

Structural Chromosome Abnormalities Associated with Obesity: Report of Four New Subjects and Review of Literature

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Abstract: Obesity in humans is a complex polygenic trait with high inter-individual heritability estimated at 40–70%. Candidate gene, DNA linkage and genome-wide association studies (GWAS) have allowed for the identification of a large set of genes and genomic regions associated with obesity. Structural chromosome abnormalities usually result in congenital anomalies, growth retardation and developmental delay. Occasionally, they are associated with hyperphagia and obesity rather than growth delay. We report four new individuals with structural chromosome abnormalities involving 10q22.3-23.2, 16p11.2 and Xq27.1-q28 chromosomal regions with early childhood obesity and developmental delay. We also searched and summarized the literature for structural chromosome abnormalities reported in association with childhood obesity.

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INTRODUCTION

Obesity is a major growing health problem facing children and adults worldwide and particularly in the Westernized world. It represents an energy imbalance in which energy intake exceeds expenditure. While decreased physical activity and increased caloric intake are the major forces behind this epidemic, there is strong evidence supporting the role of major genes and minor genomic variants in causing or contributing to human obesity. Various genetic techniques had been used to identify the genetic basis of severe early childhood obesity and with the more common forms of obesity usually seen in older individuals. To date, cytogenetic studies followed by appropriate molecular analysis in a small group of children with severe childhood obesity have shown specific structural chromosome abnormalities. Large cohorts of obese adults have also been studied using genome-wide linkage and association scans. In most of these studies, single nucleotide polymorphism (SNP) based platforms were used rather than copy number variants. Beginning in 1996, the “Human Obesity Gene Map” provided a catalogue of all known genetic variants and chromosomal loci associated with or linked to obesity-related traits [1]. The most recent update was published in 2006 [2] and included 176 single-gene mutations in 11 different genes, 50 loci related to known Mendelian syndromes, 244 murine adiposity related genes, 408 animal model based

quantitative trait loci (QTLs) and 253 human QTLs from 61 genome-wide scans.

In this report, we present our experience in a small series of individuals with childhood obesity and other health problems presenting for genetic services. Four individuals with obesity and other health problems were found to have structural chromosome abnormalities. We briefly review structural chromosome abnormalities associated with obesity reported in the literature.

SUBJECTS AND METHODS

Clinical Reports

Subject 1

At 34 years of age, this woman (Fig. 1a,b) presented with obesity since early childhood and developed idiopathic urticaria which became prednisone dependent. Therefore, multiple hives and target lesions were noted.

She was diagnosed with endometriosis at 22 years of age and a large lipoma on her upper back required resection at 34 years of age. She had recurrent facial methicillin resistant *Staphylococcus aureus* (MRSA) infection and poison ivy. She had no cognitive abnormalities. An abdominal CT scan performed at 35 years of age showed a normal gastrointestinal tract but unexpectedly marked atrophy of the right kidney was seen with bilateral renal focal clubbing and cortical scarring. Calcified renal cysts were also noted in the right kidney. Extensive laboratory workup (rheumatoid factor, aldosterone, cortisol, FSH/LH, insulin, testosterone, celiac disease antibody panel, Hepatitis B antibody profile, ferritin, *H. pylori* profile, serum protein electrophoresis, thyroid peroxidase antibody,

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anti-thyroglobulins and histamine and tryptase levels) were all within normal range. Her serum uric acid was mildly increased and an ANA screen was positive at a low titer (1 in 40, speckled pattern). Her weight was 133.36 kg (>95th centile), height was 155 cm and BMI was 55.5 kg/m². She had synophrys, a “buffalo hump” fat pattern and a recurring large lipoma on her upper back region.

A 105K-whole-genome array comparative genomic hybridization (aCGH) study revealed a 7.8 Mb duplication at chromosome 10q22.3-q23.2 (Fig. 2a) (base position: 81,281,895-89,091,213; hg18) which was absent in her mother. Her father was not available for evaluation. The duplication was confirmed by fluorescent in situ hybridization (FISH) using the BAC clone “RP11-830JJ13” (Fig. 3a).

Subjects 2 and 3

At 8 months of age, this Hispanic boy (Fig. 1c,d) was evaluated for a suspected diagnosis of Prader-Willi syndrome because of his rapid weight gain and developmental delay. He was born at term and his mother had gestational diabetes mellitus. He had feeding difficulties for the first four months of life followed by developmental delays. His weight was 11.53 kg (>95th centile), length was 73.5 cm (50-75th centile) and BMI was 21.3 kg/m² with a head circumference of 46.25 cm (75-90th centile). Frontal bossing was noted with moderate micrognathia, almond-shaped eyes, flat-nasal bridge, small appearing hands with distal tapering of fingers, deep palmar creases, one large café au lait spot on the left shoulder, undescended testes, and a head lag. DNA methylation testing for the Prader-Willi

syndrome/Angelman syndrome region at chromosome 15q11.2 was normal (not shown). Genomic DNA oligo-array CGH analysis was then performed which showed a small 16p11.2 deletion (base position: 28,730,299-29,009,896; hg18) (Fig. 2b) and confirmed by FISH analysis using the BAC clone “RP11-1136I3” (Fig. 3b).

His mother was 30 years old, weighed 58.2 kg and was 150.3 cm tall. Her BMI was 25.8 kg/m². She reported no significant health problems. Her other child (Subject 3), a 34 month old daughter with obesity and speech delay, presented for genetic evaluation. The pregnancy was complicated by preterm labor at 36 weeks gestation with a history of maternal syphilis and gestational diabetes mellitus. Birth weight was 2.43 kg (39th centile), length 45.9 cm (46th centile), BMI was 11.5 kg/m² and head circumference was 29.5 cm (6th centile). Congenital syphilis was excluded. She walked at 12 months of age. At 34 months of age, her weight was 19.9 kg (>97th centile), length was 97.5 cm (>95th centile), BMI was 20.9 kg/m² and head circumference was 50 cm (90th centile). She presented with frontal bossing, one small café au lait spot on the lower back and delayed speech (Fig. 1e). Her serum liver and lipid profiles, renal ultrasound and bone age were normal for her age. These family members also showed the same 16p11.2 deletion as Subject 2.

Subject 4

At 8 years of age, this Caucasian girl was evaluated and found to have a *de novo* germline deletion involving chromosome Xq27.1-q28 region by standard chromosome analysis (not shown). This chromosome abnormality was confirmed by aCGH analysis and a 10.69 Mb deletion was found (base position: 139,354,859-150,046,723; hg18) (Fig.

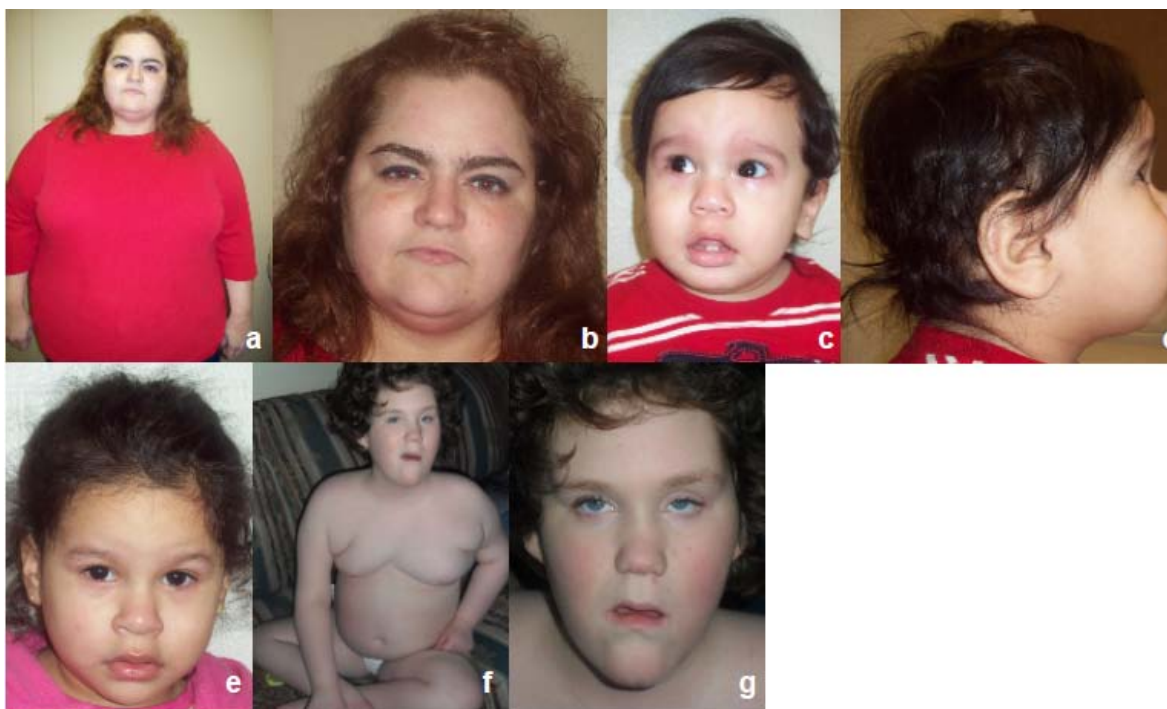


Fig. (1). Photographs of Subjects 1-4. Subject 1 (a,b) has synophrys, obesity and urticaria (not shown). Subject 2 (c,d) and his sister, Subject 3 (e) have a prominent forehead, bulky ears, micrognathia and full lips. Subject 4 (f,g) has myopathic facies, ptosis, long and narrow face, truncal obesity, a prominent forehead and prognathism.

2c). She was the product of a 37 weeks gestation complicated by maternal tobacco smoking. Delivery was spontaneous vaginal and birth weight was 2.41 kg. Postnatal health problems included a slow weight gain, hypotonia, microcephaly, global developmental delays, right eye esotropia, and chronic constipation. A brain CT scan, thyroid function, quantitative plasma amino acid and urine organic acid profiles were all normal. She also had normal *MECP2* gene sequencing, *SNRPN* gene methylation testing for PWS and *FMRI* gene methylation with the CGG repeat determination at 20 indicating one allele. Quantitative urine mucopolysaccharides levels were elevated at 20.8 (<12.0 mg/mmol Cr). Her weight was 33.7 kg (90-95th centile), height was 100 cm (<5th centile), head circumference was 50 cm, and BMI 33.7 was kg/m². She was dysmorphic (myopathic facies, dolicho-microcephaly, almond-shaped eyes, narrow, long face and nose, pinched nostrils, prominent philtrum, small mouth, small ear lobes, and a narrow palate). She had truncal obesity, small hands and feet and severe speech and cognitive delays (Fig. 1f,g). She was treated with growth hormone.

Molecular Cytogenetic Studies

In this study, four individuals were studied and found to have various chromosome aberrations associated with early onset obesity and other findings. Standard chromosome analysis of peripheral blood lymphocytes was initially performed in Subject 4. DNA was isolated according to standard procedures and used for chromosome microarray studies. FISH analysis used genomic region specific BAC clones (Table 1) for Subjects 1, 2 and 3 and obtained from The Center for Applied Genomics (TCAG, Toronto, Canada). Quantitative PCR amplification of an Xq27.1 gene was used in Subject 4 to confirm the cytogenetic deletion (not shown). Three separate Agilent Technologies (Santa Clara, CA) oligo-nucleotide CGH array platforms (105K platform in Subject 1, 180K platform in Subjects 2 and 3 and 244K platform in Subject 4) were used with genomic DNA isolated following manufacturer's recommendations and as previously described [3,4]. Each sample was subjected to one hybridization experiment using Cy3 fluorescently labeled test DNA paired with Cy5 labeled reference DNA. Probe hybridization signals were expressed as the log₂ ratio of signal intensities of a test sample versus signal intensities of a reference sample and array data were analyzed using the Nexus Copy NumberTM software

(Biodiscovery, El Segundo, CA) based on the genome content sourced from the UCSC hg18 human genome (NCBI build 36, March 2006). Array CGH studies for Subjects 1, 2 and 3 were performed at CombiMatrixTM (Irvine, CA) while Subject 4 was studied at The Children's Mercy Hospital Microarray Laboratory (Kansas City, MO).

Literature Search Discovery

To further identify structural chromosome abnormalities playing a role in the causations of obesity, we performed an online PubMed search for structural chromosome abnormalities reported in the literature using key words such obesity, chromosome deletion, duplication, translocation, inversion, and the names of leading genetics journals. The results of this search were compiled in Table 2.

RESULTS

The major clinical findings in our four individuals were summarized in Table 1 and the results of their molecular studies. While obesity is a shared clinical finding, each individual had a different complex phenotype due to their unrelated molecular genetic abnormality except for Subjects 2 and 3 who were siblings. The aCGH profiles for Subjects 1 through 4 are shown in Fig. (2a-c) representing the regions of genomic abnormality. The regions recognized segmental duplications (Fig. 2a,b) known to mediate the copy number abnormalities of the chromosomes involved are highlighted. In Fig. (3a,b), the duplication of chromosome 10q22.3-q23.2 and deletion of 16p11.2 were confirmed by FISH analysis. The BAC clones used for the FISH studies in each subject are shown in Table 1. The parents of Subject 4 had normal peripheral blood chromosomes studies.

DISCUSSION

In this group of four subjects, generalized or truncal obesity was a major clinical feature. Early feeding difficulties (Subjects 2 and 4), hypotonia (Subject 4) and developmental delays (Subjects 2 and 4) followed by rapid weight gain led to the clinical suspicion of Prader-Willi syndrome (PWS). The PWS diagnosis was largely excluded by the normal *SNRPN* gene methylation studies which ruled out genetic defects of the PWS/AS (Angelman syndrome) region. Subject 1 also presented as an adult with an unexplained complex phenotype which warranted a detailed genetic evaluation and revealed a chromosome 10q22.3-q23.2 duplication. Facial dysmorphism was noticeable in each of the four individuals but the most

Table 1. Summary of the Clinical and Molecular Findings in the Four Reported Subjects in our Study

Subject	Chromosome abnormality	FISH study/ Probe	Clinical features
1	Chr. 10q22.3-q23.2 dup (81,281,895-89,091,213bp)	Yes/ RP11-830J13	34 yr old, early onset obesity, idiopathic urticaria, endometriosis, atrophy & scarring of right kidney
2 and 3	Chr. 16p11.2 del (28,730,299-29,009,896 bp)mat	Yes/ RP11-1136I3	Early onset obesity, developmental and speech delays
4	Chr. Xq27.1-q28 del (139,354,859-150,046,723 bp)dn	No	Early onset obesity (truncal), hypotonia, microcephaly, global developmental delays, right esotropia, short stature

Table 2. Summary of Reported Chromosomal Abnormalities in the Literature from Individuals with Syndromic Obesity excluding Prader-Willi Syndrome

Chromosome	Chromosome position	Clinical Features	Reference
<i>Chr.1</i>	1p36 deletion	PWS like phenotype (hypotonia, hyperphagia, obesity, behavioral abnormality and developmental delay), dysmorphism. Hepatic steatosis & lysosomal lipofuscinosis in one patient	[37-44]
<i>Chr.2</i>	2q37.3 deletion (4 individuals)	Albright hereditary osteodystrophy (AHO): short stature, obesity, round face, brachydactyly, variable biochemical abnormalities (pseudo & pseudopseudohypoparathyroidism)	[45]
	46,XY,der(2)t(2;6)(q37.3;q26)	mental retardation, obesity, brachydactyly, short stature (subtelomeric FISH), father & sister are healthy t(2;6) carriers	[46]
	2q37 deletion as a result of maternally inherited der(2): 46,XX,ish der(2)t(2;21)(qter;qter)mat (D2S447-.D21S1146+)mat	2 sisters with Albright hereditary osteodystrophy like syndrome	[47]
<i>Chr.3</i>	46,XX,dir ins (18;3)(p11.1;q13.2→q25)	mental subnormality, short stature, multiple minor phenotypic anomalies, obesity, normal secondary sexual characteristics, speech deficit	[48]
	duplication of 3p23 as a result of maternally inherited der(9)t(3;9)(p25;p23)	hypoglycaemia, hypotonia, obesity of the trunk and thighs, mild dysmorphic features, overgrowth [features seen in both the dup(3p) and del(9p) syndromes]	[49]
	duplication of 3p25.3p26.2	PWS like: pervasive developmental disorder, delayed speech, rapid onset of obesity at age 4 years. increased expression of GHRL and PPARG genes	[50]
	constitutional complex genome rearrangement with 11 breakpoints involving chromosomes 3, 11, 12, and 21, 0.5-Mb deletion at 3q26.31 (<i>NAALADL2</i>)	mild intellectual disability, obesity, coarse facies, apparent synophrys without other distinctive dysmorphia or congenital anomalies	[51]
<i>Chr.4</i>	46,XX, r(4)(p16q35). 4p breakpoint: distal to <i>WHS</i> and <i>FGFR3</i> but proximal to D4S3359; 4q: close to the telomere as D4S2390 was not deleted	mild developmental delay, deafness, short stature, obesity, type 2 diabetes mellitus, distinctive phenotype	[52]
	<i>de novo</i> mosaic, supernumerary ring markers (G banded karyotype), 16 Mb duplication (4q10-4q13.2) by FISH & aCGH analysis	developmental delay, tall stature, obesity. Duplication includes insulin-like growth factor binding protein 7 (<i>IGFBP7</i>) gene	[53]
	7 Mb (4q35.1) deletion and 20 Mb (5p14.3) duplication	MOMES (Mental retardation, Obesity, Mandibular prognathism, Eye and Skin anomalies)	[54]
	<i>de novo</i> deletion (4q32.1q32.3) (156.6-166.3 Mb) and insertion of 0.8 Mb (160.1-160.9 Mb) and 0.11 Mb (166.8-166.5) into 5q21 [oligo aCGH & BAC-FISH]	Mild-moderate mental retardation, psychosis, obesity, broad nasal root, sparse lateral eyebrows, thin upper lip, short philtrum, micrognathia, and strabismus	[55]
<i>Chr.5</i>	<i>de novo</i> reciprocal translocation t(5;7)(q33.1;p15.1)	hypotonia, obesity, multiple congenital anomalies, and mental retardation	[56]
	<i>de novo</i> 3.7 Mb tandem microduplication: 5p13.1p13.2 (35,624,846-39,364,263) (including <i>NIPBL</i> gene)	developmental delay, autistic behavior, obesity, lymphedema, hypertension, macrocephaly, facial dysmorphism	[57]
<i>Chr.6</i>	<i>de novo</i> deletion of 6q23.3qter	craniofacial dysmorphism, truncal obesity, mental retardation, dysmorphism in the proband with 6q14q16 deletion	[58]
	familial t(6;15)(q16;q21), ins(3;6)(q12;q14q16)	6q14q16 duplication carriers: moderate mental retardation, short stature, obesity, microcephaly, brachycephaly, a short smooth philtrum, central hair whorl, simian creases, 5th finger brachydactyly, skeletal disproportion	[59]

(Table 2). Contd.....

Chromosome	Chromosome position	Clinical Features	Reference
	<i>de novo</i> interstitial deletion of 6q16.2q21	mental & psychomotor delay, obese appearance, minor craniofacial anomalies, & brain anomalies	[60]
	deletion (6)(q22.2q23.1)	Prader-Willi-like phenotype	[61]
	Paternally inherited dup(6)(q24.3q27)	Moderate-severe intellectual delay, short stature, small hands and feet, eye abnormality, small mouth, and obesity (without hyperphagia)	[62]
	46,XX,del(6)(q15-q21)	Prader-Willi-like phenotype	[63]
	<i>de novo</i> balanced t(1;6)(p22.1;q16.2), disrupts <i>SIMI</i> on 6q16.2	early-onset profound obesity (hyperphagia)	[64]
	deletion of <i>SIMI</i> gene on (6q16.2)	Prader-Willi-like phenotype	[65]
	<i>de novo</i> complex chromosomal rearrangement of chr 1, 5, 6 resulting in del 6q14	obese woman with a psychotic (schizoid) disorder	[66]
	<i>SIMI</i> gene deletion (6q16-q21)	syndromic obesity	[67]
	5 Mb microdeletion at 6q16.1-q16.3 with <i>SIMI</i> gene deletion	syndromic obesity	[68]
	*46,XY,del(6)(q16.1q21); 15.2 Mb deletion (94.349-109.625 Mb) *46,XX,del(6)(q15q21); 14.2 Mb deletion (92.102-106.363 Mb) * 46,XX,del(6)(q16.2-q21); 15 Mb deletion (98.569-113.685 Mb) *46,XY; 4.1 Mb deletion (98.569-102.689 Mb) *46,XY,del(6)(q16.1q21); 7.2 Mb deletion (95 641-102 879) <i>SIMI</i> gene responsible for obesity, <i>GRIK2</i> possibly involved in autistic-like behavior, <i>POPDC3</i> in heart development, <i>MCHR2</i> in control of feeding behavior & energy metabolism)	global DD, hypotonia, obesity, hyperphagia, and eye/vision anomalies	[69]
	11.3 Mb deletion at 6q16.1-q21 due to a paternal balanced ins(7;6)(p15;q16.1q21)	severe mental retardation, obesity, and minor anomalies	[70]
	8.73 Mb deletion (79.38-88.10 Mb) at 6q14.1-q15	developmental delay, obesity, hernia, rounded face with full cheeks, epicanthal folds, short palpebral fissures, bulbous nose, large ears, and syndactyly between toes II/III	[71]
	2.55 Mb duplication at 1p31.1 (72.618-75.171 Mb) & 4.50 Mb deletion at 6q14.1-q15 (83.890-88.391 Mb)	intact <i>SIMI</i> gene in both cases	
<i>Chr.7</i>	<i>de novo</i> 7q36→qter deletion due to paternal unbalanced t(5;7)(q35.2;q36.1)	Microcephaly, small midface (choanal narrowing), agenesis/hypoplasia of corpus callosum/septum pellucidum, thalamic fusion/single maxillary central incisor, disproportionate growth retardation, truncal obesity, facial dysmorphism	[72]
	46,XX,der(9),t(7;9)(p15;p24)	high/large forehead, hypertelorism, broad nasal bridge, hypothyroidism, obesity, cerebral palsy	[73]
<i>Chr.8</i>	46,XX,der(13)t(8;13)(q24.3;q34)	mildly mental retardation, obesity, skin atrophy of the lower limbs and mild facial dysmorphism	[74]
<i>Chr.9</i>	46, Y,der(X)t(X;9)(p22.32;p23)	chondrodysplasia punctata (brachytelephalangic type), mental retardation and obesity	[75]
	11 Mb deletion at 9p23-ter (D9S144-D9S157) & 13p11-pter due to a <i>de novo</i> translocation (9p23;13p11)	mental retardation, obesity, minor anomalies (trigonocephaly, hypertelorism, short, broad neck)	[76]

(Table 2). Contd.....

Chromosome	Chromosome position	Clinical Features	Reference
	46,XY in both children 3 Mb de novo deletion of 9q34ter (D9S158+, D9S1838-, D9S2168-) in two unrelated patients	facial dysmorphism, developmental delay, short hands, syndactyly of toes 2–3, cryptorchidism, hypospadias, partial frontal cerebral atrophy, ADHD	[77]
		obesity, developmental delay, brachycephaly, macroglossia, coarse facies, prognathism, synophrys, short nose, thin upper lip, short neck, short extremities, cryptorchidism, micropenis, hypospadias, atrial septal defect, radiographic abnormalities (small epiphyses, one rostral vertebra, mild metaphyseal enlargement)	
	<i>de novo</i> 46,XY,ish del(9)(q34.3q34.3) (D9S325-,D9S2168-)	cleft soft palate, feeding problems, recurrent pneumonia, severe developmental delay, moderate-severe conductive hearing loss, hypotonia, facial dysmorphism including fissured tongue, hypoplastic toe nails, chordee, undescended right testis, laryngomalacia, bicuspid aortic valve, secundum atrial septal defect (ASD), patent ductus arteriosus	[78]
	<i>de novo</i> 45,XY,del(9)(q34.3), der(13;14)(q10;q10), D9S2168-	dysmorphic features, jaundice, persistent tachypnoea, tetralogy of Fallot, hypotonia, bilateral retinal colobomata, developmental delay, respiratory failure & death	
	46,XY,ish del(9)(q34.3q34.3)(D9S325-, D9S2168-)	Developmental delay, hypotonia, bilateral hearing loss, laryngomalacia, pulmonary hypertension, recurrent tachypnoea, small VSD, transient pulmonary hypertension, central & obstructive sleep apnoea	
	46,XX,dup(9)(q33.3q34.1)	dysmorphism, psychomotor delays, secondary amenorrhoea and obesity	[79]
<i>Chr.10</i>	7.8 Mb (81.281-89.091 Mb) duplication at 10q22.3q23.2	obesity, idiopathic urticaria, endometriosis, atrophy & scarring of Rt. kidney	Subject 1 (current report)
<i>Chr.11</i>	deletion (11)(p12p14)	WAGR syndrome with severe obesity	[80]
	46, XY, deletion of (11)(p13p14.2), and <i>SSADH</i> (succinic semialdehyde dehydrogenase) mutations	Obesity, psychomotor retardation, WAGR, distinctive cerebral anomalies such as increased signals of the globi pallidi, internal hydrocephalus and cerebellar vermian atrophy	[81]
	deletion of (11)(p11.2p14.1)	WAGR and Potocki-Shaffer syndromes: aniridia, cataract, nystagmus, corneal ulcers and bilateral congenital ptosis, a left nephroblastoma, moderate developmental delay, growth deficiency, facial dysmorphism, multiple exostoses and cranial lacunae	[82]
	7 Mb deletion of 11p13-p14 due to <i>de novo</i> unbalanced t(11;15)(p13;p11.2)	WAGR (aniridia, bilateral ptosis, bilateral posterior capsular cataracts, nystagmus, left-sided glaucoma, microcephaly, mild unilateral hydronephrosis, poor linear growth, gross motor delay) and obesity	[83]
<i>Chr.12</i>	partial trisomy 12p13.1→12q11 due to supernumerary chromosome (SMC)	developmental delay, cerebral visual impairment, obesity and mild dysmorphic features	[84]
	1.6 Mb deletion of del(12qter)	mild mental retardation, food-seeking behavior, obesity, no significant dysmorphic facial features, abnormal hair whorl pattern, brachydactyly and mild clinodactyly	[85]
	4.5 Mb deletion of 12qter	mild mental retardation, food-seeking behavior, obesity, short stature, mild dysmorphic facial features, multicystic kidney and unilateral cryptorchidism	
<i>Chr.14</i>	47,XY +der(14)t(9;14)(p24;q13)mat	minor facial anomalies, feeding difficulties, childhood failure to thrive, severe constipation, recurrent respiratory infections, mild hypotonia, delayed psychomotor development, short stature, widely spaced teeth, multiple dental caries, normal echocardiography, hyperphagia, obesity	[86]
	Normal karyotype, gross hypomethylation of the differentially methylated regions (intergenic DMR and MEG3-DMR) at 14q32.2	UPD(14)mat-like phenotype [low birth weight, neonatal feeding problems, muscular hypotonia, motor and developmental delay, small hands and feet, and truncal obesity]	[87]

(Table 2). Contd.....

Chromosome	Chromosome position	Clinical Features	Reference
<i>Chr.15</i>	Balanced t(4;15)(q22.3;q21.3) disrupts <i>RORa1</i>	profound obesity (BMI 41-49 in a mother & her two children)	[88]
	Copy Number Variants (CNVs) at 15q11.2q13/PWSCR (<i>NDN, C15orf2, PWRNJ</i>)	3 CNVs were significantly associated with body fat mass in White individuals (a higher copy number associated with increase of 5.08-9.77 kg in body fat mass)	[89]
<i>Chr.16</i>	duplication of 16q13 [D16S419-D16S503]	severe anisomastia, mental retardation, obesity, dysmorphic facies, and digital anomalies	[90]
	deletion of 16p11.2 (including <i>SH2B1</i>)	severe early-onset obesity, developmental delay	[16-18]
	11.45 Mb duplication of 16q11.2q13 (45.026-56.507 Mb) [including <i>FTO</i>]	obesity, severe anisomastia, moderate-severe MR, ADHD, dysmorphic facies, and contractions of the small joints	[91]
	0.28 Mb (28.73-29 Mb) maternally inherited deletion of 16p11.2	obesity, developmental delay. Mother is healthy.	Subjects 2 & 3 (current report)
<i>Chr.17</i>	46,XX/47,XX,+mar,ish.p17H8+	mental retardation, obesity, short stature and minor anomalies	[92]
<i>Chr.18</i>	deletion (18)(q12.2q21.1)	Obesity and abnormal behavior	[93]
	10 patients with deletion of 18q (MC4R-ter)	18q deletion syndrome. no difference in obesity among those deleted and not deleted for the MC4R gene. involvement of MC4R in obesity may reflect a dominant negative effect.	[94]
	47, XY, i(18)(p10)	dysmorphic features, marked obesity, profound mental retardation, aggressive behavior	[95]
<i>Chr.19</i>	supernumerary marker (47,XY,+mar) derived from 19q12q13.2	morbid obesity and mental retardation	[96]
	<i>de novo</i> 1.2 Mb del on chr. 19p13.2 (14.2-15.4 Mb)	moderate MR, obesity, short stature, hypertrichosis and facial dysmorphism	[97]
	<i>de novo</i> 13.56 Mb (34.56–48.12 Mb) duplication of chr. (19) (pter) & 2.71-Mb (94.91–97.62 Mb) duplication at 2pter. 48,XX,+der(2)del(2)(p11)del(2)(q11.2), +der(14)t(14;19)(q11;q12)del(19)(q13.31) OR 48,XX,+der(2)del(2)(p11)del(2)(q11.2), +der(22)t(22;19)(q11;q12)del(19)(q13.31)	ventricular septal defect, bilateral vesico-ureteral reflux, corpus callosum agenesis, microphthalmia, and obesity	[98]
<i>Chr.20</i>	<i>de novo</i> 20q deletion: 46,XY,del(20)(q13.13q13.32),ish D20S171-	features of Albright hereditary osteodystrophy (AHO) including obesity, obesity, developmental delay, and dysmorphism, fetal growth retardation, placental insufficiency, oligohydramnios, marked hypotonia, arthrogyrosis, bilateral inguinal hernia repair, cryptorchidism,	[99]
	<i>de novo</i> 46,XX,del(20)(q13.31-q13.33),ish D20S171	marked short stature, learning difficulties, acrorhizomelic limb shortening, sister with schizencephaly, right hemiplegia & normal karyotype	
<i>Chr.21</i>	47,XY,+der(21)t(5;21)(p15.1;q22.1)	short stature, developmental delay, atypical for Down syndrome, pervasive behavioral problems and obesity	[100]
<i>Chr.22</i>	1 Mb deletion at 22q11.2	DiGeorge syndrome, obesity, aggressive behavior	[101]
	deletion of 22q11.2	DiGeorge syndrome, obesity in adolescents	[102]
<i>Chr.X</i>	mosaic deletion of 1 Mb (146.047-147.061) including <i>FMRI</i> , & comprehensive review of Xq/Xp deletions	obesity, mental retardation, hypotonia and Hunter syndrome	[20]
	two deletions (mosaic 600 bp & ~ 25 kb) in two unrelated males	seizures, obesity, large ears, mental retardation, macrocephaly	[21]

(Table 2). Contd.....

Chromosome	Chromosome position	Clinical Features	Reference
	9 Mb deletion of Xq26.3-q27.3) extending from DXS1232-DXS105 to STS-141R-DXS533 (maternally transmitted)	6-year-old mentally retarded male, obesity, anal atresia	[22,23]
	<i>de novo</i> 2.7 Mb deletion of Xq27.3-q28 including <i>FMR1</i> , <i>FMR2</i> , and <i>IDS</i> (BAC clones: RP11-37P24, RP11-949I9, RP11-489K19, RP11-164A8;)	6-year-old girl, mildly dysmorphic facies, obesity, marked developmental delay	[24]
	13 Mb deletion at Xq26.3-q27.3 (DXS1232- DXS1193) (maternally inherited)	19-year-old male, facial features c/w fragile X syndrome, profound mental and growth retardation, small testes, lower limb skeletal defects, contractures	[25]
	<i>de novo</i> 10-12 Mb deletion at Xq26.3-27.3 including <i>FMR1</i> (DXS984-DXS465/DXS1193) (no parental studies)	female with moderate-severe mental retardation, seizures, hypothyroidism	
	8.5 Mb del Xq27.1 (CDR1/sWXD2905-DXS8318/DXS7847)(maternal)	4 yr old boy, severe mental retardation, fragile X syndrome facies, hypotonia, overgrowth	[26]
	1.6 kb proximal to CGG repeat of <i>FMR1</i> gene (maternal)	11 individual family, 4 affected males and 2 expressing carrier females of the fragile X phenotype	[27]
	<i>de novo</i> 6.6 Mb deletion of <i>FMR1</i> & <i>FMR2</i> genes (DXS7536- DXS1193)	13 year old boy, severe developmental delay, epilepsy, behavioral problems, autism, marked joint hypermobility	[28]
	<i>FMR1</i> full mutation, normal 15q11-13 region	five fragile X patients with the PWS-like phenotype	[29]
	46,XX/47,XX,+mar (Xp11.2q13.1) (DXS423E/UBE1- DXS1/AR & CJB1/CCG1)	2 unrelated females with: failure to thrive in infancy, seizures, mental retardation, flat face, telecanthus, hypertelorism, low-bridged nose, small mouth, myopia, small hands & feet, tapering fingers, hypoplastic nails, clinodactyly & obesity	[30]
	46,XX/47,XX,+mar (Xp11.2q13.1) (DXS423E/UBE1- DXZ1 & DXS1/AR)		
	<i>de novo</i> 46,X,dup(X)(q23q25)	24-year old woman, Prader-Willi like syndrome (PWS)	[31]
	9.3 Mb (35.6-44.9 Mb) duplication in 46,X,Y,dup(X)(p11.3p21.1) (maternal)	Male with severe mental retardation, obesity, macrocephaly & healthy mother	[32]
	8.5 Mb (15.0-23.5 Mb) Xp22 dup in 3 males [46,X,Y,dup(X)(p22.11p22.2) (mat)	3 male (2 brothers & maternal uncle) with mental retardation. 2 healthy females (sister & mother) also carried the same duplication	
	11.1-14.4 Mb (chr.X:76.7/87.7-75.9/90.3) duplication [arr cgh Xq13.3q21.31(RP5-875J14. RP4-542O23)x2]	4-year-old male, MR & PWS like features	[33]
	<i>de novo</i> 46,X,inv(X)(q26q28),ish(wcpXp, EST Cdy 16c07+)	11-year-old girl, PWS like features	[34]
	maternally inherited pericentric inversion (X)(p11.4q11.2)	two brothers with hypogonadotropic hypogonadism (HH), obesity and short stature	[35]
	46,X,Y,der(19)t(X;19)(q11.1-11.2;p13.3) (balanced maternal translocation). BACs 372C14 & 183A17 (flank <i>XIST</i>) were mapped to der(19), while subtelomeric 19p probe mapped to der(X)	26-year-old male with epilepsy, severe learning disability, obesity, hypogonadism, periventricular nodular heterotopias	[36]
	<i>de novo</i> 10.7 Mb (139.354-150.046 Mb) deletion of Xq27.1q28	truncal obesity, hypotonia, microcephaly, global developmental delays, right eye esotropia	Subject 4, current report

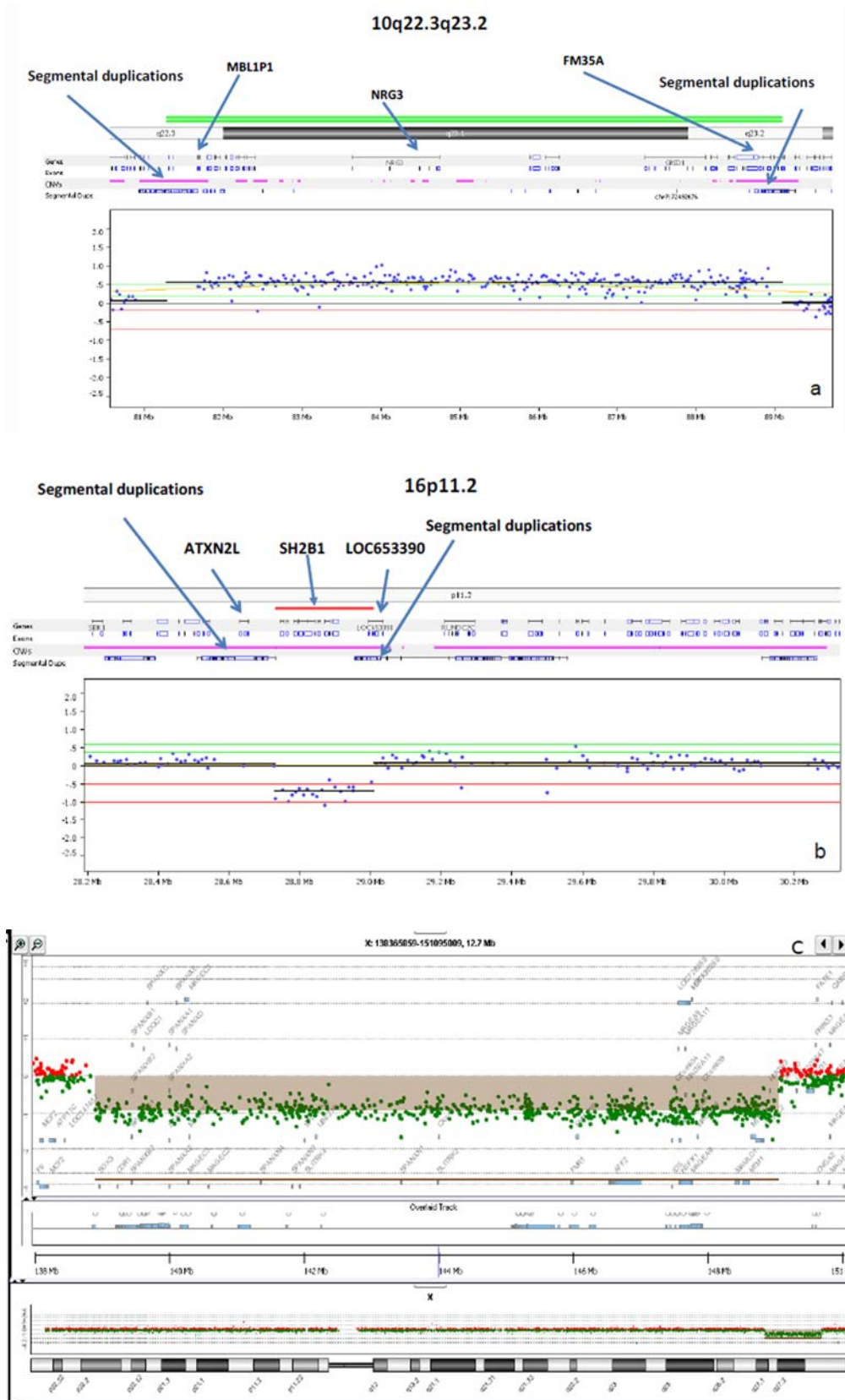


Fig. (2). Array CGH ($\log_2 R$) profiles for Subjects 1-4. Subject 1(a) has a large 7.8 Mb duplication found at 10q22.3-q23.2 between the segmental LCR3 and LCR4 regions (arrows). Subjects 2 and 3 (b) have a small maternally inherited 16p11.2 deletion found which lies within a region of segmental duplications with location of representative genes (*ATXN2L*, *SH2B1* and *LAT*) noted. Subject 4 (c) has a large 10.69 Mb deletion at Xq27.1-q28. The deleted X chromosome region detected by the array is shown above the X chromosome ideogram.

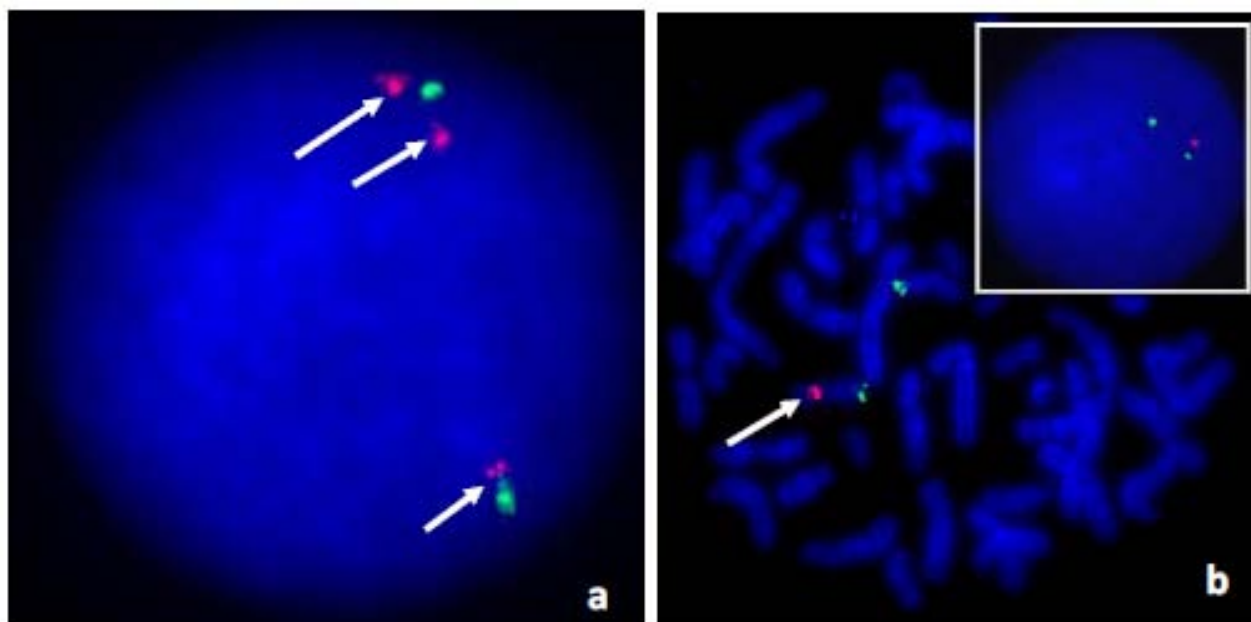


Fig. (3). Confirmatory fluorescent in situ hybridization (FISH) studies in Subjects 1, 2, and 3. In Subject 1 (**panel a**), the 10q23.2 (RP11-830J13) Rhodamine labeled BAC clone showed 3 copies (arrows) while the “control” chr. 10p11.21 FITC labeled BAC clone (RP11-876K20) showed normal hybridization pattern in interphase nuclei. Subjects 2, 3 and their mother shared the same 16p11.2 deletion (**panel b**) detected by the RP11-1136I3 (Rhodamine) BAC clone (arrow). The RP11-133L7 (FITC) BAC clone was the control probe.

striking observations were seen in Subject 4. Developmental and speech delays were present in Subjects 2, 3 and 4.

Human DNA fragments >1 kb in size and of >90% DNA sequence identity have been termed low copy repeats (LCRs) or segmental duplications which can stimulate or mediate constitutional (i.e., inherited; both recurrent and non-recurrent) and somatic genomic rearrangements [5]. The advent and application of aCGH resulted in the identification of an increasing number of genomic disorders (microdeletion/microduplication syndromes) with nonallelic homologous recombination (NAHR) as the predominant underlying molecular mechanism using the flanking LCRs as recombination substrates [5]. Examples of common copy repeat loci involved in genomic disorders due to copy number abnormalities include 7q11.2, 15q11.2, 22q11.2 and others. The phenotypic consequences observed in these disorders may result from mechanisms such as deletions or duplications of dosage sensitive genes, position effect, unmasking of recessive mutations or functional polymorphisms of the remaining allele when a deletion occurs, or through effects of transvection (interaction between alleles on homologous chromosomes) [6,7].

The 10q22.3-q23.2 region is characterized by a complex set of low-copy repeats (LCRs 3, 4), which can give rise to various genomic changes mediated by nonallelic homologous recombination. Large duplications involving the 10q22-q23 region are very rare with only four cases reported overlapping this region [8-12]. However, six microduplications within the 10q22.3-q23.3 region have been reported recently by van Bon *et al.* [13]. Subject 1 in this report has a large 7.8 Mb duplication at

10q22.3-q23.2 which is between LCR 3 and 4. It is interesting to note that the *hsa-miRNA346* gene (human microRNA) lies within this duplicated region (base position: 88,022,451-88,026,545). Microdeletion/duplications involving mirRNA genes may add another level of complexity because of their multiple target genes. For example, miRNA346 has 72 predicted targets [miRBase, 2011]. Unlike the six individuals reported by van Bon *et al.* [13], Subject 1 has severe obesity and recurrent large lipomas requiring surgical resection. She is not known to have intestinal polyposis. The 10q22.3-q23.2 duplication region seen in this subject does not include the *PTEN* and *BMPRI* genes which cause Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Juvenile Polyposis Syndrome (JPS), respectively. Lipomatosis is a known feature of BRRS. In addition, positive linkage with D10S535 (10q22.3; base position:76,240,707-76,440,904, hg19), and D10S1267 (10q24.32; chr10:104,278,612-104,478,824bp) and obesity phenotypes have been reported separately in both White and African-American individuals [14,15]. We speculate that our subject’s 10q duplication may have disrupted the expression of a dosage sensitive gene such as *PTEN* or another gene or non-coding signal in this region contributing to her recurrent lipomatosis and obesity.

The clinical and molecular findings in Subjects 2 and 3 are consistent with the recently described 16p11.2 obesity-related microdeletion syndrome (position 28.7-28.9 Mb) [16-18]. We mapped this deletion to a region of segmental duplications at 16p11.2 and found it to be maternally inherited and confirmed by FISH analysis. This deletion encompasses the *SH2B1* gene which is implicated in murine obesity [19]. The mother of these two affected children appeared to be non-penetrant for this pathogenic copy number variant, a phenomenon known to occur. This locus appears to be distinct from the more proximal 16p11.2 (29.5-30.1 Mb) autism associated locus.

Several subjects with contiguous gene deletions involving the *FMRI* gene locus have been reported and were comprehensively reviewed recently by Coffee *et al.* [20]. They cited a total of 71 deletions that were classified as small or large deletions. Subject 4 who has severe developmental delays, facial dysmorphism and truncal obesity was found to carry a *de novo* 10.69 Mb deletion at Xq27.1-q28 (Fig. 2e). Major genes within the deleted region include *FMRI*, *FMR2*, *IDS*, *MTM1* and *MTMR1*. In addition to Hunter syndrome and myotubular myopathy, other phenotypic abnormalities noted in other individuals with contiguous gene deletions including the *FMRI* are obesity [21,22,24], cherubism [23], overgrowth [25,26], and macrocephaly [27,28]. A Prader-Willi syndrome-like phenotype with obesity has been described in fragile X syndrome individuals with the CGG expansion mutation [29], indicating that the obesity is probably due to loss of *FMRI* function and interaction with other genes. In addition to these deletions, 4 duplications [30-33], 2 inversions [34,35] and 1 translocation [36] involving the X chromosome have been reported to be associated with obesity.

In Table 2, we summarized reports from the literature in which structural chromosome abnormalities were reported with syndromic obesity [20-102]. Those involving chromosome 15q11.2 and Prader-Willi syndrome were excluded as this genetic obesity syndrome will be described separately in this journal issue. The most frequently reported chromosome regions were 15q (not shown), 6q [58-71] and Xq [20-36]. Single-minded 1 (*SIM1*) gene (chr.6q16.3, position:100,836,750-100,911,551; hg19) mutations are one of the few known causes of nonsyndromic and PWS-like monogenic obesity in both humans and mice.

The mouse *Sim1* gene is expressed in the developing kidney and central nervous system and essential for formation of the supraoptic and paraventricular (PVN) nuclei of the hypothalamus implicated in the regulation of body weight. The melanocortin-4 receptor (*MC4R*) gene is expressed in these brain regions and are physiologic targets of alpha-melanocyte-stimulating hormone which inhibits food intake [103]. Michaud *et al.* [104] also demonstrated that the lethal homozygous *Sim1* (*Sim1* *-/-*) null mutation in mice causes lack of the paraventricular nucleus. However, *Sim1* heterozygotes were viable but developed early-onset hyperphagic obesity with clinical features of metabolic syndrome. A remarkable decrease in hypothalamic oxytocin (Oxt) and PVN melanocortin 4 receptor (*Mc4r*) mRNA was also demonstrated in conditional *Sim1* homozygous and germ line *Sim1* heterozygous mutant mice suggesting that hyperphagic obesity may be attributable to changes in the leptin-melanocortin-oxytocin pathway [105].

Other genes such as *MC4R*, leptin and leptin receptor, Ghrelin (*GHRL*), peroxisome proliferator-activated receptor gamma (*PPARG*), oxytocin receptor (*OXTR*), prohormone convertase-1 and proopiomelanocortin have been implicated in human obesity and will be discussed elsewhere in this journal issue. Heterozygous or bi-allelic disruptions of these genes by structural chromosome

abnormalities may potentially lead to obesity. For example, Bittel *et al.* [50] reported a boy with marked obesity and a duplication of chromosome 3p25.3-p26.2 region which contains *GHRL* and *PPARG*. They reported increased expression of these genes which appears to contribute to the obesity seen in this individual. In most of the remaining chromosomal abnormalities in individuals with obesity identified in our literature search listed in Table 2, no specific obesity-related gene was identified.

In conclusion, obesity is a highly complex multifactorial clinical phenotype with significant genetic predisposition. So far, several single genes and genomic loci scattered on most of the chromosomes except the Y chromosome have been reported and are involved in the pathogenesis of human obesity. The genetic basis of syndromic obesity in our four selected individuals was identified or confirmed using aCGH microarray analysis. Improved understanding of the specific mechanisms of these genetic predispositions will be crucial for the personalized management of individuals with various forms of obesity, particularly in early childhood.

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WEB RESOURCES

The Center for Applied Genomics (TCAG): <http://www.cag.icph.org/>

Database of Chromosome Genomic Variants (<http://projects.tcag.ca/variation>)

miRBase: the microRNA database: <http://www.mirbase.org/>

CONFLICT OF INTEREST DISCLOSURE

Karine Hovanes, Ph.D. is a Director at CombiMatrix Diagnostics: E.L.Y. and M.J.D. have no conflict of interests to disclose.

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