Obesity in adults with 22q11.2 deletion syndrome

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Purpose: To characterize the prevalence of and contributing factors to adult obesity in the most common recurrent copy-number variation (CNV), 22q11.2 deletion, given that other rare CNVs are known to have obesity phenotypes.

Methods: In 207 adults with 22q11.2 deletion syndrome (22q11.2DS), we used available height and weight measurements to calculate body mass index (BMI) and recorded associated factors that could play a role in obesity. We used the maximum BMI per subject and logistic regression to test a model predicting obesity class.

Results: The prevalence of obesity (BMI ≥30) in 22q11.2DS (n = 90, 43.5%; at median age of 26.7 years) was significantly greater than for Canadian norms (odds ratio (OR) 2.30, 95% confidence interval (CI) = 1.74–3.02, P < 0.0001), even after excluding individuals with a history of antipsychotic use. The regression model was significant (P < 0.0001). Psychotropic medication use and age, but not sex or presence of intellectual disability, were associated with higher obesity level. Ten (4.8%) individuals were diagnosed with type 2 diabetes at a median age of 39.5 years; the prevalence was higher in those with obesity (P < 0.01).

Conclusion: The results suggest that adult obesity is related to the 22q11.2 deletion. The findings expand the potential genetic causes of obesity and have important implications for management of 22q11.2DS.

Genet Med advance online publication 18 August 2016

Key Words: congenital heart disease; copy-number variation; DiGeorge syndrome; energy metabolism; hypothyroidism

INTRODUCTION

Rare copy-number variations (CNVs) are known to contribute to obesity.1–3 There are limited data, however, regarding obesity in association with the recurrent pathogenic 22q11.2 deletion. Studies examining body mass index (BMI) in 22q11.2 deletion syndrome (22q11.2DS) (OMIM 188400/192430) have focused primarily on children.4–7 Early growth faltering,4–7 possibly associated with congenital heart disease,4 does not appear to persist over time.4–7 Some studies have suggested a trend toward increased weight and obesity in adolescence and adulthood,4–7 but the numbers of adults studied are small.5–7 An early report of 78 adults with 22q11.2DS suggested that obesity may be an associated feature,8 but contributors to obesity were not examined. These are important considerations given that some of the common features of 22q11.2DS,4–9 such as intellectual disability, hypothyroidism, and psychotic illness, including schizophrenia in ~25% of adults, are also independently associated with obesity. Antipsychotic medications are known to be associated with weight gain and risk for type 2 diabetes in the general population.10,11

We sought to characterize the adult prevalence of and contributors to obesity in 22q11.2DS, and to determine the prevalence of type 2 diabetes. We hypothesized that the prevalence of obesity would be greater in those with 22q11.2DS than in the general population, and that variables that are predictive of obesity in the general population would similarly be contributors to obesity in 22q11.2DS.

MATERIALS AND METHODS

Subjects

The sample comprised 207 adults (96 males) with 22q11.2DS from a well-characterized Canadian cohort4,12,13 for whom adult BMI data were available (measured at ≥18 years of age). The 22q11.2 deletions were confirmed by standard molecular methods.8,12 The study was approved by local research ethics boards and written informed consent was obtained for each subject. As previously described,4,12 most subjects were ascertained through adult congenital cardiac, psychiatric, and/or genetics services.

Obesity prevalence

We used available lifetime medical records for all subjects to record objective measurements of height and weight and converted inches to centimeters and pounds to kilograms when necessary. Using the date of assessment and the subject’s date of birth, we calculated age at assessment. For BMI, we used the standard formula

\[ \text{BMI} = \frac{\text{weight (kg)}}{\left(\text{height (m)}\right)^2} \]

We excluded any BMI measurements calculated when the subject was >3 months pregnant and up to 6 months after

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Submitted 7 April 2016; accepted 31 May 2016; advance online publication 18 August 2016. doi:10.1038/gim.2016.98
either delivery or late miscarriage/termination. We calculated a total of 1,168 adult BMI measurements (median 4, range 1–28, per subject) for the 207 subjects; 186 (90%) had more than one BMI measurement available. To evaluate lifetime obesity, we used the maximum available adult BMI for each subject to assign the level of obesity according to the four standard categories: not obese (BMI <30), obese class I (35 > BMI ≥ 30), obese class II (40 > BMI ≥ 35), and obese class III (BMI ≥40).14

We calculated 95% confidence intervals (CIs) for the prevalence estimates of obesity in our population using the formula of Richardson et al. The median year at maximum BMI measurement was 2011 (range, 1986–2015). For comparison, we used the most recently reported population prevalence data for obesity measured in Canadian adults (≥18 years), excluding pregnant females, in 2008.16

Contributing factors to obesity
To avoid model overfitting and to focus on clinically important associations, we only considered variables for which we had a priori suspicion of a relationship with BMI based on general population data and/or if the variable was a major clinical feature of 22q11.2DS.8,9 We included variables that were present in at least five subjects. We defined lifetime history to mean presence at or before the time of maximum BMI measurement. These variables were coded as absent if they were only observed or diagnosed after maximum BMI measurement because we were interested in contributing factors to obesity rather than downstream consequences.

We considered age at assessment, sex, lifetime history of smoking (defined here as at least weekly use), presence of congenital heart disease of any severity from simple (e.g., septal defect) to complex (e.g., tetralogy of Fallot with pulmonary atresia),17 presence of intellectual disability18 (mild to severe), lifetime history of diagnosed hypothyroidism,19 and lifetime use of psychotropic medications associated with weight gain (antipsychotics, selective serotonin reuptake inhibitors, valproic acid, venlafaxine, lithium).10,11,20,21 There was substantial overlap in use of psychotropic medications within patients. We considered psychotropic medication use as a single factor to avoid multicollinearity while accounting for the maximal potential effect of any of these medications in the model. Given that smoking in conjunction with antipsychotic use has been previously associated with less weight gain,22 we also considered psychotropic medications and smoking together as an interaction term in the model. There were 202 subjects with sufficient data available to assess all contributing factors considered. The remaining five subjects were in the nonobese category.

Obesity and type 2 diabetes
With respect to potential consequences of obesity, we recorded the presence of type 2 diabetes, the age at diagnosis, and whether the subject had a history of a psychotic disorder and/or psychotropic medication use before diagnosis of diabetes.

Statistical analyses
We used an ordinal logistic regression model to identify clinical and demographic variables that were contributory factors to maximum BMI obesity class. We selected this analytic method based on consistency with existing literature, a greater level of detail than binomial logistic regression, and fewer assumptions than multiple linear regression. We reported odds ratios (ORs) and 95% CIs. All psychotropic medications showed the same direction of effect when examined individually. The variance inflation factor for each predictor included in the analysis was examined to ensure that there were no problems with multicollinearity. Pairwise interactions between predictor variables were investigated one at a time by running smaller models consisting of the two predictor terms and the corresponding interaction term. Significant interaction terms were then verified as important after accounting for the other variables of interest. Post hoc χ² or Fisher’s exact tests were used to further characterize significant effects and the prevalence of obesity in relation to type 2 diabetes. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Statistical significance was defined by a P < 0.05.

RESULTS
Prevalence of obesity in 22q11.2DS
For the 207 adults with 22q11.2DS studied, the median BMI was 29.2 (range, 16.5–57.5), which was assessed at a median age of 26.7 (range, 18.0–64.7) years (Figure 1). The prevalence of obesity was 43.5% (n = 90); 21.3% (n = 44) had class I, 15.9% (n = 33) had class II, and 6.3% (n = 13) had class III obesity. The prevalence of obesity across all classes was significantly greater than that reported for the Canadian adult population (OR 2.30, 95% CI 1.74–3.02, P < 0.0001), even after excluding those with antipsychotic medication use (OR 1.82, 95% CI 1.25–2.65, P = 0.002) (Figure 2). Using the age subgroupings provided for Canadian
population norms, and when data were sufficient (>20 subjects) in the 22q11.2DS sample, we found that for the 20- to 34-year-old group, obesity prevalence was significantly greater in 22q11.2DS (OR 3.82, 95% CI 2.57–5.66, \( P = 0.0009 \)); results were nonsignificant for the 18- to 19-year-old group when restricted to those with no antipsychotic medication exposure (Figure 2).

**Contributing factors to obesity**

The logistic regression model predicting BMI class (Table 1) in adults with 22q11.2DS was significant (likelihood ratio test: \( \chi^2 = 49.71, df = 8, P < 0.0001 \)). Lifetime use of psychotropic medications and older age were associated with higher BMI class. Results for psychotropic medication use remained significant if medications were restricted to antipsychotics (OR 2.60, 95% CI 1.31–5.13, \( P = 0.006 \)). The interaction variable of psychotropic medication use and smoking was associated with a lower BMI class. Sex and presence of intellectual disability were not significant predictors, even when considered in single variable models (data not shown) (Supplementary Figure S1 online).

Although neither congenital heart disease nor hypothyroidism alone was a significant variable (Table 1), when present together (\( n = 17 \)) the interaction variable was significantly associated with higher BMI class (OR 7.07, 95% CI 1.83–27.22, \( P < 0.01 \)), even after accounting for the other factors (data not shown). Post hoc analyses revealed that the association was only present at more severe levels of obesity: class II (FET, \( P = 0.001 \)) and class III (FET, \( P = 0.015 \)). There were no other significant pairwise interaction terms among the seven predictors.

**Prevalence of type 2 diabetes**

Ten subjects (4.8%) had a diagnosis of type 2 diabetes, which was diagnosed at a median age of 39.5 (range, 27–59) years; the three individuals with class III obesity were all diagnosed before age 35 years. The prevalence of type 2 diabetes was significantly higher in obese (9/90, 10.0%) than in nonobese subjects (1/117, 0.9%; FET, \( P = 0.003 \)). Nine (90.0%) of the 10 individuals with type 2 diabetes had a psychotic illness, and the prevalence of type 2 diabetes among those with a psychotic disorder was 10.1% (9/89).

**DISCUSSION**

The results of this study suggest that obesity is a common adult manifestation of 22q11.2DS. Consistent with our hypothesis, the prevalence of obesity was significantly greater in 22q11.2DS than in the general Canadian population. Although the presence and severity of obesity appeared to be influenced by some of the same factors, the higher prevalence of type 2 diabetes in this population suggests that novel preventive strategies may be needed.

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**Figure 2 Obesity prevalence in 22q11.2DS compared with Canadian norms.** Bar graph illustrating the obesity prevalence in 22q11.2DS, with (light grey) and without (medium grey bar) history of antipsychotic use, compared with the reported obesity prevalence in the general Canadian population (dark grey bar).

**Table 1 Contributing factors to obesity in 202 adults with 22q11.2DS**

| Contributing factors        | Not obese | Obesity class |
|----------------------------|-----------|---------------|
|                            | \( n = 202 \) | \( n = 112 \) | \( I, n = 44 \) | \( II, n = 33 \) | \( III, n = 13 \) | Logistic regression analysis |
| Age at assessment (years)   | Median IQR | Median IQR | Median IQR | Median IQR | Median IQR | Median IQR |
|------------------------------|------------|------------|------------|------------|------------|------------|
| Male                         | 23.1       | 9.8        | 31.4       | 12.5       | 32.3       | 14.2       | 31.0       | 11.7       | 1.06       | 0.60       | 1.88       | 0.836       |
| Intellectual disability\(^a\) | 94         | 54         | 48.2       | 20         | 45.5       | 15         | 45.5       | 5          | 38.5       | 1.06       | 0.60       | 1.88       | 0.836       |
| Hypothyroidism               | 117        | 71         | 63.4       | 19         | 43.2       | 21         | 63.6       | 6          | 46.2       | 0.83       | 0.46       | 1.48       | 0.524       |
| Congenital heart disease\(^b\) | 39         | 16         | 14.3       | 9          | 20.5       | 9          | 27.3       | 5          | 38.5       | 1.88       | 0.94       | 3.77       | 0.076       |
| Psychotropic medications\(^c\) | 114        | 64         | 57.1       | 21         | 47.7       | 19         | 57.6       | 10         | 76.9       | 1.82       | 0.99       | 3.34       | 0.063       |
| Smoking                      | 42         | 30         | 26.8       | 6          | 13.6       | 4          | 12.1       | 2          | 15.4       | 1.08       | 0.32       | 3.62       | 0.901       |
| Psychotropic medications × smoking | 28        | 21         | 18.8       | 3          | 6.8        | 3          | 9.1        | 1          | 7.7        | 0.13       | 0.03       | 0.60       | 0.009       |

\( ^a \)Not obese (BMI < 30), class I (35 > BMI ≥ 30), class II (40 > BMI ≥ 35), and class III (BMI ≥ 40) obesity. \(^b\)For details, see text. \(^c\)Lifetime use of antipsychotics, selective serotonin reuptake inhibitors, valproic acid, venlafaxine, or lithium. Of 119 subjects with a history of psychotropic medication use, 87 (73.1%) had a history of antipsychotic use, with \( n = 70 \) or without \( n = 17 \) other medication use. Thirty-two (26.9%) subjects had a history of using one or more of the other psychotropic medications listed (i.e., without antipsychotic use). Overall, 82 subjects had a history of SSRI, 35 of valproic acid, 12 of venlafaxine, and 9 of lithium use. CI, confidence interval; IQR, interquartile range; OR, odds ratio.
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Factors as in general population studies of obesity, the effects of the 22q11.2 deletion were evident as significantly elevated levels of obesity by early adulthood in the absence of these factors.16,23

Pediatric data available for 22q11.2DS indicated a trend toward increasing weight in late adolescence.1-7 Divergence from normal curves begins at approximately 10–12 years of age, with an ever-widening gap through adolescence.5 Consistent with later onset of obesity than that found to be associated with some other rare CNVs;7 we found that obesity prevalence was not significantly elevated in the 18–19-year-old age group in the absence of antipsychotic medication exposure compared with population norms,16 but significant differences were apparent for the 20–34-year-old group (Figure 2). Obesity in 22q11.2DS appears in the context of evidence of early growth abnormalities in terms of undergrowth, including elevated prevalence of being small for gestational age,4,5,11 and early growth faltering.4,7 This is consistent with reported patterns in other genomic disorders, including other recurrent deletions such as 16p11.2 deletions1 and Prader-Willi syndrome.14 Later onset of obesity in 22q11.2DS may be why 22q11.2 deletions have not been identified in studies of early-onset obesity.25 Interestingly, the findings for type 2 diabetes, although lower in prevalence, appeared similar for age at onset compared with the findings for adults with Prader-Willi syndrome.1 The median age of diagnosis for type 2 diabetes in 22q11.2DS was 39.5 years, which is younger by more than 14 years for all types of diabetes reported for adults in the general US population (54.2 years).26

The results suggest that psychotic illness associated with 22q11.2DS may contribute to the obesity observed. With respect to antipsychotic medication, the results for 22q11.2DS (OR 2.60) appear comparable to those observed for idiopathic schizophrenia, where 2–2.8-fold increases in obesity prevalence have been reported.27,28 This is consistent with previous findings for the antipsychotic clozapine, which indicated similar weight gain findings for 22q11.2DS and others with schizophrenia.29 The prevalence of type 2 diabetes among adults with 22q11.2DS and a history of psychotic illness (10.1%) was also similar to that reported for idiopathic schizophrenia (10.9%).30 The stronger result (OR 3.88) when all psychotropic medications were considered and the fact that the prevalence of obesity remained significantly higher for adults with 22q11.2DS than Canadian norms in the absence of any antipsychotic exposure indicate that other factors are important in the relationship of obesity and 22q11.2DS. As reported for recurrent 16p11.2 deletions,3 the presence of intellectual disability was not associated with obesity in 22q11.2DS.

Advantages and limitations
To our knowledge, this sample is the largest cohort of adults for a study of obesity for any recurrent CNV, including 16p11.2 deletions and Prader-Willi syndrome.1,3 Nonetheless, data points are still fairly scarce at ages older than 40 years. This may explain why we did not detect an effect of sex on obesity, because this emerges at approximately age 35 years in the general population.21 As for all cross-sectional, retrospective studies, it is difficult to draw causal inferences and to eliminate bias. We attempted to account for the maximal effect of each contributing factor on obesity by using maximum BMI and only examining the presence of factors prior to the maximum BMI. However, we cannot rule out that, for some factors, variability in the onset and duration of exposures could have affected results. We were unable to evaluate pediatric factors such as undergrowth and feeding difficulties due to limitations in retrospective data. We also did not include palatal anomalies in this study, most of which were repaired; and in a previous study these were previously reported to be unrelated to pediatric growth abnormalities.6 Most subjects were assessed using FISH and typical probes that would not allow analyses targeted to specific deletion extent. Excluding the four subjects assessed by microarray to have shorter nested 22q11.2 deletions from the regression analysis and population comparisons made no material difference to the main results. Future studies using larger samples with detailed molecular characterization may enable stratification based on the extent of 22q11.2 deletion to determine whether the prevalence of obesity differs between those with proximal or nested deletions compared with those with the typical A-D deletion present in 85–90% of individuals with 22q11.2DS.

Implications and future directions
The results of the current study, together with available pediatric growth curve data,3-7 support early (e.g., from age 12 years) and ongoing attempts to encourage healthy diet and exercise behaviors in 22q11.2DS. The involvement of a dietitian may be helpful, particularly in the context of other factors such as treatment with antipsychotic and other psychotropic medications. General clinical practice guidelines for schizophrenia would include active monitoring for weight gain and metabolic side effects. Medication choice should include balancing efficacy and side effects.29 Both metabolic and motor considerations may be of concern in 22q11.2DS given the predisposition to obesity and movement disorders.32,33 The results also suggest that extra attention to metabolic control may be needed for adults with hypothyroidism, especially in the presence of congenital cardiac disease. Obesity is common among individuals with intellectual disability in the general population.34 Although intellectual disability was not a contributing factor in the regression analysis, most individuals with a recurrent 22q11.2 deletion have intellectual functioning that is below average, and thus issues related to intellectual functioning may not be readily separable from the effect of the 22q11.2 deletion itself. Nonetheless, intellectual level may pose a challenge to the management of obesity (Supplementary Figure S1 online).

Our results expand the potential genetic causes of obesity to include recurrent 22q11.2 deletions. The similarities to and differences from other obesity-associated recurrent CNVs may be fruitful avenues for future research efforts. These would include satiety responsiveness,35 the trajectory of weight gain for individuals, and the development of obesity-related complications, including mortality.32,33 In addition to genetic dosage decreases in the respective microdeletion regions, there may be other contributing genetic factors and pathways to obesity expression.
that converge for CNVs with obesity phenotypes. Animal models of deletions and reciprocal duplications may assist in understanding the molecular pathways involved. To our knowledge, however, obesity has not been reported for animal models of the 22q11.2 deletion, perhaps because of the emphasis on embryonic and early development. A recent biochemical study of 11 nonobese children with 22q11.2DS implicated dysregulated energy homeostasis. Studies of such biomarker profiles and of genome-wide genetic variants in obese and nonobese adults with 22q11.2DS may shed light on factors that are important in metabolic and neuronal functions.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

ACKNOWLEDGMENTS

The authors thank the adults with 22q11.2DS and their families, as well as the many referring clinicians, for their generous contributions to this and related research studies. This work was supported by Canadian Institutes of Health Research (CIHR) grants (MOP-97800 and MOP-89066), the University of Toronto McLaughlin Centre, and National Institute of Mental Health U01 MH101723-01. A.S.B. holds the Canada Research Chair in Schizophrenia Genetics and Genomic Disorders, and the Dalglish Chair in 22q11.2 Deletion Syndrome.

DISCLOSURE

The authors declare no conflict of interest.

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