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Age- and gender-dependent obesity in individuals with 16p11.2 deletion

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Abstract

Recurrent genomic imbalances at 16p11.2 are genetic risk factors of variable penetrance for developmental delay and autism. Recently, 16p11.2 (chr16:29.5 Mb−30.1 Mb) deletion has also been detected in individuals with early-onset severe obesity. The penetrance of 16p11.2 deletion as a genetic risk factor for obesity is unknown. We evaluated the growth and body mass characteristics of 28 individuals with 16p11.2 (chr16:29.5 Mb−30.1 Mb) deletion originally ascertained for their developmental disorders by reviewing their medical records. We found that nine individuals could be classified as obese and six as overweight. These individuals generally had early feeding and growth difficulties, and started to gain excessive weight around 5−6 years of age. Thirteen out of the 18 deletion carriers aged 5 years and older (72%) were overweight or obese, whereas only two of 10 deletion carriers (20%) younger than five were overweight or obese. Males exhibited more severe obesity than females. Thus, the obesity phenotype of 16p11.2 deletion carriers is of juvenile onset, exhibited an age- and gender-dependent penetrance. 16p11.2 deletion appears to predispose individuals to juvenile onset obesity and in this case are similar to the well-described Prader−Willi syndrome (PWS). Early detection of this deletion will provide opportunity to prevent obesity.

Keywords: Obesity; Chromosome deletion; 16p11.2; Developmental delay; Autism spectrum disorders; Chromosomal microarray analysis; Genetic testing

1. Introduction

Whole genome profiling technologies such as array comparative genomic hybridization (aCGH) have enabled the accelerated discovery of novel genomic imbalances (deletions and microduplications) in patients with specific clinical phenotypes. These novel genomic disorders often exhibit additional clinical features beyond those for which they were initially ascertained. A reverse genomic or "genotype-first" approach (Ledbetter, 2008), where individuals with the same or similar genomic imbalances are further evaluated, is not only necessary to determine the penetrance and spectrum of clinical features associated with a genomic disorder but also important to effectively discover additional comorbid features critical for patient management and genetic counseling.

Deletion at 16p11.2 (chr16:29.5 Mb−30.1 Mb) is a recurrent event mediated by segmental duplication architecture, and is common among patients with developmental delay (DD), autism spectrum disorder (ASD) and other neuropsychiatric problems (Sebat et al., 2007; Christian et al., 2008; Kumar et al., 2008; Marshall et al., 2008; Weiss et al., 2008). The clinical phenotypes of individuals carrying the deletion are heterogeneous (Bijlsma et al., 2009; Fernandez et al., 2010; Hanson et al., 2010; Rosenfeld et al., 2010; Shinawi et al., 2010). The phenotypes associated with this deletion show

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incomplete and variable penetrance since the deletion has also been observed in control population (Kumar et al., 2008; Weiss et al., 2008; Bijlsma et al., 2009; Glessner et al., 2009; Rosenfeld et al., 2010) and in patients without autism spectrum disorder (Ghebranious et al., 2007; Bijlsma et al., 2009; Shimojima et al., 2009; Shiow et al., 2009; Fernandez et al., 2010; Hanson et al., 2010; Rosenfeld et al., 2010; Shinawi et al., 2010).

Overweight (defined as sex specific Body Mass Index (BMI)-for-age 85th−95th percentile) and obesity (defined as sex specific BMI-for-age ≥95th percentile) have been observed in individuals carrying 16p11.2 deletion (Ghebranious et al., 2007; Bijlsma et al., 2009; Fernandez et al., 2010; Shinawi et al., 2010; Bochukova et al., 2010; Walters et al., 2010). To evaluate the penetrance of obesity and overweight among individuals with 16p11.2 deletion, we took a genotype-first approach. We examined the growth characteristics and related clinical features of individuals carrying 16p11.2 deletion detected by diagnostic chromosome microarray analysis in a hospital setting. Our results showed that obesity is a common clinical feature of 16p11.2 deletion patients, and exhibits age-dependent penetrance suggesting that earlier diagnosis may allow for more effective intervention.

2. Materials and methods

2.1. Patient population

Individuals with 16p11.2 deletion were identified from all patients referred for diagnostic aCGH and subsequently de-identified. The study was approved by the Institutional Review Board for Human Subjects Research at the Children's Hospital Boston, USA.

2.2. aCGH analysis

aCGH was performed using Agilent 244K oligonucleotide-based CGH array (G4411B, Agilent Technologies, Palo Alto, CA, USA) following previously published protocols (Shen et al., 2007) and the manufacturer's instructions (Oligonucleotide Array-Based CGH for Genomic DNA Analysis protocol version 3 (Agilent Technologies)). The aCGH data was managed using Nexus software (V5, BioDiscovery, Inc. El Segundo, CA, USA).

2.3. Medical record review and literature data review

All available electronic medical records of the patients [mean age = 8y8m (8 years and 8 months); age range = 1y10m−21y] with 16p11.2 deletion were reviewed by a working group that consisted of a pediatric clinical geneticist, laboratory molecular geneticist, and pediatric nutrition/weight specialist. Consensus clinical features were tabulated and anthropometric data were collected to calculate the BMI percentile and Z-score (standard deviation), based on the 2000 Center for Disease Control (CDC) Growth Charts for the United States. In addition, 387 individuals (mean age = 12.9y; age range = 5y−22y) with DD/ASD without 16p11.2 deletion were randomly chosen as controls.

We also reviewed literature reports of 47 patients (mean age = 8y, age range = 2m−44y) with 16p11.2 deletion (Kumar et al., 2008; Bijlsma et al., 2009; Shimojima et al., 2009; Fernandez et al., 2010; Rosenfeld et al., 2010; Shinawi et al., 2010) for information on gender and weight-for-age percentile (Supplementary Table 1). The weight-for-age percentiles are plotted against age.

3. Results

We identified 28 patients (15 male, 13 female) with 16p11.2 deletion out of the 6680 consecutive clinical referred diagnostic cases subjected to aCGH analysis. The most common clinical indications for array testing were DD and intellectual disability (ID)(n = 3638, 54.5%), ASD (n = 2200, 32.9%) and dysmorphism or multiple congenital anomalies (n = 1412, 21%). Eighteen percent had more than two indications for testing. Thirteen deletions were *de novo* and 4 deletions (2 paternal and 2 maternal) were inherited from one of the parents. Data on parental BMI are not available. Complete parental testing was not performed for the remaining cases (n = 11) (Table 1).

3.1. Growth and development related clinical features of patients with 16p11.2 deletion

We reviewed the medical records mainly from Genetics, Neurology, Developmental Medicine (n = 28) and Nutrition Clinic visits (n = 3). Relevant clinical features are summarized in Table 1.

Pregnancy and delivery were generally uncomplicated. Six individuals weighted less than 2500 g, three of those were part of twin pregnancies. Four weighted more than 4000 g at birth; thirteen were born at appropriate weight for gestational age, and five had no birth weight recorded.

DD or ID was a common feature of 16p11.2 deletion patients. Fifteen of the 21 individuals who had formal cognitive testing were found to have ID, with a severity ranging from severe to borderline, and with the majority being mild. Ten patients also had the clinical diagnosis of ASD. Hypotonia was present in 17 of the 22 patients whose examination of muscle tone was mentioned in the medical records. Early feeding difficulty and failure to thrive were common (10 out of 22 with clinical notes describing feeding difficulties).

3.2. Overweight and obesity is an age- and gender-dependant feature

We found that overweight or obesity was frequent among patients with 16p11.2 deletion. At their most recent exam, six out of 28 were overweight and nine were obese, together comprising more than half (15/28) of the cases. The youngest overweight individual was ∼2 years of age, but overall overweight or obesity is much more prevalent in older patients. Thirteen out of 18 deletion patients aged five years

Table 1
The growth related features of patients with 16p11.2 deletion.

Patient#/ Gender	Deletion origin	Birth weight (g)	Neonatal adaptation	Hypotonia	Age at exam	Weight (kg)	Height (cm)	BMI/ percentile	Z-score	OFC (cm)	Developmental phenotype	ASD diagnosis	Eating behavior
1/M	*de novo*	2490	TTN,FTT, PWG	+	1y10m	10.15/<5th	81.5/10-25th	15.28/14th	−1.08	50/90th−95th	Mild LD; MD	NO	Poor feeding skills
2/M	*de novo*	3400	Normal	Mild	10y11m	87.5/>97th	160/>95th	34.3/99th	2.54	56/>97th	GDD; very low IQ	ASD	Avid appetite
3/M	*de novo*	3370	Respiratory distress	Mild	9y10m	76.6/>97th	151.6/75−90th	33.3/99th	2.5	54.5/90th	LD; MD; severe MR/IQ52	NO	Avid appetite
4/M	Maternal	3277	FTT, weight decline	+	4y11m	18.1/50th	105.4/54th	16.3/75th	0.67	54/98th	Mild MD, MR, LD	NO	Food aversion
5/M	NT	4540	Normal	+	5y6m	19/70th	108/50−75th	16.3/74th	0.65	51/50th	MR, MD, significant LD	ASD	Normal
6/M	*de novo*	3192	FTT	+	17y6m	139.2/>98th	168.4/10−25th	49.09/>99th	3.13	60/98th	LD, mild MD, MR/IQ 69	NO	Unknown
7/M	*de novo*	3062	Feeding difficulty	Mild	11y4m	65.2/98th	154.5/90th	25.8/97th	1.95	58/91−98th	LD / borderline IQ	ASD	Picky eater with food aversions
8/M	Paternal	Unknown	FTT,GEF	Mild	2y9m	11.09/3−5th	87.6/5−10th	15.5/5th	−1.61	47.5/10−25th	LD, MD, MR	NO	Food obsession, ravenous eating
9/M	*de novo*	1814	PWG, GEF, FTT	−	4y9m	19/75−90th	107.3/50−75th	16.5/79th	0.81	Unknown	LD, MD, MR	ASD, severe	Picky eater with poor eating habits
10/M	*de novo*	1588	PWG, GEF, FTT	+	4y8m	18.4/50−75th	107.1/50−75th	16.0/68th	0.48	50.2/90th	LD, MD, MR	ASD, severe	Picky eater; eats in large quantities
11/F	*de novo*	3657	Early FTT	+	6y6m	34.8/>97th	124.4/90th	22.5/99th	2.26	Unknown	LD	PDD-NOS	Unknown
12/F	NT	3175	Unknown	Unknown	14y	46.9/25th	148/<3rd	21.4 /64th	0.37	54.5/90th	LD	NO	Normal
13/M	*de novo*	2722	Jaundice, seizures	Unknown	19y	86/89th	176/50th	27.9/90th	1.28	57/>97th	MD	NO	Normal
14/F	NT	2296	Unknown	−	3y	14.6/50th	96.7/75th	15.6/56th	0.15	50−1/4/75−90th	Normal	NO	Unknown
15/F	Paternal	Unknown	Unknown	−	15y11m	59.9/50−75th	153.3/10−25th	25.5/90th	1.31	Unknown	Normal	NO	Normal
16/M	NT	4366	Colicky	Mild	12y6m	68.5/97th	169.3/97th	23.9/94th	1.52	57.6/98th	LD, MD	PDD-NOS	Good appetite
17/M	NT	2778	Normal	+	6y6m	44.8/>95th	126/95th	28.2/>99th	2.99	Unknown	LD, MD	Unknown	Unknown
18/F	Maternal	2722	Normal	Mild	10y8m	39/75th	149/<90th	17.6/57th	0.18	56.6/98th	LD, MD, MR	PDD-NOS	Good appetite
19/F	*de novo*	4196	GEF, poor feeding	+	2y	11/25th	85/10−25th	15.2/18th	−0.9	52.25/99th	LD, MD	No	Feeding difficulty
20/F	NT	Unknown	Normal	Unknown	14y2m	71.4/90−95th	155.8/10−25th	29.4/97th	1.85	Unknown	Mild LD	Mild ASD	Unknown
21/F	NT	2155	Poor feeding	Unknown	21y	71/>95th	146/>95th	33.3/96th	1.77	Unknown	LD, MD, MR/ IQ40	NO	Unknown
22/F	*de novo*	3941	Jaundice	+	2y4m	16.5/>97th	92/90th	19.5/98th	2	55/>97th	LD, MD	ASD	Good appetite
23/M	NT	3005	Normal	−	4y6m	18.6/75th	106.7/50−75th	16.3/75th	0.67	Unknown	LD, MR	NO	Picky eater
24/F	NT	2155	Unknown	+	5y	16.8/20−50th	105.5/25−50th	15.1/48th	−0.05	Unknown	LD	NO	Unknown
25/F	NT	Unknown	Poor feeding	+	7y	33.8/75th	138.1/75th	18/72th	0.57	54.5/90th	Learning difficulty, MD	NO	Unknown
26/M	NT	2722	Excessive cry	−	9y6m	35/77th	129/12th	21/94th	1.52	53/50th	LD, MD, MR/IQ 68	NO	Unknown
27/F	*de novo*	Unknown	Unknown	Unknown	13y	54.2/77th	150.5/10−25th	23.9/89th	1.25	Unknown	Unknown	Unknown	Unknown
28/F	*de novo*	4082	Normal	Unknown	2y4m	14/77th	88.2/50−75th	18/89th	1.24	47.8/90−97th	Unknown	NO	Unknown

TTN = transient tachypnea of newborn; FTT = failure to thrive; PWG = poor weight gain; GEF = gastro-esophageal reflux; NT = not tested; LD = language delay; MD = motor delay; MR = mental retardation; OFC = occipital-frontal circumference; IQ = intelligence quotient; GDD = global developmental delay; ASD = autism spectrum disorder; PDD-NOS = pervasive developmental disorder, not otherwise specified.

and older (72%) are overweight or obese whereas only two of the 10 patients younger than 5 years (20%) are overweight or obese. The age of onset was specifically noted in 5 patients (#3 at 6 y; #6 at 3 y; #2 and #7 at 4 y and #11 at earlier than 6 y). Thus, overweight or obesity associated with 16p11.2 is of juvenile onset and is of age-dependent penetrance (Fig. 1).

Obesity was observed in both males and females at about similar rate (∼50%), but the severity of obesity differs significantly between male patients and female patients. In this cohort, 5 male patients are obese with the mean Z-score = 2.6, four female patients are obese with the mean Z-score = 1.97, making the extent of obesity significantly more severe in male patients than in female patients (*t*-test, $P = 0.03$).

The penetrance of obesity among patients with 16p11.2 deletion older than 5 years (mean age = 11.7 y, age range = 5 y−21 y) is 47% (8/17), and is significantly higher (Fisher's exact test, $P = 0.039$) than that of DD/ASD patients of similar age range without 16p11.2 deletion (20.9% (81/387)), suggesting that the high penetrance of obesity among patients with 16p11.2 deletion is not due to a comorbid clinical diagnosis of DD or ASD.

To determine whether these findings might reflect some bias in our patient cohort, we also performed a literature review. As shown in Fig. 2, we observed similar age-dependent penetrance of obesity in patients with 16p11.2 deletion using weight-for-age percentile data: 18 of 28 individuals older than 5 years (64.3%) were overweight or obese, whereas only 2 of 22 individuals younger than 5 years (9.1%) were overweight or obese. Furthermore, the penetrance of overweight or obesity is higher in male (14/19 = 73.7%) than in female (4/9 = 44.4%) individuals with 16p11.2 deletion.

Regarding the causes of overweight or obesity among patients with 16p11.2 deletion, avid appetite was noted in 5 patients (#2, 3, 16, 18 and 22). Four other patients (#7, 9, 10 and 23) were noted as picky eaters with a very limited and rigid diet. Another patient (#8) exhibited ravenous eating behavior (this patient was not overweight or obese at 2 years of age). Excessive appetite, limited repertoire of food choices, and low level of physical activity seem to be collectively involved in the excessive weight gain of patients with 16p11.2 deletion.

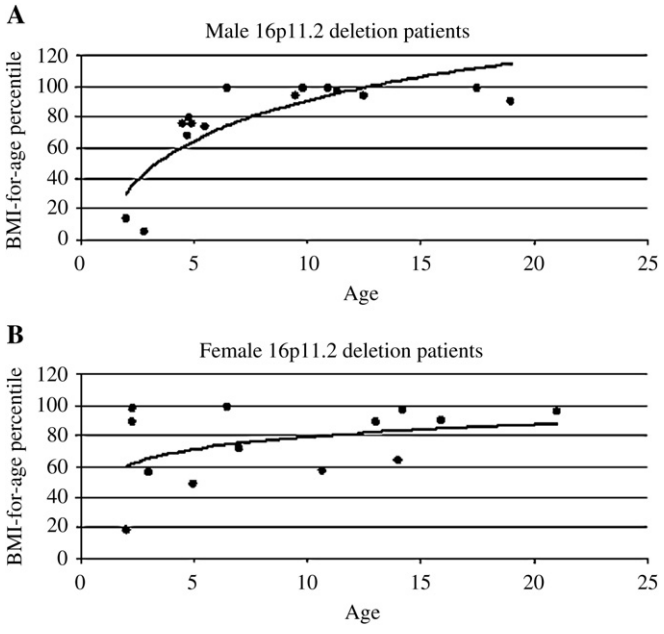

Fig. 1. The distribution of BMI-for-age percentile among 16p11.2 deletion patients of different ages. **A:** male patients; **B:** female patients.

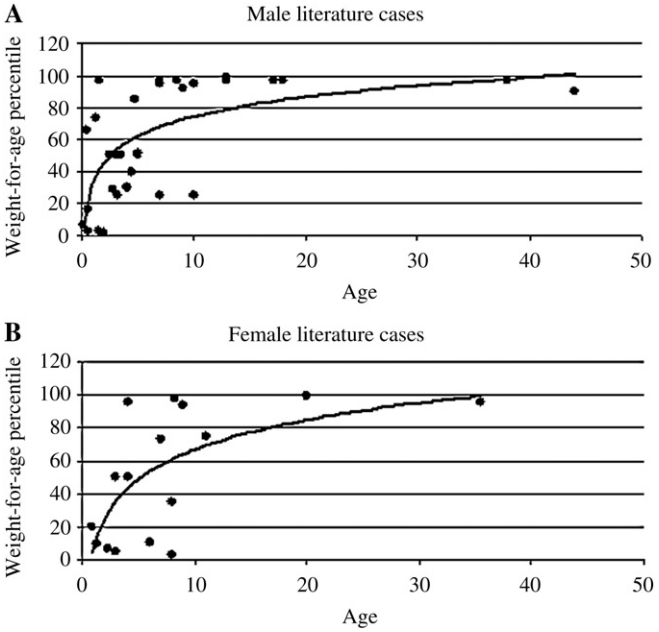

Fig. 2. The distribution of BMI-for-age percentile among literature cases with 16p11.2 deletion. **A:** male patients; **B:** female patients.

4. Discussion

While recent forward genetic studies indicated 16p11.2 deletion as a significant genetic risk factor for severe obesity (Bochukova et al., 2010; Walters et al., 2010), our reverse genetic study revealed that overweight and obesity is an age- and gender-dependent clinical phenotype among patients with 16p11.2 deletion. This finding further supports the notion that genomic imbalances can play important roles in the pathogenesis of childhood obesity, both severe and moderate. This newly discovered genomic disorder, combined with the classic human obesity syndrome, the Prader−Willi syndrome (PWS), illustrated an increasingly important genetic mechanism where dosage change of one or more genes in a contiguous genomic set can lead to the disruption of molecular pathways involved in body mass regulation. We found that the prevalence of obesity in older children exceeds 70%, which is similar to the level of other clinical features consistently associated with 16p11.2 deletion, such as developmental delay/intellectual disability (Fernandez et al., 2010; Rosenfeld et al., 2010; Shinawi et al., 2010). It is possible that our study does not represent the true penetrance of obesity because of ascertainment bias toward individuals with 16p11.2 deletion and ASD or other developmental disability. Ten out of 28 patients with

the 16p11.2 deletion in this cohort were clinically diagnosed with ASD. This raised the concern that the overweight or obese phenotype could be a secondary comorbid feature of ASD. The BMI characteristics of patients with ASD are controversial in the literature: several studies found the association of high BMI with ASD while some other studies came to the opposite conclusion (Bölte et al., 2002; Mouridsen et al., 2002; Whiteley et al., 2004; Curtin et al., 2005; Mills et al., 2007; Mouridsen et al., 2008; Xiong et al., 2009). Differences in ASD diagnostic criteria, ASD patient subgroup (e.g., Asperger syndrome *vs.* Autism), age group, sample size, gender, ethnicity and study period may all contribute to the contradictory findings. A recent study by Chen et al. (2010) using the BMI data collected by the National Survey of Children's Health (NSCH-2003) found that among several chronic conditions, ASD patients (247 patients aged 10y−17y) exhibited the highest prevalence of obesity (23.3%), double the rate of the control population without any chronic condition (12.2%). The prevalence of obesity in our cohort of 16p11.2 deletion patients aged over 5 years is 47% (8/17), four times the normal control prevalence rate and double that in unselected ASD patients. Although ASD could be a confounding factor for the obesity observed in 16p11.2 deletion patients, it does not seem to be the main causal factor for the obesity phenotype. Importantly, recent genomic studies in patients ascertained by BMI independently identified the 16p11.2 deletion as a significant genetic risk factor for obesity (Bochukova et al., 2010; Walters et al., 2010). Thus, the overall evidence supports the notion that both obesity and ASD are major clinical phenotypes of patients with 16p11.2 deletion. In the context of an energy imbalance model of obesity, 16p11.2 deletion patients exhibited both increased energy input (increased food intake and anabolic level) and reduced energy expenditure (reduced physical activity and catabolic level), which could explain the excessive weight gain. However, the mechanism by which 16p11.2 deletion leads to overeating behaviors and low energy expenditure need further investigation. Intriguingly, recent obesity GWAS studies have provided strong evidence for neuronal involvement in the pathogenesis of obesity (Willer et al., 2009), suggesting that both ASD and obesity may share similar underlying molecular and pathological mechanisms. This is an interesting hypothesis and deserves further examination. 16p11.2 deletion may serve as an ideal model for understanding the common pathways that contribute to both ASD and obesity.

Some similar clinical features were noted in comparing 16p11.2 deletion disorder and PWS. Notably several of our patients were suspected to have PWS during their clinical diagnostic visits. Shared features between the two disorders include early feeding difficulty and poor weight gain, followed by excessive eating and early childhood obesity. Motor and language problems as well as cognitive delay are common in both two disorders, as are autistic features and other neuropsychiatric disturbances. However, important differences that can be helpful for differential diagnosis do exist. In patients with PWS, early poor weight gain is often a direct consequence of poor sucking ability, usually caused by severe hypotonia. In patients with 16p11.2 deletion, hypotonia was often mild and sometimes only affected the extremities. The feeding difficulty that existed in several 16p11.2 deletion patients was mainly due to poor coordination between sucking, swallowing and gastroesophageal reflux.

In contrast to PWS, hypogonadism, short stature and flexible ligaments are not evident in individuals with 16p11.2 deletion. No characteristic facial feature has been evident with 16p11.2 deletion disorder. PWS patients tend to have smaller head size (Butler and Meaney, 1991), while patients with 16p11.2 deletion are often macrocephalic (Shinawi et al., 2010). In our cohort, 15/19 individuals are of >90% occipital-frontal circumference (Table 1). These differences are helpful for the differential diagnosis of the two disorders. A thorough comparison of the clinical features of the two disorders is warranted using larger patient cohort.

Obesity and its complications have myriad adverse effects on the health and disease prognosis of an individual. The discovery of the high risk of obesity in patients with 16p11.2 deletion will have significant direct clinical implications for patient care and management. Currently, body mass control is not a routine clinical care component for patients with 16p11.2 deletion. Among 28 deletion patients, only 3 individuals were followed in a pediatric nutrition/weight program. Since most of these patients are young, the long term consequences of obesity among these patients are currently unknown. Longitudinal follow-up studies will be necessary in order to understand the trajectory of body mass gain associated with 16p11.2 deletion and the effectiveness of body mass management schemes.

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Supplementary data

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