metaphysis of long bones. The consequence of *COL10A1* mutations is the bowing and the shortening of the long bones, *coxa vara* being usually observed. Often, the patients may develop the spine impairment, such as mild platyspondyly or other abnormalities of the vertebral body.

2.1.2.5. Skeletal dysplasia in type XI collagen abnormalities

Type XI collagen has an important interaction with type II collagen, helping in maintaining the spacing and the architecture of the type II collagen. Two polypeptide chains, α1 and α2, contribute to the formation of type XI collagen; the genes that encode these chains being *COL11A1* (1p21) and *COL11A2* (6p21.3). The mutations in these genes lead to a clinical phenotype of skeletal dysplasia overlapping with that produced by type II collagen abnormalities.

2.1.2.5.1. Stickler dysplasia type II

It is the consequence of *COL11A1* mutations. These mutations lead to a clinical picture similar to that described in Stickler syndrome type I (see Section 2.1.2.2.4), the main clinical signs being the consequence of skeletal, ophthalmologic and auditory impairments. However, the clinical severity is higher in terms of ophthalmologic (severe myopia, bilateral retinal detachment) and auditory (deafness) phenotypes [46]. The craniofacial dysmorphic features that are specific for Stickler syndrome type I or II are as follows: mid-facial hypoplasia, midline clefting and retromicrognatia (Pierre Robin syndrome). The short stature is also seen associated with hip abnormalities, such as slipped capital femoral epiphysis and mild thoracolumbar spinal abnormalities that often lead to scoliosis [47, 48]. The disease has an autosomal dominant transmission.

2.1.2.5.2. Otospondylomegaepiphyseal dysplasia (OSMED syndrome)

This dysplasia is the consequence of *COL11A2* mutations and is also called non-ocular Stickler dysplasia. The disease has an autosomal recessive transmission. Skeletal similarities with Kniest dysplasia is noticed, but without ophthalmologic involvement. However, the hearing

impairment is much more important. Thus, the clinical picture is represented by sensorineural hearing loss, disproportionate short stature with micromelia, enlarged epiphyses and spine abnormalities, and dysmorphic facial features [49].

2.1.2.6. Sulfation disorders group

In this group of disorders, the main gene mutated is *DTDST* (5q32–33) that encodes for sulphate transporter SLC26A2 that influences the sulfation of proteoglycans in cartilage matrix [50]. The pathologies of this group are autosomal recessives, in contrast to the previously presented anomalies that are characterized by autosomal dominant inheritance. The disorders produced by *DTDST* mutations are diastrophic dysplasia, achondrogenesis type IB, atelosteogenesis type II and MED type IV [11].

2.1.2.6.1. Diastrophic dysplasia

It is characterized by disproportionate growth retardation with micromelia, debuted in prenatal period [51]. Progressively, after birth, multiple joint contractures occur, especially in the shoulders, elbows, hip and interphalangeal joints [52]. At birth, the congenital club foot, the hypoplasia of the first metacarpal, thumb subluxation or cervical subluxation is also noted. Long bones are short and large [52]. There is a progressive scoliosis. Other specific features are the cysts observed at the ear pavilion [52]. Radiographic findings are metaphyseal widening and epiphyseal dysplasia.

2.1.2.7. Skeletal dysplasia in perlecan disorders

The perlecan is a heparan sulphate proteoglycan that acts as a co-receptor for *FGF2*, thus having a role in intercellular adhesion and in promoting cells proliferation and angiogenesis. The mutations of gene encoding perlecan (*PLC*, 1q36–34) induce different skeletal disorders transmitted by autosomal recessive mode: dyssegmental dysplasia, Silverman-Handmaker type; dyssegmental dysplasia, Rolland-Desbuquois type; and Schwartz-Jampel syndrome [11].

2.1.2.7.1. Dyssegmental dysplasias

They are represented by two disorders, Silverman-Handmaker and Rolland-Desbuquois, which are the forms of neo-natal short-limbed dwarfism. Both are produced by different mutations of the same gene, *PLC*. The Silverman-Handmaker type is the most severe, being lethal in peri-natal period, compared to Rolland-Desbuquois, which is less severe [53]. The skeletal abnormalities are represented by vertebral segmentation associated with long bones impairments that are shorter, larger and bowed [54]. The vertebral segmentation is observed as marked differences in size and shape of vertebral bodies. A reduced joint mobility is often associated. A cleft palate as well as the encephalocele was described.

2.1.2.7.2. Schwartz-Jampel syndrome

It is characterized by short stature, myotonic myopathy, joint contractures, *pectus carinatum*, kyphosis, *coxa valga*, myopia and blepharophimosis [55, 56]. Radiological abnormalities

include platyspondyly, short long bones with metaphyseal widening, wide epiphysis of the distal femur and tibia, and fragmented capital femoral epiphysis.

2.1.2.8. Skeletal dysplasia in aggrecan disorders

The aggrecan, also known as cartilage-specific proteoglycan core protein (CSPCP), is a chondroitin sulphate proteoglycan, the most abundant structural component in the cartilage. It leads to a normal chondroskeletal morphogenesis and it also provides a hydrated gel structure in articular cartilage that is important for its resistance [57]. Different mutations of the gene that encodes for aggrecan, *AGC1* (15q26), are responsible for different diseases: spondyloepiphyseal dysplasia, Kimberley type; spondyloepimetaphyseal and metaphyseal dysplasia, aggrecan type; and familial osteochondritis dissecans [11].

2.1.2.8.1. Spondyloepiphyseal dysplasia, Kimberley type

It leads to a proportionate short stature, osteoarthritis with early onset and sometimes to a craniofacial dysmorphia [58]. It is also defined by platyspondyly, vertebral cleft, metaphyseal widening, epiphyseal irregularities and flattening of femoral epiphysis. It is an autosomal dominant pathology.

2.1.2.9. Skeletal disorders in transient receptor potential vanilloid 4 (TRPV4) abnormalities

Transient receptor potential vanilloid 4 (12q24.1) mediates calcium influx, late in osteoclast differentiation, thus influencing bone resorption [59]. *TRPV4* mutations produce not only skeletal pathologies but also non-skeletal (such as spinal muscular atrophy, Charcot-Marie-Tooth disease). The skeletal disorders are transmitted in autosomal dominant mode and include metatropic dysplasia; spondyloepimetaphyseal dysplasia, Maroteaux type; spondylometaphyseal dysplasia, Kozlowski type; brachyolmia; and familial digital arthropathy with brachydactyly [11].

2.1.2.9.1. Metatropic dysplasia

It is a severe form of skeletal dysplasia, often lethal in the neo-natal period, and is characterized by important disproportionate short length in newborn with micromelia, wide metaphyses, platyspondyly, severe kyphoscoliosis, iliac areas in halberd, and limitations and enlargements of the joints [60].

2.1.3. Defects in intracellular structural proteins

2.1.3.1. Filamin group

Although these intracellular structural proteins are expressed in all cells, it has been observed that their mutations often induce a very severe skeletal pathologic phenotype. The filamin A and B are cytoskeleton proteins, their role being structural, in signal transduction, in transport or in intracellular and extracellular communication. Their mutations lead to the absence of some bones or to joint dislocations.

2.1.3.1.1. Filamin A disorders

Mutations of filamin A gene (*FLNA*, Xq28) lead to dominant X-linked disorders. These are: frontometaphyseal dysplasia, otopalatodigital syndromes type I and type II, Melnick-Needles syndrome and terminal osseous dysplasia with pigmentary defects [11].

Frontometaphyseal dysplasia is characterized by skeletal dysplasia, urogenital abnormalities and deafness. Otopalatodigital syndrome type I is characterized by auricular impairment, cleft palate and mild skeletal damage. Type II shows a more pronounced skeletal clinical picture associated with multiple internal malformations (brain, heart and digestive). The Melnick-Needles syndrome is the most severe disorder of filamin A group, being lethal, most often for intrauterine life.

2.1.3.1.2. Filamin B disorders

Mutations of filamin B gene (*FLNB*, 3p14.3) lead to different disorders transmitted in autosomal dominant (the majority) and recessive mode (spondylo-carpal-tarsal dysplasia). These disorders are atelosteogenesis type I, atelosteogenesis type III, Larsen syndrome and spondylocarpotarsal syndrome [11].

Many of these diseases are lethal in the early neo-natal period. In spondylocarpotarsal syndrome, spine fusions were observed. The fusions also implied the carpal and tarsal bones. On the other hand, a hyperlaxity was observed in some joints.

2.1.4. Disorders associated with SHOX gene mutations

Short stature homeobox gene belongs to the paired homeobox family and is localized in the pseudoautosomal region 1 (*PAR1*) of X (Xp22) and Y (Yp11.3) chromosomes. *SHOX* gene is expressed in hypertrophic chondrocytes of the growth plate, having a role in regulating chondrocyte differentiation [61, 62]. The diseases associated with *SHOX* gene abnormalities are Leri-Weill dyschondrosteosis (heterozygous mutations and deletions) and Langer mesomelic dysplasia (homozygous mutations). The skeletal features of Turner syndrome are also a consequence of *SHOX* gene haploinsufficiency. Otherwise, *SHOX* gene mutations were observed at 2–5% of patients with idiopathic isolated short stature [63–65].

SHOX gene is an important determinant of growth, *SHOX* deletions being associated with short stature and *SHOX* duplications with tall stature. *SHOX* gene is expressed in the first and second pharyngeal arches and also in elbow, radius, ulna, and wrist and in the equivalent bones of inferior limbs [66]. Thus, the clinical picture in *SHOX* deficiency is represented by short stature, mesomelia with shortening and bowing of the forearms and tibia, *cubitus valgus*, Madelung deformity of the wrist, brachymetacarpia, brachymetatarsia, high-arched palate, micrognathia and short neck [67]. *SHOX* gene deficiency leads to a marked phenotypic variability, even for the same mutation or in the same family. The clinical picture is more expressed in females and is usually more evident in the beginning of the puberty [68].

2.1.4.1. Leri-Weill dyschondrosteosis

It is the most common form of mesomelic dysplasia and is characterized by disproportionate short stature (145–155 cm) with mesomelia and Madelung deformity [67]. There is an important clinical variability, even in the same family, the females often being more affected. Short stature is observed from the childhood, even from the first year and usually the amplitude of the growth deficiency is correlated with the degree of wrist deformity [67]. The causes of Leri-Weill dyschondrosteosis are heterozygous mutations or deletions of *SHOX* gene.

2.1.4.2. Langer mesomelic dysplasia

It is secondary to homozygous mutations of *SHOX* gene and the clinical picture is represented by severe short stature (-6DS and -7DS) with severe abnormalities of the limbs: hypoplasia and aplasia of the ulna and fibula [67].

2.2. Genetic syndromes with primary effect on growth

2.2.1. Turner syndrome

The Turner syndrome is due to complete or partial loss of one of the two sex chromosomes, homogeneous or in mosaic, in a female patient. Only 50% of the cases present the classical homogeneous monosomy 45,X, the other half having X chromosome mosaicism, X chromosome structural abnormalities (deletions, ring chromosome and isochromosome) or Y chromosome abnormalities (2–5%). The phenotypic features are represented by short stature, dysmorphic syndrome, gonadal dysgenesis and internal malformations. There is a great variability of phenotypic traits, clinical spectrum including complete forms and more often partial forms, represented sometimes only by short stature.

Short stature is the most constant clinical sign, observed in up to 98% of patients [69, 70]. It is secondary to SHOX gene haploinsufficiency. The growth retardation might be seen in about half of patients beginning with pre-natal life [70]. In the others, the short stature will be developed usually after the age of 3–4 years, due to a diminished velocity of growth. The growth worsens progressively until 10 years and the lack of puberty growth spurt will accentuate the deficit. Finally, height will be usually between the interval 122–147 cm [71].

The dysmorphias include triangular face, epicanthus, down-slanted palpebral fissure, macrostomy, high-arched palate, dental abnormalities, micrognathia, low posterior hair insertion line 'in trident', *pterygium colli*, large thorax, *cubitus valgus*, short IV and/or V metacarpals, *genu valgum*, extremities lymphedema at birth, multiple pigmented nevi and dysplastic nails [70].

The puberty delay is one of the most common signs being observed in up to 95% of cases [70].

Most patients with Turner syndrome show a normal intellectual development, excepting those presenting ring X chromosome, who often present intellectual disability [72].

Cardiovascular malformations are particularly important in terms of evolution and prognosis, being found in 25–40% of cases [69, 70]. The most specific cardiac abnormalities are bicuspid

aortic valve and aortic coarctation. Reno-urinary malformations are observed in 40–60% of the cases, the most representative being horseshoe kidney, polycystic kidney, renal agenesis and duplicated collecting system [71].

Bone abnormalities, affecting more than 60% of patients, have a significant contribution to the external phenotype of the Turner syndrome. Typically, these patients present a lower value for upper segment/lower segment ratio, short neck, large thorax, scoliosis, kyphosis, *cubitus valgus*, Madelung deformity, congenital hip dislocation, *genu valgum*, and short IV and/or V metacarpal and metatarsal [63, 70].

2.2.2. Russell-Silver syndrome

It represents a genetic pathology in which the short stature is the most specific sign. It is very heterogeneous in terms of genetic aetiology and in many cases (about 50%) with typical clinical picture, the aetiology is unknown. Note that 40% of patients present hypomethylation of imprinting centre 1 (IC1) (*H19*, 11p15) [73, 74]. This hypomethylation could occur by epigenetic mechanisms or by duplications of maternal chromosome in 11p15 region. About 10% of patients present maternal uniparental disomy of chromosome 7 [73]. There were reported cases with 17q25 translocations, ring chromosome 2 or other structural abnormalities of 1, 15 or X chromosomes that also had a clinical phenotype of Russell-Silver syndrome [75–77].

The clinical picture is specifically represented by intrauterine growth retardation without catch-up growth in the first year of life [78]. This deficit is maintained or it gets even worse over time, the adult height being lower than -3DS for average height. At birth, the weight is more impaired than height. The head circumference is normal for age, being in contrast with a lower height, thus the patient has an appearance of macrocephaly. The craniofacial dysmorphias include triangular face, high forehead, micrognathia and down-slanted oral commissures. The limbs are often asymmetrical and a clinodactyly or a camptodactyly of one (fifth finger) or more fingers can be frequently observed. Eating difficulties in infancy, fasting hypoglycemia in infancy and childhood, global developmental delay and cognitive impairments (at about 50% of patients) were also observed. Bone age is retarded, and the radiography also shows a hypoplasia of middle phalanx of fifth finger, which give the appearance of clinodactyly (observed in up to 80% of patients). Sometimes, the patients associate urogenital (hypospadias) or cardiovascular malformations.

2.2.3. Noonan syndrome

This syndrome is very heterogeneous as aetiology, and usually, all the gene mutations described are acting on the signal transduction pathway *RAS/RAF/MEK/ERK* that has a role in regulating cell growth. About 50% of patients have mutations in *PTPN11* gene [79]. An additional percentage of 30% shows mutations in *SOS1* gene and *RAF1* gene. Other gene mutations that lead to Noonan syndrome phenotype are *KRAS*, *NRAS*, *BRAF* and *MAP2K1* [79].

The characteristic features of Noonan syndrome are short stature, craniofacial dysmorphic features, cardiac malformation and thoracic deformity. Short stature has a post-natal onset.

The dysmorphias are represented by triangular face, down-slanted palpebral fissure, hypertelorism, low-set ears and *pterygium colli*. Note that 80% of patients have cardiovascular malformations. The most frequent is pulmonary artery stenosis. About 30% of patients may present hypertrophic cardiomyopathy. Thorax deformation can be *pectus excavatum* or *pectus carinatum*. The patients can associate cryptorchidism (50% of male patients), kidney abnormalities, bleeding disorders, articular hyperlaxity, lymphedema, multiple nevi, hypotonia and epilepsy. The intellectual disability is observed in about 25% of cases.

2.2.4. Cornelia de Lange syndrome

About 50% of patients with Cornelia de Lange syndrome show mutations in *NIPBL* gene [80]. Rarer mutations have been described for *SMC1L1*, *SMC3* and *RAD21* genes [80].

It is characterized by pre- and post-natal growth retardation, characteristic craniofacial dysmorphic features (narrow forehead with low hair insertion line, synophrys, nostrils anteversion, prognathism, long philtrum, thin lips and down-slanted oral commissures) intellectual disability, upper limbs abnormalities and hypertrichosis. Male patients often present hypospadias and cryptorchidism. Cardiovascular malformations, ophthalmologic abnormalities, deafness, behaviour disorders, global developmental delay, epilepsy and ophthalmologic abnormalities were described. There is a wide phenotypic variability of the syndrome, even some cases with normal IQ have been described.

2.2.5. Rubinstein-Taybi syndrome

This syndrome is also characterized by genetic heterogeneity: *CREBBP* mutation (30–50% of cases), *CREBBP* deletion/ duplication (10–20%), 16p13.3 deletions (including CREBBP) (below 10%) and *EP300* mutation (5%) [81].

Clinically, it is characterized by short stature with post-natal onset, intellectual deficiency, characteristic craniofacial dysmorphia (prominent beaked nose, downslanted palpebral fissures, upper jaw hypoplasia, high arched palate, low-set ears, thin superior lip, microcephaly), and broad thumb with radial angulation, broad hallux, syndactyly, eating difficulties and respiratory disorders in infancy. These patients associate language retardation, hypotonia, cardiac malformations or cryptorchidism.

2.2.6. Prader-Willi syndrome

The Prader-Willi syndrome is the result of paternal loss of imprinted 15q11.2-13 region. This is produced through deletions (70% of cases), uniparental maternal disomy (28%), unbalanced translocations (1%) or mutations in imprinting centre (1%) [82]. Several genes are located in this region, whose function has been already associated with various phenotypic traits of Prader-Willi syndrome (*SNRPN* gene with brain expression, *P* gene with oculocutaneous albinism and *NDN* gene with brain expression) [83].

Most of the clinical specific signs are due to hypothalamic impairment. The clinical presentation is variable, depending on age. Infants with Prader-Willi syndrome show generalized

hypotonia, eating difficulties, males with genital abnormalities (cryptorchidism and scrotal hypoplasia) and motor acquisition delays. After the age of 2, children progressively develop obesity due to hyperphagia. A gradually slowdown in growth, the short stature being often installed before pubertal age and accentuated thereafter by the lack of pubertal growth spurt were also noticed. Most patients also have a deficiency of GH, for which a hormonal treatment is proposed, which also ameliorate the associated metabolic abnormalities. The hypothalamic involvement also induces a hypogonadotropic hypogonadism manifested by cryptorchidism and hypospadias in males or delayed puberty in both sexes, which requires hormonal substitution therapy. Often, the intellectual deficiency is mild. Lifespan is usually influenced by the complications of morbid obesity, often seen in the patients with sleep apnoea, diabetes, atherosclerosis and cardiovascular complications.

2.2.7. Kabuki syndrome

The genes involved in Kabuki syndrome are *KDM6A* (Xp11.3) and *KMT2D* (12q13.12) [84].

Clinically, it is characterized by short stature with post-natal onset, global developmental delay/intellectual disability, specific craniofacial dysmorphia (long palpebral fissures, ectropion in the third external region of the upper eyelid, sparse eyebrow in third external region, flattening of the nasal pyramid, large and prominent ears, high arched palate and cleft palate), scoliosis, fifth finger brachydactyly and persistence of finger pads. The associated skeletal abnormalities are spine anomalies, often with vertebral cleft, hip joint abnormalities and fifth finger brachydactyly. Cardiovascular malformations are associated in 50% of cases (Tetralogy of Fallot, atrial septum defects or ventricular septum defects). The characteristic craniofacial dysmorphias, post-natal growth retardation and intellectual disability are among the cardinal manifestations of the disease.

2.2.8. Williams syndrome

Williams syndrome is secondary to recurrent deletion in 7q11.23 region comprising elastin gene (*ELN*).

The specific features are craniofacial dysmorphias, cardiovascular malformation, short stature, neuropsychiatric and behavioural disorders, and idiopathic hypercalcemia [85]. Growth retardation is observed in both pre-natal and post-natal periods. The patients often present a delayed bone age and low levels of IGF1. Craniofacial phenotype is represented by stellate iris, periorbital oedema, flattening of nasal pyramid, short nose with anteverted nostrils, long philtrum, macrostomy, thick lips, microdontia, multiple diastema, dental malocclusion and micrognathia. The specific cardiovascular malformation is represented by supravalvular aortic stenosis, seen in more than 80% of patients. Other major arteries stenosis could also be seen. Other frequent signs are hyperacusis, thick voice, articular hyperlaxity, kyphoscoliosis and lordosis. Usually the intellectual disability is moderate, although sometimes, it can be very severe and there are also cases described with IQ in the normal range. These children are hypersociable and hyperactive with attention deficit, often characterized as having a 'cocktail party' personality.

3. Clinical and genetic evaluation in genetic short stature

3.1. Anamnestic data

3.1.1. Personal data

In face of a case with short stature, the anamnesis should be conducted in order to obtain the personal information, normal and pathologic, related to

- **Pre-natal period**: pre-natal echography and data on pregnancy (possible incidents and teratogen exposure).
- **Peri-natal period**: data on birth (possible incidents, type of birth), auxology at birth (weight, length, head circumference), gestational age and data on neo-natal period.
- **Infancy period**: data on nutrition, auxology, psychomotor development and others incidents.
- **Childhood period until the moment of evaluation**: data on growth - previous growth data and growth charts (height, weight, head circumference, body mass index); puberty; age at start of pubertal signs and development of these signs; psychosocial development—school performance, or data on intellectual performance, psychologic and affective status, social environment; nutrition: quantity and quality of different nutriments, particularly vitamin D and calcium intake; and level of physical activities.
- **Data on different diseases or treatment**.
- **History of short stature**: time of onset (pre-natal or post-natal), data on evolution and associated signs.

3.1.2. Familial data

The familial history is also very important, and the evaluation should obtain the data on ethnicity, consanguinity, parental height, tempo of height and puberty for the parents, reproductive history of parents and family, family history on growth disorders, familial short stature, skeletal disorders, endocrine disorders and autoimmunity.

3.2. Physical exam

3.2.1. Growth data

In every evaluation of a patient with short stature, the information on actual auxology are essential and include height, weight, head circumference, body mass index (also in standard deviation to the average) and mid-parental height. These values are put on the growth charts to evaluate the growth pattern that is also compared to midparental height.

To evaluate if the short stature is proportionate or not, the upper-to-lower segment ratio and the arm span will be evaluated. In order to see a possible Madelung deformation, the forearm will also be analysed.

3.2.2. Other associated signs

A detailed clinical exam, general and on different organs and systems, is necessary to be associated with auxologic evaluation. At adolescence, the evaluation of the puberty signs should always be attentively assessed.

There are some specific signs associated with short stature, which could give a rapid suggestion for the aetiology and diagnosis (**Table 1**) [86].

Clinical signs	Genetic syndromes
Craniofacial dysmorphy	
Midline face abnormalities: hypotelorism, midline clefting, single median incisor	-Hypophysis abnormalities and GH deficiency
Facial asimetry	-Russell Silver syndrome, 22q11.2 deletion
Elf face	-Williams syndrome
Moon face	-Hypercorticism
Synophrys and hypertrichosis	-Cornelia de Lange syndrome
Short nose and anteverted nostrils	-Smith-Lemli-Opitz syndrome
High arched palate	-SHOX deletion, Turner syndrome, 22q11.2 deletion
Pterygium colli	-Turner syndrome, Noonan syndrome
Tegument and adipose tissue abnormalities	
Multiple nevi	-Turner syndrome, Noonan syndrome
Morbid obesity	-Prader Willi syndrome
Skeletal signs	
Disproportionate short stature	-Skeletal dysplasia
Limbs asymmetry	-Russell-Silver syndrome
Cubitus valgum	-Turner syndrome
Madelung deformity	-SHOX deletion, Turner syndrome
4th and/or 5th brachymetacarpia	-SHOX deletion, Turner syndrome, pseudohypoparathyroidism
Broad thumb	-Rubinstein-Taybi syndrome
5th finger clinodactyly	-Russell Silver syndrome
Cardio-vascular malformation	
Bicuspid aortic valve, aortic coarctation	-Turner syndrome
Supravalvulary aortic stenosis	-Williams syndrome
Pulmonary stenosis	-Noonan syndrome
Urogenital malformation	
Cryptorchidism	-Prader Willi syndrome, Noonan syndrome, Rubinstein Taybi syndrome
Micropenis	-Prader Willi syndrome, congenital GH deficiency
Shawl scrotum	-Aarskog syndrome

Table 1. Clinical signs indicating different genetic syndromes in patients with short stature [86].

Clinical feature	Skeletal dysplasia
Limbs	
Rhizomelic shortening	-achondroplasia, thanatophoric dysplasia, diastrophic dysplasia, spondyloepiphyseal dysplasia (SED)
Mesomelic shortening	-Langer mesomelic dysplasia
Acromelic shortening	-acrodysostosis
Micromelia	-achondrogenesis, Kniest dysplasia, dyssegmental dysplasia
Short trunk	-Kniest syndrome, metatropic dysplasia, SED
Thorax/ribs	
Long or narrow thorax	-Metatropic dysplasia
Pear-shaped chest	-Thanatophoric dysplasia, short-rib polydactyly syndrome
Radial ray defects	-Cornelia de Lange syndrome
Polydactyly	-Chondroectodermal dysplasia, short-rib polydactyly
Hands and feet	
Hitchhiker thumb	-Diastrophic dysplasia
Clubfoot	-Diastrophic dysplasia, Kniest dysplasia, OI
Nails	
Hypoplastic nails	-Chondroectodermal dysplasia
Joints	
Multiple joint dislocations	-Larsen and otopalatodigital syndrome
Long bone fractures	-OI, hypophosphatasia, achondrogenesis type I
Skull	
Macrocephaly	-Achondroplasia, achondrogenesis, thanatophoric dysplasia
Craniosynostosis	-Craniosynostosis syndromes, hypophosphatasia
Cloverleaf skull	-Thanatophoric dysplasia, craniosynostosis
Caput membranaceum	-Hypophosphatasia, osteogenesis imperfecta (OI)
Multiple wormian bones	-Cleidocranial dysplasia, osteogenesis imperfecta
Eyes	
Congenital cataract	-Chondrodysplasia punctata
Myopia	-Kniest dysplasia and spondyloepiphiseal dysplasia
Mouth	
High arched/cleft palate	-Kniest dysplasia, diastrophic dysplasia, metatropic dysplasia
Ears	
Acute swelling of the pinnae	-Diastrophic dysplasia
Heart	
Atrial septal defect	-Chondroectodermal dysplasia
Patent ductus arteriosus	-Lethal short-limbed skeletal dysplasias
Mental retardation	
	-Genetic syndromes—Rubinstein-Taybi syndrome
	-Cranium pathology—craniostenosis
	-Metabolic disorders—lysosomal storage diseases

Table 2. Clinical signs indicating different skeletal dysplasias in patients with short stature [87].

If the patient presents skeletal dysplasia, some clinical signs could orient to the aetiology (**Table 2**) [87].

3.3. Investigations

3.3.1. Imagistic investigations

When evaluating a child with short stature, an X-ray of hand and fist is needed to assess bone age and growth potential. In primary short stature, the bone age is usually not delayed, compared to secondary or idiopathic short stature where a retarded bone age is observed. The bone age is necessary to obtain the predicted height for one patient. This examination is also indicated in parents, if they also have short stature and bone deformities.

If the patient shows clinical signs of skeletal dysplasia, supplementary radiographs are needed to assess long bones, spine and skull, in particular, the forearm (AP), pelvic radiographs (AP), radiographs of the knee (AP) and spine (AP, lateral). Thus, in disproportionate short stature, the radiographs could bring important indicators to establish the diagnosis of the type of skeletal dysplasia, according to the affected area.

Sometimes, at radiography, there are not significant skeletal changes, but even so it cannot rule out skeletal dysplasia, radiological monitoring being required, with repeated radiographs, which may change over time.

3.3.2. Laboratory analysis

Represent the first-line tests indicated in patients with short stature, particularly not elucidated by clinical signs. These analyses must always evaluate the most common causes responsible for somatic developmental delay: anaemic syndrome (erythrocytes, haemoglobin, haematocrit, iron); inflammatory syndrome (erythrocyte sedimentation rate, leucocytes); kidney function and bone metabolism abnormalities (creatinine, urea, sodium, potassium, calcium, magnesium, phosphor and alkaline phosphatase); renal tubular acidosis (acid-base balance); other renal disorders (urinalysis); malabsorption syndrome (iron, ferritin, total protein and albumin); celiac disease (IgA anti-endomysium and anti-transglutaminase, total IgA); hypothyroidism (TSH, T4 free); and growth hormone deficiency (IGF1).

3.4. Genetic testing

Genetic testing follows to the routine non-specific laboratory analysis. It should be performed after an informed consent for genetic testing is obtained. If all the routine tests are negative and clinical examination is not suggestive for certain pathology, a karyotype to any female patient with short stature is routinely indicated. For a male patient with isolated short stature, there is no consensus on routine testing by karyotype; however, an argument in performing the karyotype being to detect a possible syndrome 45,X/46,XY.

If there are no clinical, imagistic or laboratory suggestions for a specific disease, a whole genome analysis of copy number variants by CGH array (array based comparative genomic

hybridization) or SNP array (array based single nucleotide polymorphism genotyping) will be indicated. When there is the possibility, an analysis based on massive parallel sequencing technology that will evaluate the whole exome or a panel of genes well known to be implicated in short stature will be proposed. The algorithm of a genetic evaluation in short stature is described in **Figure 1**.

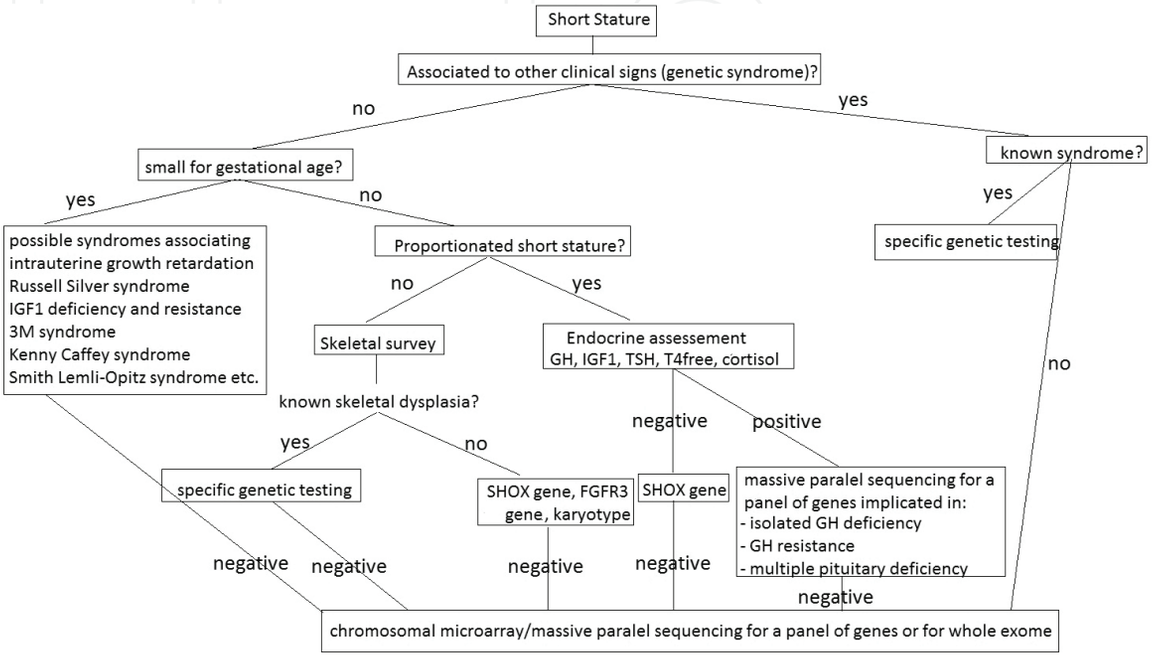

Figure 1. Algorithm for genetic testing in short stature [4, 88].

In a patient with isolated proportioned short stature, the most common causes are numeric abnormalities of X chromosome, SHOX gene mutations, discrete skeletal dysplasia, endocrine disorders, SGA without catch-up growth, constitutional growth retardation and familial short stature. Thus, the genetic testing should take into consideration these aspects.

The patients with SGA without catch-up growth are a special category of patients with short stature, usually proportioned. The majority of patients with SGA (90%) recuperate the deficit by the age of 1, maximum 2 years. Still about 10% of these patients remain with somatic deficit. Often, these patients present associated dysmorphic signs. The main syndromes that have to be taken into consideration in this situation are Russell-Silver syndrome, Bloom syndrome, Nijmegan breakage syndrome, Cockayne syndrome, Dubowitz syndrome, deficit in IGF1, resistance to IGF1, Kenny-Caffey syndrome, Schimke dysplasia or Smith-Lemli-Opitz syndrome [88].

4. Conclusions

Short stature is a strongly genetically determined pathology. The group of genetic disorders with primary effect on growth is very heterogeneous and comprises two important categories

of pathologies: skeletal dysplasia and different genetic syndromes with primary effect on growth. Their diagnosis is often difficult, thus, knowledge of the main clinical signs of each syndrome and the algorithm for clinical diagnosis and genetic testing will practically lead to an easier clinical and etiologic diagnosis.

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References

[1] Silventoinen K, Sammalisto S, Perola M, Boomsma DI, Cornes BK, Davis C, et al. Heritability of adult body height: a comparative study of twin cohorts in eight countries. Twin Res. 2003;6(5):399–408. DOI: 10.1375/136905203770326402

[2] Roche AF. Secular trends in human growth, maturation, and development. Monogr Soc Res Child Dev. 1997;44(3–4):1–120.

[3] Ogata T. Genetics of human growth. Clin Pediatr Endocrinol. 2006;15(2):45–53. DOI: 10.1297/cpe.15.45

[4] Dauber A, Rosenfeld RG, Hirschhorn JN. Genetic evaluation of short stature. J Clin Endocrinol Metab. 2014;99(9):3080–3092. DOI: 10.1210/jc.2014-1506

[5] Lango Allen H, Estrada K, Lettre G, Berndt SI, Weedon MN, Rivadeneira F, et al. Hundreds of variants clustered in genomic loci and biological pathways affect human height. Nature. 2010;467(7317):832–838. DOI: 10.1038/nature09410

[6] Weedon MN, Lango H, Lindgren CM, Wallace C, Evans DM, Mangino M, et al. Genome-wide association analysis identifies 20 loci that influence adult height. Nat Genet. 2008;40(5):575–583. DOI: 10.1038/ng.121

[7] Sovio U, Bennett AJ, Millwood IY, Molitor J, O'Reilly PF, Timpson NJ, et al. Genetic determinants of height growth assessed longitudinally from infancy to adulthood in the northern Finland birth cohort 1966. PLoS Genet. 2009;5(3):e1000409. DOI: 10.1371/journal.pgen.1000409

[8] Song KC, Jin SL, Kwon AR, Chae HW, Ahn JM, Kim DH, et al. Etiologies and characteristics of children with chief complaint of short stature. Ann Pediatr Endocrinol Metab. 2015;20(1):34–39. DOI: 10.6065/apem.2015.20.1.34

[9] Flechtner I, Lambot-Juhan K, Teissier R, Colmenares A, Baujat G, Beltrand J, et al. Unexpected high frequency of skeletal dysplasia in idiopathic short stature and small for gestational age patients. Eur J Endocrinol. 2014;170(5):677–684. DOI: 10.1530/EJE-13-0864

[10] Rappold G, Blum WF, Shavrikova EP, Crowe BJ, Roeth R, Quigley CA, et al. Genotypes and phenotypes in children with short stature: clinical indicators of SHOX haploinsufficiency. J Med Genet. 2007;44(5):306–313. DOI: 10.1136/jmg.2006.046581

[11] Warman ML, Cormier-Daire V, Hall C, Krakow D, Lachman R, LeMerrer M, et al. Nosology and classification of genetic skeletal disorders: 2010 revision. Am J Med Genet A. 2011;155A(5):943–968. DOI: 10.1002/ajmg.a.33909

[12] Su N, Jin M, Chen L. Role of FGF/FGFR signaling in skeletal development and homeostasis: learning from mouse models. Bone Res. 2014;2:14003. DOI: 10.1038/boneres.2014.3

[13] Peters K, Ornitz D, Werner S, Williams L. Unique expression pattern of the FGF receptor 3 gene during mouse organogenesis. Dev Biol. 1993;155(2):423–430. DOI: 10.1006/dbio.1993.1040

[14] Shiang R, Thompson LM, Zhu YZ, Church DM, Fielder TJ, Bocian M, et al. Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. Cell. 1994;78(2):335–342. DOI: 10.1016/0092-8674(94)90302-6

[15] Rousseau F, Bonaventure J, Legeai-Mallet L, Pelet A, Rozet JM, Maroteaux P, et al. Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. Nature. 1994;371(6494):252–254. DOI: 10.1038/371252a0

[16] Bellus GA, Hefferon TW, Ortiz de Luna RI, Hecht JT, Horton WA, Machado M, et al. Achondroplasia is defined by recurrent G380R mutations of FGFR3. Am J Hum Genet. 1995;56(2):368–373.

[17] Wilkin DJ, Szabo JK, Cameron R, Henderson S, Bellus GA, Mack ML, et al. Mutations in fibroblast growth-factor receptor 3 in sporadic cases of achondroplasia occur exclusively on the paternally derived chromosome. Am J Hum Genet. 1998;63(3):711–716. DOI: 10.1086/302000

[18] Bober MB, Bellus GA, Nikkel SM, Tiller GE. Hypochondroplasia [Internet]. 15/07/1999 [Updated: 26/09/2013]. Available from: www.ncbi.nlm.nih.gov/books/NBK1477/ [Accessed: 02/03/2016]

[19] Mullis PE, Patel MS, Brickell PM, Hindmarsh PC, Brook CG. Growth characteristics and response to growth hormone therapy in patients with hypochondroplasia: genetic linkage of the insulin-like growth factor I gene at chromosome 12q23 to the disease in a subgroup of these patients. Clin Endocrinol (Oxf). 1991;34(4):265–274. DOI: 10.1111/j.1365-2265.1991.tb03765.x

[20] Walker BA, Murdoch JL, McKusick VA, Langer LO, Beals RK. Hypochondroplasia. Am J Dis Child. 1971;122(2):95–104. DOI: 10.1001/archpedi.1971.02110020029001

[21] Bellus GA, Bamshad MJ, Przylepa KA, Dorst J, Lee RR, Hurko O, et al. Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN): phenotypic analysis of a new skeletal dysplasia caused by a Lys650Met mutation in fibroblast growth factor receptor 3. Am J Med Genet. 1999;85(1):53–65.

[22] Zankl A, Elakis G, Susman RD, Inglis G, Gardener G, Buckley MF, et al. Prenatal and postnatal presentation of severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) due to the FGFR3 Lys650Met mutation. Am J Med Genet A. 2008;146A(2):212–218. DOI: 10.1002/ajmg.a.32085

[23] Xue Y, Sun A, Mekikian PB, Martin J, Rimoin DL, Lachman RS, et al. FGFR3 mutation frequency in 324 cases from the International Skeletal Dysplasia Registry. Mol Genet Genomic Med. 2014;2(6):497–503. DOI: 10.1002/mgg3.96

[24] Tavormina PL, Shiang R, Thompson LM, Zhu YZ, Wilkin DJ, Lachman RS, et al. Thanatophoric dysplasia (types I and II) caused by distinct mutations in fibroblast growth factor receptor 3. Nat Genet. 1995;9(3):321–328. DOI: 10.1038/ng0395-321

[25] Langer LO, Yang SS, Hall JG, Sommer A, Kottamasu SR, Golabi M, et al. Thanatophoric dysplasia and cloverleaf skull. Am J Med Genet Suppl. 1987;3:167–179. DOI: 10.1002/ajmg.1320280521

[26] Pannier S, Martinovic J, Heuertz S, Delezoide AL, Munnich A, Schibler L, et al. Thanatophoric dysplasia caused by double missense FGFR3 mutations. Am J Med Genet A. 2009;149A(6):1296–1301. DOI: 10.1002/ajmg.a.32880

[27] Shaker JL, Albert C, Fritz J, Harris G. Recent developments in osteogenesis imperfecta. F1000Res. 2015;4(F1000 Faculty Rev):681. DOI: 10.12688/f1000research.6398.1

[28] Exposito JY, Cluzel C, Garrone R, Lethias C. Evolution of collagens. Anat Rec. 2002;268(3):302–316. DOI: 10.1002/ar.10162

[29] Gelse K, Pöschl E, Aigner T. Collagens-structure, function, and biosynthesis. Adv Drug Deliv Rev. 2003;55(12):1531–1546. DOI: 10.1016/j.addr.2003.08.002

[30] Kadler KE, Baldock C, Bella J, Boot-Handford RP. Collagens at a glance. J Cell Sci. 2007;120(Pt 12):1955–1958. DOI: 10.1242/jcs.03453

[31] Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet. 1979;16(2):101–116. DOI: 10.1136/jmg.16.2.101

[32] Krakow D, Rimoin DL. The skeletal dysplasias. Genet Med. 2010;12(6):327–341. DOI: 10.1097/GIM.0b013e3181daae9b

[33] Nishimura G, Haga N, Kitoh H, Tanaka Y, Sonoda T, Kitamura M, et al. The phenotypic spectrum of COL2A1 mutations. Hum Mutat. 2005;26(1):36–43. DOI: 10.1002/humu.20179

[34] Chan D, Cole WG, Chow CW, Mundlos S, Bateman JF. A COL2A1 mutation in achondrogenesis type II results in the replacement of type II collagen by type I and III collagens in cartilage. J Biol Chem. 1995;270(4):1747–1753. DOI: 10.1074/jbc.270.4.1747

[35] Godfrey M, Hollister DW. Type II achondrogenesis-hypochondrogenesis: identification of abnormal type II collagen. Am J Med Genet. 1988;43(6):904–913.

[36] Wynne-Davies R, Hall C. Two clinical variants of spondylo-epiphysial dysplasia congenita. J Bone Joint Surg Br. 1982;64(4):435–441.

[37] Gilbert-Barnes E, Langer LO, Opitz JM, Laxova R, Sotelo-Arila C. Kniest dysplasia: radiologic, histopathological, and scanning electronmicroscopic findings. Am J Med Genet. 1996;63(1):34–45. DOI: 10.1002/(SICI)1096-8628(19960503)

[38] Snead MP, Yates JRW. Clinical and molecular genetics of Stickler syndrome. J Med Genet. 1999;36(5):353–359. DOI: 10.1136/jmg.36.5.353

[39] Robin NH, Moran RT, Ala-Kokko L. Stickler Syndrome [Internet]. 09/06/2000 [Updated: 26/11/2014]. Available from: www.ncbi.nlm.nih.gov/books/NBK1302 [Accessed: 02/03/2016]

[40] Holden P, Meadows R S, Chapman KL, Grant ME, Kadler KE, Briggs MD. Cartilage oligomeric matrix protein interacts with type IX collagen, and disruptions to these interactions identify a pathogenetic mechanism in a bone dysplasia family. J Biol Chem. 2001;276(8):6046–6055. DOI: 10.1074/jbc.M009507200

[41] Hecht JT, Hayes E, Haynes R, Cole WG. COMP mutations, chondrocyte function and cartilage matrix. Matrix Biol. 2005;23(8):525–533. DOI: 10.1016/j.matbio.2004.09.006

[42] Unger SL, Briggs MD, Holden P, Zabel B, Ala-Kokko L, Paassilta P, et al. Multiple epiphyseal dysplasia: radiographic abnormalities correlated with genotype. Pediatr Radiol. 2001;31(1):10–18. DOI: 10.1007/s002470000362

[43] Unger S, Hecht JT. Pseudoachondroplasia and multiple epiphyseal dysplasia: new etiologic developments. Am J Med Genet. 2001;106(4):244–250. DOI: 10.1002/ajmg.10234

[44] Seo SG, Song H-R, Kim HW, Yoo WJ, Shim JS, Chung CY, et al. Comparison of orthopaedic manifestations of multiple epiphyseal dysplasia caused by MATN3 versus COMP mutations: a case control study. BMC Musculoskelet Disord. 2014;15:84. DOI: 10.1186/1471-2474-15-84

[45] Shen G. The role of type X collagen in facilitating and regulating endochondral ossification of articular cartilage. Orthod Craniofac Res. 2005;8(1):11–17. DOI: 10.1111/j.1601-6343.2004.00308.x

[46] Poulson AV, Hooymans JMM, Richards AJ, Bearcroft P, Murthy R, Baguley DM, et al. Clinical features of type 2 Stickler syndrome. J Med Genet. 2004;41(8):e107. DOI: 10.1136/jmg.2004.018382

[47] Rose PS, Ahn NU, Levy HP, Magid D, Davis J, Liberfarb RM, et al. The hip in Stickler syndrome. J Pediatr Orthop. 2001;21(5):657–663. DOI: 10.1097/01241398-200109000-00020

[48] Rose PS, Ahn NU, Levy HP, Ahn UM, Davis J, Liberfarb RM, et al. Thoracolumbar spinal abnormalities in Stickler syndrome. Spine. 2001;26(4):403–409. DOI: 10.1097/00007632-200102150-00017

[49] Harel T, Rabinowitz R, Hendler N, Galil A, Flusser H, Chemke J, et al. COL11A2 mutation associated with autosomal recessive Weissenbacher-Zweymuller syndrome: molecular and clinical overlap with otospondylomegaepiphyseal dysplasia (OSMED). Am J Med Genet A. 2005;132A(1):33–35. DOI: 10.1002/ajmg.a.30371

[50] Hästbacka J, de la Chapelle A, Mahtani MM, Clines G, Reeve-Daly MP, Daly M, et al. The diastrophic dysplasia gene encodes a novel sulfate transporter: positional cloning by fine-structure linkage disequilibrium mapping. Cell. 1994;78(6):1073–1087. DOI: 10.1016/0092-8674(94)90281-X

[51] Ayoubi JM, Jouk PS, Pons JC. Diastrophic dwarfism and pregnancy. Lancet. 2001;358(9295):1778. DOI: 10.1016/S0140-6736(01)06806-4

[52] Bonafe L, Mittaz-Crettol L, Ballhausen D, Superti-Furga A. Diastrophic Dysplasia [Internet]. 15/11/2004 [Updated: 18/07/2013]. Available from: www.ncbi.nlm.nih.gov/books/NBK1350 [Accessed: 02/03/2016]

[53] Aleck KA, Grix A, Clericuzio C, Kaplan P, Adomian GE, Lachman R, et al. Dysssegmental dysplasias: clinical, radiographic, and morphologic evidence of heterogeneity. Am J Med Genet. 1987;27(2):295–312. DOI: 10.1002/ajmg.1320270208

[54] Rieubland C, Jacquemont S, Mittaz L, Osterheld M-C, Vial Y, Superti-Furga A, et al. Phenotypic and molecular characterization of a novel case of dyssegmental dysplasia, Silverman-Handmaker type. Eur J Med Genet. 2010;53(5):294–298. DOI: 10.1016/j.ejmg.2010.06.005

[55] Stum M, Davoine CS, Fontaine B, Nicole S. Schwartz-Jampel syndrome and perlecan deficiency. Acta Myol. 2005;24(2):89–92.

[56] Spranger J, Hall BD, Häne B, Srivastava A, Stevenson RE. Spectrum of Schwartz-Jampel syndrome includes micromelic chondrodysplasia, kyphomelic dysplasia, and Burton disease. Am J Med Genet. 2000;94(4):287–295. DOI: 10.1002/1096-8628(20001002)94:4<287::AID-AJMG5>3.0.CO;2-G

[57] Kiani C, Chen L, Wu YJ, Yee AJ, Yang BB. Structure and function of aggrecan. Cell Res. 2002;12(1):19–32. DOI: 10.1038/sj.cr.7290106

[58] Anderson IJ, Tsipouras P, Scher C, Ramesar RS, Martell RW, Beighton P. Spondyloepiphyseal dysplasia, mild autosomal dominant type is not due to primary defects of type II collagen. Am J Med Genet. 1990;37(2):272–276. DOI: 10.1002/ajmg.1320370223

[59] Masuyama R, Vriens J, Voets T, Karashima Y, Owsianik G, Vennekens R, et al. TRPV4-mediated calcium influx regulates terminal differentiation of osteoclasts. Cell Metab. 2008;8(3):257–265. DOI: 10.1016/j.cmet.2008.08.002

[60] Geneviève D, Le Merrer M, Feingold J, Munnich A, Maroteaux P, Cormier-Daire V. Revisiting metatropic dysplasia: presentation of a series of 19 novel patients and review of the literature. Am J Med Genet A. 2008;146A(8):992–996. DOI: 10.1002/ajmg.a.32191

[61] Munns CJF, Haase HR, Crowther LM, Hayes MT, Blaschke R, Rappold G, et al. Expression of SHOX in human fetal and childhood growth plate. J Clin Endocrinol Metab. 2004;89(8):4130–4135. DOI: 10.1210/jc.2003-032230

[62] Marchini A, Marttila T, Winter A, Caldeira S, Malanchi I, Blaschke RJ, et al. The short stature homeodomain protein SHOX induces cellular growth arrest and apoptosis and is expressed in human growth plate chondrocytes. J Biol Chem. 2004:279(35):37103–37114. DOI: 10.1074/jbc.M307006200

[63] Rao E, Weiss B, Fukami M, Rump A, Niesler B, Mertz A, et al. Pseudoautosomal deletions encompassing a novel homeobox gene cause growth failure in idiopathic short stature and Turner syndrome. Nat Genet. 1997:16(1):54–63. DOI: 10.1038/ng0597-54

[64] Rappold GA, Fukami M, Niesler B, Schiller S, Zumkeller W, Bettendorf M, et al. Deletions of the homeobox gene SHOX (short stature homeobox) are an important cause of growth failure in children with short stature. J Clin Endocrinol Metab. 2002;87(3):1402–1406. DOI: 10.1210/jcem.87.3.8328

[65] Stuppia L. SHOX mutations detected by FISH and direct sequencing in patients with short stature. J Med Genet. 2003;40(2):e11. DOI: 10.1136/jmg.40.2.e11

[66] Hintz RL. SHOX mutations. Rev Endocr Metab Disord. 2002;3(4):363–367.

[67] Leka SK, Kitsiou-Tzeli S, Kalpini-Mavrou A, Kanavakis E. Short stature and dysmorphology associated with defects in the SHOX gene. Hormones (Athens). 2006;5(2):107–118.

[68] Ogata T. SHOX haploinsufficiency: lessons from clinical studies. Curr Opin Endocrinol Diabetes. 2002;9(1):13–20. DOI: 10.1097/00060793-200202000-00003

[69] Elsheikh M, Dunger DB, Conway GS, Wass JAH. Turner's syndrome in adulthood. Endocr Rev. 2002;23(1):120–140. DOI: 10.1210/edrv.23.1.0457

[70] Cabrol S. Turner syndrome. Ann Endocrinol (Paris). 2007;68(1):2–9. DOI: 10.1016/j.ando.2006.12.002

[71] Sybert VP, McCauley E. Turner's syndrome. N Engl J Med. 2004;351(12):1227–38. DOI: 10.1056/NEJMra030360

[72] Migeon BR, Luo S, Jani M, Jeppesen P. The severe phenotype of females with tiny ring X chromosomes is associated with inability of these chromosomes to undergo X inactivation. Am J Hum Genet. 1994;55(3):497–504.

[73] Fuke T, Mizuno S, Nagai T, Hasegawa T, Horikawa R, Miyoshi Y, et al. Molecular and clinical studies in 138 Japanese patients with Silver-Russell syndrome. PLoS One. 2013;8(3):e60105. DOI: 10.1371/journal.pone.0060105

[74] Eggermann T. Russell-Silver syndrome. Am J Med Genet C Semin Med Genet. 2010;154C(3):355–364. DOI: 10.1002/ajmg.c.30274

[75] Dörr S, Midro AT, Färber C, Giannakudis J, Hansmann I. Construction of a detailed physical and transcript map of the candidate region for Russell-Silver syndrome on chromosome 17q23-q24. Genomics. 2001;71(2):174–181. DOI: 10.1006/geno.2000.6413

[76] van Haelst MM, Eussen HJFMM, Visscher F, de Ruijter JLM, Drop SLS, Lindhout D, et al. Silver-Russell phenotype in a patient with pure trisomy 1q32.1-q42.1: further delineation of the pure 1q trisomy syndrome. J Med Genet. 2002;39(8): 582–585. DOI: 10.1136/jmg.39.8.582

[77] Li CC, Chodirker BN, Dawson AJ, Chudley AE. Severe hemihypotrophy in a female infant with mosaic Turner syndrome: a variant of Russell-Silver syndrome? Clin Dysmorphol. 2004;13(2):95–98. DOI: 10.1097/00019605-200404000-00008

[78] Price SM, Stanhope R, Garrett C, Preece MA, Trembath RC. The spectrum of Silver-Russell syndrome: a clinical and molecular genetic study and new diagnostic criteria. J Med Genet. 1999;36(11):837–842. DOI: 10.1136/jmg.36.11.837

[79] Ferrero GB, Baldassarre G, Delmonaco AG, Biamino E, Banaudi E, Carta C, et al. Clinical and molecular characterization of 40 patients with Noonan syndrome. Eur J Med Genet. 2008;51(6):566–572. DOI: 10.1016/j.ejmg.2008.06.011

[80] Ramos FJ, Puisac B, Baquero-Montoya C, Gil-Rodríguez MC, Bueno I, Deardorff MA, et al. Clinical utility gene card for: Cornelia de Lange syndrome. Eur J Hum Genet. 2015;23(10):1431. DOI: 10.1038/ejhg.2014.270

[81] Milani D, Manzoni FMP, Pezzani L, Ajmone P, Gervasini C, Menni F, et al. Rubinstein-Taybi syndrome: clinical features, genetic basis, diagnosis, and management. Ital J Pediatr. 2015;41:4. DOI: 10.1186/s13052-015-0110-1

[82] Driscoll DJ, Miller JL, Schwartz S, Cassidy SB. Prader-Willi Syndrome [Internet]. 06/10/1998 [Updated: 04/02/2016]. Available from: www.ncbi.nih.gov/books/NBK1330/ [Accessed: 02/03/2016]

[83] MacDonald HR, Wevrick R. The necdin gene is deleted in Prader-Willi syndrome and is imprinted in human and mouse. Hum Mol Genet. 1997;6(11):1873–1878. DOI: 10.1093/hmg/6.11.1873

[84] Arnaud M, Barat-Houari M, Gatinois V, Sanchez E, Lyonnet S, Touitou I, et al. Kabuki syndrome: update and review. Arch Pediatr. 2015;22(6):653–660. DOI: 10.1016/j.arcped.2015.03.020

[85] Pober BR. Williams-Beuren syndrome. N Engl J Med. 2010;362(3):239–252. DOI: 10.1056/NEJMra0903074

[86] Oostdijk W, Grote FK, de Muinck Keizer-Schrama SMPF, Wit JM. Diagnostic approach in children with short stature. Horm Res. 2009;72(4):206–217. DOI: 10.1159/000236082

[87] Chen H. Skeletal Dysplasia [Internet]. [Updated: 02/03/2015]. Available from: emedicine.medscape.com/article/943343-clinical#b4 [Accessed: 02/03/2016]

[88] Seaver LH, Irons M. ACMG practice guideline: genetic evaluation of short stature. Genet Med. 2009;11(6):465–470. DOI: 10.1097/GIM.0b013e3181a7e8f8