16p11.2 Locus modulates response to satiety before the onset of obesity

AM Maillard1,19, L Hippolyte1,19, B Rodriguez-Herreros1,2, SJRA Chawner3, D Dremmel4, Z Agüera5,6, AB Fagundo5,6, A Pain1, S Martin-Brevet1,2, A Hilbert7, S Kurz4, R Etienne1, B Draganski2,8, S Jimenez-Murcia5,6,9, K Männik10,11, A Metspalu10, A Reigo10, B Isidor12, C Le Caignec12,13, A David12, C Mignot14,15,16, B Keren17, 16p11.2 European Consortium20, MBM van den Bree3, S Munsch4, F Fernandez-Aranda5,6,9, JS Beckmann1,18, A Reymond11 and S Jacquemont1,21

1Service de Génétique Médicale, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland; 2LREN—Département des Neurosciences Cliniques, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland; 3MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, UK; 4Department of Psychology, Clinical Psychology and Psychotherapy, University of Fribourg, Fribourg, Switzerland; 5CIBER Fisiopatologia Obesidad y Nutrición (CIBERObn), Instituto de Salud Carlos III, Barcelona, Spain; 6Department of Psychiatry, Bellvitge University Hospital-IDIBELL, Barcelona, Spain; 7Integrated Research and Treatment Center Adiposity Diseases, Department of Medical Psychology and Medical SocCiology, University of Leipzig Medical Center, Leipzig, Germany; 8Department of Neurology, Max-Planck Institute for Human Cognitive and Brain Science, Leipzig, Germany; 9Clinical Sciences Department, School of Medicine, Barcelona, Spain; 10Estonian Genome Center, Tartu University Hospital, Tartu, Estonia; 11Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland; 12Service de Génétique Médicale, CHU-Nantes, Nantes, France; 13INSERM UMR957, Faculté de Médecine, Nantes, France; 14AP-HP, Hôpital Pitié-Salpêtrière, Département de Génétique et de Cytogénétique, Unité Fonctionnelle de Génétique Clinique, Paris, France; 15Centre de Référence Déficiences Intellectuelles de Causes Rares, Paris, France; 16Groupe de Recherche Clinique Déficience Intellectuelle et Autisme, UPMC, Paris, France; 17Groupe Hospitalier Pitié Salpêtrière, AP-HP, Department of Genetics and Cytogenetics, Paris, France and 18SIB Swiss Institute of Bioinformatics, Lausanne, Switzerland. Correspondence: Professor S Jacquemont, Service de Génétique Médicale, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Vaudois Avenue Pierre-Decker 2, Lausanne 1011, Switzerland.
E-mail: sebastien.jacquemont@umontreal.ca
19These authors contributed equally to this work.
20The 16p11.2 European Consortium collaborators are listed before references.
21Current address: Département de Pédiatrie, Faculté de Médecine, Université de Montréal, Montréal, QC, Canada.

INTRODUCTION

Copy number variants (CNVs) are stretches of DNA with a deletion or duplication.1 They are important contributors to mental illness and affect cognition in the general population.2–4 CNVs at the 16p11.2 locus (600 kb BP4-BP5 breakpoints; 29.6–30.2 Mb; GRCh37/hg19) have been associated with neurodevelopmental and psychiatric disorders. Although the duplication has been associated with autism spectrum disorder and schizophrenia,5,6 carrying the deletion is a risk factor for autism spectrum disorder.6–8 We and others also demonstrated that the number of genomic copies at this locus correlates with body mass index (BMI) and brain volume.5,9–14 Specifically, while deletion carriers present a 43-fold increased risk of morbid obesity, duplication carriers have an eightfold risk of being underweight.12–14 Murine models engineered to carry deletions and duplications that are paralogous to the 16p11.2 rearrangements show BMI phenotypes that are inverse to those observed in human, with deletion and duplication mice being under- and overweight, respectively.15,16

Obesity has been associated with cognitive as well as reward dysfunction in the literature.17 Numerous studies have investi-gated the relationship between cognition, behavior and BMI.18 More specifically, deficits in inhibition and decision making have been associated with higher BMI in both children and adults.19–22

Study of these reciprocal CNVs with large effects is a unique opportunity to investigate high-risk individuals before and after the onset of obesity, as well as the relationships with cognitive and behavioral comorbidities. Recent studies suggest that diminished response to satiety is a strong contributor mediating genetic forms of obesity in childhood.23–26 To date, only one study27 reported eating behavior in 16p11.2 deletion carriers. Using a parental report questionnaire investigating aspects of disinhibited eating, the authors found that the deletion was associated with eating in the absence of hunger and that this association was primarily driven by two factors: sensitivity to external cues and boredom. Interestingly, these findings were independent of parental feeding practices.

In this study, we hypothesize that the deletion is associated with altered eating behavior and that cognitive deficits (in particular, executive dysfunctions) are associated with more extreme BMI. We therefore aimed at: (1) assessing eating behavior through self- and parent report in deletion and duplication carriers, as compared with controls, (2) comparing deletion carriers with individuals presenting with obesity or binge eating/loss of control disorder or bulimia and (3) investigating the relationship between BMI and cognition.

SUBJECTS AND METHODS

Subjects

The study was reviewed and approved by the local Ethics committee of each site conducting the study. Informed written consents were obtained from participants or legal caregivers before inclusion in the study. Clinical characteristics of the adult and pediatric samples are presented in Table 1. Pediatric samples. We collected data on 73 deletion carriers (59 families), 42 controls (18 intrafamilial and 24 extrafamilial) and 39 duplication carriers (31 families) ascertained through two different cohorts: 16p11.2 European Consortium and the Experiences of Children with Copy Number Variants (ECHO) study in Cardiff, United Kingdom (Supplementary Table 1).

Participants from the 16p11.2 European Consortium were taking part in a larger phenotyping project on the deletion/duplication of the 16p11.2 region. Most carriers were referred to the study by the clinical geneticist who had initially established the genetic diagnosis (whole-genome arrays) in the context of a neurodevelopmental disorder. The inclusion criteria include the presence of a 16p11.2 deletion or duplication comprising the BP4-BP5 region (29.6–30.2—according to the human genome build GRCh37/hg19). Intrafamilial controls were non-carriers sibling from the same family. Extrafamilial controls were recruited in the general popula-tion. Intra- and extrafamilal controls have a BMI z-score between − 2.5 and 2.5 s.d. Given the absence of significant differences between intrafamilial and extrafamilial controls, we merged both samples into a single control group for statistical analyses (Supplementary Table 1). The exclusion criteria include none beside age o3 years.

Data were also available from the ECHO study, which recruited through medical genetics clinics across the United Kingdom, various charities, word of mouth and the ECHO study website (http://medicine.cardiff.ac.uk/psychological-medicine-neuroscience/areas-research/copy-number-variant-research/research-projects/). The presence of the 16p11.2 CNV was confirmed from medical records and/or by the laboratory of the Institute of Psychological Medicine and Clinical Neurosciences at the Cardiff University. Intrafamilial controls were non-carrier siblings closest in age to the child with the CNV (one invited per family). To examine the specificity of eating behavior in CNV carriers, we compared results with a group of 26 children who met the criteria for loss of control over eating according to the diagnosis criteria adapted for children.28 All children participated in a research project (Swiss University Study of Nutrition, SUN) at the Fribourg University, Switzerland. Detailed description of the study and recruitment methods can be found in Kurz et al.29 Children with loss of control over eating were older than deletion carriers (P=0.005), but there were no difference in gender or BMI z-score (Supplementary Table 2).

Adult samples. We examined a total of 25 adult deletion carriers (21 families), 28 duplication carriers (21 families) and 38 intrafamilial controls (spouse of carriers from 26 families) from the 16p11.2 European Consortium (Table 1). Inclusion and exclusion criteria were the same as the ones used for the pediatric sample. To examine the specificity of eating behavior in CNV carriers, we compared results to a group with obesity (OB, N=232), a group with diagnosis of binge eating disorder (BED, N= 154) and a group with bulimia nervosa (BN, N=274). They were diagnosed by experienced psychologists and psychiatrists according to the DSM-5 criteria.30 The three cohorts were recruited from the Eating Disorder Unit in the Department of Psychiatry at the University Hospital of Bellvitge, Barcelona, Spain.

Deletion carriers were younger than the OB group but did notdifferfromthetwootherclinical groups (BN and BED). There was no difference in education level. Deletion carriers had a higher BMI z-score compared with the BN cohort but they did not significantly differ from the OB or BED groups. Finally, there was a balanced gender distribution in the deletion group, whereas there were considerably more females in the two clinical and obese groups (Supplementary Table 3).

Anthropometric measures

BMI z-scores were computed for all data using a gender, age and geographically matched reference population as previously described in Zufferey et al.14

Neuropsychological measures

Overall cognitive functioning was measured using either the Wechsler Intelligence Scales for Children (WISC-IV)31 or the Wechsler Intelligence Scale for Adults (WAIS-III)32 with participants assessed in Lausanne. The Wechsler Abbreviated Scale of Intelligence (WASI)33 was used with participants from the ECHO study. We used the Full Scale Intellectual Quotient (FSIQ) as outcome measure. Verbal inhibition skills were assessed with the Stroop test34 (⩾ age 8 years) and motor inhibition with a computerized version of the Go-Nogo task35 (⩾ age 7 years). Raw score for error numbers was used as outcome measure in both tasks.

Table 1. Clinical description of the pediatric and adult samples

	Pediatric sample			*Adult sample*		
	Deletion, n = 73	*Control, n = 42*	*Duplication, n = 39*	*Deletion, n = 25*	*Control, n = 38*	*Duplication, n = 28*
Age (years) (mean ± s.d.)	9.6 ± 3.3	11.1 ± 3.1[∞]	9.1 ± 1	34.7 ± 11.9	36.6 ± 11.4	37.5 ± 12.3
Gender (M/F)	46/27	16/26[†]	26/13	12/13	16/ 22	15/13
BMI *z*-score (mean ± s.d.)	1.5 ± 1.7[≋]	0.45 ± 0.78	-0.4 ± 1.5[§]	2.8 ± 1.3*	0.4 ± 1.2	− 0.8 ± 1.5[♦]
FSIQ (mean ± s.d.)	70 ± 15 (*n* = 62)	104 ± 14[‡] (*n* = 18)	64 ± 24 (*n* = 31)	74 ± 14	92 ± 15[¶]	74 ± 20

Abbreviations: BMI, body mass index; FSIQ, Full Scale Intellectual Quotient. *P*-values are uncorrected. *Pediatric cohort*: [§]Significantly different from control ($P = 0.004$). [≋]Significantly different from control ($P = 1.4e-05$) and duplication ($P = 7.4e-08$). [∞]Significantly different from deletion ($P = 0.014$) and duplication ($P = 0.015$). [†]Significantly different from deletion ($P = 3.8e-10$) and duplication ($P = 2e-09$). [†]Significantly different from deletion (Fisher's exact test, $P = 0.012$) and duplication (Fisher's exact test, $P = 0.014$). *Adult cohort*: *Significant different from control ($P = 2.6e-9$) and duplication ($P = 4.1e-12$). [♦]Significantly different from control ($P = 0.002$). [¶]Significantly different from deletion ($P = 1.7e-5$) and duplication ($P = 0.0004$).

Eating behavior assessment

Pediatric cohort. Parent report was used to assess food-related behaviour in children or young adults (⩽20 years) unable to complete self-report because of low cognitive level.

Child Eating Behavior Questionnaire (CEBQ, age ⩾ 3):36 This parent report instrument (35 items) includes four subscales related to children's food approach behaviors—Food Responsiveness, Emotional Over Eating, Enjoyment of Food and Desire to Drink—and four subscales assessing avoidant-type responses—Satiety Responsiveness, Slowness in Eating, Emotional Under Eating and Food Fussiness. Response to each question is given on a 5-point Likert scale (1 = never to 5 = always). We used the mean raw score on each subscale as the outcome measure.

Adult cohort. Data on eating behavior were acquired through self-reports on the following measures:

Eating Disorder Inventory-2 referral form (⩾ age 12 years):37 This questionnaire is a self-report measure to assess symptomatology of eating problems (three subscales) and more general psychological difficulties (five subscales). In this study, we only used the subscales related to eating problems: Drive for Thinness, Bulimia and Body Dissatisfaction. Responses are given using a 6-point Likert scale (1 = never to 6 = always). We used total raw scores of each subscale as the outcome measure.

Dutch Eating Behavior Questionnaire—Externality subscale (⩾ age 10 years):38 This 10-item subscale assesses whether participants are attracted to food stimuli and tend to eat regardless of the internal state of hunger or satiety. Each item consists of a 5-point Likert scale (1 = never to 5 = very often). We used the mean raw score as outcome measure.

Statistical analyses

Effect of CNVs on eating behavior traits. To estimate the effect of the 16p11.2 on eating behavior, we conducted linear mixed models to compare eating disorder behavior in the deletion versus control, deletion versus duplication and duplication versus control, whereas accounting for correlated measures within families

(familial clustering). We systematically controlled for age, gender and FSIQ (Supplementary Tables 4 and 5), and only significant covariates were included in the final statistical model. Linear regression model was used to compare deletion carriers with clinical groups (obesity, BN and BED), while controlling for age, gender and education level (Supplementary Table 6). Given the high collinearity between BMI z-score and the number of genomic copies, we subsequently added BMI z-score as an explanatory variable. Finally, we assessed the inheritance factor on eating behavior by introducing inheritance in the statistical model as a covariate (de novo or inherited from a parent).

Relationship between BMI, eating behavior scores and cognition within CNV groups. Pearson's correlation analyses explored the relationship between BMI and cognition (FSIQ, executive functions), as well as BMI and eating behavioral traits within a group. We used similar analysis to assess the correlation between FSIQ and eating behavior scores. Bonferroni-corrected P-values were obtained by multiplying the original P-values by the number of possible comparisons (n= 3): P-values $\leqslant$0.016 were considered significant in the pediatric and adult cohorts when comparing CNVs carriers with controls, whereas P-values $\leqslant$ 0.0083 were considered significant when comparing adult deletion carriers with the clinical and obese groups (n=6 comparisons). Owing to missing data, the sample size might differ between outcome measures. Statistical analyses were conducted using IBM SPSS (version 21.0, released 2012; IBM Corp., SPSS Statistics for Windows, Armonk, NY, USA) and R 3.1.1 (The R Project for Statistical Computing; http://www.R-project.org/).

RESULTS

Children: Eating behavior differences between CNV carriers and controls

CEBQ scores are described in Supplementary Table 7. Three out of the nine CEBQ subscales show differences between deletion carriers and controls, as well as duplication carriers (Figures 1a–c and Supplementary Table 8). Deletion carriers show lower level of satiety responsiveness, increased responsiveness to food and higher sensitivity to emotional overeating compared with the two other groups. As previously reported in the literature,6 BMI z-scores are negatively correlated to the number of genomic copies (Table 1). When BMI z-score is included in the model, differences in satiety responsiveness between groups are no longer significant (Supplementary Table 9). None of the other subscales (Enjoyment of Food, Emotional Undereating, Food Fussiness, Slowness in Eating, Desire to Drink) showed significant difference between groups (Supplementary Figure 1 and Supplementary Table 8).

Children who carry a deletion: Relationship between eating behavior, BMI and age

Age does not affect satiety responsiveness in deletion carriers, whereas BMI z-scores increase progressively with age (P= 0.003), as we previously reported14 (Figure 2a). Satiety responsiveness does not correlate with BMI z-score in children $\leqslant$ 10 years, but a decrease in the levels of satiety responsiveness is significantly associated with higher BMI z-score in adolescents 410 years of age (P=0.003; Figure 2b). The relationship between the satiety response and BMI z-score in adolescents is not specific to the deletion group and this correlation is also present in controls (P= 0.002).

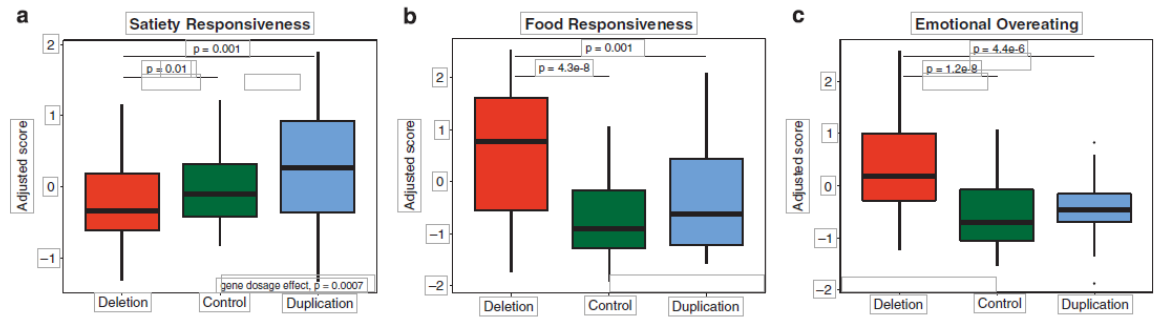

Figure 1. CEBQ scores in deletion and duplication carriers. Boxplots represent scores for satiety responsiveness (**a**), food responsiveness (**b**) and emotional overeating (**c**), in 73 deletion (red), 39 duplication carriers (blue) and 42 controls (green). The bold line shows the median, the bottom and top of the box, the 25th (Q1) and the 75th (Q3) percentile, respectively. The upper whisker ends at highest observed data value within the span from Q3 to Q3+1.5 times the interquartile range (IQR; Q3–Q1), lower whiskers end at lowest observed data value within the span for Q1 to Q1–(1.5 × IQR). Significant group differences (*p*-corrected threshold = 0.016) are represented by solid lines with exact *P*-values above. Age, gender and FSIQ were systematically controlled for in the linear mixed model. Scores are adjusted for age and family as a random factor in the final models.

Similar analyses show that increased scores of food respon-siveness and emotional overeating appear with age and do not correlate with BMI z-score in deletion carriers (Supplementary Figure 2). These two measures are correlated across all groups (r240.4), and both negatively correlate with satiety responsive-ness in deletion carriers (Supplementary Figure 3).

We further compared deletion carriers with a group of children with an eating disorder defined as loss of control over eating. We found no differences between these two groups on the CEBQ subscales (Supplementary Table 10 and Supplementary Figure 4).

Adults: Body perception and eating disorder traits differences between CNV carriers and controls

Deletion carriers show increased body dissatisfaction and drive for thinness compared with controls and duplication carriers (Figures 3a and b and Supplementary Tables 11 and 12). Bulimia score (Figure 3c) and externality scale from the Dutch Eating Behavior Questionnaire were comparable between the three groups (Supplementary Table 12). When BMI z-score is included in the model, group differences are no longer present, suggesting that the above-mentioned effects are mainly related to BMI (Supplementary Table 13).

To further understand these eating disorder traits in deletion carriers, we compared them with three other groups including individuals with OB, BN or BED. Bulimia and Body dissatisfaction scores are similar in deletion carriers and the OB group, and both groups score significantly lower compared with the BN and BED cohorts (Figures 4a and b). Interestingly, deletion carriers show a significantly lower drive for thinness compared with the three other groups (Figure 4c and Supplementary Tables 14 and 15).

Subsequently, we investigated whether the specificity of the relationship between BMI z-score and eating disorder differs across groups (deletion carriers, BN, BED and OB). A differential effect of BMI z-score across groups is only seen for body dissatisfaction: both eating disorder groups show a positive correlation between BMI z-score and body dissatisfaction (BN: r2 = 0.16, P=6.5e − 11; BED: r2 = 0.04, P= 0.01), whereas this relationship is not seen neither in OB nor in deletion carriers.

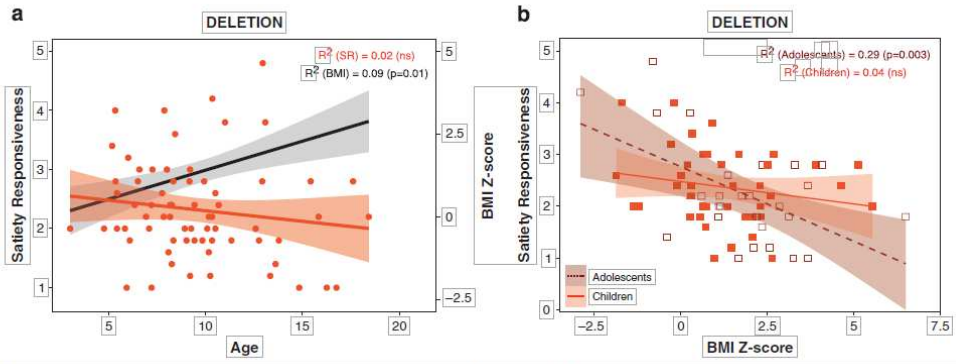

Figure 2. BMI *z*-score, age and satiety responsiveness. (**a**) Scatterplot for the deletion group representing satiety responsiveness (Y axis) and BMI *z*-score (Z axis) as a function of age (X axis). For BMI *z*-score, only the fitted regression line (solid black) and standard error (gray surface) is represented. (**b**) Scatterplot shows the relationship between BMI *z*-score (X axis) and satiety responsiveness (Y axis) for children and adolescents in deletion group. Shaded areas depict the 95% confidence intervals of the regression line.

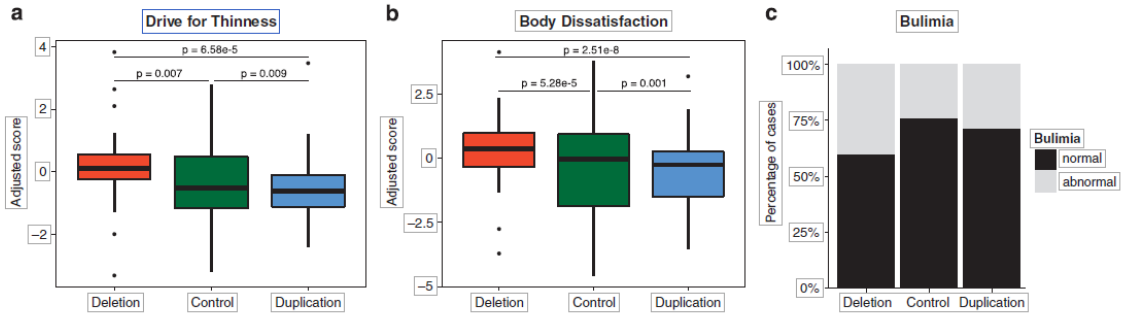

Figure 3. Gene dosage and group comparison on Eating Disorder Inventory-2 (EDI-2) measures. Boxplots represent scores for (**a**) Drive for Thinness and (**b**) Body Dissatisfaction subscales (EDI-2) in 25 deletion, 28 duplication carriers and 38 intrafamilial controls. The bold line shows the median, the bottom and top of the box, the 25th (Q1) and the 75th (Q3) percentile, respectively. The upper whisker ends at highest observed data value within the span from Q3 to Q3+1.5 times the interquartile range (IQR; Q3 – Q1), lower whiskers end at lowest observed data value within the span for Q1 to Q1–(1.5 × IQR). Significant group differences are represented by solid lines with exact *P*-values above. Group contrasts are estimated in regression analyses models (binomial mixed model). Age, gender and FSIQ were systematically controlled for. Scores are adjusted for gender and family as a random factor in the final models. (**c**) Stackplots illustrate the percentage of participants with an abnormal score (> 2) on the bulimia scale (EDI-2) in each group.

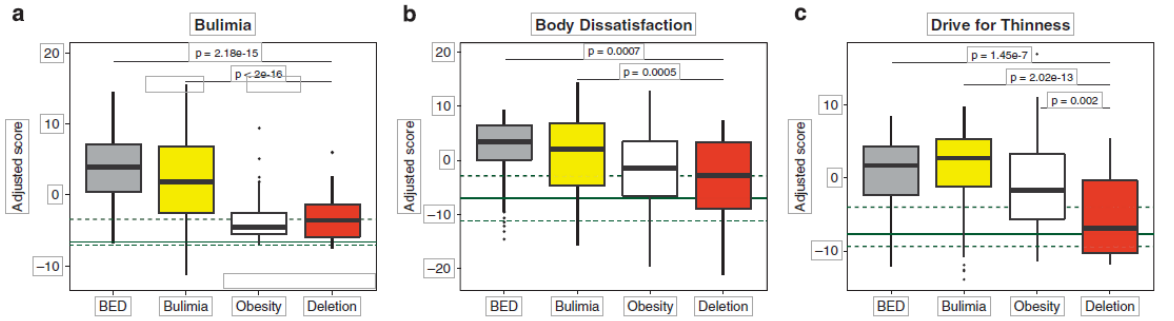

Figure 4. Comparing deletion carriers and individuals with a diagnosis of eating disorder. Boxplots (**a–c**) represent Drive for Thinness, Body dissatisfaction and Bulimia subscales (Eating Disorder Inventory-2 (EDI-2)) adjusted for gender and BMI *z*-score, in deletion carriers ($n = 25$), 'constitutional' obesity ($n = 232$) and two eating disorders: BED ($n = 154$) and BN ($n = 274$). The bold line in the boxes shows the median, the bottom and top of the box, the 25th (Q1) and the 75th (Q3) percentile, respectively. The upper whisker ends at highest observed data value within the span from Q3 to Q3+1.5 times the interquartile range (IQR; Q3 – Q1), lower whiskers end at lowest observed data value within the span for Q1 to Q1 – (1.5 × IQR). Significant group differences are represented by solid lines with exact *P*-values above. The solid lines flanked by the dashed lines in green represent the median, 1st and 3rd quartile of the extrafamilial group control group ($n = 128$).

Global cognition, executive functions and BMI

FSIQ of CNV carriers is about 2 s.d. lower compared with intrafamilial controls (Table 1). We do not find significant relationships between BMI z-score and FSIQ. Analyses of verbal and motor inhibition also show no relationship with BMI. There also is no correlation between cognitive scores and eating behavior scales in any of the groups.

Finally, we sought to explore the potential impact of family environment on eating behavior and obesity by comparing families where the deletion is de novo or inherited. In the latter case, transmitting parents also present cognitive impairments and obesity. The inheritance status was only available in children. Inheritance neither affects BMI z-score nor eating behavior. This analysis was not performed in the duplication because of the small sample size (de novo = 7; inherited = 24; unknown = 7).

DISCUSSION

The present study investigates the relationship between eating behavior and BMI in carriers of a 16p11.2 BP4-BP5 CNV, who are at risk of obesity or being underweight.12,13 Children who carry a deletion present altered satiety responsiveness, which is already present before any diagnosis of obesity. The correlation between response to satiety and BMI z-score becomes significant in adolescents supporting the notion that satiety response in young deletion carriers is associated with future increase in BMI z-score. The relevance of satiety

responsiveness to obesity has been documented by longitudinal studies showing that appetitive traits in infancy are correlated with subsequent weight gain.39,40 Our findings are also consistent with data on the relationship between satiety/satiety responsiveness and genetic factors associated with obesity.24,26,41 Recent studies in the general population using polygenic risk scores demonstrated that common genetic risk for higher BMI also correlates with satiety responsiveness in children even after the exclusion of FTO and MC4R, two major genes associated with obesity.25 Along with our results, this suggests that genes that are risk factors for obesity might act through appetitive mechanisms.

Although we interpret our results as a primary effect of satiety, we also show alterations in food responsiveness and emotional overeating, two components related to reward sensitivity. A previous study on 16p11.2 deletion carriers also reported subjective alteration of reward (eating in the absence of hunger and sensitivity to boredom or external cues in deletion carriers).27 We recently demonstrated that CNV in the 16p11.2 region is associated with altered brain structures (orbitofrontal cortex, insula, putamen and thalamus) implicated in reward.9 A large body of research has also demonstrated that satiety influences the subjective value of reward.42 Our current inter-pretation of these data is that increased responsiveness to food and emotional overeating observed in 16p11.2 deletion carriers may be the consequence of altered satiety response.

Adult deletion carriers do not present with eating disorder as defined in the DSM-5 (BN, BED). Body dissatisfaction and bulimia symptoms in deletion carriers are equal to that observed in individuals of the obese group and contrast with behaviors observed in the BN and BED groups. Interestingly, deletion carriers present with significantly lower drive for thinness compared with the obese group with similar BMI. Studies of personality traits known to correlate with drive for thinness (e.g. harm avoidance, anxiety) may shed light on this difference.43

Although several studies have demonstrated a correlation between BMI and executive dysfunction in obesity, we show no association between BMI z-score and overall cognitive functioning. These results replicate earlier reports in 16p11.2 CNV carriers.14 The fact that loss of control over eating children and deletion carriers do not differ on any of the behavioral CEBQ dimensions suggests similar underlying mechanisms for their energy imbalance. Similarly, we did not find any relationship between BMI z-score and inhibition, corroborating previous findings in extreme weight conditions such as anorexia nervosa and obesity.20 This is analogous to findings for the 22q11.2 deletion CNV showing that psychopathology and cognitive deficits are independent sequelae.44

One of the limitations of this work is our reliance on parent- and self-report ratings of eating behavior, which are subjective in nature. Possible under- or over-reporting on these measures would have implications for our analyses on BMI z-scores. The lack of longitudinal data prevents us from concluding how response to satiety evolves over time. Furthermore, the measures of eating behavior varied between the pediatric and adult cohorts. However, the study of a high-risk pediatric cohort offers the possibility to explore behavioral phenotypes that are not the consequence of long-standing obesity. We observed fewer significant effects of the duplication on eating behaviors that may be due to smaller sample size of the duplication group.

To conclude, our findings provide further insights into the behaviors underlying or associated with energy imbalance in 16p11.2 CNV carriers. Altered satiety response is potentially a primary mechanism contributing to later obesity in deletion carriers but co-occurring changes in the reward system may also have a role. Study of these reciprocal 16p11.2 CNVs and how they affect clinical traits is a powerful tool to shed light on common phenotypes such as obesity. For clinicians, a comprehensive characterization of eating behavior will guide care of patients presenting with this genetic disorder.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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16P11.2 EUROPEAN CONSORTIUM

Addor, M-C, Service de Génétique Médicale, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland; Andrieux, J, Institut de Génétique Médicale, Hôpital Jeanne de Flandre, CHRU de Lille, France; Baujat, G, Centre de Référence Département de Génétique, Hôpital Necker-Enfants malades, Paris, France; Belfiore, M, Laboratoire de cytogénétique, Service de Génétique Médicale, CHUV, Lausanne, Switzerland; Bonneau, D, Service de génétique médicale, CHU-Angers, France; Bouquillon, S, Institut de Génétique Médicale, Hôpital Jeanne de Flandre, Lille, France; Boute, O, Hôpital Jeanne de Flandre, CHRU de Lille, France; Brusco, A, University of Torino, Department of Medical Sciences, Turin, Italy; Bussat, J, Service of Medical Genetics, Centre Hospitalier Universitaire Vaudois, Lausanne University, Switzerland; Campion, D, Service de psychiatrie, Centre hospitalier de Rouvray, Sotteville lès Rouen, France; Delrue, M-A, Univ. Bordeaux, Maladies Rares: Génétique et Métabolisme, Service de Génétique Médicale, CHU-Bordeaux, France; Dervaux, G, Unité de Médecine et Chirurgie de l'obésité, Centre Hospitalier de Béthune, France; Doco-Fenzy, M, Service de Génétique, CHU, EA3801 SFR-CAP Santé Reims, France; Edery, P, Service de Génétique, Hospices Civils de Lyon, Hôpital Femme-Mère-Enfant et Centre de Recherche en Neurosciences de Lyon, Université Claude Bernard Lyon 1, Villeurbanne, France; Fagerberg, C, Department of Clinical Genetics, Odense Universitetshospital, Odense, Denmark; Fellmann, F, Service de Génétique Médicale, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland; Ferrarini, A, Department of Pediatrics, San Giovanni Hospital, Bellinzona, Switzerland; Forzano, F, SSD Genetica Medica, E Ospedali Galliera, Genova, Italy; Gérard, M, Département de Génétique, Hôpital Robert Debré, AP-HP, Paris, France; Giachino, D, Genetica Medica, Azienda Ospedaliera Universitaria San Luigi Gonzaga Orbassano, Torino, Italy; Gilbert-Dussardier, B, Service de Génétique Médicale, Centre de Référence Anomalies du Développement-Ouest, CHU de Poitiers; EA 3808, Université de Poitiers, France; Héron, D, Département de Génétique, Hôpital Pitié-Salpêtrière, Université Pierre et Marie Curie, Paris, France; Holder, M, Hôpital Jeanne de Flandre, CHRU de Lille, France; Jacquette, A, Département de Génétique, groupe hospitalier Pitié-Salpétrière, Paris, France; Journel, H, Génétique médicale, Centre Hospitalier Bretagne Atlantique, Vannes, France; Kutalik, Z, IUMSP, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; Lacombe, D, Department of Medical Genetics, CHU of Bordeaux, Université de Bordeaux, France; Lazaro, L, CH Côte-Basque, Service de pédiatrie, Bayonne, France; Lemaître, M-P, Service de Neuropédiatrie, Centre Hospitalier Régional Universitaire, Lille, France; Lespinasse, J, Service génétique médicale, CH Chambéry, France; Macé, A, Department of Medical Genetics, University of Lausanne, Switzerland; Mandrile, G, Genetica Medica, Azienda Ospedaliera Universitaria San Luigi Gonzaga Orbassano, Torino, Italy; Martinet, D, Laboratoire de cytogénétique, Service de Génétique Médicale, CHUV, Lausanne, Switzerland; Minet, J-C, Department of Pediatrics, Hôpital du Jura, Délémont, Switzerland; Moerman, A, Institut de Génétique Médicale, Hôpital Jeanne de Flandre, Lille, France; Morice-Picard, F, Department of Medical Genetics, Centre Hospitalier Universitaire de Bordeaux, GH Pellegrin, Bordeaux, France; Motte, J, Neurologie Pédiatrique, Pôle Femme-Mère-Enfant, American Memorial Hospital, Reims, France; Olivier-Faivre, L, Centre de référence Anomalies du développement et Syndromes Malformatifs de l'Interrégion Est, Hôpital

d'Enfants, CHU de Dijon et Université de Bourgogne, Dijon, France; Pasquier, L, Service de Génétique Clinique, Hôpital sud, CHU de Rennes, Université Rennes 1, UMR 6290 CNRS, Groupe GPLD, Rennes, France; Petit, F, Hôpital Jeanne de Flandre, CHRU de Lille, France; Plessis, G, Service de Génétique clinique, CHU Caen, France; Ragona, F, Department of Pediatric Neuroscience, IRCCS Foundation Neurological Institute C Besta, Milan, Italy; Ramelli, G-P, Department of Pediatrics, San Giovanni Hospital, Bellinzona, Switzerland; Van Haelst, MM, Department of Medical Genetics, University Medical Center, Utrecht, Netherlands; Van Maldergem, L, Centre de Génétique humaine, CHU-Besançon, France.

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