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Pseudoacromegaly

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ABSTRACT

Individuals with acromegaloid physical appearance or tall stature may be referred to endocrinologists to exclude growth hormone (GH) excess. While some of these subjects could be healthy individuals with normal variants of growth or physical traits, others will have acromegaly or pituitary gigantism, which are, in general, straightforward diagnoses upon assessment of the GH/IGF-1 axis.

However, some patients with physical features resembling acromegaly – usually affecting the face and extremities –, or gigantism – accelerated growth/tall stature – will have no abnormalities in the GH axis. This scenario is termed pseudoacromegaly, and its correct diagnosis can be challenging due to the rarity and variability of these conditions, as well as due to significant overlap in their characteristics.

In this review we aim to provide a comprehensive overview of pseudoacromegaly conditions, highlighting their similarities and differences with acromegaly and pituitary gigantism, to aid physicians with the diagnosis of patients with pseudoacromegaly.

1. Pseudoacromegaly or acromegaloidism

Patients with excess of growth hormone (GH), usually due to a pituitary adenoma, generally show three major attributes: (i) characteristic physical appearance with prominent facial features and typical alterations in their extremities; (ii) tall stature, if the disease started at a young age; and (iii) elevated insulin-like growth factor-1 (IGF-1) levels and an elevated glucose-suppressed GH (Katznelson et al., 2014). In most cases the diagnosis of acromegaly is straightforward based on history, past photographs and clinical features, and confirmed by measuring serum IGF-1 levels, assessing nadir GH levels during an oral glucose tolerance test (OGTT) and by performing a pituitary MRI scan (Katznelson et al., 2014).

The term pseudoacromegaly describes patients with features of acromegaly or gigantism but without GH/IGF-1 axis abnormalities (Albuquerque et al., 2017; Chakraborty et al., 2017; Kumar et al., 2012; Marques et al., 2018b; Stratakis et al., 2001). This term is similar to other conditions, where the 'pseudo' prefix is used to describe cases with features of a certain disease, but without the characteristic pathophysiological mechanisms and key biochemical hallmarks, such as pseudohypoparathyroidism (Mantovani, 2011) or pseudo-Cushing syndrome (Findling and Raff, 2017). Pseudoacromegaly designates a heterogeneous group of disorders in which patients share some features with patients who have GH excess causing acromegaly or gigantism in the absence of GH axis abnormalities.

Acromegaloidism is a term first used in the Seventies, and defined as a "bodily condition resembling acromegaly but not due to a pituitary (or hypothalamic) disorder" (Mims, 1978). In an elegant study on 15 patients referred for evaluation of acromegaly, baseline and dynamic GH tests were negative, patients were characterized by acromegaloid facies and acral enlargement as well as prognathism, visceromegaly, hypertension, fatigue, headaches, arthralgias, paresthesias, hyperhidrosis, oily odorous skin, hypertrichosis, hyperpigmentation and dysphonia (Mims, 1978). The pathogenesis of acromegaloidism was not determined in this study. Another study suggested the presence of an unidentified 70,000 Da growth factor in the serum of 5 patients with acromegaloidism (Ashcraft et al., 1983). Its growth promoting activity was demonstrated *in vitro* on human erythroid cell progenitors, an effect independent of epidermal, nerve, fibroblast or platelet-derived growth factors, IGF-1, IGF-2, insulin or GH, but its identity remains to be defined (Ashcraft et al., 1983). Earlier reports of patients with acromegaloid features without acromegaly are also available in the literature (Girard et al., 1953; Marabini et al., 1956; Robecchi and Einaudi, 1957; Weber and Loewy, 1926). Many of these historical cases with acromegaloid appearance without GH axis abnormalities could belong to one of the syndromes we describe in this review, where advanced molecular, genetic and clinical studies lead to the correct diagnosis. For instance, a family reported originally in 1996 with 'hypertrichosis acromegaloid facial appearance syndrome' (Irvine et al., 1996) was

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recently shown to harbor an *ABCC9* mutation and belongs to the Cantú syndrome phenotypic spectrum (Marques et al., 2018b). Sotos syndrome was initially described as cerebral gigantism in a child with overgrowth and acromegaloid appearance (Sotos et al., 1964), while currently it is a well-defined overgrowth syndrome (Baujat and Cormier-Daire, 2007) which can be considered as a pseudoacromegaly condition (Dahlqvist et al., 2017).

One of the most common pseudoacromegaly conditions is severe insulin resistance and hyperinsulinemia with characteristic acromegaloid features. The underlying pathophysiological mechanism was highlighted as insulin-mediated pseudoacromegaly in the 1990s (Dib et al., 1998; Flier et al., 1993). The scope of pseudoacromegaly has been further expanded when applied to patients with other conditions presented with acromegaloid features, such as pachydermoperiostosis (Karimova et al., 2017), Sotos syndrome (Dahlqvist et al., 2017), Cantú syndrome (Marques et al., 2018b), X-tetrasomy (Alvarez-Vazquez et al., 2006), Klippel-Trenaunay syndrome (Lowman and Mooradian, 2008), primary hypothyroidism (Kumar et al., 2012), Fabry disease (Hogarth et al., 2013), non-islet cell tumor induced hypoglycemia syndrome (Trivedi et al., 1995), or exposure to minoxidil (Nguyen and Marks, 2003) or phenytoin (Mishriki, 1998).

Pseudoacromegaly cases are often referred to pediatric or adult endocrinologists for investigation of possible GH excess or other hormonal disturbances affecting growth, such as precocious puberty, hypogonadism or thyrotoxicosis, or syndromic conditions such as Sotos, Weaver or Beckwith-Wiedemann syndromes. The diagnosis of many of these pseudoacromegaly conditions, especially the syndromic forms, will be established by experienced geneticists or dedicated pediatricians, but some may present first to pediatric or adult endocrinologists, where their main role is to rule out GH axis abnormalities and to aid in establishing the underlying diagnosis.

The differential diagnosis of pseudoacromegaly can be challenging due to the long list of sometimes overlapping and rare conditions (Supplemental Fig. 1). Key facial features characterize for example Sotos syndrome (Baujat and Cormier-Daire, 2007), distinctive forehead skin folds and joint abnormalities help the diagnosis of pachydermoperiostosis (Pan et al., 2016), severe hypoglycemia would be typical in IGF-2-secreting tumors (Ries et al., 2006), while generalized infant-onset hirsutism indicate Cantú syndrome (Marques et al., 2018b). We have compiled a comparative table of pseudoacromegaly conditions denoting similarities and distinctive features differentiating them from acromegaly and pituitary gigantism (Supplemental Table 1), and we provide diagnostic flow charts for differential diagnosis of pseudoacromegaly (Figs. 1 and 2). Examples of typical faces and hands of many conditions we discuss in this review are shown in Figs. 3 and 4. While the most prominent pseudoacromegaly conditions mimic acromegaly or gigantism more closely, other conditions may show some acromegaloid features but overall unlikely to masquerade as acromegaly. In Fig. 5 we divided the conditions we discuss in this review to high or low likelihood of imitating acromegaly or gigantism.

Human growth results from a complex interaction of factors including genetic background, hormones and growth factors, and environmental influences (Wood et al., 2014). Height is a polygenic trait with 50–90% of variation attributed to genetic factors (Ambler, 2002; Lango Allen et al., 2010; Wood et al., 2014). Tall stature is defined as height of more than 2 standard deviations (SD) above the average for gender and age, or as height with more than 2 SD above the mid-parental height (Albuquerque et al., 2017). Normal variants in stature, constitutional (familial) tall stature or constitutional advance of growth, are the most common cause for tall children or adults (Albuquerque et al., 2017). Constitutional tall stature is the most common diagnosis among tall individuals and results probably from several hundreds polymorphisms linked to human stature (Wood et al., 2014). Subjects with constitutional tall stature grow along the same high height percentile from infancy attaining an increased final height, in the absence of any recognizable pathological condition (Ambler, 2002; Skogland et al., 1985). Constitutional advance of growth is also common, particularly in obese children, in which the individuals have increased height velocity from birth to the age of 4 years when they become tall, with growth velocity running along the 97th centile between the ages of 5 and 9 years, and then dropping to the 50th centile thereafter until puberty which tends to occur earlier in this setting (Albuquerque et al., 2017; Dickerman et al., 1984; Papadimitriou et al., 2010).

Diseases causing accelerated growth and tall stature must be differentiated from normal height variants. Disorders of the GH axis can lead to abnormal growth and height, the most classical of which is pituitary gigantism usually due to a GH-secreting pituitary adenoma manifesting before the epiphyseal closure (Rostomyan et al., 2015). However, pathological accelerated growth and/or tall stature can be unrelated to the GH axis, and may occur in isolation or as part of a syndrome, such as the overgrowth syndromes, Klinefelter syndrome or Marfan syndrome (Albuquerque et al., 2017). Overgrowth syndromes are typically characterized by accelerated growth, macrocephaly, distinctive facial appearance and a certain degree of intellectual disability (Tlemsani et al., 2016). The genetic bases of many overgrowth conditions have now been identified (we refer to the excellent reviews of Albuquerque et al. (2017) and Edmondson and Kalish (2015)). Due to the overlapping features, genetic testing is commonly offered as an 'overgrowth panel test' (Albuquerque et al., 2017; Ambler, 2002; Tlemsani et al., 2016).

In this review we aim to provide a comprehensive overview of the pseudoacromegaly conditions, focusing mainly on their clinical aspects and highlighting their similarities and differences regarding acromegaly/pituitary gigantism, to aid physicians with the differential diagnosis of patients with pseudoacromegaly. Pseudoacromegaly conditions are arranged into 4 sections on the basis of acromegaloid facial features with tall, normal or short stature and tall stature without acromegaloid features.

2. Acromegaloid appearance with accelerated growth/tall stature

2.1. Beckwith-Wiedemann syndrome

Beckwith–Wiedemann syndrome is the most common overgrowth syndrome (Bentov and Werner, 2004), with prevalence estimated at 1:13,700 live births (Engstrom et al., 1988; Thorburn et al., 1970); however, the current incidence might be higher than initial estimations, as this disorder is now more routinely identified (Greer et al., 2008). The frequency is similar between males and females (Choufani et al., 2010; Pettenati et al., 1986). Most cases occur sporadically, but up to 15% can be familial with an autosomal dominant inheritance (Choufani et al., 2010; Wiedemann, 1964).

Beckwith-Wiedemann syndrome is caused by a dysregulation of imprinted growth-regulatory genes on chromosome 11p15.5. Perturbation of those genes occur by different mechanisms: uniparental disomy, chromosomal translocations and inversions, paternal duplications and epigenetic defects (Ambler, 2002; Choufani et al., 2010; Weksberg et al., 2003). The 11p15.5 region is organized into 2 imprinted domains, separated by a non-imprinted region (Choufani et al., 2010). In domain 1, *IGF2* is expressed only from the paternal allele, which is counterbalanced by the maternally expressed *H19* gene that encodes an untranslated RNA polymerase II transcript involved in growth restriction (Guo et al., 2008; Hao et al., 1993). The most common description for reciprocal imprinting of *IGF2* and *H19* is "enhancer competition" between these genes, where a shared enhancer downstream of *H19* drives RNA expression from the maternal allele. On the paternal allele methylation of *H19* promoter allows the enhancer to interact instead with *IGF2* gene (Maher and Reik, 2000). *IGF2* promotes fetal growth, while *H19* prevents overgrowth (Jones et al., 2001). *IGF2* overexpression is one of the leading causes of Beckwith-Wiedemann syndrome (Brown et al., 1996). In domain 2 there are around 10

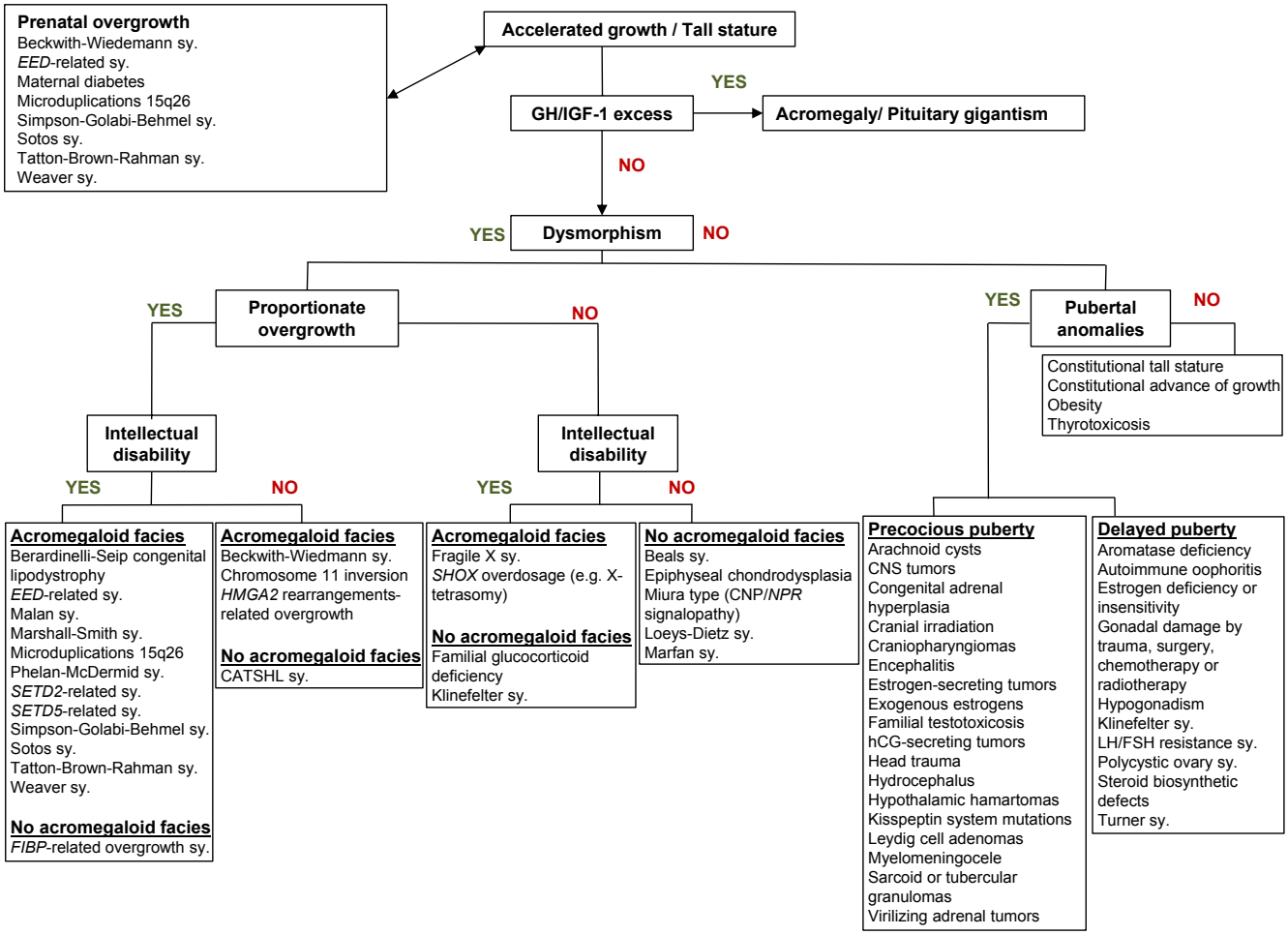

Fig. 1. Diagnostic flow chart for evaluation of individuals with accelerated growth/tall stature in the absence of GH/IGF-1 excess taking into account the main differential diagnoses. CATSHL sy., camptodactyly, tall stature and hearing loss syndrome; CNP, C-type natriuretic peptide; CNS, central nervous system; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; IGF-2, insulin-like growth factor 2; LH, luteinizing hormone; sy., syndrome.

imprinted genes, 2 of them involved in this condition: *CDKN1C* (cyclin-dependent kinase inhibitor 1C coding for p21) and *KCNQ1QT1* (potassium channel KQT). Loss of maternal methylation of imprinting center 2 is associated with expression of the normally silent maternal allele of *KCNQ1QT1*, and any disturbance in domain 2 results in decreased *CDKN1C* expression (Choufani et al., 2010; Cooper et al., 2005).

The following manifestations support the diagnosis: overgrowth, macroglossia, distinctive facial features, abdominal wall defects, hemihyperplasia, ear or renal anomalies and embryonal tumors (Ambler, 2002; Choufani et al., 2010; Elliott et al., 1994). Prenatal and postnatal overgrowth can affect the body as a whole, or can be regional affecting only some parts. Overgrowth is usually apparent at birth, with most newborns displaying length and weight above +2 SD. Growth velocity is above the 90th centile until the age of 4–6 years and tends to normalize at puberty, reaching a final height between 50 and 90th centiles; advanced bone age is common (Pettenati et al., 1986; Shuman et al., 1993; Weng et al., 1995). Patients may have facial features (Hikita et al., 2014), such as coarse long facies, prominent mandible often due to macroglossia, anterior open bite, earlobe grooves, infra-orbital recession and midfacial hypoplasia (Fig. 3) (Gurrieri et al., 2013; Kawafuji et al., 2011; Shuman et al., 1993).

Organomegaly is common, involving one or more organs including the liver, spleen, kidneys, pancreas, heart and adrenals where adrenocortical cytomegaly (large polyhedral cells with eosinophilic granular cytoplasm and enlarged nuclei) is a pathognomonic feature (Elliott et al., 1994; Shuman et al., 1993). Hyperinsulinemic hypoglycemia is frequent, tends to be transient but may be severe (Engstrom et al., 1988; Pettenati et al., 1986). Cleft palate, cardiomyopathy, nevus simplex, hemangiomas, brain abnormalities and hearing loss are less common (Elliott et al., 1994; Shuman et al., 1993). The malignancy risk is increased, particularly for Wilms tumors and hepatoblastomas (Mussa et al., 2016), but neuroblastomas, nephroblastomas, rhabdomyosarcomas and adrenal cortical carcinomas have been reported (DeBaun and Tucker, 1998; Wiedemann, 1997). A patient was diagnosed with an ACTH-secreting pituitary microadenoma in which a somatic *USP8* mutation was identified (Brioude et al., 2016).

2.2. Sotos syndrome

Sotos syndrome, also known as cerebral gigantism syndrome, is one of the most common overgrowth disorder, first described in 1964 (Sotos et al., 1964) and with a prevalence estimated at 1:10,000 to 1:50,000 (Leventopoulos et al., 2009). Most cases are sporadic, but autosomal dominant pedigrees have been reported (Chen et al., 2002; de Boer et al., 2004a; Winship, 1985). The diagnosis was based on clinical criteria until 2002 when haploinsufficiency of *NSD1* (nuclear receptor binding SET domain protein 1) was identified, and now genetic testing plays a key role in the diagnosis (Kurotaki et al., 2002). Sotos syndrome is caused by heterozygous loss-of-function *NSD1* pathogenic variants (Kurotaki et al., 2002). *NSD1* is translated into a 2696 amino-acid protein, present in fetal/adult brain, skeletal muscle, kidney, thymus, spleen, lung and leukocytes (Kurotaki et al., 2001) which is a SET-domain histone lysine methyltransferase that interacts with nuclear

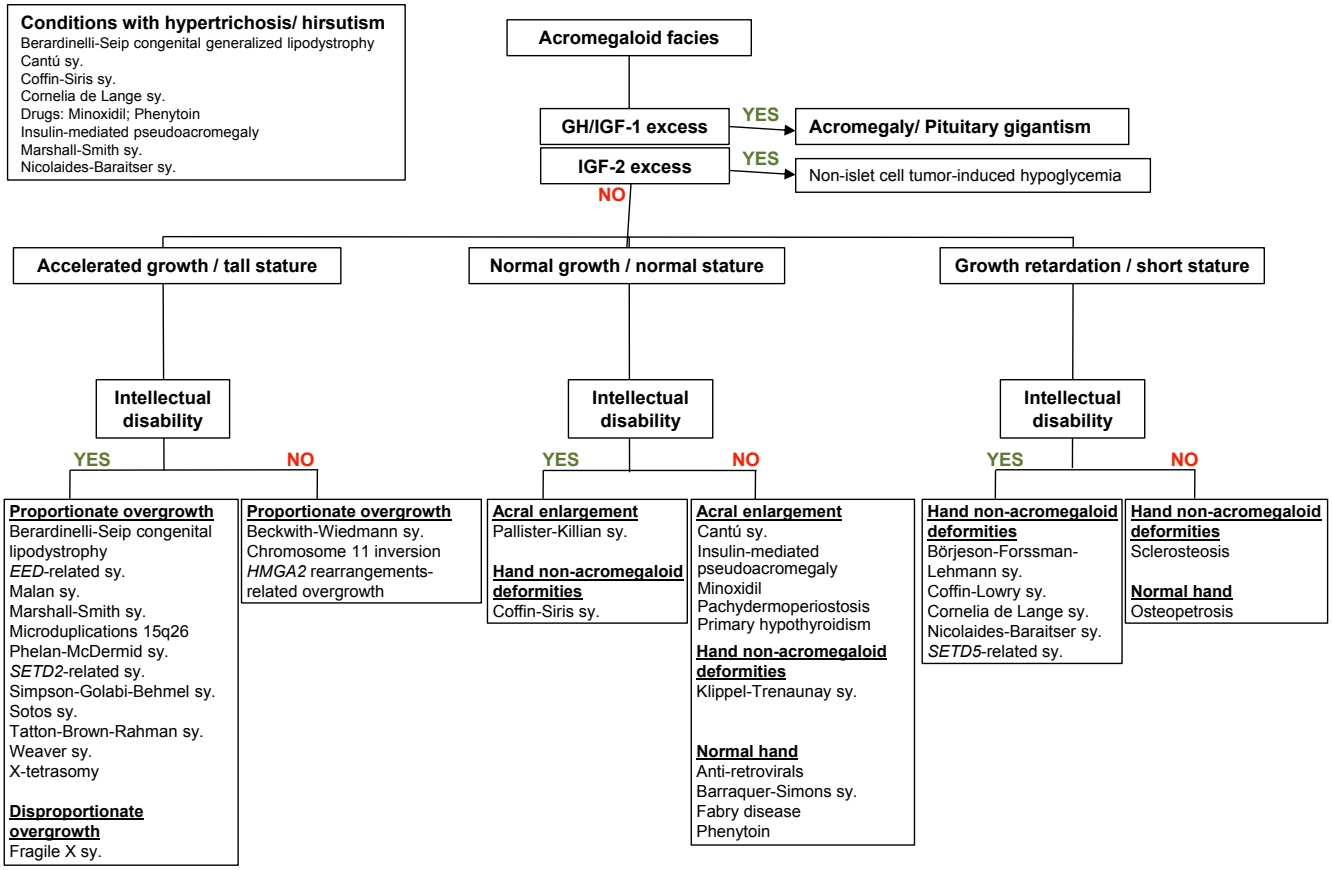

Fig. 2. Diagnostic flow chart for evaluation of individuals with acromegaloid features in the absence of GH/IGF-1 excess taking into account the main differential diagnoses. GH, growth hormone; IGF-1, insulin-like growth factor 1; IGF-2, insulin-like growth factor 2; sy., syndrome.

receptors and can activate or repress transcription (Baujat and Cormier-Daire, 2007; Faravelli, 2005; Huang et al., 1998). The exact mechanism leading to overgrowth remains unknown, but has been suggested that *NSD1* mutations may cause loss of the silencing of some unidentified growth promoting genes (Nielsen et al., 2004; Rayasam et al., 2003). MAPK-ERK pathway is determinant for longitudinal growth in the epiphyseal plates, and deregulation of this pathway may involved in the overgrowth (Visser et al., 2012). Modest increases in plasma IGFBP-2 and IGFBP-6 levels, and reduced IGF-1 and IGF-2 levels were detected in some patients, findings which otherwise are more closely related with short rather than tall stature; moreover, proliferation and mitogenic responses to IGFs were reduced in Sotos syndrome patient fibroblasts, suggesting that GH/IGF-1 axis is unlikely to play a role (De Boer et al., 2004b). *NSD1* mutation type is influenced by ethnicity, with Europeans typically harboring point mutations, while more than 50% of Japanese patients have microdeletions (Kurotaki et al., 2003; Kurotaki et al., 2002; Saugier-Veber et al., 2007). Overgrowth is less prominent in the microdeletion group than in the point mutations group (height +2.2 vs +3.3 SD, respectively) (Nagai et al., 2003; Rio et al., 2003; Tatton-Brown et al., 2005).

Sotos syndrome is characterized by the following key clinical features, present in more than 90% of patients: overgrowth, macrocephaly, characteristic facial appearance and learning difficulties (Tatton-Brown et al., 2005). Other manifestations affecting more than 15% of cases include premature teeth eruption, high palate, hypotonia, neonatal jaundice and poor feeding, scoliosis, cardiac, renal or central nervous system (CNS) abnormalities (Schaefer et al., 1997). More rarely astigmatism, cataracts, strabismus, myopia, hypermetropia, nystagmus, hearing loss, chronic otitis media, cholesteatoma, inguinal and umbilical hernia, craniosynostosis, pectus excavatum, genu valgum, syndactyly, hemangiomas, neonatal hypoglycemia, hypo/hyperpigmentation, hypoplastic nails, hypospadias and phimosis can be found (Gaudreau et al., 2013; Tatton-Brown et al., 2005; Tatton-Brown and Rahman, 2004).

Overgrowth is seen at birth with reported SD for birth length, weight and occipito-frontal circumference as +3.2, +1.0 and +1.8, respectively (Cole and Hughes, 1994), although up to 15% of cases have normal birth length (Ambler, 2002; Edmondson and Kalish, 2015; Tatton-Brown and Rahman, 2004). In infancy, growth velocity is particularly excessive in the first year, then slows between the ages of 2–6 years remaining consistently above the 97th centile, and at puberty tends to normalize due to epiphyseal fusion induced by sex steroid hormones. In most cases, the final height is within the upper limit of normal range (Agwu et al., 1999; Baujat and Cormier-Daire, 2007). The bone age is advanced during the childhood, but normalizes after puberty (Sotos, 1997). Characteristic facial features may resemble acromegaly (Dahlqvist et al., 2017), and typically include macrodolichocephaly (head longer than the width), frontal bossing, prominent mandibles, long face, high frontal hairline, scarce hair, pointy chin, inverted triangular face and downslanting palpebral fissures (Fig. 3) (Ambler, 2002; Baujat and Cormier-Daire, 2007). Other acromegaloid characteristics include macroglossia, large feet and hands (Fig. 4) and hoarse voice (Dahlqvist et al., 2017). Learning disability affects most patients (Baujat and Cormier-Daire, 2007; Lane et al., 2016) and there is an increased risk for saccrococcygeal teratomas, ganglioneuromas and neuroblastomas (Al-Mulla et al., 2004; Hersh et al., 1992; Tatton-Brown et al., 2005).

2.3. Weaver syndrome

Weaver syndrome was first reported in 1974 (Weaver et al., 1974), and its prevalence is not yet established, with most cases being sporadic, although autosomal dominant familial cases are reported

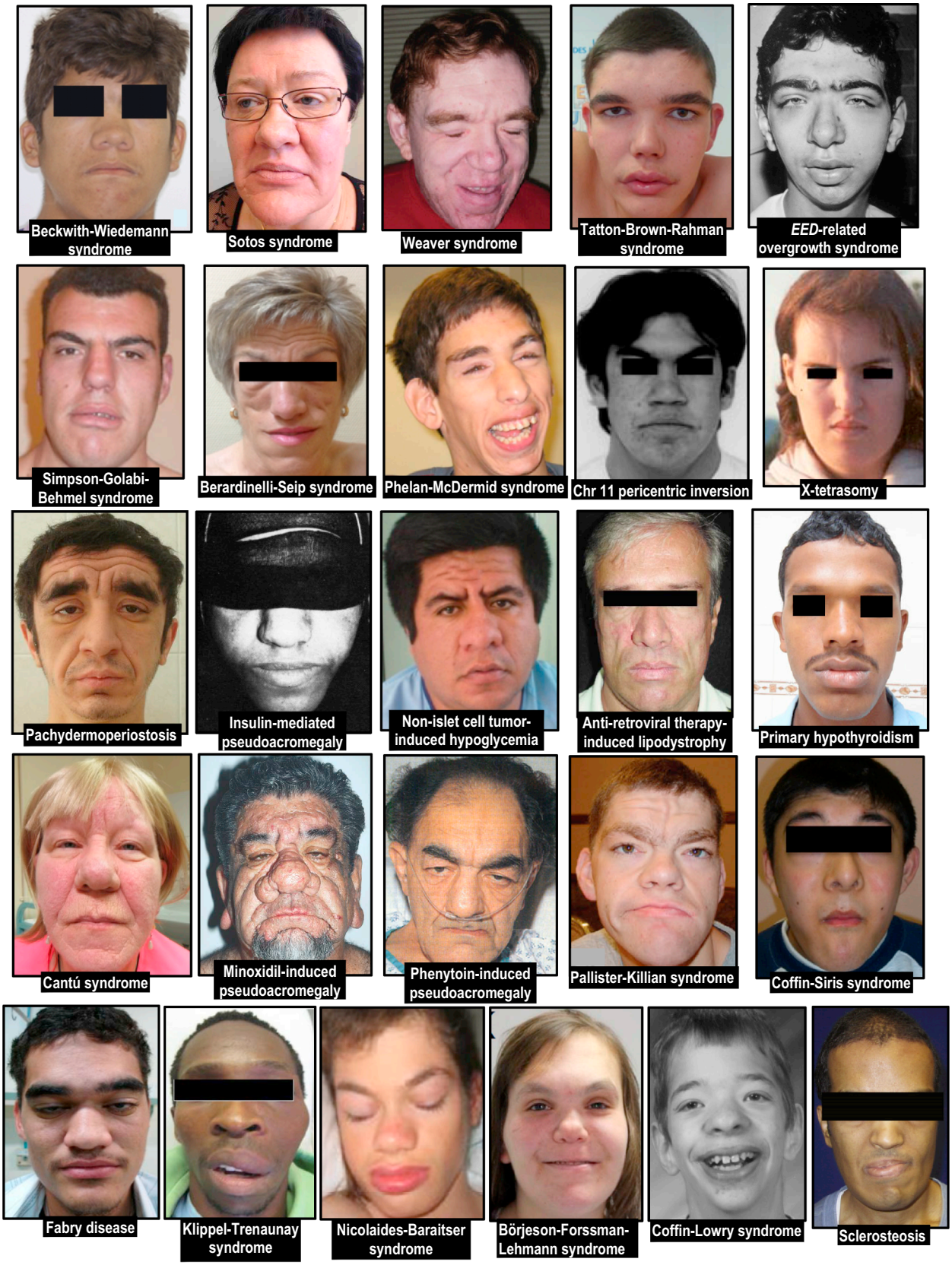

Fig. 3. Facial appearance in different pseudoacromegaly conditions. The source of each illustrative case is provided in the Supplemental Table 2.

Fig. 4. Hands in different pseudoacromegaly conditions. The source of each illustrative case is provided in the Supplemental Table 2.

(Fryer et al., 1997; Proud et al., 1998). Definitive diagnosis can be established by the detection of a heterozygous *EZH2* (enhancer of zeste homolog-2) mutation (Tatton-Brown et al., 2011; Tatton-Brown and Rahman, 2013). *EZH2* codes a SET-domain-containing histone methyltransferase which plays an important role in epigenetic modification of histones, determining chromatin compaction and transcriptional activity. EZH2 binds to histone binding proteins RBBP4 (retinoblastoma binding proteins 4) and RBBP7 to create the PRC2 (polycomb repressive complex). *EZH2* mutations lead to reduced PRC2 activity which is the main pathogenic mechanism (Cohen et al., 2016). PRC2 catalyzes the transfer methyl groups to lysine 27 of histone H3 (H3K27), therefore repressing gene transcription to which trimethylated H3K27 is bound (Cao et al., 2002; Kuzmichev et al., 2002; Tatton-Brown and Rahman, 2013). EZH2 has a role in stem cell maintenance, lineage determination and in osteogenesis, myogenesis, lymphopoiesis and hematopoiesis (Chou et al., 2011). EZH2 also interacts with other pathways relevant for cell growth, such as PI3K/mTOR pathway (Dazert and Hall, 2011; Lindhurst et al., 2011). More than 90% *EZH2* mutations are missense truncating mutations, and there is no genotype-phenotype correlation (Tatton-Brown et al., 2011).

Patients typically display exuberant prenatal and postnatal overgrowth, being remarkably tall during the infancy/childhood (up to +8 SD) (Tatton-Brown et al., 2011; Tatton-Brown and Rahman, 1993, 2013), as well as advanced skeletal maturation, intellectual disability

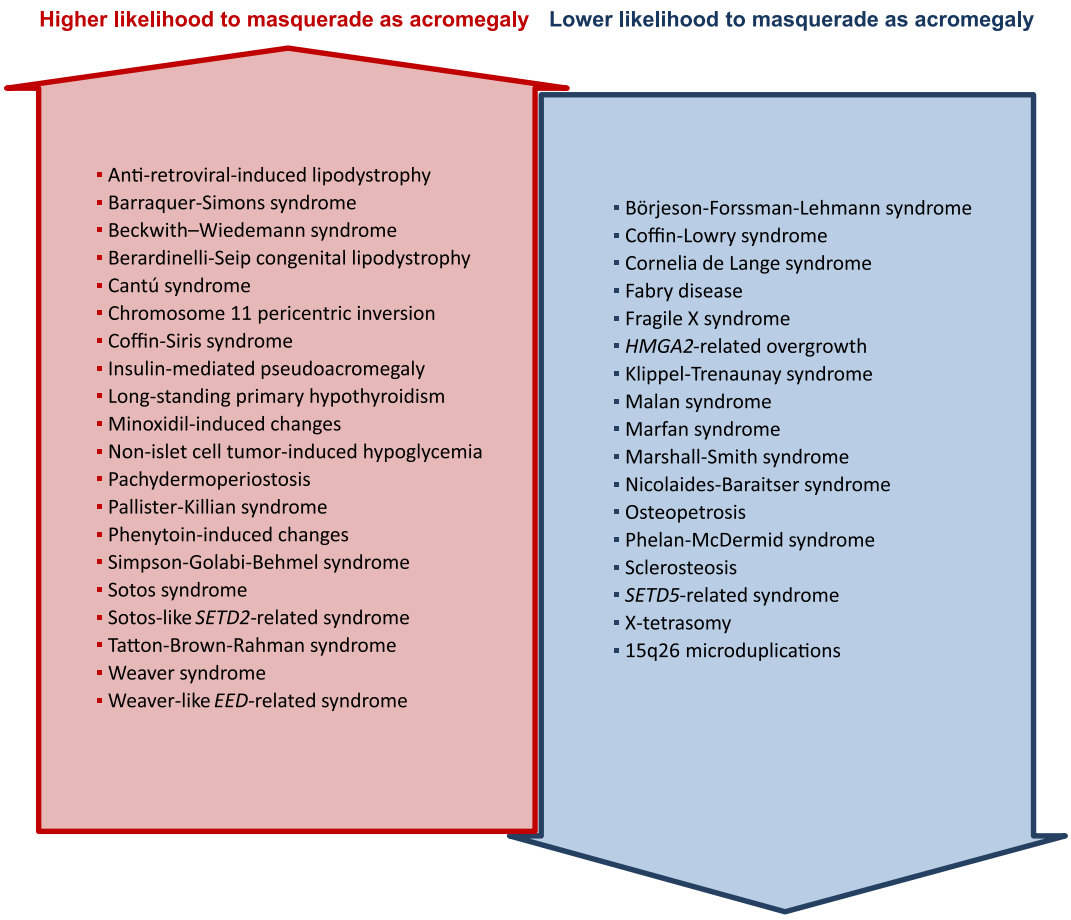

Fig. 5. Likelihood of each pseudoacromegaly condition to masquerade as acromegaly. Pseudoacromegaly conditions with acromegaloid physical features are divided to high likelihood to masquerade as acromegaly (red box on the left) or lower likelihood to masquerade as acromegaly (blue box on the right), taking into account the lower or higher prominence and likelihood of acromegaloid features as well as the presence of remarkable features that distinguish them from acromegaly. Conditions are listed in alphabetical order in each box.

and characteristic facial features such as macrocephaly, prominent forehead, flat occiput, micrognathia, prominent chin crease, ocular hypertelorism and large ears (Fig. 3). Mild limb abnormalities, joint contractures, deep-set nails, camptodactyly, large hands (Fig. 4) and feet, macroglossia, gingival edema, hoarse voice, soft skin and hypertonia are common (Gibson et al., 2012; O'Carroll et al., 2001; Tatton-Brown and Rahman, 2013; Wyngaarden et al., 2011). Patients may have oral and parodontal problems, such as generalized heavy plaque with subgingival calculus, malocclusion, maxillary atresia and bifid uvula (Miller et al., 2015), congenital cardiac and renal anomalies, scoliosis, talipes equinovarus, ligamentus laxity, poor neonatal feeding, umbilical hernia and seizures (Gibson et al., 2012; Tatton-Brown et al., 2011; Tatton-Brown and Rahman, 1993, 2013). The malignancy risk is increased (Tatton-Brown and Rahman, 2013), mostly for hematological malignancies and neuroblastomas (Tatton-Brown et al., 2011; Usemann et al., 2016). Hypothyroidism has been reported (Gibson et al., 2012; Iatrou et al., 2008).

The phenotype is variable, with some patients displaying only isolated overgrowth or mild facial features (Tatton-Brown and Rahman, 1993), many of them shared with Sotos syndrome, making the differential diagnosis between these entities challenging and the molecular testing crucial for an accurate diagnosis (Baujat et al., 2005; Douglas et al., 2003).

2.4. Tatton-Brown-Rahman syndrome

Tatton-Brown-Rahman syndrome is a Sotos-like autosomal dominant disorder due to heterozygous germline loss-of-function mutations in the *DNMT3A* (DNA methyltransferase 3A) gene (Tatton-Brown et al., 2014). *DNMT3A*, located on chromosome 2p23.3, encodes a DNA-methyltransferase essential in the genome-wide DNA methylation maintenance (Kaneda et al., 2004; Okano et al., 1999). All mutations are located in the functional domains damaging the methyltransferase activity (Lemire et al., 2017; Okamoto et al., 2016; Tatton-Brown et al., 2014; Xin et al., 2017).

Patients display tall stature, distinctive facial features and intellectual disability (Tatton-Brown et al., 2014). All patients show tall stature, on average +3 SD (Lemire et al., 2017), the tallest case with 206 cm (+5.25 SD) (Xin et al., 2017). The overgrowth tends to occur postnatally, although patients may born with increased length and weight (Lemire et al., 2017; Tlemsani et al., 2016; Xin et al., 2017). Facies is typically coarse with horizontal eyebrows, narrow palpebral fissures, large forehead, gingival hyperplasia, broad or small nose, thick nasal alae, long philtrum, high arched palate, thin upper vermillion, low-set ears, overcrowding teeth, hypertelorism and malar flush (Fig. 3) (Kosaki et al., 2017; Lemire et al., 2017; Shen et al., 2017; Xin et al., 2017). Other features includes hypotonia, large hands and feet, joint hypermobility, scoliosis, pes plannus, advanced bone age, obesity, acne, sparse frontotemporal hair, myopia, astigmatism, nystagmus, laryngomalacia, umbilical hernia, heart defects, hydronephrosis, cryptorchidism and depression (Kosaki et al., 2017; Lemire et al., 2017; Shen et al., 2017; Tatton-Brown et al., 2014; Xin et al., 2017). Neurological abnormalities include a small optic chiasm, optic nerve hypoplasia, focal encephalomalacia, hydrocephaly and Chiari type 1 malformations (Kosaki et al., 2017; Shen et al., 2017). One patient was found with combined GH, TSH and gonadotropin deficiency, but ACTH

and prolactin secretion were normal (Tlemsani et al., 2016). A young patient developed acute myeloid leukemia raising concerns for increased risk of hematological malignancies (Hollink et al., 2017; Shen et al., 2017).

2.5. Sotos-like SETD5-related overgrowth syndrome

A syndrome characterized by intellectual disability, leg length discrepancy and facial dysmorphism, among other Sotos-like features (Drumheller et al., 1996; Green et al., 2017; Szczaluba et al., 2016) has been associated with *SETD5* loss-of-function subsequent to microdeletions in chromosome 3 and intragenic *SETD5* variants (Grozeva et al., 2014; Kuechler et al., 2015). *SETD5* (Kleefstra et al., 2006), encodes the SET domain-containing protein 5 responsible for methylation of histone H3 and H4 lysine residues, having thus an important role in gene expression and chromatin remodelling (Green et al., 2017; Kuechler et al., 2015).

Craniofacial features include brachycephaly, prominent forehead, striking full/broad eyebrows, long nose, bulbous nasal tip, anteverted nares, large ears, hypertelorism, long philtrum, open mouth with an everted full lower lip and micrognathia (Green et al., 2017; Kuechler et al., 2015; Szczaluba et al., 2016). Long and thin fingers, prominent finger joints, broad distal phalanges, tapering fingers or clinodactyly are often seen (Green et al., 2017). Leg length discrepancy is characteristic, but other skeletal anomalies such as scoliosis, kyphosis, lordosis, pectum excavatum are more common (Green et al., 2017; Kuechler et al., 2015). Growth parameters are usually normal at birth, but patients often display growth retardation during childhood (Green et al., 2017; Kuechler et al., 2015); however, tall individuals are reported (Kuechler et al., 2015). Other manifestations include hypotonia, abnormal gait, myopia, astigmatism, strabismus, amblyopia, microphthalmia, heart defects, inguinal hernias, cryptorchidism, hypospadias, vesico-ureteral reflux, cleft palate, bifid uvula and recurrent infections (Green et al., 2017; Kuechler et al., 2015). Congenital primary hypothyroidism has been reported (Malhotra et al., 2011; Yagasaki et al., 2017).

2.6. Sotos-like SETD2-related overgrowth syndrome

Some patients exhibiting a Sotos-like phenotype negative for mutations in *NSD1* and *EZH2*, tested positive for *SETD2* (SET domain containing-2) mutations (Luscan et al., 2014). *SETD2*, located at 3p21.31, encodes a protein that catalyses H3K36 methylation leading to transcription activation (Edmunds et al., 2008; Lucio-Eterovic et al., 2010). Eight patients have been reported, and tall stature seen in seven (Lumish et al., 2015; Luscan et al., 2014; O'Roak et al., 2012; Tlemsani et al., 2016), while one was short (Lumish et al., 2015). Postnatal overgrowth (+2.5 SD), macrocephaly (+4 SD), obesity (> +4 SD), advanced bone age, joint hyperlaxity, speech delay, hypotonia and polycystic ovaries have been described (Luscan et al., 2014). While tall stature and intellectual disability are constant manifestations, facial dysmorphism is variable and include features such as long face, high forehead with bitemporal retraction, macrocephaly, prominent mandible, high frontal hairline, long or bulbous nose, malar hypoplasia, hypertelorism and downslanting palpebral fissures (Lumish et al., 2015; Luscan et al., 2014; O'Roak et al., 2012; Tlemsani et al., 2016).

2.7. Weaver-like EED-related overgrowth syndrome

Recently, 3 patients with a Weaver-like phenotype negative for *EZH2* and *NSD1* mutations were found to carry mutations in the *EED* gene (Cohen et al., 2016; Cohen, 2003; Cooney et al., 2017). *EED*, located at 11q14.2, encodes the epigenetic regulator protein EED which is an EZH2 partner essential for its methyltransferase activity (Cohen et al., 2016; Cooney et al., 2017; Morey and Helin, 2010). Overlapping phenotypes associated to *NSD1*, *EZH2*, *EED*, *DNMT3A*, *SETD5* and *SETD2* loss-of-function may be explained by a unifying pathogenic mechanism consisting in epigenetic disruption, mainly histone methylation (Cooney et al., 2017; Luscan et al., 2014; Tlemsani et al., 2016).

The overgrowth was either noticeable at birth or only postnatally. Throughout the childhood and adolescence, growth does not consistently remain above the 95th centile, but the childhood excessive height can be prominent up to +5.1 SD (Cohen et al., 2015). The final height tends to be above the 95th centile (Cohen and Gibson, 2016; Cohen et al., 2015). Facial features become more prominent in adulthood, typically including macrocephaly, large bifrontal diameter, hypertelorism, large ears, downslanting palpebral fissures, prominent and/or long philtrum, pointed chin and retrognathia (Fig. 3) and large hands (Fig. 4) (Cohen and Gibson, 2016; Cooney et al., 2017). Hypernasal and hoarse speech, poor coordination, developmental delay, hyper/hypotonia, seizures, hearing loss, camptodactyly, kyphoscoliosis, advanced bone age, osteopenia, small nails, pigmented nevi, widely spaced nipples, cryptorchidism, umbilical hernia, bidif uvula, genitourinary, cardiac and ophthalmic anomalies can be seen (Cohen and Gibson, 2016; Cohen et al., 2015; Cooney et al., 2017).

2.8. Simpson-Golabi-Behmel syndrome

Simpson-Golabi-Behmel syndrome is a rare X-linked overgrowth syndrome with unknown prevalence, first reported by Simpson et al. (1975), with additional cases by Golabi et al. (1984) and Behmel et al. (1984). There are 2 types: type 1 associated to mutations in *GPC3* (glypican 3) and the lethal type 2 associated to genetic anomalies at Xp22.2 (Tenorio et al., 2014) recently attributed to *PIGA* (phosphatidylinositol glycan class A) (Fauth et al., 2016). Here, we review the type 1 syndrome. *GPC3* is mapped to Xq26 and encodes a membrane associated cell surface heparan sulfate proteoglycan named glypican 3. Glypicans are proteoglycans that are bound to the cell surface by a GPI anchor (Filmus and Capurro, 2014). GPC3 plays a role in cell cycle, apoptosis and growth, through the inhibition of Hedgehog pathway, modulation of bone morphogenetic proteins, fibroblast growth factors (FGFs) and WNT signaling (Capurro et al., 2009; Filmus and Capurro, 2008). Overgrowth is independent of IGF-1 pathway (Song et al., 1997; Tenorio et al., 2014). Most of cases follow an X-linked inheritance pattern; however, some are *de novo* cases and at least one family with germinal mosaicism (Romanelli et al., 2007). The penetrance is 100%, with all *GPC3* mutated males being clinically affected (Tenorio et al., 2014). One patient was identified with a *GPC4* duplication, suggesting that *GPC4* can be also involved (Waterson et al., 2010).

Increased prenatal and postnatal growth is common in type 1 Simpson-Golabi-Behmel syndrome (Cottereau et al., 2013). Coarse and square face, wide mouth, everted lower lip, large forehead and nose (Fig. 3) are seen in 95% of patients (Cottereau et al., 2013). Macroglossia with a midline furrow of the tongue is present in up to 50% of patients, macrocephaly in 70% (Tenorio et al., 2014) and macrognathia, usually not observed in neonates or infants, becomes evident in childhood and prominent in adults (Cottereau et al., 2013). Other less common features includes cleft lip or palate, subcutaneous lipomas, flat nevus flammeus, hypertelorism, anteverted nares, macrostomia, odontogenic keratocysts and ear anomalies (Cottereau et al., 2013; Tenorio et al., 2014). Broad and/or short hands are found in more than 80% of cases (Fig. 4); index finger hypoplasia, nail dysplasia, broad fingertips, finger syndactyly and brachydactyly, postaxial polydactyly are also common (Cottereau et al., 2013; Tenorio et al., 2014). Other skeletal abnormalities include a deep V-shaped sella turcica, rib malformations, vertebral anomalies, chest deformity and scoliosis (Cottereau et al., 2013; Rodriguez-Criado et al., 2005; Tenorio et al., 2014). Genitourinary complications include urinary tract malformations, renal dysplasia/cysts, hypospadias, hydrocele, cryptorchidism and penoscrotal transposition (Cottereau et al., 2013). Nephromegaly, splenomegaly and hepatomegaly are common, whereas diaphragmatic, umbilical or inguinal hernias, neonatal liver or biliary disease are less common

(Tenorio et al., 2014). Heart and cardiovascular problems (Lin et al., 1999), supranumerary nipples (Tenorio et al., 2014), generalized hypotonia, intellectual disability, hydrocephalus, epilepsy and speech disorders have been reported (Tenorio et al., 2014; Young et al., 2006). Simpson-Golabi-Behmel syndrome predisposes for embryonic cancers including Wilms tumors, hepatoblastomas, adrenal neuroblastomas, gonadoblastomas and medulloblastomas (Lapunzina, 2005; Tenorio et al., 2014; Thomas et al., 2012).

2.9. Berardinelli-Seip congenital generalized lipodystrophy

Lipodystrophies are a heterogeneous conditions in which the defect lies in a generalized or partial absence of subcutaneous adipose tissue, congenital or acquired in origin (reviewed by Garg (2000, 2011)). Metabolic derangements, also common in acromegaly, include premature cardiovascular disease, diabetes, polycystic ovary syndrome (PCOS), acanthosis nigricans due to insulin resistance, and eruptive xanthomas, fatty liver or acute pancreatitis due to hypertriglyceridemia (Handelsman et al., 2013). Hyperinsulinemia secondary to insulin resistance, similarly to insulin-mediated pseudoacromegaly (Section 3.2), may give rise to an acromegaloid phenotype, including coarse facial appearance, hand and feet enlargement, muscular hypertrophy, macroglossia and genitalia enlargement (Handelsman et al., 2013; Huang-Doran et al., 2010; Quinn and Purcell, 2017; Van Maldergem, 1993). An acromegaloid appearance is more typical in Berardinelli-Seip congenital generalized lipodystrophy, but can be found in acquired partial lipodystrophy (Chakraborty et al., 2016b; Kumar et al., 1996; Quinn and Purcell, 2017). Berardinelli-Seip lipodystrophy is discussed here, while Barraquer-Simons syndrome and acquired partial lipodystrophy secondary to anti-retroviral therapy will be discussed in Section 3.4.

Berardinelli-Seip congenital lipodystrophy, reported by Berardinelli (Berardinelli, 1954) and further characterized by Seip (1959), is an autosomal recessive disorder with four distinct types depending on which gene is involved: type 1, *AGPAT2* (1-acylglycerol 3-phosphate-O-acyltransferase 2); type 2, *BSCL2* (Berardinelli-Seip congenital lipodystrophy 2); type 3, *CAV1* (caveolin-1); type 4, *PTRF* (polymerase I and transcript release factor) (Garg, 2004, 2011). Mutations in the AGPAT2, a key enzyme in triglyceride and phospholipid synthesis, cause lipodystrophy by inhibiting triacylglycerol synthesis and storage in adipocytes and increasing lysophosphatidic acid level that negatively affects adipocytes (Agarwal and Garg, 2006; Van Maldergem, 1993). Seipin encoded by *BSCL2* plays a role in lipid droplet formation and adipocyte differentiation (Garg, 2011). Caveolin-1 is a caveolae component which binds fatty acids and translocates them to lipid droplets. *PTRF* regulates caveolins 1 and 3 (Garg, 2000, 2004, 2011).

In Berardinelli-Seip generalized lipodystrophy functional adipocytes are absent leading to lipid storage in other tissues such liver and muscle resulting in metabolic complications (Van Maldergem, 1993). Mechanisms behind acromegaloid features may involve: hyperinsulinemia resulting in activation of the mitogenic MAPK pathway and resistance of the metabolic phosphoinositide 3-kinase (PI3K) pathway (Sam et al., 2011); GH resistance (Bereket et al., 1999; Douyon and Schteingart, 2002); hyperinsulinemia reduces IGF binding proteins therefore increasing IGF-1/binding protein ratio allowing a relatively unopposed IGF-1 action on peripheral IGF-1 receptors (Janssen et al., 1998).

Major diagnosis criteria include: (1) acromegaloid features, including coarse face (Fig. 3), tall stature, large hands and feet, clitoromegaly, enlarged external genitalia, muscular hypertrophy and advanced bone age; (2) generalized lipoatrophy mainly affecting the face, trunk and limbs; (3) hepatomegaly secondary to fatty liver; (4) hypertriglyceridemia; (5) insulin resistance, reflected by acanthosis nigricans. Minor criteria include: hypertrophic cardiomyopathy, psychomotor retardation or intellectual impairment, hirsutism, phlebomegaly, bone cysts and precocious puberty in females (Gomes et al., 2009; Van Maldergem, 1993). The diagnosis is established in the presence of 3 major criteria, or 2 major and 2 minor criteria, and/or by detecting a pathogenic variant in a related gene (Garg, 2011; Van Maldergem, 1993). Berardinelli-Seip congenital lipodystrophy is usually diagnosed at birth or soon after. Clinical presentation in the first months of life typically include failure to thrive, lipoatrophy, acromegaloid facies, macroglossia, hepatomegaly, muscular appearance, large hands and feet or developmental delay (Garg, 2011; Gomes et al., 2009; Van Maldergem, 1993). In a series of 54 cases, acromegaloid facies was reported in 95.5%, with atrophic cheeks and prognathism described in 97.7% and 90.9%, respectively (Lima et al., 2016). A review involving childhood-onset cases reported rates of acromegaloid features and prominent musculature of 76% and 97%, respectively (Gupta et al., 2017). Hypermetabolism is an important feature (Magage et al., 2007), leading to increased appetite and body temperature, hyperhidrosis, organomegaly and muscle hypertrophy (Gomes et al., 2009; Van Maldergem, 1993), also common in acromegaly. Children have accelerated growth. Precocious puberty is common in females, but delayed menarche and irregular menstruation may also be found, while fertility may be impaired in women but usually not in men (Gomes et al., 2009; Van Maldergem, 1993).

2.10. NFIX-related disorders: Malan and Marshall-Smith syndrome

Malan and Marshall-Smith syndromes are overgrowth conditions that result from distinctive *NFIX* pathogenic variants (Gurrieri et al., 2015). *NFIX* (nuclear factor I-X), located at 19p13.3, is a member of the NFI transcription factor family consisting of 4 closely-related genes (*NFIA, NFIB, NFIC* and *NFIX*), which encodes proteins capable of binding DNA and interacting with other proteins such RNA polymerase subunits (Gurrieri et al., 2015). NFIX proteins are involved in brain development (Campbell et al., 2008; Driller et al., 2007), chondrocyte differentiation and in endochondral ossification suggesting that *NFIX* act as negative regulator of ossification. *NFIX* pathogenic variants may dysregulate bone proliferation and differentiation (Malan et al., 2010). In most cases, there is a phenotypic separation between Malan and Marshall-Smith syndromes, which may be explained by the abnormal protein fate: while in Malan syndrome phenotype results from *NFIX* haploinsufficiency, in Marshall-Smith syndrome there is a dominant-negative effect of the truncated NFIX proteins, which can dimerize with the wild-type protein leading to a more severe phenotype (Malan et al., 2010; Martinez et al., 2015). The major distinction between the two forms is the prognosis, favorable in Malan syndrome but poor in Marshall-Smith syndrome (Gurrieri et al., 2015).

Malan syndrome overgrowth is typically postnatal (Klaassens et al., 2015), and macrocephaly, prominent forehead and chin, downslanting palpebral fissures and high anterior hairline, advanced bone age, scoliosis, mental retardation, seizures and neonatal hypotonia are common features (Klaassens et al., 2015). Pectus excavatum, strabismus, nystagmus and optic disc hypoplasia are frequently seen while episodic ataxia and migraines affect a minority of patients (Klaassens et al., 2015). There are no reports of neoplasia (Klaassens et al., 2015).

Marshall-Smith syndrome is characterized by dysmorphic facial features, accelerated skeletal maturation, respiratory difficulties, failure to thrive and mental retardation (Aggarwal et al., 2017). Facial features include prominent forehead, flat midface, prominent maxilla, micro and retrognathia, short nose, long philtrum, everted full lips, gingival hyperplasia, large and protuberant tongue and irregular teeth. Large eyes and shallow orbits may lead to proptosis; myopia, glaucoma and optic nerve hypoplasia are common (Shaw et al., 2010). Stature is usually normal in childhood, but after puberty height gradually diverges from normal and final height is, in some cases, more than -6 SD below the mean, partly due to thoracic kyphoscoliosis. Advanced bone age is invariably reported. The proximal and middle phalanges are usually wide, whereas terminal phalanges are short and narrow (Fig. 4) (Shaw et al., 2010). Recently, a young girl was reported with progressive thelarche, high growth velocity and abnormal GnRH stimulation test indicative of central precocious puberty, with no sellar region

abnormalities (Aggarwal et al., 2017). Choanal stenosis, laryngomalacia, laryngeal stenosis, glottis stenosis are common (Gomez-Santos et al., 2014; Shaw et al., 2010). Hypertrichosis, cryptorchidism, hypospadias, genital labia hypoplasia, vesicoureteral reflux, pigmentary skin defects, umbilical hernia, pyloric stenosis, IgA deficiency, mental disability, truncal hypotonia and peripheral hypertonia, CNS anomalies and Wilms tumors have been reported (Gomez-Santos et al., 2014; Shaw et al., 2010; Travan et al., 2008; van Balkom et al., 2011).

2.11. Phelan-McDermid syndrome

Phelan-McDermid syndrome, also known as 22q13.3 deletion syndrome, equally affects females and males (Phelan and Rogers, 1993) and is caused by either a 22q13 chromosome deletion involving the *SHANK3* (SH3 and multiple ankyrin repeat domain) gene or by a mutation in this gene (Phelan and McDermid, 2012; Phelan, 2008). *SHANK3* encodes a protein that connects ion channels and receptors in the post-synaptic membrane playing a key role in the CNS (Luciani et al., 2003; Wilson et al., 2003).

Neonatal hypotonia and developmental delay (often the earliest manifestations), dysmorphic features and postnatal accelerated growth affect more than 95% of patients (Phelan, 2008). Birth growth parameters are usually normal, children are tall during childhood and adolescence (+2 or +3 SD), while adult height is frequently normal (Phelan and Rogers, 1993; Phelan, 2008; Rollins et al., 2011). Macrocephaly can be found, but microcephaly is more common (Rollins et al., 2011). Craniofacial features includes wide nasal bridge, supraorbital fullness, hypertelorism, deep set-eyes, large ears, long philtrum, full lips, pointed chin, dolichocephaly, epicanthal folds, full cheeks, full brow, wide spaced teeth and malocclusion (Fig. 3). The face coarsens over time, with adults displaying a prominent square jaw. The hands tend to be large and fleshy with normal fingernails (Hopkin et al., 2008), although dysplastic toenails are described (Phelan and McDermid, 2012; Phelan and Rogers, 1993; Phelan, 2008). Decreased perspiration and tendency to overheat is seen in half of patients (Phelan, 2008). Endocrinopathies include precocious or delayed puberty and hypothyroidism (Kolevzon et al., 2014). Infertility is not typical but hypergonadotropic hypogonadism was reported (Misceo et al., 2011). Other features include lymphedema, renal anomalies, hearing loss, arachnoid cysts, frontal lobe hypoplasia, corpus callosum agenesis, ventriculomegaly, seizures, ptosis and cardiac defects (Phelan, 2008).

2.12. Chromosome 11 pericentric inversion

Stratakis et al. identified a chromosome 11 pericentric inversion in a young male referred with a possible diagnosis of acromegaly. Acromegaloid facial features with prominent supraorbital ridges and coarse facies (Fig. 3), together with symmetrical overgrowth, advanced bone age, sleep apnea, oily skin, acne, submucosal cleft palate and a diaphragmatic hernia were described in this patient. Acromegaloid features of variable severity, overgrowth and palatal cleft were also identified in his mother and sister, who had the same chromosomal abnormality. The etiology of acromegaloidism in this family remains unknown (Stratakis et al., 2001).

2.13. Fragile X syndrome

Fragile X syndrome is an X-linked dominant disorder caused by a loss-of-function pathogenic variant in the *FMR1* (fragile X mental retardation 1) gene, with subsequent loss of its encoded protein, FMRP. FMRP regulates many proteins involved in neuronal synaptic connections (Rajaratnam et al., 2017; Saul and Tarleton, 1993). There is a remarkable gender difference, with males presenting a more severe phenotype than females (Lozano et al., 2014; Saul and Tarleton, 1993). The most common facial features include long face and prominent forehead (83%), macrocephaly (50–81%), large ears (75%) and prominent jaw (80%) (Rajaratnam et al., 2017; Saul and Tarleton, 1993). Growth velocity in boys with fragile X syndrome is higher during the prepubertal period, but tend to decelerate after puberty and final height tends to be normal (Kidd et al., 2014; Loesch et al., 1995). Normal growth have also reported in this setting (Butler et al., 1992). Female carriers are predisposed to premature ovarian failure. Other features include obesity, strabismus, seizures, hypotonia, intellectual disability, gastrointestinal problems, mitral valve prolapse, aortic root dilation and recurrent otitis (Loesch and Hagerman, 2012; Rajaratnam et al., 2017; Saul and Tarleton, 1993).

2.14. SHOX overdosage

The *SHOX* (short stature homeobox containing) gene (Rao et al., 1997) is mainly expressed in bone marrow fibroblasts of the distal limb bones, and functions as a linear growth promoter and as a repressor of growth plate fusion (Ogata et al., 2000; Ogata et al., 2001). *SHOX* is a pseudoautosomal gene with a dosage effect in structural or numeric sex chromosome aberrations (Ogata et al., 2001; Rao et al., 1997). Overdosage (extra copies) of *SHOX* in combination with gonadal dysgenesis and estrogen deficiency lead to tall stature (Binder et al., 2001; Nishi et al., 2008; Ogata et al., 2000). These patients display tall stature, long limbs, long hands and feet, and amenorrhea. Females with 3 copies of *SHOX* and gonadal dysgenesis usually have an adult stature of between +2.0 and +2.9 SD (Nakamura et al., 2001), and are 5–10 cm taller than the general population (Ogata and Matsuo, 1993). Patients grow normally in the prepubertal period but for an extended period because of delayed growth plate fusion in the background of estrogen deficiency (Binder et al., 2001; Ogata et al., 2002, 2001). Acromegaloid features with normal GH secretion were described in a female with *SHOX* overdosage due to X-tetrasomy who was referred with presumed acromegaly following changes in her appearance, mainly progressive face coarsening (Fig. 3) (Alvarez-Vazquez et al., 2006).

2.15. Microduplications 15q26

Overgrowth is rarely associated with chromosomal inbalances (Zollino et al., 1999), and in fact, most patients with chromosomal abnormalities are short (Kant et al., 2007). Trisomy and tetrasomy of chromosome 15 distal end has been associated with overgrowth (Kant et al., 2007; Tatton-Brown et al., 2009). Duplication of this region results in duplication of *IGF1R* (IGF-1 receptor) gene, thought to represent the main cause of overgrowth (Faivre et al., 2003; Kant et al., 2007; Nagai et al., 2002). Accelerated growth was observed in fibroblasts from a patient with 3 *IGF1R* copies (Okubo et al., 2003). Conversely, inactivating *IGF1R* mutations are associated with growth failure (Abuzzahab et al., 2003). However, not all cases with 15q26-qter trisomy have overgrowth (Roggenbuck et al., 2004; Zollino et al., 1999), and some tall patients have 15q26.3 microduplications not involving *IGF1R*, suggesting that other genes may also be involved (Leffler et al., 2016), or some features may depend on specific breakpoints (Roggenbuck et al., 2004). Leffler et al. raised the possibility for a second candidate, *LRRK1* (leucine-rich repeat kinase 1), which encodes ROCO protein (Leffler et al., 2016) thought to regulate cell proliferation and endocytic receptor trafficking (Harada et al., 2005).

Postnatal overgrowth is more frequent, but prenatal overgrowth has been reported (Faivre et al., 2004; Kant et al., 2007; Leffler et al., 2016). Length at birth is usually in the upper half of normal range (Kant et al., 2007) or increased (Faivre et al., 2002) as high as +4.2 SD (Okubo et al., 2003); few patients have low birth length (Nagai et al., 2002). Growth velocity is usually increased during childhood (Faivre et al., 2002), and the final height above +3 SD (Faivre et al., 2002; Kant et al., 2007; Leffler et al., 2016). Facial features include frontal bossing, high forehead, elongated face, pointed or large chin, wide nasal bridge, triangular facies, low-set ears and downslanting eyes (Faivre et al., 2002; Kant et al., 2007). Large wrists and ankles, short

thumbs, arachnodactyly, hyperlaxity, scoliosis, hearing loss, mental retardation, kidney and heart defects have been reported (Faivre et al., 2002; Wieczorek et al., 1998). Endocrine abnormalities are uncommon (Faivre et al., 2002; Kant et al., 2007), although a young girl was reported with precocious puberty (Kant et al., 2007).

3. Acromegaloid appearance with normal growth/stature

3.1. Pachydermoperiostosis

One of the most striking pseudoacromegaly conditions is pachydermoperiostosis (also known as primary hypertrophic osteoarthropathy or Touraine-Soulente-Golé syndrome) (Abdullah et al., 2017; Chakraborty et al., 2016a; Karimova et al., 2017; Mahy and Wiggins, 1992; Mangupli et al., 2017), a rare genetic disorder caused by prostaglandin excess (Castori et al., 2005), distinct from secondary hypertrophic osteoarthropathy in many cardiac or pulmonary diseases (Zhang et al., 2013b). Pachydermoperiostosis can be inherited both by an autosomal dominant and recessive manner (Castori et al., 2005; Diggle et al., 2012; Zhang et al., 2014; Zhang et al., 2013b), and the diagnosis made on clinical grounds can be genetically confirmed. Type 1 pachydermoperiostosis (due to mutations in *HPGD*, which encodes the hydroxyprostaglandin dehydrogenase) occur in early childhood, males and females are equally affected, and usually elevated urinary prostaglandin E2 but low/undetectable prostaglandin E2 metabolites are found. Type 2 pachydermoperiostosis (due to mutations in *SLCO2A1*, which encodes prostaglandin E2 transported SLCO2A1 (solute carrier organic anion transporter family member 2A1) allowing prostaglandin cytoplasmic degradation by HPGD) manifests in the second decade of life, with a more severe phenotype (prominent cutis verticis gyrate and hypocellular myelofibrosis) and elevated urinary prostaglandin and its metabolite (Diggle et al., 2012; Seifert et al., 2012; Tuysuz et al., 2014; Yuan et al., 2015). Prostaglandin E2 osteogenic effect is likely mediated by vascular endothelial growth factor and/or by abnormal platelet activation via prostaglandin E receptor subtype 3 (Fabre et al., 2001; Harada et al., 1994). Prostaglandin E2 can promote fibroblast growth and increase collagen and extracellular matrix (ECM) production resulting in the typical connective tissue manifestations (Matucci-Cerinic et al., 2000).

The major diagnostic features are digital clubbing, joint problems and pachydermia (thickening and furrowing of the skin). These manifestations are usually progressive for 5–20 years before becoming stationary or resolve later in life (Castori et al., 2005; Zhang et al., 2013b). Digital clubbing is the most specific sign present in most cases (Fig. 4). Arthralgia affects up to 40% of patients, with knees, ankles and wrists being the major affected joints. Synovial effusions, periosteal changes, acroosteolysis and ligaments/interosseous membranes ossification are common (Martinez-Lavin et al., 1988). Skin involvement is characterized by facial coarsening, dermal hypertrophy and pachydermia of the forehead, face and scalp skin (cutis verticis gyrate) especially in type 2, sometimes described as leonine face (Fig. 3) (Ghosn et al., 2010). Sebaceous gland hypertrophy leads to seborrhea, acne, hyperhidrosis and blepharoptosis. Non-steroid anti-inflammatory drugs block prostaglandin E2 synthesis, and are effective in relieving joints pain and inflammation, as well as in improving hyperhidrosis, seborrhea (Castori et al., 2005; Giancane et al., 2015), pachydermia and coarse facies (Li et al., 2016). Botulinum toxin type A may improve pachydermia in some cases (Ghosn et al., 2010). Other pachydermoperiostosis complications, include anemia, myelofibrosis, hypoalbuminemia, chronic gastritis, peptic ulcer, Ménétrier disease, Crohn's disease, gastric or colon cancer (Castori et al., 2005; Guda et al., 2014; Zhang et al., 2013b), and watery diarrhea, particularly induced by cold drinks, greasy food or sexual intercourse (Zhang et al., 2013a). Corneal leukoma, hypoplastic internal genitalia, gynecomastia and follicular thyroid cancer are rare (Cantatore et al., 1995; Jajic et al., 2001; Tavarelli et al., 2015).

3.2. Insulin-mediated pseudoacromegaly

Insulin-mediated pseudoacromegaly is characterized by severe insulin resistance, acanthosis nigricans and acromegaloid features in the absence of GH excess (Baynes et al., 2000; Flier et al., 1993; Sam et al., 2011). Insulin-mediated pseudoacromegaly is associated with a selective post-receptor insulin signaling defect in which the insulin metabolic actions are impaired but its mitogenic actions are preserved (Yaqub and Yaqub, 2008). The first study was conducted on skin fibroblasts from a patient with insulin-mediated pseudoacromegaly (Flier et al., 1993), and later studies provided evidence for impaired insulin-stimulated PI3K activity but preserved insulin-mediated mitogenesis (Dib et al., 1998; Kausch et al., 1999). When insulin binds to its receptor causes phosphorylation of IRS-1 (insulin-receptor substrate 1) and Shc. Shc binds to PI3K activating downstream metabolic pathways (Lizcano and Alessi, 2002), and IRS-1 activates RAS-RAF-MEK-MAPK pathway relevant for cell growth (Dib et al., 1998). Hence, in insulin-mediated pseudoacromegaly the metabolic actions of insulin are reduced resulting in hyperinsulinemia, whilst insulin mitogenic actions are preserved leading to acromegaloid appearance (Dib et al., 1998; Kausch et al., 1999). Other mechanisms may have a contributory role: when insulin binds to its receptor activates farnesyltransferase, an intracytoplasmic enzyme that mediates the availability of farnesylated RAS on the plasma membrane; in hyperinsulinemia, increased farnesylated RAS availability enhances the mitogenic potential of insulin and other growth factors (Goalstone and Draznin, 1996; Goalstone et al., 1998a; Goalstone et al., 1998b). Insulin and IGF-1 receptors share a number of biological activities which may contribute further for cell growth: IGF-1 binding to its receptor results in IRS-1 phosphorylation and RAS-RAF-MEK-MAPK pathway activation, similarly as to insulin (Lee and White, 2004); insulin and IGF-1 exhibit affinity for each other's receptor, and thus high insulin levels resultant from insulin resistance may act on the type 1 IGF receptor (Sam et al., 2011); α and β subunits of insulin and type 1 IGF receptors are able to form hybrid receptors with increased affinity for its ligands (Bailyes et al., 1997; Moxham et al., 1989; Sachdev and Yee, 2007; Samani et al., 2007; Slaaby et al., 2006).

Insulin resistance and hyperinsulinemia occur in obesity (Cruz et al., 2005), diabetes, lipodystrophies such as Berardinelli-Seip congenital generalized lipodystrophy (Garg, 2004), PCOS (Bhathena, 2011; Fox et al., 1991), or in complex syndromes such as Bardet-Biedl, Bloom or Werner syndromes (Semple et al., 2011). Genetic abnormalities in the insulin receptor results in hyperinsulinemia, diabetes and often acromegaloid features, a condition first described by Kahn *et al.* and termed as acromegaloid variant of type A insulin resistance (Kahn et al., 1976; Kumar et al., 1996). Insulin resistance type A is caused by heterozygous, homozygous, or compound heterozygous mutations in insulin receptor gene, and as insulin shares structural homology with IGF-1, insulin cross-receptor activation is regarded as the main mechanism. Several patients have been reported (Flier et al., 1993; Flier et al., 1980; Low et al., 1989), but most do not have acromegaloid features (Ardon et al., 2014). Some patients identified clinically with acromegaloid variant of type A insulin resistance do not carry mutations in the insulin receptor gene (Krook et al., 1994; Kumar et al., 1996).

The clinical picture in insulin-mediated pseudoacromegaly may include face coarsening (Fig. 3), frontal bossing, macroglossia, separated teeth, prognathism, large ears, acral enlargement (Fig. 4), reduced subcutaneous fat on arms and legs, well-developed muscles, weight gain, acanthosis nigricans, skin tags, acne, hirsutism, hyperhidrosis, oligoamenorrhea and PCOS (Flier et al., 1993; Kumar et al., 1996; Sam et al., 2011). Adenomatous colonic polyps and multinodular goitre have been reported (Sam et al., 2011). Acromegaloid bone changes were described in a woman with PCOS and severe hyperinsulinemia (Fox et al., 1991). Increased intimal and medial complex thickness of common carotid artery was reported in a 17-years old patient (Fukunaga et al., 1997), linking hyperinsulism with premature

atherosclerosis (Fukunaga et al., 1997; Stout, 1996). Clinical features in insulin-mediated pseudoacromegaly overlap with acromegaly, but IGF-1 levels and GH suppression on OGTT are usually normal. These patients usually have hyperinsulinemia, hyperglycemia, hypertriglyceridemia, increased nonesterified fatty acids (Kumar et al., 1994), as well as increased LH levels and hyperandrogenism with increased total, free testosterone and low sex hormone binding globulin (Kumar et al., 1996; Sam et al., 2011). These patients assessment can be complicated when incidental pituitary adenomas are found (Famuyiwa and Sulimani, 1993; Hernan Martinez et al., 2014; Yaqub and Yaqub, 2008). Their management is challenging, particularly the diabetes as usually requires high insulin doses in combination with insulin-sensitizing antidiabetic drugs (Sam et al., 2011). Antilipolytic drugs such as nicotinic acid analogues or fibric acid derivatives have been shown to be beneficial and and may reverse diabetes, at least in part, by suppressing nonesterified fatty acids (Kumar et al., 1994; Kumar et al., 1996).

3.3. Non-islet cell tumor-induced hypoglycemia

Non-islet cell tumor-induced hypoglycemia is a rare paraneoplastic entity, described in 1929 (Daughaday et al., 1988; de Groot et al., 2007), classically seen in patients with tumors of mesenchymal origin (Bertherat et al., 2000; Dutta et al., 2013; Trivedi et al., 1995), although can arise from any neoplasm (de Groot et al., 2007; Iglesias and Diez, 2014). Mesenchymal tumors, such mesotheliomas, solitary fibrous tumors, gastrointestinal stromal tumors, hemangiopericytomas and fibrosarcomas are responsible for nearly 40% of cases, whereas 40% are due to epithelial tumors such lung, prostate or colon cancer, as well as endocrine and neuroendocrine tumors (de Groot et al., 2007; Dutta et al., 2013). The pathogenic mechanism is related to *IGF2* overexpression and aberrant tumoral secretion of “big” or pro-IGF-2 (incompletely processed IGF-2 precursors) resulting in persistent insulin-like activity (de Groot et al., 2007; Iglesias and Diez, 2014). Circulating pro-IGF-2 binds poorly to binding proteins, therefore increased ability to penetrate tissues (de Groot et al., 2007; Iglesias and Diez, 2014; Morioka et al., 2014). Pro-IGF-2 suppresses GH, insulin, IGF-1 and IGF-binding protein 3. The elevated IGF-2 bioavailability increases glucose consumption and decreases hepatic gluconeogenesis leading to hypoglycemia, and its interaction with IGF-1 receptors explains the acromegaloid features (de Groot et al., 2007; Iglesias and Diez, 2014).

Non-islet cell tumor-induced hypoglycemia present usually in the fifth to sixth decade of life. Hypoglycemia is a cardinal feature (de Groot et al., 2007; Iglesias and Diez, 2014) which can be the presenting symptom or appear later during the disease course (Dutta et al., 2013; Fukuda et al., 2006). Patients commonly develop acromegaloid features (Ries et al., 2006), such as facial changes including coarse facies, thick lips, bumpy nose, soft tissue facial swelling, rhinophyma (Fig. 3), acral swelling, skin tags and oily skin, which typically regress after treatment of the underlying tumor (de Groot et al., 2007; Dutta et al., 2013; Trivedi et al., 1995). In a series of 6 cases, an acromegaloid phenotype was found in two (Jannin et al., 2018). Despite somatostatin receptors may be present in up to 40–55% of the underlying tumors, somatostatin analogues are unable to restore glucose levels and reverse acromegaloid features (Cebon et al., 2006; Morbois-Trabut et al., 2004; Perros et al., 1996; Reubi et al., 1999); nonetheless, somatostatin infusion reduced the tumoral pro-IGF-2 secretion in a patient with a hemangiopericytoma (Chung and Henry, 1996).

3.4. Acquired partial lipodystrophy: Barraquer-Simons syndrome and anti-retroviral therapy-induced lipodystrophy

Before the recognition of anti-retroviral therapy-induced lipodystrophy, Barraquer-Simons syndrome was the most common acquired partial lipodystrophy (Garg, 2004, 2011). **Barraquer-Simons syndrome** typically occurs before the age of 15 years, affects more prominently females, and the fat loss progress gradually, first affecting the subcutaneous tissue of face, then neck, upper extremities and trunk, but sparing the lower abdomen and legs (Garg, 2011). Metabolic complications such dyslipidemia, insulin resistance, acanthosis nigricans, diabetes, hirsutism or menstrual irregularities are seldom seen. One third of the patients have mesangiocapillary glomerulonephritis, and other autoimmune diseases may be found (Garg, 2000, 2011). The fat loss appears to involve an autoimmune-mediated destruction of adipocytes, with more than 80% of these patients having low serum complement 3 and detectable circulating antibodies thought to promote adipocyte lysis (Garg, 2011).

Over the past decades, **anti-retroviral therapy** became the most common cause of acquired partial lipodystrophy. Anti-retroviral therapy-induced lipodystrophy appears after 2 or more years of treatment with protease inhibitors or nucleoside analogues (Van Maldergem, 1993), especially thymidine analogues such as stavudine or zidovudine (de Waal et al., 2013). Protease inhibitors may cause lipodystrophy by inhibiting zinc metallopeptidase STE24, an enzyme involved in the formation of lamin A, with subsequent accumulation of toxic farnesylated prelamin A, by altering the expression of transcription factors involved in lipogenesis and adipocyte differentiation, and by inducing insulin resistance through the downregulation of glucose transporter type 4 (Bastard et al., 2002; Hudon et al., 2008), whereas nucleoside transcriptase inhibitors-induced lipodystrophy has been linked to mitochondrial toxicity (Lee et al., 2003). Most patients gradually lose subcutaneous fat from the face (the most commonly affected region) (Fig. 3), arms and legs (Soares and Costa, 2011). The fat loss worsens with ongoing anti-retroviral therapy, and does not reverse after its discontinuation; however, features may ameliorate by switching for tenofovir DF or abacavir (Moyle et al., 2006), but some cases require surgery (Soares and Costa, 2011; Wu et al., 2016).

3.5. Primary hypothyroidism

Acromegaloid features due to long-standing and/or severe primary hypothyroidism have been reported (Chakraborty et al., 2017; Kumar et al., 2012; Ruchala et al., 2009). The hypothyroidism-related acromegaloid features typically involve skin and soft tissues. These patients may develop coarse facies, prominent supraorbital ridges, broad nose, thick lips, macroglossia and prognathism (Fig. 3), as well as acral enlargement (Chakraborty et al., 2017; Kumar et al., 2012). Other acromegalic features such as snoring, joint pain, lethargy, skin tags and decreased libido have been reported (Chakraborty et al., 2017).

Hypothyroidism is associated with dermal deposition of mucopolysaccharides leading to myxedematous changes in the face and extremities (Heymann, 1992; Kumar et al., 2012). Another mechanism behind the soft tissue changes in long-standing hypothyroidism relies on the stimulation of TSH receptors present in fibroblasts leading to increased production of glycosaminoglicans (Hari Kumar et al., 2011; Kumar et al., 2012). However, unlike the acromegalic oily skin, in hypothyroidism the skin is pale, dry and hyperkeratotic with superficial scaling. Macroglossia is another common feature in hypothyroidism and acromegaly (Chakraborty et al., 2017). Severe primary hypothyroidism in childhood may lead to precocious puberty with delayed bone age (Van Wyk-Grumbach syndrome) (Baranowski and Hogler, 2012). The clinical picture in hypothyroidism-related pseudoacromegaly may get further complicated by the radiological evidence of pituitary enlargement and hyperprolactinemia, which results from the lack of thyroid hormone negative feedback and subsequent high TRH-driven stimulation of pituitary thyrotrophs and lactotrophs (Chakraborty et al., 2017; Kumar et al., 2012). Restoration of euthyroidism resolves the pituitary hyperplasia and reverts the acromegaloid features (Kumar et al., 2012; Passeri et al., 2011).

3.6. Cantú syndrome

Cantú syndrome, also named hypertrichotic osteochondrodysplasia, first described in 1982 (Cantu et al., 1982; Scurr et al., 2011), is caused by gain-of-function mutations in *ABCC9* or less commonly in its partner *KCNJ8* (Brownstein et al., 2013; Cooper et al., 2014; Harakalova et al., 2012; Marques et al., 2018b). Cantú syndrome prevalence is unknown, males and females are equally affected, and is inherited in an autosomal dominant manner (Cooper et al., 2015; Nichols et al., 2013).

Earlier reports used different terms for a few phenotypically overlapping conditions with Cantú syndrome, such as acromegaloid facial appearance syndrome (da-Silva et al., 1998; Dallapiccola et al., 1992; Hughes et al., 1985; Kini and Clayton-Smith, 2004; Zelante et al., 2000), or hypertrichosis acromegaloid facial features syndrome, but many of these were later found to have *ABCC9* mutations (Irvine et al., 1996; Marques et al., 2018b). In fact, these represent a spectrum of the same disease with alteration in a common molecular pathway, gain-of-function mutations in *ABCC9* or *KCNJ8* (Brownstein et al., 2013; Cooper et al., 2014; Harakalova et al., 2012; Marques et al., 2018b). *ABCC9,* located at 12p12.1, encodes a member of the adenosine triphosphate (ATP)-binding cassette transporter subfamily C, commonly referred to as SUR2 (sulfonylurea receptor 2) (Nichols et al., 2013). This protein functions as a ATP-sensitive potassium channel subunit involved in potassium transport in cardiac, skeletal, vascular smooth muscle and other tissues (Nichols et al., 2013). Co-expression of SUR2 with the pore-forming inward rectifier proteins, Kir6.1 (encoded by *KCNJ8*) or Kir6.2 (*KCNJ11*) generates the functional channels, which encloses 4 subunits of each protein (Cooper et al., 2014; Cooper et al., 2015; Nichols et al., 2013). The *ABCC9* pathogenic variants reported to date are gain-of-function missense mutations (Cooper et al., 2015; Harakalova et al., 2012; Hiraki et al., 2014; Nichols et al., 2013). *ABCC9* activation reduces ATP-mediated potassium channel inhibition, therefore opens the channel (Cooper et al., 2015; Harakalova et al., 2012; Nichols et al., 2013). There are 2 mechanisms by which these mutations lead to an overactive channel: decreased ATP sensitivity and enhanced magnesium-ADP expression (Cooper et al., 2015). More rarely, Cantú syndrome is caused by mutations in the *KCNJ8* gene (Brownstein et al., 2013; Cooper et al., 2014).

It is unclear how *ABCC9* mutations lead to acromegaloid features, hypertrichosis, cardiovascular anomalies and osteochondrodysplasia, but the involvement of this pathway is strengthened by the phenotypic overlap between Cantú syndrome and minoxidil effects (Section 3.7) (Grange et al., 2006; Nichols et al., 2013). Minoxidil is an ATP-sensitive potassium channel agonist which binds to SUR2 subunit resulting in channel opening, and therefore mimicking the effects of *ABCC9* gain-of-function mutations (Grange et al., 2006; Nichols et al., 2013). Prolonged minoxidil treatment can lead to hypertrichosis, acromegaloid facial features, pericardial effusions, fluid retention and edema (Mehta et al., 1975; Nguyen and Marks, 2003). Minoxidil promotes proliferation of keratinocytes and glycosaminoglycans synthesis (Mori et al., 1991), leads to elastin production from skin fibroblasts, prominent folliculosebaceous units and blood vessels proliferation (Nguyen and Marks, 2003; Tajima et al., 1995). Minoxidil also increases the amount of fibroblasts, mucin and connective tissue depositions in soft tissues (Nguyen and Marks, 2003), these are histopathologic findings also described in acromegaly (Ben-Shlomo and Melmed, 2006; Thiboutot, 1995). Regarding hypertrichosis, the opening of potassium channels with consequent vasodilation may increase blood supply, oxygen and nutrients to the hair follicles leading to telogen phase follicles to be shed and replaced by new thicker hair (Nichols et al., 2013; Shorter et al., 2008). SUR2 is expressed in follicular dermal papillae and its activation may promote hair growth (Shorter et al., 2008). Cardiovascular effects are due to reduced vascular tone, which may explain pericardial effusions and peripheral edema seen in Cantú syndrome (Grange et al., 1993; Nichols et al., 2013). ATP-sensitive potassium channels are expressed in chondrocytes and osteoblasts (Kawase et al., 1996; Rufino et al., 2013), but their role in bone is unknown, thus skeletal abnormalities remain unexplained (Nichols et al., 2013).

Patients present with acromegaloid facial appearance and the hallmark feature is early-onset hypertrichosis. Other features include cardiac (cardiomegaly, pericardial effusion, ventricular hypertrophy, mitral valve regurgitation, patent ductus arteriosus, cardiac failure, pulmonary hypertension, myocarditis) or skeletal abnormalities (thickened calvarium, craniosynostosis, broad ribs, narrow thorax, pectus carinatum, scoliosis, coxa vara, osteopenia, delayed bone age, hypoplastic bones, joint hyperextensibility), summarized elsewhere (Marques et al., 2018b). Acromegaloid facial features progress over time and include coarse facies, broad nasal bridge, bulbous nose, prominent mouth with thick lips, prominent forehead and supraorbital ridges, epicanthal folds, long philtrum, prognathism, thick lips, gingival hyperplasia, macroglossia, enlargement of submandibular and parotid glands (Fig. 3) (Marques et al., 2018b; Pachajoa et al., 2018), and hands may also enlarge (Fig. 4) (Czeschik et al., 2013; Scurr et al., 2011). Macrocephaly is common, and neonatal macrosomia has been reported, although the final height is usually normal (Grange et al., 1993; Marques et al., 2018b). No major endocrinopathies have been consistently reported (Scurr et al., 2011). GH axis is normally intact (Afifi et al., 2016; Czeschik et al., 2013; Ghazi et al., 2013; Grange et al., 2006; Nichols et al., 2013; van Bon et al., 2012), but there is one *KCNJ8* mutation-positive patient with GH deficiency (Cooper et al., 2014). In another *ABCC9* mutation-positive family, two members harbor non-functioning pituitary macroadenomas, although is unclear if these represent a Cantú syndrome feature (Marques et al., 2018b) or a coincidental finding (Marques and Korbonits, 2017). One patient was identified with pituitary gland enlargement extending into the suprasellar cistern but no adenoma (Scurr et al., 2011).

3.7. Minoxidil-induced pseudoacromegaly

Minoxidil is a vasodilator that was used to treat hypertension; locally it is used for baldness as a result of its stimulatory effects in hair growth (Rossi et al., 2012). Minoxidil lead to acromegaloid features by altering the composition of skin, soft connective or adipose tissues particularly in the face (Fig. 3) (Mehta et al., 1975; Nguyen and Marks, 2003). The pathophysiological mechanism is analogous with that of Cantú syndrome (Section 3.6), as minoxidil stimulates the ATP potassium channel. The development of such features occur after chronic exposure to high minoxidil doses (Nguyen and Marks, 2003), but may become apparent within a few months of minoxidil treatment (Mehta et al., 1975). The acromegaloid features may improve after discontinuation pf minoxidil therapy (Nguyen and Marks, 2003).

3.8. Phenytoin-induced pseudoacromegaly

Phenytoin is an anticonvulsant agent used to treat focal and tonic clonic generalized seizures, associated with a range of adverse effects affecting the skin and connective tissues (Scheinfeld, 2004). Chronic exposure to phenytoin may lead to coarse facial features including large nose and thickened lips (Fig. 3), gingival hyperplasia, calvaria thickening and hirsutism (Falconer and Davidson, 1973; Lefebvre et al., 1972; Mishriki, 1998; Scheinfeld, 2004). In a study involving 222 patients, coarse facial features were noted in one third, and about 30% of patients with coarse features had calvarial thickening (Lefebvre et al., 1972). The pathogenic mechanism is unknown, but tissue culture studies have shown that phenytoin stimulates fibroblast proliferation and collagen formation (Shafer, 1960; Standish and Clark, 1962).

3.9. Pallister-Killian syndrome

Pallister-Killian syndrome is a rare mosaic condition, first described in 1977 (Pallister et al., 1977), caused by the presence of extra copies of chromosome 12 (Izumi and Krantz, 2014). Isochromosome 12p is present in a tissue-limited mosaic pattern (Izumi and Krantz, 2014). The mechanism responsible for isochromosome 12p remains to be elucidated, but probably arises from maternal or more rarely paternal meiosis II nondisjunction (Izumi and Krantz, 2014). The percentage of cells containing isochromosome 12p is tissue-dependent, with lower mosaicism in lymphocytes in comparison to fibroblasts (Wilkens et al., 2012). Cytogenetic diagnosis can be challenging due to the possibility of isochromosome absence in lymphocytes, requiring sampling of other tissues. New methodologies, such CGH and SNP arrays, more readily detect low mosaicism levels and thus are more reliable to establish the diagnosis (Izumi and Krantz, 2014).

Pallister-Killian syndrome can affect any body organ or system (Schinzel, 1991; Wilkens et al., 2012). Facial features are the most useful diagnostic criteria, and includes frontal bossing, fronto-parietal alopecia, epicanthal folds, hypertelorism, long philtrum, large mouth with Cupid's bow appearance, flat nasal bridge, spare eyebrows or eyelashes, anteverted nares and ear abnormalities (Fig. 3) (Blyth et al., 2015; Izumi and Krantz, 2014; Wilkens et al., 2012). In a series of 22 patients, coarse facies was apparent in 52%, becoming more common with age: coarse facial appearance was described in 36% of patients below the age of 10 years and in 86% of older patients (Blyth et al., 2015). Micrognathia may be seen in younger patients, but enlarged mandible and prognathism are common in adults (Blyth et al., 2015; Wilkens et al., 2012). Scalp alopecia often seen in children tends to resolve during childhood or adolescence (Izumi and Krantz, 2014). Extremities abnormalities are common, such as lymphedema, soft tissue deposition, broad thumbs and toes, polydactyly, joint contractures or hip dislocations (Blyth et al., 2015; Wilkens et al., 2012). Patients are born usually with high-normal growth parameters, most having weight, height and head circumference above the 50th centile, followed by a postnatal growth deceleration in the first years of life (Blyth et al., 2015; Izumi et al., 2015; Wilkens et al., 2012). The cause for this has not been clarified, but could be due to growth advantage of normal cells over the isochromosome 12p cells (Izumi and Krantz, 2014), or due to high IGF binding protein-2 levels which can attenuate IGF-1 action (Izumi et al., 2015). Seizures and brain malformations are frequent, and most patients have hypotonia during infancy, although hypertonia and spasticity can be found in older individuals. Intellectual disability, skin pigmentation abnormalities, cardiac (Tilton et al., 2014; Wilkens et al., 2012), gastrointestinal and skeletal anomalies, most typically delayed ossification of vertebral bodies and pubic bones, triradiate cartilage, flaring of anterior ribs ends, and long bones metaphyseal broadening, are often seen (Jamuar et al., 2012; Schinzel, 1991). Hearing loss, strabismus, nystagmus, myopia, supranumerary nipples, small genitalia and cryptorchidism have also been described (Blyth et al., 2015; Wilkens et al., 2012).

3.10. Coffin-Siris syndrome

The list of disorders related with BRG1/BRM (BRM/SW12 related gene 1 and Brahma) associated factor (BAF), also known as SWItch/Sucrose Non-Fermentable (SWI/SNF), includes the overlapping Coffin-Siris and Nicolaides-Baraitser syndromes (Sokpor et al., 2017). In both acromegaloid features are recognizable, but in Coffin-Siris syndrome growth is normal, whereas Nicolaides-Baraitser syndrome patients usually have growth retardation (Santen et al., 2012). The BAF complex plays a role in chromatin remodelling and transcription regulation (Hargreaves and Crabtree, 2011). This complex is composed by 2 ATPase subunits, SMARCA2 and SMARCA4 (also known as BRG1 and BRM, respectively), and other subunits with DNA- and histone-binding domains involved in transcription (ARID1A, ARID1B, ARID2, SMARCB1, SMARCE1, SOX11, AT-hook proteins, zinc finger, plant homeodomain and helicase/SANT-associated domain) (Santen et al., 2012; Sokpor et al., 2017). BAF complex is involved in cell cycle regulation, cell survival and DNA repair (Santen et al., 2012; Wilson and Roberts, 2011), and is implicated in the CNS development and cognitive functions (Sokpor et al., 2017). Coffin-Siris syndrome is a rare autosomal dominant disorder described in 1970 (Coffin and Siris, 1970), with an unknown prevalence and more females reported thus far (Kosho et al., 2014; Santen et al., 2014), caused by pathogenic variants in BAF complex-related genes *AIRD1A*, *ARID1B*, *SMARCA4*, *SMARCA2*, *SMARCB1*, *SMARCE1* and *SOX11* (Miyake et al., 2014; Tsurusaki et al., 2014a; Tsurusaki et al., 2014b).

Dysmorphic facial features, present at birth in 30% of cases, usually coarsen over time and become apparent in up to 95% of cases (Kosho et al., 2014; Santen et al., 2014). Typical features includes wide mouth with thick and everted lips, broad nasal bridge with broad nasal tip, anteverted nares, thick alae nasi, broad philtrum, thick eyebrows, long eyelashes and large ears (Fig. 3) (Santen et al., 2014; Schrier et al., 2012; Vergano and Deardorff, 2014). The face of patients with *SMARCA4* mutations is less coarse than *SMARCB1*-mutated cases (Kosho et al., 2014). Prenatal growth is usually normal but can be mildly impaired. However, childhood height is below the 50th centile in most patients, in 20% below the 5th centile (Kosho et al., 2014). Bone age is often delayed. Hypoplasia of the fifth digits/nails is the most typical finding (Fig. 4); however, some patients have little or no fifth digit involvement; other skeletal anomalies include clinodactyly, joint laxity and scoliosis (Kosho et al., 2014; Santen et al., 2013). Hypertrichosis, present in up to 95% of patients, often coexists with low anterior hairline, sparse scalp hair or thin hair. Cognitive impairment, hypotonia, seizures, CNS malformations (Kosho et al., 2014; Santen et al., 2013; Santen et al., 2014; Schrier et al., 2012), cardiac, renal and genitourinary anomalies, ptosis, strabismus, myopia and hearing anomalies are often seen (Kosho et al., 2014; Santen et al., 2013). These patients have increased risk for small-cell hypercalcemic type carcinoma of the ovary (Errichiello et al., 2017), hepatoblastoma, papillary thyroid cancer and schwannomatosis (Kosho et al., 2014; Schrier et al., 2012; Vengoechea et al., 2014). Obesity, hyperinsulinism, PCOS (Sonmez et al., 2016; Vals et al., 2014), premature thelarche (Brunetti-Pierri et al., 2003; Flynn and Milunsky, 2006), pituitary hypoplasia with GH deficiency (Baban et al., 2008), hypoglycemia (Imaizumi et al., 1995), hyperphosphatasia (Rabe et al., 1991) and biotinidase deficiency (Burlina et al., 1990) have been reported.

3.11. Fabry disease

Fabry disease, described in 1898 (Fabry, 2002), is a rare inherited X-linked lysosomal storage disorder, with incidences ranging from 1:476,000 and 1:117,000 (Meikle et al., 1999; Poorthuis et al., 1999), affecting both men and women, although men usually have a more severe phenotype (Germain, 2010). Fabry disease is caused by loss-of-function mutations in the *GLA* gene, resulting in a deficiency of the lysosomal enzyme α-galactosidase (Mehta and Hughes, 1993). Deficient or absent α-galactosidase activity results in accumulation of glycosphingolipids within lysosomes in different cells (Germain, 2010) triggering a cascade of events including cell death, vessel injury, oxidative stress, compromised energy metabolism, dysfunctional autophagosome maturation, tissue ischemia and fibrosis (Das and Naim, 2009; Germain, 2010; Lucke et al., 2004). Fabry disease is caused by a wide range of missense and nonsense mutations, splicing mutations, small deletions and insertions (Germain, 2010),

Fabry disease should be suspected in males or females with the following features: periodic crises of severe pain in the extremities (acroparesthesias), angiokeratomas (vascular cutaneous lesions which appear as clusters of punctate, dark red to blue-black angiectases in the skin, often the earliest manifestation), sweating abnormalities (anhidrosis, hypohidrosis or rarely hyperhidrosis), corneal and lenticular

opacities, unexplained stroke, left ventricular hypertrophy, arrhythmia or angina, or kidney dysfunction, proteinuria or glomerulosclerosis (Mehta and Hughes, 1993). Craniofacial features have been described including prominent supraorbital ridges, periorbital fullness, increased bitemporal width, bushier eyebrows, ptosis, broader nasal base and bulbous nose, full lips, prognathism (Fig. 3) (Cox-Brinkman et al., 2007; Hogarth et al., 2013; Ries et al., 2006), thus potentially mimicking acromegaloid facial appearance (Hogarth et al., 2013). Facial features seems to affect more commonly men, and in women tend to be more subtle (Hogarth et al., 2013). The growth pattern is usually normal, although patients may grow slower in late childhood or adolescence; no GH/IGF-1 axis abnormalities have been reported (Faggiano et al., 2006; Germain, 2010). Endocrine dysfunctions include adrenal insufficiency, hypothyroidism, impaired spermatic count and azoospermia, and menstrual abnormalities or miscarriage affecting up to 89% of females (Faggiano et al., 2006; Germain, 2010). Other features includes cold and heat intolerance as result of autonomic neuropathy and dysfunctional sweating, tinnitus, hearing loss (Hogarth et al., 2013; Mehta and Hughes, 1993), vomiting, diarrhea, abdominal pain, intestinal malabsorption (Hoffmann et al., 2007), dyspnea, chronic bronchitis, obstructive lung disease (Magage et al., 2007), lymphedema, varices, priapism, hemorrhoids, osteoporosis, anemia, depression and fatigue (Germain, 2010; Mehta and Hughes, 1993).

3.12. Klippel-Trenaunay syndrome

Klippel-Trenaunay syndrome is a rare disorder affecting approximately 1:100,000 live births (Lorda-Sanchez et al., 1998) with unknown cause (Oduber et al., 2008). Most cases are sporadic (Aelvoet et al., 1992; Oduber et al., 2008); however, isolated vascular malformations or hemihypertrophy have been reported in family members of patients suggesting that this condition may be inherited with incomplete penetrance or phenotypic variability (Aelvoet et al., 1992; Lorda-Sanchez et al., 1998). Most patients have a normal karyotype, but there are cases identified with chromosomal anomalies (Tian et al., 2004; Whelan et al., 1995). A pathogenic variant of *AGGF1* (angiogenic factor with G patch and FHA domains 1) have been identified in 5 out of 130 patients (Timur et al., 2004), but a polygenic cause seems plausible and may explain why this syndrome occurs mainly sporadically (Oduber et al., 2008). Several copy number variations were identified in chromatin modification genes (*HDAC9*, *SALL2*, *DNMT3A* and *ING5*) (Dimopoulos et al., 2017).

The main manifestation is capillary malformation (98%) which is represented by port-wine stains and cutaneous hemangiomata, varicose veins and dilated lymphatic vessels (Oduber et al., 2008), in association with asymmetric overgrowth of extremities (macromelia) affecting more frequently the lower limbs leading to prominent macrodactyly (Fig. 4) (Oda et al., 2018; Oduber et al., 2008). Hypertrophy and vascular abnormalities involving the face, jaws and oral soft tissues are not uncommon leading to craniofacial dysmorphic features (Fakir et al., 2009). Asymmetric overgrowth of the craniofacial skeleton (Dhamecha and Edwards-Brown, 2001; Hallett et al., 1995) may result in unilateral facial hypertrophy, asymmetric prognathism, micro/macrocephaly, hypertrophy of alveolar processes, prominent cheeks, thick lips, gingival hypertrophy, macroglossia, gingival fibromas, palatal anomalies, dental diastema, premature teeth eruption, anterior open bite, dental cross bite and malocclusion (Fig. 3) (Fakir et al., 2009). Facial skin anomalies such as telangiectasias, papillomata, hyperpigmentation, cutis marmorata, lymphangiomas or hemangiomas are not uncommon (Auluck et al., 2005; Fakir et al., 2009). Hemimegalencephaly is often seen, and usually manifested by brain hemihypertrophy and thickening of the overlying ventricle and frontal bone (Cristaldi et al., 1995; Dhamecha and Edwards-Brown, 2001; Fakir et al., 2009). Facial features may progress rapidly during puberty, but usually do not evolve in the adulthood (Auluck et al., 2005; Bathi et al., 2002). Other manifestations include bleeding diatheses, thrombocytopenia, thromboembolism (Fakir et al., 2009; Horbach et al., 2017), gross hematuria and vascular malformations in the bladder and genitalia (Furness et al., 2001), cellulitis, hearing loss, hydrocephalus, cerebral calcifications or atrophy, cavernomas, seizures and mental retardation (Ishimoto et al., 2002; Renard et al., 2013).

4. Acromegaloid appearance with growth retardation/short stature

4.1. Nicolaides-Baraitser syndrome

Nicolaides-Baraitser syndrome is a BAF-related complex autosomal dominant disorder, described in 1993 (Nicolaides and Baraitser, 1993), with all reported cases displaying a *de novo SMARCA2* pathogenic variant (Sousa et al., 2009; Sousa et al., 2014). Genetic and molecular aspects of BAF complex are discussed in Section 3.10. While facial features in Nicolaides-Baraitser syndrome are similar to those of Coffin-Siris syndrome, digital features are the most useful in differentiating these conditions: patients with Nicolaides-Baraitser syndrome have prominent interphalangeal joints but no fifth digit hypoplasia is found in Coffin-Siris syndrome; in addition, Coffin-Siris syndrome patients usually have normal stature, whereas growth retardation is common in Nicolaides-Baraitser syndrome (Sousa et al., 2009; Sousa et al., 2014). Nicolaides-Baraitser syndrome facial features includes wide mouth, thick lower lip vermilion, long philtrum, anteverted nares, broad nasal base, thick alae nasi, upturned nasal tip, gum hypertrophy and widely spaced teeth (Fig. 3). Face coarsening occurs over time and may be only recognizable later in childhood or adolescence, affecting 75% of patients (Sousa et al., 2014; Van Houdt et al., 2012). Other striking features are skin wrinkling and decrease in subcutaneous fat tissue, particularly noticeable below the orbits and in cheeks (Sousa et al., 2014). About one third of patients are small-for-gestational-age, and one fifth have length at birth below -2 SD. Postnatally, short stature is seen in 50% of cases, the majority having a height below the 5th centile (Sousa et al., 2014). Other features include sparse hair, microcephaly, prominence and widening of interphalangeal joints and distal phalange, delayed tooth eruption, seizures, ptosis, intellectual disability, visual and hearing impairment, reduced skin pigmentation, hypertrichosis, scoliosis, pectus excavatum, joint laxity, cryptorchidism and heart malformations (Sousa et al., 2014; Van Houdt et al., 2012). Insulin resistance and multiple cerebral cavernous malformations have been described (Pretegiani et al., 2016).

4.2. Börjeson-Forssman-Lehmann syndrome

Börjeson-Forssman-Lehmann syndrome is a rare X-linked intellectual disability syndrome, first described in 1962 (Borjeson et al., 1962), which diagnosis is based on clinical history and examination, but can be confirmed finding loss of function mutations in *PHF6* (PHD-like finger protein 6) gene (Jahani-Asl et al., 2016; Lower et al., 2002). PHF6 contains two PHD-like zinc fingers, and nuclear and nucleolar localization sequences, suggesting a role in transcription and epigenetic regulation (Jahani-Asl et al., 2016; Zweier et al., 2014). It is involved in neuronal migration and in formation of cerebral cortex (Jahani-Asl et al., 2016). However, the exact pathogenic mechanism is not established (Jahani-Asl et al., 2016; Todd et al., 2015).

Facial features are absent or difficult to recognize at birth, becoming more prominent in adolescence or adult life (Turner et al., 2004; Zweier et al., 2014), and include frontal bossing, prominent supraorbital ridges, large ears, deep-set eyes, bitemporal narrowing, marked zygomatic arch, highly arched eyebrows, wide or short nose with bulbous nasal tip, skin thickening, large mouth and widely spaced teeth (Fig. 3) (Turner et al., 2004; Zweier et al., 2013; Zweier et al., 2014); in some cases mild hypertelorism is noted (Berland et al., 2011; Di Donato et al., 2014). Female facial appearance display some differences in comparison to males, particularly frontotemporal sparse hair, more pronounced supraorbital region, more prominent highly arched eyebrows

and less prominent ears (Zweier et al., 2014). Deep and hoarse voice is common (Zweier et al., 2013; Zweier et al., 2014) and is due to extensive frontal sinus pneumatization (Kasper et al., 2017). Growth tends to be normal, although moderate short stature may be found in 35–50% of males (Berland et al., 2011; Carter et al., 2009; Turner et al., 2004; Zweier et al., 2013). Body height above +2 SD have been reported in two females (Crawford et al., 2006; Zweier et al., 2013). Increased weight/truncal obesity is a hallmark in male patients (Turner et al., 2004; Zweier et al., 2013; Zweier et al., 2014), but is rarely seen in females (Crawford et al., 2006; Zweier et al., 2013). In a series 2 out of 7 females had mild obesity (Zweier et al., 2013), and 1 obese female patient had hyperphagia (Crawford et al., 2006). Other features are skeletal and limb anomalies, including tapered fingers, (brachy)clinodactyly of the fourth and fifth fingers, hypoplastic nails, hyperextensible joints (Fig. 4), short/broad toes, advanced bone age, vertebral anomalies, kyphoscoliosis, cone-shaped epiphyses (Zweier et al., 2014), linear skin pigmentation and sparse hair (Turner et al., 2004; Zweier et al., 2013; Zweier et al., 2014). Endocrine abnormalities are common: oligoamenorrhea or primary/secondary amenorrhea occur in most females, whereas males frequently have small genitalia, cryptorchidism and gynecomastia (Crawford et al., 2006; Gecz et al., 2006; Turner et al., 2004; Weber et al., 1978); primary hypothyroidism (Crawford et al., 2006), hypopituitarism and pituitary abnormalities (small pituitary, absent pituitary stalk) have been reported (Birrell et al., 2003; Gecz et al., 2006; Kasper et al., 2017; Turner et al., 2004). Other rarer findings include persistent ductus arteriosus, ectopic or horseshoe kidney, neurogenic bladder, strabism, nystagmus, myopia, hyperopia, hearing impairment, seizures, hypotonia and brain anomalies (Kasper et al., 2017; Zweier et al., 2014).

4.3. Coffin-Lowry syndrome

Coffin-Lowry syndrome, with an estimated prevalence of 1:50,000 to 1:100,000 (Pereira et al., 2010; Temtamy et al., 1975), is caused by loss-of-function mutations in *RPS6KA3* (ribosomal protein S6 kinase alpha-3) gene and is inherited in an X-linked dominant manner (Rogers and Abidi, 1993). *RPS6KA3*, located to Xp22.2, encodes the kinase RPS6KA3 involved in some pathways related to cell differentiation, proliferation and survival, DNA repair and neurotransmitters release (Hauge and Frodin, 2006; Pereira et al., 2010; Rogers and Abidi, 1993; Zeniou-Meyer et al., 2010).

Cardinal features are intellectual disability, characteristic facial appearance, growth retardation and skeletal anomalies (Field et al., 2006; Pereira et al., 2010). Affected newborn males have normal or mild craniofacial traits, with typical coarse face apparent from the second year of life (Pereira et al., 2010; Rogers and Abidi, 1993). Other features include prominent forehead and supraorbital ridges, thick eyebrows, hypertelorism with downslanted palpebral fissures, epicanthic folds, large ears, broad nose, anteverted nares, wide mouth and thick everted lips (Fig. 3) (Pereira et al., 2010), usually more prominent in males (Hanauer and Young, 2002; Rogers and Abidi, 1993). With age, retrognathia seen in younger children tends to be replaced by prognathism (Rogers and Abidi, 1993). Extremities and digital anomalies include large fleshy hands often with hyperextensible fingers, and a transverse palmar crease, as well as tapering stubby fingers with tufted drumstick-like appearance of the distal phalanges, small nails, flat feet and forearm fullness (Herrera-Soto et al., 2007; Pereira et al., 2010; Rogers and Abidi, 1993). Other skeletal anomalies include thickened skull with large frontal sinuses, kyphoscoliosis, pectus carinatum/excavatum, a narrow pelvis, narrowing of intervertebral spaces, delayed bone development and calcification of ligament flava (Herrera-Soto et al., 2007; Pereira et al., 2010). Prenatal growth is usually normal, but growth failure occurs early in the postnatal period (Hunter, 2002; Touraine et al., 2002). Loss of muscle mass, progressive spasticity or even paraplegia, deep tendon reflexes alterations, seizures, stroke, corpous callosum anomalies, increased intraventricular, subarachnoid and Virchow-Robin spaces, hearing loss, optic atrophy, anxiety and cognitive deficits were reported (Hanauer and Young, 2002; Kondoh et al., 1998; Pereira et al., 2010; Rogers and Abidi, 1993). Although occurring only in 20% of patients, stimulus-induced drop attacks (lower limbs brief collapse following an unexpected tactile or auditory stimuli) are typical of Coffin-Lowry syndrome (Nakamura et al., 2005; Rogers and Abidi, 1993). Other features include cardiac valves anomalies, congestive heart failure, aorta dilation, rectal or uterine prolapse, hernias, jejunal and colonic diverticuli, pyloric stenosis and renal agenesis (Hunter, 2002; Pereira et al., 2010).

4.4. Cornelia de Lange syndrome

Cornelia de Lange syndrome, originally described in 1916 (Kline et al., 2007), with prevalence estimated at 1:50,000 (Barisic et al., 2008), is caused by pathogenic variants on cohesion pathway-related genes: *NIPBL*, *SMC1A*, *SMC3*, *RAD21* and *HDAC8* (Boyle et al., 2015). Mutations in *NIPBL*, *SMC3* and *RAD21* lead to the autosomal dominant form, whereas *SMC1A* and *HDAC8* are responsible for X-linked Cornelia de Lange syndrome (Boyle et al., 2015). The cohesin complex consists of 4 main subunits: RAD21 (human homolog of *Schizosaccharomyces pombe* radiation sensitive mutant 21), STAG1 and 2 (stromal antigen 1 and 2), SMC1A and SMC3 (structural maintenance of chromosomes 1A and 3, respectively). Other proteins are involved in its functional activity, such NIPBL (nipped-B-like protein) and HDAC8 (histone deacetylase 8) (Deardorff et al., 2012a; Deardorff et al., 2007; Deardorff et al., 2012b). This complex is important for chromosome segregation, transcription regulation and DNA repair. Mutations in these elements affect the role of this complex in transcriptional regulation and in sister chromatid cohesion (Boyle et al., 2015). Mutations in *NIPBL* account for 80% of cases, who often carry the classical phenotype, including the typical facial appearance (Boyle et al., 2015).

Key manifestations include typical facial appearance (Froissart et al., 2003), growth failure, limb anomalies, intellectual disability, present in more than 95% of cases, and hypertrichosis in more than 80% of patients (Boyle et al., 2015). Craniofacial features (Rohatgi et al., 2010) include highly arched eyebrows, long and thick eyelashes, depressed or wide nasal bridge, upturned nasal tip with anteverted nares, long and smooth philtrum, thin vermillion of the upper lip with a midline 'drip' appearance, widely spaced teeth, micrognathia, low-set posteriorly rotated and hirsute ears (Boyle et al., 2015; Jackson et al., 1993; Kline et al., 2007). Growth failure starts prenatally becoming more prominent by the age of 6 months (Kline et al., 1993); GH therapy may be useful in some cases (de Graaf et al., 2017). Upper limb extremities are primarily involved, with relatively spared lower limbs, and the deficiencies vary from severe reduction defects with lack of forearms, to different forms of oligodactyly, small hands, proximally placed thumbs or fifth finger clinodactyly (Fig. 4) (Boyle et al., 2015; Jackson et al., 1993; Kline et al., 2007). Other problems (Boyle et al., 2015; Kline et al., 2007) include gastroesophageal reflux, pneumonitis, seizures, temperature intolerance, decreased pain sensation, hearing loss, ptosis, myopia, astigmatism, strabismus, nystagmus, glaucoma, optic atrophy, coloboma, nasolacrimal duct stenosis, recurrent infections, low-pitched cry, cutis marmorata, hypoplastic nipples, single palmar creases, scoliosis, chest deformities, heart disease, cryptorchidism, hypoplastic genitalia and bicornuate uterus (Boyle et al., 2015; Jackson et al., 1993; Kline et al., 2007).

4.5. Osteopetrosis

Osteopetrosis, also known as marble bone disease, encloses a group of disorders that vary in presentation and severity, typically characterized by increased bone density due to a defect in bone resorption by dysfunctional osteoclasts (Stark and Savarirayan, 2009; Tolar et al., 2004). Osteopetrosis has been categorized in 3 types: infantile or "malignant" osteopetrosis inherited in an autosomal recessive manner

known as autosomal recessive osteopetrosis (ARO); “intermediate” ARO; and autosomal dominant osteopetrosis (Tolar et al., 2004). A fourth X-linked form in association with ectodermal dysplasia, lymphedema and immunodeficiency has been also described (Del Fattore et al., 2008). Osteopetrosis is caused by mutations (mostly loss-of-function) in at least 10 different genes involved in osteoclast differentiation and function, impairing trafficking and/or fusion of lysosome-related organelles to the osteoclastic ruffled border. Pathogenic variants in *TCIRG1* (osteoclast vacuolar proton pump) and *CLCN7* (chloride channel 7) account for 70% of ARO cases, but disease-causing mutations in other genes (*OSTM1*, *RANK*, *RANKL*, *CAII*, *PLEHKM1*, *LEMD3*, *NEMO*, *MITF, SNX10*) were also described (Del Fattore et al., 2008; George et al., 2016; Tolar et al., 2004; Wu et al., 2017).

Increased bone density leads paradoxically to weak bones resulting in fractures, deformities, degenerative arthritis and osteomyelitis, as well as longitudinal bone growth impairment resulting in short stature (Stark and Savarirayan, 2009; Wu et al., 2017). Craniofacial bone abnormalities, including macrocephaly, frontal bossing, hypertelorism, cranial hyperostosis are common (Lucke et al., 2004) resulting in a typical facial appearance (Del Fattore et al., 2008; Hamdan et al., 2006; Stark and Savarirayan, 2009). The expanding bone can narrow nerve foramina leading to blindness, deafness, anosmia, facial palsy or facial sensory changes (Steward, 2003; Wu et al., 2017). Other manifestations include hydrocephalus, headache, small orbits, exophthalmos, strabismus, ptosis, recurrent otitis, vertigo, sinuses agenesis, malocclusion, tooth eruption defects, oral fistulas or jaw osteitis (Detailleur et al., 2016; Hamdan et al., 2006; Krithika et al., 2009; Wu et al., 2017). Children are at risk of hypocalcemia due to defective osteoclasts unable to mobilize calcium from bone, with compensatory secondary hyperparathyroidism, and basal ganglia calcifications. The most severe complication is bone marrow suppression subsequent to abnormal bone expansion impairing hematopoiesis, and hepatosplenomegaly as a result of compensatory extramedullary hematopoiesis (Stark and Savarirayan, 2009; Wu et al., 2017).

4.6. SOST-related sclerosing bone dysplasias

SOST-related sclerosing bone dysplasias are bone remodeling disorders due to loss-of-function *SOST* (coding for sclerostin) mutations resulting in osteoblast hyperactivity. *SOST* mutations results in deficiency of sclerostin, a protein secreted by osteoblasts, osteocytes, chondrocytes, cementocytes embedded in the bone matrix that regulates bone growth, density and mechanosensing anabolic responses (Lin et al., 2009; Moustafa et al., 2009; Robling et al., 2008). Patients present with skeletal overgrowth, affecting more prominently the mandible and skull, leading to asymmetric mandibular hypertrophy, teeth malalignment, frontal bossing and proptosis (Fig. 3) (Beighton et al., 1993; Stephen et al., 2001). Skull foramina narrowing may cause entrapment of the seventh cranial nerve (facial palsy) and eighth cranial nerve (deafness) (Hamersma et al., 2003; Hamersma and Hofmeyr, 2007). Accelerated growth is occasionally seen usually in childhood (Beighton et al., 1993). Variable cutaneous or bony syndactyly, usually bilateral and affecting the index and third middle fingers (Fig. 4), radial deviation of terminal phalanges and dysplastic or absent nails are occasionally seen (Tholpady et al., 2014). Classical radiographic findings include bone widening (hyperostosis) and increased bone density (sclerosis) mainly affecting the calvarium, skull base and tubular bones shafts (Gardner et al., 2005; Hamersma et al., 2003). Serum calcium is normal, but alkaline phosphatase, urinary cross-linked N-telopeptide, serum procollagen peptide and osteocalcin are usually elevated (Beighton et al., 1993; Wergedal et al., 2003).

5. Accelerated growth/tall stature without acromegaloid appearance

5.1. Endocrinopathies associated with accelerated growth and/or tall stature

In addition of the GH axis-related disorders, many other endocrinopathies may lead to accelerated growth and tall stature during childhood or adolescence by increasing the growth velocity due to hormonal action on bone growth and maturation (sex steroids, adrenal steroids or thyroid hormone) or by delaying the epiphyses closure thus prolonging the growth period. Nevertheless, the final stature tends to be reduced or normal particularly when these endocrinopathies are successfully treated (Albuquerque et al., 2017).

Sexual precocity, i.e. early onset of estrogen or androgen secretion and subsequent excessive sex steroid circulating levels, results in increased height velocity and bone growth and maturation, as reflected by the prominent advanced bone age typical in this setting. Moreover, estrogens enhance GH secretion, particularly during puberty; however, they can also accelerate chondrocyte senescence in the growth plate, leading to its premature fusion. Androgens mediate growth through their conversion to estrogens or also due to their own direct action in the growth plate (Nilsson et al., 2005). Thus, sexual precocity can lead to the paradox of a tall child and a short adult (Albuquerque et al., 2017). These conditions include gonadotropin-releasing hormone (GnRH)-independent entities such as congenital adrenal hyperplasia, virilizing adrenal tumors, ovarian cysts, estrogen-secreting ovarian neoplasms or Sertoli cell tumors found in Peutz-Jeghers syndrome, Leydig cell adenomas, McCune-Albright syndrome, familial testotoxicosis due to LH-receptor activating mutations, human chorionic gonadotropin-secreting tumors (germinomas, teratomas, hepatomas, choriocarcinomas, chorioepitheliomas), or inadvertent exposure to estrogens in food, drugs or cosmetics. Premature activation of the hypothalamic GnRH pulse generator results in GnRH-dependent precocious puberty conditions including CNS tumors as optic gliomas, hypothalamic astrocytomas or hamartomas, craniopharyngiomas, encephalitis, brain abscess, sarcoid or tubercular granulomas, hydrocephalus, arachnoid cysts, myelomeningocele, head trauma, cranial irradiation, and genetic conditions, such as mutations in the kisspeptin pathway (Bridges et al., 1994; Eugster, 2009; Latronico et al., 2016; Marques et al., 2000) or due to *MKRN3* mutations (Lima et al., 2016).

Hypogonadism leads to prolonged growth due to delayed growth plate fusion, and contrarily to patients with sexual precocity, these cases do not display a growth spurt due to reduced, absent of or resistance to sex steroids. Growth velocity is low, but as the growth plate fusion is delayed, these patients grow for longer periods into adulthood developing tall stature (Jee and Baron, 2016). Hypogonadotropic hypogonadism can be congenital or acquired, can be isolated or combined with other pituitary deficiencies, encompasing several entities such as Kallmann syndrome, LHRH receptor or kisspeptin pathway genetic abnormalities, congenital adrenal hypoplasia due to *DAX1* mutations, isolated LH or FSH deficiencies, CNS tumors, Langerhans histiocytosis, lymphocytic hypophysitis, vascular abnormalities, irradiation and trauma (Marques et al., 2000; Seminara et al., 1998). Conditions associated with hypergonadotrophic hypogonadism include Klinefelter and Turner syndromes, chemotherapy, radiotherapy, trauma/surgery, steroid biosynthetic defects, LH/FSH resistance syndromes, cryptorchidism, autoimmune oophoritis or PCOS (Friedman et al., 1983). Aromatase deficiency or estrogen resistance due to mutations in the estrogen receptor gene, as well as exposure to aromatase inhibitors, share similar phenotypes, with tall stature in both males and females as a result from the marked epiphyseal closure delay, in addition to other

problems such low bone density, genital ambiguity or poor breast development in women (Bulun, 2014; Miedlich et al., 2016; Rochira and Carani, 2009; Smith et al., 1994).

Hyperthyroidism or excessive thyroid hormones from overtreatment with exogenous thyroxine, leads to an increased growth velocity and advanced bone age as a result of their stimulatory effect in bone growth. Hyperthyroid children can be above +2 SD for height, but usually reach normal adult height when adequately treated (Albuquerque et al., 2017; Wong et al., 1999).

Obesity is related to tall stature during childhood, with several studies showing that obese children are taller than their normal-weight counterparts, with a mean height difference comprised between 4 and 5 cm. In addition to increased growth velocity, obese children have earlier puberty which may contribute for this difference. However, the growth velocity tends to decrease earlier during adolescence, and there is no significant statural differences between obese, overweight or normal-weight adults (Johnson et al., 2012; Stovitz et al., 2011). Patients with monogenic obesity, such as those with *MC4R* (melanocortin receptor 4) mutations, are characterized by increased linear growth greater than expected for the obesity degree (Farooqi et al., 2003). Martinelli et al. reported increased height in MC4R-deficient children under the age of 5 years in comparison with controls, an effect that remained throughout childhood, and a final height greater in MC4R-deficient men and women (Martinelli et al., 2011). The mechanism by which obesity influences growth is has not yet been elucidated (Fennoy, 2013; Martinelli et al., 2011).

Maternal diabetes is the most common cause of large-for-gestational-age infants, defined as birth length or weight greater than the 90th centile for gestational age, with approximately 45% of infants from diabetic mothers preseting macrosomia at birth (Ballard et al., 1993). An infant from a diabetic mother is exposed to sustained maternal hyperglycemia in case of unrecognized or poorly-controlled maternal diabetes, which may result in beta-cell hyperplasia and hyperinsulinism leading to fetal macrosomia. Birth length and weight are typically increased, with more pronounced weight increase (Ambler, 2002; Ballard et al., 1993; Djelmis et al., 1998). Infants from diabetic mothers are at higher risk of prematurity, postnatal hypoglycemia, hyaline membrane disease, hyperbilirubinemia, thrombosis and transient cardiomyopathy, as well as of congenital anomalies such as heart defects, skeletal anomalies and microcephaly (Martinez-Frias, 1994; Neave, 1984).

5.2. Klinefelter syndrome

The most common chromosome aneuploidy is XXY in Klinefelter syndrome, affecting 1 in 660 men (Groth et al., 2013; Tuttelmann and Gromoll, 2010). Most genes from the extra X chromosome undergo inactivation, but some genes, particularly those from the pseudoautosomal regions, escape X inactivation and serve as the putative genetic cause and phenotype of Klinefelter syndrome. Examples of genes escaping X inactivation are the *SHOX* genes (Groth et al., 2013; Tuttelmann and Gromoll, 2010). Tall stature results from the presence of 3 copies of *SHOX*, an important element in controlling linear growth and growth plate fusion, although other factors such as concomitant primary hypogonadism may contribute to increased final height (Kant et al., 2007; Ogata et al., 2001; Tuttelmann and Gromoll, 2010).

Klinefelter syndrome is remarkably underdiagnosed or diagnosed late in life, and its key clinical findings, in addition to tall stature, include cognitive impairment, learning disabilities, hypergonadotrophic hypogonadism, small testes, cryptorchidism, infertility, gynecomastia, decreased facial and pubic hair, osteopenia and osteoporosis, abdominal adiposity, diabetes, metabolic syndrome, congenital malformations (such as cleft palate, inguinal hernias), mitral valve prolapse, and increased risk for breast cancer (in adults) and for mediastinal cancers (in children) (Groth et al., 2013). Acromegaloid appearance was reported in a male with a variant type of Klinefelter syndrome (48, XXYY karyotype) who presented with tall stature, hypogonadism and acromegaloid facial and acral appearance, as well as acne and voice changes, but no GH axis abnormalities (Yamane et al., 1993).

5.3. Familial glucocorticoid deficiency

Familial glucocorticoid deficiency is an autosomal recessive disorder resulting from mutations in the genes encoding either the ACTH receptor (melanocortin 2 receptor, MC2R), its accessory protein MRAP (melanocortin 2 receptor accessory protein, MRAP) or involved in this pathway. Familial glucocorticoid deficiency is classified as type 1 when *MC2R* mutations are identified, or type 2 in the presence of *MRAP* mutations (Chan et al., 2008; Chung et al., 2010). *MC2R* mutations result in reduced expression of this receptor and therefore decreased ACTH signaling, whereas *MRAP* mutations are associated with MC2R retainment in the cell endoplasmic reticulum and complete failure of receptor function (Chung et al., 2010; Chung et al., 2008). Familial glucocorticoid deficiency is characterized by severe glucocorticoid deficiency due to lack of an appropriate response to ACTH, but no mineralocorticoid deficiency (Chan et al., 2008; Metherell et al., 2006).

Some of the familial glucocorticoid deficiency type 1 patients exhibit tall stature in the presence of normal GH axis (Chan et al., 2008; Chung et al., 2010; Clark and Weber, 1998; Elias et al., 2000; Slavotinek et al., 1998; Weber et al., 1995). This excessive growth is more prominent prior to the initiation of glucocorticoid treatment, and although hydrocortisone seems to bring the height back towards the mid-parental target height, these children become tall adults (Clark and Weber, 1998). Weber *et al.* reported 3 patients from different ethnic backgrounds, with remarkable tall stature at diagnosis (Weber et al., 1995). In Chung *et al.* series, the height of familial glucocorticoid deficiency type 1 patients at presentation was 1.76 ± 1.52 SD, whereas in type 2 was 0.12 ± 2.35 SD (Chung et al., 2010). Tall stature and increased height velocity has also been reported in familial glucocorticoid deficiency patients without *MC2R* mutations (Imamine et al., 2005), and not all patients with *MC2R* mutations are tall (Imamine et al., 2005), they can even be short (Selva et al., 2004). The mechanism for tall stature is not fully understood, but may be related to the direct action of excessive ACTH levels on melanocortin receptors in bone or cartilage (Elias et al., 2000; Imamine et al., 2005; Metherell et al., 2006), or indirectly by increasing estradiol levels (Imamine et al., 2005), or acting on bone factors such as aromatase (Slavotinek et al., 1998). One tall girl with familial glucocorticoid deficiency type 1 and dysmorphic features, particularly a broad nasal bridge and small tapering fingers, was reported (Slavotinek et al., 1998).

5.4. Epiphyseal chondrodysplasia Miura type (CNP/NPR signalopathy)

Animal models (Chusho et al., 2001; Tsuji and Kunieda, 2005; Yasoda et al., 1998) and GWAS studies (Estrada et al., 2009; Gudbjartsson et al., 2008; Lango Allen et al., 2010) support the involvement of C-type natriuretic peptide (CNP) and its receptor NPR-B (natriuretic peptide receptor-B, coded by *NPR2*) as well as the clearance receptor NPR-C (coded by *NPR3*) in growth. Gain-of-function *NPR2* mutations (Hannema et al., 2013; Miura et al., 2014; Miura et al., 2012), loss-of-function mutations in *NPR3* (Boudin et al., 2018) or CNP overexpression are associated with extreme tall stature and long halluces (Bocciardi et al., 2007; Moncla et al., 2007; Tassano et al., 2013). CNP is encoded by *NPPC* (natriuretic peptide precursor C) located at 2q37.1. The translated pre-pro-CNP is processed by the endoprotease furin into a 50 amino-acid amino-terminal peptide (NT-proCNP) and an active 53 amino-acid peptide (CNP-53). Both NT-proCNP and CNP-53 are secreted, and CNP-53 is cleaved once again resulting in the mature 22 amino-acid CNP (Olney, 2006; Wu et al., 2003). While other natriuretic peptide family members are associated to natriuresis and cardiovascular actions, CNP lacks natriuretic functions and is involved in endochondral bone growth, promoting synthesis of cartilage matrix

and stimulating chondrocyte differentiation and proliferation (Bocciardi and Ravazzolo, 2009; Mericq et al., 2000; Nakao et al., 2015; Pejchalova et al., 2007). CNP binds preferentially to NPR-B, a G-protein coupled receptor (Chusho et al., 2001; Olney, 2006; Yamashita et al., 2000). CNP knockout mice have disproportionate dwarfism due to impaired ossification (Chusho et al., 2001), while CNP overexpression lead to excessive linear growth (Kake et al., 2009; Yasoda et al., 2004). NPR-B knockout mice have similar phenotype displaying low proliferative chondrocytes (Tamura et al., 2004; Tsuji and Kunieda, 2005). NPR-C is almost exclusively expressed in the cartilage hypertrophic zone and is responsible for CNP clearance and thus its availability to bind NPR-B (Olney, 2006; Pejchalova et al., 2007; Yamashita et al., 2000). NPR-C knockout mice display overgrowth, with elongated long bones, metatarsals and digits, vertebrae and tails (Matsukawa et al., 1999).

The phenotype of patients with CNP overexpression or *NPR2* gain-of-function mutations is characterized by tall stature, with height SD ranging between +3.0 − +5.2 SD, and increased birth length in some cases (Bocciardi et al., 2007; Hannema et al., 2013; Miura et al., 2014; Miura et al., 2012; Moncla et al., 2007; Tassano et al., 2013). Long halluces is a hallmark feature of CNP/*NPR* system-related conditions, but is not always present (Hannema et al., 2013). Skeletal manifestations include also long hands and feet (Fig. 4), arachnodactyly, camptodactyly, clinodactyly, syndactyly, feet deformities, tibia and femur bowing, unstable slipped capital femoral epiphysis, scoliosis, hyperlordosis, dorsal dysmorphism, multiple hernias, wide vertebral canal and low bone mineral density (Bocciardi et al., 2007; Hannema et al., 2013; Miura et al., 2014; Miura et al., 2012; Moncla et al., 2007; Tassano et al., 2013). Some patients are severely affected (Miura et al., 2014), whereas others have minor manifestations (Hannema et al., 2013). Height and skeletal phenotype appears to be consistent within affected members displaying the same *NPR2* mutation (Miura et al., 2014; Miura et al., 2012). CNP overexpression has not been reported in a familial setting.

While distinguishing CNP overexpression or *NPR2* activating mutations relying only on clinical features is not practical due to high heterogeneity, but biochemical measurements of NTproCNP can be useful. NTproCNP is expected to be lower in the context of increased *NPR2* activity due to reduced CNP production (Hannema et al., 2013; Vasques et al., 2014). This CNP feedback loop is present in patients with loss-of-function *NPR2* mutations, who normally display increased plasma CNP levels (Olney et al., 2006; Prickett et al., 2005). In CNP overexpression, normal or increased levels of NT-proCNP and CNP-22 are expected (Bocciardi et al., 2007; Tassano et al., 2013; Vasques et al., 2014). CNP synthesis is closely related to linear growth in healthy children, therefore CNP and NTproCNP levels vary considerably according to gender and age (Olney et al., 2012).

Recently, four individuals from 3 different families were identified with a bi-allelic loss-of-function mutation in *NPR3*, with a phenotype characterized by tall stature, long digits, extra epiphyses in hands and feet, and joint hyperlaxity. Biochemical analysis from 2 individuals revealed a reduced plasma NTproCNP/CNP ratio and high cGMP levels (Boudin et al., 2018).

5.5. Marfan syndrome

Marfan syndrome, originally described in 1896 (Verstraeten et al., 2016), is a connective tissue disorder (Dietz, 1993; Kumar and Agarwal, 2014) with prevalence estimated at 1:5000 to 1:10,000, affecting equally both genders (Dietz, 1993; Kumar and Agarwal, 2014; Verstraeten et al., 2016), and is caused by pathogenic variants in the *FBN1* gene (Faivre et al., 2003; Vollbrandt et al., 2004). Marfan syndrome is inherited in an autosomal dominant manner, with 75% of patients having an affected parent, while 25% have a *de novo* mutation (Dietz, 1993). Microfibrils, made of fibrillin-1, fibrillin-2 and elastin, provide force-bearing structural support and elasticity in tissues (Callewaert et al., 2009; Giusti and Pepe, 2016). Mutated forms of fibrillin-1 alter tissue mechanical properties, increase transforming growth factor-β signaling, overexpress matrix metalloproteinases, resulting in ECM abnormalities and the various clinical features in Marfan syndrome (Kumar and Agarwal, 2014).

Clinical scores to facilitate its diagnosis have been established (Dietz, 1993; Loeys et al., 2010; Radke and Baumgartner, 2014). Typical skeletal manifestations are joint laxity and excessive linear growth resulting in tall stature. However, Marfan syndrome adults are not always taller than the general population, but are usually taller than their predicted height. The growth spurt and skeletal maturation tend to occur earlier, with the puberty-associated growth velocity peak occurring 2.4 and 2.2 years earlier in male and female patients, respectively (Erkula et al., 2002). The extremities are typically disproportionately long for trunk size (dolichostenomelia) leading to increased arm span-to-height and the lower-to-upper segment ratios (Dietz, 1993; Verstraeten et al., 2016). Pectus carinatum or excavatum, scoliosis, pes plannus or cavus and long fingers are common (Dietz, 1993; Kumar and Agarwal, 2014). Skeletal manifestations can be present in young children and progress in periods of rapid growth (Dietz, 1993). Facial features include narrow and long face, enophthalmos, downslanting palpebral fissures, malar hypoplasia and micro/retrognathia although prognathism may be present in 30% of patients (Dietz, 1993; Poole, 1989; Ting et al., 2010). There are no gender differences regarding facial traits (Dolci et al., 2018). Pituitary gigantism and non-pituitary gigantism due to Marfan syndrome has been described in an *AIP* mutation-positive family, highlighting diagnostic challenges in the scenario of overlapping features (tall stature in this case) between GH excess and GH-unrelated conditions, particularly when coexisting in the same kindred (Marques et al., 2018a). Myopia is the most common ocular finding, but ectopia lentis is the hallmark feature seen in nearly 60% of cases (Nahum and Spierer, 2008). Cardiovascular findings include dilation of the aorta, predisposition to aortic rupture, enlarged pulmonary artery and mitral valve prolapse (Radke and Baumgartner, 2014). Other features include dural ectasia with nerve entrapment and bone erosion, headache and intracranial hypertension caused by cerebrospinal fluid leaking from a dural sac (Bassani et al., 2014; Foran et al., 2005), as well as skin striae, muscle hypoplasia, fat pads, pneumothorax and intellectual disability (Bolar et al., 2012; Dietz, 1993; Verstraeten et al., 2016).

Other Marfanoid-like connective tissue conditions, such Beals syndrome due to *FBN2* mutations (reviewed in (Callewaert et al., 2009)) and Loeys-Dietz syndrome with mutations in various genes in the transforming growth factor-β pathway (reviewed in (Loeys and Dietz, 1993)), may also lead to skeletal overgrowth and tall stature (Albuquerque et al., 2017; Erkula et al., 2010; Matyas et al., 2014).

5.6. CATSHL syndrome (camptodactyly, tall stature and hearing loss)

FGFs are a family of growth factors involved in various processes including mitogenesis and angiogenesis, by interacting with their cell-surface FGF-receptors 1, 2 and 3. FGFR3 is a regulator of endochondral bone growth (Keegan et al., 1991; Toydemir et al., 2006). Most *FGFR3* mutations are activating causing short-limbed bone dysplasias due to impaired bone growth (Makrythanasis et al., 2014). On other hand, loss-of-function *FGFR3* mutations are associated with camptodactyly, tall stature and hearing loss, denoting this condition as CATSHL syndrome (Escobar et al., 2016; Makrythanasis et al., 2014; Toydemir et al., 2006). Tall stature is present in all cases, with mean height in males of 195 cm and females of 178 cm (Toydemir et al., 2006). Bone overgrowth has been observed in animals with loss-of-function *FGFR3* mutations (Beever et al., 2006; Colvin et al., 1996; Deng et al., 1996), consistent with the human phenotype (Escobar et al., 2016; Makrythanasis et al., 2014; Toydemir et al., 2006). Other features include microcephaly, pectus excavatum, kyphoscoliosis, broad femur metaphyses, osteochondromas, high palate and intellectual disability

(Escobar et al., 2016; Toydemir et al., 2006).

5.7. FIBP-related overgrowth syndrome

Two reports identified mutations in *FIBP* (acidic fibroblast growth factor intracellular binding protein) in patients with a rare autosomal recessive overgrowth syndrome (Akawi et al., 2016; Thauvin-Robinet et al., 2016). The phenotype includes tall stature, macrocephaly, retinal coloboma, varicose veins, intellectual disability, nephromegaly or dysplastic cystic kidneys, and one case of Wilms tumor (Akawi et al., 2016; Thauvin-Robinet et al., 2016). Fibroblasts from affected individuals have increased proliferation rate compared to control fibroblasts (Akawi et al., 2016; Thauvin-Robinet et al., 2016). Although the mechanism of disease is not elucidated, it is postulated that *FIBP* play a role in FGFR3 pathway, and its loss causes an increased proliferation (Akawi et al., 2016; Thauvin-Robinet et al., 2016).

5.8. HMGA2 rearrangements-related overgrowth

HMGA2 encodes a protein belonging to the HMGA (High Mobility Group A) family, which are non-histone chromatin-associated proteins that bind to DNA in AT-rich regions regulating transcription and gene expression (Cleynen and Van de Ven, 2008). *HMGA2* is upregulated in a number of benign tumors, including lipomas, uterine leiomyomas, pleomorphic salivary gland adenomas, pulmonary hamartomas and thyroid tumors (Cleynen and Van de Ven, 2008; Klemke et al., 2014), as well as in pituitary adenomas, particularly prolactinomas (Fedele et al., 2002; Finelli et al., 2002). *HMGA2* plays a role in growth with several *HMGA2* variants/polymorphisms linked with increased height across different ethnicities (Lettre et al., 2008; Weedon et al., 2008; Weedon et al., 2007; Yang et al., 2010). A young boy with a pericentric inversion of chromosome 12 truncating *HMGA2* had tall stature (at the age of 8 years he had a noteworthy height of 169 cm, +7.5 SD), facial dysmorphic features, multiple lipomas, advanced bone age and a cerebellar tumor (Ligon et al., 2005), while transgenic mice with *Hmga2* truncation show 15% increase in body length (Arlotta et al., 2000; Battista et al., 1999). Facial features include flat supraorbital ridges, hypertelorism, large ears, prominent nasal bridge, alveolar ridges hypertrophy, gum hypertrophy and retrognathia. Brachydactyly, enlarged interphalangeal joints and redundant nail have been described (Fig. 4) (Ligon et al., 2005).

6. Conclusions

Individuals with acromegaloid appearance or tall patients may be referred to endocrinologists to exclude GH excess. While some of these cases are healthy individuals with normal variants of physical traits or growth, others indeed will have pituitary gigantism or acromegaly. However, some cases with clinical features of GH excess will not have any abnormality in the GH/IGF-1 axis. The differential diagnosis of pseudoacromegaly can be challenging due to the numerous pseudoacromegaly conditions and the significant overlap between some of these conditions. While history and clinical examination provides essential clues to the diagnosis, these often can be confirmed with genetic testing.

7. Disclosure summary

The authors declare no conflict of interest.

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Appendix A. Supplementary material

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