A Clinical Review of Generalized Overgrowth Syndromes in the Era of Massively Parallel Sequencing

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Keywords

Large stature · Macrocephaly · Macrosomia · Obesity · Overgrowth · Tall stature

Abstract

The overgrowth syndromes are important to diagnose, not just for accurate genetic counseling, but also for knowledge surrounding cancer surveillance and prognosis. There has been a recent expansion in the number of genes associated with a mendelian overgrowth phenotype, so this review updates previous classifications of overgrowth syndromes. We also describe a clinical and molecular approach to the investigation of individuals presenting with overgrowth. This review aims to assist the clinical diagnosis of generalized overgrowth syndromes by outlining the salient features of well-

known overgrowth syndromes alongside the many syndromes that have been discovered and classified more recently. We provide key clinical “handles” to aid clinical diagnosis and a list of genes to aid with panel design when using next generation sequencing, which we believe is frequently needed due to the overlapping phenotypic features seen between overgrowth syndromes.

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The term “overgrowth” is in common use in clinical genetics practice, but there is no formal definition. Overgrowth can be generalized (involving the whole body) or localized to one part of the body (segmental). Typically, generalized overgrowth is symmetrical whereas segmental overgrowth is asymmetrical. We concentrate on gen-

Table 1. A list of chromosomal conditions often associated with generalized overgrowth

Condition	Possible genes involved in pathogenesis	References
Translocation 2q37	<i>NPCC</i>	Moncla et al., 2007
3q13.31 deletion	<i>ZBTB20</i>	Molin et al., 2012
4p16.3 duplication	<i>FGFR3, FGFR1</i>	Partington et al., 1997
5q35.3 deletion	<i>NSD1</i>	Hirai et al., 2011
9q22.3 deletion	<i>PTCH1</i>	Kosaki et al., 2011
Maternal deletion or paternal UPD or paternal duplication of 11p15.5	<i>CDKN1C, KCNQ1, KCNQ1OT1, IGF2, H19</i>	Choufani et al., 2010
13q13q21 deletion	multiple	Tosca et al., 2011; Kamien et al., 2015
13q31.3 duplication	<i>GPC5</i>	Kannu et al., 2013
15q26 overgrowth syndrome (duplication)	<i>IGF1R</i>	Tatton-Brown et al., 2009
19p13.13 deletion	<i>NFIX</i>	Dolan et al., 2010
Phelan-McDermid (22q13 deletion)	<i>SHANK3</i>	Phelan et al., 2001; Sarasua et al., 2014; Soorya et al., 2013
Xq26.3 duplication, X-linked acroigantism	<i>GPR101</i>	Trivellin et al., 2014
UPD, uniparental disomy.		

eralized, symmetrical overgrowth syndromes in this review.

There have been several suggestions regarding the definition of generalized overgrowth. Perhaps the most sensible suggestion came from Cohen [1998] who recommended that classification remain “loose,” simply serving as an organizing principle for review and discussion. Operationally, this accommodates the considerable phenotypic and etiologic heterogeneity in this domain. For example, approximately 10% of the children with Sotos syndrome have a height <97th centile [Tatton-Brown et al., 2005].

More formal definitions have been proposed, however, and more recent definitions suggest overgrowth should be considered if there are dysmorphic features and a height and head circumference greater +2 SD, the target height (calculated on the basis of mid-parental height) is greater +2 SD, or if a patient has the typical dysmorphic features of a known “overgrowth syndrome” [Visser et al., 2009; Neylon et al., 2012]. Verge and Mowat [2010] provided a similar definition but also suggested overgrowth should be considered if birth weight was >4.5 kg [Verge and Mowat, 2010].

The overgrowth syndromes presented all have intellectual disability as a key feature, although it is possible that borderline or low-normal intellect could be seen. It is important to note that some causes of overgrowth, macrosomia, tall stature, macrocephaly, or obesity are not seen in the context of syndromes. When intellect is normal, the most common causes of overgrowth are: (1) familial, (2) growth acceleration driven by over-nutrition (includes infants of diabetic mothers), (3) endocrine conditions (such

as precocious puberty, hyperthyroidism, congenital adrenal hyperplasia, growth hormone-secreting adenoma, familial glucocorticoid deficiency, and aromatase deficiency) [Verge and Mowat, 2010].

The overgrowth syndromes are important to diagnose, not just for accurate genetic counseling, but also for knowledge surrounding cancer surveillance and prognosis.

Procedure

An OMIM search of abstracts with the word “overgrowth” returned 192 entries, and a search for “macrosomia” returned 41 entries. We also searched PubMed using the search terms “overgrowth” and “macrosomia” to identify conditions. Previous review articles on overgrowth, obesity, macrocephaly, and tall stature were also examined to ensure no syndromes were missed [Cohen, 1998; Sotos and Argente, 2008; Williams et al., 2008; Verge and Mowat, 2010; Sabin et al., 2011; Argente and Sotos, 2012; Neylon et al., 2012; Durand and Rappold, 2013; Tatton-Brown and Weksberg, 2013]. From this, we classified each disorder as either: (1) a generalized overgrowth condition, (2) a segmental overgrowth condition, (3) a condition associated with fetal and neonatal macrosomia but not usually overgrowth in childhood and later life, (4) a condition mostly associated with tall stature, (5) a condition mostly associated with macrocephaly, or (6) a condition mostly associated with obesity. We used this classification system to identify core overgrowth conditions as well as to report on differential diagnoses or conditions that mimic overgrowth.

Table 2. Syndromes associated with macrosomia but not usually overgrowth in later life

Syndrome	Gene	Inheritance	Clinical features
Cantu	<i>ABCC9</i>	AD	Polyhydramnios (~50%) Congenital hypertrichosis Distinctive facial appearance (coarse facies, prominent forehead, long philtrum, epicanthic folds, long and curly eyelashes, anteverted nares, flat and broad nasal bridge, thick lips, short neck) Cardiomegaly Skeletal involvement (wide ribs, platyspondyly, hypoplastic ischiopubic branches, small obturator foramen, bilateral coxa valga, enlarged medullary canal (Erlenmeyer flask-like long bones), generalized osteopenia [Gilissen et al., 2012; Scurr et al., 2011; van Bon et al., 2012])
Costello (and other RASopathies)	<i>HRAS</i>	AD	Initial polyhydramnios, edema, and macrosomia are followed by failure to thrive, growth deficiency, macrocephaly, and developmental delay Craniofacial: coarse face, low set ears, thick lobes, downslanting palpebral fissures, thick lips, macroglossia, full cheeks, short bulbous nose Skin: cutis laxa, curly hair, teeth abnormalities Perioral, nasal and anal papillomas, deep palmar and plantar creases Cardiac: pulmonary stenosis and other congenital heart disease [Gripp and Lin, 2017]
Elejalde (Acrocephalopoly-dactylous dysplasia)	unknown	AR	Lethal multiple congenital abnormality disorder with increased birth weight, globular body with thick skin, organomegaly, and fibrosis in multiple tissues [Phadke et al., 2011]
Familial hyperinsulinism	<i>ABCC8</i> , <i>KCNJ11</i> , <i>GCK</i> , <i>HADH</i> , <i>GLUD1</i> , <i>SLC16A1</i> , <i>HNF4A</i> , <i>HNF1A</i>	usually AR, sometimes AD	Severe hypoglycemia at birth often associated with macrosomia [Kapoor et al., 2013; Glaser, 2017]
Infant of diabetic mother or maternal overweight	–	–	In addition to macrosomia, infants of diabetic mothers have a 2- to 3-fold increase in congenital abnormalities (6–9%) including: neural tube defects, congenital heart disease, renal and skeletal anomalies [Ornoy, 2011]
Pallister-Killian	extra isochromosome 12p	somatic mosaicism	Pallister-Killian is frequently mentioned in review articles as an overgrowth syndrome. However, only ~30–40% of patients have 2 of Ht, Wt or HC >90th centile at birth usually followed by postnatal reduction to the lower centiles. Clinical features include severe developmental delay, sparse scalp hair, prominent forehead, slow coarsening, hypertelorism, upslanting palpebral fissures, epicanthic folds, ptosis, strabismus, short nose, anteverted nostrils, large ears, short neck, skin streaks, accessory nipples [Wilkens et al., 2012]
Perlman	<i>DIS3L2</i>	AR	Often have polyhydramnios Hypotonia Organomegaly High risk of Wilms tumor High perinatal mortality Characteristic facial appearance (inverted V-shaped upper lip; prominent forehead; deep-set eyes; broad, flat nasal bridge, and low-set ears) [Astuti et al., 2012]

AD, autosomal dominant; AR, autosomal recessive; HC, head circumference; Ht, height; Wt, weight.

Results

Based on a literature review, syndromes commonly associated with generalized overgrowth are covered in the discussion below and are also listed in online supplementary Table 1 (for all online suppl. Tables, see www.karger.com/doi/10.1159/000484532). To cover diagnoses made by chromosomal microarray, chromosomal

conditions often associated with overgrowth are listed in Table 1. Regarding differential diagnoses to outline conditions that are not overgrowth syndromes by strict definition, Table 2 presents syndromes associated with macrosomia at birth that later usually progress to normal growth parameters or failure to thrive. Online supplementary Table 2 lists syndromes associated with segmental overgrowth. Online supplementary Table 3 lists condi-

tions that can mimic overgrowth but would usually only show a significant increase in only 1 of the 3 parameters (height, weight, and head circumference).

Many overgrowth, macrocephaly, and obesity syndromes have an association with neoplasia because of widespread alterations in gene expression and cell-signaling pathways; the associated tumor risk of some of these syndromes is presented in Table 3.

The syndromes listed below represent the currently known monogenic forms of overgrowth. We present the syndromes in order of expected frequency of presentation to a clinical genetics unit, although accurate data on prevalence and proportion coming to medical attention are not available for most conditions.

Beckwith-Wiedemann Syndrome

Suggested clinical diagnostic criteria require the presence of at least 2 major and 1 minor criteria. However, with advances in molecular testing, it is now recognized that subtle phenotypes are possible, so Beckwith-Wiedemann syndrome (BWS; OMIM 130650) should be considered if there is one or more of the following major features: macrosomia, hemihyperplasia, macroglossia, visceromegaly, ear creases/pits, infraorbital creases, embryonal tumors, omphalocele, neonatal hypoglycemia, renal abnormalities, cytomegaly of the fetal adrenal cortex, cleft palate (rare), and cardiomegaly or structural cardiac anomalies. Minor findings include polyhydramnios during pregnancy, nevus simplex, diastasis recti, and advanced bone age. Facial features can be subtle and include infraorbital creases and midface retrusion. Linear growth slows around the age of 8 years, and the facial and physical features become less obvious with age. BWS methylation studies involve techniques such as methylation sensitive MLPA which examines DNA methylation and copy number within subregions of 11p15.5. This detects methylation abnormalities such as: (1) loss of methylation of the imprinting center 2 on the maternal chromosome, (2) gain of methylation of imprinting center 1 on the maternal chromosome, and (3) paternal uniparental disomy of 11p15.5. In addition, Sanger or next generation sequencing methods are needed to detect *CDKN1C* mutations that are present in only 5% of sporadic BWS cases but in 40% of patients with a family history of BWS [Baujat et al., 2005; Greer et al., 2008; Choufani et al., 2010].

Sotos Syndrome

Sotos syndrome (OMIM 117550) is characterized by pre- and postnatal overgrowth with intellectual disability that is usually mild to moderate, but can be severe. The

characteristic facial gestalt includes prominent forehead, downslanting palpebral fissures, and malar flushing. At birth, the mandible appears small, but by childhood it is pointed, and in adulthood, often prominent and square. Patients often have advanced bone age, congenital heart disease (20%), ventriculomegaly or other central nervous system abnormalities identified at MRI, renal abnormalities (15%), scoliosis (30%), seizures (25%), and tumors (3%). Heterozygous mutations of *NSD1* are responsible, and it is estimated that a mutation will be detected in over 90% of the patients (5–10% are larger deletions detected by MLPA or cytogenetic studies) following accurate phenotyping [Tatton-Brown and Rahman, 2004, 2007; Cecconi et al., 2005; Douglas et al., 2005; Tatton-Brown et al., 2005; Fickie et al., 2011; Hirai et al., 2011].

Simpson-Golabi-Behmel Syndrome

Pre- and postnatal overgrowth is present often with polyhydramnios in pregnancy (~95%). Craniofacial features of Simpson-Golabi-Behmel syndrome (SGB; OMIM 312870) include macrocephaly (~75%), coarse facial features and square face (~90%), downslanting palpebral fissures, hypertelorism (~50%), epicanthic folds, short nose/broad nasal bridge (~80%), ear lobe creases (~70%), macrostomia (~85%), macroglossia, midline groove in lower lip/deep midline groove in the tongue (~50%). Skeletal findings include postaxial polydactyly (~20%), syndactyly (~20%), brachydactyly (~50%), nail hypoplasia (~25%), broad/short hands (~80%), and vertebral defects (~30%). Other findings can include thin muscular body habitus, organomegaly, supernumerary nipples (~50%), congenital heart disease (~35%), cardiac conduction defects (~15%), cryptorchidism, herniae, diaphragmatic hernia (~30%), and cleft lip or palate (~25%). Intellectual disability can be mild to severe. The condition is X-linked involving mutations in *GPC3* [Neri et al., 1998; Li et al., 2001; Sakazume et al., 2007; Cottureau et al., 2013]. *GPC4* duplication detected by MLPA has been reported in 2 individuals from one family with a clinical diagnosis of SGB syndrome [Cottureau et al., 2013]. It remains to be seen if *GPC4* is important in SGB. Clinical diagnosis of SGB can be challenging. For example, Cottureau et al. [2013] described that over 90% of the samples referred to their laboratory with suspected SGB did not have *GPC3* mutations.

Weaver Syndrome

Patients with Weaver syndrome (OMIM 277590), also known as *EZH2*-related overgrowth, have some clinical overlap with features resembling Sotos syndrome includ-

Table 3. Overgrowth syndromes and macrocephaly syndromes with increased risk of neoplasia

Beckwith-Wiedemann	5–10% of children develop neoplasia, particularly Wilms tumor and hepatoblastoma. Other reported tumors include neuroblastoma, adrenocortical carcinoma, and rhabdomyosarcoma. The tumor risk is mostly in the first 8 years of life although later tumors have been reported including pheochromocytoma, adrenal adenoma, thyroid cancer, breast cancer, and AML. These later onset tumors may or may not be related to BWS [Greer et al., 2008]. Tumor risks were highest in the IC1 (H19/IGF2:IG-DMR) hypermethylation subgroup (28%) and pUPD subgroup (16%) and were lower in the KCNQ1OT1:TSS-DMR (IC2) subgroup (2.6%), CDKN1C (6.9%) subgroup, and in clinically diagnosed patients in whom no molecular defect was detectable (6.7%) [Maas et al., 2016].
Costello	Approximately 15% lifetime risk of solid tumors including rhabdomyosarcoma, neuroblastoma, and transitional cell carcinoma of the bladder [Kratz et al., 2011].
Gorlin	90% of patients develop jaw keratocysts, 90% develop basal cell carcinoma, 5% develop primitive neuroectodermal tumor, 20% of females develop ovarian fibroma, 2% develop cardiac fibromas. Lymphoma and meningioma have been reported [Cowan et al., 1997; Gorlin, 2004; Watson et al., 2004].
PIK3CA-related overgrowth spectrum (PROS)	Further evidence of neoplasia risk is needed. There are case reports of leukemia, meningioma, retinoblastoma, and Wilms tumor. Benign vascular tumors are common [Gripp et al., 2016].
NF1	Neurofibromas occur in the majority of patients. Plexiform neurofibromas occur in ~50%. Optic nerve gliomas in ~10–15%. Brain tumors in ~1%. Malignant peripheral nerve sheath tumors occur in ~10% of patients. Women have a 3.5-fold increased risk of developing breast cancer overall. Other reported tumors include leukemia, pheochromocytoma, gastrointestinal stromal tumors, malignant melanoma, and glomus tumor [Sharif et al., 2007; Wang et al., 2012; Friedman, 2017].
Perlman	64% risk of Wilms tumor in surviving children [Astuti et al., 2012].
Proteus	The exact tumor risk is difficult to quantify. The most common tumors include monomorphic adenomas of the parotid glands, and bilateral ovarian cystadenomas. Other reported tumors include meningioma and ovarian tumors [Biesecker, 2006].
PTEN hamartoma tumor syndrome	The lifetime risk of developing breast cancer is 25–50%, The lifetime risk for thyroid cancer (usually follicular) is ~10%. The risk of endometrial cancer may approach 5–10%. Other benign tumors include multiple types of skin lesion, hamartomatous intestinal polyps, fibrocystic disease of the breast, lipomas, fibromas, angioliomas, hemangiomyolipomas, and brain tumors. Malignant tumors include renal cell carcinoma, melanoma, and colorectal cancer [Ngeow et al., 2011; Tan et al., 2012].
RASA1-related disorders (Parkes-Weber)	Revenu et al. [2008] reported that 7/101 (6.9%) <i>RASA1</i> positive patients had tumors. Tumors included vestibular schwannoma, neurofibroma, non-small cell lung cancer, angiolioma, lipoma, superficial basal cell carcinoma, optic glioma.
Schimmelpenning-Feuerstein-Mims	Secondary tumors can often develop in an epidermal nevus (~24%). However, the exact tumor incidence in Schimmelpenning-Feuerstein-Mims syndrome is currently unknown [Groesser et al., 2012].
Simpson-Golabi-Behmel	Tumor frequency of perhaps 10% including Wilms tumor, hepatoblastoma, hepatocellular carcinoma, adrenal neuroblastoma, gonadoblastoma [Li et al., 2001; Lapunzina et al., 2005]. Recent data suggests the tumor frequency could be lower as 1/34 patients developed Wilms tumor and 1/34 patients developed leukemia [Cottreau et al., 2013].
Sotos	The exact tumor risk remains controversial and is perhaps 3%. Reported tumors include sacrococcygeal teratoma, neuroblastoma, presacral ganglioma, ALL, retinoblastoma, and small cell lung cancer [Tatton-Brown et al., 2005, 2017a; Fickie et al., 2011].
Sotos-like syndrome (NFI)	1/9 reported patients had a Wilms tumor. More information is required before attributing a neoplasia risk to <i>NFI</i> mutations [Malan et al., 2010].
Tatton-Brown-Rahman	AML reported in one patient [Kosaki et al., 2017].
Weaver	Tumor frequency of perhaps 4% including neuroblastoma, acute lymphoblastic leukemia, ovarian endodermal sinus tumor, sacrococcygeal teratoma, and lymphoma [Baujat et al., 2005; Basel-Vanagaite, 2010; Gibson et al., 2012; Tatton-Brown and Rahman, 2013; Tatton-Brown et al., 2013]. No specific protocol for cancer surveillance has yet been validated.

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BWS, Beckwith-Wiedemann syndrome. IC1/2, imprinting center 1/2.

ing pre- and postnatal overgrowth. Over 80% of reported patients have intellectual disability. Craniofacial features include a broad forehead and face, wide-spaced eyes, almond-shaped and downslanting palpebral fissures, prominent wide philtrum, retrognathia, and a deep horizontal chin groove. The latter often gives the chin a “stuck-on” appearance. The facial features can become less recognizable with age. Other findings can include scoliosis, large hands and feet, camptodactyly (~45%), advanced bone age, deep-set nails, hypotonia (45%), hypertonia (~30%), low-pitched cry (~35%), umbilical hernia (~45%), and soft doughy skin (~50%). Neuronal migration defects can be seen as well as seizures. Embryonal and hematologic tumors may occur in up to 5% of the patients [Baujat et al., 2005; Basel-Vanagaite, 2010; Tatton-Brown et al., 2011; Gibson et al., 2012; Tatton-Brown and Rahman, 2013; Tatton-Brown et al., 2013], though no specific protocol for cancer surveillance has yet been validated.

EED-Associated Overgrowth and SUZ12-Associated Overgrowth

Patients with mutations in these genes have phenotypes resembling Weaver syndrome. Four patients have been reported with *EED* mutations and 1 patient with a *SUZ12* mutation. The patients had overgrowth from birth, developmental delay/mild to moderate intellectual disability, and facial features resembling Weaver syndrome (round face, long philtrum, and retrognathia with “stuck-on” chin). Other features reported include large ears, prominent crease between the lower lip and chin, scoliosis, osteopenia, large hands and feet with slender fingers and toes, flexion deformities of fingers, multiple nevi, cleft palate (1 patient), posterior ear pits (1 patient), inguinal and femoral herniae (1 patient), epilepsy (1 patient), and constipation (1 patient) [Cohen et al., 2015; Cohen and Gibson, 2016; Cooney et al., 2017; Imagawa et al., 2017].

Tatton-Brown-Rahman Syndrome

Twenty patients with heterozygous *DNMT3A* mutations have been reported. Clinical features of Tatton-Brown-Rahman syndrome (OMIM 615879) include tall stature, macrocephaly, intellectual disability, characteristic facial features including a round face, heavy horizontal eyebrows, and narrow, small or downslanting palpebral fissures. A “marked philtrum with triangular interpillar space” has been described. Some patients had atrial septal defects, seizures, and scoliosis. Low tone and joint hypermobility are common findings [Tatton-Brown et al., 2014; Tlemsani et al., 2016].

Bannayan-Riley-Ruvalcaba Syndrome

Bannayan-Riley-Ruvalcaba syndrome (OMIM 153480) is also known as *PTEN*-related disorders. Macrocephaly at birth is commonly seen, but growth may slow down in childhood. However, significant macrocephaly persists throughout life. Enlarged penis, testicles, and macules on the glans penis are occasionally present. Facial and physical findings may include a prominent forehead, downslanting palpebral fissures, supernumerary nipples, joint hypermobility, and pectus excavatum. Intestinal hamartomatous polyposis and lipomas may be detected in childhood. The condition is allelic to Cowden syndrome, so later onset of benign and malignant tumors such as thyroid, breast, and endometrium may occur. Skin lesions such as trichilemmomas, acral keratoses, papillomatous lesions, and mucosal lesions can also occur [Marsh et al., 1997; Longy et al., 1998; Lachlan et al., 2007].

Primrose Syndrome

Intellectual disability, enlarged and calcified external ears as well as distal muscle wasting are the main features of this condition. Microphthalmia, cataract, congenital heart disease, sparse body hair, diabetes, deafness, hypothyroidism, and corpus callosum hypoplasia can be seen. Primrose syndrome (OMIM 259050) is associated with progressive neurological deterioration with ataxia and/or pyramidal signs. Characteristic facial features include deeply set eyes, downslanting palpebral fissures, ptosis, and a high nasal bridge. MRI may show basal ganglia calcifications. The condition is caused by *ZBTB20* mutations [Cordeddu et al., 2014; Mattioli et al., 2016].

Sotos Syndrome 2

Patients with haploinsufficiency caused by whole gene deletions of *NFIX* or mutations within *NFIX* exhibit postnatal overgrowth that is sometimes also present prenatally. Reported patients with Sotos Syndrome 2 (OMIM 614753), also known as Sotos-like and Malan syndrome, have a long/narrow face, high forehead, downslanting palpebral fissures, small mouth, and an everted lower lip. Other findings include scoliosis, pectus excavatum, advanced bone age, slender body habitus, intellectual disability, hypotonia, and autistic traits. Since first reported in 2010, there have been 3 publications with 11 reported patients [Malan et al., 2010; Yoneda et al., 2012; Klaassens et al., 2015].

Macrosomia, Obesity, Macrocephaly, and Ocular Abnormalities Syndrome

Only 8 cases have been reported in the literature. The syndrome consists of macrosomia, obesity, macrocephaly, ocular abnormalities (MOMO; OMIM 157980) including retinal or choroidal coloboma, microphthalmia, or optic atrophy, and mild to moderate intellectual impairment. A high forehead, up- or downslanting palpebral fissures, hypogenitalism, and seizures may also be seen. Four patients had normal height or short stature, and MOMO syndrome may be alternatively classified as an obesity syndrome or macrocephaly syndrome. The etiology is currently unknown [Di Donato et al., 2012; Vu et al., 2012].

PPP2R5B, PPP2R5C, and PPP2R5D-Related Overgrowth

Five genes encode PP2A-B56 subunit proteins, *PPP2R5A*, *PPP2R5B*, *PPP2R5C*, *PPP2R5D*, and *PPP2R5E*. Exome sequencing in 363 patients with overgrowth detected 3 mutations in *PPP2R5D*, 1 mutation in *PPP2R5B*, and 1 mutation in *PPP2R5C*. All 5 patients exhibited overgrowth or tall stature with mild to moderate intellectual disability, although their facial features were not particularly distinct, and there was no consistent recognizable phenotype. Hypospadias and poor feeding, Parkinsonism, and facial asymmetry were each reported in only 1 patient, respectively [Loveday et al., 2015]. Eleven other patients with *PPP2R5D* mutations have been reported and most did not have overgrowth, but 7 patients had macrocephaly. However, the other patients had normal head size or microcephaly [Houge et al., 2015].

Susceptibility to Autism 18

From an autism cohort of 3,730 children, 15 individuals with mutations in *CHD8* (Susceptibility to autism 18; OMIM 615032) were identified. Of these, 86% were tall, and 80% of individuals had macrocephaly. Physical findings included prominent supraorbital ridges, downslanting palpebral fissures, a broad nose with full nasal tip, pointed chin, tall slender build, and flat feet. Constipation, sleep disturbance, and seizures were reported in some patients [Bernier et al., 2014].

Tenorio Syndrome

Six patients from 4 families were described with overgrowth present from birth. Some of the patients had hypoglycemia, hypotonia, and macroglossia at birth. Five out of 6 patients had mild to moderate intellectual disability. Slightly dilated ventricles were present on MRI.

Three out of 6 patients had autoimmune features such as Raynaud phenomenon and keratoconjunctivitis. A common facial phenotype was not reported aside from a broad forehead. Review of clinical photographs showed features such as thick eyebrows and a wide, upturned nose. The condition is caused by heterozygous mutations in *RNF125* (Tenorio syndrome; OMIM 616260) [Tenorio et al., 2014].

Macrocephaly, Dysmorphic Facies, and Psychomotor Retardation

Overgrowth and intellectual disability have been reported in 5 patients homozygous for *HERC1* mutations (Macrocephaly, dysmorphic facies, and psychomotor retardation; OMIM 617011). Dysmorphic findings include a long face with a high forehead, up- or downslanting palpebral fissures, wide-spaced eyes, and sparse flared eyebrows. Joint laxity and hypotonia (5 patients) as well as kyphoscoliosis (3 patients) have been reported. Seizures were present in 2 patients. MRI may be normal or may demonstrate a thick corpus callosum, cerebellar hypoplasia, or ventriculomegaly [Ortega-Recalde et al., 2015; Aggarwal et al., 2016; Nguyen et al., 2016].

Macrocephaly, Macrosomia, Facial Dysmorphism Syndrome

Only 6 patients have been reported with Macrocephaly, macrosomia, facial dysmorphism syndrome (OMIM 614192) in 2007, so caution may be required when ascribing pathogenicity to dominant mutations in *RNF135*. Patients may have mild to moderate postnatal overgrowth, a broad forehead, downslanting palpebral fissures, broad nasal tip, long philtrum, thin upper lip, and a full lower lip. Intellectual disability may be mild to severe but *RNF135* mutations can be inherited from an intellectually normal parent with only mild features of overgrowth [Douglas et al., 2007]. More research is required as *RNF135* mutations may not be a common finding in patients with overgrowth [Visser et al., 2009].

Rahman Syndrome (MIM # 617537)

A recent paper by Tatton-Brown et al. [2017b] performed exome sequencing on 710 individuals. Five patients had mutations in *HIST1H1E*. Clinical findings of Rahman syndrome (OMIM 617537) included mild to moderate intellectual disability, full cheeks, high hairline, and telecanthus. Overgrowth present early in life may not persist beyond early childhood.

X-Linked Mental Retardation 93

One percent of individuals in the overgrowth cohort presented by Tatton-Brown et al. [2017b] have a mutation in the X-linked *BRWD3* gene. Clinical features of X-linked mental retardation 93 (OMIM 300659) in previously reported families included macrocephaly, tall stature, a long face, pointed chin, and large, prominent ears [Field et al., 2007].

Luscan-Lumish Syndrome

Only 4 patients with a *SETD2* mutation have been reported in the medical literature, so caution is required when ascribing overgrowth to this gene. Luscan-Lumish syndrome (OMIM 616831) has been linked to mild to moderate intellectual disability and/or autism spectrum disorder, a prominent forehead with a high frontal hairline as well as long and large hands/feet [Luscan et al., 2014; Lumish et al., 2015; Tlemsani et al., 2016].

Thauvin-Robinet-Faivre Syndrome

Four patients from 2 families have been reported with overgrowth and mild to severe intellectual disability. Other clinical findings reported include congenital heart disease (2 patients), retinal coloboma (2 patients), renal malformations (2 patients), chronic neutropenia (2 patients), cataract (1 patient), strabismus (1 patient), severe varicose veins (1 patient), sensorineural hearing loss (1 patient), and Wilms tumor (1 patient). Mild dysmorphic findings in some patients included downslanting palpebral fissures, epicanthic folds, flat midface and full/thick lips, large hands and feet, large thumbs, and spatulate digits. Thauvin-Robinet-Faivre syndrome (OMIM 617107) is autosomal recessive due to mutations in *FIBP* [Akawi et al., 2016; Thauvin-Robinet et al., 2016].

Kosaki Overgrowth Syndrome

Four patients with gain-of-function mutations in *PDGFRB* have been reported. Patients with Kosaki overgrowth syndrome (OMIM 616592) had a similar phenotype consisting of tall stature, long lower segment, long hands and feet, hyperelastic fragile skin, scoliosis, white matter lesions, and neurologic deterioration. Facial features included sparse hair, prominent forehead, proptosis, downslanting palpebral fissures, wide nasal bridge, thin upper lip, and a pointed chin. Lipodystrophy and premature aging appearance was also noted [Takenouchi et al., 2015; Minatogawa et al., 2017]. The head circumferences of the patients were not included in the research article, and this condition may be better classified

as a genetic syndrome associated with tall stature and postnatal bony overgrowth. Further phenotypic reports will clarify this.

TCF20 Mutations

TCF20 mutations have been implicated in autism spectrum disorder [Babbs et al., 2014]. Two patients have been reported with a postnatal overgrowth phenotype and a *TCF20* de novo mutation. Clinical features included intellectual impairment and hypotonia. Minor dysmorphic or abnormal physical findings included a prominent forehead, downturned corners of the mouth, and inverted nipples. One patient had epilepsy, and one patient had an advanced bone age, mild scoliosis, and small penis [Schäffgen et al., 2016].

Diagnostic Approach

Based on this review, we created a flow chart and provide examples of facial phenotypes to aid with the clinical diagnosis of overgrowth patients (Fig. 1). A glossary of “diagnostic handles” is also presented in Table 4. When possible, chromosomal microarray and other molecular investigations should follow.

Discussion

The tables classifying overgrowth syndromes reveal a large number of conditions, and the underlying genetic mechanisms have been elucidated in the majority of these. Clinical acumen and accurate phenotyping should diagnose the more common syndromes such as BWS, Sotos, and Weaver syndrome. However, molecular genetic confirmation and molecular classification is important as the number of overgrowth syndromes is now large, and the phenotypes often overlap with patients exhibiting similar facial findings [Baujat et al., 2005]. Exome sequencing or gene panel design will therefore be the most useful investigation. This review provides an overgrowth syndrome gene list to prioritize variants examined at exome sequencing. The current list we suggest is: *ABCC9*, *BRWD3*, *CDKN1C*, *CHD8*, *DIS3L2*, *DNMT3A*, *EED*, *EZH2*, *FIBP*, *GPC3*, *HERC*, *HIST1H1*, *MTOR*, *NFIX*, *NSD1*, *PDGFRB*, *PIK3CA*, *PPP2R5B*, *PPP2R5C*, *PPP2R5D*, *PTCH1*, *PTEN*, *RNF125*, *RNF135*, *TCF20*, *SETD2*, *SUZ12*, and *ZBTB20*.

In the era of massively parallel sequencing, accurate clinical diagnosis can limit the number of genes to be an-

Fig. 1. Flow chart showing a diagnostic approach to generalized overgrowth. **A, B** Facial findings in a patient with Sotos syndrome showing prominent forehead, frontotemporal hair sparsity, and prominent and narrow jaw. **C, D** A patient with BWS who has infraorbital creases, a small midface, macroglossia, and anterior linear ear lobe creases. **E, F** Facial findings in a patient with SGB syndrome demonstrating wide-spaced eyes, epicanthic folds, downslanting palpebral fissures, low-set ears, and macroglossia. **G** Facial features of a patient with Weaver syndrome (*EZH2* mutation) demonstrating almond-shaped and downslanting palpebral fissures. **H, I** A patient with Weaver syndrome due to an *EED* mutation showing almond-shaped and downslanting palpebral fissures as well as retrognathia. **J** A patient with possible Luscan-

Lumish syndrome with a variant of unknown significance [SETD2 (NM_014159.6): c.3229A>G, p.(Thr1077Ala)] but probably pathogenic. He has a prominent forehead and a high frontal hairline. Facial features resemble patients with Sotos syndrome. **K** A patient with a *PPR2R5B* pathogenic mutation with a prominent forehead, high frontal hairline, strabismus, wide-spaced eyes, and open-mouthed expression. **L** Facial findings in a patient with a small chromosomal microdeletion including the *NFIX* gene with a high forehead and downslanting palpebral fissures. **M, N** A patient with Cantu syndrome showing a low anterior hairline, wide-spaced eyes, and a flat nasal bridge. BWS, Beckwith-Wiedemann syndrome; SGB, Simpson-Golabi-Behmel syndrome; WES, whole exome sequencing.

Table 4. Diagnostic “handles” suggestive of various overgrowth syndromes

Features	Syndromes
Autoimmune phenomenon	Tenorio
Basal ganglia calcification	Primrose
Camptodactyly	CATSHL, Weaver
Cataract	Primrose, Thauvin-Robinet-Faivre
Coarse facial features	Cantu, Costello, Tatton-Brown-Rahman, Gorlin, Pallister-Killian, Perlman, SGB, Weaver
Cleft palate	BWS, SGB
Coloboma	MOMO, Thauvin-Robinet-Faivre
Congenital heart disease	BWS, infant of diabetic mother, Tatton-Brown-Rahman, Thauvin-Robinet-Faivre, Perlman, Ras/MAPK-related disorders, SGB, Sotos, Weaver
Cryptorchidism	Perlman, SGB, Weaver
Downslanting palpebral fissures	Bannayan-Riley-Ruvalcaba, Kosaki overgrowth, Macrocephaly, macrosomia, facial dysmorphism, MOMO, Primrose, Ras/MAPK-related disorders, SGB, Sotos, Sotos syndrome 2, Weaver
Ear calcification	Primrose
Ear lobe creases	BWS, SGB
Fetal fingertip pads	Cantu, Weaver
Forehead broad or prominent	Luscan-Lumish, Macrocephaly, macrosomia, facial dysmorphism, Sotos, Sotos syndrome 2, Tenorio, Weaver
Gap between central incisors	Clark-Baraitser
Groove in lower lip or tongue	SGB
Hemangiomas/nevus flammeus	BWS, MCAP, MPPH, Perlman, PTEN-related disorders, RASA1
Herniae	BWS, Perlman
Hypertrichosis	Cantu
Low-pitched voice	Weaver
Macroglossia	BWS, SGB
Microphthalmia	Primrose, MOMO
Muscular build	Cantu, SGB
Neutropenia	Thauvin-Robinet-Faivre
Polydactyly	Bardet-Biedl, Carpenter, Greig, infant of diabetic mother, MPPH, PTEN-related disorders, SGB
Renal abnormalities	Infant of diabetic mother, Sotos
Scoliosis	CATSHL, Kosaki overgrowth, Macrocephaly, dysmorphic facies, and psychomotor retardation, <i>NPR2</i> gene gain-of-function mutation, Tatton-Brown-Rahman, SGB, Sotos, Sotos syndrome 2, Weaver
Slender build	CATSHL, Kosaki overgrowth, Sotos syndrome 2, Susceptibility to autism 18
Spasticity	Pallister-Killian, Weaver
Spotted penis	PTEN-related disorders
“Stuck-on” chin	<i>EED</i> -associated overgrowth, Weaver
Supernumerary nipples	Pallister-Killian, PTEN-related disorders, SGB
Syndactyly	Carpenter, Greig, MCAP, MPPH, SGB
Synophrys	Cantu, Tatton-Brown-Rahman

BWS, Beckwith-Wiedemann syndrome; CATSHL, camptodactyly, tall stature, scoliosis, and hearing loss syndrome; MCAP, megalencephaly-capillary malformation syndrome; MOMO, macrosomia, obesity, macrocephaly, and ocular abnormalities syndrome; MPPH, megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome; SGB, Simpson-Golabi-Behme syndrome.

alyzed resulting in faster reporting of molecular results and fewer variants of uncertain significance.

Newer technologies such as genome wide methylation studies are emerging, but are not yet part of routine clinical practice. However, these technologies could be useful when a genetic variant of uncertain significance is detected [Choufani et al., 2015].

As molecular diagnoses increase, more phenotypic information will be gathered for the recently described syndromes to better inform management and prognosis of these diagnoses.

There are still gaps in diagnosis, and many overgrowth patients will remain undiagnosed even with exome sequencing. Tatton-Brown et al. [2017b] demonstrated a

50% detection rate in an overgrowth cohort of 710 individuals. However, 34% had *NSD1* mutations; 4.8% had *EZH2* mutations, and it could be argued that clinical diagnosis prior to exome sequencing was possible for most of these patients. The next order in frequency of mutation identification was *DNMT3A* (2.5%), *PTEN* (2.3%), *NFIX* (2.0%), *CHD8* (1.7%), *BRWD3* (1.0%), *HIST1H1E* (0.7%), *PPP2R5D* (0.4%), *EED* (0.3%), *GPC3* (0.3%), and *MTOR* (0.3%) [Tatton-Brown et al., 2017b].

More genes associated with an overgrowth phenotype may be discovered in the future, and this explains why some patients do not achieve a diagnosis even with accurate phenotyping and exome sequencing. We hypothesize that many patients with an apparent overgrowth phenotype have familial tall stature and a separate cause of intellectual disability. Also, the large stature seen in patients with intellectual disability may have polygenic causes.

Lastly, this review has enabled identification of some common molecular themes seen in some of the overgrowth syndromes. The presumed pathological basis be-

hind overgrowth involves an increase in cell numbers, cell size, or both. The interplay between the multiple mechanisms involved in growth regulation remains incompletely understood at a molecular level, but classifying and studying overgrowth syndromes provides insight into the control of cellular growth and also tumor formation often observed in patients with overgrowth [Neylon et al., 2012; Tatton-Brown and Rahman, 2013; Tatton-Brown and Weksberg, 2013]. One of the most important mechanisms in overgrowth is perturbation of epigenetic regulation. The following genes are involved in histone modification, chromatin modeling, or DNA methylation: *DNMT3A*, *EED*, *EZH2*, *HIST1H1E*, *NSD1*, *SETD2*, and *SUZ12*. The PI3K/AKT/mTOR pathway is also important [Imagawa et al., 2017; Tatton-Brown et al., 2017b].

Disclosure Statement

The authors have no conflicts of interest or ethical conflicts to disclose.

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