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Review

Review

The Spectrum of the Prader–Willi-like Pheno- and Genotype: A Review of the Literature

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Abbreviations: ASD, autism spectrum disorder; CHS, Chitayat–Hall syndrome; GH, growth hormone; PWL, Prader–Willi-like; PWS, Prader–Willi syndrome; SNP, single nucleotide polymorphism; SNV, single nucleotide variant; SYS, Schaaf–Yang syndrome.

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Abstract

Prader–Willi syndrome (PWS) is a rare genetic syndrome, caused by the loss of expression of the paternal chromosome 15q11-q13 region. Over the past years, many cases of patients with characteristics similar to PWS, but without a typical genetic aberration of the 15q11-q13 region, have been described. These patients are often labelled as Prader–Willi-like (PWL). PWL is an as-yet poorly defined syndrome, potentially affecting a significant number of children and adults. In the current clinical practice, patients labelled as PWL are mostly left without treatment options. Considering the similarities with PWS, children with PWL might benefit from the same care and treatment as children with PWS. This review gives more insight into the pheno- and genotype of PWL and includes 86 papers, containing 368 cases of patients with a PWL phenotype. We describe mutations and aberrations for consideration when suspicion of PWS remains after negative testing. The most common genetic diagnoses were Temple syndrome (formerly known as maternal uniparental disomy 14), Schaaf–Yang syndrome (truncating mutation in the *MAGEL2* gene), 1p36 deletion, 2p deletion, 6q deletion, 6q duplication, 15q deletion, 15q duplication, 19p deletion, fragile X syndrome, and Xq duplication. We found that the most prevalent symptoms in the entire group were developmental delay/intellectual disability (76%), speech problems (64%), overweight/obesity (57%), hypotonia (56%), and psychobehavioral problems (53%). In addition, we propose a diagnostic approach to patients with a PWL phenotype for (pediatric) endocrinologists. PWL comprises a complex and diverse group of patients, which calls for multidisciplinary care with an individualized approach.

Key Words: Prader–Willi-like, PWL, PWS-like, PW-like, Temple syndrome, Schaaf–Yang syndrome

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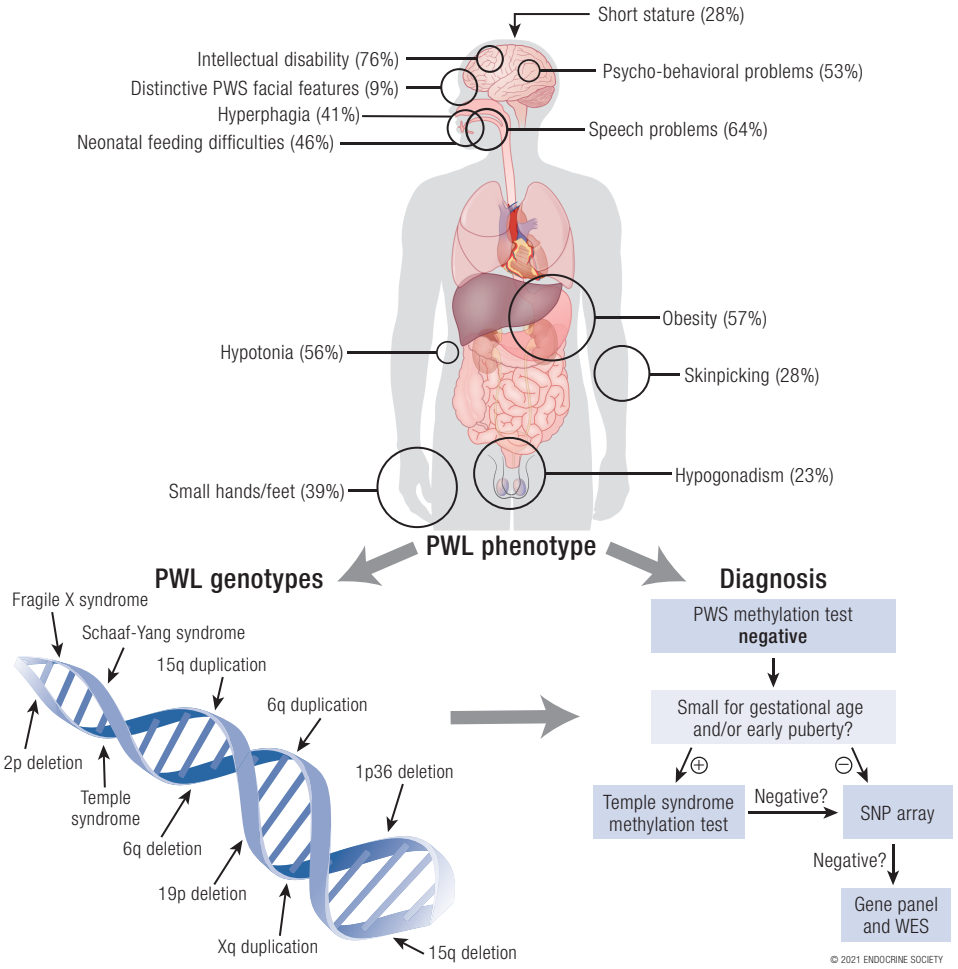
Graphical Abstract



ESSENTIAL POINTS

- The Prader–Willi-like (PWL) phenotype comprises a broad range of clinical symptoms, but most often described are obesity/overweight, psychobehavioral problems, intellectual disability/developmental delay, speech problems, and hypotonia.
- The underlying genetic aberrations and syndromes that are most frequently linked to PWL in the literature are Temple syndrome, Schaaf–Yang syndrome, 1p36 deletion, 2p deletion, 6q deletion, 6q duplication, 15q deletion, 15q duplication, 19p deletion, fragile X syndrome, and Xq duplication.
- The most striking similarities to Prader–Willi syndrome (PWS) are found in Temple syndrome (formerly known as maternal uniparental disomy of chromosome 14) and we recommend testing for Temple syndrome if the patient has a neonatal period resembling that of PWS, especially in a child born small for gestational age and/or presenting with early puberty in childhood.
- Most genetic aberrations discussed in this paper can be diagnosed with a single nucleotide polymorphism array, but syndromes such as Temple syndrome and Schaaf–Yang syndrome would need additional testing, namely a methylation study or next-generation sequencing panel/whole exome sequencing.
- The complexity and diversity of the range of symptoms linked to the PWL phenotype calls for multidisciplinary care with an individualized approach.

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Prader–Willi Syndrome (PWS) is caused by the loss of paternal expression of the 15q11-q13 region. This loss of expression can be due to different mechanisms, namely a (type 1 or 2) deletion of the 15q11-q13 region, a maternal uniparental disomy of chromosome 15, an (unbalanced) translocation, or an imprinting center defect (1). PWS is a genetic syndrome characterized by hypotonia, feeding problems in early infancy, hypogonadism, neuropsychomotor developmental delay, and an insatiable appetite leading to morbid obesity without proper management. Short stature, scoliosis, small hands and feet, and characteristic facial features are common (2).

In the last decade, there have been reports about children and adolescents with symptoms similar to patients with PWS, but without the typical Prader–Willi genotype. In some of these patients other genetic aberrations were found, which appear to be associated with the Prader–Willi phenotype. These patients are generally described as Prader–Willi-like (PWL).

One of the common genetic aberrations associated with the PWL phenotype is Temple syndrome, which is most often caused by a maternal uniparental disomy of chromosome 14, but can also have a copy number change or epigenetic error as the underlying mechanism (3). Alterations in the 6q16 region have also been linked to PWL (4). This region houses the single minded homolog 1 (*SIM1*) gene. *SIM1* is part of the central molecular leptin–melanocortin pathway that regulates body mass. It has been postulated that loss-of-function variants in *SIM1* may cause obesity with or without PWL features (5). Interestingly, not all reported individuals with a PWL phenotype and a 6q16 deletion have a deletion that encompasses *SIM1*, and not all patients with a *SIM1* deletion have a PWL phenotype (6).

Other papers describing a PWL phenotype point to 1p36 deletions, which is the most common subtelomeric deletion syndrome seen in humans (7). The 2pter region is also of interest, containing the myelin transcription factor 1 like (*MYT1L*) gene, which has been implicated in intellectual disability and obesity (8). Deletions in the 15qter region, distally from the PWS region, have also been described, as have deletions in the 22q11.2 region (9), or alterations of the X chromosome, such as Xq duplications (10) or even fragile X syndrome (11). There can also be small genetic defects in the PWS critical region which do not qualify as a molecular diagnosis of PWS, but may produce a PWS phenotype. This has been described in patients with a nonsense or frameshift mutation in *MAGEL2* (12), known as Schaaf–Yang syndrome (SYS) and in patients with a 15q11.2q13.1 duplication (13).

Knowledge about PWS has much improved and treatment options for children and adults with PWS continue to advance. Currently, very young children start GH therapy right after being diagnosed with PWS and receive multidisciplinary care by a team of physicians, nurses, dieticians, physiotherapists, speech therapists, and other specialists. In contrast to this, there is a lot unknown about PWL. A clear definition is missing for most patients and, most importantly, treatment options are lacking. Finding a cause for the PWL phenotype can be crucial for further treatment and for determining and advising on the prognosis. It is unknown if patients with a phenotype similar to PWS, might benefit from the same multidisciplinary approach, including growth hormone (GH) therapy and early dietary intervention, all led by a multidisciplinary team.

Because the symptoms in children with PWS are age dependent and some characteristics are also common in other disorders, it is difficult to determine the phenotypic definition. Here, we present an in-depth review of all the available literature on patients demonstrating a PWL phenotype. By bundling all the case series and reports, we aimed to obtain a more complete view of what is considered PWL and which distinguishing features several genetic defects might have, providing a diagnostic roadmap for current and future patients.

Materials and Methods

The public PUBMED database was searched according to a 4-step protocol, which is summarized in Fig. 1.

Relevant publications from January 1963 to May 2020 were identified using the following search terms: ("developmental disabilities" [Mesh] or "learning disabilities" [Mesh] or "intellectual disability" [Mesh:noexp] or "mental retardation, X-linked" [Mesh]) and ("obesity"[mesh] or "hyperphagia" [Mesh:noexp]) and ("genetic variation" [Mesh] or "phenotype" [Mesh]) or ("prader-willi-like" [tiab] or "PWS-like" [tiab] or "PW-like" [tiab]). Terms were combined using "OR" and "AND" logic. The search resulted in an initial pool of 375 papers. There were no duplicates and all 375 papers were initially screened by title and abstract.

To be included for review, studies had to meet at least the following criteria: (1) case report or series providing information on the clinical features of the patients, (2) containing original data (no literature review), (3) published in English, (4) full text available.

Studies were excluded if they reported cases on syndromes that do not show a PWL phenotype, such as Cohen syndrome or Wilms tumour, Aniridia, Genitourinary anomalies, mental Retardation, obesity (WAGRO) syndrome. An exception to these criteria were syndromes that are historically known as PWL or otherwise linked to PWS, such as Temple syndrome and SYS. Papers that reported patients with atypical deletions in the PWS region (15q11.2-q15) were also excluded for this review, because patients with atypical deletions are often considered as having PWS and

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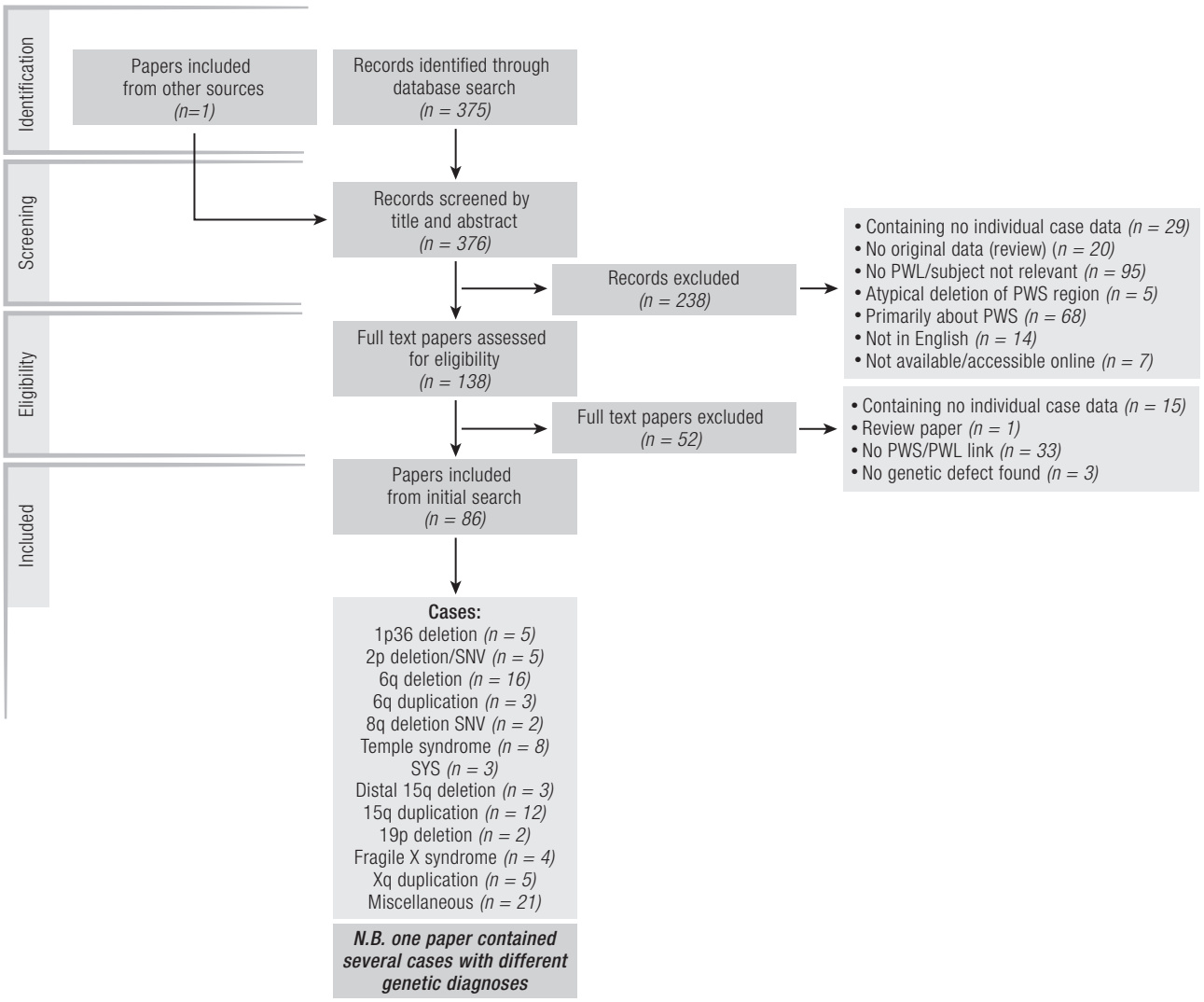

Figure 1. Flow diagram of the literature review and paper inclusion pathway.

can be diagnosed by methylation testing of the PWS region. Articles were excluded if the primary focus was on (typical) PWS, such as intervention trials or studies about the behavioral phenotype. A few studies carried out testing for a specific genetic defect in a cohort of PWL patients (14-16), but identified no variants in their patients. These papers did not provide any individual case data and were also excluded for review. Finally, a number of papers reported patients with obesity and intellectual disability, but had no mention of PWS/PWL as a considered cause for the phenotype. These papers did not provide any other connection between PWS/PWL and the genetic defect eventually found. The cases in these papers could therefore not be considered "PWL" and were excluded.

The remaining 86 papers were included in the review and the following data were extracted: study size, gender of participants, genetic diagnosis, clinical features similar to PWS, and additional clinical features. The features similar to PWS were the following: obesity/overweight, developmental delay/intellectual disability, psychobehavioral problems, hypotonia, neonatal feeding difficulties, hypogonadism, hyperphagia, dysmorphic facial features typical to PWS, speech (articulation) problems/delay, skin picking, sleep problems/apnea, short stature, small hands/feet, eye abnormalities.

Results

The initial search yielded 376 records, of which 86 were suitable for inclusion. The resulting pool of articles contained data for 368 individual cases and 35 separate genetic diagnoses.

Tables 1 and 2 summarize the clinical findings, subdivided into genetic defects that were reported in more than 1 of the reviewed papers. The genetic defects that were described in only 1 paper reviewed for this purpose can

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Table 1. Summary of clinical features of genetic defects linked to the PWL phenotype

Genetic defect	1p36 deletion	2p25 deletion/ LoF SNV	6q deletion/LoF SNV	6q duplication	Temple syndrome	Schaaf–Yang syndrome	(distal) 15q deletion
Number of papers	5	5	16	3	8	3	3
Number of cases	11	17	67	7	48	22	4
Gender (M/F)	4/7	5/12	39/28	2/5	26/22	12/10	3/1
References	(7, 17-20)	(21-25)	(4-6, 25-37)	(25, 38, 39)	(40-47)	(48-50)	(51-53)
Clinical features, occurrence/n, (%)							
Hypotonia	**10/11 (91)**	7/15 (47)	27/56 (48)	**1/1 (100)**	**36/48 (75)**	**18/22 (82)**	**3/3 (100)**
Infantile feeding problems/FTT	3/9 (33)	3/15 (20)	16/52 (31)	**1/1 (100)**	**33/47 (70)**	**19/22 (86)**	1/2 (50)
Hyperphagia	7/11 (64)	**13/17 (76)**	28/67 (42)	0/1 (0)	4/38 (11)	4/18 (22)	**2/3 (67)**
Overweight/obesity	6/11 (55)	**13/17 (76)**	**54/67 (81)**	**6/7 (86)**	12/48 (25)	5/19 (26)	**3/4 (75)**
Distinctive facial features	3/11 (27)	1/17 (6)	4/56 (7)	**5/7 (71)**	2/47 (4)	1/22 (5)	0/4 (0)
DD/ID	**11/11 (100)**	**17/17 (100)**	**60/67 (90)**	**5/7 (71)**	18/48 (38)	**18/22 (82)**	**4/4 (100)**
Psychobehavioral problems	7/11 (64)	**14/17 (82)**	38/66 (58)	0/1 (0)	8/46 (17)	11/22 (50)	2/4 (50)
Speech problems	**10/11 (91)**	**16/17 (94)**	33/52 (63)	3/7 (43)	**9/13 (70)**	**1/1 (100)**	**3/4 (75)**
Skin picking	1/3 (33)	0/1 (0)	0/18 (0)	NA	2/10 (20)	7/18 (39)	NA
Sleep disturbances/ apnea	1/4 (25)	4/16 (25)	10/43 (23)	NA	0/2 (0)	9/18 (50)	**1/1 (100)**
Short stature	4/11 (36)	0/17 (0)	7/56 (13)	2/7 (29)	**42/48 (88)**	11/19 (58)	2/4 (50)
Hypogonadism	0/6 (0)	1/5 (20)	12/65 (18)	2/7 (29)	2/48 (4)	11/21 (52)	**2/3 (67)**
Small hands/feet	4/10 (40)	3/7 (43)	17/44 (39)	1/7 (14)	**39/47 (83)**	12/21 (57)	**2/3 (67)**
Eye abnormalities	**9/11 (82)**	9/17 (53)	27/51 (53)	0/1 (0)	0/3 (0)	11/18 (61)	1/3 (33)
Distinguishing features	Seizures, strabismus	seizures, CNS malformations	Skull abnormalities, scoliosis, seizures	macrosomia	SGA, recurring otitis, precocious puberty, irregular teeth, prominent forehead, scoliosis	joint contractures, ASD, GER, scoliosis	seizures

Bold: occurrence of 67% and higher.

Abbreviations: NA, information not available/provided in the paper; LoF, loss of function; FTT, failure to thrive; SNV, single nucleotide variant; DD, developmental delay; ID, intellectual disability; CNS, central nervous system; SGA, small for gestational age; ASD, autism spectrum disorder; GER, gastro-esophageal reflux.

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Table 2. Summary of clinical features of genetic defects linked to the PWL phenotype

Genetic defect	15q duplication	19p deletion	Fragile X syndrome	Xq duplication	Total
Number of papers	12	2	4	5	66
Number of cases	86	2	23	5	292
Gender (M/F)	47/39	0/2	23/0	4/1	165/127
References	(13,54-64)	(65, 66)	(11, 67-69)	(10, 70-73)	
Clinical features, occurrence/n (%)					
Hypotonia	26/64 (40)	NA	7/23 (30)	**4/5 (80)**	139/248 (56)
Infantile feeding problems/FTT	3/27 (11)	NA	4/15 (27)	**5/5 (100)**	88/195 (45)
Hyperphagia	2/13(15)	0/1 (0)	**14/14 (100)**	**2/3 (67)**	76/186 (41)
Overweight/obesity	7/38 (18)	**2/2 (100)**	**23/23 (100)**	3/5 (60)	134/241 (56)
Distinctive facial features	2/41 (5)	0/1 (0)	0/15 (0)	1/5 (20)	19/226 (8)
DD/ID	**58/86 (67)**	**2/2 (100)**	**23/23 (100)**	**5/5 (100)**	**220/292 (75)**
Psychobehavioral problems	41/62 (66)	**2/2 (100)**	**14/15 (93)**	2/4 (50)	139/251 (55)
Speech problems	48/83 (58)	**1/1 (100)**	11/22 (50)	**5/5 (100)**	140/216 (65)
Skin picking	2/13 (15)	NA	6/11 (55)	**2/2 (100)**	20/76 (26)
Sleep disturbances/apnea	8/41 (20)	NA	NA	1/3 (33)	34/128 (27)
Short stature	7/67 (10)	0/2 (0)	2/23 (9)	**4/5 (80)**	81/259 (31)
Hypogonadism	3/64 (5)	NA	15/23 (65)	**4/5 (80)**	52/247 (21)
Small hands/feet	2/43 (5)	**1/1 (100)**	9/23 (39)	2/4 (50)	92/210 (44)
Eye abnormalities	5/26 (19)	NA	1/13 (8)	**2/2 (100)**	65/145 (45)
Distinguishing features	ASD, anxiety	NA	Tall stature, obsessive behavior and ASD	Facial hypotonia, cryptorchidism, seizures, microcephaly, low birth weight	

Bold: occurrence of 67% and higher.
Abbreviations: NA, information not available/provided in the paper; LoF = loss-of-function; FTT, failure to thrive; SNV, single nucleotide variant; DD, developmental delay; ID, intellectual disability; CNS, central nervous system; SGA, small for gestational age; ASD, autism spectrum disorder.

be found in Tables 3 to 5. The tables are arranged in a chromosome 1 to 22 order and in the following paragraphs we summarize the characteristics and symptoms of the genetic defects, with a final paragraph dedicated to defects that were only reported in 1 paper.

1p36 Deletion

In 5 papers, 11 patients with terminal 1p36 deletions were reported (7, 17-20). All patients had developmental delay and 10 out of 11 (91%) had neonatal hypotonia, with only 33% also exhibiting feeding difficulties in the neonatal period. Speech problems were common (91%), as was strabismus (82%). Several patients presented with hyperphagia (64%). Five patients were diagnosed with epileptic seizures (7, 17). One patient also had subnormal GH secretion (7). Short stature was reported in 4 patients (7, 18, 19).

2p Deletion

Patients with deletions or single nucleotide variants (SNVs) in the 2p25.3 region (21-25) typically presented with intellectual disability and/or motor delay (100%), speech delay (94%), and obesity (76%). The severity of the intellectual disability varied, with some patients not able to read and write or perform self-care activities (23, 25). The onset of obesity often occurred as early as 12-24 months of age (21, 22, 24). A significant number of cases also had hyperphagia (76%). Many patients had behavioral problems, often described as aggressive, autistic, and hyperactive (21, 23, 25). Epileptic seizures were common (23, 24). Features that were less frequently reported were (neonatal) hypotonia and eye abnormalities, including strabismus. There was no shared, distinctive facial dysmorphology reported.

The genes of interest in the 2p25 region, specifically 2p25.3 are the myelin transcription factor 1 like (*MYTL1L*) gene and *TMEM18* gene. Loss-of-function SNVs in the *MYT1L* gene were reported in several of the case reports that we reviewed (21-23).

6q Deletion

In 16 papers (4-6, 25-37), a total of 67 patients with a 6q deletion were described. Most, but not all of the deletions were of the 6q16 band and encompassed the single-minded homolog 1 (*SIM1*) gene. The similarities which most cases of 6q deletions have with PWS lie in

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Table 3. Clinical features of miscellaneous genetic defects

	Vauthier et al., 2012	Hyder et al, 2019	Cooke et al., 1995	D'Angelo et al., 2013	Alsters et al., 2015	Chantot-Bastaraud et al., 2004	Marangi et al., 2013	Tinkle et al., 2003	Kleefstra et al., 2000	Yeo et al, 2004*
Genetic defect	1p31.3 deletion	1q deletion	2q11.2-q21 duplication	3p26.3 deletion +11q22.3q25 duplication	4q32.3 SNV CPE gene	SMC chromosome 7	8q24 SNV	8q12.2q21.1 deletion	trisomy 8qter + terminal deletion 13q	9q21.33 SNV NTRK2 gene
Study size, n	1	1	1	1	1	2	2	1	2	1
Gender (M/F)	M	M	M	M	F	1/1	0/2	M	0/2	M
Reference	(104)	(105)	(84)	(25)	(106)	(107)	(108)	(109)	(110)	(111)
Clinical features										
Hypotonia	–	+	–	+	NA	NA	2/2	NA	1/2	+
Infantile feeding problems/FTT	NA	+	–	+	NA	NA	NA	NA	NA	NA
Hyperphagia	+	+	+	NA	NA	NA	NA	+	NA	+
Overweight/ obesity	+	+	–	+	+	1/2	2/2	+	2/2	+
Distinctive facial features	–	–	–	+	–	0/2	2/2	–	0/2	–
DD/ID	+	+	+	+	+	2/2	2/2	+	2/2	+
Psychobehavioral problems	NA	+	+	–	–	1/2	1/2	+	2/2	+
Speech problems	+	+	+	NA	NA	1/2	2/2	+	2/2	+
Skin picking	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sleep disturbances/ apnea	NA	+	+	NA	NA	NA	2/2	NA	NA	NA
Short stature	–	–	–	–	NA	0/2	0/2	+	0/2	–
Hypogonadism	+	–	–	+	+	NA	NA	NA	NA	NA
Small hands/feet	–	–	–	NA	NA	NA	0/2	–	NA	NA
Eye abnormalities	NA	NA	NA	NA	NA	NA	NA	+	1/2	NA
Distinguishing features	seizures	Low birth weight, aggressive outbursts	Hyperactivity, poor sleep	cryptorchidism, early onset obesity (< 1 of age)	Type 2 diabetes mellitus, primary amenorrhea	Long fingers, hyperactive behavior	Seizures, brachycephaly	Blepharophimosis, seizures, ASD, cataract, scoliosis	Genu valgum, muscle weakness	Abnormal nociception, early-onset obesity, seizures

Abbreviations: NA, information not available/provided in the paper; FTT, failure to thrive; SNV, single nucleotide variant; SMC, small marker chromosome; DD, developmental delay; ID, intellectual disability; ASD, autism spectrum disorder.

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Table 4. Clinical features of miscellaneous genetic defects

	Gawlik-Kuklinska et al., 2007	Sofos et al., 2012	D'Angelo et al., 2013	Niyazov et al., 2007	D'Angelo et al., 2013	D'Angelo et al., 2013	D'Angelo et al., 2013	Bachmann-Gagescu et al., 2010	Parente et al., 2017	Vergult et al., 2012
Genetic defect	9q34 duplication	11p15.4 duplication	12q15q21.2 deletion	12q subtelomeric deletion	12q21.32q23.1 duplication	14q12 deletion	14q11.2 duplication	16p11.2 deletion	17p13.1 SNV NLGN2	17q24.2 deletion
Study size, n	1	1	1	2	1	1	1	6	1	4
Gender (M/F)	F	M	F	2/0	F	F	M	NA	M	0/4
Reference	(74)	(112)	(25)	(113)	(25)	(25)	(25)	(114)	(115)	(75)
Clinical features										
Hypotonia	+	+	+	NA	+	+	+	1/6	NA	1/4
Infantile feeding problems/ FTT	+	–	NA	NA	NA	NA	NA	NA	NA	3/4
Hyperphagia	+	NA	+	2/2	+	–	+	1/6	+	NA
Overweight/ obesity	+	+	+	2/2	+	+	+	4/6	+	2/4
Distinctive facial features	–	–	–	0/2	–	–	–	0/6	+	0/4
DD/ID	+	+	+	2/2	+	+	+	6/6	+	4/4
Psycho-behavioral problems	NA	+	–	2/2	+	–	+	3/6	+	2/4
Speech problems	+	+	+	1/2	+	+	+	3/6	+	3/4
Skin picking	+	NA	NA	1/2	NA	NA	NA	NA	NA	NA
Sleep disturbances/ apnea	+	NA	NA	NA	+	NA	NA	NA	NA	1/4
Short stature	–	–	–	1/2	–	–	+	0/6	–	3/4
Hypogonadism	+	NA	+	1/2	NA	–	+	0/6	–	NA
Small hands/feet	–	–	+	0/2	+	NA	+	NA	NA	1/4
Eye abnormalities	NA	NA	+	NA	+	NA	+	1/6	NA	1/4
Distinguishing features	Secondary amenorrhea, absent speech, sleep apnea	SGA, aggressive behavior, large hands	Oligodontia, hypoplasia labia majora	Cryptorchidism, hyperactivity	Microcephaly, tooth agenesis, aggression, strabismus	Seizures, hypothyroidism, hypoglycemia	Microcephaly, strabismus, aggression, genital hypoplasia	Tall stature, precocious puberty	Self-injurious behavior, ADHD, OCD, macrocephaly	Visual and auditory hallucinations, epilepsy, hearing loss

Abbreviations: NA, information not available/provided in the paper; FTT, failure to thrive; SNV, single nucleotide variant; DD, developmental delay; ID, intellectual disability; SGA, small for gestational age; ADHD, attention deficit hyperactivity disorder; OCD, obsessive compulsive disorder.

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Table 5. Clinical features of miscellaneous genetic defects

	Zung et al., 2007	D'Angelo et al., 2013	Tarpey et al., 2007	Kleefstra et al., 2002	Tumer et al., 1998	Total
Genetic defect	19q12q13.3 duplication	Xp22.12p22.13 del	Xq24 SNV	Xq28 SNV *MECP* gene	SMC X	25 papers
Study size, n	1	1	39	1	2	76 cases
Gender (M/F)	M	F	39/0	M	0/2	M/F: 53/17
Reference	(116)	(25)	(117)	(118)	(119)	
Clinical features						
Hypotonia	–	+	NA	+	NA	16/28 (57%)
Infantile feeding problems/FTT	NA	NA	NA	NA	1/2	7/11 (64%)
Hyperphagia	–	NA	NA	NA	NA	8/20 (40%)
Overweight/obesity	+	+	15/39	+	2/2	46/76 (61%)
Distinctive facial features	–	–	NA	–	0/2	4/37 (11%)
DD/ID	+	+	22/39	+	2/2	**59/76 (78%)**
Psycho-behavioral problems	–	–	12/39	+	1/2	33/74 (45%)
Speech problems	+	+	18/39	+	1/2	46/74 (62%)
Skin picking	NA	NA	NA	NA	NA	**2/3 (67%)**
Sleep disturbances/ apnea	+	NA	NA	NA	NA	**8/11 (73%)**
Short stature	–	–	7/39	–	NA	13/73 (18%)
Hypogonadism	–	NA	10/39	NA	0/2	17/55 (31%)
Small hands/feet	–	–	7/39	+	2/2	14/61 (23%)
Eye abnormalities	NA	–	NA	+	1/2	9/20 (45%)
Distinguishing features	Hypertonia, seizures, onset obesity <1 year	Absent speech, seizures, preauricular pit	Macrocephaly, seizures	Gynecomastia, strabismus, seizures	Gynecomastia, strabismus, hypermetropia, seizures	

Bold, occurrence of 67% and higher.

Abbreviations: NA, information not available/provided in the paper; FTT, failure to thrive; SNV, single nucleotide variant; SMC, small marker chromosome; DD, developmental delay; ID, intellectual disability.

the presented symptoms of developmental delay/intellectual disability (90%), obesity/overweight (81%), speech problems (63%), behavioral problems (58%), and eye abnormalities, namely strabismus (53%). One feature that is often reported in cases with 6q deletions is the presence of a skull abnormality, such as brachycephaly (4, 5), macrocephaly (5, 32), or microcephaly (6, 37). Hypotonia was reported in 49% of all cases. Apparently, neonatal hypotonia and feeding difficulties were more often found in patients with larger deletions (5, 32, 34-36) and far less common in patients with smaller deletions (33) or in those with single-nucleotide mutations (26, 28, 31). Most patients had a normal birth weight (6, 33, 37), but some cases had a birth weight below the third centile (29, 30, 36).

Several patients had short stature (4, 6, 25, 26, 29, 30, 32), and a few patients presented with endocrine abnormalities, such as hypothyroidism and/or insufficient GH secretion (29, 34, 37).

Some less frequently reported symptoms are genital anomalies, namely cryptorchidism (5, 29), seizures (6, 30, 37), scoliosis (30), and congenital defects, including cardiac and renal abnormalities (6).

Three reports describe patients with a point mutation in the *SIM1* gene (26, 28, 31). Two patients with a loss-of-function single-nucleotide mutation in the *SIM1* gene presented with (not early-onset) obesity (28). Neither of these patients had dysmorphic features, including skull abnormalities. Five individuals with base pare substitutions in *SIM1*, presented in a separate paper, had no symptoms other than morbid obesity, while 4 patients were categorized as PWL (31). Blackburn et al., presented 2 patients with the same missense variant in *SIM1*. One of the patients had a PWL phenotype, but this individual also had

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Table 6. Total occurrence of clinical features in all cases

Number of cases	**368**
Gender (M/F)	218/144
Clinical features	
Hypotonia	**155/276 (56%)**
Infantile feeding problems/FTT	95/206 (46%)
Hyperphagia	84/206 (41%)
Overweight/obesity	**180/317 (57%)**
Distinctive facial features	23/263 (9%)
DD/ID	**279/368 (76%)**
Psycho-behavioral problems	**172/325 (53%)**
Speech problems	**186/290 (64%)**
Skin picking	22/79 (28%)
Sleep disturbances/apnea	42/139 (30%)
Short stature	94/332 (28%)
Hypogonadism	69/302 (23%)
Small hands/feet	106/271 (39%)
Eye abnormalities	74/165 (45%)

Bold: occurrence of 50% and higher.
Abbreviations: FTT, failure to thrive; DD, developmental delay; ID, intellectual disability.

a mutation in the *CHD2* gene, which might have been the cause of the developmental delay (26).

6q Duplication

Seven patients with 6q duplications were reported in 3 papers (25, 38, 39), though 2 of them had an additional chromosomal aberration, namely a 10p duplication (38) and a 10p deletion (25). Most patients had obesity (86%), developmental delay/intellectual disability (71%), and speech delay, with articulation defects and little language development (43%). In 1 family, 5 members had the duplication and 4 were born with macrosomia (39).

Temple Syndrome

For this review, 8 papers, presenting 48 cases of patients with Temple syndrome, were evaluated (40-47). Thirty-six out of the 48 patients (75%) had hypotonia and 33 out of 47 (70%) had infantile feeding problems. Notably, during pregnancy intrauterine growth restriction can be detected and all patients were born small for gestational age (40-47). One paper reported on the presence of a hypoplastic placenta (41). In 42 out of 48 patients (88%), the growth retardation persisted in childhood and 83% also had small hands and feet. Many patients developed central precocious puberty (41, 46, 47). Other common symptoms were recurrent middle ear infections (41, 43, 46), scoliosis (41, 47), and hyperextensible joints (42, 43), and in 1 report, 3 out of 7 patients were noted to have microcephaly postnatally, whereas 1 patient had macrocephaly (43). Several patients had a single palmar crease (43, 46).

Obesity/overweight was present in 25% of the cases, with food-seeking behavior (40, 41, 47) or without (40, 46).

The severity of developmental problems varied, with cases reporting limited gross motor developmental delay without severe intellectual disability (40, 43) and cases with intellectual disability (41-43). Many patients were said to have speech and expressive language delay (40, 44).

Schaaf–Yang Syndrome

SYS is caused by a truncating mutation in the *MAGEL2* gene, located on chromosome 15q11.2. Patients present with hypotonia (82%), feeding difficulties (86%), hypogonadism (52%), developmental delay (82%), behavioral abnormalities (50%), short stature (58%), and small hands and feet (57%) (48-50). The phenotype can vary, with some patients presenting with more generalized hypopituitarism (48, 49) and respiratory difficulties in the early infantile period (49). Most patients with SYS have joint contractures, a feature that is not seen in PWS (50). The psychobehavioral profile is also distinct from PWS; most patients with SYS have autism spectrum disorder (ASD), whereas the typical PWS hyperphagia and consequent obesity is often absent or only mildly present in SYS (50). Less common, but still prevalent in patients with SYS are symptoms like scoliosis, chronic constipation, gastroesophageal reflux, and eye abnormalities (50). The dysmorphic features are unlike those seen in PWS and inconsistent across individual patients (50).

(Distal) 15q Deletion

A few papers report on patients with deletions distally located from the PWS region on chromosome 15 (51-53). In the reports reviewed, the most prevalent symptoms were hypotonia (100%), hypogonadism (67%), hyperphagia (67%), overweight/obesity (75%), developmental delay (100%), speech problems (75%), and small hands and feet (67%). One report described a male patient with a complex aberration, consisting of a 15q26.2 deletion together with an 18q23 duplication, showing a PWL phenotype with growth retardation, developmental delay, rapid weight gain, sleep disorders, and speech problems. He had delayed pubertal development and did not show any specific behavioral phenotype (51). In another report, both patients had a moderate intellectual disability, behavioral disorder with aggressive and autistic features, epilepsy, scoliosis, and truncal obesity (52).

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15q Duplication

A total of 12 papers found in our search, report on 86 patients with a 15q duplication (13, 54-64). Thirty patients were described in a single paper (13). They had developmental delay, speech delay and psychobehavioral problems, such as ASD, auto-aggression, anxiety and attention deficit hyperactivity disorder as the most common features. Indeed, when considering all 86 patients, the most common symptoms were developmental delay in 67%, psychobehavioral problems in 66%, and speech problems in 58% of patients. Hypotonia was not rare, with an occurrence of 26 in 64 patients (40%). Obesity was only found in 7 out of 38 (18%) and hyperphagia was only reported in 2 out of 13 patients (15%).

Almost half of the group of 30 patients described by Al Ageeli et al. (13) presented with a seizure disorder. This also occurred in many of the other patients described in other reports (55, 56, 58, 61-64). Notably, in 1 family, consisting of 12 individuals carrying an interstitial duplication, seizures and ASD were only present in 1 patient with a severe phenotype (55). Several papers describe phenotypically normal individuals with a duplication of the long arm of chromosome 15 (13, 55, 57, 60, 62), occasionally stating that these patients had a smaller duplication than the affected patients (62).

19p Deletion

We reviewed a few case reports of patients with a 19p13 deletion (65, 66), but the deletions did not have any overlapping regions. Two patients presented with developmental delay and severe obesity (65, 66) with 1 of the 2 also presenting overgrowth with macrocephaly in childhood (66).

Fragile X Syndrome

The 4 papers concerning fragile X syndrome and a PWL phenotype report a total of 23 cases (11, 67-69). The most common symptoms were hyperphagia (100%), overweight/obesity (100%), developmental delay/intellectual disability (100%), behavioral problems (93%), and hypogonadism (65%). A distinguishing feature of fragile X syndrome is tall stature, thus very few patients had short stature (9%), yet a few more had small hands and feet (39%). One paper reported that all 13 cases had behavioral problems, including obsessive tendencies, food seeking, skin picking, and characteristics of ASD. Two out of the 13 patients also had seizures (67). In a report of 8 patients, 6 had hypogonadism, often described as pubertal delay (11).

Xq Duplication

There were several reports on patients with Xq duplications (10, 70-73), mostly affecting males. Not all of the reported duplications had overlapping regions. The most common symptoms were hypotonia (80%), neonatal feeding problems (80%), hypogonadism (80%), which was reported in all male patients, developmental delay (100%), speech problems (100%), and eye abnormalities (100%), characterized as poor eyesight requiring glasses (71) and myopia (10). At least 3 patients had a relatively low birth weight on or below, the third centile (10, 72, 73). Two patients were noted to have evident facial hypotonia, next to the axial hypotonia (70, 72), and 2 presented with gynecomastia (70, 71). Two patients developed microcephaly (71, 72). Three patients had undescended testes and a small penis and/or hypoplastic scrotum (70-72), with 1 patient showing hypogonadotropic hypogonadism (71). Three patients were overweight/obese (10, 71, 73). Notably, 1 patient also had typical Prader–Willi facial features, namely almond shaped eyes, narrow bifrontal diameter, and a small mouth (73).

Other Genetic Defects

The last group of papers are those describing miscellaneous genetic defects that could not be grouped and can be found in Table 6. They comprise a heterogeneous group of rare genetic disorders. We are not able to ascertain if patients with these disorders have a uniform phenotype, as it goes beyond the scope of this review. For this group, the clinical features cannot be summarized, but there were a few striking cases that stand out among the rest, such as a woman with a 9q34 duplication (74), who exhibited hypotonia and feeding difficulties after birth and presented with truncal obesity, food-seeking behavior from age 3 years, skin picking, obstructive sleep apnea, and secondary amenorrhea. Another remarkable report, described 4 patients with a 17q24.2 deletion (75). All 4 patients had developmental delay and only 2 were obese. Three had neonatal feeding difficulties, speech problems, and short stature. One of them was clinically diagnosed with Silver–Russel syndrome and had a robust response to GH treatment, despite having a normal response to GH stimulation testing. Two patients had epilepsy and the same 2 presented with visual and auditory hallucinations. In 3, conductive hearing loss was diagnosed.

Discussion

By reviewing papers reporting on patients with a PWL phenotype, we found the most common symptoms to be intellectual disability/developmental delay, speech problems,

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obesity/overweight, hypotonia, and psychobehavioral problems. Other symptoms specific and quintessential to PWS, such as neonatal feeding difficulties, hypogonadism, hyperphagia, and short stature, were much less frequently described.

Phenotype

The broad range of clinical symptoms in the group of patients with PWL underlines the importance of multidisciplinary care for this group of patients, as many will show additional features and symptoms that might require expertise and treatment by mental health specialists, neurologists, physiotherapists, and dieticians, next to the care provided by a physician. There was a number of additional features that might provide professionals with a framework to differentiate between various causes of the PWL phenotype, such as skull abnormalities as a distinct feature of 6q deletions, and pre- and postnatal growth retardation and precocious central puberty in Temple syndrome (41, 43, 46), joint contractures and ASD in SYS (50), tall stature in fragile X syndrome (11, 67), and an emphasis on psychobehavioral problems such as anxiety in 15q duplications (13, 55). Several of the reported genetic defects were associated with epileptic seizures, such as 1p36 deletions, 2p25 deletions, 6q deletions, 8q deletions, distal 15q deletions, and Xq duplications, whereas epilepsy is uncommon in PWS (76).

The most striking similarities to PWS are found in Temple syndrome, where patients follow a similar course as patients with PWS, with feeding problems in early life and a tendency to overeat in later childhood. In the neonatal period, the 2 syndromes can hardly be distinguished from one another, aside from patients with Temple syndrome having on average a lower birth weight than patients with PWS (3). The feeding problems often persist throughout infancy. It is unclear how much obesity and hyperphagia contribute to the Temple syndrome phenotype. Several papers report very few patients with these symptoms (41, 43), while others state it is a significant part of the phenotype (40, 47). It can be argued that this aspect of the syndrome takes shape in later childhood, which could explain the low frequency in cohorts of relatively young patients (41). Short stature is often described, but with most patients starting puberty very early, physicians should be alert to an equally early pubertal growth spurt which might disguise this feature of short stature in later childhood, while eventually the child would end up with a short adult height. Early puberty might also be a sign of an isolated mutation in the *MKRN3* gene (located in the Prader–Willi region of chromosome 15) or the *DLK1* gene (77), which might be found with a precocious puberty gene panel. In patients with these mutations, it is likely that the precocious puberty is an isolated symptom, without additional signs of PWL.

SYS was one of the first syndromes to be linked to PWS and has many similarities to PWS. SYS is caused by truncating point mutations of the paternal copy of the *MAGEL2* gene, located within the Prader–Willi region on chromosome 15. While PWS and SYS share many common features, such as neonatal hypotonia and feeding difficulties in infancy, there are also some striking distinct features. Patients with SYS often present with joint contractures, which is not commonly described in PWS, and patients with SYS demonstrate a higher prevalence of ASD. Hyperphagia and obesity are far less often seen in SYS than in PWS (50). The results of this review do reinforce these findings, with only 22% of cases with SYS showing hyperphagia and 26% being overweight or obese. There is evidence that the *MAGEL2* gene is involved in the MC4R pathway (78), with *MAGEL2* knockout mice displaying an elevated percentage of fat mass accompanied by high leptin levels. These mice did not show a significant difference in body weight, which is similar to what is seen in most patients with SYS (79). Whole gene mutations of *MAGEL2* appear to have a milder phenotype than the truncating mutations that are seen in SYS, therefore the *MAGEL2* gene knockout mice might not provide a perfect model for SYS (80).

In 2018, it was found that a different genetic syndrome, Chitayat–Hall syndrome (CHS), is also caused by variants in *MAGEL2* (81). The main characteristics of CHS are distal arthrogryposis, hypopituitarism, intellectual disability, and facial dysmorphias (82). Compared with SYS, the following characteristics were less often described in CHS: temperature instability, use of nasogastric feeding in infancy, and hyperphagia/obesity (83). CHS and SYS have strongly overlapping phenotypes and it has been postulated that the differences are due to intrasyndrome variability, suggesting that SYS and CHS are likely the same disorder (83).

Also in patients with 1p36 deletions, hyperphagia and obesity were not always apparent. It has been proposed that patients with larger deletions in this region have more severe disabilities and are unable to feed themselves or seek food. Thus in these patients hyperphagia and obesity might be clinically masked due to severe psychomotor developmental delay (19).

Patients with duplications in the long arm of the X chromosome also form an especially interesting, albeit small, group. They show a striking resemblance to patients with PWS with their infantile feeding problems, hypotonia, cryptorchidism, developmental delay, and behavioral problems, including self-injurious behavior (and skin picking)

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(10, 70-73). Many, but not all, eventually developed hyperphagia and obesity (10, 71, 73).

In our search, we found the largest group of patients to be those with 15q duplications (86 cases), which was remarkable, because although most patients have behavioral and psychological problems, such as anxiety and ASD, a large number of patients are asymptomatic. Possibly, the cases with small duplication are those with a normal phenotype (62). Overall, the PWL phenotype was not very pronounced in patients with this defect, but historically patients with a 15q duplication are described as PWL or even as PWS (63, 64).

Genetic Testing

Many of the genetic aberrations described in this review could be detected by single nucleotide polymorphism (SNP) array testing, but there are a few that might be missed. The most important one is probably Temple syndrome. It has been proposed that the incidence of Temple syndrome is much higher than was initially thought (43) and with the syndrome being so similar to PWS in the neonatal period, one could consider to always test for Temple syndrome if PWS could not be detected. If in addition to showing the typical neonatal phenotype, a child is also born small for gestational age with a birth weight below the third centile, Temple syndrome testing might even be prioritized over testing for PWS. There are also several single gene defects, such as the truncating mutations in the *MAGEL2* gene in SYS or single nucleotide variations in the *MYT1L* gene, that would be missed in SNP array testing, but can often be detected in obesity gene panels available in many laboratories. In Fig. 2, we propose a genetic diagnostic approach to the patient presenting with a PWL phenotype.

Future Research

There were several important problems that were often only briefly mentioned in the reports, but not discussed extensively. One of these is psychobehavioral problems, which in many patients were described as hyperactivity/hyperkinetic behavior, ASD, and/or aggression. The former is one not often seen in PWS. Very few papers gave more insight on the behavioral phenotype (13, 21, 57, 67, 75, 84) and it would be interesting to have more in-depth data on the scope of the behavioral problems, as these are often characterized as having a major influence on the quality of life of not only the patient, but the entire family. A second gap in information was found in the endocrine status of the reported cases. In some patients more extensive endocrine testing was described (41, 42, 85), such as thyroid function testing or GH stimulation testing, but there were often no endocrine function tests described. As patients with PWS have endocrine abnormalities, testing a larger group of patients with PWL for their endocrine status would add to the knowledge we have so far. This would add to providing more clarity on the pathophysiological mechanisms underlying the PWL conditions. Hypothalamic dysfunction accounts for many of the clinical aspects of the PWS phenotype (86). This is also suggested to be the cause of most symptoms in Temple syndrome (87), but uncertainty persists and this should be assessed in future studies. In other genetic defects with a potential PWL phenotype,

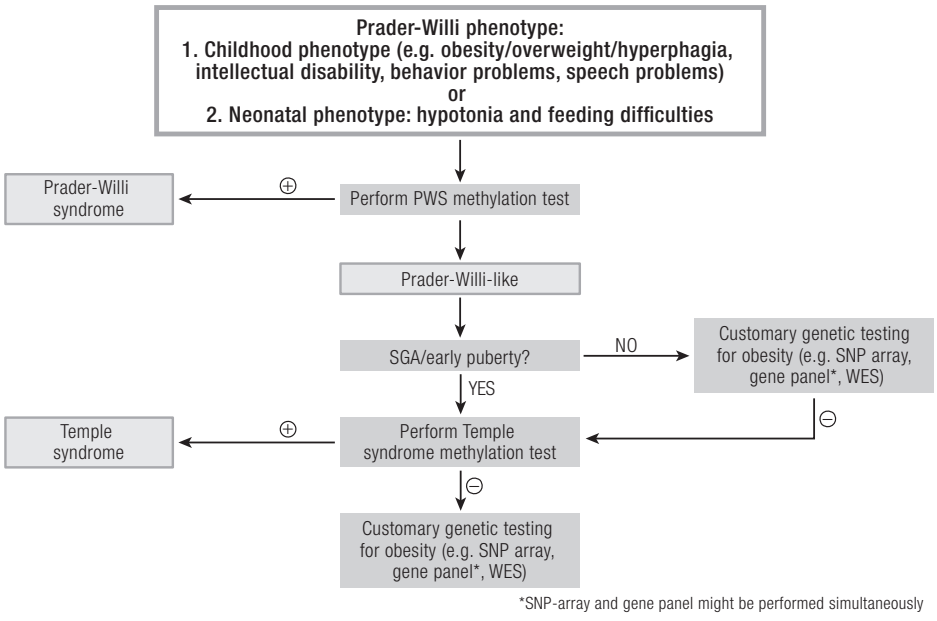

Figure 2. Genetic diagnostic approach to the patient with a PWL phenotype. *SNP-array and gene panel might be performed simultaneously. SNP: single nucleotide polymorphism, WES: whole exome sequencing.

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there may be involvement of the MC4 signaling pathway, such as in mutations of the *SIM1* gene (88), the *PHIP* gene (89), and, as mentioned before, in SYS (78). It is likely that there is not a single, overlapping pathophysiology of the PWL phenotype, but more likely several mechanisms that can lead to the same outcome of characteristics and symptoms.

Potential Treatment Options

There are several treatment options that could be explored in patients with PWL. GH treatment has been extensively investigated in PWS and proven effective in improving body composition by decreasing fat mass and increasing lean-body mass, as well as normalizing height (90-93). While there is a lot of literature supporting GH treatment in PWS, there is very little research done in children with PWL. In a small group of patients with Temple syndrome, GH treatment was shown to improve growth (94). In a retrospective study in 26 patients with SYS, of which 14 had been treated with GH, it was shown that GH increased body height and decreased body mass index in the first months of treatment (95). The rationale behind treating patients with PWS with GH is to improve the body composition. This aspect of GH treatment has barely been investigated in the PWL group.

Medication used for treatment of obesity could also be of interest, such as glucagon-like peptide-1 receptor agonist (eg, liraglutide), and MC4R agonists (eg, setmelanotide). Though liraglutide has been shown effective in the treatment of obesity for adults (96) and adolescents (97), there is no to very little evidence supporting its effect in patients with PWS or PWL. Similarly, setmelanotide has been tested in groups with both monogenetic obesity (98, 99) and syndromic obesity (100), and found effective, but no trials have been performed in children with PWS and PWL. Setmelanotide has been proven to decrease hunger scores (98-100) and could be of specific interest for the PWL phenotypes that present with severe hyperphagia.

Bariatric surgery is rarely performed in pediatric patients (101). There is some research done in small groups of patients with PWS, but results were inconclusive (102, 103). The option of bariatric surgery might be explored in PWL patients with severe obesity and comorbidities due to the overweight, but the cognitive and behavioral profile of the patients should always be taken into account.

Concerning pharmacotherapeutic and surgical treatment of patients with PWL, more research is needed to determine which (sub)group might benefit from different treatment options. Most of the PWL syndromes are quite rare, which makes it difficult to carry out (randomized, controlled) pharmacotherapeutic trials. The evidence for specific treatment options might therefore remain weak. We commend including patients with rare PWL syndromes, such as Temple syndrome and SYS, in trials for patients with PWS and/or other (syndromic) obesity conditions.

As a baseline for treatment, we advise multidisciplinary care with involvement of, at least, a physician, dietician, and psychologist. The focus should be on management of weight and complications due to overweight/obesity, while giving appropriate treatment for behavioral problems which might be linked to eating and food. Most children with PWL will present with intellectual disability and/or disharmonic intelligence profiles. As hospital visits can be difficult to navigate for these patients, it is important that they receive useful preparation and that the visits are predictable and familiar.

New Insights in the Definition of PWL

As been mentioned before, PWL lacks a clear and explicit definition. While it is tempting to provide criteria for this condition, it is also limiting. Determining that a patient has a PWL phenotype depends on too many factors and with adhering very strictly to criteria, we have found that patients might be falsely diagnosed or missed. An example can be patients with Temple syndrome, who often have an average total intelligence quotient, but do present with cognitive deficits, preventing them from functioning independently in daily life and affecting their performance in school. If PWL would be defined as a condition with intellectual disability, these patients could be overlooked. We advise expert opinion to take precedence over predetermined criteria in diagnosing a patient with PWL.

Conclusion

This review summarizes the current knowledge about PWL conditions, the differential diagnosis, and it informs on the identification of and testing for PWL. It gives insight into which mutations and aberrations could be considered when suspicion of PWS remains after negative testing, leading to the recommendation to always test for Temple syndrome if the patient has a neonatal period resembling that of PWS, especially if the child is born small for gestational age. In Fig. 2, we aim to clarify this recommendation and propose a diagnostic approach to patients with a PWL phenotype. There are many aspects of the PWL phenotype that need to be further unraveled, especially with regard to the behavioral phenotype, the endocrine status, and the possibilities for treatment, but, most importantly, we ascertain that the diversity and complexity of the range of symptoms linked to the PWL phenotype calls for multidisciplinary care with an individualized approach.

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Additional Information

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