From NSD1 to Sotos syndrome : a genetic and functional analysis

Visser, R.

Chapter 2

Overgrowth syndromes: from classical to new

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Abstract

Overgrowth syndromes are a group of growth disorders which have gained joint attention from the fields of pediatrics, endocrinology and genetics. Major progress such as the identification of genetic causes has recently enhanced the delineation of the characteristic and non-characteristic manifestations, phenotype-genotype correlations and knowledge of the underlying pathophysiological mechanisms. As a consequence, the possibilities for distinction between the different overgrowth disorders have increased. Patients with either typical or non-typical features in whom no molecular abnormalities are found, form a basis for further research. Identification of new pathogenic alterations in these patients, best exemplified by the Marfan-related syndromes, has provided further understanding of the regulatory gene network involved.

In light of the recent developments and as an aid to the diagnostic process, the aim of this review is to give a comprehensive overview of the clinical, molecular genetic and pathophysiological aspects of each of the classic and new overgrowth syndromes.

Introduction

Longitudinal growth is a complex process which is influenced pre- and postnatally by an interaction of genetic, endocrine, nutritional, environmental and socioeconomic factors (1). Due to the complexity to attain normal height, usually disturbance of even a single factor results in a delayed growth velocity and short stature. Less common are conditions causing increased height. However, from a patient's and physician's perspective concerning diagnosis, prognosis, counselling and therapy, tall stature, either as the only symptom or as part of an overgrowth syndrome, is not less important. In the last two decades, the causative genetic defects in the classic overgrowth syndromes such as Beckwith-Wiedemann, Simpson-Golabi-Behmel and Sotos syndrome have been identified (2-4). These discoveries have resulted in the delineation of the phenotypic spectrum and genotype-phenotype correlations. They also stimulated and still stimulate further research in patients with either characteristic or non-characteristic manifestations but without a confirmed genetic defect. A successful example of these investigations is the identification of transforming growth factor beta receptor (*TGFBR1* and *TGFBR2)* mutations; originally detected in patients with Marfan-like syndromes and subsequently also in classic Marfan syndrome patients without a fibrillin 1 (*FBN1)* mutation (5,6). Furthermore, genes implicated in overgrowth syndromes resulted in the identification of reciprocal short stature syndromes; hypomethylation of an imprinting center region at 11p15 was identified as a cause of Silver-Russell syndrome, while hypermethylation of the same region is responsible for 2-7% of patients with Beckwith-Wiedemann syndrome (7,8). In accordance with this, other reports of patients with gene alterations leading to an opposite growth phenotype have emerged recently, for example a missense mutation of the fibroblast growth factor receptor 3 (*FGFR3)* gene is thought to cause a tall stature syndrome (9) while activating mutations of *FGFR3* are well-known to be responsible for several growth deficient disorders such as hypochondroplasia and achondroplasia (10). Furthermore, a duplication of the insulin-like growth factor 1 receptor (*IGF1R)* is associated with tall stature while haploinsufficiency results in short stature (11).

With regard to the recent progress, this review gives a comprehensive overview of the clinical, molecular genetic and pathophysiological aspects of the classic overgrowth syndromes and new overgrowth disorders. The syndromes are selected based on the fact that during the process of diagnosis they should be considered and hence distinguished from each other. Although in the past classificatory schemes have been postulated (reviewed in (12)), these

seem nowadays artificial by absence of good grouping definitions other than the common classification “overgrowth syndrome”. Endocrine disorders and skeletal dysplasias with an overgrowth component will not be discussed here.

Diagnosis of overgrowth syndromes

The starting point for diagnostic evaluation of an overgrowth problem is usually tall stature, which is defined as a height of > +2 standard deviation score (SDS; i.e. ~98th percentile) above the mean height for that age, corrected for sex and ethnicity. It is important also to suspect children growing outside their target height range (> +2 SDS of the mid-parental height corrected for gender- and secular trend) of having a growth disorder. Furthermore, recent growth acceleration warrants further diagnostic analysis as well, with specific attention for endocrine disorders with tall stature (reviewed in (13)). However, it should be noted that although tall stature is used as a common denominator, many patients of the so called overgrowth syndromes might not fulfil the > + 2 SDS criterion. Therefore we propose that typical dysmorphic features either with or without tall stature should be a second starting point for diagnostic consideration of the overgrowth syndromes discussed in this review. A diagnostic flow chart is shown in Figure 1 and the respective diagnostic tests for the overgrowth disorders are shown in Table 1. Detailed recording and description of the dysmorphic features will be indispensable to discern the correct clinical diagnosis. Afterwards, molecular confirmation of a defect of the involved gene should be undertaken. In groups belonging to the same molecular pathways, for example the Marfan-related syndromes, a stepwise screening of the candidate genes known in this pathway is recommended. In other overgrowth syndromes, routine molecular screening of multiple genes implicated in overgrowth syndromes cannot be advised based on the very low and often zero detection rate. Therefore, molecular testing for different genes should be reserved for patients with overlapping features of different overgrowth syndromes.

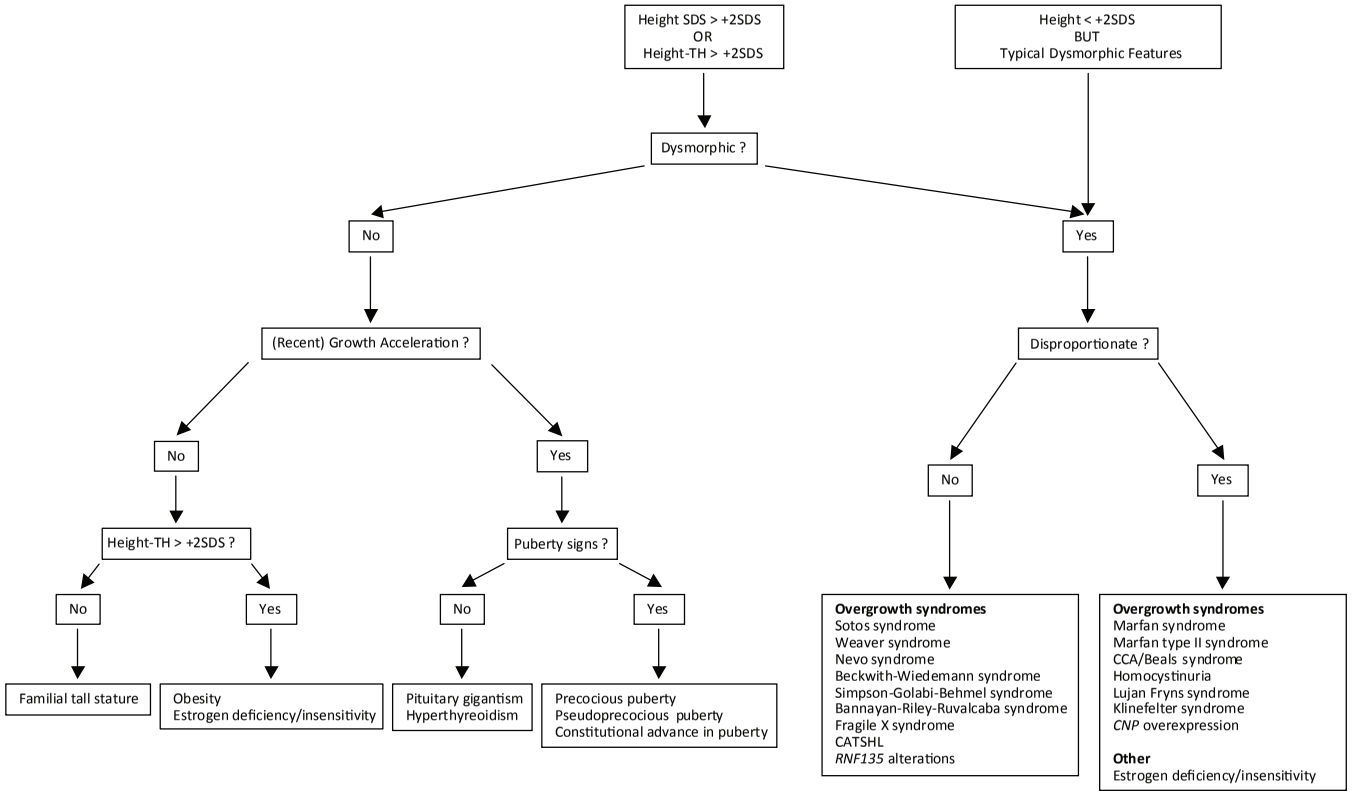

Figure 1. Diagnostic flow chart for the differential diagnosis of tall stature and overgrowth syndromes

Figure 1 is modified from (14,15). CCA: Congenital Contractural Arachnodactyly; CNP: C-type natriuretic peptide

Table 1. Overgrowth causing disorders and their respective diagnostic tests

Disorders without dysmorphic features[1]	**Diagnostic Test**
Familial tall stature	Family history
Obesity	BMI, BA
Estrogen deficiency/insensitivity	LH, FSH, estradiol, testosterone
Pituitary gigantism	GH (suppression by glucose), IGF-I, IGFBP-3, pituitary imaging
Hyperthyreoidism	Free T4, TSH
Precocious puberty	LH, FSH, GnRH test , estradiol or testosterone
Pseudoprecocious puberty	ACTH, Androstenedione, DHEAS, estrone, 17OHP, estradiol or testosterone
Dysmorphic features without disproportions[1]	
Sotos syndrome	DNA (*NSD1*)
Weaver syndrome	DNA (Exclusion o*f NSD1* mutations)
Nevo syndrome	DNA (*PLOD1*)
Beckwith-Wiedemann syndrome	DNA (*locus 11p15)*
Simpson-Golabi-Behmel syndrome	DNA (*GPC3*)
Bannayan-Riley-Ruvalcaba syndrome	DNA (*PTEN*)
Fragile X syndrome	DNA (*FMR1*)
CATSHL	DNA (*FGFR3*)
RNF135 syndrome	DNA (*RNF135*)
Dysmorphic features with disproportions[1]	
Marfan syndrome	DNA (*FBN1* and consider *TGFBR2* and *TGFBR1*)
Marfan type II syndrome	DNA (*TGFBR2*)
CCA/Beals syndrome	DNA (*FBN2*)
Homocystinuria	Serum and urine levels of homocysteine, DNA (*CBS*)
Lujan Fryns syndrome	DNA (*MED12, UPF3B*)
Klinefelter's syndrome	Karyotyping
CNP overexpression	Karyotyping, DNA (*NPPC*), serum levels of CNP

[1] Order of disorders is according the diagnostic flow chart presented in Figure 1.

Abbreviations: 17OHP: 17 hydroxyprogesterone; ACTH: adrenocorticotropic hormone; BA: bone age; BMI: body mass index; DHEAS: dehydroepiandrosterone sulphate; FSH: follicle-stimulating hormone; GH: Growth Hormone; GnRH: gonadotropin releasing hormone; IGF-I: Insulin-like Growth Factor I; IGFBP-3: Insulin-like Growth Factor Binding Protein 3; LH: luteinizing hormone; TSH: thyroid-stimulating hormone

Classic syndromes

Marfan syndrome

Marfan syndrome (MFS; OMIM 154700) is an autosomal dominant connective tissue disorder with an estimated incidence of 2-3 per 10.000 individuals (16). It is caused by pathogenic mutations of the fibrillin 1 (*FBN1*) gene at 15q21.1 (17) and approximately 25% of the mutations occur *de novo* (16). In MFS multi-organ systems are affected with manifestations primarily in the skeletal (Marfan habitus), cardiovascular (aortic root dilatation and mitral valve prolaps and regurgitation) and ocular systems (ectopia lentis). Also the skin/integument, lung or dura can be affected (18). The characteristic Marfan habitus includes a tall disproportionate stature with long slender limbs (dolichostenomelia), arachnodactyly with a positive thumb and wrist sign and pectus excavatum or carinatum (19). Typical craniofacial features are a long and narrow face, downslant of the palpebral fissures, enophtalmos, malar hypoplasia, micrognathia or retrognathia and a high-arched palate (16). Other prominent manifestations are scoliosis, pes planus, joint laxity and lumbosacral dural ectasia (20). Acute dissection of the ascending aorta due to progressive dilatation is the major cause of mortality in MFS. The clinical diagnosis is made on the criteria defined by the Ghent nosology (Table 2) (18). For the diagnosis of MFS, a major criterion in two different organ systems and involvement of a third is required. Since the occurrence of certain Marfan features such as aortic dilation and ectopia lentis are age-related, caution is warranted to use this nosology for the exclusion of MFS in patients younger than 18 years (19). Furthermore, the phenotypic expression can vary greatly between affected family members or between affected members of different families.

Although height itself is not included in the Ghent nosology, the mean birth length for boys and girls with clinically MFS is near the 90th percentile (21). Boys then continue to grow approximately between the 50th en 95th percentiles for the first three years of life. Girls show similar increased body length in the first year of life with a further increase along the 95th percentile between 1 and 3 years of age. Height of boys and girls after three years of age till adulthood is consistently above the 95th percentile of the normal population. Furthermore, the peak of the pubertal growth spurt is advanced on average with 2.4 and 2.2 years for boys and girls, respectively (21).

Table 2. Diagnostic criteria of Marfan syndrome and frequencies of common features with confirmed *FBN1* alterations

Clinical diagnosis of MFS requires a major criterion in two systems and involvement of a third

Skeletal system	Major criterion:	Presence of at least 4 of the major features
	Involvement:	Presence of 2 of the major features or 1 of the major plus 2 of the minor features

Major features		**Minor features**	
Pectus carinatum, or excavatum requiring surgery	32%	Pectus excavatum of moderate severity	29%
Reduced upper to lower segment ratio <0.86 or arm span to height ratio > 1.05	55%	Joint hypermobility	63%
Positive wrist and thumb sign	78%	Characteristic face	49%
Scoliosis of >20° or spondylolisthesis	53%	Highly arched palate with dental crowding	69%
Reduced extenstion at the elbows <170°	15%		
Pes planus	47%		
Protrusio acetabulae	23%		

Ocular system	Major criterion:	Ectopia lentis present (54%)
	Involvement:	At least 2 of the minor features present

Major features		**Minor features**	
Ectopia lentis	54%	Flat cornea	9%
		Myopia	52%
		Iris or ciliary muscle hypoplasia	n.r.[1]

Cardiovascular system	Major criterion:	At least 1 major feature
	Involvement:	At least 1 minor feature

Major features		**Minor features**	
Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses Valsalva	77%	Mitral valve prolapse	54%
Dissection of the ascending aorta	14%	Dilatation of the main pulmonary artery before 40 years	n.r.
		Mitral annulus calcification < 40 years	n.r.
		Dilatation or dissection of the descending thoracic or abdominal aorta < 50 years	7%

Table 2. ***(continued)***

Pulmonary system	Involvement:		At least 1 minor feature	
Major features			**Minor features**	
None			Spontaneous pneumothorax or apical blebs	7%
Skin and integument system	Involvement:		At least 1 minor feature	
Major features			**Minor features**	
None			Striae atrophicae	47%
			Recurrent or incisional herniae	10%
Dura system	Major criterion: Involvement:		Lumbosacral dural ectasia present At least 1 minor feature	
Major features			**Minor features**	
Lumbosacral dural ectasia		53%	None	
Family system	Major criterion: At least 1 major feature present			
Major features			**Minor features**	
First degree family member independently fulfilling criteria		51%	None	
Carrier pathogenic *FBN1* mutation				
Inheritance of DNA marker haplotype linked to Marfan syndrome in the family				

Table 2 was adapted from Faivre et al. (20) with permission from BMJ Publishing Group Ltd. Diagnostic criteria are according the Ghent nosology (18)

[1] n.r. : not reported

The detection rate of *FBN1* mutations varies widely from 9-90%, depending on the type of screening method employed as well as on the criteria used (reviewed in (22)). A strong association between the Ghent nosology and the rate of *FBN1* mutations is shown by two large studies which detected *FBN1* mutations in 51-66% in patients fulfilling the Gent criteria versus 12% not meeting the diagnostic criteria (23,24). *FBN1* mutations consist mainly of missense mutations (~56%) and the majority of the missense mutations are located in the

calcium-binding epidermal growth factor domains (cb-EGF; in 74%) or in the transforming growth factor β binding protein-like domain (TB; in 15%) (25). Approximately 60% of the missense mutations substitute or create a cysteine residue and consequentially affect disulfide bonds and the tertiary protein structure (25). Mutations in *FBN1* have been also found in a broad group of disorders including for example isolated ectopia lentis, Shprintzen-Goldberg craniosynostosis, familial thoracic aortic aneurysms and dissections (TAAD) and autosomal dominant Weill-Marchesani syndrome (reviewed in (22)).

Until recently, no strong genotype-phenotype correlation had been established in MFS, except for the association of mutations in exons 24-32 with a neonatal form of MFS (26). This neonatal presentation is more severe with additional manifestations such as flexion contractures, pulmonary emphysema and loose skin and most patients do no survive 2 years of life. A recent large study of 1013 *FBN1* mutation carriers showed that mutations in exons 24-32 were also correlated with a more severe phenotype in MFS patients with a younger age at diagnosis and shorter survival (25). Furthermore, a higher probability to develop ectopia lentis, ascending aortic root dilatation, mitral valve defects and scoliosis was found for this region. In the same study, missense mutations affecting a cysteine residue were correlated with a higher probability of ectopia lentis compared to other missense mutations.

FBN1 encodes for a large extracellular matrix (ECM) protein and this monomer fibrillin-1 polymerizes in bundles of microfibrils. In interaction with other ECM proteins these bundles form an assembly and give elasticity to the connective tissues (27). Although the exact mechanisms are not clear, the loss of connective tissue integrity in MFS could be explained by either a reduced incorporation of fibrillin-1 in the microfibrils or that after incorporation of mutated fibrillins an increased loss of tissue, possibly due to proteolysis, would occur. The molecular biology of fibrillin and fibrillinopathies has been extensively reviewed elsewhere (22). However, the loss of connective tissue integrity would not provide enough support for manifestations such as increased statural growth and other skeletal features. Interestingly, an interaction between fibrillin and the latent TGFβ binding protein 1 (LTBP1) has been reported and a model was proposed in which LTBP1 by sequestering latent TGFβ complexes regulates TGFβ bioactivity in the ECM (28). This involvement of TGFβ signaling is further supported by the detection of TGFβ receptor 2 *(TGFBR2)* mutations as the cause of MFS type II (29) (see further). In addition, *TGFBR1* and *TGFBR2* mutations have been identified in individuals fullfiling the Ghent criteria (5,6), emphasizing the shared underlying pathogenic

mechanism. However conflicting data exists, showing a decreased signaling activity for mutations found in MFS type 2 (29) while increased signaling was found in the related Loeys-Dietz syndrome (LDS) (30) and in the lungs of *Fbn1* deficient mice (31). Nevertheless, from *in vitro* studies the role of TGFβ in chondrogenesis has been well established (32) and perturbation of this signaling pathway is likely to contribute to the skeletal manifestations in MFS.

Marfan syndrome type II / Loeys-Dietz syndrome

Marfan syndrome type II (MFS2 ; OMIM 154705) is a dominant autosomal disorder and was first described in a large French family (33). Similar involvement as in Marfan syndrome was found for the skeletal system (tall stature, increased arm span, arachnodactyly and chest deformities, scoliosis) and the cardiovascular system (aortic root dilatation, aortic dissection or rupture, mitral valve prolapse), but without involvement of the ocular system.

A cosegregating loss-of-function missense mutation of *TGFBR2* at 3p24.1 was identified as the cause in this family (29) and *TGBR2* mutations were detected in several other patients with features of Marfan-syndrome but without major ocular involvement (5,6,34,35). However, recently one member of the original French family was reported to have ectopia lentis (36). Furthermore, *TGFBR2* and also *TGFBR1* mutations were found in LDS (type I and II) which is characterised by arterial tortuosity and aneurysms, hypertelorism, bifid uvula and cleft palate (30,37) and in a spectrum of other disorders (36). Whether MFS2 should be regarded as the phenotypic spectrum of classic MFS or of LDS remains a topic for discussion (29,37). With regard to molecular diagnosis, it is important to consider *TGFBR2* and *TGFBR1* analysis in patients with features of MFS without *FBN1* abnormalities.

TGFBR2 encodes a transmembrane receptor with an intracellular kinase domain. Primarily missense mutations are detected which cluster in or close to the serine-threonine kinase domain and alter TGFβ signaling (29,30,37). For discussion on TGFβ signaling we refer to MFS.

Congenital contractural arachnodactyly / Beals syndrome

Congenital contractural arachnodactyly or Beals syndrome (CCA; OMIM 121050) is an autosomal dominantly inherited disorder with overlapping manifestations with MFS. CCA is caused by abnormalities of the fibrillin 2 (*FBN2*) gene at 5q23.3 (38). Characteristic features

include multiple congenital contractures (knees, elbows, fingers), arachnodactyly, tall stature with dolichostenomelia, severe kyphoscoliosis, muscular hypoplasia and crumpled ears (22). Although initially aortic involvement was thought to be absent in CCA, aortic root dilatation has been reported in four patients (39).

Mutations in *FBN2* cluster in exons 24 through 34 which is associated in *FBN1* with neonatal MFS and a more severe phenotype (see MFS). Mutations are primarily located in the cbEGF domains or are affecting splicing (39). Although the pathogenesis is thought to be in general similar to *FBN1* defects, differences in spatial and temporal gene expression for *FBN1* and *FBN2*, which might underlie the different phenotypic manifestations, have been shown (22).

Homocystinuria

Homocystinuria (OMIM 236200) is an autosomal recessive disorder of sulfur amino acid metabolism and is caused by a cystathionine β-synthase (CBS) deficiency due to mutations of the CBS gene at 21q22.3 (40). The clinical features include skeletal (Marfanoid habitus, osteoporosis and scoliosis), ocular (ectopia lentis and myopia), vascular manifestations (thromboembolism, malar flush and livido reticularis) and manifestations affecting the central nervous system (mental retardation and psychiatric disorders) (41). Height is at or above the 95th percentile in 50% of the patients (42). Extremely high plasma levels of total homocysteine and high levels of methionine are measured with decreased levels of cystathionine and cysteine (40). Treatment options include pyridoxine (vitamin B6), betaine and restriction of dietary methionine. In a small study group, a correlation between growth and free homcysteine levels was found with a mean height SDS of -0.01 SDS ± 0.81 in the optimally treated group and +1.73 SDS ± 0.88 in the suboptimally treated group (43).

Interestingly, an interaction between FBN1 and homocysteine was detected, in which homocysteine reduces the disulfide bonds of the cbEGF domains of FBN1 and consequentially modifies protein folding and increases proteolytic degradation of the protein (44,45). This interaction would explain why in homocystinuria patients, manifestations similar to Marfan syndrome are part of the phenotype.

Lujan-Fryns syndrome

Lujan-Fryns syndrome (LFS ; OMIM 309520) is a rare X-linked mental retardation syndrome which is characterised by a marfanoid habitus becoming evident after puberty (tall stature, long thin hyper-extensible fingers and toes), typical craniofacial dysmorphism (a long, narrow face, prominent forehead, maxillary hypoplasia, a small mandible) and behavioural problems (46). Recently mutations in the *MED12* gene and in the *UPF3B* gene were found as the cause of Lujan-Fryns syndrome (47,48). Furthermore, mutations in the *ZDHHC9* gene cause another X-linked mental retardation syndrome with a marfanoid habitus and should be considered in the differential diagnosis of LFS (49).

Sotos syndrome

Sotos syndrome (SoS; OMIM 117550) is an autosomal dominant disorder and has an estimated incidence of 1 in 15.000 newborns (50). It is caused by haploinsufficiency of the nuclear receptor binding SET domain protein 1 (*NSD1*) at 5q35.2-35.3 (4). The cardinal features (i.e. ≥ 90% of the patients) for the diagnosis of SoS are characteristic facial features, overgrowth (height and/or head circumference ≥ 98th percentile) and a certain degree of learning disability (51). The characteristic Sotos craniofacial features include a triangular shaped ("inverted pear-like") face with a prominent chin, macrodolichocephaly, frontal bossing with a high hairline, (apparent) hypertelorism and downslanting of the palpebral fissures. These facial features are probably the most consistent diagnostic criterion (52), but become less apparent in adolescence and adulthood. SoS is furthermore associated with a large variety of additional features such as advanced bone age, scoliosis, seizures and neonatal problems (Table 3) (51-53). Cardiac and genitourinary anomalies are also frequently reported. The overall tumor incidence in patients with an *NSD1* abnormality is ~2% with an increased incidence of neural crest tumors and sacrococcygeal teratomas (54). Although the risk for malignancy in SoS is very low, some patients carrying an *NSD1* alteration have been described with acute lymphoblastic leukaemia, T-cell lymphoma, neuroblastoma, hepatoblastoma and small-cell lung cancer (52,54).

The growth pattern shows an accelerated growth, which starts pre- or postnatally and is especially increased in the early years of childhood. The final adult height however is found to be within the (high) normal range (53). Although overgrowth is a cardinal feature, children carrying a pathogenic *NSD1* mutation with normal heights and normal head circumference

Table 3. Clinical diagnostic criteria and common features in Sotos syndrome with confirmed *NSD1* abnormalities

Cardinal features (present in ≥ 90% of the patients) (51)		
Characteristic facial features		
Height and/or head circumference ≥ 98th percentile		
Learning disability		
Major features (present in ≥ 15% of the patients)[1]	**Number of patients**	**Percentage**
Neonatal hypotonia	76/91	84
Neonatal feeding problems	85/103	83
Advanced bone age	n.r.[2]	76
Neonatal hyperbilirubinemia	61/85	71
Scoliosis	43/101	43
Seizures/Epilepsy	55/184	30
Cardiac anomalies	30/178	17
Genitourinary anomalies	26/164	16
Hyperlaxity/pes planus	n.r.	n.r.
Cranial MRI or CT abnormalities	n.r.	n.r.
Maternal pre-eclampsia	n.r.	n.r.

[1] Major features were adapted from (51-53)
[2] n.r.: not reported

have been described (51,52). The degree of learning disability varies widely, from mild to severe.

Pathogenic alterations of *NSD1* are found in approximately 60-90% of the patients depending on the stringency of the inclusion criteria used (reviewed in (55)). Most of the alterations occur *de novo*, but familial cases with autosomal dominant inheritance have also been described. The main causes are intragenic point mutations (~80-85%) , whole-gene microdeletions (~10%) and exon-deletions (~5%) (55). However, based on ethnicity this spectrum can be different. In the Japanese population a common 1.9 Mb-microdeletion encompassing *NSD1* and neighbouring genes is the main cause and is detected in ~50% of the patients while intragenic point mutations only account for ~10% (56,57). As an explanation,

we have suggested that a genomic inversion polymorphism increases the susceptibility to microdeletions in the Japanese population (57). Mutations resulting in protein truncation are found throughout the *NSD1* gene without specific hotspot locations. In contrast, missense mutations are preferentially located in the functional domains of *NSD1* (reviewed in *(55)*). Statistically convincing data are lacking but a correlation between a milder phenotype and missense mutations compared with truncating mutations has been suggested (52). This would possibly explain the preferential detection of missense mutations in familial cases (51). Although SoS is primarily caused by a reduced level of proper functioning NSD1, a correlation for a more severe level of mental impairment and smaller height has been found for patients harboring a microdeletion in comparison with patients carrying a point-mutation (51,58). Furthermore, anomalies of the cardiovascular and genitourinary systems seem correlated with microdeletions (52,58).

NSD1 alterations have also been detected in 6 Weaver syndrome patients (59,60), in two patients with Beckwith-Wiedemann (61) and in one patient with Nevo syndrome (62). Without additional patients reported so far, it seems likely that these patients should be considered as having overlapping phenotypic features, rather than *NSD1* alterations being responsible for a subset of patients with these respective syndromes.

NSD1 was identified as interacting with nuclear hormone receptors (retinoic receptor, thyroid receptor, retinoid X and estrogen receptors) through its nuclear receptor interaction domains (63). It was postulated that NSD1 could interact both as a co-repressor and co-activator of nuclear hormone receptors and would therefore be a bifunctional transcriptional regulator (63). Additionally, NSD1 is able to control chromatin transcription through the histone methyltransferase activity of its SET domain (Su(var) 3-9, Enhancer of zeste, Trithorax domain) (64) and through its interaction with the NIZP1 protein (65). In this function as a transcriptional regulator it can be hypothesized that NSD1 reduces the transcription of growth promoting genes and loss of this activity would consequentially result in overgrowth (4). Unfortunately no further evidence for the involvement of NSD1 in growth regulation could be derived from mouse models since heterozygous *Nsd1* mutant mice did not express an overgrowth phenotype and homozygous *Nsd1* deficient mice died during embryogenesis (64). We detected endocrine and paracrine changes in the IGF-system between SoS patients with a confirmed *NSD1* defect and controls, although the actual contribution of these differences to overgrowth is unclear (66).

Weaver syndrome

Weaver syndrome (OMIM 277590) is a rare disorder with less than hundred patients described in the literature. It is characterized by pre- or postnatal overgrowth, typical craniofacial features, developmental delay, a hoarse low-pitched cry, advanced bone maturation and finger- and nail abnormalities such as camptodactyly and deep set nails (67-70). The craniofacial features include macrocephaly, flat occiput, hypertelorism, micrognathia, long and prominent philtrum and large ears. There is a phenotypical overlap with Sotos syndrome and six Weaver syndrome patients have indeed been reported to carry an *NSD1* point mutation (59,60),although two of them were later reclassified as typical Sotos and one as Sotos-like (51). In 16 additional patients no alterations were detected (59,60,71-73) and it can be questioned whether *NSD1* abnormalities are the cause of classical Weaver syndrome (51). Furthermore, no *RNF135* (see further) abnormalities were found in classical Weaver syndrome patients.

Nevo syndrome / Ehlers-Danlos type VIA

Nevo syndrome (OMIM 601451) is a rare autosomal recessive disorder and is characterized by an increased perinatal length, kyphoscoliosis, talipes calcaneovalgus, generalized hypotonia, volar edema and spindle shaped fingers (74-76). In 2005, a homozygous *PLOD1* mutation (p.R319X) was found in 6 patients from Arab ancestry and one Dutch patient carried a homozygous deletion of exon 17 (77). Deficiency of the procollagen-lysine 1, 2-

Table 4. Clinical diagnostic criteria in Ehlers-Danlos Kyphoscoliosis Type[1]

Major clinical diagnostic criteria	Minor clinical diagnostic criteria
Generalized joint laxity	Tissue fragility, including atrophic scars
Severe muscle hypotonia at birth	Easy bruising
Scoliosis at birth, progressive	Arterial rupture
Scleral fragility and rupture of the ocular globe	Marfanoid habitus
	Microcornea
	Radiologically considerable osteopenia
	Family history, i.e. affected sibs

[1] Revised nosology, Villefranche 1997 (78)

oxoglutarate 5-dioxygenase 1 (*PLOD1)* gene was previously described in the kyphoscoliotic type of Ehlers-Danlos syndrome (EDS VIA; OMIM 225400) which is characterized by severe muscular hypotonia present at birth, progressive kyphoscoliosis, joint hypermobility, scleral fragility and an elevated ratio of total lysyl pyridinoline to hydroxylysyl pyridinoline in the urine (Table 4) (78). It was therefore concluded that Nevo syndrome and EDS VIA were a single entity (77).

Nevo syndrome was originally regarded as an overgrowth syndrome, but this remains equivocal since height information of patients with confirmed *PLOD1* abnormalities is scarce. Four patients were reported to have birth lengths > 90th percentile, three between the 50th-90th percentile and one at the 10th percentile (77,79,80). Follow-up height in infancy or childhood in 7 of these patients varied between the 25th-90th percentile, while two patients had a height >90th percentile. However, progressive kyphoscoliosis might have influenced follow-up height measurements.

PLOD1 is located on chromosome 1p36.22 and encodes for a protein which hydroxylates specific lysyl residues in collagen proteins (81). These residues are attachment sites for carbohydrates and are essential for the formation of collagen cross-links. Deficiency of PLOD1 results in a weakened cross-linking formation and consequentially an impaired biomechanical instability of the connective tissues (79). However, also since *Plod1* $^{-}$/$^{-}$ mice did not show overgrowth (82), it is not known how PLOD1 would be involved in longitudinal growth.

Beckwith-Wiedemann syndrome

Beckwith-Wiedemann syndrome (BWS; OMIM 130650) is characterised by three cardinal features: neonatal macrosomia or postnatal overgrowth, abdominal wall defects and macroglossia. Additional features include ear abnormalities (earlobe creases or posterior helical pits), neonatal hypoglycaemia, nevus flammeus, hemihypertrophy, organomegaly, polyhydramnios, midfacial hypoplasia, cardiomyopathy and embryonal tumors (83,84). Although there are no consensus diagnostic criteria, in general the diagnosis can be made if three of the cardinal features are present or two cardinal and one of the additional features (Table 5) (85). BWS has an estimated incidence of approximately 1 in 13700 newborns (86). Approximately 85% of the patients with BWS are sporadic while 10-15% show an autosomal inherited pattern with a preferential maternal transmission (8).

Table 5. Clinical diagnostic criteria in BWS and common features

The diagnosis is made if three of the sentinel features are present[1]. If less than three are present the additional features may support the diagnosis.

Sentinel features	**Percentage[2]**
Macrosomia (prenatal and/or postnatal gigantism)	77-88
Macroglossia	91-100
Abdominal wall defects (omphalocele>umbilical hernia>diastasis recti)	77-91
Hemihyperplasia	14-24
Embryonal tumors	7.5
Adrenocortical cytomegaly	100[3]
Ear anomalies (anterior linear earlobe creases, posterior helical pits)	65-76
Visceromegaly	86-100
Renal abnormalities	60-88
Neonatal hypoglycemia	50-63
Cleft palate	2.5-5
Positive family history	11-42
Additional features	
Polyhydramnios	29-43
Prematurity	27
Enlarged placenta	n.r.[4]
Cardiomegaly or structural cardiac anomalies	6.5-18
Nevus flammeus	54-82
Advanced bone age	60
Characteristic facies with midfacial hypoplasia	88-94
Monozygotic twinning	n.r.

[1] Clinical diagnostic criteria are according to (85). No consensus clinical criteria exist. Cohen (84) suggested at least the combination of macrosomia, macroglossia and abdominal wall defects or two of those in combination with hypoglycaemia, hemihyperplasia, ear anomalies, midface hypoplasia, nevus flammeus, cardiomegaly and enlarged placenta/long umbilical cord and/or polyhydramnios, advanced bone age and tumors.

[2] Common features are adapted from (83,84,86,87) and references therein. Percentages include data from clinical studies (83,84,86,87) without molecular confirmation.

[3] Only 9 patients reported in (86)

[4] n.r. not reported

Increased infant mortality is caused by hypoglycaemia, respiratory or feeding problems due to macroglossia, prematurity or cardiovascular problems. Usually there is a normal mental development in BWS, although moderate to severe developmental delay has been reported in 4% (83). There is an estimated tumor risk of 5-10% with a predisposition for embryonal tumors, specifically Wilms tumor (54).

In a review of 134 clinically diagnosed patients, the average birth length and weight for boys was above the 95th percentile and height was at or above the 95th percentile throughout adolescence, parallel to the growth curve of the normal population (87). Weight followed the 95th percentile, but weight follow-up data was only available till three years of age. For girls, average birth length and weight was at the 75th percentile and increased towards the 95th percentile at 18 months of age. The statural growth throughout adolescence was similar to the males, while weight data were only available till nine years of age. There is an advanced bone maturation especially during the first 4 years of life and adult height is supposed to be within the normal range (84).

BWS is caused by abnormalities, either cytogenetic, molecular genetic or epigenetic, of a cluster of imprinted genes on 11p15 (reviewed in (8,88)). This cluster can be divided into two domains. The telomeric domain 1 contains the genes *H19* and insulin-like growth factor 2 (*IGF2*) and is regulated by the imprinting center region 1 (ICR1 or DMR1; differentially methylated region 1). The centromeric domain 2 contains *CDKN1C*, *KCNQ1* and *KCNQ1OT1* as the most important genes and is regulated by imprinting center region 2 (ICR2 or DMR2). In a normal situation, these imprinting centres are differentially methylated which means that instead of bi-allelic expression either the genes from the paternal allele (*IGF2*, *KCNQ1OT1*) or from the maternal allele (*H19*, *CDKN1C* and *KCNQ1*) are expressed and that the genes on the opposite allele are silenced. In general, disturbance of this differentially regulated gene-expression pattern is the cause of BWS. In sporadic BWS patients, loss of methylation at the DMR2 accounts for 50-60%, intragenic-point mutations of *CDKN1C* for 5-10% and hypermethylation of DMR1 and *H19* for 2-7% of the abnormalities detected (reviewed in (8,88)). In approximately 20% of the sporadic patients, paternal uniparental disomy (UPD) with loss of the maternal allele is found. In autosomal dominant pedigrees, intragenic-point mutations of *CDKN1C* are found in ~30-50% of the patients. Less frequent causes, either sporadic and/or inherited, include balanced chromosomal translocations, duplications or inversions involving 11p15 and microdeletions of DMR1 and DMR2. In 10-15% of the

patients the etiology is unknown. Recently, constitutional DMR2 defects were shown to be also responsible for 3% of patients with sporadic Wilms tumor but without features of BWS (89). This suggests that defects in this region might result in a broad phenotypic spectrum.

Interestingly, hypomethylation of DMR1 has been found to be the cause of Silver-Russell syndrome (7). This syndrome is characterised by intrauterine and postnatal growth retardation, dysmorphic facial features and frequent body asymmetry, an opposite phenotype of the BWS (90). No abnormalities, except for a maternal duplication in a single patient (91), have been detected so far in the centromeric 11p15 domain.

In BWS, genotype/epigenotype-phenotype correlations show a strong association of UPD with hemihypertrophy (92), which is probably due to that fact that many cases of UPD display somatic mosaicism. Different associations can be found for the two imprinting centers with exomphalos being associated with an DMR2 alteration or a *CDKN1C* defect (92,93), a higher birth weight with DMR1 defects (92) and a higher risk of tumors for patients with DMR1 alterations and UPD patients (92,94,95). Although there is a lower risk, in patients with DMR2 defects tumors such as hepatoblastoma and rhabdomyosarcoma have still been reported (54). On the other hand, the risk for Wilms tumor for patients with an DMR2 defect seems very low and in fact no such patients have yet been reported (54,92).

Originally increased expression of *IGF2* was thought to be the cause of the BWS phenotype (2,96). This was supported by transgenic mice overexpressing *Igf2* which showed prenatal and postnatal overgrowth, macroglossia, polyhydramnios and organomegaly (97). In addition, loss of imprinting and increased *IGF2* expression was found in Wilms tumor (98). However, significant biallelic expression of *IGF2* was also observed in the leukocytes of 10% of normal individuals without a BWS phenotype (99) and detection of abnormalities in BWS patients at DMR2 and in *CDKN1C* called for a more complex explanatory mechanism. Evidence came from a mouse model with a null-mutation in *CDKN1C* and loss of imprinting of *Igf2*, which showed features reminiscent of BWS (100), while mice carrying *CDKN1C* mutations alone exhibited omphalocele and kidney dysplasia but no macrosomia (101). Additional support for an interaction model can be derived from the data that increased *IGF2* expression causes decreased *CDKN1C* expression both *in vitro* and *in vivo* (102). Therefore, both genes seem to act in a concerted fashion influencing the same biochemical pathway and perturbation of this signaling cascade is likely to be the cause of BWS.

Simpson-Golabi-Behmel syndrome

Simpson-Golabi-Behmel syndrome (SGBS; OMIM 312870) is an X-linked condition and is caused by defects of the glypican 3 (*GPC3*) gene at Xq26.2 (3). Characteristic features are pre- and postnatal overgrowth, a "coarse" facial appearance (short nose with anteverted nares, low set posteriorly rotated ears, hypertelorism, downslanting of the palpebral fissures and epicanthic folds), supernumerary nipples and congenital heart defects (Table 6). Other common features include skeletal, hand and renal tract anomalies, macroglossia, midline groove of the lower lip and or tongue, macrognathia, cleft palate and inguinal and umbilical hernias (103-105). There is a predisposition for embryonal tumors especially Wilms tumor and furthermore hepatoblastoma and nephroblastomatosis (104). Although speech and fine and/or gross motor delay are commonly found, mental development can be normal in SGBS-patients (103). The phenotypic spectrum varies from very mild in female carriers to early lethal forms in affected boys (106). Due to the neonatal macrosomia, macroglossia, abdominal wall defects and a predisposition for Wilms tumor, BWS is usually considered in the differential diagnosis although the coarse facial features, supernumerary nipples, cardiac defects, polydactyly and an X-linked inheritance pattern are more typical of SGBS (106).

The mutational spectrum of GPC3 abnormalities includes microdeletions affecting a variable number of exons (most frequently), deletions of the whole gene and intragenic point mutations (3,104,107). In roughly 40-70% of the typical SGBS patients alterations of *GPC3* were identified (104,108) and no genotype-phenotype correlation was observed, which leaves nonfunctional GPC3 as the most likely cause of SGBS (107). In contrast, the causative role of GPC3 in Wilms tumor is less clear because no abrogating alterations of *GPC3* were detected (109) and even an increased expression of *GPC3* was found (110). A second SGBS locus was mapped to ~6Mb region on chromosome Xp22 in a family expressing a more severe from of SGBS, so called SGBS type 2 (111). Recently a novel X-linked mental retardation syndrome including macrocephaly and ciliary dysfunction was described by Budney et al. which was caused by mutation in the *OFD1* gene (112). This gene is also responsible for the oral-facial-digital syndrome type 1 (113). Because of the overlapping phenotype of their families and the fact that *OFD1* is located in the 6Mb region on Xp22, Budney et al. speculated that *OFD1* might be the responsible gene in SGBS type 2 (112).

GPC3 is one of the six members of the glypican family, which is a group of heparan sulphate proteoglycans (HSPG). These proteins are involved in the regulation of heparin-

Table 6. Common features (>10%) in Simpson-Golabi-Behmel syndrome with confirmed *GPC3* alterations

Major features[1]	Number of patients	Percentage
Prenatal overgrowth	41/42	98
Coarse face	36/42	86
Postnatal overgrowth	27/39	69
Hand anomalies	23/35	66
Speech delay	21/39	54
Supernumerary nipples	22/42	52
Macroglossia	21/42	50
Hernia (inguinal, umbilical)	18/42	43
Fine/Gross motor delay	17/39	44
Cardiac defects	13/42	31
Pectus excavatum	11/35	31
Renal dysplasia/nephromegaly	11/35	31
Cleft lip/palate	12/42	29
Macrognathia	8/35	23
Polyhydramnios	7/35	20
Cryptorchidism	7/35	20
Syndactyly/polydactyly	7/35	20
Hydroureters/hydronephrosis	5/34	15
Embryonal tumors	5/42	12
Hernia diaphragmatica	5/42	12
Rib anomaly/13 ribs	4/35	11

[1] Major features are adapted from (103), (122) and references therein.

binding growth factors, such as Wnts and fibroblast growth factors (reviewed in (114)). It was demonstrated *in vitro* that GPC3 binds directly to IGF2 and sequestering of this ligand might inhibit its activity (3). Recently this direct interaction between GPC3 and IGF2 and additionally also with the IGF1R was shown again (115). A model was proposed in which absent GPC3 would result in high level of IGF2 signaling, resulting in overgrowth in a fashion similar to BWS (3,116). This model was supported by double mutant mice overexpressing

Igf2 due to absence of the Igf receptor type 2 (*Igf2r*; a downregulator of Igf2) and the *H19* locus (117). These mice demonstrated BWS features but additionally also skeletal defects and cleft palate reminiscent of SGBS. In contrast, in a rat model the direct interaction between GPC3 and IGF2 could not be reproduced (118). In addition, Gpc3 mutant mice which did exhibit an increased body size, did not show elevated levels of circulating Igf2 or an increased expression in tissues (119) and overgrowth due to *Gpc3* deficiency was postulated to occur without directly influencing Igf2 signaling (120). It remains therefore unclear if and to what extent increased IGF2 signaling is responsible for SGBS. Alternative explanations such as the regulation by GPC3 of other heparin-binding growth factors (for example Wnts, fibroblast growth factors, bone morphogenetic proteins and hepatocyte growth factors) should be taken into consideration (105,114). Recently, deficient GPC3 was shown to cause upregulation of Hedgehog signaling and it was suggested that hyperactivation of this pathway plays a role in overgrowth in SGBS (121).

Bannayan-Riley-Ruvalcaba syndrome

Bannayan-Riley-Ruvalcaba syndrome (BRRS; OMIM 153480) is an autosomal dominant disorder of unknown incidence which is caused by haploinsufficiency of the phosphatase and tensin homolog (*PTEN*) gene at 10q23.31 (123,124). Diagnostic criteria were defined as at least two of the following features: macrocephaly, hamartomas (including at least one lipoma, haemangioma or intestinal polyp) and penile macules in males (125) or as at least three of the four following characteristics: macrocephaly, lipomatosis, haemangiomas and pigmented macules of the glans penis in males (126) (Table 7). The latter criteria were found to result in a more sex-biased diagnosis towards males (127). Other common detected features in *PTEN*-mutation positive patients include developmental delay/mental retardation, hypotonia, downslanting of the palpebral fissures, postnatal childhood overgrowth, a high arched palate and joint hypermobility (125,128) (Table 7). Mental retardation is reported in *PTEN*-mutation positive patients in 93-100% (125,128). However, this might be an overestimation due to ascertainment bias as two recent studies showed learning difficulties in only 2 of 17 non-proband patients (12%) and mental retardation or global development delay in 3 of 26 patients (12%), respectively (127,129).

Abnormalities of *PTEN* are detected in approximately 57-60% of the BRRS patients (126,130,131). In the majority, intragenic point-mutations are found, while only a few patients have been described carrying exonic or whole *PTEN*-gene deletions (132). *PTEN*

Table 7. Clinical diagnostic criteria and common features in BRRS

Clinical diagnostic criteria used by Parisi et al. (125)		
At least two of the following features:		
Macrocephaly		
Hamartomas (including at least one lipoma, haemangioma or intestinal polyp)		
Penile macules in males		
Clinical diagnostic criteria used by Marsh et al. (126)		
At least three of the four following characteristics:		
Macrocephaly		
Lipomatosis		
Haemangiomas		
Pigmented maculae of the glans penis in males		
Common features of BRRS with a confirmed *PTEN* mutation, adapted from (128) and references therein		
	Number of patients	**Percentage**
Sex ratio	**20 males : 7 females**	
Macrocephaly	27/27	100
Developmental delay/Mental retardation	25/27	93
Pigmented maculae of the glans penis	17/20	85
Lipomas	10/27	37
Hypotonia	8/27	30
Hamartomatous polyps	6/27	22
Hemangiomas	5/27	19
Seizures	4/27	15
Downslanting palpebral fissures	4/27	15
Additional features (present >50%) from three BRRS families with a confirmed *PTEN* mutation (125)		
High arched palate	8/8	100
Overgrowth	8/9	89
Joint hypermobility	7/8	88

abnormalities are also responsible for ~80% of Cowden syndrome syndrome (CS) patients (131). This is an adult-onset hamartomatous disorder with pathognomic mucocutaneous lesions including trichilemmomas (133). There is an increased incidence of malignancy with lifetime risks of 3-10% for thyroid cancer, 25-50% for breast cancer and an unknown risk for endometrial cancer (reviewed in (134)). Because of the overlapping features between BRRS and CS, the fact that they are caused by alterations of the same gene and the lack of consistent genotype-phenotype correlations, it was suggested that BRRS and CS are the same entity with a variable expression and age-related penetrance (126,127). It was proposed that they should be classified as the "PTEN-hamartoma-tumour syndrome" (PHTS) (126). In relation to this and since a correlation was found with cancer or breast fibroadenoma in BRRS and BRRS/CS families (126), BRRS patient should undergo similar cancer surveillance as proposed for CS (133,135). *PTEN* aberrations are further reported in Proteus syndrome (~20%) and Proteus-like syndrome (~60%) (136) although in other Proteus(like) populations no *PTEN* mutations could be detected (137-139). Furthermore, somatic *PTEN*-alterations were found in a variety of sporadic neoplasias (reviewed in (135)).

The *PTEN*-gene encodes for a tumor suppressor protein which exerts phosphatase activity (i.e. removal of phosphate groups from macromolecules) targeting both proteins as well as lipids (reviewed in (140)). PTEN has an inhibitory function on the PI3K/Akt pathway and decreased signaling activity of this pathway usually limits proliferation and cell survival. Furthermore, PTEN dephosphorylates the focal adhesion factor (FAK) which is involved in inhibiting cell migration and spreading (141). Hence, loss of function of PTEN would consequentially promote cell growth, survival and migration. Most of the functional studies were performed to elucidate the role of PTEN in neoplasias and much less is known about its role in skeletogenesis. However, recently mice lacking *Pten* in their osteo-chondroprogenitor cells were reported (142). These mice displayed an increased skeletal size, especially enlargement of the vertebrae, and disorganised epiphyseal growth plates. Furthermore, there was a significant increase in the amount of trabecular and cortical bone. In a second report, mice deficient for *Pten* in their osteoblasts were of normal size but showed a highly increased bone mass (143). In both studies an increased PI3K/Akt signaling was demonstrated. These reports are very interesting because they provide the first direct evidence of the role of *PTEN* in skeletogenesis and create an explanatory basis for the macrocephaly and longitudinal overgrowth found in BRRS.

Fragile X syndrome

Fragile X syndrome (FXS; OMIM 300624) is an X-linked disorder and is caused by a silenced expression of the fragile X mental retardation 1 (*FMR1*) gene at Xq27.3. It has a prevalence of approximately 1 in 4000 - 9000 Caucasian males and 1 in 8000-9000 females (144), although a higher frequency of the full mutation allele (see further) of approximately 1 in 2500 individuals (males and females) is proposed (145). FXS is therefore the most common inherited cause of cognitive impairment. The degree of mental retardation is however variable; from mild learning difficulties with normal IQ to very severe mental impairment (146). The dysmorphic facial features can be subtle and include a narrow and elongated face, high forehead, prominent lower jaw and large protruding ears (Table 8) (147). Other physical features are macroorchidism and hyperextensibility of the joints (147). In general, the craniofacial features and macroorchidism become more outspoken in adolescence and adulthood. In males, the head circumference is consistently increased compared to the normal population and although height is close to the normal growth charts (148,149), childhood and preadolescent height and/or weight overgrowth has been associated with FXS (148,150,151). Adult height for males and females is lower than normal (148,151). Behavioural problems are frequent in FXS and include hyperactivity, impulsivity, sensory oversensitivity, tactile defensiveness, shyness, hand flapping and biting and autism spectrum disorders (147,152). In general, females are more mildly affected, probably due to X-inactivation. Diagnostic testing for FXS is advised in all individuals with mental retardation, developmental delay or autism, especially when other features of FXS are present or if there is a positive family history (153).

FXS is caused by hypermethylated CGG repeat expansions in the 5'UTR of the *FMR1* gene at Xq27.3 (154). These repeats co-localise with a constriction of the long arm seen in metaphases which is known as the fragile site at chromosome X (FRAXA) (155). In addition to transcriptional silencing due to repeat expansions, less frequently microdeletions of (parts of) *FMR1* and intragenic mutations have been described as well (reviewed in (156)). Nowadays, four allelic classes of repeat expansions can be distinguished: normal or common (6-44 repeats), intermediate (45-54 repeats), premutation (55-200 repeats) and full mutation (> 200 repeats) (146). The full mutation is hypermethylated and consequentially results in a silenced transcription. The premutation is non-methylated and is meiotically but also mitotically instable and can expand to larger repeats or to full mutations in the next generation (157). Full-mutation expansions were detected in the female germline and not in sperm cells,

Table 8. Common features of FXS with confirmed full mutation[1]

	Prepubertal		Postpubertal	
Physical features	**Nr. of patients (n=96)**	**Percentage**	**Nr. of patients (n=64)**	**Percentage**
Flat feet	79	82	38	60
Hyperextensible joints	78	81	31	49
Prominent ears	75	78	42	66
Long face	61	64	51	80
Double-jointed thumb	56	58	30	48
Macroorchidism	52	54	59	92
High-arched palate	49	51	40	63
Palmar crease	25	26	14	22
Long ears	24	25	32	50
Hand calluses	17	18	33	52
Heart murmer/click	15	16	19	29
Behavioural features				
Perseverate	91	95	64	100
Hyperactivity	85	89	41	64
Poor eye contact	84	88	63	98
Hand flapping	82	85	52	81
Imitational	75	78	53	83
Tactile defensiveness	73	76	55	86
Anxiety	61	64	51	79
Hand biting	61	64	41	64
Shyness	58	60	39	61
Aggression	55	57	35	55
Violent outbursts	24	25	27	42
Panic attacks	24	25	25	39

[1] Common features are adapted from (149)

which would explain why expansion from premutation to full-mutation only occurs through female transmission (158). Although premutation carriers do not exhibit a characteristic FXS phenotype, mild physical manifestations have been reported and neurocognitive and behavioural functioning might be affected (reviewed in (159)). Furthermore, premutations are associated with premature ovarian failure and with Fragile-X Tremor Ataxia Syndrome (FXTAS) (159). This is a late-onset neurological disorder characterized by cerebellar ataxia, intention tremor and a progressive cognitive decline.

FMR1 is widely expressed, especially in the brain and the testis (160). The protein (FMRP) exhibits selective RNA binding capacity and controls local protein production by inhibiting translation of mRNA (reviewed in (161)). In addition, the translational control by FMRP might be mediated by influencing a microRNA pathway, although this needs further investigation (161). The suppression of local protein synthesis takes place at the neuron dendrites, which have been shown to display structural and numerical anomalies in FXS (162). One identified mechanism is that deficiency of FMRP results in an increased signaling of group I metabotropic receptors (mGluR) with an increased synaptic protein production and consequentially affecting synaptic plasticity and neuronal signal transmission (163). Since most of the functional research is focussing on the role of FMRP in mental retardation and neuronal development, the role in growth regulation is yet an unexplored field. Although Fmr1 deficient knockout mice showed macroorchidism and behavioural abnormalities similar to FXS, no other features were reported (164). Recently, evidence of a direct involvement of FMRP in skeletogenesis was shown by a zebrafish *fmr1* knockdown model in which mild craniofacial abnormalities were demonstrated to be caused by abnormal cartilage formation (165).

Klinefelter syndrome

Klinefelter syndrome (KS) is the most common disorder of sex chromosome aneuploidy with a prevalence of 1.09 - 1.72 per 1000 newborns (166). It is caused by an extra X chromosome which usually results in a 47,XXY karyotype. Other karyotypes observed include 48,XXXY; 48,XXYY; 49,XXXXY and 46,XY/47,XXY mosaicism. The classical pubertal KS phenotype is characterised by tall stature and features of androgen deficiency such as eunuchoidal body proportions with an increased arm span and long legs, sparse or absent pubic and axillary hair, decreased muscle mass, small testis and reduced penile length, infertility, a feminine distribution of adipose tissue and gynecomastia (Table 9) (167). A recent study identified

Table 9. Common features of KS[1]

Major features of KS	**Percentage**
Infertility/Azoospermia	93-100
Small testes	76-100
Elevated gonadotropin levels	90-100
Gynecomastia	26-75
Central obesity	75
Increased height	73
Speech therapy	42- 69
Reading difficulties	55-77
Decreased testosterone levels	65-85
Decreased facial hair	60-80
Decreased pubic hair	30-60
Decreased penile length	10-92
Taurodontism	40
Decreased bone mineral density	25
Varicose veins	20
Cryptorchidism	17
Additional features from a study of 55 patients from (168)	
Hypotonia	76
Clinodactyly	74
Hypertelorism	69
High-arched palate	37
Elbow dysplasia (mild)	36

[1] Common features are adapted from (167), (168), (169), (183) and references therein.

clinodactyly, hypertelorism, elbow dysplasia, a high arched palate and hypotonia as additional frequent findings (168). Although birth length was reported to be less compared to controls (169), from around 2 years of age there is a tall stature with a mean height just below or at +1 SDS (168,170). Associations of KS with breast cancer, autoimmune and endocrine disorders, venous disease, osteoporosis and taurodontism have been observed (reviewed

in (167)). The overall cognitive development is apparently normal (171), but delayed speech and language development are common findings in KS patients (169,171). Although there is no characteristic personality or behavioural phenotype, most KS boys were observed to be quiet, unassertive, passive, with an increased level of anxiety and a tendency of withdrawing from group activities (reviewed in (171)).

In early puberty, serum testosterone levels are normal, while at a later age in mid-pubertal patients levels are decreased with increased levels of LH, FSH and estradiol (172). These hormonal imbalances are addressed by testosterone replacement at the beginning of puberty, which improves the secondary sex characteristics, body proportions, bone mineral density and strength but does not improve fertility, testicular size or gynecomastia (173).

Nondisjunction during meiotic divisions in parental gametogenesis or during early mitotic cell divisons cause the extra X chromosome in KS. Paternal nondisjunction at meiosis I accounts for 53% of the cases, while maternal nondisjunction occurs either during meiosis I (34%) or meiosis II (9%) (174). Postzygotic disjunction errors during mitosis accounts for 3% of the cases (174). In some studies, a correlation was observed between the maternal age and nondisjunction at meiosis I (174-176) and between the paternal age and meiosis I (176), but no association with parental age was found in another study (177).

The exact molecular mechanisms underlying KS remain to be elucidated. On testicular biopsy of adult KS patients, fibrosis and hyalinization of the seminiferous tubules is found (reviewed in (178)). It is however not known whether testicular disfunction is due to intrinsic germ cell defects or that Sertoli cells are not able to support normal spermatogenesis (177,178). Furthermore, expressed phenotypic features such as height, gynaecomastia and smaller testes were reported to be regulated by the activity of the X-located androgen receptor (179). A positive correlation was found with a long CAGn repeat in this receptor, which is thought to result in decreased functionality of the receptor and consequentially in stronger effects of the androgen deficiency. However, only a correlation with penile length was found in another study (180). Because haploinsufficiency of the short stature homeobox (*SHOX*) gene is shown to be the cause of Leri-Weill syndrome, short stature in Turner syndrome and in a subset of patients with idiopathic short stature (181), a plausible explanation for the increased height in KS is the overdosage of *SHOX* in combination with hypogonadism (182).

New syndromes

Overexpression of the natriuretic peptide precursor C (*NPPC*) gene

Recently, three patients were described each carrying a unique balanced translocation of the same 2q37.1 locus and chromosomes 7, 8 and 13, respectively (184,185). These patients presented with a similar phenotype of postnatal statural overgrowth (>97th percentile), a marfanoid habitus, scoliosis, very long halluces and metaphyseal-epiphyseal dysplasia. All three translocation breakpoints localized in the vicinity of the *NPPC* gene, which encodes for the C-type natriuretic peptide (CNP). An increased expression of *NPPC* was found in fibroblasts, chondrocytes and lymphoblasts of these patients (184,185). It was proposed that the translocations caused a separation of *NPPC* from a negative regulatory element, hence resulting in overexpression (185). This finding is in line with transgenic mice overexpressing *NPPC* in growth-plate cartilage, which showed general skeletal overgrowth (186), while *Npcc* $^{-}$/$^{-}$ mice were dwarfed (187). Chondrocytic overexpression of CNP was also shown to be able to rescue achondroplasia in mice with an activated fibroblast growth factor receptor 3 (*Fgfr3*) in their cartilage (188). Furthermore, homozygous loss-of-function mutations of the *NPR2*, the membrane receptor with the highest affinity for CNP, cause acromesomelic dysplasia type Maroteaux with a disproportionate short stature and radiographic skeletal changes (189). Heterozyogous *NPR2* mutations have been associated with proportionate, short stature (190). In general it can be concluded that CNP plays an important role in the regulation of endochondral bone growth and cartilage homeostasis (reviewed in (191)).

CATSHL syndrome

In a large pedigree of 27 living affected family members spanning four generations an autosomal dominant syndrome was identified which was characterised by *C*amptodactyly (18/20; 90%), *T*all stature (13/14 93%) and Sensoneurinal *H*earing Loss (17/20; 85%). (CATSHL; OMIM 610474) (9). Height was >97th percentile for 5 out of 5 affected males and 8 out of 9 affected females. Additional features were development delay (12/20; 60%), microcephaly, scoliosis and/or pectus excavatum. A heterozygous missense mutation (p.R621H) in the tyrosine kinase domain of the fibroblast growth factor receptor 3 (*FGFR3*) was found, which is thought to impair the signaling function of FGFR3 through a negative dominant mechanism (9). Furthermore, *Fgfr3*$^{-}$/$^{-}$ mice showed a reminiscent skeletal phenotype in combination with deafness (192). In contrast, gain-of-function alterations of the *FGFR3* gene are found in several well-known growth failure disorders due to impaired endochondral bone formation

such as achondroplasia and hypochondroplasia (reviewed in (10)).

RNF135 alterations

Recently a new overgrowth disorder due to haploinsufficiency of the ring finger protein 135 (*RNF135*) (OMIM 611358) was reported in six patients (193). The alterations detected included four heterozygous truncating mutations, one missense mutation and a microdeletion including four neighbouring genes of *RNF135*. The patients showed a postnatal overgrowth phenotype with tall stature (height > +2.0 SDS) and macrocephaly (head circumference ≥ +2.0 SDS). The height of the single patient carrying a missense mutation was within normal range (+1.1 SDS). Dysmorphic characteristics included a broad forehead, anti-mongoloid slant of the eyes, a broad nasal tip, a long philtrum, a thin upper lip and a full lower lip. Furthermore, a spectrum of additional features was reported: for example advanced bone age (3/6), hearing problems (2/6) and eye abnormalities (2/6). A varying degree of developmental delay was present. The fathers or the mothers and also two siblings were carriers of the mutations as well. However, the dysmorphic features of these carriers were, except for macrocephaly, less distinctive and three of them showed a normal intellectual development.

RNF135 is located on 17q11.2 and and expression is found in several tissues (193). It is one of the 14 genes deleted in the common 1.4 Mb microdeletion, which causes neurofibromatosis type 1 (NF1) in approximately 5% of the cases (194,195). Due to the tall stature phenotype of these patients in comparison to patients with intragenic *NF1* mutations, *RNF135* was considered as a candidate gene responsible for this overgrowth (193,196). Furthermore, a Weaver syndrome-like phenotype was described in two familial patients carrying a deletion of the *NF1* region (197). However, investigations of *RNF135* mutations in classical Weaver syndrome patients did not yield positive results (193). Due to the phenotypic overlap with Sotos syndrome, a cohort of 160 patients referred for *NSD1* analysis on suspicion of Sotos syndrome features was investigated, but no *RNF135* abnormalities were detected (198). Additional patients harbouring pathogenic *RNF135* alterations are necessary for a further phenotype-delineation and also for elucidation of the very mild phenotype found in carrier-parents.

Conclusion and future perspective

In this review we have given a comprehensive overview of the classical and new overgrowth disorders with a delineation of the clinical phenotype and the molecular genotype. Whether the new disorders will actually justify their position within the group of classic overgrowth syndromes, will largely depend on the discovery of additional patients. However, based on for example the unequivocal importance of proper CNP signaling in both under-and overgrowth, it is likely that additional patients with defects affecting the same pathway indeed will be identified. Furthermore, we expect that technological developments such as high resolution genome-wide array approaches targeting copy number variations and increased capacity of long range sequencing will result in the identification of additional defects of known genes as well as in the discovery of new genes. With regard to this, a combined approach with studies in the fields of genetics, genomics and proteomics are necessary to elucidate the underlying pathophysiological mechanisms. However, despite technological advances, thorough clinical assessment of a patient suspected of an overgrowth syndrome remains the first important step in the diagnostic process. This will not only increase the likelihood of attaining a molecular diagnosis for the patient, but will also create the basis for further research targeting new molecular defects in patients with certain features but without a confirmed molecular abnormality.

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