Interstitial Deletions at 6q14.1–q15 Associated with Obesity, Developmental Delay and a Distinct Clinical Phenotype

C. Wentzel^a S.A. Lynch^b E.-L. Stattin^c F.H. Sharkey^d G. Annerén^a
A.-C. Thuresson^a

^aDepartment of Genetics and Pathology, Uppsala University, Uppsala, Sweden; ^bNational Centre for Medical Genetics, OLCHC, Dublin, Ireland; ^cDepartment of Medical Biosciences, Medical and Clinical Genetics, Umeå University, Umeå, Sweden; ^dMicroarray Unit, Cytogenetics Laboratory, Western General Hospital, Edinburgh, UK

Key Words

6q Deletion • Learning disability • Mental retardation • Obesity

Abstract

Background: Interstitial deletions of the long arm of chromosome 6 have been described in several patients with obesity and a Prader-Willi-like phenotype. Haploinsufficiency of the *SIM1* gene located at 6q16.3 is suggested as being responsible for the regulation of body weight. Here we report on 2 patients with interstitial deletions at 6q14.1–q15 presenting with obesity and symptoms strikingly similar to those reported for deletions involving the *SIM1* gene despite not having a deletion of this gene. **Methods:** Array comparative genomic hybridisation was used to diagnose 2 children with obesity and developmental delay, revealing 2 interstitial deletions at 6q14.1–q15 of 8.73 and 4.50 Mb, respectively, and a region of overlap of 4.2-Mb. **Results:** The similar phenotype in the 2 patients was most likely due to a 4.2-Mb common microdeletion at 6q14.1–q15. Another patient has previously been described with an overlapping deletion. The 3 patients share several features, such as developmental delay, obesity, hernia, rounded face with full cheeks, epicanthal folds, short palpebral fissures, bulbous nose, large ears, and syndactyly between toes II and III. **Conclusions:** Together

with a previously reported patient, our study suggests that the detected deletions may represent a novel clinically recognisable microdeletion syndrome caused by haploinsufficiency of dosage-sensitive genes in the 6q14.1–q15 region.

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Introduction

For several years, rare copy number variants (CNV) have been known to be the cause of many developmental diseases [Lee and Lupski, 2006], and many new syndromes have been discovered since genomic arrays were implemented as a diagnostic tool in clinical settings to search for the cause of idiopathic mental retardation in children. Several rare CNVs have been detected in patients suffering from mental retardation and early-onset obesity [Bonaglia et al., 2008; Bochukova et al., 2010; Walters et al., 2010]. A number of single nucleotide polymorphisms (SNPs) has, in recent genome-wide association studies, also been associated with obesity [Walley et al., 2009].

In the reported cases with deletions at chromosome 6q, there are large phenotypic variations due to differences in the size and location of the deletion [Turleau et

Fig. 1. **A** Patient 1 at the age of 17 years. **B** Patient 2 at the age of 12.5 years. **C** Ear. **D** Foot with brachymetatarsalia of the 4th toe of patient 1. **E** Patient 2.

al., 1988; Villa et al., 1995; Stein et al., 1996; Hopkin et al., 1997; Gilhuis et al., 2000; Faivre et al., 2002; Grati et al., 2005; Le Caignec et al., 2005; Varela et al., 2006; Klein et al., 2007; Bonaglia et al., 2008]. In a review of 60 patients by Hopkin et al. [1997], 3 distinct phenotypes were described on the basis of the location of the 6q deletion. In group A, del(6)(q11–q16), there was a high incidence of hernias, up-slanting palpebral fissures and thin lips. This deletion was also associated with microcephaly, micrognathia and cardiac malformations.

So far, reports on 8 patients presenting with a 6q deletion and a Prader-Willi-like phenotype, including obesity, have been published. Seven of the 8 patients featured a deletion of the 6q16.2–q16.3 region. Haploinsufficiency of the *SIM1* gene (MIM 603128), located in this region, has been suggested as a possible cause of the obesity [Villa et al., 1995; Faivre et al., 2002; Bonaglia et al., 2008].

In this report, we present 2 patients with developmental delay with an interstitial deletion of 6q14.1–6q15. Although these patients did not have a deletion at the 6q16.3 region encompassing the *SIM1* gene, they have most of the symptoms in common with these patients, suggesting that other genes might cause the obesity in these patients.

Another patient has previously been reported with a deletion overlapping this region and a phenotype similar to the patients in this study [Turleau et al., 1988]. The shared clinical features of the 3 patients include developmental delay, obesity, hernia, rounded face with full cheeks, epicanthal folds, short palpebral fissures, bulbous nose, large ears, and syndactyly between toes II and III.

Materials and Methods

Patients

The clinical investigations and genetic analyses were performed according to the guidelines in the Declaration of Helsinki and were approved by the ethics committee at Uppsala University. Informed consent was obtained from the families. Genomic DNA was extracted from peripheral blood leukocytes from patients using standard procedures.

Array Comparative Genomic Hybridisation

Microarray-based comparative genomic hybridisation (array CGH) was performed using the CytoChip (BlueGnome Ltd., Cambridge, UK), as previously described [Wentzel et al., 2008]. To confirm the results and map breakpoints, an Affymetrix® Genome-Wide SNP Array 6.0 (Affymetrix Inc., Santa Clara, Calif., USA) was performed in accordance with the manufacturer's instructions. Data analysis of Affymetrix data was carried out with Genotyping Console 3.0.2.

MLPA

Confirmation of array CGH data and parental analysis of patient 1 was carried out by using 3 specifically designed synthetic MLPA probes designed to cover the region of interest [Stern et al. 2004], as previously described [Thuresson et al., 2007]. Data analysis was performed with GeneMarker software 1.85 (Softgenetics, State College, PA, USA).

FISH

Confirmation of array CGH data and maternal analysis of patient 2 was performed by FISH analysis using bacterial artificial chromosome probes within the deleted region and using standard techniques [Chong et al. 1997].

Case Reports

Patient 1

This 17-year-old girl (fig. 1A, C, D) is the first child born to non-consanguineous, healthy parents. The mother's brother had mental retardation, probably due to a viral infection in the neonatal period. The father's 2 cousins, born by the same parents, were mentally retarded; the causes for the retardation remain unknown.

The pregnancy was described as uneventful, apart from a few days of severe maternal vertigo at the end of

the pregnancy period. The proband was born by vaginal delivery after the 42nd week of gestation. Her birth weight was 2,800 g (-2 SD), length 49 cm (-0.5 SD) and head circumference 37 cm ($+2$ SD). She had muscle hypotonia with failure to thrive during the neonatal period. During childhood she was short in stature but grew according to her growth chart.

Psychomotor development was delayed. At 17 months, she had reached the developmental milestones of a 7–10-month-old child. She started to crawl at the age of 2–3 years, to sit at 4 years and to walk, with support, at 4.5 years of age. At 7 years of age, she was still not able to walk without support. She spoke her first words when she was 3 years old. Clinical examination at the age of one year showed the following dysmorphic features: a large head with a prominent occipital and frontal region and a narrow bi-temporal diameter, thin hair, full round cheeks, short and down-slanting palpebral fissures, epicanthal folds, entropion of one lower eyelid, a broad nasal bridge, a bulbous nose tip, a high palate, a thin upper lip, and a tented mouth. The hands and feet were small and obese with fragile nails. She had syndactyly between the second and the third toe bilaterally. At birth, she had an umbilical hernia and a fistula in the sacral region, later both healed spontaneously. From about the age of 7 years, she started to become obese. At 5 years of age, bilateral hyperopia was found and at 15 years progressive cataract in the right eye was diagnosed. She had a hearing deficiency of 30 db bilaterally. Menarche occurred at 15 years of age.

There was a heart murmur, but cardiac ultrasonographic findings were normal. Her renal function was deficient as a result of chronic pyelonephritis and a malformation of the right kidney; she was treated with daily antibiotics. Routine biochemical and metabolic screening was normal. Cerebral CT showed wide ventricles and a partial corpus callosum agenesis. She attended a special school for children with developmental delay.

At re-evaluation at the age of 4, her weight was 18.2 kg and height 98 cm (BMI 19); at 4 years and 9 months, weight was 20.1 kg and height 102 cm (BMI 19.3); at 5 years and 11 months, weight was 25.2 kg and height 109 cm (BMI 21.2); at 7 years, weight was 33.7 kg and height 116.5 cm (BMI 25). Her occipito-frontal head circumference (OFHC) at birth was ± 2 SD; at 9 months ± 3 SD, at 4 years ± 2 SD and at 8 years ± 3 SD. At the last clinical examination at 17 years of age, the patient (fig. 1A, C, D) was able to walk without support for a short distance; she spoke in short sentences of 2–3 words but understood much more. Her height was 151 cm, which was short compared with her target height of 165 cm. Her weight was 70 kg (BMI

30.7), and she still ate a lot, but she was not ‘bottomless’ and said no to food when she was full. She had attention deficit and aggressive tantrums. OFHC was ± 3 SD.

Patient 2

This male patient (fig. 1B) was born by ventouse delivery at 42 weeks after an unremarkable pregnancy. The birth weight was 3,630 g (± 0 SD). There were early feeding difficulties. He was noted to have camptodactyly of the 3 middle fingers of his right hand. He had a right inguinal hernia corrected by operative surgery at 9 months. His eyes were deep-set and appeared shut, resulting in early referral to ophthalmology. He was noted to have a very small angle esophoria with fine horizontal nystagmus. He had hyperopic astigmatism and mild ptosis. The rest of his ocular examination was normal. He had surgery for a twisted epididymis when he was 4 years old. He had grommets and adenoids removed in early childhood. He was noted to have early scoliosis which improved later in childhood. He had mild to moderate developmental delay and a severe dyspraxia. He entered puberty at the appropriate age and there are no signs of hypogonadism. He can walk and run but is described as awkward. Fine motor skills, such as holding a pencil, are poor. He cannot ride a bike but can manage a go-cart. He can dress himself but tends to put clothes on back to front and inside out. He cannot read or write and can only produce 3-worded sentences. He is hyperactive and exhibits food-seeking behaviour. The kitchen is locked at night. He started to become obese when he was 5 years old.

At re-evaluation at 3.3 years of age, his weight was 23 kg ($+3$ SD), height 106.5 cm ($+2$ SD; BMI 20.3) and OFHC 52.5 cm ($+2$ SD); at 13 years and 10 months, his weight was 79.6 kg, height 173 cm (BMI 26.6) and OFHC 58 cm. He wore size 43 shoes at the age of 14. He had fixed flexion deformities of both elbows, restriction in pronation in the right forearm and restriction in supination in the left forearm. He had a mild pectus excavatum, inverted nipples and a café au lait patch on the right side of his chest. Due to pectus excavatum an X-ray of the chest was performed, which showed suspected cardiomegaly. The ultrasound of the heart was normal, but the ECG revealed mild right ventricular conduction delay.

Results

Patient 1

Chromosomal karyotyping was normal. Owing to the obesity and the Prader-Willi-like phenotype, a Prader-

Fig. 2. A Idiogram of chromosome 6 displaying the deletions at 6q14.1–q15 in patients 1, 2, and patient 140 reported in DECIPHER. **B** Enlargement of deleted region of present 2 cases and patient 140 in DECIPHER and genes involved in the region of interest.

Willi syndrome methylation test was carried out and proved normal. At 16 years of age, array CGH-analysis revealed a de novo deletion at 6q14.1–q15. To further refine the breakpoints, an Affymetrix SNP Array 6.0 analysis was performed, which determined the centromeric breakpoint to be located at 79,381,592 (hg18)(SNP_A-2113875) at 6q14.1, and the telomeric breakpoint at 88,101,121 (hg18)(SNP_A-1882803) at 6q15 (fig. 2A). The size of the deletion was estimated to be 8.73 Mb.

Patient 2

Chromosomal karyotyping and telomeres by MLPA were normal. Array CGH analysis revealed 2 CNVs, one duplication at 1p31.1 and one deletion at 6q14.1–q15. To further refine the breakpoints, an Affymetrix SNP Array 6.0 analysis was performed, which determined the 1p31.1 duplication to encompass the region between 72,618,778–75,171,956 (hg18; SNP_A-8687482 to CN_500319) and the 6q14.1–q15 deletion to be located between 83,890,115–88,391,069 (CN_1200346 to CN_1189450) (fig. 2A). The estimated sizes of the CNVs were 2.55 Mb and 4.50 Mb, respectively. The CNVs could not be detected in the mother. DNA from the father was not available.

Discussion

Prader-Willi syndrome is the most well-known obesity-associated syndrome and is characterised by hypotonia, craniofacial abnormalities, hypogonadism, a short stature, small hands and feet, hyperphagia, and developmental delay. The incidence is 1/15–25,000 per live births. Early-onset obesity in combination with a developmental disorder was recently also reported in patients with a deletion at 16p11.2 [Bochukova et al., 2010; Walters et al., 2010] and has also been observed in a majority of patients with deletions within the 6q15–q23.1 region [Turleau et al., 1988; Villa et al., 1995; Stein et al., 1996; Gilhuis et al., 2000; Faivre et al., 2002; Varela et al., 2006; Bonaglia et al., 2008].

Here we report on 2 patients with interstitial deletions at 6q14.1–q15 which have early-onset obesity and a developmental delay. Patient 2 also has an additional duplication at 1p31.1. In the literature, there has been a report on a patient with an overlapping deletion at 6q14–q16.2 [Turleau et al., 1988]. Comparing the phenotype of these 3 patients, the common features present are striking (fig. 1A, B; table 1). Apart from the developmental delay present in

Table 1. Summary of clinical features of present and previously reported cases with a deletion at 6q14–q23.1

	Present patient 1	Present patient 2	Turleau et al.	Hopkin et al. group A	Total results
Sex	F	M	F		
6q deletion	q14.1–q15	q14.1–q15	q14–q16.2	q11–q16	
Feeding problems	+	+	–	83%	2/3
Developmental delay	+	+	+	13	3/3
Motor delay	+	+	+		3/3
Hypotonia	+	–	+	90%	2/3
Behavioural problems	+	+			2/2
Brain anomalies	+		– (CT)	33%	1/3
Cardiac abnormalities	–	+	–	28%	1/3
Obesity	>6y	+	>6m		3/3
Hernia	+ (um)	+ (ing)	+ (um)	71% hernias	3/3
Macrocephaly	+	+	–		2/3
Prominent forehead	+	+	–	0%	2/3
Rounded face/full cheeks	+	+	+		3/3
Almond-shaped eyes	–	–	+	42%	1/3
Short palpebral fissures	+	+	+	28%	3/3
Up-slanting palpebral fissures	–	–	+	86%	1/3
Down-slanting palpebral fissures	+	+	–	0%	2/3
Epicanthal folds	+	+	+	64%	3/3
Thick upper eyelids	+	+			2/2
Strabismus	–	+	+		2/3
Bulbous nose	+	+	+	57%	3/3
Large ears	+	+	+	83%	3/3
Small mouth	+	–	+	21%	2/3
Everted lower lip	–	–	+		1/3
Thin lips	+	–	–	57%	1/3
High-arched palate	+	–		42%	1/3
Small hands/feet	+	–	+	78%	2/3
Syndactyly (toe II-III)	+	+	+		3/3
Brachymetatarsia	+				1/1

+ = Feature present; – = feature absent; F = female; M = male; m = months; y = years; CT = computer tomography; US = ultrasound; AC = Arnold-Chiari; ing = inguinal; um = umbilical.

all 3 patients, all have an early onset of obesity, motor delay, hernia, rounded face with full cheeks, epicanthal folds, short palpebral fissures, bulbous nose, large ears, and syndactyly between toes II and III. Many of these findings are consistent with what has previously been reported from a review of 60 patients presenting with deletions encompassing the long arm of chromosome 6 [Hopkin et al., 1997]. In this review, 3 distinct phenotypes were described on the basis of the location of the 6q deletion. All 3 of the above-mentioned patients would have been assigned to group A, del(6)(q11–q16), where hernias, epicanthal folds, bulbous nose, and large ears were also commonly reported features. Our findings suggest that the genes causing this common phenotype would be located in the 6q14 region.

In the DECIPHER database (<https://decipher.sanger.ac.uk/>), there is a patient reported, patient 140, partially overlapping with patient 1. The main symptom described in that patient, apart from the developmental delay, is joint laxity, which could not be observed in our 2 patients. The main symptoms described in our patients were not present in that patient [H. van Esch and E. Rosser, personal communication].

Twenty-three genes are located within the 4.2 Mb commonly deleted region (fig. 2B), of which some are interesting and might play a role for the phenotype of these patients. *HTR1E* (MIM 182132) is a receptor for a serotonin neurotransmitter thought to play a role in various cognitive and behavioural functions including feeding,

sleep, pain, depression, and learning, and it might explain the behavioural problems and food-seeking behaviour seen in our 2 patients. Association studies have implicated *HTR1E* as a candidate gene in ADHD patients [Lasky-Su et al., 2008; Oades et al., 2008] and to be located in close proximity to the breakpoint in a schizophrenia-like psychosis patient with a balanced translocation, t(6;11)(q14.2;q25) [Jeffries et al., 2003]. *ME1* (MIM 154250) encodes a NADP-dependent cytosolic enzyme, expressed in white adipose tissue and involved in modulating lipogenesis. Altered *Me1* enzyme activity has been associated with obesity in mouse and rat models [Vidal et al., 2006; Qian et al., 2008]. A recent study could show decreased body weight in a knockout mouse model [Yang et al., 2009].

Other genes of interest might be *CYB5R4* (MIM 608343), a widely expressed reductase, believed to cause insulin-deficient diabetes [Xie et al., 2004] and *SNX14*, a membrane protein belonging to the sorting nexin family. *SNX14* is mainly expressed in cells of the neuronal lineage and is involved in several stages of intracellular trafficking [Carroll et al., 2001; Worby and Dixon, 2002].

The 1p31.1 duplication detected in patient 2 contains some genes that could explain the cardiac abnormality not present in patient 1 and in the patient of Turleu et al. [1988]. One of the genes in this region is *TNNI3K*, a TNNI3-interacting kinase, which has been implemented to a role in cardiac physiology. However, it is not likely that the duplication in this patient contributes to the phenotype shared by our 2 patients and the one by Turleu et al. [1988] and also seen in group A by Hopkins et al. [1997].

Haploinsufficiency of the gene *SIM1*, located at 6q16.3, has been suggested as being responsible for the severe obesity [Villa et al., 1995; Faivre et al., 2002; Bonaglia et al., 2008]. Previous studies in mice have shown that expression of the *SIM1* gene is involved in the regulation of

body weight [Michaud et al., 1998]. Moreover, the commonly deleted region reported here might affect the gene expression of *SIM1* and thereby causing the obesity through alteration of the chromatin structure. Recent studies showed that CNVs can have an effect on gene expression of genes as far as 2–7 Mb away from the CNV by influencing the transcriptome [Henrichsen et al., 2009]. However, in our 2 patients the deletion is 13 Mb upstream of the *SIM1* gene, thus, altered *SIM1* expression is less probable and thereby might not explain the obesity seen in our 2 patients.

In spite of this difference, in the location of the deletion our patients bare a striking resemblance to the other reported patients with haploinsufficiency of the *SIM* gene, suggesting that other genes might also have been responsible for the obesity and specific phenotype seen in our patients. In conclusion, the deletion at 6q14.1q15 seen in our 2 patients and the one previously reported by Turleu et al. [1988], suggest that this might represent a new clinically recognisable microdeletion syndrome characterised by developmental delay, early-onset obesity, hernia, rounded face with full cheeks, epicanthal folds, short palpebral fissures, bulbous nose, large ears, and syndactyly between toes II and III. This is further supported by the patients in group A in the review by Hopkins et al. [1997]. Further high-resolution studies of patients with deletions in the 6q14q15 region will facilitate genotype-phenotype correlations for specific genes responsible for the obesity and specific phenotype seen in these patients.

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