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Abstract

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 the different forms and focuses more in detail on the five most common ones for which the genetics are partially or completely determined: PWS and the PWL phenotype, BBS, AS, WAGR syndrome and 16p11.2 microdeletions. 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, a lot of 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: Syndromic obesity; Genetics; Clinics; Therapy.

Introduction

Obesity is a metabolic disorder characterized by an imbalance between energy intake and expenditure resulting in an excess of adipose tissue. Since 1980, the prevalence of obesity is more than doubled. World Health Organisation (WHO) figures of 2014 showed that 58.6% of adults are considered overweight (body mass index (BMI) = 25.0 – 29.9 kg/m²) and even 23% is obese (BMI ≥ 30 kg/m²) in Europe. The problem also affects children in whom 41 million under the age of 5 were overweight or obese in 2014 worldwide. If current trends continue, the number of overweight or obese infants and young children will increase to 70 million by 2025[1]. This high prevalence is very alarming as obesity can contribute to several adverse consequences like cardiovascular disease, type II diabetes mellitus (T2DM) and even thirteen different types of cancer[1, 2]. Due to the increased risk of developing the abovementioned comorbidities and the high, still increasing, prevalence, obesity has a major impact on global health and consequently represents a significant expenditure of national health-care budgets. Moreover, obese individuals accrued medical costs approximately 30% higher than their normal weight peers[3].

In 1973 Coleman and Hummel demonstrated for the first time that, to a certain extent, genetic factors are responsible for the familial aggregation of obesity[4]. Several years later twin and adoption studies confirmed this and estimated the heritability of BMI at 40 – 70%[5-7]. In most cases, a combination of genetic and environmental factors such as a high-fat diet and sedentary lifestyle causes the development of obesity, which is called common or complex obesity. To date, genome-wide association studies (GWAS) identified 97 loci related to complex obesity which account for approximately 2.7% of BMI variation[8]. On the other hand, an even more severe and rare form of obesity is monogenic obesity in which individuals exhibit one mutation in one of the known disease causing genes. Most of these affected genes are part of the leptin-melanocortin signaling pathway in the hypothalamus which has an important function in maintaining energy homeostasis[9]. Heterozygous mutations in the *melanocortin-4 receptor* (*MC4R*) gene, coding for a G protein-coupled

receptor (GPCR) that plays an important role in this signaling pathway, are the most common causes of monogenic forms of obesity and cumulates to approximately 2-5%[10].

Syndromic obesity

Syndromic obesity refers to obesity occurring in the context of a distinct set of associated clinical phenotypes such as intellectual disability, dysmorphic features and organ-specific developmental abnormalities[11, 12]. Up to now over 25 syndromic forms of obesity have been identified[13] (Table 1). As shown in table 1, the genetics of these disorders is extremely heterogeneous[14] and different molecular mechanisms lie at the basis of the syndromes. In case of 'pleiotropy' one single gene is responsible for the presence of two or more distinct and seemingly unrelated traits in the patient[15]. Secondly, 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[16].

This review includes recent data of the five most common forms for which the genetic background is completely or partially determined: 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 microdeletions (Table 2).

Prader Willi syndrome

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 intellectual disability (average IQ of 65). PWS patients also show characteristic facial features like almond-shaped eyes, a thin upper lip, downturned corners of the mouth and/or a narrow face. Also behavioral problems (e.g. temper tantrums, stubbornness and skin picking), small hands and feet and short stature are frequently described features[95-99].

In order to clinically diagnose PWS, Holm and colleagues developed a scoring system based on the abovementioned features. Characteristics were divided into three groups: major criteria (1 point), minor criteria (0.5 point) and supportive criteria (no points). When younger than three years of age, five points (at least four of them major) are required to diagnose PWS. Eight points (at least five of them major) are needed when 3 years or older[144]. Gunay-Aygun and colleagues later modified these clinical criteria to help identify appropriate patients for further diagnostic testing of PWS and which criteria are characteristic at different ages[96].

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%)[95, 97]. Two main deletion types, I and II, are described. The type I deletion, occurring in approximately 40% of patients, is located between breakpoint (BP) I and BP III 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 BP II and BP III[145, 146] (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 three molecular genetic classes, however, it won't identify the genetic subtype[99]. Therefore, to diagnose deletions, additional cytogenetic analyses such as fluorescence in situ hybridization (FISH) can be performed, however nowadays chromosomal microarrays are increasingly used in clinical genetics and may replace the FISH analysis in the future[146, 147]. 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[147]. This can be done with the use of the MS-MLPA assay or sequencing the 4.3kb smallest region of overlap for the PWS imprinting center[146, 148, 149]. In extremely rare cases also gene mutations (<0.1%) and a(n) (un)balanced translocation (0.1%) can be the cause of PWS in an individual. When the breakpoint 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[98, 147] (Figure 2).

An additional advantage of the MS-MLPA technique is that it can differentiate PWS from Angelman Syndrome or 'Happy Puppet' syndrome (1 in 15.000 – 20.000), a condition genetically related to PWS[99, 150, 151]. In contrary to PWS, Angelman Syndrome 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 Angelman Syndrome due to a deletion, paternal uniparental disomy, imprinting defects or intragenic mutations[151, 152]. Characteristic features of Angelman Syndrome are severe developmental delay, jerky movements, seizures and a happy disposition[153, 154].

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 two balanced translocations,

though a rare cause of PWS, excluded the gene as a primary candidate[155-157]. 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[157-159]. Consequently, a significant role for the snoRNA genes in the PWS phenotype emerged. In 2008, Sahoo and colleagues identified for the first time a microdeletion of SNORD116 and a substantial segment of the SNORD115 cluster in a patient with PWS characteristics[159]. Since 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[160, 161]. 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[162]. Even more recently, Bieth and colleagues 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[163]. Up to now, four research groups also studied a PWS mouse mutant line which carries a Snord116 deletion[164-167]. Heterozygous mice exhibiting a paternally inherited deletion show postnatal growth retardation and hyperphagia[164, 165]. Mice with a biallelic deletion of Snord116 have low birth weight with an increase in body weight, energy expenditure and hyperphagia in early adulthood[167]. Overall, both mice models show important characteristics of the PWS phenotype, supporting a significant role for SNORD116 in PWS pathogenesis[157].

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[95, 98, 168]. 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[98, 169, 170]. A still investigational therapy is the administration of intranasal oxytocin 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[171-173]. Important to mention, restrictive bariatric surgery is not recommended in PWS as it is associated with high complication rates and even mortality[174, 175]. Other beneficial therapies for PWS 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[95, 168, 176]. Noteworthy, since the genes and pathways disrupted in PWS are highly conserved in zebrafish, in the future zebrafish could serve as a promising model for high-throughput screening in order to quickly identify and deliver potential curative pharmacotherapies for PWS patients[177].

Prader Willi like

Once a clinical diagnosis of PWS cannot be confirmed molecularly with the use of MS-MLPA or additional techniques, patients are classified as Prader Willi *like* (PWL). These patients have similar characteristics as PWS individuals but occasionally show heart defects or neurological defects like seizures or hearing loss[103, 178, 179]. Clinically but also genetically the PWL phenotype is heterogeneous as it has already been associated with copy number variations (CNVs) on different chromosomes such as 1p36, 2p21, 9q34 and X as well as maternal uniparental disomy of chromosome 14[180-184]. However, deletions at chromosome 6q are most frequently reported. In 1988, Turleau and colleagues linked the PWL phenotype with a 6q deletion for the first time[185]. Several years later, similar reports appeared which enlarged the role of chromosome 6q in the PWL phenotype[103, 148, 178, 179, 186-193]. In these studies most 6q deletions encompass *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[103, 148, 178, 179, 190-193]. This hypothesis was substantiated further in an eighteen 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' promotor 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[194]. 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[195-198]. 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* in the PWL phenotype[199].

More recently, Kasher and colleagues also identified small deletions encompassing *POU3F2*, and not *SIM1*, at chromosome 6q in ten individuals from six families with developmental delay, intellectual disability, 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[200]. In extremely rare cases, heterozygous truncating mutations in *MAGEL2*, occurring on the paternal allele, are reported in individuals with features resembling the PWS/PWL phenotype which is called the Schaaf-Yang syndrome[201, 202]. Also the Magel2-null mouse model indicates a role in PWS and obesity[203]. However, in contrast to this findings, Buiting and colleagues identified two deletions including *MAGEL2* and not the *SNRPN/SNORD116* locus in two patients who do not have PWS or PWL characteristics and consequently concluded that the role of *MAGEL2* in PWS/PWL still remains unclear[204, 205].

Bardet-Biedl syndrome

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[21, 22, 206]. Apart from obesity, BBS patients are primarily characterized by cone-rod dystrophy, postaxial polydactyly, cognitive impairment, hypogenitalism and renal abnormalities. Secondary features are speech deficits, olfaction disorders (anosmia or hyposmia), psychiatric problems, T2DM and ataxia or impaired coordination[21-25]. At birth, most of these symptoms are not noticeable, however they appear and progressively worsen during the first and second decade of life[25]. E.g.: For children with BBS the visual prognosis is poor. At age seven to eight years, patients usually develop night blindness which eventually leads to legal blindness by the age of 20 years in more than 60% of patients[21, 207, 208].

As for PWS, BBS is also diagnosed based on clinical findings. BBS diagnosis is assigned to patients bearing at least four primary criteria. When only three major features are present, two minor criteria are required to confirm the presence of the disorder[25, 208, 209]. However, since many characteristics are not yet noticeable at birth, early genetic testing is highly essential to molecularly diagnose BBS. To date, 21 genes (*BBS1* – *BBS20* and *NPHP1*) have been identified to be associated with BBS and which are all involved in primary cilia functioning[25]. 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[24, 210, 211]. Disease-causing mutations in other BBS genes have a prevalence below 10% and even in most cases ≤5% (overview in Suspitsin *et al.* 2016[25]). 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 one BBS family and two heterozygous *BBS2* nonsense mutations and a *BBS6* nonsense mutation in BBS patients in three other families[212]. This triallelic model was supported by some research groups[213-216], as others do not underpin the triallelic inheritance hypothesis[217-222]. 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[25, 212, 215, 223]. 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[224]. 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[21, 225-228]. 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[216, 229].

BBS therapy mainly exist of the treatment of the patient's symptoms. The first therapy that is being performed, is the removal of the accessory digit(s) when necessary. In most children this happens within the first two years of age. Secondly, 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[21]. One study also discovered a positive effect of the diet on renal function, however it only may slow the progression of renal failure[230]. Consequently, a renal transplantation is the only method to successfully treat the renal problems[21]. In addition, another rather exceptional case report of a 21-month-old girl diagnosed with BBS also showed a remarkably improvement of her vision, obesity, behavior and mood when subjected to appropriate nutritional correction[231]. Thirdly, 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 by a specialist. However, an experimental set-up of subretinal injection of BBS-containing adenovirus constructs in mice demonstrated encouraging results so far[21, 25]. As for PWS patients, a hormonal replacement therapy in order to produce adequate secondary sexual characteristics at puberty can also be used in BBS patients[21].

Alström syndrome

Alström syndrome (AS) was first described in 1959[232] and is, as BBS, included in the ciliopathies group[233]. It is a rare autosomal recessive disorder with a prevalence estimated at one to nine cases per 1.000.000 individuals. To date, approximately 950 cases are described worldwide[233, 234]. AS shows a wide clinical variability even within the same family. It does share some features with BBS such as obesity, cone-rod dystrophy and renal anomalies and is additionally characterized by progressive sensorineural hearing impairment, male hypogonadism/female hyperandrogenism, adult short stature, T2DM and dilated or restrictive cardiomyopathy[17, 18]. A clinical distinction between AS and BBS can be made based on the timing of the onset of visual problems and the presence of postaxial polydactyly. AS patients usually show vision difficulties before the age of two years, whereas in BBS this appears on average 6.5 years later. Polydactyly, which is common in BBS, has not been described in AS[17]. However, since both ciliopathies show considerable phenotypic overlap, especially in early infancy, molecular techniques such as an array- or next generation sequencing-based technology can be used to clearly differentiate AS from BBS[226, 235, 236].

AS is caused by homozygous or compound heterozygous mutations in *Alström syndrome protein 1* (*ALMS1*) on chromosome 2p13[19]. Recently, however, Ozantürk and colleagues also reported triallelic mutations in *ALMS1* in Turkish AS cases who incredibly did not show more severe characteristics[237]. To date, more than 200 mutations have been reported of which exon 8, 10 and 16 are the three big hotspots for *ALMS1* mutations (overview Supplemental S1 Table in Marshall *et al.* 2015[238]). The most pathogenic ones are frameshift or nonsense mutations occurring downstream of exon 7 resulting in an early termination of ALMS1 and subsequently a non-functional protein[233, 238]. In addition, also splice-site mutations[239], deletions[240, 241], one *Alu* transposon insertion[242] and one balanced translocation[243] 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[17, 237, 244, 245]. Secondly, it is also hypothesized that ALMS1 could play a role in β-cell function and/or peripheral insulin signaling

pathways since AS patients are more likely to develop T2DM in contrast to BBS patients despite the fact that obesity levels are equivalent in both syndromes[246, 247]. Unfortunately, up till now the precise molecular mechanism underlying the AS phenotype has not been fully elucidated[238].

In the past, molecular diagnosis of AS in patients was done by first performing mutation analysis of the gene hotspots (exon 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[233, 235]. Nevertheless, as the NGS methodology is rapidly growing and gradually replacing above-mentioned 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[233, 248, 249].

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[233]. 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, in the end patients should be prepared for the development of blindness. Secondly, weight gain can be controlled with the use of a healthful, reduced calorie diet and regular exercise taking into account the vision limitations of the patient[17]. Also beneficial effects of rhGH on body composition and liver fat content were reported in a 15-year-old AS patient[250]. Renal problems can be detected when proteinuria is noted. 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[17, 251]. 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[17], though valuable results are already obtained with a combined therapy comprising a high dose of metformin and rosiglitazone[252].

WAGR syndrome

Wilms tumor, Aniridia, Genitourinary malformations and mental Retardation or WAGR syndrome, first described in 1964 by Miller *et al.*[253], is an autosomal dominant disorder with an estimated prevalence of 1 in 1.000.000 individuals[139, 254]. The main characteristics are stated in the acronym: Wilms tumor (an embryonal malignancy of the kidney), aniridia, genitourinary malformations and mental retardation or intellectual disability. Obesity or severe hyperphagia has also been described in a subgroup of these patients, in which case the condition is often called WAGRO[131-137]. Secondary features often seen in WAGR patients are renal problems, cardiopulmonary defects and behavioral difficulties[135]. It 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[254]. 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[135, 255]. There is also a possibility that *PAX6* deficiency results in brain and pancreas defects[256-259]. Both genes are located at approximately 4 Mb from the *Brain-derived Neurotrophic Factor* (*BDNF*) gene at chromosome 11p14.1[137, 254]. 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[137] (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[9, 260, 261]. 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[262-265]. In addition, since its neural function, the protein is widely distributed in the central nervous system including the hypothalamus[9, 254]. 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[266, 267]. 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[268].

Genetic testing for WAGR syndrome is typically performed in children presented with aniridia[135]. To identify large deletions or translocations of chromosome 11p13, high-resolution cytogenetics is an appropriate method[139, 269]. Small deletions, however, cannot be recognized with this technique. In this case, FISH, Multiplex Ligation-dependent Probe Amplification (MLPA) or array Comparative Genomic Hybridization (CGH) are more suitable[135, 137, 255, 269].

Once genetic tests confirm the diagnosis of WAGR syndrome, ultrasound screening for Wilms tumor is initiated every three months until the age of five to six years to allow early detection[135, 269, 270]. The prevalence of Wilms tumor in WAGR patients is estimated between 45%[271] and 57%[135]. 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[135, 269]. Aniridia should be managed by regular eye examinations by an expert ophthalmologist[269, 272]. 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[272]. That's why implantation of an artificial iris-intraocular lens is nowadays suggested[272, 273]. Genitourinary malformations such as gonadoblastoma can only be treated with surgical intervention[269].

16p11.2 microdeletions

Due to the presence of flanking homologous segmental duplications, the chromosome 16p region is particularly prone to rearrangements leading to copy number changes[53]. The recurrent proximal ~593kb deletions (and duplications) are among the most frequent genetic etiologies of autism spectrum disorders (ASD)[274-276], schizophrenia[277] and neuropsychiatric disorders[278]. The prevalence is estimated at approximately 1% in all ASD cases[274]. In addition, the microdeletion syndrome also

cosegregates with severe early-onset obesity[54, 279], developmental delay[280], intellectual disability[281, 282], hypotonia[283], epilepsy[280, 282-284], behavioral problems[104, 280] and even a high prevalence of speech articulation abnormalities[104, 283]. On the contrary, patients harboring a ~593kb 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 593kb region is pointed forward to clarify the obesity/underweight phenotype[285]. In addition, larger deletions of 1.7Mb encompassing the 593kb proximal deletion are also reported in patients harboring similar characteristics[54, 286, 287] supplemented with or without secondary features such as dysmorphism, heart defects[287], Batten disease[288] or Hirschsprung disease[289]. Noteworthy, this 1.7Mb deletion also includes a second 220kb distal deletion which in literature mainly is associated with severe early-onset obesity as well as obesity with developmental delay[53-56] (Figure 4). Additionally, dysmorphic features, behavioral problems, seizures, speech and motor delays and autism are also commonly reported[53, 290]. All four CNVs (593kb deletion, 593kb duplication, 1.7Mb deletion and 220kb deletion) are inherited in an autosomal dominant matter, either due to a *de novo* event or inherited from one of the (even healthy) parents[53, 54, 286, 291].

For the distal 16p11.2 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[285] as other genes within the 220kb region might clarify the presence of the additional features[292]. Previous research in a yeast two-hybrid system demonstrated that SH2B1 is a Janus kinase 2 (JAK2)-binding protein[293]. 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[294, 295] indicating that SH2B1 could act as a positive regulator of leptin signaling and consequently might be implicated in energy homeostasis[292]. 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[296, 297]. 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[55, 298, 299]. 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[300-302]. Own research, on the other hand, showed an equal presence of rare non-synonymous *SH2B1* variations in both lean and obese individuals[292] which was also seen in a Chinese study population[303]. 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)[53, 290-292].

Noteworthy, patients with a 220kb and 593kb deletion share a comparable phenotype such as individuals with a 220kb and 593kb duplication do. Due to this phenomenon, Loviglio and colleagues suggested a genomic interaction between the distal (220kb) and proximal (593kb) region and in fact observed a complex chromatin looping between the genes located in the 220kb 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[304].

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. Developmental delay is preferably monitored by a clinical psychologist with the use of neuropsychological testing. 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[291]. As ASD is not 'curable', the primary goals for

treatment of ASD is to manage the cornerstones of the disorder. Therefore, 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, naturalistic behavioral methodologies and developmental-pragmatic approaches are effective. A visit to a speech-language pathologist is usually an appropriate first step[305].

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 a lot of information on the molecular genetics of these disorders and the obesity phenotype which ultimately leads to a more individualized treatment of the patients. However, a lot of questions still remain unanswered. At this point, the big challenge for clinicians and scientists is to differentiate all syndromic forms of obesity more clearly to correctly diagnose the patients as quickly as possible. 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. However, this would help to provide conclusive genetic explanations to eventually deliver accurate genetic counseling and treatment instead of only treating the patient's symptoms[146, 306]. In addition, signs and symptoms of PWS and PWL are also common to other syndromes such as BBS, AS, but also Fragile X syndrome, Cohen syndrome and even Temple syndrome[307, 308] which makes it even more difficult to determine in which circumstances the MS-MLPA analysis for PWS diagnosis should be performed. As the absence of a correct diagnosis may result in inappropriate treatment of the disease, an update in the phenotypic and genetic information of these patients is important and will be helpful to recognize the appropriate syndrome in an individual[146, 306]. In addition, further delineation of (the functions of) the underlying genes will be helpful to unravel the mechanisms of energy metabolism in the general population[22]. Previous research mostly focused on simple screening methods like Sanger sequencing and FISH. 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[14, 309]. Furthermore, also chromosomal microarrays are increasingly utilized in clinical genetics and are already replacing the previously used FISH analysis[146, 147].

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Table 1. Overview of the most important main and secondary clinical features and the responsible gene(s) or chromosomal region of known obesity syndromes.

DISEASE	INHERITANCE	RESPONSIBLE GENE(S) OR CHROMOSOMAL REGION	MAIN CLINICAL FEATURES	SECONDARY CLINICAL FEATURES
Alström Syndrome[17-20]	Autosomal recessive	*ALMS1*	Obesity, cone-rod dystrophy, renal anomalies, progressive sensorineural hearing impairment, male hypogonadism/female hyperandrogenism, adult short stature, type II diabetes mellitus (T2DM) and dilated or restrictive cardiomyopathy.	/
Bardet-Biedl Syndrome[21-27]	Autosomal/Oligogenic recessive	*BBS1* – *BBS20* and *NPHP1*	Obesity, cone-rod dystrophy, postaxial polydactyly, cognitive impairment, hypogenitalism and renal abnormalities.	Speech deficits, olfaction disorders (anosmia or hyposmia), psychiatric problems, T2DM and ataxia or impaired coordination.
Borjeson-Forssman-Lehmann Syndrome[28-30]	X-linked recessive	*PHF6*	Mild to severe intellectual disability (ID), hypogonadism, hypometabolism, obesity with marked gynaecomastia, facial dysmorphism, tapered fingers, broad shortened toes, small genitalia and short stature.	Microcephaly or macrocephaly and epileptic seizures.
Carpenter Syndrome[31-35]	Autosomal recessive	*RAB23* and *MEGF8*	Craniofacial features, mild to moderate ID, increased birth weight (90% of CS patients obese later in life), central nervous system abnormalities, dental	Omphalocele and umbilical hernia.

			problems, cardiovascular malformations, foot and hand syndactyly/brachydactyly, hip, knee, and ankle deformities and clinodactyly, undescended or underdeveloped testicles.	
Choroideremia-deafness-obesity Syndrome or Ayazi Syndrome[36-39]	X-linked recessive	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[40-43]	X-linked dominant Isolated cases	*RPS6KA3*	Growth and psychomotor retardation, hypotonia, hyperlaxity of joints, characteristic facial and digital abnormalities, progressive skeletal alterations, microcephaly, (severe) cognitive deficiency, impaired speech development.	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[44-46]	Autosomal dominant	*AFF4*	Cognitive impairment, coarse facies, heart defects, obesity, pulmonary involvement and short stature and skeletal dysplasia.	/
Cohen Syndrome[47-50]	Autosomal recessive	*VPS13B*	Facial dysmorphism, microcephaly, truncal obesity, intellectual disability, progressive retinopathy, and intermittent congenital neutropenia.	Childhood hypotonia, joint laxity, cheerful disposition.

Colobomatous microphtalmia-obesity-hypogenitalism intellectual disability Syndrome[51, 52]	Autosomal dominant	N.A.	Colobomatous microphthalmia, obesity, hypogonadism/genitalism and intellectual disability.	/
Distal 16p11.2 microdeletion Syndrome[53-57]	Autosomal dominant	16p11.2 (*SH2B1*)	Severe early-onset obesity, developmental delay.	/
Fragile X Syndrome[58-63]	X-linked dominant	*FMR1*	Mild to severe intellectual disability, cognitive and developmental impairment (e.g. 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, ADHD), obesity, otitis media, hyperextensible finger joints.	Recurrent otitis, (childhood) seizures, pes planus, strabismus, mitral valve prolapse, scoliosis.
Hydrocephalus-obesity-hypogonadism or Sengers-Hamel-Otten Syndrome[64]	X-linked recessive	N.A.	Congenital hydrocephalus, centripetal obesity, hypogonadism, intellectual deficit and short stature.	/
Intellectual disability-obesity-brain malformations-facial dysmorphism Syndrome[65, 66]	Autosomal recessive	*TRAPPC9*	Obesity, hypotonia, microcephaly, moderate to severe ID, brain abnormalities.	Peculiar facial appearance, epilepsy.
Intellectual disability-obesity-prognathism-eye and skin anomalies syndrome or MOMES Syndrome[67-70]	Autosomal recessive	4q35.1-qter del and 5pter-5p14.3 dup	Intellectual disability, 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)	
Intellectual disability-seizures-macrocephaly-obesity Syndrome[71-76]	N.A.	der(8)t(8;12)(p23.1;p13.31) (*GNB3*)	Intellectual disability, developmental delay, obesity, seizures, hypotonia, dysmorphic features, macrocephaly, excema, poor coordination, ocular problems, social personality.	Abnormal gait, dental/palate abnormalities, hypertelorism, scoliosis.
X-linked intellectual disability-epileptic seizures-hypogenitalism-microcephaly-obesity syndrome or MEHMO Syndrome[77-81]	X-linked recessive Mitochondrial inheritance	Xp21.1 – p22.13	Intellectual disability, developmental delay, severe postnatal growth delay, seizures, hypogonadism and -genitalism, microcephaly and infancy-onset obesity.	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[82-85]	Autosomal recessive	*PCNT*	Severe intrauterine and postnatal growth retardation, disproportionate short stature (adult height < 100cm), skeletal abnormalities, microcephaly, dysmorphic features (e.g.: retrognathia, upward-slanting palpebral fissures, prominent nose, …), truncal obesity, intellectual disability, scoliosis, unusual pigmentation (e.g. café-au-lait spots), high-pitched voice.	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-	Autosomal dominant	N.A.	Macrocephaly, obesity, overgrowth, intellectual disability	Behavioral disorders (aggressiveness, self-

mental disability-ocular abnormalities (MOMO) Syndrome or Macrosomia-obesity-macrocephaly-ocular abnormalities Syndrome[86-91]			and ocular abnormalities (retinal coloboma and nystagmus), macrosomia, downslanting palpebral fissures, hypertelorism, broad nasal root, high and broad forehead and delayed bone maturation.	mutilation, excessive shyness), short stature, recurvation of femur or straight femur, autism, developmental issues, clavicular pseudoarthrosis.
Mental retardation (Intellectual disability)-truncal obesity-retinal dystrophy-micropenis (MORM) Syndrome[92-94]	Autosomal recessive	*INPP5E*	Moderate intellectual disability, truncal obesity, congenital nonprogressive retinal dystrophy, micropenis	/
Prader Willi Syndrome[95-101]	Isolated cases	15q11.2 – q13 (imprinting region)	Severe neonatal hypotonia, feeding difficulties followed by hyperphagia and excessive weight gain, developmental delay, hypogonadism, intellectual disability, characteristic facial features (almond-shaped eyes, a thin upper lip, downturned corners of the mouth and/or a narrow face), behavioral problems (e.g. 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[100, 102-105]	Isolated cases	1p36, 2p21, 6q, 9q34, X, maternal uniparental disomy of chromosome 14	see Prader-Willi Syndrome	see Prader-Willi Syndrome + heart defects, neurological defects (seizures, hearing loss).
Pseudohypoparathyroidism (PHP) with Albright hereditary osteodystrophy (AHO)[106-113]	Autosomal dominant	*GNAS1* (loss-of-function on maternal allele)	Resistance to parathyroid hormone, thyroid-stimulating hormone, growth hormone–releasing hormone and	Intellectual disability, mild developmental delay.

			gonadotropins, AHO: short stature, obesity, dysmorphic features (round face, nystagmus, low nasal bridge, short neck), hypocalcaemia, subcutaneous ossifications, brachydactyly (hands/feet), osteoporosis, hypogonadism, calcified choroid plexus, hypocalcemic tetany.	
Rubinstein-Taybi Syndrome or Broad Thumb-Hallux Syndrome[114-120]	Autosomal dominant	*CREBBP* and *EP300*	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 intellectual disability, obesity after puberty, speech delay, delayed bone age, strabismus, cryptorchidism, recurrent infections.	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 developmental delay Syndrome[121-123]	Autosomal recessive	*PRMT7*	Short stature, obesity, symmetrical shortening of the digits and posterior metacarpals and metatarsals, global developmental delay, mild intellectual disability	/
Diploid Triploid Mosaicism[124-130]	Mosaicism	N.A.	Developmental delay, intellectual disability, 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	
Wilms tumor, Aniridia, Renitourinary malformations and mental Retardation (WAGR) Syndrome[131-139]	Autosomal dominant	11p13 (*WT1* and *PAX6*)	Wilms tumor, aniridia, genitourinary malformations (hypospadias, cryptorchidism), intellectual disability.	Obesity or severe hyperphagia, renal problems, cardiopulmonary defects, behavioral difficulties.
Wilson-Turner or X-linked intellectual disability-gynaecomastia-obesity Syndrome[140-143]	X-linked recessive	*LAS1L*	Mild to moderate intellectual disability, dysmorphic facial features, hypogonadism, short stature, truncal obesity, gynaecomastia, speech impairment, tapering fingers, behavioral problems (e.g. emotional lability), small feet.	Seizures.

Table 2. Overview of clinical features, molecular analysis and treatment of the five most common forms for which the genetic background is completely or partially determined: 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 microdeletions.

DISEASE	CLINICAL FEATURES	MOLECULAR ANALYSIS	TREATMENT
Prader Willi Syndrome **Prader Willi like Syndrome**	Main features: Severe neonatal hypotonia, feeding difficulties followed by hyperphagia and excessive weight gain, developmental delay, hypogonadism, intellectual disability, characteristic facial features (almond-shaped eyes, a thin upper lip, downturned corners of the mouth and/or a narrow face), behavioral problems (e.g. temper tantrums, stubbornness, skin picking), small hands and feet, short stature. Secondary features: type II diabetes mellitus (T2DM), sleep abnormalities, apnea, hypothyroidism, delayed language development, respiratory infections, hypopigmentation of hair, eyes, and skin, strabismus, hip dysplasia, scoliosis, psychosis, heart defects, neurological defects (seizures, hearing loss).	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 4.3kb 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	Main features: Obesity, cone-rod dystrophy, postaxial polydactyly, cognitive impairment, hypogenitalism and renal abnormalities. Secondary features: Speech deficits, olfaction disorders (anosmia or hyposmia), psychiatric problems, T2DM and ataxia or impaired coordination.	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	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.	Past: Mutation analysis of the gene hotspots (exon 8, 10 and 16) in *ALMS1*. Present/Future: Array- or next generation sequencing-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	Main features: Wilms tumor, aniridia, genitourinary malformations (hypospadias, cryptorchidism), intellectual disability. Secondary features: Obesity or severe hyperphagia, renal problems, cardiopulmonary defects, behavioral difficulties.	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 ○ Nutritional management: Low calorie and/or protein diet, daily physical activity ○ ACE inhibitors
16p11.2 microdeletions ***593 kb deletion*** ***220 kb deletion***	Main features: Autism spectrum disorders, schizophrenia, neuropsychiatric disorders Secondary features: Severe early-onset obesity, developmental delay, intellectual disability, hypotonia, epilepsy, behavioral problems, speech articulation abnormalities. Main features: Severe early-onset obesity, developmental delay.	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.	○ 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

Figures

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) I and BP III 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 BP II and BP III. AS = Angelman Syndrome, IC = Imprinting center, CEN = centromere, TEL = telomere.

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.

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 the WAGR patients exhibit a deletion also including the *Brain-derived Neurotrophic Factor* (*BDNF*) gene located at approximately 4Mb 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.

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