The spectrum of the Prader-Willi-like pheno- and genotype

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Background

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 multidisciplinary care and treatment as children with PWS. In order to gain more knowledge on PWL, we provide a complete overview of published cases of patients with the PWL phenotype.

Methods

We conducted a Pubmed Search to identify papers published between January 1963 and May 2020 using the keywords overweight, obesity and intellectual disability. This lead to inclusion of 86 papers for review. Data extraction focused on clinical features related to PWS, distinguishing clinical features of PWL and genetic diagnoses.

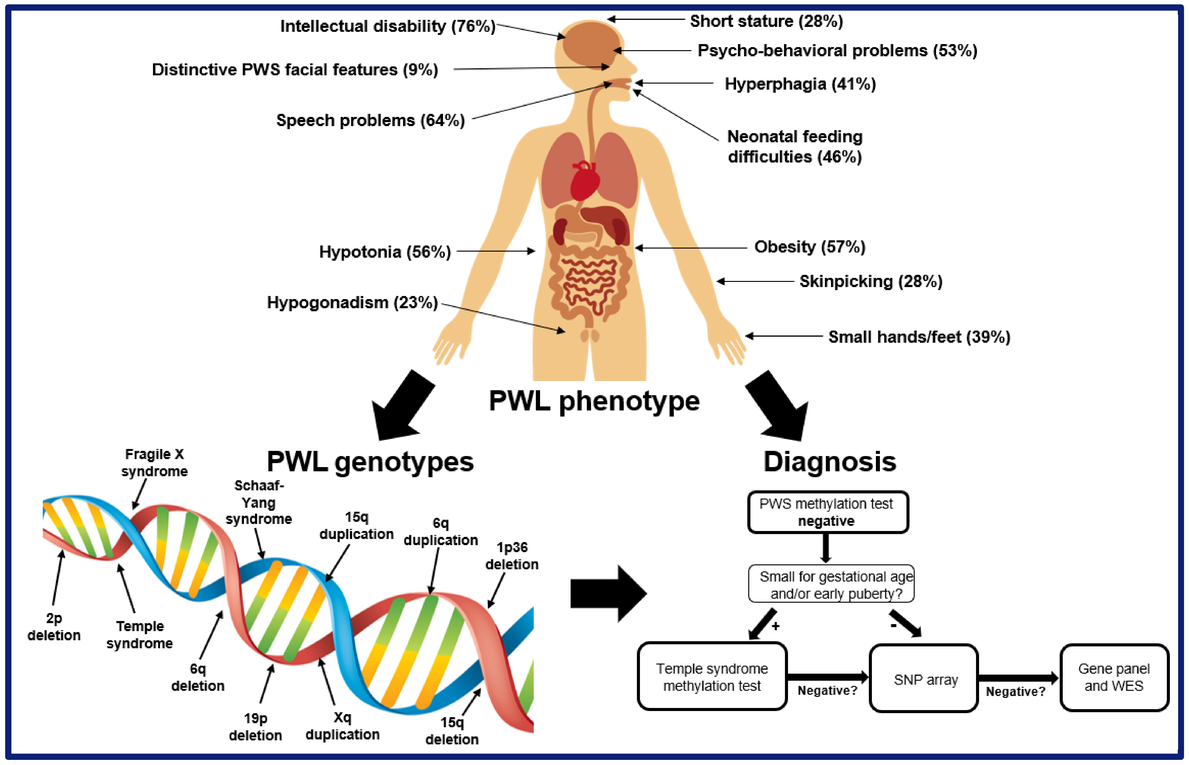
Results

Overall, 368 individual cases with 35 distinct genetic diagnoses were included. 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.

Total occurrence of clinical features

Number of cases	368
Sex (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%)

Note: FFT: failure to thrive; DD: developmental delay; ID: intellectual disability.
Bold: occurrence of 50% and higher



Key points:

- The PWL phenotype comprises a broad range of clinical symptoms, but most often described are obesity/overweight, psycho-behavioral problems, intellectual disability/developmental delay, speech problems and hypotonia.
- The most striking similarities to 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 but no genetic aberration of 15q11-q13, especially in a child born small for gestational age and/or presenting with early puberty in childhood.
- Most underlying genetic aberrations can be diagnosed with a SNP-array, but specified methylation testing might be required.
- **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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