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Compulsions in Prader-Willi syndrome: occurrence and severity as a function of genetic subtype

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Introduction. Compulsions are among the most typical behaviors in Prader-Willi syndrome (PWS). The most frequent causes of PWS are deletion of the genes located in the segment 15q11-q13 of the paternal allele and maternal uniparental disomy of cromosome 15. The aim of the present work was to study compulsive behavior in a sample of adults with PWS and analyze potential differences as a function of the genetic cause/subtype.

Material and methods. In the 27 study participants, existence of type I deletion (n=7), type II deletion (n=13), and maternal disomy (n=7) was determined by means of genetic tests. The Yale-Brown Obsessive Compulsive Scale, the Compulsive Behavior Checklist, and the Repetitive Behavior Questionnaire were used to assess occurrence and severity of compulsions.

Results. Most of the participants showed compulsive behavior, the most frequent compulsions were those of inappropriate grooming (skin picking) and order (hoarding). The occurrence of compulsions was less frequent in the maternal disomy group than in the deletion groups. Severe compulsions were more frequent in those participants with type II deletion than in the other groups.

Conclusions. Differences in occurrence and severity of compulsions exist as a function of PWS genetic subtype. Our results support the idea that individuals with maternal disomy are less affected by compulsive behavior. More research on the severity of compulsions as a function of deletion type should be done, as the studies conducted so far have shown contradictory results.

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Compulsiones en el síndrome de Prader-Willi: presencia y gravedad en función del subtipo genético

Introducción. Las compulsiones forman parte de las conductas más características del síndrome de Prader-Willi (SPW). Las causas más frecuentes del SPW son la deleción de los genes localizados en el segmento 15q11-q13 del alelo paterno y la disomía uniparental materna del cromosoma 15. El objetivo de este trabajo fue estudiar las conductas compulsivas en una muestra de adultos con SPW y analizar posibles diferencias en función de la causa/subtipo genético.

Material y métodos. En los 27 participantes del estudio, la presencia de deleción tipo I (*n*=7), deleción tipo II (*n*=13), y disomía materna (*n*=7) fue determinada mediante pruebas genéticas. La presencia y gravedad de las compulsiones fueron evaluadas mediante los cuestionarios *Yale-Brown Obsessive Compulsive Scale, Compulsive Behavior Checklist,* y *Repetitive Behavior Questionnaire.*

Resultados. La mayoría de los participantes presentaba conductas compulsivas, las más frecuentes eran las de cuidado inapropiado (excoriación) y orden (acumulación). La presencia de compulsiones era menor en el grupo con disomía materna que en los grupos de deleción. Las compulsiones graves eran más frecuentes en los participantes con deleción tipo II que en los otros grupos.

Conclusiones. Existen diferencias en la presencia y gravedad de compulsiones en función del subtipo genético del SPW. Los resultados apoyan la idea que las personas

con disomía materna están menos afectadas por las conductas compulsivas. Hay que seguir investigando sobre la gravedad de las compulsiones en función de los dos tipos de deleción, ya que los hallazgos de los distintos estudios son contradictorios.

Palabras clave: Síndrome Prader-Willi, Conducta Compulsiva, Deleción Genética, Disomía Uniparental

INTRODUCTION

Prader-Willi syndrome (PWS) is a genetic disorder due to the lack of expression of the genes from the locus 15q11-q13 of the paternal chromosome. The PWS phenotype includes neonatal hypothonia, dysmorphic features, and hypothalamic insufficiency causing endocrinological problems such as obesity, hypogonadism, and short stature. The syndrome shows a wide behavioral expression, including hyperphagia, severe tantrums, and obsessive-compulsive symptoms, as well as borderline, mild, or moderate, intellectual disability[1]. Three main genetic mechanisms result in the occurrence of PWS. Deletion or loss of the genes located at the 15q11-q13 region of the paternal chromosome is the most frequent cause (65-75% of the cases). This is followed by maternal uniparental disomy (20-30% of the cases), in which both copies of chromosome 15 come from the mother. Finally, an imprinting defect preventing the expression of the genes located at the 15q11-q13 region coming from the father occurs in 1-3% of the cases. Deletion is further subdivided in type I and type II; the former affecting the chromosome 15 segment between breakpoint (BP) 1 and BP3, and the latter affecting the segment included between BP2 and BP3. Thus, gene loss is larger in type I than in type II deletion[2,3].

Compulsions are highly frequent among individuals with PWS, and they cannot be explained only by hyperphagia or intellectual disability[4,5]. These may involve a significant deterioration in the quality of life of both individuals with PWS and their carers[6,7]; and they may even cause severe physical problems, such as in the case of skin picking[8]. In fact, skin picking is one of the most frequent compulsive behaviors in this group[9], together with hoarding and arranging. On the other hand, individuals with PWS show a lower frequency of cleaning and checking compulsions, which are typical of obsessive-compulsive disorder (OCD)[5]. A study conducted by our group showed abnormalities in the functional connectivity between the prefrontal cortex and the basal ganglia, and between subcortical structures, in participants with PWS compared to healthy controls. These abnormalities were associated with the occurrence and severity of compulsive behavior (including skin picking), and they showed some similarities with the abnormalities in functional connectivity previously seen in individuals with OCD[10].

Following the improvement in the methods used for identifying the PWS subtypes, several studies have focused on potential differences in compulsive behavior as a function of the three most frequent genetic subtypes (type I deletion, type II deletion, and maternal disomy). While it seems clear that individuals with maternal disomy show a smaller frequency and severity of compulsions than individuals with deletion[11,12], the available data on the potential differences between the two deletion types are inconsistent. In accordance with the larger number of genes affected in type I deletion, some results showed that this deletion type was associated with a greater compulsion severity than type II deletion[13,14]. Conversely, other studies found no differences[15,16].

Studying differences in compulsive behavior as a function of the distinct genetic mechanisms involved in PWS may help to enhance the support given to the affected individuals, particularly by preventing misguided attributions about the compulsion causes. In addition, the acquired knowledge might help to better understand the genetic basis of the obsessive-compulsive psychopathology, both in individuals with PWS and in other populations. Thus, the aim of the present research was to study the compulsive behavior of individuals with PWS and to identify potential differences as a function of genetic subtype. Based on previous findings, it was hypothesized a lower occurrence and severity of compulsive behavior in participants with maternal disomy than in participants with deletion. Given the heterogeneous results concerning the two deletion types, no specific hypotheses were made about the potential differences between participants in each of these two groups.

METHOD

Participants

Participants were recruited by means of a convenience sampling method in two centers of reference: Parc Taulí Health Corporation (Sabadell) and Specialized Service in Mental Health and Intellectual Disability of the health region of Girona (Salt). Associació Prader-Willi Catalunya (Barcelona) and Fundación Prader-Willi (Madrid) also helped in the recruitment. Those individuals with severe sensory impairment, central nervous system impairment unrelated to PWS (e.g., head injury, stroke, or brain tumor), substance abuse, and non-treated illnesses with associated cognitive deficits (e.g., hypothyroidism, B12 vitamin deficiency, or diabetes mellitus), were excluded. In addition, those individu-

als with PWS due to genetic imprinting defects were also excluded (*n*=3). The final sample was composed of 27 participants (mean age=27.30 years, standard deviation=8.25; 14 women, 51.9%) with PWS due to deletion (*n*=20) or maternal disomy (*n*=7). Seventeen participants were taking psychoactive medication: selective serotonin reuptake inhibitors (*n*=9), topiramate or other antiepileptics (*n*=14), antipsychotics (*n*=6), and/or benzodiazepines (*n*=1). All of them were on a stable medication regime for at least the three months before the study.

Procedure

All potential participants were informed about the study, and those who were part of the final sample and their legal tutors gave their informed assent/consent. PWS diagnosis was confirmed by the absence of the paternal allele at 15q11-q13, by means of a specific PCR methylation. Deletion was determined by means of in situ fluorescence hybridization. Designation of deletion type (I or II) was identified by means of a multiplex ligation-dependent probe amplification (MRC-Holland). In order to identify maternal disomy, an analysis of multiple microsatellite markers distributed within the 15q11-q13, and along chromosome 15, was conducted in both the proband and their parents.

A psychiatrist conducted the psychopathological assessment, guided by the PAS-ADD-10 interview[17], as well as the assessment of compulsive traits by means of standardized questionnaires, which were answered by the carer of each participant with PWS (see Instruments section). A neuropsychologist assessed intellectual disability, using the DSM-5 criteria[18] in order to determine the level of impairment. In addition, she conducted an extensive neuropsychological assessment by means of the Barcelona Test for Intellectual Disability (BT-ID)[19]. Both professionals are experts in mental health and intellectual disability.

The clinical research ethics committee in Parc Taulí Health Corporation approved the study protocol, and its development was thoroughly supervised by the principal investigator, ensuring adherence to the principles of the Declaration of Helsinki.

Instruments

Yale-Brown Obsessive Compulsive Scale (Y-BOCS)

This standardized scale is the most frequently used to assess obsessions and compulsions in psychiatric patients[20]. In addition, it has been extensively used in studies of PWS[4,5,12-14,16]. In the present study, it was used to obtain a severity score of the compulsive symptoms, based on five items assessing the time spent doing compulsions, the degree of distress produced by them, the degree of interference in social activities, and the ability to resist and control them. Every item has five options of *Likert*-type response, from 0 to 4. Therefore, scores vary between 0 (absence of symptoms) and 20 (maximum symptom severity).

Compulsive Behavior Checklist (CBC)

List of 25 compulsive behaviors specifically designed to assess individuals with intellectual disability[21]. It has been frequently used in studies of PWS[13,14,22-24]. The specific behaviors are grouped in five categories: ordering, completeness, cleaning, checking and touching, and deviant grooming.

Repetitive Behavior Questionnaire (RBQ)

It evaluates the occurrence of 19 repetitive behaviors that are typical of both autism spectrum disorders and OCD. These are grouped in five categories: stereotyped behavior, compulsive behavior, restricted preferences, repetitive speech, and insistence on sameness. In the present study, those behaviors that were performed at least with a daily frequency were analyzed, as this frequency is considered the clinical cutoff[25].

Data analysis

Given that the quantitative variables did not show normal distributions, they were summarized with medians (*Md*) and interquartile ranges (*IQR*). Absolute frequencies and percentages were computed for the categorical variables. The Fisher's exact test was used in order to analyze potential differences in the frequency distributions as a function of genetic subtype. When a significant effect was found, standardized residuals were computed in order to ascertain which groups differed from the others ($\pm$ 1.96 cutoff). In addition, odds ratios (OR) with their 95% confidence intervals (CI) were computed in order to confirm the observed associations. The statistical significance level was set at $p \leq 0.05$. The overall *n* in the data from the CBC decreased to 25 due to the existence of missing values in two participants. Data were analyzed by means of Stata 12.0 software.

RESULTS

Seven participants showed type I deletion, 13 type II deletion, and the remaining seven participants showed ma-

Table 1 Age, gender, and level of intellectual disability of participants with Prader-Willi syndrome, as a function of genetic subtype

	Type I deletion (*n*=7)	Type II deletion (*n*=13)	Maternal disomy (*n*=7)
Age, Md (IQR)	25 (19–35)	30 (23–36)	22 (18–26)
Gender, n (%)			
Men (n=13)	2 (28.6%)	8 (61.5%)	3 (42.9%)
Women (n=14)	5 (71.4%)	5 (38.5%)	4 (57.1%)
Level of intellectual disability, n (%)			
Mild (n=21)	5 (71.4%)	11 (84.6%)	5 (71.4%)
Moderate (n=6)	2 (28.6%)	2 (15.4%)	2 (28.6%)

Md: median; IQR: interquartile range.

ternal disomy. Table 1 shows the distributions of age, gender, and level of intellectual disability as a function of genetic subtype. No statistically significant differences were found concerning these characteristics. One participant with type II deletion had been diagnosed with affective disorder, while another participant with disomy had been diagnosed with psychotic disorder.

Compulsive behavior in the whole sample

Table 2 shows the scores of the questionnaires used to study the compulsive behaviors. Y-BOCS showed a moderate level of compulsion severity (*Md*=7). Figure 1 shows the distribution of the response options for each of the Y-BOCS items. Around half of the participants had selected a response option that reflected a certain degree of severity in each item. This group of participants spent a moderate amount of time (1-3 hours per day) doing compulsions, which caused them moderate levels of distress and interference. In addition, these participants did not show any resistance to compulsions, and they had little or no control over them.

Participants showed a median of 2 compulsions as measured by the CBC, and at least one compulsion was recorded for most of them (76.0%). Deviant grooming, which included an item about skin picking ("Picks at face/body to point of gouging skin"), was the most frequent category (56.0% of participants), followed by ordering (48.0%), and cleaning compulsions (44.0%). On the other hand, completeness (28.0%), and checking and touching (24.0%), appeared less frequently (Table 2).

Concerning the RBQ data, participants carried out a median of 2 repetitive behaviors at least once a day. Two thirds of the participants showed at least one daily repetitive behavior. Within the different categories, compulsive behaviors were performed by the largest percentage of participants (55.6%), followed by stereotyped behavior (44.4%). Those behaviors belonging to the remaining categories (restricted preferences, repetitive speech, and insistence on sameness) were seen in less than 20% of the participants (Table 2).

Effects of PWS genetic subtype

Table 3 shows those results in which effects of genetic subtype were found. Based on its distribution, the Y-BOCS compulsion severity score was dichotomized in severity score=0 and severity score>0. The dichotomized score showed a statistically significant association with genetic subtype, Fisher's test=6.08, p=0.04. The standardized residuals showed that this association existed because of a larger percentage of individuals with severity scores > 0 in the type II deletion group (76.9%, standardized residual=2.51), compared to the type I deletion and maternal disomy groups (28.6% in both cases). The response options of the Y-BOCS individual items were also dichotomized. The analyses showed that genetic subtype was significantly associated with the time spent doing compulsions and the ability to control them, Fisher's tests=6.08, ps=0.04. Specifically, the type II deletion group showed a larger percentage of individuals spending time doing compulsions and not having control over them (76.9% in all cases, standardized residuals=2.51) in comparison with the type I deletion and disomy groups (28.6% in all cases). In addition, a trend to a statistically significant association between genetic subtype and resistance to compulsions was also seen, Fisher's test=6.18, p=0.06. Again, the type II deletion group distinguished from

Tabla 2 **Medians (Md), together with their 95% confidence intervals (95% CI), and interquartile ranges (IQR) of the scores obtained with the compulsion questionnaires. Absolute frequencies and percentages of participants with Prader-Willi syndrome who had the different compulsions and repetitive behaviorsa**

	Md (95% CI) / *n*	IQR / %
Y-BOCS compulsion severity	7 (3.97–10.03)	0-13
CBC overall compulsions	2 (-0.20–4.20)	1-4
CBC presence of compulsions	19	76.0%
Deviant grooming	14	56.0%
Ordering	12	48.0%
Cleaning	11	44.0%
Completeness	7	28.0%
Checking and touching	6	24.0%
RBQ overall repetitive behaviorsb	2 (0.18–1.82)	0-4
RBQ presence of repetitive behaviors	18	66.7%
Compulsive behavior	15	55.6%
Stereotyped behavior	12	44.4%
Repetitive speech	5	18.5%
Insistence on sameness	5	18.5%
Restricted preferences	3	11.1%

[a]Overall n=27. Except in the CBC data, for which the overall n=25.
[b]According to the clinical cutoff, those repetitive behaviors that occurred at least once a day were counted.

the other two, with a larger percentage of individuals not offering a complete resistance to compulsions (69.2% in the type II deletion group, vs 14.3% and 28.6% in the type I and maternal disomy groups, respectively, standardized residual=2.50). The OR confirmed the differences found between those participants with type II deletion and the rest. Compared to the other participants, the type II deletion group showed a positive association with severity, time, and lack of resistance (all OR=8.33, 95% CI=1.47–47.23), and low control over compulsions (OR=8.25, 95% CI=1.45–46.86).

According to the CBC data, a statistically significant association existed between presence of compulsive behaviors and genetic subtype, Fisher's test=6.62, p=0.03. This association involved a smaller percentage of individuals with compulsive behaviors in the maternal disomy group (33.3%, standardized residual=-2.81), compared to type I (85.7%) and type II (91.7%) deletion groups. When the compulsion categories were considered separately, no genetic subtype effects were found.

Regarding the RBQ data, a statistically significant association existed between daily occurrence of repetitive behaviors and genetic subtype, Fisher's test=6.00, p=0.04. Again, the association was due to a smaller percentage of individuals doing daily repetitive behaviors in the disomy group (28.6%, standardized residual=-2.84) compared to type I (71.4%) and type II (84.6%) deletion groups. In addition, genetic subtype also showed a trend to a statistically significant association with daily occurrence of compulsive behaviors, Fisher's test=6.18, p=0.06. This trend was due to a smaller percentage of individuals with compulsive behaviors in the maternal disomy group (14.3%, standardized residual=-2.55) compared to the other groups (71.4% in type I deletion, and 69.2% in type II deletion). No effects of genetic subtype were seen in the remaining categories of repetitive behaviors.

The OR showed that, relative to the deletion groups, the maternal disomy group showed a negative association with the occurrence of compulsive behaviors according to the data from the CBC (OR=0.06, 95% CI=0.01–0.55) and with a daily occurrence of repetitive behaviors (OR=0.10, 95% CI=0.01–0.75) and compulsive behaviors (OR=0.02, 95% CI=0.01–0.32) according to the data from the RBQ.

Lastly, although there were no significant differences in the distributions of age, gender, and intellectual disability, as a function of genetic subtype; analyses were conducted in order to test whether these variables were associated with the measures of compulsive behaviors. Given that age did not show a normal distribution, Mann-Withney tests (U) were used in order to analyze potential differences in the distribution of this variable as a function of the dichotomized scores. These analyses revealed that those participants with a Y-BOCS severity score>0 were older than those with a score=0, *Md*=29 (*IQR*=22–36) vs *Md*=22 (*IQR*=18–28), U=47.50, p=0.03. Age also showed a significant association with the dicothomized scores of some Y-BOCS individual items. Those participants who spent time in doing compulsions, did not show a lot of resistance, and were not completely in control, were older than those who did not spent time doing compulsions [*Md*=29 (*IQR*=22–36) vs *Md*=22 (*IQR*=18–28), U=47.50, p=0.03], showed a lot of resistance [*Md*=32 (*IQR*=22–36) vs *Md*=24 (*IQR*=18–27), U=49.50, p=0.03], and were completely in control [*Md*=29 (*IQR*=22–36) vs *Md*=22 (*IQR*=18–28), U=47.50, p=0.03]. Regarding the CBC data, a trend to significantly older ages was seen in

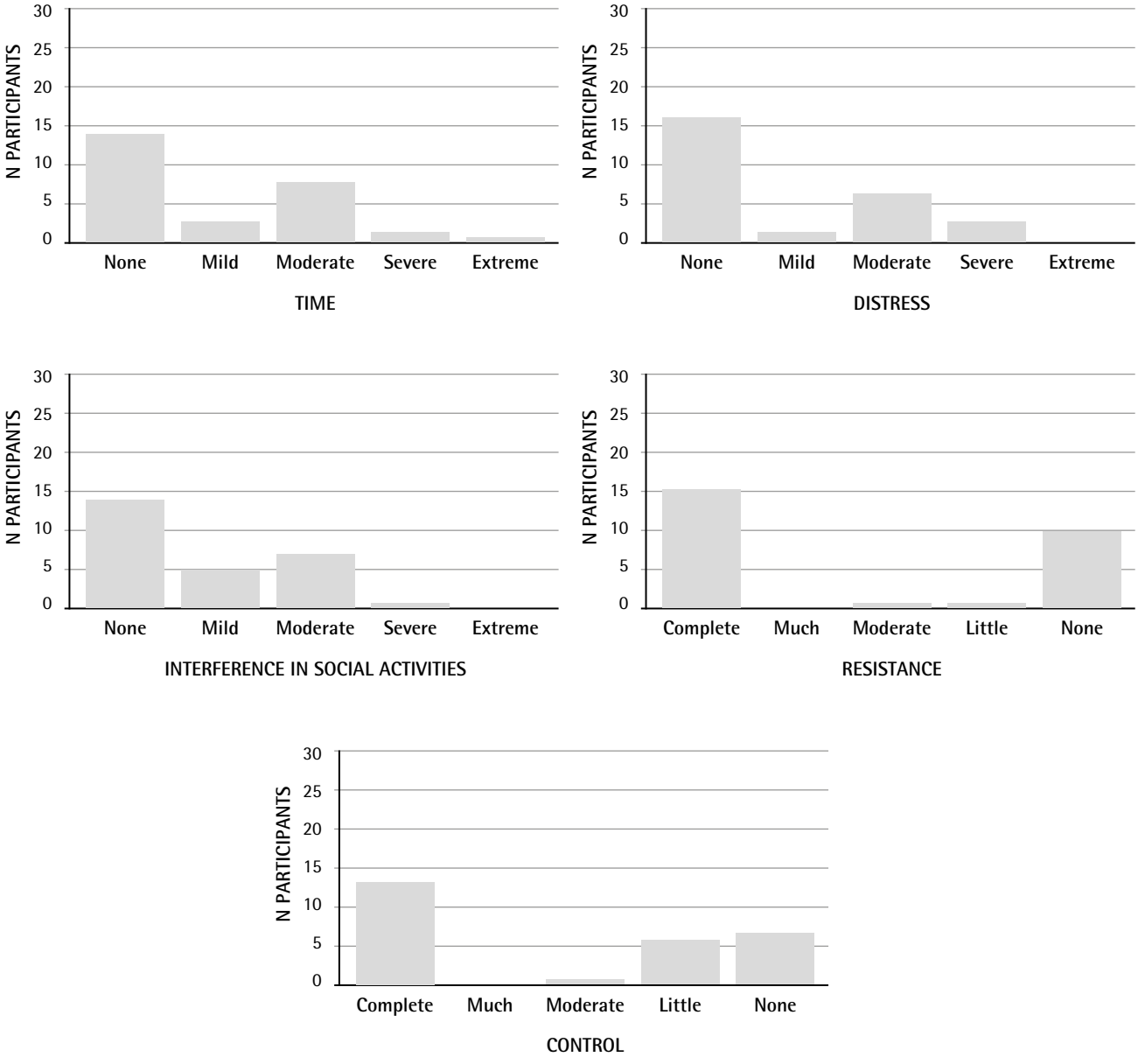

Figure 1 | *Y-BOCS compulsion severity*

those participants who showed some of the compulsive behaviors compared to those who did not show any, *Md*=27 (*IQR*=22–35) vs *Md*=19 (*IQR*=17–27), *U*=28.50, *p*=0.07. In addition, those participants who showed ordering compulsions were older than those who did not show them, *Md*=29 (*IQR*=24–35) vs *Md*=20 (*IQR*=18–30), *U*=42.00, *p*=0.05. Regarding gender, the percentage of men with ordering compulsions was higher than that of women (85.7% vs 14.3%, Fisher's test=6.87, *p*=0.02). No other significant associations existed between compulsive behaviors and age, gender, or level of intellectual disability.

CONCLUSIONS

The aim of the present work was to study the frequency and severity of compulsions in a sample of adults with PWS, and to analyze potential differences as a function of genetic subtype (type I deletion, type II deletion, and maternal

Table 3 Variables in which participants' distribution differed as a function of the genetic subtype of Prader-Willi syndrome. Absolute frequencies and percentages are shown

	Type I deletion (*n*=7)	Type II deletion (*n*=13)[a]	Maternal disomy (*n*=7)[a]	Fisher's test	*p*
Y-BOCS compulsion severity					
Overall score>0[b]	2 (28.6%)	10 (76.9%)	2 (28.6%)	6.08	0.04
Time>None[b]	2 (28.6%)	10 (76.9%)	2 (28.6%)	6.08	0.04
Resistance<Complete[b]	1 (14.3%)	9 (69.2%)	2 (28.6%)	6.18	0.06
Control<Complete[b]	2 (28.6%)	10 (76.9%)	2 (28.6%)	6.08	0.04
CBC					
Presence of repetitive behaviors[c]	6 (85.7%)	11 (91.7%)	2 (33.3%)	6.62	0.03
RBQ					
Daily presence of repetitive behaviors[c]	5 (71.4%)	11 (84.6%)	2 (28.6%)	6.00	0.04
Daily presence of compulsive behavior[c]	5 (71.4%)	9 (69.2%)	1 (14.3%)	6.18	0.06

[a]In the RBQ data, type I deletion n=12 and maternal disomy n=6.

[b]The standardized residuals of the type II deletion group (all>2.49) showed that the differences in each variable were due to the fact that a larger percentage of participants in that group had the levels shown on the table, compared to participants from the other groups.

[c]The standardized residuals of the maternal disomy group (all<-2.47) showed that the differences in each variable were due to the fact that a smaller percentage of participants in that group showed the studied behaviors, compared to participants from the other groups.

disomy). Most of the participants showed at least one of the compulsive behaviors assessed by the CBC. Deviant grooming behaviors (which included skin picking) were the most frequent, followed by ordering compulsions (which included hoarding), and cleaning. On the other hand, completeness compulsions, and checking and touching, were seen less frequently. These results are in line with those described in previous studies conducted with individuals with PWS. Stein et al.[9] showed that skin picking was the most frequent compulsive symptom, and secondly came hoarding. Dykens et al.[5] found that the most frequent type of compulsion was hoarding, while the least frequent was checking. In that study, participants with PWS were compared with individuals with OCD, and in the latter group the most frequent symptom was checking, while the least frequent was hoarding. Therefore, they showed opposite patterns. Despite this difference, participants with PWS showed a presence and severity of compulsions similar to those of participants with OCD. Clarke et al.[4] also showed that checking (and counting) were the type of compulsions that were most frequently seen in a sample of individuals with PWS. These authors compared participants with PWS with a group of individuals with a similar level of intellectual disability and body mass index, and they found a greater occurrence of compulsions in the former group.

Regarding the genetic subtype effects, the present study confirms previous findings showing that individuals with maternal disomy are less affected by compulsive behaviors[11,12]. Thus, the occurrence of compulsions in the disomy group was lower than in the deletion groups, and their severity was lower than in the type II deletion group. However, and against what has been reported so far in the literature, the type II deletion group showed a greater compulsion severity than the type I deletion group. These results add more complexity to the current evidence on the potential differences as a function of deletion types. On the one hand, Butler et al.[13] found that type I deletion was linked to more difficulties in controlling compulsions and larger interferences in social activities (as assessed with the severity items of the CBC). The latter difference was also reported by Zarcone et al.[14]. On the other hand, Milner et al.[15] found no differences in the overall compulsion severity score of the Children's Y-BOCS. Similarly, Dykens et al.[16] did not find differences in the overall severity score of the Y-BOCS for adults. Thus, it appears that the selected questionnaire might have an influence in the differences: From greater severity in type I deletion using the CBC to a lack of differences –or in our study greater severity in type II deletion– with the (Children's) Y-BOCS. On the other hand, the sample of the current study consisted of adults (18–36 years), while the other studies were conducted using participants with a

much wider age range (including both minors and adults up to 50 years). Age might also be an important factor when it comes to explain the discrepancies between studies. In fact, Dykens et al.[16] found an association between age and several measures of compulsions and problem behaviors as function of genetic subtype.

The main limitation of the present study was the small sample size in the type I deletion and maternal disomy groups (n=7). However, the three study groups were comparable regarding some characteristics that could potentially be associated to compulsive behavior (such as age, level of intellectual disability, and gender) and showed a homogeneous age range. In addition, the present study was not concerned with obsessions. Still, they were not investigated in most of the related studies. This can be attributed to the existing difficulties in assessing obsessions in a reliable way in individuals with intellectual disability[26]. In fact, strong difficulties exist when it comes to detect obsessive thoughts, as well as resistance, mental control, or avoidance behavior; which are required ICD-10 criteria to diagnose OCD. In this sense, the authors of the present study suggest using the diagnostic category obsessive-compulsive spectrum disorders (OCSD), which includes symptoms reminiscent of OCD yet excluding the typically egodystonic nature of those symptoms[27].

The present study shows that there are differences in the presence and severity of compulsions as a function of the PWS genetic subtype. The results support the idea that individuals with maternal disomy are less affected by compulsive behavior. On the other hand, adults with type II deletion may show more severe compulsions than adults with type I deletion. In that sense, and given the discrepancy of the results published so far, it is important to study which characteristics may have an influence in compulsion severity as a function of the two deletion types. Distinguishing whether these behaviors are real compulsions in an OCD, impulses, or just typical rituals in PWS (behavioral phenotype), is a difficult but necessary work, with important implications for providing an appropriate treatment.

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CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

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