Two New Cases of 1p21.3 Deletions and an Unbalanced Translocation t(8;12) among Individuals with Syndromic Obesity

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Key Words

Deletion of 1p21.3 · *GNB3* · Intellectual disability · *MIR137* · Obesity · t(8;12)

Abstract

Obesity is a highly heritable but genetically heterogeneous disorder. Various well-known microdeletion syndromes (e.g. 1p36, 2q37, 6q16, 9q34, 17p11.2) can cause this phenotype along with intellectual disability (ID) and other findings. Chromosomal microarrays have identified 'new' microdeletion/duplication syndromes often associated with obesity. We report on 2 unrelated patients with an overlapping region of deletion at 1p21.3p21.2, and a third patient with a de novo recurrent unbalanced translocation der(8)t(8;12)(p23.1;p13.31), detected by 180K array CGH in a prospective cohort of syndromic obesity patients. Deletion of 1p21.3 is a rare condition, and there have been only 11 cases of the same recurrent translocation between chromosomes 8 and 12 [t(8;12)] reported to date. The former has been associated with ID, autistic spectrum disorder (ASD) and mild dysmorphic features, and in 4 patients who were obese or had a tendency to obesity, a minimal overlapping region of 2 genes, *DPYD* and *MIR137*, was detected; t(8;12) has recently been recognized to cause a childhood obesity syndrome

due to duplication of the *GNB3* gene. Thus, our findings add to the existing literature on the clinical description of these new syndromes, providing additional support that these loci are associated with syndromic obesity. We suggest that heterozygous loss of *MIR137* may contribute to obesity as well as ID and ASD.

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Several syndromes arising from copy number variants (CNVs) have obesity as a common component of their clinical phenotype, often including developmental delay (DD)/intellectual disability (ID), dysmorphic features or congenital anomalies. Prader-Willi syndrome (PWS; MIM 176270) is the most common; deletions of 1p36 (MIM 607872), 2q37 (MIM 600430), 6q16 (MIM 603128), 9q34 (MIM 610253), and 17p11.2 (MIM 182290) are included in the same category. Genotype-phenotype correlations in these syndromes have resulted in the identification of genes within these chromosomal regions involved in the pathogenesis of obesity (e.g. *SIM1*). Since the implementation of chromosomal microarray analysis, the number of new candidate loci and microdeletion/duplication syndromes associated with obesity has grown [Bochukova et al., 2010; Davidsson et al., 2010; Walters et

Fig. 1. Pictures of patients 1 (**A, B**) and 2 (**C, D**) with deletions involving the 1p21.3 band and patient 3 (**E–G**) with t(8;12), showing facial features and obesity. Patients 1 and 2 have a high forehead,

deeply set eyes and full cheeks. Patient 3 at the age of 6 years (**E**) has a round face, thin upper lip, short nose, and long philtrum. Note the periorbital fullness in patient 3 at the age of 12 years (**F**).

al., 2010; Wentzel et al., 2010; Dasouki et al., 2011; Shinawi et al., 2011; Vergult et al., 2012; D'Angelo et al., 2013; Doco-Fenzy et al., 2014; Vuillaume et al., 2014].

Deletions in chromosome 1p21.3 are rare but have been associated with ID, autism spectrum disorder (ASD) and often obesity [Carter et al., 2011; Willemsen et al., 2011; Pinto et al., 2014]. A critical region of 1.22 Mb, linked to ID and/or ASD, has been delimited within which *DPYD* and *MIR137* (the gene encoding the microRNA miR-137) are mapped. The recurrent unbalanced translocation der(8)t(8;12)(p23.1;p13.31) [t(8;12)] has recently emerged as a new syndromal entity with ID, seizures and obesity, but there have been only 11 cases reported so far [Segel et al., 2006; Ou et al., 2011; Margari et al., 2012; Goldlust et al., 2013]; the 12p duplicated region harbors the *GNB3* gene, coding for a G-protein highly expressed in the brain, which was found to be responsible for the obesity phenotype.

In an ongoing study of undiagnosed patients with syndromic obesity (i.e. obesity with at least one other feature such as DD/ID, congenital anomalies or dysmorphic fea-

tures), we identified 2 unrelated individuals by chromosomal microarray analysis with an overlapping region of deletion at 1p21.3p21.2, including *DPYD* and *MIR137*, and a third patient with t(8;12). Our findings add to the existing literature on the clinical description of these new syndromes and provide additional evidence that gene(s) in the chromosomal regions involved may play a role in the development of obesity.

Patients and Methods

Case Reports

All 3 patients were referred to analysis for obesity and ID. The study protocol was reviewed and approved by our local institutional human research committee (CEP/IB/021/2004). Parents or guardians also provided written informed consent.

Patient 1, a 15-year-old girl (fig. 1A, B), is the second child born to unrelated healthy parents at 40 weeks of gestation by cesarean section. Her birth weight was 3,650 g (50–75th percentile). She had neonatal hypotonia, psychomotor and speech delay (walked and spoke at the age of 2 years). She presented with brachycephaly, high forehead, myopia, and clinodactyly (5th fingers). She had no

distinct facial features. Physical examination showed a height of 162 cm (50–75th percentile), a weight of 97 kg (>97th percentile), an occipital frontal circumference (OFC) of 59 cm (>98th percentile), and a body mass index (BMI) of 37.0 (>95th percentile). Menarche occurred at the age of 10 years. She had hyperphagia with food-seeking behavior. She has had special education since the age of 5 years, yet she was unable to read and write.

Patient 2 was an 8-year- and 8-month-old female (fig. 1C, D) born at 39 weeks of gestation to unrelated healthy parents after an uneventful pregnancy. At birth, her weight was 4,500 g (97th percentile) and her length 52 cm (75th percentile). There was rapid weight gain during the first weeks of life, and she was put on a calorie-restricted diet at 3 months of age. She had psychomotor delay (walked at 20 months) and spoke her first words at the age of 2 years. She presented with ID, severe language delay, pervasive developmental disorder, and marked hyperphagia with excessive weight gain. At the age of 6 years, her weight was 46 kg (>97th percentile), her height 123 cm (90–95th percentile), OFC 54.5 cm (>98th percentile), and BMI 30.4 (>95th percentile). At the age of 8 years and 8 months, she manifested signs of precocious puberty and advanced bone age (consistent with 11 years). Her weight was 65 kg (>97th percentile), height 140 cm (90–95th percentile) and BMI 33.2 (>95th percentile). She had large hands (>97th percentile). No dysmorphic features were noted. Her plasmatic iron level was low (40 µg/dl; normal range 50–150 µg/dl).

Patient 3 was a 6-year-old male (fig. 1E, G), and the first child born to unrelated healthy parents with a history of repetitive spontaneous abortions. He was born at 36 weeks of gestation by normal delivery. At birth, his weight was 4,030 g (>97th percentile), length 48 cm (50th percentile) and his OFC was 36 cm (97th percentile). The infant had feeding difficulties and hypotonia. He also had psychomotor delay (sat at 30 months and walked >4 years) and had delayed language skills with short sentences at 5 years of age. At the same age, he could not read or write and needed special education. His weight was 57.4 kg (>97th percentile), height 131 cm (>97th percentile), OFC 55 cm (>98th percentile), and BMI 33.4 (>95th percentile). He presented with seizures, brachycephaly, large ears, rounded facies, short and beaked nose, thin upper lip, high-arched palate, short neck, clinodactyly (5th fingers), micropenis and cryptorchidism. Additionally he has flat feet and hypopigmented patches of skin. He also manifested sleep disturbance and hyperphagia.

Methods

Chromosomal microarray analysis was performed using an 180,000 60-mer-oligonucleotide array (CytoSure ISCA 4×180K microarrays, Oxford Gene Technology, Oxford, UK) according to the manufacturer's instructions. A dye-reversal experiment of the dye labels for the control and test DNA was performed for each patient sample. Scanned images of the arrays were processed using Agilent Feature Extraction software and analyzed with Genomic Workbench software (both from Agilent Technologies), with the statistical algorithm ADM-2, and sensitivity threshold 6.7. At least 3 consecutive oligonucleotides had to exhibit aberrant log₂ ratios of the same sign to be recognized by the software. All genomic breakpoints were based on the human genome build GRCh37 (hg19). FISH analysis was performed on metaphase chromosomes of patients 1 and 3 (and on both of their parents), using RP11-146P11 (1p21.3), RP11-45M12 (8p23.2), RP11-433L7 (8p22), RP11-320N7 (12p13.32), and RP11-434C1 (12p13.2).

Results

As part of an ongoing study using chromosomal microarrays in patients with syndromic obesity of unknown etiology, we detected a female proband (patient 1) with a 5.9-Mb (chr1:93,919,217–99,846,176) deletion at 1p22.1p21.2. The deletion was further confirmed by FISH using the BAC clone RP11-146P11 which localizes within the deleted region. FISH analysis using the same probe on the parental samples showed that the deletion was de novo. In a second unrelated female (patient 2), a 12-Mb (chr1:95,696,444–107,755,879) deletion of the 1p21.3p13.3 region was detected. No parental samples were available. The smallest region of overlap between these 2 individuals is estimated to be 4.1 Mb located at 1p21.3p21.2 and encompasses 17 RefSeq genes, including *DPYD* and *MIR137* (fig. 2). In a third case (patient 3), a 7.7-Mb deletion of 8p23.3p23.1 (chr8:0,176,464–7,881,234) was detected in addition to an 8.2-Mb duplication of 12p13.33p13.31 (chr12:0,148,375–8,309,473). The deletion and concurrent duplication were confirmed by FISH using BAC clones specific for the 8p deletion (RP11-45M12) and 12p duplication (RP11-320N7). We confirmed the unbalanced translocation by dual-color FISH using differentially labeled BAC clones from 8p22 (RP11-433L7, present) and 12p13.32 (RP11-320N7, duplicated). We analyzed the inheritance of t(8;12) by FISH and found that the translocation was de novo.

Discussion

Deletions of chromosome band 1p21.3 are rare. Including our own cases, about 12 patients with overlapping deleted regions in chromosome 1p21.3 identified by genome-wide array analysis have been reported in the literature (fig. 2; table 1). Carter et al. [2011] reported 4 patients from 3 families presenting with ASD and severe speech delay. Among these patients, 3 had de novo 1p21.3 deletions ranging from ~1.1 to 1.5 Mb that included the *DPYD* gene, and one patient presented with an intragenic *DPYD* deletion which was inherited from a healthy mother. All 4 patients had normal motor development, absence of major medical problems or a recognizable pattern of dysmorphic features. Furthermore, the identical deletion in 2 siblings cosegregated with obesity for one and with ID for the other. Five other cases have been reported in 3 adult siblings and 2 unrelated patients with ID sharing a 1p21.3 deletion with a smallest region of overlap estimated at 1.22 Mb involving *DPYD* and *MIR137* genes.

Fig. 2. Screenshot of UCSC hg19 build 37 showing the smallest region of deletion overlap at 1p21.3p21.2 detected in our patients and the overlapping deleted segments of patients from DECIPHER, Carter et al. [2011], Willemsen et al. [2011] and Pinto et al. [2014]. Obese/overweight patients with ID and/or ASD

(dark gray bars), and patients with no reported obesity (middle gray bars) are represented. Patients from DECIPHER excluded from further analysis are shown in light gray bars. The relative position of the candidate gene *MIR137* is indicated by a vertical blue line.

The patients in this report had similarities in facial appearance, including long ears (4/4), thick lower lip (4/4), broad nasal tip (3/4), obesity/overweight (4/4), ocular problems (3/4), and similar behavior characteristics such as shy and friendly behavior (4/4), tendency to overeating (3/4) and features of autism (3/4). Recently, Pinto et al. [2014] reported a de novo 2.7-Mb deletion of the 1p21.3p21.2 region involving *MIR137* in an autistic individual with overweight and ID.

The present study involves 2 unrelated patients who have a common region of deletion of 4.15 Mb within 1p21.3p21.2 overlapping with those in the patients described above. The patients share phenotypic characteristics, such as ID, delayed speech, macrocephaly, obesity, and hyperphagia, while features of autism were only seen in patient 2. We found 12 additional patients in the DECIPHER database (<http://decipher.sanger.ac.uk/>) with available clinical features and deletions partially overlapping with the smallest region of overlap observed in this

report (fig. 2). However, the deletions in 4 cases (258241, 270230, 270491, and 282720) lack neither *DPYD* nor *MIR137* and were inherited in 2 other cases with ataxia (261617) and impulsivity (287915) as the only reported clinical features. In addition, patient 279246 was described with a much larger deletion in 1p21.3p13.2, while patient 288739 showed a 4.51-Mb deletion at 1p22.1p21.3 and 2 additional CNVs of unknown inheritance. Among the remaining patients, 2 were reported with ID and obesity (256941 and 282571) and 2 others with autistic behavior co-occurring with ID (254871) or delayed speech (274360). They showed a de novo 4.58-Mb deletion at 1p22.1p21.3 and an inherited variant from a normal parent (case 256941), a de novo pure 1p21.3p13.3 deletion of 11.19 Mb (case 282571), a de novo pure 1p21.3p21.1 deletion of 5.43 Mb (case 254871), and a pure 9.98-Mb deletion at 1p21.3p13.3 of unknown inheritance (case 274360).

Carter et al. [2011] and Willemsen et al. [2011] suggested a possible causative role of *DPYD* and *MIR137*

Table 1. Main clinical and molecular features in our patients 1 and 2 and previously reported patients with overlapping 1p21.3 micro-deletions

Features	Our patients	Patients 1–4 Carter et al. [2011]	Patients 1–5 Willemsen et al. [2011]	Patient 8658_201 Pinto et al. [2014]
Gender	2 F	3 M/1 F	3 M/2 F	–
Size of deletions	5.9–12 Mb	10 kb–1.5 Mb	1.75–2.45 Mb	2.75 Mb
Cytoband range	1p22.1p13.3	1p21.3	1p21.3	1p21.3p21.2
Overlapping region	95.69–99.84 Mb	98.16–98.17 Mb	97.72–98.94 Mb	–
Candidate genes in the critical regions	<i>DPYD</i> , <i>MIR137</i>	<i>DPYD</i>	<i>DPYD</i> , <i>MIR137</i>	<i>MIR137</i>
Age at clinical presentation	8 ys 8 mo–15 ys	5 ys–13 ys 9 mo	18 ys–42 ys ^a	–
High birth weight	1/2	0/4	–	–
Postnatal macrocephaly	2/2	3/– ^b	–	no
Postnatal obesity	2/2	1/3 ^c	4/4 ^d	overweight
ID	2/2	2/4	5/5	yes
Features of ASD	1/2	4/4	3/4	yes
Aggressive behavior	1/2	1/–	3/4	–
Shy and friendly	–	–	4/4	–
Speech deficits	2/2	4/4	2/2	no
Tendency to overeating	2/2 (hyperphagia)	–	3/4	–
Dysmorphic features	1/2	2/3	4/4	–
Ocular problems	1/2	–	3/4	–

Patients 2 and 3 from Carter et al. [2011] and patients 1–3 from Willemsen et al. [2011] are siblings. mo = Months; ys = years.

^a Age at clinical presentation was not informed for patient 3.

^b OFC of patients 2 and 3 was at the 95 and 98th percentiles, respectively, and above 1 SD for patient 4. The deletions of patients 2 and 3 were de novo and both parents had OFC >95th percentile.

The deletion of patient 4 was inherited from a healthy mother with OFC + 1 SD.

^c Patient 3 weighted above 4 SD. His younger sister's weight was at the 75th percentile.

^d Patients 1 and 2, 4 and 5 were obese or overweight (≥90th percentile); weight data was not available for patient 3.

genes in autism and ID. These candidate genes are deleted in our patients and DECIPHER cases showing these phenotypes, further reinforcing their causative role in ASD and/or ID. However, a likely role for *MIR137* haploinsufficiency in both conditions, as pointed out by Willemsen et al. [2011], is further reinforced by the patient's distal deletion breakpoint reported in the paper by Pinto et al. [2014], which was located proximally from and did not include *DPYD*. Regarding the obesity phenotype, miR-137 was shown to be downregulated in 4 obese/overweight patients with ID reported by Willemsen et al. [2011], while 3 downstream targets of miR-137 were upregulated. The miR-137 has also been shown to regulate a large number of autism candidate genes [Devanna and Vernes, 2014] and genes implicated in schizophrenia [Collins et al., 2014]. Various studies have found a shared molecular basis for the coexistence of obesity in individuals with developmental disabilities, including ID and ASD. For example, a recurrent microdeletion of 16p11.2 frequently cosegregates with obesity, ID and ASD (MIM 611913). Therefore, it can be hypothesized that dysregu-

lation of miR-137 in particular is involved in the etiology of obesity, autism and ID in patients with 1p21.3 deletions. Another gene that may play a role in the obesity associated with 1p21.3 deletions is *PTBP2*, as polymorphisms in this gene have been recognized as a risk factor for obesity [Speliotes et al., 2010].

Additionally, we report on a patient with monosomy 8p23.1pter and trisomy 12p13.31pter resulting from a de novo unbalanced translocation. It was previously shown that this translocation arises by nonallelic homologous recombination mediated by interchromosomal paralogous low-copy repeats shared between chromosome bands 8p23.1 and 12p13.31 [Ou et al., 2011]. Recurrent unbalanced t(8;12) is, however, rare. Nine cases with clinical data, including our own, have been published so far (table 2). For the other 3 cases with t(8;12) reported in the literature, clinical information was unavailable [Segel et al., 2006; Ou et al., 2011].

A single case of t(8;12) was described by Margari et al. [2012] in an 11-year-old patient with high birth weight, hypotonia, mild ID, significant language impairment,

Table 2. Phenotypic features of the present case 3 compared to those found in the published 8 cases of der(8)t(8;12)(p23.1;p13.31) with clinical data

Features	Present case 3	Patient 1 Margari et al. [2012]	Patients 1–7 Goldlust et al. [2013]
Gender	M	F	4 M/3 F
Age at clinical presentation	6 ys	11 ys	4 ys 8 mo–29 ys
High birth weight	+	+	
ID/DD	+	+	+ (7/7)
Hypotonia	+	+	+ (5/7)
Seizures	+	+	+ (5/7)
Height ≥90th percentile	+	–	+ (3/6)
Weight ≥90th percentile	+	–	+ (5/6)
OFC ≥90th percentile	+	+	+ (6/6)
BMI >95th percentile	+		+ (5/6)
Dysmorphic features	+	+	+ (7/7)
Brachycephaly	+		
Large forehead	–		+ (1/*)
Round facies/facial fullness/broad or prominent cheeks	+	+	+ (3/*)
Coarse facies	–		+ (1/*)
Prominent eyebrows	–		+ (1/*)
Hypertelorism	–		+ (1/*)
Ptosis	–		+ (2/*)
Epicanthal folds	+		+ (1/*)
Down-slanting eyes	–		+ (1/*)
Periorbital fullness	+		+ (1/*)
Telecanthus	–		+ (1/*)
Prominent nasal bridge	+		+ (1/*)
Flat broad nasal bridge	–	+	+ (1/*)
Beaked nose	+		+ (1/*)
Short nose	+		+ (1/*)
Small mouth	–		+ (1/*)
Thin upper lip	+		
Prominent lower lip	–		+ (1/*)
Micrognathia	–		+ (1/*)
Large ears	+		
Posteriorly rotated ears	–		+ (1/*)
Low-set ears	–	+	
Short neck	+		
Inverted nipples	*		+ (1/*)
Fifth-finger clinodactyly	+		+ (1/*)
Abnormal gait	+		+ (4/7)
Poor coordination	+	+	+ (5/5)
Ocular problems ^a	+		+ (5/6)
Eczema	–		+ (6/7)
Behavioral disturbances ^b	+	+	+ (1/*)
Sleep disturbances	+		
Social personality	*	+	+ (6/7)
Speech articulation problems/language impairment	+	+	+ (1/*)
Dental/palate abnormalities ^c	+	+	+ (4/7)
Foot deformities ^d	+		+ (2/*)
Constipation	–		+ (3/*)
Hypogenitalism	+		
Abnormal regulation of body temperature ^e	–		+ (2/*)
Enuresis	+		+ (2/*)
Left hemiparesis	*		+ (2/*)
Vasovagal episodes	*		+ (1/*)

Table 2 (continued)

Features	Present case 3	Patient 1 Margari et al. [2012]	Patients 1–7 Goldlust et al. [2013]
Excess saliva	+		+ (1/*)
Respiratory difficulties ^f	+	+	+ (3/*)
Impaired hearing	*		+ (1/*)
Brain MRI abnormalities ^g	+	+	+ (3/*)
Heart disease ^h	–	–	+ (1/*)

ys = Years; mo = months; + = patients exhibiting features; – = features are not present. * Features not formally evaluated.

^a Amblyopia, astigmatism, iris disorders, strabismus, exophoria, exotropia, delayed visual development.

^b Aggressiveness, obsessive-compulsive disorder, repetitive and stereotyped behaviors, hyperactivity, social skill delays.

^c Narrow, high-arched palate; dental crowding; poor occlusion; supernumerary, crooked, late erupting teeth.

^d Varus and valgus deformity, flat feet.

^e Poor body temperature regulation and heat intolerance.

^f Obstructive sleep apnea, paroxysmal nocturnal dyspnea, croup, recurrent respiratory infections, asthma.

^g Mild atrophy of cerebral hemispheres, reduced volume of white matter in the cerebral hemispheres, thinning of the corpus callosum, pineal gland cyst, porencephalic cyst, hydrocephalus.

^h Mitral valve prolapse.

seizures, macrocephaly, and mild dysmorphic features (table 2). Seven other t(8;12) cases reported by Goldlust et al. [2013] presented with a unique phenotype with ID, seizures, macrocephaly, and obesity (table 2). In the latter work the authors have demonstrated that duplication of the *GNB3* gene is linked to the obesity phenotype in patients with t(8;12). These clinical features are shared by our patient with t(8;12). In addition, our patient showed common facial features with cases of pure and complete 12p duplication, such as a round face, short nose, thin upper lip, and short neck, which is in agreement with previous studies showing that the facial features of trisomy 12p syndrome are linked to genes at the distal 12p region [Segel et al., 2006; Izumi et al., 2012; Poirsier et al., 2014]. Our patient also manifested increased birth weight and neonatal complications such as hypotonia, poor feeding, and hypoglycemia resembling those of trisomy 12p.

The most common symptoms among the reported patients with t(8;12) are ID/DD (9/9), hypotonia (7/9), seizures (7/9), macrocephaly (8/8), obesity (6/7), abnormal gait (5/8), poor coordination (7/7), ocular problems (6/7), eczema (6/8), dental/palate abnormalities (6/9), outgoing personality (7/8), and mild dysmorphisms (9/9) with rounded facies and broad/prominent cheeks being more common. Several patients also displayed accelerated growth, brain MRI abnormalities and respiratory difficulties. Interestingly, many of these features are frequently seen in 12p duplication, such as DD, hypotonia, seizures, 'social' behavior, macrocephaly, and some of the facial features [Segel et al., 2006; Izumi et al., 2012; Poir-

sier et al., 2014], suggesting the presence of genes on 12p responsible for various aspects of t(8;12) phenotype.

In conclusion, we identified 2 patients with an overlapping region of deletion at 1p21.3p21.2 and one new case of a de novo t(8;12) in a prospective cohort of syndromic obesity patients. The deletions in this report reinforce the hypothesis that one or more genes in the 1p21.3 region are involved in obesity as well as ID and ASD, and lead us to speculate that miR-137 dysregulation might be the underlying genetic basis. Our findings justify the use of chromosomal microarrays in the evaluation of patients with obesity associated with a nonspecific phenotype, aiming to describe novel chromosomal etiologies for syndromic obesity.

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