Received: 19 February 2018 | Revised: 5 April 2018 | Accepted: 16 April 2018

DOI: 10.1111/cge.13367

WILEY CLINICAL GENETICS

REVIEW

Clinical, molecular genetics and therapeutic aspects of syndromic obesity

E. Geets | M.E.C. Meuwissen | W. Van Hul

Department of Medical Genetics, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium

Correspondence
Prof. Dr. Wim Van Hul, Department of Medical Genetics, University of Antwerp, Prins Boudewijnlaan 43, B-2650 Edegem, Belgium.
Email: wim.vanhul@uantwerpen.be

Obesity has become a major health problem worldwide. To date, more than 25 different syndromic forms of obesity are known in which one (monogenic) or multiple (polygenic) genes are involved. This review gives an overview of these forms and focuses more in detail on 6 syndromes: Prader Willi Syndrome and Prader Willi *like* phenotype, Bardet Biedl Syndrome, Alström Syndrome, Wilms tumor, Aniridia, Genitourinary malformations and mental Retardation syndrome and 16p11.2 (micro)deletions. Years of research provided plenty of information on the molecular genetics of these disorders and the obesity phenotype leading to a more individualized treatment of the symptoms, however, many questions still remain unanswered. As these obesity syndromes have different signs and symptoms in common, it makes it difficult to accurately diagnose patients which may result in inappropriate treatment of the disease. Therefore, the big challenge for clinicians and scientists is to more clearly differentiate all syndromic forms of obesity to provide conclusive genetic explanations and eventually deliver accurate genetic counseling and treatment. In addition, further delineation of the (functions of the) underlying genes with the use of array- or next-generation sequencing-based technology will be helpful to unravel the mechanisms of energy metabolism in the general population.

KEYWORDS

clinics, genetics, syndromic obesity, therapy

1 | INTRODUCTION

Obesity is a metabolic disorder characterized by an imbalance between energy intake and expenditure resulting in an excess of adipose tissue. In 1973 Coleman and Hummel showed for the first time that, to a certain extent, genetic factors are responsible for the familial aggregation of obesity.[1] Several years later twin and adoption studies confirmed this and estimated the heritability of body mass index (BMI) at 40% to 70%.[2–4] There are several types of obesity. The most common is a polygenic type of obesity, which is caused by a combination of genetic and environmental factors such as high-fat diet and sedentary lifestyle, with alarming prevalence and serious complications. This type of obesity is called common or complex obesity. To date, genome-wide association studies (GWAS) identified 97 loci related to complex obesity that account for approximately 2.7% of BMI variation.[5] On the other hand, an even more severe and rare form of obesity is monogenic (non-syndromic) obesity; individuals carry mutations in a single gene that cause the obesity phenotype. Most of the genes affected in monogenic obesity are part of the leptin-melanocortin signaling pathway in the hypothalamus which has an important function in maintaining energy homeostasis.[6] In the European population heterozygous mutations in the *melanocortin-4 receptor* (*MC4R*) gene, coding for a G protein-coupled receptor that plays an important role in this signaling pathway, are the most common causes of monogenic forms of obesity and cumulates to approximately 2% to 5%.[7] However, even for monogenic obesity it has been clear there is an effect of the obesogenic environment on the penetrance.[8] Yet, this manuscript concentrates on a third, rare form of obesity in which genetics play a dominant role: syndromic obesity.

1.1 | Syndromic obesity

Syndromic obesity refers to obesity occurring in the context of a distinct set of associated clinical phenotypes such as intellectual

disability (ID), dysmorphic features and organ-specific developmental abnormalities.[9,10] Up to now over 25 syndromic forms of obesity have been identified.[11] As shown in Table 1, syndromic obesity is extremely heterogeneous[144] and different molecular mechanisms underlie the various syndromes. In case of "pleiotropy" one single gene is responsible for the presence of 2 or more distinct and seemingly unrelated traits in the patient.[145] Second, a contiguous gene syndrome (CGS) is a clinical phenotype caused by the absence of a contiguous set of genes with each of the genes underlying one of the unrelated clinical features. The segmental aneuploidy syndrome is a special type of CGS usually originated from non-allelic homologous recombination between low copy repeats that flank the region. A good example of this is the Prader Willi syndrome (PWS).[146]

In Table 1 the most important aspects of all syndromic forms of obesity are described. In addition, 6 syndromes were selected for a more detailed discussion. The selection was made in order to illustrate frequent causes, phenotypic overlap, both monogenic causes as well as contiguous gene effects and different types of molecular mechanisms underlying obesity. PWS and Bardet-Biedl syndrome (BBS) were selected because they are the most prevalent (non-X-linked) obesity syndromes. The Prader Willi *like* (PWL) phenotype and 16p11.2 (micro)deletions were included due to their clinical similarity with PWS, therefore being important differential diagnostic considerations. Additionally, we also choose Alström syndrome (AS) due to its phenotypic overlap with BBS. Finally, Wilms tumor, Aniridia, Genitourinary malformations and mental Retardation (WAGR) syndrome was selected as it is an excellent example of a CGS (Table 2).

2 | PRADER WILLI SYNDROME

PWS is the most common form of syndromic obesity with a prevalence of 1 in 10 000-30 000 live births. It is mainly characterized by severe neonatal hypotonia, feeding difficulties followed by hyperphagia and excessive weight gain, hypogonadism and ID with an average IQ of 65. Characteristic facial features are almond-shaped eyes, a thin upper lip, downturned corners of the mouth and/or a narrow face. Also behavioral problems (eg, temper tantrums, stubbornness and skin picking), sleep abnormalities, small hands and feet and short stature are frequently described features.[12,13,147–149]

In order to clinically diagnose PWS, Holm et al developed a scoring system based on the abovementioned features. Characteristics were divided into 3 groups: major criteria (1 point), minor criteria (0.5 point) and supportive criteria (no points). When younger than 3 years of age, 5 points (at least 4 of them major) are required to diagnose PWS. Eight points (at least 5 of them major) are needed when 3 years or older.[14] Gunay-Aygun et al[148] later modified these clinical criteria to help identify appropriate patients for further diagnostic testing of PWS and which criteria are characteristic at different ages.

In spite of the accuracy of this clinical scoring system, a DNA methylation analysis is always performed to confirm the PWS diagnosis. PWS is caused by the absence of expression of the paternal genes (*small nuclear ring finger* [*SNURF*], *small nuclear ribonucleoprotein polypeptide N* [*SNRPN*], *makorin ring finger protein 3* [*MKRN3*], *MAGE family member 2* [*MAGEL2*] and *necdin MAGE family member* [*NDN*]) on the imprinting region 15q11.2-q13 due to a paternal deletion (70%-75%), maternal uniparental disomy (UPD) (20%-25%) or an imprinting defect of the critical region (1%-3%).[147,149] Two main deletion types, I and II, are described. The type I deletion, occurring in approximately 40% of patients, is located between breakpoint (BP) 2 and BP3 with a mean size of 6.6 Mb. Deletion type II occurs in the remaining 60% of patients spanning a region of 5.3 Mb between BP2 and BP3[15,16] (Figure 1).

Methylation-specific-multiplex ligation-dependent probe-amplification analysis (MS-MLPA) targeting the 5′ CpG island of the *SNURF-SNRPN* locus is the gold standard technique for diagnosing PWS in all 3 molecular genetic classes, however, it won't identify the genetic subtype.[13] Therefore, to diagnose deletions, additional cytogenetic analyses such as fluorescence in situ hybridization (FISH) can be performed; however, nowadays chromosomal microarrays are routinely used in clinical genetics and have replaced the FISH analysis in most centers.[16,17] If MS-MLPA shows an abnormal methylation pattern but it does not indicate a paternal deletion, additional microsatellite analysis can be performed in order to characterize UPD (heterodisomy or isodisomy) or imprinting defects. If this technique shows a biparental pattern, a mutation (0.85%-0.9%) or microdeletion (0.1%-0.15%) in the imprinting center is present. Testing for the presence of a microdeletion is important, as the recurrence risk can be 50% when the father also harbors the deletion.[17] This can be done with the use of the MS-MLPA assay or sequencing the 4.3 kb smallest region of overlap for the PWS imprinting center.[16,18,19] In extremely rare cases a(n) (un)balanced translocation (0.1%) can be the cause of PWS in an individual. When the BP of the translocation is located in the 15q11.2-q13 PWS region, it can be indicated with the use of the karyotype of the patient in association with the MS-MLPA results or using FISH analysis[12,17] (Figure 2).

An additional advantage of the MS-MLPA technique is that it can differentiate PWS from Angelman Syndrome (AnS) (1 in 15 000-20 000), a condition genetically related to PWS.[13,20,21] In contrary to PWS, AnS patients show an absence of expression of the maternal genes *ubiquitin protein ligase E3A* (*UBE3A*) and *ATPase Phospholipid Transporting 10A (Putative)* (*ATP10A*) on the imprinting region 15q11.2-q13. Later, the disruption of the *UBE3A* gene is identified as the cause of AnS due to a deletion, paternal UPD, imprinting defects or intragenic mutations.[21,22] Characteristic features of AnS are severe developmental delay (DD), hypotonia in infancy, jerky movements, seizures and a happy disposition.[23,24]

Because of hypotonia, AnS and Fragile X Syndrome need to be considered as a differential diagnosis of PWS in infants. Other differential diagnoses are BBS, Cohen Syndrome, AS, Borjeson-Forssman-Lehmann syndrome, PWL syndrome and 16p11.2 (micro)deletions.

Which gene effectively is responsible for the PWS phenotype is not clear yet. Initially, *SNRPN* was designated as a strong candidate gene, however, further research of 2 balanced translocations, although a rare cause of PWS, excluded the gene as a primary candidate.[25–27] Located within the introns of very long transcripts extending downstream of *SNRPN* are clusters of C/D box-containing small nucleolar RNA (snoRNA) genes of which the expression (especially in the brain) is controlled by the SNRPN promoter.[27–29] Consequently, a significant role for the snoRNA genes in the PWS

TABLE 1 Overview of the prevalence, inheritance, the responsible gene(s) or chromosomal region and most important cardinal and additional clinical features of known obesity syndromes

Disease	Prevalence	Inheritance	Gene(s) or region	Main clinical features	Additional clinical features
Alström syndrome (AS)[12–15]	1-9 in 1 000 000	Autosomal recessive	*ALMS1* (mutations)	Obesity, cone-rod dystrophy, renal anomalies, progressive sensorineural hearing impairment, male hypogonadism/female hyperandrogenism, adult short stature, T2DM, and dilated or restrictive cardiomyopathy, shortened life expectancy (40-50 years)	/
Bardet-Biedl syndrome (BBS)[16–25]	1 in 13 500 (Israel and Arab counties) 1 in 160 000 (Switzerland)	Autosomal/ Oligogenic recessive	*BBS1—BBS20*, *NPHP1*, *FBN3* and *CEP19* (mutations)	Obesity, cone-rod dystrophy, postaxial polydactyly, cognitive impairment, hypogenitalism and renal abnormalities, shortened life expectancy (men = 43 years, women = 46 years)	Speech deficits, olfaction disorders (anosmia or hyposmia), psychiatric problems, T2DM and ataxia or impaired coordination
Borjeson-Forssman-Lehmann syndrome[26–28]	<1 in 1 000 000	X-linked recessive	*PHF6* (mutations)	Mild to severe ID, hypogonadism, hypometabolism, obesity with marked gynaecomastia, facial dysmorphism, hypotonia, tapered fingers, broad shortened toes, small genitalia and short stature	Microcephaly or macrocephaly and epileptic seizures
Carpenter syndrome (CS)[29–33]	<1 in 1 000 000	Autosomal recessive	*RAB23* and *MEGF8* (mutations)	Craniofacial features, mild to moderate ID, increased birth weight (90% of CS patients obese later in life), central nervous system abnormalities, dental problems, cardiovascular malformations, foot and hand syndactyly/brachydactyly, hip, knee, and ankle deformities and clinodactyly, undescended or underdeveloped testicles, shortened life expectancy but extremely variable	Omphalocele and umbilical hernia
Choroideremia-deafness-obesity syndrome or Ayazi syndrome[34–37]	<1 in 1 000 000	X-linked recessive	Deletion of Xq21 including at least the CHM and POU3F4 genes	Choroideremia (males: progressive nyctalopia and eventual central blindness; females: Retinal changes), obesity, moderate ID and congenital mixed (sensorineural and conductive) deafness	/
Coffin-Lowry syndrome[38–41]	1 in 50 000-100 000	X-linked dominant and de novo cases	*RPS6KA3* (mutations)	Growth and psychomotor retardation, hypotonia, hyperlaxity of joints, characteristic facial and digital abnormalities, progressive skeletal alterations, microcephaly, (severe) cognitive deficiency, impaired speech development, shortened life expectancy	Obesity, psychiatric illness (depression, psychotic behavior and schizophrenia), sensorineural hearing deficit, mitral regurgitation, seizures
Cognitive impairment-coarse facies-heart defects-obesity-pulmonary involvement-short stature-skeletal dysplasia (CHOPS) syndrome[42–44]	N.A.	Autosomal dominant	*AFF4* (mutations)	Cognitive impairment, coarse facies, heart defects, obesity, pulmonary involvement and short stature and skeletal dysplasia	/
Cohen syndrome[45–48]	N.A.	Autosomal recessive	*VPS13B* (deletion or mutation)	Facial dysmorphism, microcephaly, truncal obesity, ID, progressive retinopathy, and intermittent congenital neutropenia	Childhood hypotonia, joint laxity, cheerful disposition
Colobomatous microphtalmia-obesity-hypogenitalism ID syndrome[49,50]	<1 in 1 000 000	Autosomal dominant	N.A.	Colobomatous microphthalmia, obesity, hypogonadism/genitalism and ID	/
16p11.2 (micro)deletion syndrome (220 kb, 593 kb and 1.7 Mb deletion)[51–56]	N.A.	Autosomal dominant	Deletion of 16p11.2 (*SH2B1*)	Severe early-onset obesity, developmental delay (DD), autism spectrum disorders (ASD), schizophrenia, neuropsychiatric disorders	ID, hypotonia, epilepsy, behavioral problems, speech articulation abnormalities
Fragile X syndrome[57–62]	1 in 4000-5000	X-linked dominant	*FMR1* ([pre]mutations)	Mild to severe ID, cognitive and developmental impairment (eg, delayed or absent speech), physical features including macroorchidism and facial dysmorphisms (elongated face, prominent ears and forehead), behavioral problems (hyperactivity, impulsivity, attention problems, anxiety, mood lability, autistic features, attention deficit hyperactivity disorder [ADHD]), obesity, otitis media, hyperextensible finger joints	Recurrent otitis, (childhood) seizures, pes planus, strabismus, mitral valve prolapse, scoliosis

TABLE 1 (Continued)

Disease	Prevalence	Inheritance	Gene(s) or region	Main clinical features	Additional clinical features
Hydrocephalus-obesity-hypogonadism or Sengers-Hamel-Otten syndrome[63]	<1 in 1 000 000	X-linked recessive	N.A.	Congenital hydrocephalus, centripetal obesity, hypogonadism, intellectual deficit and short stature	/
ID-obesity-brain malformations-facial dysmorphism syndrome[64,65]	<1 in 1 000 000	Autosomal recessive	*TRAPPC9* (mutations)	Obesity, hypotonia, microcephaly, moderate to severe ID, brain abnormalities	Peculiar facial appearance, epilepsy
ID-obesity-prognathism-eye and skin anomalies syndromeor MOMES syndrome[66–69]	<1 in 1 000 000	Autosomal recessive	4q35.1-qter deletion and 5pter- 5p14.3 duplication	ID, speech delay, obesity, macrocephaly, maxillary hypoplasia, mandibular prognathism, crowding of teeth, ocular anomalies (blepharophimosis, blepharoptosis, decreased visual acuity, abducens palsy, hyperopic astigmatism and accommodative esotropia), chronic atopic dermatitis, lateral deviation of the great toes and cone-shaped epiphyses (toes 2, 3 and 4)	/
ID-seizures-macrocephaly-obesity syndrome[68,70–74]	<1 in 1 000 000	N.A.	der(8)t(8;12)(p23.1;p13.31)(*GNB3*)	ID, DD, obesity, seizures, hypotonia, dysmorphic features, macrocephaly, eczema, poor coordination, ocular problems, social personality	Abnormal gait, dental/palate abnormalities, hypertelorism, scoliosis
X-linked ID-epileptic seizures-hypogenitalism-microcephaly-obesity syndrome or MEHMO syndrome[64,65,75–78]	<1 in 1 000 000	X-linked recessive	*EIF2S3* (mutations)	ID, DD, severe postnatal growth delay, seizures, hypogonadism and -genitalism, microcephaly and infancy-onset obesity, life expectancy is less than 2 years	Characteristic facies, diabetes, hypertonia and hyperreflexia, nystagmus, agitated and irritable behavioral pattern
Microcephalic osteodysplastic primordial dwarfism (MOPD) type II or Majewski osteodysplastic primordial dwarfism type II[79–82]	N.A.	Autosomal recessive	*PCNT* (mutations)	Severe intrauterine and postnatal growth retardation, disproportionate short stature (adult height <100 cm), skeletal abnormalities, microcephaly, dysmorphic features (eg: retrognathia, upward-slanting palpebral fissures, prominent nose, …), truncal obesity, ID, scoliosis, unusual pigmentation (eg, café-au-lait spots), high-pitched voice, shortened life expectancy (30 years)	Severe microdontia, rootless molars, malformation of mandibular premolars, narrow chest, increased susceptibility to infections, aneurysms, Moya Moya disease, elevated platelet counts, vascular anomalies (can affect neurovasculature in childhood and renal and coronary arteries in adulthood), T2DM
Macrocephaly-obesity-mental disability-ocular abnormalities (MOMO) syndrome or macrosomia-obesity-macrocephaly-ocular abnormalities syndrome[83–89]	<1 in 1 000 000	Autosomal dominant	Balanced reciprocal translocation (16;20)(q21;p11.2)(*LINC00237*?)	Macrocephaly, obesity, overgrowth, ID and ocular abnormalities (retinal coloboma and nystagmus), macrosomia, downslanting palpebral fissures, hypertelorism, broad nasal root, high and broad forehead and delayed bone maturation	Behavioral disorders (aggressiveness, self-mutilation, excessive shyness), short stature, recurvation of femur or straight femur, autism, developmental issues, clavicular pseudoarthrosis
Mental retardation (ID)-truncal obesity-retinal dystrophy-micropenis (MORM) syndrome[90–92]	N.A.	Autosomal recessive	*INPP5E* (mutations)	Moderate ID, truncal obesity, congenital non-progressive retinal dystrophy, micropenis	/
Prader Willi syndrome[93–99]	1 in 10 000-30 000	Familial inheritance as well as de novo cases	15q11.2-q13 (imprinting region)	Severe neonatal hypotonia, feeding difficulties followed by hyperphagia and excessive weight gain, DD, hypogonadism, ID, characteristic facial features (almond-shaped eyes, a thin upper lip, downturned corners of the mouth and/or a narrow face), behavioral problems (eg, temper tantrums, stubbornness, skin picking), small hands and feet, short stature	T2DM, sleep abnormalities, apnea, hypothyroidism, delayed language development, respiratory infections, hypopigmentation of hair, eyes, and skin, strabismus, hip dysplasia, scoliosis, psychosis
Prader Willi *like* syndrome[98,100–103]	N.A.	Familial inheritance as well as de novo cases	1p36.3, 2p21, 3p26.3, 6q (*SIM1*, *MRAP2*, *POU3F2*), 9q34, 10q26, 12q, maternal	See Prader-Willi syndrome	See Prader-Willi syndrome + heart defects, neurological defects (seizures, hearing loss)

TABLE 1 (Continued)

Disease	Prevalence	Inheritance	Gene(s) or region	Main clinical features	Additional clinical features
			uniparental disomy (UPD) of chromosome 14 and X, heterozygous truncating mutations in *MAGEL2*		
Pseudohypoparathyroidism (PHP) with Albright hereditary osteodystrophy (AHO)[104–112]	N.A.	Autosomal dominant	*GNAS1* (mutations or duplication)	Resistance to parathyroid hormone, thyroid-stimulating hormone, growth hormone-releasing hormone and gonadotropins, AHO: short stature, obesity, dysmorphic features (round face, nystagmus, low nasal bridge, short neck), hypocalcaemia, subcutaneous ossifications, brachydactyly (hands/ft), osteoporosis, hypogonadism, calcified choroid plexus, hypocalcemic tetany	ID, mild DD
Rubinstein-Taybi syndrome or broad thumb-hallux syndrome[113–119]	1 in 100 000-125 000	Autosomal dominant as well as de novo cases	*CREBBP* and *EP300* (deletions or mutations)	Craniofacial features (microcephaly, low anterior hairline, downslanted palpebral fissures, broad nasal bridge/beaked nose, low hanging columella, high palate, grimacing smile, talon cusps), hypotonia, broad and often angulated thumbs and great toes, short stature, gastroesophageal reflux, moderate to severe ID, obesity after puberty, speech delay, delayed bone age, strabismus, cryptorchidism, recurrent infections, shortened life expectancy in children with heart defects	Behavioral and psychiatric problems, intrauterine growth retardation, increased fractures, orthopedic problems (scoliosis, kyphosis, lordosis), renal malformations, congenital heart defects, vascular anomalies, hirsutism, nocturnal obstructive apnea, increased risk of benign and malignant tumors, increased risk of leukemia, seizures
Short stature-brachydactyly-obesity-global DD syndrome[120–122]	<1 in 1 000 000	Autosomal recessive	*PRMT7* (mutations)	Short stature, obesity, symmetrical shortening of the digits and posterior metacarpals and metatarsals, global DD, mild ID	/
Diploid triploid mosaicism[123–129]	N.A.	Mosaicism	N.A.	DD, ID, learning difficulties, seizures, hearing loss, depression, short stature, truncal obesity, hypotonia, syndactyly or camptodactyly, facial features (small chin or lower jaw, broad/prominent forehead, small mouth, low set ears), scoliosis, genital anomalies, patches or streaks of darker or lighter skin, shortened life expectancy	/
Wilms tumor, Aniridia, Renitourinary malformations and mental retardation (WAGR) syndrome[130–139]	1 in 1 000 000	Autosomal dominant	Deletion of 11p13-p14.1 (*WT1*, *PAX6* and *BDNF*)	Wilms tumor, aniridia, genitourinary malformations (hypospadias, cryptorchidism), ID	Obesity or severe hyperphagia, renal problems, cardiopulmonary defects, behavioral difficulties like autism
Wilson-Turner or X-linked ID-gynaecomastia-obesity syndrome[140–143]	N.A.	X-linked recessive	*LAS1L* and *HDAC8* (mutations)	Severe ID, dysmorphic facial features, hypogonadism, short stature, truncal obesity, gynaecomastia, speech impairment, tapering fingers, behavioral problems (eg, emotional lability), small feet	Seizures

Abbreviations: ID, intellectual disability; T2DM, type 2 diabetes mellitus.

TABLE 2 Overview of prevalence, clinical features, responsible gene(s) or chromosomal region, molecular analysis and treatment of the 6 selected syndromic obesity forms: Prader Willi syndrome (PWS) and the Prader Willi *like* (PWL) phenotype, Bardet-Biedl syndrome (BBS), Alström syndrome (AS), Wilms tumor, Aniridia, genitourinary malformations and mental retardation (WAGR) syndrome and 16p11.2 (micro)deletions

Disease	Prevalence	Clinical features	Gene(S) or region	Molecular analysis	Treatment
Prader Willi syndrome Prader Willi *like* phenotype	*PWS:* 1 in 10 000-30 000 *PWL:* N.A.	*Main features:* Severe neonatal hypotonia, feeding difficulties followed by hyperphagia and excessive weight gain, DD, hypogonadism, ID, characteristic facial features (almond-shaped eyes, a thin upper lip, downturned corners of the mouth and/or a narrow face), behavioral problems (eg, temper tantrums, stubbornness, skin picking), small hands and feet, short stature. *Additional features:* T2DM, sleep abnormalities, apnea, hypothyroidism, delayed language development, respiratory infections, hypopigmentation of hair, eyes, and skin, strabismus, hip dysplasia, scoliosis, psychosis, heart defects, seizures, hearing loss.	*Prader Willi syndrome*: 15q11.2-q13 (imprinting region) *Prader Willi like phenotype:* 1p36.3, 2p21, 3p26.3, 6q (*SIM1*, *MRAP2*, *POU3F2*), 9q34, 10q26, 12q, maternal UPD of chromosome 14 and X, heterozygous truncating mutations in *MAGEL2*	*Present:* Methylation-specific-multiplex ligation-dependent probe-amplification analysis (MS-MLPA) in combination with karyotyping, fluorescence in situ hybridization (FISH) or chromosomal microarray, DNA polymorphism analysis, microsatellite analysis or sequencing the 4.3 kb smallest PWS region.	• Nutritional management: low calorie diet and/or protein diet, daily physical activity, locking kitchen, refrigerator and/or cupboards • Recombinant human growth hormone (rhGH) • Intranasal oxytocin • Hormonal replacement therapy • Serotonin reuptake inhibitors
Bardet-Biedl syndrome	1 in 13 500 (Israel and Arab counties) 1 in 160 000 (Switzerland)	*Main features:* Obesity, cone-rod dystrophy, post-axial polydactyly, cognitive impairment, hypogenitalism and renal abnormalities. *Additional features:* Speech deficits, olfaction disorders (anosmia or hyposmia), psychiatric problems, T2DM and ataxia or impaired coordination.	*BBS1—BBS20*, *NPHP1*, *FBN3* and *CEP19* (mutations)	*Past:* Restriction enzyme digests and/or amplification-refractory mutation system (ARMS) assays. *Present/future:* Targeted high-throughput sequencing such as next-generation sequencing (NGS) panels.	• Nutritional management: low calorie and/or protein diet, daily physical activity and behavioral therapies • Low vision aids and mobility training or even subretinal injection • Removal of the accessory digit(s) • Hormonal replacement therapy • Renal transplantation
Alström syndrome	1-9 in 1 000 000	*Main features:* Obesity, cone-rod dystrophy, renal anomalies, progressive sensorineural hearing impairment, male hypogonadism/ female hyperandrogenism, adult short stature, T2DM and dilated or restrictive cardio-myopathy.	*ALMS1* (mutations)	*Past:* Mutation analysis of the gene hotspots (exons 8, 10 and 16) in *ALMS1*. *Present/future:* Array- or NGS-based technology.	• Nutritional management: Low calorie and/or protein diet, daily physical activity • RhGH • Red-orange tinted lenses • Angiotensin-converting-enzyme (ACE) inhibitors or renal transplantation • Myringotomy • Metformin and rosiglitazone • Cardiac transplantation
WAGR syndrome	1 in 1 000 000	*Main features:* Wilms tumor, aniridia, genitourinary malformations (hypospadias, cryptorchidism), ID. *Additional features:* Obesity or severe hyperphagia, renal problems, cardiopulmonary defects, behavioral difficulties.	Deletion of 11p13-p14.1 (*WT1*, *PAX6* and *BDNF*)	*Present:* FISH, MLPA, multiplex amplicon quantification (MAQ), chromosomal microarray (single-nucleotide polymorphism [SNP]-based array or array comparative genomic hybridization [CGH]) or high-resolution cytogenetics.	• Chemotherapy, radiotherapy or even nephrectomy • Colored, tinted contact lenses or implantation of an artificial iris-intraocular lens • Surgical intervention for genitourinary malformations

TABLE 2 (Continued)

Disease	Prevalence	Clinical features	Gene(S) or region	Molecular analysis	Treatment
					• Nutritional management: low calorie and/or protein diet, daily physical activity • ACE inhibitors
16p11.2 593 kb deletion 220 kb deletion 1.7 Mb deletion	N.A.	*Main features:* ASD, schizophrenia, neuropsychiatric disorders. *Additional features:* Severe early-onset obesity, DD, ID, hypotonia, epilepsy, behavioral problems, speech articulation abnormalities. *Main features:* Severe early-onset obesity, DD. Combination of features seen in 593 kb deletion and 220 kb deletion	Deletion of 16p11.2 (*SH2B1*)	*Present:* FISH, MLPA, MAQ, chromosomal microarray (SNP-based array or array CGH) or high-resolution cytogenetics.	• Neuropsychological testing • Nutritional management: controlling food intake and physical activity • Epileptic medication • Behavioral strategies and habilitative therapies • Didactic, naturalistic behavioral methodologies and developmental-pragmatic approaches

Abbreviations: DD, developmental delay; ID, intellectual disability; UPD, uniparental disomy, T2DM, type 2 diabetes mellitus.

phenotype emerged. In 2008, Sahoo et al[29] identified for the first time a microdeletion of SNORD116 and a substantial segment of the SNORD115 cluster in a patient with PWS characteristics. As previously identified deletions of the SNORD115 cluster did not show a clear PWS phenotype with paternal inheritance, the SNORD116 cluster was designated as the most likely candidate to cause PWS.[30,31] One year later, a research group in the United Kingdom confirmed the role of the SNORD116 cluster in PWS and particular in human energy homeostasis, growth and reproduction.[32] Even more recently, Bieth et al[33] identified the first restricted deletion of the SNORD116 cluster in a patient with PWS features increasing the contributing role of SNORD116 in the pathogenesis of PWS. Up to now, 4 research groups also studied a PWS mouse mutant line which carries a Snord116 deletion.[34–37] Heterozygous mice exhibiting a paternally inherited deletion show postnatal growth retardation and hyperphagia.[34,35] Mice with a biallelic deletion of Snord116 have low birth weight with an increase in body weight, energy expenditure and hyperphagia in early adulthood.[37] Overall, both mice models show important characteristics of the PWS phenotype, supporting a significant role for SNORD116 in PWS pathogenesis.[27]

Therapeutically, there are no opportunities yet to address the primary cause of PWS, however, symptoms can be treated. In order to lower the risk of developing obesity and its comorbidities, nutritional management is crucial. In general, a well-balanced, low calorie diet together with daily physical activity is a fundamental therapy. From early childhood (age of 2 years) PWS patients also tend to sneak and hoard food with the result that locking the kitchen, refrigerator and/or cupboards is necessary in order to control their dietary intake.[12,38,147] Another promising therapy is the administration of recombinant human growth hormone (rhGH). Besides its beneficial effect on weight gain (decrease in adipose tissue and increase in lean body mass), rhGH also normalizes the patient's height and improves respiratory function and physical activity.[12,13,39,40] The effects of liraglutide, a glucagon-like peptide (GLP)-1 analog approved by the US Food and drug Administration and the European Medicines Agency for weight management in obese adults, were also investigated in PWS individuals with type 2 diabetes mellitus (T2DM). Liraglutide therapy leads to a decrease in plasma ghrelin levels and BMI; however, the long-term effects of such treatment in individuals with PWS are uncertain and further studies on a larger number of patients are required.[41–43] De Waele et al also examined the effect of long-acting octreotide treatment in PWS. As for liraglutide a decrease in ghrelin concentrations was noticed after octreotide administration for 16 weeks, however, it did not affect weight, appetite or compulsive behavior toward food in the PWS subjects.[44] Another still investigational therapy is the administration of intranasal oxytocin (OXT) to treat hyperphagia. Despite contradictory results of different clinical trials so far, a promising effect on food-related behavior was seen in children with PWS younger than 11 years of age.[45–47] This hormone shows a high expression in the hypothalamus and, as seen in functional magnetic resonance imaging scans, this brain region also shows a significant delay in activation in PWS patients[48] so further research of the effects of intranasal OXT administration on the hypothalamic activity is still necessary. In addition, different studies in whole-room indirect calorimeters also indicated a significant reduction in total, resting, sleep and activity

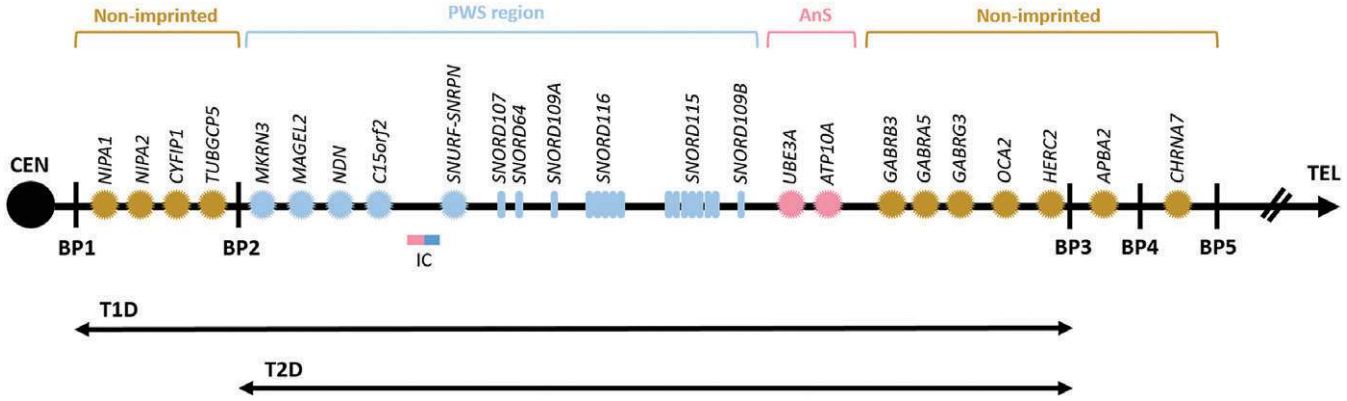

FIGURE 1 Schematic representation of chromosomal region 15q11.2-q13. The region involved in Prader Willi syndrome (PWS) is depicted in blue. The type I deletion (T1D), occurring in approximately 40% of patients, is located between breakpoint (BP) 1 and BP3 with a mean size of 6.6 Mb. Deletion type II (T2D) occurs in the remaining 60% of patients spanning a region of 5.3 Mb between BP2 and BP3. AnS = Angelman syndrome, IC = imprinting center, CEN = centromere, TEL = telomere

energy expenditure in PWS patients compared to age-, sex- and BMI-matched subjects. This decrease can be attributed to reduced activity but also to lower energy utilization due to reduced lean body mass which primarily consists of muscle.[49,50] These results highlight the importance of daily physical activity in PWS patients.

Important to mention, restrictive bariatric surgery is not recommended in PWS as it is associated with high complication rates and even mortality.[51,52] Also in a case report Fonkalsrud and Bray describe the limited success of a truncal vagotomy to treat obesity in PWS patients as the subject initially lost 29 kg but regained most of this in almost a year time due to almost continuous ingestion of small quantities of food.[53] Other therapies that may benefit PWS patients are the use of serotonin reuptake inhibitors to manage behavioral disorders, especially obsessive-compulsive symptoms and a hormonal replacement therapy in order to produce adequate secondary sexual characteristics at puberty. The latter, however, is somewhat controversial due to the effects of, that is, testosterone replacement on behavior.[38,54,147]

Noteworthy, recently Kim et al reported a first epigenetics-based therapy for PWS. In a PWS mice model, they restored the expression from the maternal copies of PWS-associated genes by targeting the histone methyltransferase G9a with the use of 2 small molecules UNC0638 and UNC0642. Administration of UNC0642 resulted in the improvement of survival and growth of the pups. However, the effect of the drug on other disease symptoms such as hyperphagia and obesity still needs to be evaluated.[55]

As an additional remark, because the genes and pathways disrupted in PWS are also highly conserved in zebrafish, in the future zebrafish could also serve as a promising model for high-throughput screening in order to quickly identify and deliver potential curative pharmacotherapies for PWS patients.[56]

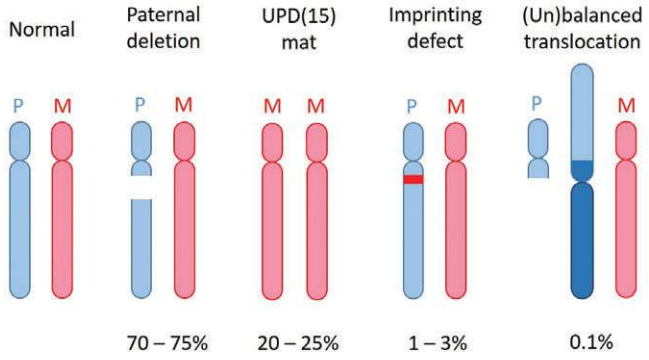

FIGURE 2 Ideograms showing possible causes of chromosomal abnormalities in Prader Willi syndrome. Blue = paternal chromosome 15, pink = maternal chromosome 15. UPD(15)mat = maternal uniparental disomy of chromosome 15

2.1 | Prader Willi like

Patients with a PWL phenotype have similar clinical characteristics as PWS individuals but occasionally show heart defects or neurological defects like seizures or hearing loss.[57–59] Consequently, MS-MLPA and/or additional techniques are always performed in order to exclude PWS in these patients. Once the clinical diagnosis of PWS cannot be confirmed molecularly, the patients are considered PWL. Clinically but also genetically the PWL phenotype is heterogeneous. In literature, the phenotype has already been associated with copy number variations (CNVs) on different chromosomes such as 1p36.3,[60] 2p21,[61] 3p26.3,[62,63] 6q,[18,57–59,62,64–74] 9q34,[75] 10q26,[76] 12q[76] and X[76] as well as maternal UPD of chromosome 14.[76] Therefore, the use of chromosomal microarrays is recommended in order to identify any of these CNVs. Noteworthy, deletions at chromosome 6q are most frequently reported. In 1988, Turleau et al linked the PWL phenotype with a 6q deletion for the first time.[64] Several years later, similar reports appeared which enlarged the role of chromosome 6q in the PWL phenotype.[18,57–59,65–68,70,71,73,74] In these studies most 6q deletions encompass *Single-minded 1* (*SIM1*) which is part of the leptin-melanocortin signaling pathway that regulates energy homeostasis. This ultimately led to the identification of haploinsufficiency of the *SIM1* gene as a possible cause for obesity in these patients.[18,57–59,67,68,70,71] This hypothesis was substantiated further in an 18-month old girl with early-onset severe obesity who presented with a de novo balanced translocation between chromosome 1p22.1 and 6q16.2 separating the 5′ promoter region and basic helix-loop-

helix (bHLH) domain from the 3′ PER-ARNT-SIM (PAS) region and putative transcriptional regulating domains of the *SIM1* gene.[77] In addition, different research groups, including our own, reported loss-of-function point mutations and variants in *SIM1* in obese individuals with or without PWL features, indicating a possible contribution of the *SIM1* gene in the development of obesity and the PWL syndrome.[78–81] Moreover, Wentzel et al[82] identified 2 interstitial deletions of 8.73 and 4.50 Mb at chromosome 6q14.1-q15 in 2 children with a PWL phenotype. The overlapping region of 4.2 Mb encompasses the *Melanocortin 2 Receptor Accessory Protein 2* (*MRAP2*) gene. By sequencing the coding regions and intron/exon boundaries of the gene, Asai et al[83] also revealed 4 rare heterozygous variants in 4 severely obese children of which 1 (E24X) was clearly disruptive. In contrast to this, own CNV and mutation analysis in a cohort of 109 PWL patients only showed a limited involvement of copy number and sequence variation in *SIM1* and *MRAP2* in the PWL phenotype.[84] More recently, Kasher et al also identified small deletions encompassing *POU Class 3 Homeobox 2* (*POU3F2*), and not *SIM1*, at chromosome 6q in 10 individuals from 6 families with DD, ID, neonatal hypotonia, susceptibility to obesity and hyperphagia, characteristics resembling the PWL phenotype. In addition, with the use of morpholino and mutant zebrafish models, they showed that the gene lies downstream of *SIM1* in the leptin-melanocortin signaling pathway which indicates that *POU3F2* also has a potentially interesting role in the obesity phenotype of PWL patients.[85] In extremely rare cases, heterozygous truncating mutations in *MAGE Family Member L2* (*MAGEL2*), occurring on the paternal allele, are reported in individuals with features resembling the PWS/PWL phenotype which is called the Schaaf-Yang syndrome.[86,87] Also the Magel2-null mouse model indicates a role in PWS and obesity.[88] However, in contrast to this findings, Buiting et al identified 2 deletions including *MAGEL2* and not the *SNRPN/SNORD116* locus in 2 patients who do not have PWS or PWL characteristics and consequently concluded that the role of *MAGEL2* in PWS/PWL still remains unclear.[89,90]

As for PWS, PWL therapy is mainly focused on the treatment of the symptoms. As these symptoms are largely comparable, the corresponding treatment of both phenotypes is similar. In addition, depending on the patient's phenotype, specific treatment of epilepsy or cardiovascular abnormalities can be indicated. In case of hearing loss a cochlear hearing device implantation could be a solution.

3 | BARDET-BIEDL SYNDROME

BBS is a pleiotropic recessive disorder belonging to the family of ciliopathies with a prevalence of 1 in 13 500 (Israel and Arab counties) to 1 in 160 000 (Switzerland) individuals. The big difference in prevalence can be attributed to a high rate of consanguinity in the first population group.[91–93] Apart from obesity, BBS patients are primarily characterized by cone-rod dystrophy, post-axial polydactyly, cognitive impairment, hypogenitalism and renal abnormalities. Secondary features are speech deficits, olfaction disorders (anosmia or hyposmia), psychiatric problems, T2DM and ataxia/impaired coordination.[91,92,94–96] At birth, several major diagnostic clues such as the ophthalmological features and obesity are not noticeable yet; however, they appear and progressively worsen during the first and second decade of life.[96] For example: for children with BBS the visual prognosis is poor. At age 7 to 8 years, patients usually develop night blindness which eventually leads to legal blindness by the age of 20 years in more than 60% of patients.[91,97,98]

As for PWS, BBS is also diagnosed based on clinical findings. BBS diagnosis is assigned to patients bearing at least 4 primary criteria. When only 3 major features are present, 2 secondary criteria are required to confirm the presence of the disorder.[96,98,99]

A substantial clinical overlap exists with other ciliopathies like AS and McKusick-Kaufman syndrome. Due to the evolving phenotype of BBS in time, the clinical overlap with other disorders, and the increasing possibilities of large-scale genetic testing, molecular diagnostics is becoming more important in establishing a diagnosis of BBS. To date, 23 genes (*BBS1—BBS20*, *Nephrocystin 1* [*NPHP1*], *Fibrillin 3* [*FBN3*][100] and *Centrosomal Protein 19* [*CEP19*][101]) have been identified to be associated with BBS and which are all involved in primary cilia functioning.[96] Most BBS cases can be attributed to mutations in *BBS1* and *BBS10* accounting for 23.2% and 20% in the populations of Europe and North America.[95,102,103] Disease-causing mutations in other BBS genes have a prevalence below 10% and even in most cases ≤5% (overview in Suspitsin et al[96]). Early studies suggested a classical mode of autosomal recessive inheritance for BBS in which a biallelic mutation in one of the affected genes gives rise to the disorder. However, as the years proceeded, the genetics of BBS became more complex. Katsanis et al was the first to propose a "triallelic inheritance" to manifest the phenotype. They identified a homozygous *BBS6* mutation in combination with a heterozygous *BBS2* mutation in 1 BBS family and 2 heterozygous *BBS2* nonsense mutations and a *BBS6* nonsense mutation in BBS patients in 3 other families.[104] This triallelic model was supported by some research groups,[105–108] as others do not underpin the triallelic inheritance hypothesis.[109–114] In addition, cases are reported in which even healthy individuals carry a biallelic mutation in one of the known BBS genes which suggests incomplete penetrance for at least some genes and/or types of mutations.[96,104,107,115] The only way to achieve molecular confirmation of BBS is the use of clinically available tests. In the past, the most frequently reported mutations, such as p.M390R in *BBS1* and p.C91Lfs*5 in *BBS10*, were identified with the use of simple screening methods such as restriction enzyme digests and/or amplification-refractory mutation system (ARMS) assays.[116] Nowadays targeted high-throughput sequencing, such as next-generation sequencing (NGS) panels, offer the most feasible and effective approach to provide high diagnostic yields as previously used mutation screening techniques are too time-consuming and expensive due to the broad genetic locus heterogeneity of the disease.[91,117–120] To date, a clear genotype-phenotype correlation is not yet identified in BBS; however, patients with *BBS1* mutations do show a milder phenotype compared to patients harboring mutations in other BBS genes.[108,121]

BBS therapy mainly exists of the treatment of the patient's symptoms. Polydactyly can be surgically corrected. In most children this happens within the first 2 years of age. Second, the management of obesity is initiated at an early age with the use of a low calorie and/or protein diet, exercise and behavioral therapies.[91] One study also discovered a positive effect of the diet on renal function; however, it

only may slow the progression of renal failure.[122] Due to the high incidence of renal malformations and abnormal renal function that can lead to end-stage renal disease (ESRD), renal function must be monitored closely. In case of ESRD a renal dialysis and/or renal transplantation are warranted.[91] Third, up till now researchers are unable to prevent the development of blindness in BBS patients. With the use of low vision aids and mobility training they are being prepared to progressive visual loss and possibly blindness by a specialist. However, an experimental set-up of subretinal injection of BBS-containing adenovirus constructs in mice showed encouraging results so far.[91,96] In case of abnormal gonadotropin or sex hormone levels at puberty, a hormonal replacement therapy in order to produce adequate secondary sexual characteristics can be used in BBS patients.[91]

4 | ALSTRÖM SYNDROME

AS was first described in 1959[123] and is, as BBS, included in the ciliopathies group.[124] It is a rare autosomal recessive disorder with a prevalence estimated at 1 to 9 cases per 1 000 000 individuals. To date, approximately 950 cases are described worldwide.[124,125] AS shows a wide clinical variability even within the same family. It does share some features with BBS such as obesity, cone-rod dystrophy, renal anomalies, male hypogonadism/female hyperandrogenism and adult short stature, suggesting BBS as an important differential diagnostic consideration. Additionally, AS is characterized by progressive sensorineural hearing impairment, T2DM and dilated or restrictive cardiomyopathy.[126,127] A clinical distinction between AS and BBS can be made based on the timing of the onset of visual problems and the presence of post-axial polydactyly. AS patients usually show vision difficulties before the age of 2 years, whereas in BBS this appears on average 6.5 years later. Polydactyly, which is common in BBS, has not been described in AS.[126] However, since both ciliopathies show considerable phenotypic overlap, especially in early infancy, molecular techniques are crucial to clearly differentiate AS from BBS.[118,128,129]

AS is caused by homozygous or compound heterozygous mutations in *Alström syndrome protein 1* (*ALMS1*) on chromosome 2p13.[130] Recently, however, Ozantürk et al[131] also reported triallelic mutations in *ALMS1* in Turkish AS cases who incredibly did not show more severe characteristics. To date, more than 200 mutations have been reported of which exons 8, 10 and 16 are the 3 big hotspots for *ALMS1* mutations (overview table S1in Marshall et al[132]). The mutations with the largest impact on the ALMS1 protein are frameshift or nonsense mutations occurring downstream of exon 7 resulting in an early termination of ALMS1 and subsequently a non-functional protein.[124,132] In addition, also splice-site mutations,[133] deletions,[134,135] one *Alu* transposon insertion[136] and one balanced translocation[137] have been identified in *ALMS1*.

As ALMS1 localizes to centrosomes and basal bodies of ciliated cells, a role in microtubule organization, intracilia transport, endosome recycling and cell cycle regulations is suggested.[126,131,138,139] Second, it is also hypothesized that ALMS1 could play a role in β-cell function and/or peripheral insulin signaling pathways because AS patients are more likely to develop T2DM in contrast to BBS patients despite the fact that obesity levels are equivalent in both syndromes.[140,141] Unfortunately, up till now the precise molecular mechanism causing the AS phenotype has not been fully elucidated.[132]

In the past, the first step in the molecular diagnosis of AS in patients was to perform mutation analysis of the gene hotspots (exons 8, 10 and 16) in *ALMS1*. When this approach did not reveal any mutation, an array-based technology, which includes a set of known mutations in *ALMS1*, was often carried out.[124,128] Nevertheless, as the NGS methodology is rapidly growing and gradually replacing abovementioned technologies, whole-exome and whole-genome sequencing are nowadays the most widely used approaches to identify the causal mutation and secondly also exclude mutations in other genes in the differential diagnosis.[124,142,143]

As for PWS and BBS, the only therapy for AS patients is restricted to the management of the clinical symptoms and the improvement of the quality of life.[124] Between birth and age 15 months most patients become very sensitive to light (photodysphoria) which can be reduced with the use of red-orange tinted lenses. However, almost all patients have decreasing visual accuracy with loss of light perception around the age of 20 years, although the progression rate is variable. Second, weight gain can be controlled with the use of a healthy, reduced calorie diet and regular exercise taking into account the vision limitations of the patient.[126] Also beneficial effects of rhGH on body composition and liver fat content were reported in a 15-year-old AS patient.[150] Urinary analysis for proteinuria is warranted in order to detect decreased renal function. In this case, angiotensin-converting-enzyme (ACE) inhibitors are often prescribed, which are also used for the treatment of the dilated or restrictive cardiomyopathy. Unfortunately, in select cases a renal and/or cardiac transplantation is the only viable therapeutic option.[126,151] Myringotomy, a surgical procedure in which a tiny incision is created in the tympanic membrane, or the implantation of an cochlear hearing device can improve the hearing impairment in the patients. Lastly, when T2DM is present a treatment as in the general population is recommended,[126] although valuable results are already obtained with a combined therapy comprising a high dose of metformin and rosiglitazone.[152]

5 | WILMS TUMOR, ANIRIDIA, GENITOURINARY MALFORMATIONS AND MENTAL RETARDATION SYNDROME

WAGR syndrome, first described in 1964 by Miller et al,[153] is an autosomal dominant disorder with an estimated prevalence of 1 in 1 000 000 individuals.[154,155] The main characteristics are stated in the acronym: Wilms tumor (an embryonic malignancy of the kidney), aniridia, genitourinary malformations and mental retardation or ID. Obesity or severe hyperphagia has also been described in a subgroup of these patients, in which case the condition is often called WAGRO.[156–162] Secondary features often seen in WAGR patients are renal problems, cardiopulmonary defects and behavioral difficulties like autism.[160,163] Due to the specific combination of manifestations, the differential diagnosis of WAGR is very limited.

WAGR is caused by a de novo heterozygous deletion on chromosome 11p13 in which haploinsufficiency of *Wilms tumor 1* (*WT1*) and *paired box 6* (*PAX6*) is responsible for the core features of the

disorder.[155] Evidence is shown that a deletion of *WT1* is associated with an increased risk of Wilms tumor, genitourinary anomalies and nephropathies, whereas *PAX6* deletions give rise to eye abnormalities.[160,164] There is also a possibility that *PAX6* deficiency results in brain and pancreas defects.[165–168] Both genes are also located at approximately 4 Mb from the *brain-derived neurotrophic factor* (*BDNF*) gene at chromosome 11p14.1.[155,162] More than half the WAGR patients exhibit a deletion also including this gene who notably all show childhood obesity compared to only 20% of the patients without a *BDNF* encompassing deletion[162] (Figure 3). Consequently, it is suggested that *BDNF* is a key player in the obesity phenotype seen in WAGR patients and even in overall energy homeostasis in humans. BDNF encodes a member of the nerve growth factor family which is involved in neuronal proliferation, differentiation and survival of specific neuronal populations.[6,169,170] Its role in energy homeostasis has extensively been investigated resulting in the development of different *Bdnf* animal models exhibiting an obese phenotype and marked hyperphagia.[171–174] In addition, as its neural function, the protein is widely distributed in the central nervous system including the hypothalamus.[6,155] It is believed that BDNF functions within the ventromedial hypothalamic leptin-melanocortin signaling pathway as a downstream target of MC4R and, as a result, is an important effector in the control of energy balance.[175,176] On the other hand, a recent study determined more severe neurocognitive impairments in WAGR syndrome patients with *BDNF* haploinsufficiency which shows that BDNF could also be involved in cognitive functioning.[177]

Genetic testing for WAGR syndrome is typically performed in children presented with aniridia.[160] To identify large deletions or translocations of chromosome 11p13, high-resolution cytogenetics is an appropriate method.[154,178] Small deletions, however, cannot be recognized with this technique. In this case, FISH, MLPA or array comparative genomic hybridization (CGH) are more suitable.[160,162,164,178]

Once genetic tests confirm the diagnosis of WAGR syndrome, ultrasound screening for Wilms tumor is initiated every 3 months until the age of 5 to 6 years to allow early detection.[160,178,179] The prevalence of Wilms tumor in WAGR patients is estimated between 45%[180] and 57%.[160] Depending on the stage of the tumor, patients may require chemotherapy, radiotherapy or even nephrectomy (surgical removal of the kidney). Other renal problems are also frequently reported in which proteinuria or mild hypertension can be an early indication of renal insufficiency and subsequently can be treated with ACE inhibitors.[160,178] Aniridia should be monitored by an expert ophthalmologist.[178,181] Colored, tinted contact lenses can be worn to reduce light sensitivity and restore a more normal appearance of the eye, however, due to poor ocular surface and reduced tear production, difficulties can be experienced.[181] That is why implantation of an artificial iris-intraocular lens is nowadays suggested.[181,182] In case of gonadal dysgenesis, prophylactic removal of the gonads is warranted to prevent the occurrence of gonadoblastoma.[178]

6 | 16P11.2 (MICRO)DELETIONS

Due to the presence of flanking homologous segmental duplications, the 16p region is particularly prone to rearrangements leading to copy number changes.[183] The recurrent proximal ~593 kb deletions (and duplications) are among the most frequent genetic etiologies of autism spectrum disorders (ASD),[184–186] schizophrenia[187] and neuropsychiatric disorders.[188] The prevalence is estimated at approximately 1% in all ASD cases.[184] In addition, the microdeletion syndrome also cosegregates with severe early-onset obesity,[189,190] DD,[191] ID,[192,193] hypotonia,[194] epilepsy,[191,193–195] behavioral problems[191,196] and even a high prevalence of speech articulation abnormalities.[194,196] On the contrary, patients harboring a ~593 kb microduplication share some characteristics with the deletion phenotype, however, confer an increased risk for being underweight indicating that haploinsufficiency and triplosensitivity at the 16p11.2 locus clearly has opposite effects on BMI. To date, no particular candidate gene located within the 593 kb region is pointed forward to clarify the obesity/underweight phenotype.[197] In addition, larger deletions of 1.7 Mb encompassing the 593 kb proximal deletion are also reported in patients harboring similar characteristics[189,190,198,199] supplemented with or without secondary features such as dysmorphism, heart defects[199] or Hirschsprung disease.[200] Noteworthy, this 1.7 Mb deletion also includes a

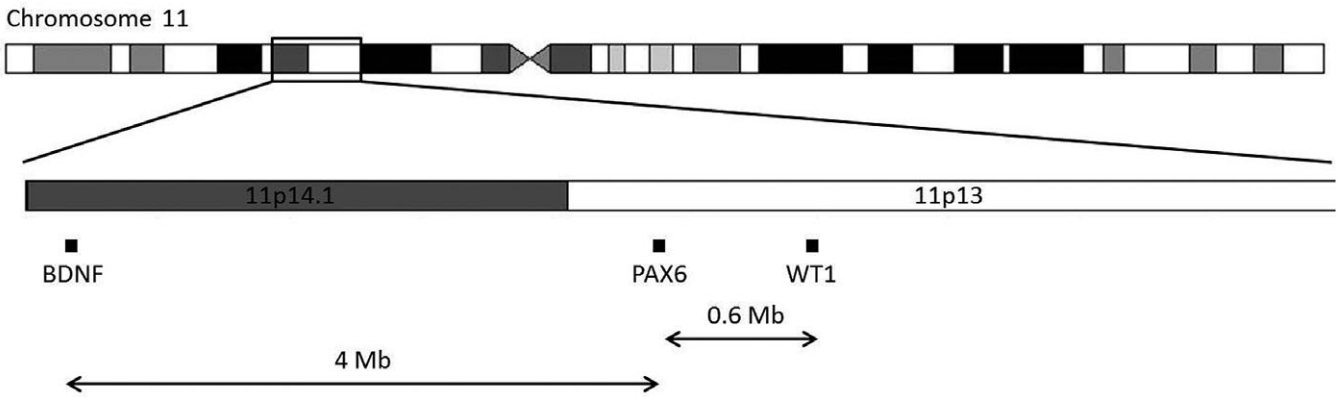

FIGURE 3 Schematic representation of the critical region of Wilms tumor, Aniridia, genitourinary malformations and mental retardation (WAGR) syndrome on chromosome 11p. WAGR syndrome is caused by a de novo heterozygous deletion of *Wilms tumor 1* (*WT1*) and *paired box 6* (*PAX6*) on chromosome 11p13. More than half of the WAGR patients exhibit a deletion also including the *Brain-derived Neurotrophic Factor* (*BDNF*) gene located at approximately 4 Mb from *WT1* and *PAX6* at chromosome 11p14.1. Notably, these patients all show childhood obesity compared to only 20% of the patients without a *BDNF* encompassing deletion

second 220 kb distal deletion which in literature mainly is associated with severe early-onset obesity as well as obesity with DD[183,189,201,202] (Figure 4). Additionally, dysmorphic features, behavioral problems, seizures, speech and motor delays and autism are also commonly reported.[183,203]

In case of obesity in association with DD or ID, PWS or PWL should be considered as a differential diagnosis. However, as nowadays genome-wide microarray analysis is a routine diagnostic screening method, 16p11.2 (micro)deletions are unlikely to be missed. Therefore extensive differential diagnosis is useless.

All 4 CNVs (593 kb deletion, 593 kb duplication, 1.7 Mb deletion and 220 kb deletion) are inherited in an autosomal dominant matter, either due to a de novo event or inherited from one of the (even healthy) parents.[183,189,198,204]

For the distal 16p11.2 deletion (and the overlapping 1.7 Mb deletion) there is increasing evidence that haploinsufficiency of the *Sarcoma* (*Src*) *homology 2B adaptor protein 1* (*SH2B1*) gene could induce the obesity phenotype seen in the patients[197] as other genes within the 220 kb region might clarify the presence of the additional features.[205] Previous research in a yeast 2-hybrid system showed that SH2B1 is a Janus kinase 2 (JAK2)-binding protein.[206] Later on, the same research group showed that, in response to the binding of leptin to its receptor, SH2B1 not only binds to JAK2 but also promotes its activation[207,208] indicating that SH2B1 could act as a positive regulator of leptin signaling and consequently might be implicated in energy homeostasis.[205] This hypothesis was substantiated further with the generation of a *SH2B1* deficient mouse model in which a significant decrease in leptin signaling in the hypothalamus was indicated. The *SH2B1*$^{-/-}$ mice also clearly developed an obesity phenotype with hyperphagia, hyperlipidemia, hyperglycemia, hyperleptinemia, hyperinsulinemia, hepatic steatosis and glucose intolerance.[209,210] Further genetic evidence appeared in 2009 when GWAS reported an association of the A484T variant (rs7498665) in *SH2B1* with BMI which could also be replicated in our own Belgian cohort.[202,211,212] Published mutation analyses of *SH2B1* in both obese and lean study populations, however, show conflicting results. Two research groups identified potentially causative mutations in approximately 1% of severe obese subjects whereas no private variants were identified in lean control populations.[213–215] Own research, on the other hand, showed an equal presence of rare non-synonymous *SH2B1* variations in both lean and obese individuals[205] which was also seen in a Chinese study population.[216] Both concluded that it seems unlikely that *SH2B1* variants do confer risks for obesity; however, further research is necessary to clarify the contradictory findings.

As for the WAGR syndrome, genetic screening for a 16p11.2 microdeletion in patients can include chromosomal microarray (single-nucleotide polymorphism [SNP]-based array or array CGH) or targeted deletion analysis using FISH, MLPA or multiplex amplicon quantification (MAQ).[183,203–205]

Noteworthy, the deletion patients (either with a 220 or 593 kb deletion) and duplication patients (either with a 220 or 593 kb duplication) share a common phenotype. Due to this phenomenon, Loviglio et al suggested a genomic interaction between the distal (220 kb) and proximal (593 kb) region and in fact observed a complex chromatin looping between the genes located in the 220 kb region and those mapped to the proximal region. This observation indicates that the Chromosome Conformation Capture technique can be proposed as a new and effective tool to identify genes and/or pathways that are perturbed in patients harboring, for example, an overlapping obesity phenotype.[217]

Therapeutically, as for the foregoing disorders, treatment should target the specific features identified. Before excessive weight gain begins, controlling food intake and physical activity at an early age is essential in order to avoid the development of obesity. A neurologist is seen when epilepsy is suspected who will prescribe epileptic medication based on the patient's age, seizure type, electroencephalography (EEG) and side effect profiles.[204] For the management of autism spectrum disorders, different educational interventions such as behavioral strategies and habilitative therapies are used. In addition, to improve communication skills and speech deficits in patients with 16p11.2 microdeletions, different didactic methodologies and developmental-pragmatic approaches are effective. A visit to a speech-language therapist is usually an appropriate first step.[218]

7 | CONCLUSIONS AND FUTURE PERSPECTIVES

Due to its increasing prevalence and the associated comorbidities, obesity has become a major health problem worldwide. As shown in this review, several genes/chromosomal regions are associated with energy homeostasis. Many years of research already resulted in more information on the molecular genetics of these disorders and the obesity phenotype, however, as discussed in detail for the 6 selected syndromes, treatment of all syndromic forms is only restricted to the

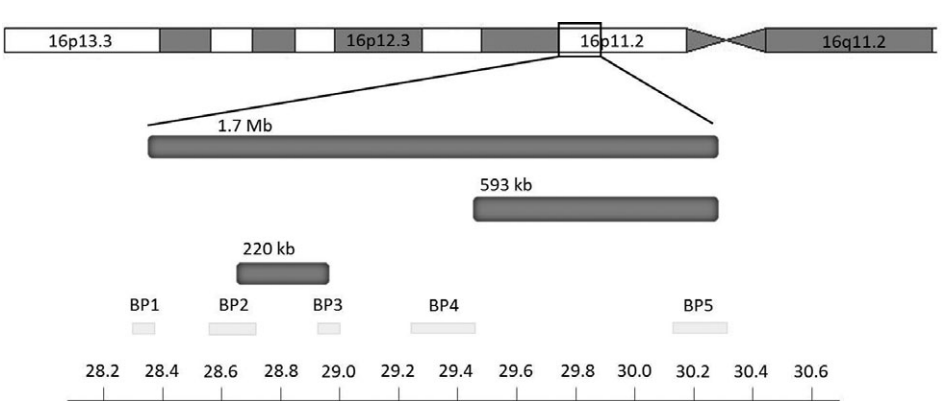

FIGURE 4 Schematic representation of the proximal (593 kb), distal (220 kb) and overlapping 1.7 Mb copy number variations on chromosome 16p11.2

management of the patient's symptoms. Due to the important phenotypic overlap between various obesity syndromes, it remains very difficult to make an appropriate syndromic diagnosis solely based on clinical phenotype. A good example of this is the differentiation between PWS and the PWL phenotype. So far, a clear difference between both phenotypes on clinical level is not yet made.[16,76] In addition, signs and symptoms of PWS and PWL are also common to other syndromes such as BBS, AS, 16p11.2 (micro)deletions but also Fragile X syndrome, Cohen syndrome and even Temple syndrome[219,220] which makes it even more difficult to determine in which circumstances the MS-MLPA analysis for PWS diagnosis should be performed. A correct and fast diagnosis, however, is of great importance. An update in the phenotypic and genetic information of these patients is therefore of great use to recognize the appropriate syndrome in an individual.[16,76] In general, early diagnosis of an obesity syndrome is important as this would result in the delivery of accurate genetic counseling for parents. This will help in a better understanding of their child's condition. In addition, it can influence family planning and can help in the identification of other family members at risk of having a similar genetic condition. Furthermore, when a patient can be diagnosed with a syndromic form of obesity early in life, appropriate screening, follow-up and treatment of other associated medical problems can be offered. Examples are follow-up of renal function or ophthalmological problems in BBS or AS. Also, early observation of eating behavior of a patient is important as this would make it possible to intervene in time and even refer the patient to a specialized team.

Lastly, further delineation of (the functions of) the underlying genes will be helpful to unravel the mechanisms of energy metabolism in the general population as well.[92] Previous research mostly focused on simple screening methods like Sanger sequencing and FISH; however, due to the extremely heterogeneous character of the different syndromic obesity forms, these techniques are becoming too expensive and time-consuming to screen for disease-causing mutations. Yet nowadays, with the advent of automated DNA sequencing instruments, the NGS technology provides a new method for molecular diagnosis allowing the sequencing of gene panels, whole exomes and even whole genomes.[144,221] Furthermore, also chromosomal microarrays are routinely utilized in most clinical genetics centers and are already replacing the previously used FISH analysis.[16,17] To conclude, syndromic obesity is likely to be a monogenic or contiguous gene disorder. Due to its great heterogeneity, nowadays molecular diagnostics is increasingly important in order to make a fast and accurate diagnosis, because an appropriate diagnosis based solely on clinical signs is difficult. Chromosomal microarrays and NGS technology are being introduced as important diagnostic methods. In the near future, it will even be possible to use whole-genome sequencing in order to detect both genomic mutations as well as translocations. However, understanding the clinical phenotypes still remains crucial for accurate counseling of families coping with syndromic obesity and appropriate follow-up of patients.

Conflict of interest

The authors declare no conflict of interest.

Author contribution

E.G., M.E.C.M. and W.V.H. wrote the manuscript and contributed to the discussion. They all read and approved the final version of the manuscript.

ORCID

E. Geets https://orcid.org/0000-0002-4057-0564

REFERENCES

1. Coleman DL, Hummel KP. The influence of genetic background on the expression of the obese (Ob) gene in the mouse. *Diabetologia*. 1973;9(4):287-293.
2. Stunkard AJ, Foch TT, Hrubec Z. A twin study of human obesity. *JAMA*. 1986;256(1):51-54.
3. Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. *Behav Genet*. 1997;27(4):325-351.
4. Luke A, Guo X, Adeyemo AA, et al. Heritability of obesity-related traits among Nigerians, Jamaicans and US black people. *Int J Obes Relat Metab Disord*. 2001;25(7):1034-1041.
5. Locke AE et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015;518(7538):197-206.
6. Zegers D, van Hul W, van Gaal LF, Beckers S. Monogenic and complex forms of obesity: insights from genetics reveal the leptin-melanocortin signaling pathway as a common player. *Crit Rev Eukaryot Gene Expr*. 2012;22(4):325-343.
7. Hinney A, Volckmar AL, Knoll N. Melanocortin-4 receptor in energy homeostasis and obesity pathogenesis. *Prog Mol Biol Transl Sci*. 2013;114:147-191.
8. Stutzmann F, Tan K, Vatin V, et al. Prevalence of melanocortin-4 receptor deficiency in Europeans and their age-dependent penetrance in multigenerational pedigrees. *Diabetes*. 2008;57(9):2511-2518.
9. Mutch DM, Clement K. Unraveling the genetics of human obesity. *PLoS Genet*. 2006;2(12):e188.
10. Ichihara S, Yamada Y. Genetic factors for human obesity. *Cell Mol Life Sci*. 2008;65(7–8):1086-1098.
11. Chung WK. An overview of mongenic and syndromic obesities in humans. *Pediatr Blood Cancer*. 2012;58(1):122-128.
12. Elena G et al. Prader-willi syndrome: clinical aspects. *J Obes*. 2012;2012:473941.
13. Angulo MA, Butler MG, Cataletto ME. Prader-Willi syndrome: a review of clinical, genetic, and endocrine findings. *J Endocrinol Investig*. 2015;38(12):1249-1263.
14. Holm VA, Cassidy SB, Butler MG, et al. Prader-Willi syndrome: consensus diagnostic criteria. *Pediatrics*. 1993;91(2):398-402.
15. Butler MG, Fischer W, Kibiryeva N, Bittel DC. Array comparative genomic hybridization (aCGH) analysis in Prader-Willi syndrome. *Am J Med Genet A*. 2008;146A(7):854-860.
16. Cheon CK. Genetics of Prader-Willi syndrome and Prader-Will-Like syndrome. *Ann Pediatr Endocrinol Metab*. 2016;21(3):126-135.
17. Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. *Genet Med*. 2012;14(1):10-26.
18. Izumi K, Housam R, Kapadia C, et al. Endocrine phenotype of 6q16.1-q21 deletion involving SIM1 and Prader-Willi syndrome-like features. *Am J Med Genet A*. 2013;161A(12):3137-3143.
19. Ohta T, Gray TA, Rogan PK, et al. Imprinting-mutation mechanisms in Prader-Willi syndrome. *Am J Hum Genet*. 1999;64(2):397-413.
20. Clayton-Smith J, Driscoll DJ, Waters MF, et al. Difference in methylation patterns within the D15S9 region of chromosome 15q11-13 in first cousins with Angelman syndrome and Prader-Willi syndrome. *Am J Med Genet*. 1993;47(5):683-686.
21. Jiang Y, Lev-Lehman E, Bressler J, Tsai TF, Beaudet AL. Genetics of Angelman syndrome. *Am J Hum Genet*. 1999;65(1):1-6.

22. Glenn CC, Driscoll DJ, Yang TP, Nicholls RD. Genomic imprinting: potential function and mechanisms revealed by the Prader-Willi and Angelman syndromes. *Mol Hum Reprod*. 1997;3(4):321-332.
23. Angelman H. 'Puppet' children. A report of three cases. *Dev Med Child Neurol*. 1965;7:681-688.
24. Williams CA, Driscoll DJ, Dagli AI. Clinical and genetic aspects of Angelman syndrome. *Genet Med*. 2010;12(7):385-395.
25. Schulze A, Hansen C, Skakkebæk NE, Brøndum-Nielsen K, Ledbetter DH, Tommerup N. Exclusion of SNRPN as a major determinant of Prader-Willi syndrome by a translocation breakpoint. *Nat Genet*. 1996;12(4):452-454.
26. Wirth J, Back E, Hüttenhofer A, et al. A translocation breakpoint cluster disrupts the newly defined 3′ end of the SNURF-SNRPN transcription unit on chromosome 15. *Hum Mol Genet*. 2001;10(3): 201-210.
27. Duker AL, Ballif BC, Bawle EV, et al. Paternally inherited microdeletion at 15q11.2 confirms a significant role for the SNORD116 C/D box snoRNA cluster in Prader-Willi syndrome. *Eur J Hum Genet*. 2010;18(11):1196-1201.
28. Runte M, Hüttenhofer A, Gross S, Kiefmann M, Horsthemke B, Buiting K. The IC-SNURF-SNRPN transcript serves as a host for multiple small nucleolar RNA species and as an antisense RNA for UBE3A. *Hum Mol Genet*. 2001;10(23):2687-2700.
29. Sahoo T, del Gaudio D, German JR, et al. Prader-Willi phenotype caused by paternal deficiency for the HBII-85 C/D box small nucleolar RNA cluster. *Nat Genet*. 2008;40(6):719-721.
30. Burger J et al. Familial interstitial 570 kbp deletion of the UBE3A gene region causing Angelman syndrome but not Prader-Willi syndrome. *Am J Med Genet*. 2002;111(3):233-237.
31. Runte M, Varon R, Horn D, Horsthemke B, Buiting K. Exclusion of the C/D box snoRNA gene cluster HBII-52 from a major role in Prader-Willi syndrome. *Hum Genet*. 2005;116(3):228-230.
32. de Smith AJ, Purmann C, Walters RG, et al. A deletion of the HBII-85 class of small nucleolar RNAs (snoRNAs) is associated with hyperphagia, obesity and hypogonadism. *Hum Mol Genet*. 2009;18(17): 3257-3265.
33. Bieth E, Eddiry S, Gaston V, et al. Highly restricted deletion of the SNORD116 region is implicated in Prader-Willi syndrome. *Eur J Hum Genet*. 2015;23(2):252-255.
34. Skryabin BV, Gubar LV, Seeger B, et al. Deletion of the MBII-85 snoRNA gene cluster in mice results in postnatal growth retardation. *PLoS Genet*. 2007;3(12):e235.
35. Ding F, Li HH, Zhang S, et al. SnoRNA Snord116 (Pwcr1/MBII-85) deletion causes growth deficiency and hyperphagia in mice. *PLoS One*. 2008;3(3):e1709.
36. Lassi G, Priano L, Maggi S, et al. Deletion of the Snord116/SNORD116 alters sleep in mice and patients with Prader-Willi syndrome. *Sleep*. 2016;39(3):637-644.
37. Qi Y, Purtell L, Fu M, et al. Snord116 is critical in the regulation of food intake and body weight. *Sci Rep*. 2016;6:18614.
38. Irizarry KA, Miller M, Freemark M, Haqq AM. Prader Willi syndrome: genetics, metabolomics, hormonal function, and new approaches to therapy. *Adv Pediatr Infect Dis*. 2016;63(1):47-77.
39. Myers SE, Carrel AL, Whitman BY, Allen DB. Sustained benefit after 2 years of growth hormone on body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome. *J Pediatr*. 2000;137(1):42-49.
40. Burman P, Ritzen EM, Lindgren AC. Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. *Endocr Rev*. 2001;22(6):787-799.
41. Senda M, Ogawa S, Nako K, Okamura M, Sakamoto T, Ito S. The glucagon-like peptide-1 analog liraglutide suppresses ghrelin and controls diabetes in a patient with Prader-Willi syndrome. *Endocr J*. 2012;59(10):889-894.
42. Cyganek K, Koblik T, Kozek E, Wojcik M, Starzyk J, Malecki MT. Liraglutide therapy in Prader-Willi syndrome. *Diabet Med*. 2011;28(6): 755-756.
43. Fintini D, Grugni G, Brufani C, Bocchini S, Cappa M, Crinò A. Use of GLP-1 receptor agonists in Prader-Willi syndrome: report of six cases. *Diabetes Care*. 2014;37(4):e76-e77.
44. De Waele K et al. Long-acting octreotide treatment causes a sustained decrease in ghrelin concentrations but does not affect weight, behaviour and appetite in subjects with Prader-Willi syndrome. *Eur J Endocrinol*. 2008;159(4):381-388.
45. Einfeld SL, Smith E, McGregor I, et al. A double-blind randomized controlled trial of oxytocin nasal spray in Prader Willi syndrome. *Am J Med Genet A*. 2014;164A(9):2232-2239.
46. Kuppens RJ, Donze SH, Hokken-Koelega AC. Promising effects of oxytocin on social and food-related behaviour in young children with Prader-Willi syndrome: a randomized, double-blind, controlled crossover trial. *Clin Endocrinol*. 2016;85:979-987.
47. ClinicalTrials.gov: A service of the U.S. National Institutes of Health. https://clinicaltrials.gov. Accessed October 2016.
48. Shapira NA, Lessig MC, He AG, James GA, Driscoll DJ, Liu Y. Satiety dysfunction in Prader-Willi syndrome demonstrated by fMRI. *J Neurol Neurosurg Psychiatry*. 2005;76(2):260-262.
49. Butler MG, Theodoro MF, Bittel DC, Donnelly JE. Energy expenditure and physical activity in Prader-Willi syndrome: comparison with obese subjects. *Am J Med Genet A*. 2007;143A(5):449-459.
50. Alsaif M, Elliot SA, MacKenzie ML, Prado CM, Field CJ, Haqq AM. Energy metabolism profile in individuals with Prader-Willi syndrome and implications for clinical management: a systematic review. *Adv Nutr*. 2017;8(6):905-915.
51. Papavramidis ST, Kotidis EV, Gamvros O. Prader-Willi syndrome-associated obesity treated by biliopancreatic diversion with duodenal switch. Case report and literature review. *J Pediatr Surg*. 2006;41(6):1153-1158.
52. Scheimann AO, Butler MG, Gourash L, Cuffari C, Klish W. Critical analysis of bariatric procedures in Prader-Willi syndrome. *J Pediatr Gastroenterol Nutr*. 2008;46(1):80-83.
53. Fonkalsrud EW, Bray G. Vagotomy for treatment of obesity in childhood due to Prader-Willi syndrome. *J Pediatr Surg*. 1981;16(6): 888-889.
54. Hellings JA, Warnock JK. Self-injurious behavior and serotonin in Prader-Willi syndrome. *Psychopharmacol Bull*. 1994;30(2):245-250.
55. Kim Y, Lee HM, Xiong Y, et al. Targeting the histone methyltransferase G9a activates imprinted genes and improves survival of a mouse model of Prader-Willi syndrome. *Nat Med*. 2017;23(2):213-222.
56. Spikol ED et al. Zebrafish models of Prader-Willi syndrome: fast track to pharmacotherapeutics. *Diseases*. 2016;4(1):13.
57. Faivre L, Cormier-Daire V, Lapierre JM, et al. Deletion of the SIM1 gene (6q16.2) in a patient with a Prader-Willi-like phenotype. *J Med Genet*. 2002;39(8):594-596.
58. Bonaglia MC, Ciccone R, Gimelli G, et al. Detailed phenotype-genotype study in five patients with chromosome 6q16 deletion: narrowing the critical region for Prader-Willi-like phenotype. *Eur J Hum Genet*. 2008;16(12):1443-1449.
59. Rosenfeld JA, Amrom D, Andermann E, et al. Genotype-phenotype correlation in interstitial 6q deletions: a report of 12 new cases. *Neurogenetics*. 2012;13(1):31-47.
60. Tsuyusaki Y, Yoshihashi H, Furuya N, et al. 1p36 deletion syndrome associated with Prader-Willi-like phenotype. *Pediatr Int*. 2010;52(4): 547-550.
61. Martens K, Derua R, Meulemans S, et al. PREPL: a putative novel oligopeptidase propelled into the limelight. *Biol Chem*. 2006;387(7): 879-883.
62. D'Angelo CS, Kohl I, Varela MC, et al. Obesity with associated developmental delay and/or learning disability in patients exhibiting additional features: report of novel pathogenic copy number variants. *Am J Med Genet A*. 2013;161A(3):479-486.
63. Ben-Abdallah-Bouhjar I, Hannachi H, Labalme A, et al. Chromosomal microarray analysis of functional Xq27-qter disomy and deletion 3p26.3 in a boy with Prader-Willi like features and hypotonia. *Eur J Med Genet*. 2012;55(8–9):461-465.
64. Turleau C et al. 6q1 monosomy: a distinctive syndrome. *Clin Genet*. 1988;34(1):38-42.
65. Villa A, Urioste M, Bofarull JM, Martínez-Frías ML. De novo interstitial deletion q16.2q21 on chromosome 6. *Am J Med Genet*. 1995; 55(3):379-383.

66. Gilhuis HJ et al. Interstitial 6q deletion with a Prader-Willi-like phenotype: a new case and review of the literature. *Eur J Paediatr Neurol*. 2000;4(1):39-43.
67. Varela MC, Simões-Sato AY, Kim CA, Bertola DR, de Castro CIE, Koiffmann CP. A new case of interstitial 6q16.2 deletion in a patient with Prader-Willi-like phenotype and investigation of SIM1 gene deletion in 87 patients with syndromic obesity. *Eur J Med Genet*. 2006;49(4):298-305.
68. Klein OD, Cotter PD, Moore MW, et al. Interstitial deletions of chromosome 6q: genotype-phenotype correlation utilizing array CGH. *Clin Genet*. 2007;71(3):260-266.
69. Wang JC, Turner L, Lomax B, Eydoux P. A 5-Mb microdeletion at 6q16.1-q16.3 with SIM gene deletion and obesity. *Am J Med Genet A*. 2008;146A(22):2975-2978.
70. Spreiz A, Müller D, Zotter S, et al. Phenotypic variability of a deletion and duplication 6q16.1 --> q21 due to a paternal balanced ins(7;6)(p15;q16.1q21). *Am J Med Genet A*. 2010;152A(11):2762-2767.
71. Vignoli A, Scornavacca GF, Peron A, la Briola F, Canevini MP. Interstitial 6q microdeletion syndrome and epilepsy: a new patient and review of the literature. *Am J Med Genet A*. 2013;161A(8):2009-2015.
72. El Khattabi L et al. Incomplete penetrance and phenotypic variability of 6q16 deletions including SIM1. *Eur J Hum Genet*. 2015;23(8):1010-1018.
73. Stein CK, Stred SE, Thomson LL, Smith FC, Hoo JJ. Interstitial 6q deletion and Prader-Willi-like phenotype. *Clin Genet*. 1996;49(6):306-310.
74. Le Caignec C et al. Interstitial 6q deletion: clinical and array CGH characterisation of a new patient. *Eur J Med Genet*. 2005;48(3):339-345.
75. Cormier-Daire V, Molinari F, Rio M, et al. Cryptic terminal deletion of chromosome 9q34: a novel cause of syndromic obesity in childhood? *J Med Genet*. 2003;40(4):300-303.
76. Rocha CF, Paiva CL. Prader-Willi-like phenotypes: a systematic review of their chromosomal abnormalities. *Genet Mol Res*. 2014;13(1):2290-2298.
77. Holder JL, Butte NF, Zinn AR. Profound obesity associated with a balanced translocation that disrupts the SIM1 gene. *Hum Mol Genet*. 2000;9(1):101-108.
78. Bonnefond A, Raimondo A, Stutzmann F, et al. Loss-of-function mutations in SIM1 contribute to obesity and Prader-Willi-like features. *J Clin Invest*. 2013;123(7):3037-3041.
79. Ramachandrappa S, Raimondo A, Cali AMG, et al. Rare variants in single-minded 1 (SIM1) are associated with severe obesity. *J Clin Invest*. 2013;123(7):3042-3050.
80. Montagne L, Raimondo A, Delobel B, et al. Identification of two novel loss-of-function SIM1 mutations in two overweight children with developmental delay. *Obesity*. 2014;22(12):2621-2624.
81. Zegers D, Beckers S, Hendrickx R, et al. Mutation screen of the SIM1 gene in pediatric patients with early-onset obesity. *Int J Obes*. 2014;38(7):1000-1004.
82. Wentzel C, Lynch SA, Stattin EL, Sharkey FH, Annerén G, Thuresson AC. Interstitial deletions at 6q14.1-q15 associated with obesity, developmental delay and a distinct clinical phenotype. *Mol Syndromol*. 2010;1(2):75-81.
83. Asai M, Ramachandrappa S, Joachim M, et al. Loss of function of the melanocortin 2 receptor accessory protein 2 is associated with mammalian obesity. *Science*. 2013;341(6143):275-278.
84. Geets E, Zegers D, Beckers S, et al. Copy number variation (CNV) analysis and mutation analysis of the 6q14.1-6q16.3 genes SIM1 and MRAP2 in Prader Willi like patients. *Mol Genet Metab*. 2016;117(3):383-388.
85. Kasher PR, Schertz KE, Thomas M, et al. Small 6q16.1 deletions encompassing POU3F2 cause susceptibility to obesity and variable developmental delay with intellectual disability. *Am J Hum Genet*. 2016;98(2):363-372.
86. Schaaf CP, Gonzalez-Garay ML, Xia F, et al. Truncating mutations of MAGEL2 cause Prader-Willi phenotypes and autism. *Nat Genet*. 2013;45(11):1405-1408.
87. Soden SE et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci Transl Med*. 2014;6(265):265ra168.
88. Bischof JM, Stewart CL, Wevrick R. Inactivation of the mouse Magel2 gene results in growth abnormalities similar to Prader-Willi syndrome. *Hum Mol Genet*. 2007;16(22):2713-2719.
89. Buiting K, di Donato N, Beygo J, et al. Clinical phenotypes of MAGEL2 mutations and deletions. *Orphanet J Rare Dis*. 2014;9:40.
90. Kanber D, Giltay J, Wieczorek D, et al. A paternal deletion of MKRN3, MAGEL2 and NDN does not result in Prader-Willi syndrome. *Eur J Hum Genet*. 2009;17(5):582-590.
91. Forsythe E, Beales PL. Bardet-Biedl Syndrome. In: Pagon RA et al., eds. *GeneReviews(R)*. University of Washington, Seattle (WA); 1993.
92. Gunay-Aygun M, Cassidy SB, Nicholls RD. Prader-Willi and other syndromes associated with obesity and mental retardation. *Behav Genet*. 1997;27(4):307-324.
93. M'Hamdi O, Ouertani I, Chaabouni-Bouhamed H. Update on the genetics of bardet-biedl syndrome. *Mol Syndromol*. 2014;5(2):51-56.
94. Braun JJ, Noblet V, Durand M, et al. Olfaction evaluation and correlation with brain atrophy in Bardet-Biedl syndrome. *Clin Genet*. 2014;86(6):521-529.
95. Khan SA, Muhammad N, Khan MA, Kamal A, Rehman ZU, Khan S. Genetics of human Bardet-Biedl syndrome, an updates. *Clin Genet*. 2016;90(1):3-15.
96. Suspitsin EN, Imyanitov EN. Bardet-Biedl Syndrome. *Mol Syndromol*. 2016;7(2):62-71.
97. Klein D, Ammann F. The syndrome of Laurence-Moon-Bardet-Biedl and allied diseases in Switzerland. Clinical, genetic and epidemiological studies. *J Neurol Sci*. 1969;9(3):479-513.
98. Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. *J Med Genet*. 1999;36(6):437-446.
99. Putoux A, Attie-Bitach T, Martinovic J, Gubler MC. Phenotypic variability of Bardet-Biedl syndrome: focusing on the kidney. *Pediatr Nephrol*. 2012;27(1):7-15.
100. Wang Y, Garraoui A, Zeng L, et al. FBN3 gene involved in pathogenesis of a Chinese family with Bardet-Biedl syndrome. *Oncotarget*. 2017;8(49):86718-86725.
101. Yildiz Bolukbasi E et al. Homozygous mutation in CEP19, a gene mutated in morbid obesity, in Bardet-Biedl syndrome with predominant postaxial polydactyly. *J Med Genet*. 2018;55(3):189-197.
102. Katsanis N. The oligogenic properties of Bardet-Biedl syndrome. *Hum Mol Genet*. 2004;13 Spec No 1:R65-R71.
103. Stoetzel C, Laurier V, Faivre L, et al. BBS8 is rarely mutated in a cohort of 128 Bardet-Biedl syndrome families. *J Hum Genet*. 2006;51(1):81-84.
104. Katsanis N, Ansley SJ, Badano JL, et al. Triallelic inheritance in Bardet-Biedl syndrome, a Mendelian recessive disorder. *Science*. 2001;293(5538):2256-2259.
105. Katsanis N, Eichers ER, Ansley SJ, et al. BBS4 is a minor contributor to Bardet-Biedl syndrome and may also participate in triallelic inheritance. *Am J Hum Genet*. 2002;71(1):22-29.
106. Badano JL, Kim JC, Hoskins BE, et al. Heterozygous mutations in BBS1, BBS2 and BBS6 have a potential epistatic effect on Bardet-Biedl patients with two mutations at a second BBS locus. *Hum Mol Genet*. 2003;12(14):1651-1659.
107. Beales PL, Badano JL, Ross AJ, et al. Genetic interaction of BBS1 mutations with alleles at other BBS loci can result in non-Mendelian Bardet-Biedl syndrome. *Am J Hum Genet*. 2003;72(5):1187-1199.
108. Hjortshoj TD et al. Bardet-Biedl syndrome in Denmark--report of 13 novel sequence variations in six genes. *Hum Mutat*. 2010;31(4):429-436.
109. Fauser S, Munz M, Besch D. Further support for digenic inheritance in Bardet-Biedl syndrome. *J Med Genet*. 2003;40(8):e104.
110. Mykytyn K, Nishimura DY, Searby CC, et al. Evaluation of complex inheritance involving the most common Bardet-Biedl syndrome locus (BBS1). *Am J Hum Genet*. 2003;72(2):429-437.
111. Hichri H, Stoetzel C, Laurier V, et al. Testing for triallelism: analysis of six BBS genes in a Bardet-Biedl syndrome family cohort. *Eur J Hum Genet*. 2005;13(5):607-616.

112. Laurier V, Stoetzel C, Muller J, et al. Pitfalls of homozygosity mapping: an extended consanguineous Bardet-Biedl syndrome family with two mutant genes (BBS2, BBS10), three mutations, but no triallelism. *Eur J Hum Genet*. 2006;14(11):1195-1203.
113. Smaoui N, Chaabouni M, Sergeev YV, et al. Screening of the eight BBS genes in Tunisian families: no evidence of triallelism. *Invest Ophthalmol Vis Sci*. 2006;47(8):3487-3495.
114. Abu-Safieh L, al-Anazi S, al-Abdi L, et al. In search of triallelism in Bardet-Biedl syndrome. *Eur J Hum Genet*. 2012;20(4):420-427.
115. Estrada-Cuzcano A, Koenekoop RK, Senechal A, et al. BBS1 mutations in a wide spectrum of phenotypes ranging from nonsyndromic retinitis pigmentosa to Bardet-Biedl syndrome. *Arch Ophthalmol*. 2012;130(11):1425-1432.
116. Billingsley G, Deveault C, Heon E. BBS mutational analysis: a strategic approach. *Ophthalmic Genet*. 2011;32(3):181-187.
117. Janssen S, Ramaswami G, Davis EE, et al. Mutation analysis in Bardet-Biedl syndrome by DNA pooling and massively parallel resequencing in 105 individuals. *Hum Genet*. 2011;129(1):79-90.
118. Redin C, Le Gras S, Mhamdi O, et al. Targeted high-throughput sequencing for diagnosis of genetically heterogeneous diseases: efficient mutation detection in Bardet-Biedl and Alstrom syndromes. *J Med Genet*. 2012;49(8):502-512.
119. Gonzalez-Del Pozo M et al. Deciphering intrafamilial phenotypic variability by exome sequencing in a Bardet-Biedl family. *Mol Genet Genomic Med*. 2014;2(2):124-133.
120. Ece Solmaz A, Onay H, Atik T, et al. Targeted multi-gene panel testing for the diagnosis of Bardet Biedl syndrome: identification of nine novel mutations across BBS1, BBS2, BBS4, BBS7, BBS9, BBS10 genes. *Eur J Med Genet*. 2015;58(12):689-694.
121. Daniels AB, Sandberg MA, Chen J, Weigel-DiFranco C, Fielding Hejtmancic J, Berson EL. Genotype-phenotype correlations in Bardet-Biedl syndrome. *Arch Ophthalmol*. 2012;130(7):901-907.
122. Dervisoglu E, Isgoren S, Kasgari D, Demir H, Yilmaz A. Obesity control and low protein diet preserve or even improve renal functions in Bardet-Biedl syndrome: a report of two cases. *Med Sci Monit*. 2011; 17(1):CS12-CS14.
123. Alstrom CH et al. Retinal degeneration combined with obesity, diabetes mellitus and neurogenous deafness: a specific syndrome (not hitherto described) distinct from the Laurence-Moon-Bardet-Biedl syndrome: a clinical, endocrinological and genetic examination based on a large pedigree. *Acta Psychiatr Neurol Scand Suppl*. 1959; 129:1-35.
124. Alvarez-Satta M, Castro-Sanchez S, Valverde D. Alstrom syndrome: current perspectives. *Appl Clin Genet*. 2015;8:171-179.
125. Orpha.net: Alström syndrome. http://www.orpha.net/consor/cgi-bin/Disease_Search_Simple.php?lng=EN&diseaseGroup=Alstrom. Accessed October 10, 2016.
126. Marshall JD et al. Alstrom Syndrome. In: Pagon RA et al., eds. *GeneReviews(R)*. University of Washington, Seattle (WA); 1993.
127. Marshall JD, Bronson RT, Collin GB, et al. New Alstrom syndrome phenotypes based on the evaluation of 182 cases. *Arch Intern Med*. 2005;165(6):675-683.
128. Pereiro I, Hoskins BE, Marshall JD, et al. Arrayed primer extension technology simplifies mutation detection in Bardet-Biedl and Alstrom syndrome. *Eur J Hum Genet*. 2011;19(4):485-488.
129. Aliferis K, Hellé S, Gyapay G, et al. Differentiating Alstrom from Bardet-Biedl syndrome (BBS) using systematic ciliopathy genes sequencing. *Ophthalmic Genet*. 2012;33(1):18-22.
130. OMIM: Alstrom syndrome; ALMS. http://www.omim.org/entry/203800. Accessed October 10, 2016.
131. Ozanturk A et al. The phenotypic and molecular genetic spectrum of Alstrom syndrome in 44 Turkish kindreds and a literature review of Alstrom syndrome in Turkey. *J Hum Genet*. 2015;60(1):1-9.
132. Marshall JD, Muller J, Collin GB, et al. Alstrom syndrome: mutation spectrum of ALMS1. *Hum Mutat*. 2015;36(7):660-668.
133. Sanyoura M, Woudstra C, Halaby G, et al. A novel ALMS1 splice mutation in a non-obese juvenile-onset insulin-dependent syndromic diabetic patient. *Eur J Hum Genet*. 2014;22(1):140-143.
134. Bond J, Flintoff K, Higgins J, et al. The importance of seeking ALMS1 mutations in infants with dilated cardiomyopathy. *J Med Genet*. 2005;42(2):e10.
135. Lee NC, Marshall JD, Collin GB, et al. Caloric restriction in Alstrom syndrome prevents hyperinsulinemia. *Am J Med Genet A*. 2009; 149A(4):666-668.
136. Taskesen M et al. Novel Alu retrotransposon insertion leading to Alstrom syndrome. *Hum Genet*. 2012;131(3):407-413.
137. Hearn T, Renforth GL, Spalluto C, et al. Mutation of ALMS1, a large gene with a tandem repeat encoding 47 amino acids, causes Alstrom syndrome. *Nat Genet*. 2002;31(1):79-83.
138. Collin GB, Cyr E, Bronson R, et al. Alms1-disrupted mice recapitulate human Alstrom syndrome. *Hum Mol Genet*. 2005;14(16):2323-2333.
139. Jagger D, Collin G, Kelly J, et al. Alstrom syndrome protein ALMS1 localizes to basal bodies of cochlear hair cells and regulates cilium-dependent planar cell polarity. *Hum Mol Genet*. 2011;20(3): 466-481.
140. Girard D, Petrovsky N. Alstrom syndrome: insights into the pathogenesis of metabolic disorders. *Nat Rev Endocrinol*. 2011;7(2):77-88.
141. Lodh S, Hostelley TL, Leitch CC, O'Hare EA, Zaghloul NA. Differential effects on beta-cell mass by disruption of Bardet-Biedl syndrome or Alstrom syndrome genes. *Hum Mol Genet*. 2016;25(1):57-68.
142. Katagiri S, Yoshitake K, Akahori M, et al. Whole-exome sequencing identifies a novel ALMS1 mutation (p.Q2051X) in two Japanese brothers with Alstrom syndrome. *Mol Vis*. 2013;19:2393-2406.
143. Long PA, Evans JM, Olson TM. Exome sequencing establishes diagnosis of Alstrom syndrome in an infant presenting with non-syndromic dilated cardiomyopathy. *Am J Med Genet A*. 2015; 167A(4):886-890.
144. Albuquerque D, Stice E, Rodríguez-López R, Manco L, Nóbrega C. Current review of genetics of human obesity: from molecular mechanisms to an evolutionary perspective. *Mol Gen Genomics*. 2015; 290(4):1191-1221.
145. He X, Zhang J. Toward a molecular understanding of pleiotropy. *Genetics*. 2006;173(4):1885-1891.
146. Strachan T, Read A. *Human Molecular Genetics*. 4th ed. New York, NY: Garland Science, Taylor & Francis Group; 2011.
147. Driscoll DJ et al. Prader-Willi Syndrome. In: Adam MP et al., eds. *GeneReviews(R)*. University of Washington, Seattle (WA); 1993.
148. Gunay-Aygun M, Schwartz S, Heeger S, O'Riordan MA, Cassidy SB. The changing purpose of Prader-Willi syndrome clinical diagnostic criteria and proposed revised criteria. *Pediatrics*. 2001;108(5):E92.
149. Buiting K. Prader-Willi syndrome and Angelman syndrome. *Am J Med Genet C Semin Med Genet*. 2010;154C(3):365-376.
150. Tai TS, Lin SY, Sheu WH. Metabolic effects of growth hormone therapy in an Alstrom syndrome patient. *Horm Res*. 2003;60(6):297-301.
151. Goerler H, Warnecke G, Winterhalter M, et al. Heart-lung transplantation in a 14-year-old boy with Alstrom syndrome. *J Heart Lung Transplant*. 2007;26(11):1217-1218.
152. Sinha SK, Bhangoo A, Anhalt H, et al. Effect of metformin and rosiglitazone in a prepubertal boy with Alstrom syndrome. *J Pediatr Endocrinol Metab*. 2007;20(9):1045-1052.
153. Miller RW, Fraumeni JF Jr, Manning MD. Association of Wilms's tumor with Aniridia, hemihypertrophy and other congenital malformations. *N Engl J Med*. 1964;270:922-927.
154. Orpha.net: WAGR syndrome. http://www.orpha.net/consor/cgi-bin/Disease_Search_Simple.php?lng=EN&diseaseGroup=WAGR. Accessed October 10, 2016.
155. Han JC. Rare syndromes and common variants of the brain-derived neurotrophic factor gene in human obesity. *Prog Mol Biol Transl Sci*. 2016;140:75-95.
156. Marlin S, Couet D, Lacombe D, Cessans C, Bonneau D. Obesity: a new feature of WAGR (del 11p) syndrome. *Clin Dysmorphol*. 1994; 3(3):255-257.
157. Tiberio G, Digilio MC, Giannotti A. Obesity and WAGR syndrome. *Clin Dysmorphol*. 2000;9(1):63-64.
158. Amor DJ. Morbid obesity and hyperphagia in the WAGR syndrome. *Clin Dysmorphol*. 2002;11(1):73-74.
159. Gul D et al. Third case of WAGR syndrome with severe obesity and constitutional deletion of chromosome (11)(p12p14). *Am J Med Genet*. 2002;107(1):70-71.
160. Fischbach BV, Trout KL, Lewis J, Luis CA, Sika M. WAGR syndrome: a clinical review of 54 cases. *Pediatrics*. 2005;116(4):984-988.

161. Jung R, Rauch A, Salomons GS, et al. Clinical, cytogenetic and molecular characterization of a patient with combined succinic semialdehyde dehydrogenase deficiency and incomplete WAGR syndrome with obesity. *Mol Genet Metab*. 2006;88(3):256-260.
162. Han JC, Liu QR, Jones MP, et al. Brain-derived neurotrophic factor and obesity in the WAGR syndrome. *N Engl J Med*. 2008;359(9):918-927.
163. Justice ED, Barnum SJ, Kidd T. The WAGR syndrome gene PRRG4 is a functional homologue of the commissureless axon guidance gene. *PLoS Genet*. 2017;13(8):e1006865.
164. Xu S, Han JC, Morales A, Menzie CM, Williams K, Fan YS. Characterization of 11p14-p12 deletion in WAGR syndrome by array CGH for identifying genes contributing to mental retardation and autism. *Cytogenet Genome Res*. 2008;122(2):181-187.
165. Glaser T, Jepeal L, Edwards JG, Young SR, Favor J, Maas RL. PAX6 gene dosage effect in a family with congenital cataracts, aniridia, anophthalmia and central nervous system defects. *Nat Genet*. 1994;7(4):463-471.
166. Yasuda T, Kajimoto Y, Fujitani Y, et al. PAX6 mutation as a genetic factor common to aniridia and glucose intolerance. *Diabetes*. 2002;51(1):224-230.
167. Mitchell TN, Free SL, Williamson KA, et al. Polymicrogyria and absence of pineal gland due to PAX6 mutation. *Ann Neurol*. 2003;53(5):658-663.
168. Talamillo A, Quinn JC, Collinson JM, et al. Pax6 regulates regional development and neuronal migration in the cerebral cortex. *Dev Biol*. 2003;255(1):151-163.
169. Barde YA. The nerve growth factor family. *Prog Growth Factor Res*. 1990;2(4):237-248.
170. McAllister AK. Neurotrophins and neuronal differentiation in the central nervous system. *Cell Mol Life Sci*. 2001;58(8):1054-1060.
171. Lapchak PA, Hefti F. BDNF and NGF treatment in lesioned rats: effects on cholinergic function and weight gain. *Neuroreport*. 1992;3(5):405-408.
172. Lyons WE, Mamounas LA, Ricaurte GA, et al. Brain-derived neurotrophic factor-deficient mice develop aggressiveness and hyperphagia in conjunction with brain serotonergic abnormalities. *Proc Natl Acad Sci USA*. 1999;96(26):15239-15244.
173. Rios M, Fan G, Fekete C, et al. Conditional deletion of brain-derived neurotrophic factor in the postnatal brain leads to obesity and hyperactivity. *Mol Endocrinol*. 2001;15(10):1748-1757.
174. Unger TJ, Calderon GA, Bradley LC, Sena-Esteves M, Rios M. Selective deletion of Bdnf in the ventromedial and dorsomedial hypothalamus of adult mice results in hyperphagic behavior and obesity. *J Neurosci*. 2007;27(52):14265-14274.
175. Xu B, Goulding EH, Zang K, et al. Brain-derived neurotrophic factor regulates energy balance downstream of melanocortin-4 receptor. *Nat Neurosci*. 2003;6(7):736-742.
176. Bariohay B, Roux J, Tardivel C, Trouslard J, Jean A, Lebrun B. Brain-derived neurotrophic factor/tropomyosin-related kinase receptor type B signaling is a downstream effector of the brainstem melanocortin system in food intake control. *Endocrinology*. 2009;150(6):2646-2653.
177. Han JC, Thurm A, Golden Williams C, et al. Association of brain-derived neurotrophic factor (BDNF) haploinsufficiency with lower adaptive behaviour and reduced cognitive functioning in WAGR/11p13 deletion syndrome. *Cortex*. 2013;49(10):2700-2710.
178. Clericuzio C, Hingorani M, Crolla JA, van Heyningen V, Verloes A. Clinical utility gene card for: WAGR syndrome. *Eur J Hum Genet*. 2011;19(4).
179. Dome JS, Huff V. Wilms Tumor Predisposition. In: Pagon RA et al., eds. *GeneReviews(R)*. University of Washington, Seattle (WA); 1993.
180. Muto R, Yamamori S, Ohashi H, Osawa M. Prediction by FISH analysis of the occurrence of Wilms tumor in aniridia patients. *Am J Med Genet*. 2002;108(4):285-289.
181. Hingorani M, Moore A. Aniridia. In: Pagon RA et al., eds. *GeneReviews(R)*. University of Washington, Seattle (WA); 1993.
182. De Grande V et al. Artificial iris-intraocular lens implantation for traumatic aniridia and aphakia assisted by silicone oil retention sutures. *J Cataract Refract Surg*. 2012;38(11):2045-2048.
183. Bachmann-Gagescu R, Mefford HC, Cowan C, et al. Recurrent 200-kb deletions of 16p11.2 that include the SH2B1 gene are associated with developmental delay and obesity. *Genet Med*. 2010;12(10):641-647.
184. Weiss LA, Shen Y, Korn JM, et al. Association between microdeletion and microduplication at 16p11.2 and autism. *N Engl J Med*. 2008;358(7):667-675.
185. Kumar RA, KaraMohamed S, Sudi J, et al. Recurrent 16p11.2 microdeletions in autism. *Hum Mol Genet*. 2008;17(4):628-638.
186. Marshall CR, Noor A, Vincent JB, et al. Structural variation of chromosomes in autism spectrum disorder. *Am J Hum Genet*. 2008;82(2):477-488.
187. McCarthy SE et al. Microduplications of 16p11.2 are associated with schizophrenia. *Nat Genet*. 2009;41(11):1223-1227.
188. Zufferey F, Sherr EH, Beckmann ND, et al. A 600 kb deletion syndrome at 16p11.2 leads to energy imbalance and neuropsychiatric disorders. *J Med Genet*. 2012;49(10):660-668.
189. Bochukova EG, Huang N, Keogh J, et al. Large, rare chromosomal deletions associated with severe early-onset obesity. *Nature*. 2010;463(7281):666-670.
190. Walters RG, Jacquemont S, Valsesia A, et al. A new highly penetrant form of obesity due to deletions on chromosome 16p11.2. *Nature*. 2010;463(7281):671-675.
191. Shinawi M, Liu P, Kang SHL, et al. Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size. *J Med Genet*. 2010;47(5):332-341.
192. Bijlsma EK, Gijsbers ACJ, Schuurs-Hoeijmakers JHM, et al. Extending the phenotype of recurrent rearrangements of 16p11.2: deletions in mentally retarded patients without autism and in normal individuals. *Eur J Med Genet*. 2009;52(2–3):77-87.
193. Mullen SA, Carvill GL, Bellows S, et al. Copy number variants are frequent in genetic generalized epilepsy with intellectual disability. *Neurology*. 2013;81(17):1507-1514.
194. Steinman KJ, Spence SJ, Ramocki MB, et al. 16p11.2 deletion and duplication: characterizing neurologic phenotypes in a large clinically ascertained cohort. *Am J Med Genet A*. 2016;170(11):2943-2955.
195. Olson H, Shen Y, Avallone J, et al. Copy number variation plays an important role in clinical epilepsy. *Ann Neurol*. 2014;75(6):943-958.
196. Rosenfeld JA, Coppinger J, Bejjani BA, et al. Speech delays and behavioral problems are the predominant features in individuals with developmental delays and 16p11.2 microdeletions and microduplications. *J Neurodev Disord*. 2010;2(1):26-38.
197. D'Angelo CS, Koiffmann CP. Copy number variants in obesity-related syndromes: review and perspectives on novel molecular approaches. *J Obes*. 2012;2012:845480.
198. Hanson E, Nasir RH, Fong A, et al. Cognitive and behavioral characterization of 16p11.2 deletion syndrome. *J Dev Behav Pediatr*. 2010;31(8):649-657.
199. Ballif BC, Hornor SA, Jenkins E, et al. Discovery of a previously unrecognized microdeletion syndrome of 16p11.2-p12.2. *Nat Genet*. 2007;39(9):1071-1073.
200. Sampson MG, Coughlin CR II, Kaplan P, et al. Evidence for a recurrent microdeletion at chromosome 16p11.2 associated with congenital anomalies of the kidney and urinary tract (CAKUT) and Hirschsprung disease. *Am J Med Genet A*. 2010;152A(10):2618-2622.
201. OMIM: Chromosome 16p11.2 deletion syndrome, 220-KB. http://omim.org/entry/613444. Accessed October 10, 2016.
202. Thorleifsson G, Walters GB, Gudbjartsson DF, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet*. 2009;41(1):18-24.
203. Barge-Schaapveld DQ, Maas SM, Polstra A, Knegt LC, Hennekam RC. The atypical 16p11.2 deletion: a not so atypical microdeletion syndrome? *Am J Med Genet A*. 2011;155A(5):1066-1072.
204. Miller DT et al. 16p11.2 Recurrent Microdeletion. In: Pagon RA et al., eds. *GeneReviews(R)*. University of Washington, Seattle (WA); 1993.
205. Aerts E, Beckers S, Zegers D, et al. Genetic and structural variation in the SH2B1 gene in the Belgian population. *Mol Genet Metab*. 2015;115(4):193-198.

206. Rui L, Mathews LS, Hotta K, Gustafson TA, Carter-Su C. Identification of SH2-Bbeta as a substrate of the tyrosine kinase JAK2 involved in growth hormone signaling. *Mol Cell Biol*. 1997;17(11):6633-6644.
207. Duan C, Li M, Rui L. SH2-B promotes insulin receptor substrate 1 (IRS1)- and IRS2-mediated activation of the phosphatidylinositol 3-kinase pathway in response to leptin. *J Biol Chem*. 2004;279(42):43684-43691.
208. Li Z, Zhou Y, Carter-Su C, Myers MG Jr, Rui L. SH2B1 enhances leptin signaling by both Janus kinase 2 Tyr813 phosphorylation-dependent and -independent mechanisms. *Mol Endocrinol*. 2007;21(9):2270-2281.
209. Ren D, Li M, Duan C, Rui L. Identification of SH2-B as a key regulator of leptin sensitivity, energy balance, and body weight in mice. *Cell Metab*. 2005;2(2):95-104.
210. Duan C, Yang H, White MF, Rui L. Disruption of the SH2-B gene causes age-dependent insulin resistance and glucose intolerance. *Mol Cell Biol*. 2004;24(17):7435-7443.
211. Willer CJ, Speliotes EK, Loos RJ, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet*. 2009;41(1):25-34.
212. Beckers S, Zegers D, van Gaal LF, van Hul W. Replication of the SH2B1 rs7498665 association with obesity in a Belgian study population. *Obes Facts*. 2011;4(6):473-477.
213. Doche ME, Bochukova EG, Su HW, et al. Human SH2B1 mutations are associated with maladaptive behaviors and obesity. *J Clin Invest*. 2012;122(12):4732-4736.
214. Volckmar AL, Bolze F, Jarick I, et al. Mutation screen in the GWAS derived obesity gene SH2B1 including functional analyses of detected variants. *BMC Med Genet*. 2012;5:65.
215. Pearce LR, Joe R, Doche ME, et al. Functional characterization of obesity-associated variants involving the alpha and beta isoforms of human SH2B1. *Endocrinology*. 2014;155(9):3219-3226.
216. Zheng Z, Hong L, Huang X, et al. Screening for coding variants in FTO and SH2B1 genes in Chinese patients with obesity. *PLoS One*. 2013;8(6):e67039.
217. Loviglio MN et al. Chromosomal contacts connect loci associated with autism, BMI and head circumference phenotypes. *Mol Psychiatry*. 2017;22(6):836-849.
218. Myers SM, Johnson CP, American Academy of Pediatrics Council on Children With Disabilities. Management of children with autism spectrum disorders. *Pediatrics*. 2007;120(5):1162-1182.
219. Cassidy SB, Driscoll DJ. Prader-Willi syndrome. *Eur J Hum Genet*. 2009;17(1):3-13.
220. Severi G, Bernardini L, Briuglia S, et al. New patients with Temple syndrome caused by 14q32 deletion: genotype-phenotype correlations and risk of thyroid cancer. *Am J Med Genet A*. 2016;170A(1):162-169.
221. Marian AJ. Molecular genetic studies of complex phenotypes. *Transl Res*. 2012;159(2):64-79.

How to cite this article: Geets E, Meuwissen MEC, Van Hul W. Clinical, molecular genetics and therapeutic aspects of syndromic obesity. *Clin Genet*. 2019;95:23–40. https://doi.org/10.1111/cge.13367