**Title: Are Angelman and Prader-Willi Syndromes more Similar than we Thought? Food-related Behavior Problems in Angelman, Cornelia de Lange, Fragile X, Prader-Willi and 1p36 Deletion Syndromes**

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### ABSTRACT

Food-related behavior problems are well documented in Prader-Willi syndrome (PWS), with impaired satiety, preoccupation with food and negative food-related behaviors (such as taking and storing food) frequently reported as part of the behavioral phenotype of older children and adults. Food-related behavior problems in other genetic neurodevelopmental syndromes remain less well studied, including those seen in Angelman Syndrome (AS), the ’sister imprinted disorder’ of PWS.

 Food-related behavior problems were assessed in 152 participants each with one of five genetic neurodevelopmental syndromes – PWS, AS, 1p36 deletion, Cornelia de Lange and fragile X. Predictably, levels of food-related behavior problems reported in participants with PWS significantly exceeded those of at least one other groups in most areas (impaired satiety; preoccupation with food; taking and storing food; composite negative behavior). However, the AS group were also reported to display significantly more food-related behavior problems than at least one comparison group on measures of taking and storing food, composite negative behaviors, impaired satiety and preoccupation with food. In some areas people with AS were reported to display food-related problems at least as severe as those with PWS. Over 50% of participants in the AS group scored above the median point of the distribution of PWS scores on a measure of taking and storing food. These findings indicate further investigation of eating problems in AS are warranted and have implications for current theoretical interpretations of the behavioral differences between AS and PWS.

**INTRODUCTION**

Atypical and problematic eating- and food-related behaviors feature in the descriptions of a number of genetic syndromes, but are most prominently associated with the behavioral phenotype of Prader-Willi Syndrome (PWS). PWS is caused by absence or lack of expression of a region of the paternally-derived proximal long arm of chromosome 15q (15q11-q13). The phenotype [see, e.g., Whittington & Holland, 2010] includes initial feeding difficulties and failure to thrive [e.g., Greenberg, Elder, & Ledbetter, 1987], followed by the onset in early childhood of hyperphagia and obesity. This may relate to (amongst other factors) impaired satiety, with difficulties possibly underlain by altered function of the feeding pathways of the hypothalamus and/or altered regulation of genes related to energy balance [see McAllister, Whittington, & Holland, 2011, for a review]. A number of related behavioral difficulties typically become apparent, including preoccupation with food and behaviors such as taking [Donaldson, Chu, Cooke, Wilson, Greene & Stephenson, 1994] and hoarding [Dykens, Leckman, & Cassidy, 1996] food items.

Russell & Oliver [2003] introduced the Food-Related Problems Questionnaire (FRPQ) to assess three dimensions of disordered eating in PWS: impaired satiety, preoccupation with food and composite negative behaviors. The composite negative behaviors scale can be subdivided into three areas: taking and/or storing food inappropriately, eating inedible items and responding in an inappropriate way when food is not available or is restricted. Russell and Oliver [2003] reported that people with PWS displayed significantly higher scores on all subscales of this questionnaire than groups of people with similar levels of intellectual disability due to other causes.

Phenotypic food-related behaviors found in other syndrome groups remain relatively unexamined, despite the fact that in a number of other syndromes there are reports of disordered eating behaviors, including some signs typically associated with PWS. These groups include 1p36 deletion syndrome, in which clinical similarities with PWS have been noted [e.g., D’Angelo, Da Paz, Kim, Bertola, Castro, Varela & Koiffmann, 2006; Tsuyusaki , Yoshihashi, Furuya, Adachi, Osaka, Yamamoto & Kurosawa, 2010; although see also Rodríguez, Mazzucato, & Pina-Neto, 2008], and fragile X Syndrome (FXS), some people with which are reported to display a ‘Prader-Willi Phenotype’, including obesity and hyperphagia [Nowicki, Tassone, Ono, Ferrant, Croquette, Goodlin-Jones & Hagerman, 2007; De Vries, Fryns, Butler, Canziani, Wesby-van-Swaay, van-Hemel & Oostra, 1993]. In addition, Angelman syndrome (AS) has been reported to be associated with food fads, gorging on or stealing food, eating non-food items [e.g., Berry, Leitner, Clarke, & Einfeld, 2005], and obesity [Clayton-Smith, 1993], although food-related behaviors have not received extensive or systematic study in this population. AS has sometimes been regarded as a ‘sister imprinted disorder’ to PWS [Cassidy, Dykens, & Williams, 2000] in that, whilst PWS is associated with a loss of (or loss of expression of) genetic material in the 15q11-q13 region of the paternally-derived chromosome 15q, AS is associated with loss in maternally-derived genetic material within the same region [Cassidy et al., 2000]. The substantial differences between the behavioral phenotypes of AS and PWS have been interpreted in the light of their respective paternal and maternal genetic origins [Haig & Wharton, 2003; Haig, 2014].

Comparisons between different genetic disorders are considered crucial to the development of understanding of behavioral phenotypes [e.g., Hodapp & Dykens, 2001]. The aim of the present study was therefore to examine the nature and extent of food-related behavior problems traditionally associated with PWS across a number of other syndrome groups – AS, 1p36 deletion syndrome and FXS – in relation to each other and in relation to a group of participants with PWS. A further comparison group of participants with Cornelia de Lange syndrome (CdLS) was also included, since the behavioral phenotype of this syndrome [e.g., Oliver, Arron, Hall, & Sloneem, 2008] is not commonly considered to include the types of problematic eating behaviors seen in PWS (whilst problems with feeding can be major management issues in people with CdLS [Hawley, Jackson, & Kurnit, 1985], the types of difficulty reported in this syndrome group relate more to inadequate food intake, and to disorders of the digestive tract, than to behavior problems related to excessive interest or consumption).

We used the FRPQ [Russell & Oliver, 2003], a measure already established for use with people with PWS and known to have favorable psychometric properties, to assess a range of problematic food-related behaviors. Whilst the FRPQ was developed primarily for use with people with PWS, a comparison group of people without PWS in residential care was also used when establishing its psychometric properties (which were deemed sufficiently robust for use of the instrument in future research) [Russell & Oliver, 2003]. Its status as an informant report measure (in contrast with many other measures of disordered eating) makes the FRPQ suitable for those with intellectual disabilities of differing severities.

**MATERIALS AND METHODS**

**Participants**

A total of 729 participants, each with one of four genetic syndromes (127 Angelman (AS), 157 Cornelia de Lange (CdLS), 220 Fragile X (FXS), 204 Prader-Willi (PWS) syndromes), were contacted as part of a longitudinal follow-up study. These participants had initially been contacted via relevant syndrome support groups, at which point the diagnosis of each participant was confirmed by information from a clinical geneticist, paediatrician, neurologist or general practitioner [for further information about initial recruitment, see Arron, Oliver, Moss, Berg, & Burbidge, 2011; Burbidge, Oliver, Moss, Arron, Berg, Furniss, Hill, Trussler & Woodcock, 2010; Moss, Oliver, Arron, Burbridge, & Berg, 2009; Oliver, Berg, Moss, Arron, & Burbidge, 2011]. 54 participants with 1p36 deletion syndrome were contacted through a syndrome support group, and their diagnoses were similarly confirmed by information from one of the professionals listed above.

Return rates for syndrome groups were: 27.6% AS; 21.0% CdLS; 13.6% FXS; 18.1% PWS; 38.9% 1p36. In total, 156 participants took part in the current study, representing an overall return rate of 21.4 %. The data for four participants could not be analysed due to an insufficient number of completed questions, leaving a sample of 152. Table I shows the number, age, gender distribution, mobility and verbal ability in participants across syndrome groups.

**Procedure**

Parents and carers of prospective participants received a pack containing a covering letter, information sheet, consent form, questionnaire set and prepaid envelope. They were asked to return completed questionnaires along with the consent form.

**Measures**

Questionnaires administered to parents and carers included a demographic questionnaire, the Wessex Scale [Kuschlick, Blunden, & Cox, 1973] and the Food Related Problems Questionnaire (FRPQ) [Russell & Oliver, 2003].

*Demographic Questionnaire.* The demographic questionnaire assessed gender, age and diagnostic status as well as verbal ability and mobility.

*Wessex Scale* [Kushlick et al., 1973]. The Wessex Scale assessed social and physical abilities in individuals with intellectual disabilities. Subscales include mobility, self-help skills, continence and literacy skills. This scale has good inter-rater reliability at subscale level [Kushlick et al., 1973]. The self-help score on the Wessex scale can be used as an estimate of an individual’s level of intellectual disability [e.g., Oliver, Arron, Hall & Sloneem, 2008].

*Food Related Problems Questionnaire* [Russell & Oliver, 2003]. The FRPQ is an informant-based questionnaire to assess the presence of food related issues in people with PWS. This is a 16-item questionnaire split into three subscales: impaired satiety (score range 0-30), preoccupation with food (score range 0-18) and composite negative behaviors (score range 0-48). The negative behavior composite can be further subdivided into ‘takes and stores food’ (score range 0-18), ‘eats inedible items’ (score range 0-12) and ‘inappropriate behavior’ (score range 0-18) subcategories. Items are scored on a 7 point likert scale ranging from 0 (never) to 6 (always) representing the frequency of a given behavior. Three items require reverse scoring and scores for the preoccupation with food and impaired satiety subscales require prorating for non-verbal individuals, for whom scoring is not possible on some items. Subscale test-retest reliability and inter-rater reliability are acceptable and internal consistency was reported at .86 using Chronbach’s alpha coefficient. This scale has been shown to have good criterion validity; participants with PWS score consistently higher on all subscales than a cohort of individuals with intellectual disability without the syndrome [Russell & Oliver, 2003].

**Data Analysis**

One way analyses of covariance (ANCOVAs) were conducted to identify differences in subscale scores on the FRPQ between syndrome groups. Subscale scores were included as dependent variables, with syndrome group (5 levels) as an independent variable. Age was included as a covariate and gender as a fixed factor in all ANCOVAs. Planned between-group contrasts were run using Bonferroni corrections. Since FXS is X-linked, and thus much more common in males than females, ANCOVAs were repeated without inclusion of gender as a covariate to assess for between-group differences for the FXS group

ANCOVAs (and Bonferroni-corrected between group contrasts) were also run including the self-help score on the Wessex scale (which can be used as an estimate of intellectual disability [e.g., Oliver et al., 2008]) as a covariate.

In addition to analyses assessing differences between groups in their mean scores on the subscales, we ascertained the proportions of participants in the AS, 1p36, FXS and CdLS groups whose scores indicated levels of problematic food-related behavior similar to or exceeding what might be expected of people with PWS. 50th percentile (i.e., median) cut-off points were identified within the distribution of PWS scores, on each subscale of the FRPQ. The proportions of each of the remaining four syndrome groups attaining scores at or above the median for the PWS group were identified, and these were compared using Chi square analyses.

**RESULTS**

**Basic Characteristics of sample**

Data summarising age, gender, mobility and verbal ability for each syndrome group are presented in Table I. Where significant differences were identified between groups (in age, mobility and verbal ability), post hoc contrasts were performed; the results of these are displayed in Table II, alongside the self-help ability of the groups. Significant group differences are in keeping with known characteristics of the syndrome groups.

**Food Related Problems Questionnaire scores**

*Initial analysis – simple assessment of group differences*

Means and standard deviations on FRPQ subscales in the five groups can be seen in Figure 1. There were significant differences between syndrome groups on measures of ‘preoccupation with food’ [*F*(4,141)= 14.52, *p* < .001] and ‘impaired satiety’ [*F*(4,138) = 5.90, *p* < .001]. ‘Composite negative behavior’ also differed significantly across syndrome groups [*F*(4,137) = 5.44, *p* < .001]. Within the negative behavior composite, there was a significant effect of group on the ‘takes and stores food’ [*F*(4, 140)=8.68, *p* < .001] and ‘eats inedible items’ [*F*(4,138)=3.11, *p* < .05] subscales within this measure. There was not a significant effect of group on the ‘inappropriate responses’ subscale (F < 1.5).

There was a significant effect of age on the ‘eats inedible items’ subscale, [*F*(4,138)=6.85, *p* < .05]. Apart from this, neither age nor gender had a significant effect on any of the FRPQ subscale scores.

Table III shows results of planned contrasts for subscales in which there was a significant effect of group. On measures of impaired satiety, preoccupation with food, taking and storing food and the negative behaviour composite, the PWS group scored significantly higher than one or more other syndrome groups. Interestingly, on all of these measures, the scores of the AS group also significantly exceeded those of at least one other group. On the ‘negative behavior composite’, ‘eats inedible items’ and ‘inappropriate negative behavior’ subscales, there was a trend towards greater scores in the AS than the PWS group.

*Group differences with self-help ability scores as covariate*

All significant main effects of syndrome group within the ANCOVAs (see above) remained significant after inclusion of the Wessex self-help score as a covariate to explore the potential role of level of intellectual disability (min. F = 3.24). There also remained the same pattern of significant differences between specific groups for the ‘takes and stores food’ and ‘preoccupation with food’ and subscales For ‘composite negative behaviour’ and ‘impaired satiety’, there were differences in the patterns of significant differences between groups after addition of self-help scores (see Table III).

There was a significant effect of Wessex self-help score on the ‘eating inedible items’, ‘inappropriate negative responses’ and ‘composite negative behavior’ subscales.

**50th percentile cut-off**

Fiftieth percentile (median) cut-off scores for the PWS group on subscales of the FRPQ were calculated. Figure 2 shows the percentage of participants in each of the other four groups who met or exceeded these cut-off scores.

Scoring within the upper 50% of PWS scores on measures of impaired satiety, preoccupation with food or inappropriate behavior was not significantly associated with syndrome group. However, the frequency with which a score met or exceeded the PWS median for negative composite behaviors, taking/storing food and eating inedible items was significantly associated with syndrome group ([χ2(3) =15.70, *p* = .001]; [χ2(3) = 14.27, *p* = .002]; [χ2(3) = 17.62, *p* = .001] respectively). Scores at or above the 50th percentile of the PWS score distribution were most likely if the participant was in the AS cohort for all of these subscales. Post hoc analyses indicated that for the ‘takes and stores food’ subscale, the proportion of the AS group meeting or exceeding the 50th percentile of PWS scores was significantly greater than that in the CdLS, FXS and 1p36 groups. On the ‘composite negative behavior’ subscale, a significantly greater proportion of the AS group met or exceeded the median score for PWS than in the CdLS and FXS groups. On the ‘eats inedible items’ subscale, a greater proportion of the scores of people with AS and 1p36 deletion syndrome met or exceeded the 50th percentile than did those of participants with FXS.

**DISCUSSION**

 As might be expected, food-related behavior problems reported for participants with PWS exceeded those shown in other groups in many areas: reported preoccupation with food was significantly greater in participants with PWS than in any other group, the PWS group had the highest mean score on impaired satiety (significantly greater than the CdLS group and also, after addition of self-help skills as a covariate, the 1p36 and AS groups); scores on measures of taking and storing food and on a measure of composite negative behavior each exceeded those in at least one other group. These results are broadly commensurate with current understanding of the behavioral phenotype of PWS [e.g., Whittington & Holland, 2010].

 Interestingly, the AS group also displayed significantly higher scores than at least one other group on the composite negative behavior scale, taking and storing food, preoccupation with food and impaired satiety. There were trends towards higher scores in the AS than PWS groups on the negative behavior composite and, within this, measures of inappropriate negative behavior and eating inedible items. Over 65% of the AS group scored at or above the 50th percentile of PWS group scores on the composite negative behaviors measure, a proportion which significantly exceeded that identified in the FXS and CdLS groups. More than 50% of participants in the AS group scored at or above the 50th percentile in relation to the PWS group on measures of taking and storing food, a proportion significantly exceeding that in all three other groups (FXS, 1p36, CdLS). These data indicate that a large proportion of people with AS may be displaying high levels of problematic food-related behaviors, perhaps even in relation to those with PWS, a syndrome in which food-related behavior problems have been considered a cardinal feature.

 AS is known to be associated with low intellectual functioning, a finding which was reflected in our data, with the AS group showing significantly lower levels of self-help ability (used as a proxy for level of intellectual ability) than two other groups (PWS and FXS). This raises the possibility that low levels of intellectual ability contribute to the AS group’s high levels of food-related behavior problems. It is very difficult to account for such possibilities when comparing genetic neurodevelopmental syndrome groups, since ability level will necessarily be confounded with other syndrome-specific elements of the behavioral phenotype. However, it should be noted that 1p36 and CdLS are also associated with low levels of intellectual ability, that there were no significant differences between the self-help scores of the AS, 1p36 and CdLS groups, and that participants in the CdLS and 1p36 groups did not display any significant elevation in scores on any subscale of the FRPQ. PWS, the syndrome group most associated with high levels of food-related behavior problems, is associated with only relatively mild intellectual disability, confirming that factors other than low intellectual disability are important in determining such behaviors. In the current data, the patterns of results were broadly similar when self-help ability was added as a covariate in the analyses (see Table III), with syndrome group remaining an important determinant of food-related problem behaviors. The relationships between food-related behavior problems and other factors (including intellectual disability) in AS and other syndrome groups remains to be explored in future research.

The possible theoretical implications of significant eating problems in AS, overlapping with the types seen in PWS, are intriguing. Much has been made of the significance of the maternally- and paternally- derived nature of the two syndromes in relation to the allocation of resources (including food) elicited by their phenotypic behaviors [e.g., Haig and Wharton, 2003; Haig, 2014]. Whilst we are in the early stages of understanding of the nuances of disordered eating in AS, our data suggest that similarities between AS and PWS in the extent and type of problematic food-related behaviors may be greater than has previously been thought. The similarities and differences between the eating-related issues in AS and PWS should be examined in further detail, both empirically and theoretically, in future work. Such work should also consider eating behavior in relation to the specific genetic mechanisms underlying AS and PWS in individuals; the lack of such available information in the current study is a significant limitation.

Whilst the data indicated food-related behavioral problems in participants with PWS and AS (in relation to other syndrome groups), there was no evidence on any subscale that the 1p36 syndrome group displayed significantly higher scores than other groups. This is intriguing in the context of the reported associations of mutations of this genetic region with hyperphagia and obesity [e.g., D’Angelo et al., 2006; 2009]. However, it may be that only a small proportion of people diagnosed with 1p36 syndrome are affected by these symptoms [see also Rodrigues et al., 2008], and it may be that there is an effect of genetic subtype, a factor not explored in the current analysis. The data were also not suggestive of any elevated scores in the FXS group relative to any other. This may be commensurate with the notion that PWS-like phenotype is rare in FXS [e.g., Garcia-Nonell et al., 2009]. The CdLS group did not show any significantly elevated scores relative to any other group on any subscale of the FRPQ, a result which would be expected on the basis of the relative absence of the types of food-related behaviors seen in PWS in the reported behavioral phenotypes of this syndrome group.

**Limitations**

A major factor to consider in interpretation of the current data is that the FRPQ was designed to capture the aspects of problematic food-related behavior typically seen in PWS. This means that further aspects of food- and eating-related behavior problems which are potentially characteristic of other syndrome groups (e.g., inadequate food intake as seen in CdLS) are not gauged in our analysis, and there may be more subtle, as-yet unexplored features of eating behaviors in the other four groups. It should also be noted that the sample sizes are relatively small (a common difficulty when researching rare syndrome groups), impeding detection of possible differences between the syndrome groups in their food-related behaviors. Whilst different syndrome groups display intriguingly different profiles of potential difficulty across the domains of the FRPQ (see Figure 2), these require statistical verification and further exploration in future studies.

The use of a questionnaire measure can also introduce reporting biases, and the varied levels of ability of participants contributes to potential variations in the manner in which caregivers can assess factors such as satiety [although see Russell & Oliver, 2003, for analysis of how the FRPQ can accommodate differing levels of ability]. These problems could be addressed in future studies by collection of more direct (e.g., observational/experimental) data. It should also be noted that participants were recruited via syndrome support groups. It has been hypothesized that families caring for individuals showing challenging behaviors are more likely to join support groups [Hyman, Oliver, & Hall, 2002], although if this is the case, then the bias is comparable across groups and therefore comparisons may remain valid. Finally, collection of individuals’ genetic data within the syndrome groups is a crucial next step, to elucidate the degree to which different genetic variants may be differently associated with problematic eating behaviors. Further assessments of eating behavior in AS and PWS in relation to people with other genetic diagnoses associated with hyperphagia and obesity (e.g., 16p11.2 microdeletions [Bachmann-Gagescu et al., 2010; Walters et al., 2010]) will also be important in determining the specific profiles of behavior associated with specific genetic aberations.

In summary, this study confirms and extends our understanding of the presence of food-related difficulties in AS. At least some of these difficulties bear similarities to those found in PWS and in some areas may approach or even exceed them in extent. Further research addressing the physiological (e.g., hormonal), neurological and psychological underpinnings of food-related behavioral problems in AS is also now warranted. Clinically, it may be that greater attention should be paid to disordered eating behaviors in AS, that techniques, including close control of the food environment [e.g., Hoffman, Aultman, & Pipes, 1992; Goldberg et al., 2002], thought to help in PWS could be considered for some people with AS, and that future studies should assess the efficacy of treatments for problematic food-related behaviors specifically associated with AS. Given the postulated genetic relationships between AS and PWS, the common and distinct mechanisms underlying their associated food-related problems should also be explored.

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**FIGURE LEGENDS**

**Figure 1.** Mean scores of syndrome groups on subscales of the Food Related Problems Questionnaire.

**Figure 2.** Percentage of participants scoring at or above the 50th percentile of scores attained by individuals with Prader-Willi syndrome on subscales of the FRPQ.

**FIGURES**

**Figure 1.**

\*[Type a quote from the document or the summary of an interesting point. You can position the text box anywhere in the document. Use the Drawing Tools tab to change the formatting of the pull quote text box.]

\*[Type a quote from the document or the summary of an interesting point. You can position the text box anywhere in the document. Use the Drawing Tools tab to change the formatting of the pull quote text box.]

\* = significantly exceeds score in one or more other syndrome group

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**Figure 2.**

**TABLES**

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| **Table I.** Participant characteristics for each syndrome group |
| Syndrome Group | *Nµ* | Mean age*β* (*SD*)\* | % female1 | % mobile\* | % verbal\* |
| Angelman | 35 | 10.5 (3.3) | 51.4 | 65.7 | 2.9 |
| Cornelia de Lange | 32 | 10.2 (4.0) | 33.3 | 72.7 | 36.4 |
| Fragile X  | 28 | 13.6 (1.3) | 3.7 | 100.0 | 92.8 |
| Prader-Willi  | 37 | 10.7 (2.3) | 32.4 | 94.6 | 94.6 |
| 1p36 deletion | 20 | 7.9 (4.2) | 65.0 | 55.0 | 35.0 |
| µ *N* may vary across analysis due to missing data*β* In years\* significant group differences at p < 0.011 no significant differences between groups. The Fragile X group was excluded from the gender analysis due to the X-linked nature of the condition.

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| **Table II.** Results of post hoc comparisons for variables on which significant group differences were identified.  |
| Demographic characteristic | Results of post hoc analysis *p* < .01 |
| Age | FXS > AS, CdLS, 1p36, PWSPWS> 1p36 |
| Number of mobile participants | FXS > AS, 1p36PWS>1p36 |
| Number of verbal participantsWessex self-help score | AS < CdLS, FXS, PWS, 1p36CdLS < FXS, PWS1p36 < FXS, PWSPWS > 1p36, AS, CdLSFXS > 1p36, AS, CdLS |
| *FXS* Fragile X syndrome*, AS* Angelman syndrome*, CdLS* Cornelia de Lange syndrome*, 1p36* 1p36 deletion syndrome*, PWS* Prader-Willi Syndrome |

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| Table III. Syndrome group differences in FRPQ subscales.ANCOVAs including chronological age as covariate and gender as fixed factor. \* significant at 0.01 (Bonferroni-corrected p value)µ also significant after inclusion of self-help skills as a covariateγ significant only after inclusion of self-help skills as covariateα significant only when gender not included in analysis (FXS group only) |
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| **FRPQ subscale** | **Bonferroni-corrected contrasts (p<0.05 after Bonferroni corrections)** |
| Takes and stores foodSignificant effect of group \* µ | AS > CdLS\*µ; 1p36µPWS > CdLS\*µ; 1p36\*µ |
| Eats inedible itemsSignificant effect of group  µ | AS > FXS\*α |
| Composite negative behaviourSignificant effect of group \* µ | AS > CdLS\*µ; 1p36µPWS > CdLSµ; 1p36γ  |
| Impaired satietySignificant effect of group \* µ | AS > CdLSPWS > CdLS\*µ; 1p36γ; ASγ; FXSα |
| Preoccupation with foodSignificant effect of group \* µ | AS > CdLSµ, PWS > CdLS\*µ; 1p36\*µ; AS\*µ; FXSµ  |