LETTER TO JMG

Deletion of the *SIM1* gene (6q16.2) in a patient with a Prader-Willi-like phenotype

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Apart from Prader-Willi syndrome, which is a well delineated imprinting disorder of the 15q11-q12 region, other chromosome anomalies have been described in a small number of patients with features reminiscent of Prader-Willi syndrome, including hypotonia, progressive obesity, small extremities, and delayed developmental milestones. Among these chromosome anomalies are some cases of interstitial deletion of chromosome 6q[1–5] and haploinsufficiency of the *SIM1* gene (6q16.2) has been proposed as a candidate gene for obesity.[6] Here, we report a fifth case of Prader-Willi-like phenotype associated with an interstitial chromosome 6q deletion (6q16.1-q21) detected only by high resolution banding techniques. This suggests that a subgroup of patients with features reminiscent of Prader-Willi syndrome and an interstitial deletion of chromosome 6q16.2 could be delineated.

CASE REPORT

The proband was the only child of a 27 year old mother and a 32 year old father. Intrauterine growth retardation, oligohydramnios, and a left club foot were noted during the third trimester of pregnancy. He was born at term after a normal delivery. His growth parameters were weight 2350 g (−2.5 SD), length 47 cm (−1.5 SD), and OFC 33 cm (−1.5 SD). He was described as floppy and had feeding difficulties in early infancy. He sat at the age of 2 years, walked at 3½ years, and had no speech when we first saw him aged 5 years. Excessive weight gain began at 3 years, with a big appetite and food seeking behaviour. There were no sleep disturbances. His behaviour was hyperactive, with a short attention span and intolerance to frustration. Interaction with other children was non-existent.

At physical examination, weight was +5.5 SD, height was −1 SD, and OFC was +2.5 SD. He had generalised obesity, slightly dysmorphic features including a square and flat face, a large forehead with a protruding metopic ridge, small palpebral fissures, mild strabismus, a thin nose, and thin lips (fig 1). The ears were low set with very small lobes. The hands and feet were small with low implanted thumbs, the external genitalia were normal, and a dry skin with livedo was noted. No malformations were found. Clumsiness and a wide based gait were noted at neurological examination. Metabolic screening and fragile X studies were normal, as was a cerebral MRI. Bone age was 3½ years at the age of 5. Psychometric evaluation showed performance at a 2½ year level (DQ = 50).

Cytogenetic and molecular analyses

In order to rule out Prader-Willi syndrome, a methylation assay of the *SNRPN* gene and a FISH study with the *SNRPN* probe were performed. Both analyses showed normal results, as well as standard cytogenetic and telomere analyses using microsatellite polymorphic markers. However, high resolution banding analysis performed on cultured peripheral blood lymphocytes using R and G banding techniques showed a 46,*XY*, del(6)(q16.1q21) karyotype (fig 2A). Karyotypes of the parents were normal. Comparative genomic hybridisation study confirmed the deletion (fig 2B). Molecular studies using microsatellite polymorphic markers D6S1709, D6S1580, and D6S447 (6q16.3-q21) were fully informative and showed that the 6q deletion was paternal in origin. In addition, molecular studies using an intragenic microsatellite polymorphic marker within the *SIM1* gene (primers 5′-GGCTGGCTCCAACTCGG-3′ and reverse 5′-GATCAGCAGGCAGGAGAG-3′) were fully informative and showed that the *SIM1* gene was deleted (fig 2C).

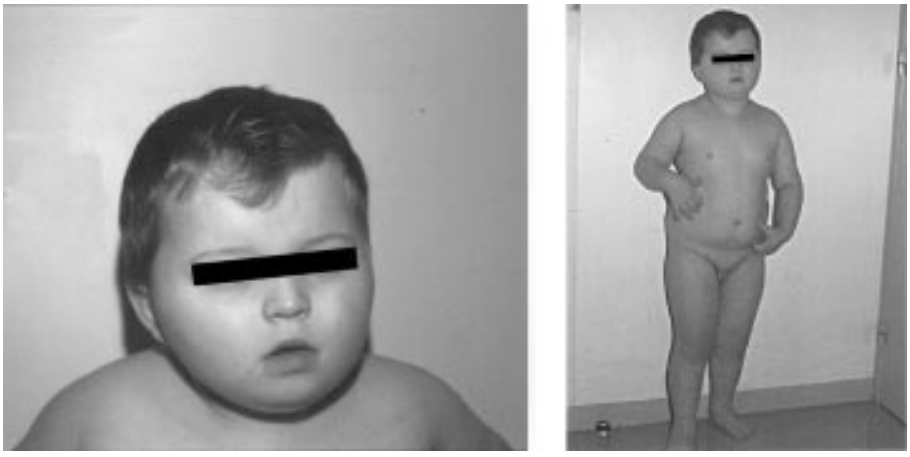

Figure 1 Picture of the child at the age of 5 years. Note generalised obesity, slightly dysmorphic features including a square and flat face, large forehead with protruding metopic ridge, small palpebral fissures, mild strabismus, thin nose, low set ears and thin lips, and small hands and feet.

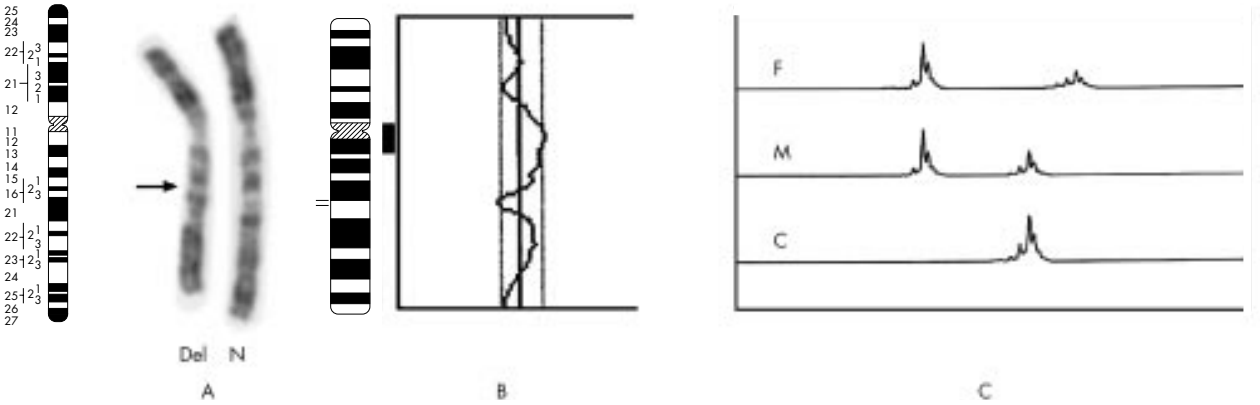

Figure 2 (A) High resolution banding of chromosome 6, showing the non-deleted chromosome on the left and the deleted chromosome on the right. (B) Comparative genomic hybridisation studies confirming the 6q deletion. (C) Molecular analysis using intragenic polymorphic microsatellite marker of the *SIM1* gene showing the deletion of paternal origin (F: father, M: mother, C: child).

Table 1 Clinical features observed in Prader-Willi syndrome and five cases of interstitial deletion of chromosome 6q associated with Prader-Willi-like phenotype

	Prader-Willi syndrome	Patients with interstitial 6q deletion and a Prader-Willi-like phenotype
Hypotonia	+	4/4
Feeding problems in infancy	+	3/3
Obesity	+	5/5
Facial dysmorphism	Mild	Moderate
Hypogonadism	+	4/5
Developmental delay	Mild	Severe
Hyperphagia	+	2/5
Short extremities	+	5/5
Cardiac defects	-	2/5
CNS abnormalities	-	3/5

DISCUSSION

Here we report on the fifth case of chromosome 6q deletion in association with a Prader-Willi-like phenotype. A review of five patients with an interstitial chromosome 6q deletion and a Prader-Willi-like phenotype showed that they all shared the following features with Prader-Willi syndrome patients: obesity, hypotonia, short extremities, and developmental delay.[2–5] However, there are also distinct differences. For example, excessive appetite was seen in only two patients and cardiac (bicuspid aortic valve, aortic stenosis, right branch block) as well as neurological abnormalities (polygyria, leucomalacia, seizures, hearing loss, Arnold-Chiari malformation) were found in 2/5 and 3/5 patients, respectively. These differences are summarised in table 1.

Interestingly, four out of five patients described have a 6q16.2 deletion (fig 3). This suggests that the 6q16.2 subband could be regarded as a region of interest for obesity related genes. In addition, a balanced translocation between chromosomes 1p22.1 and 6q16.2 has been reported in a patient with profound obesity.[6] The authors cloned and sequenced both translocation breakpoints. While the translocation did not appear to affect any transcription unit on 1p22.1, it disrupted the *SIM1* gene on 6q16.2. They hypothesised that haploinsufficiency of *SIM1*, possibly acting upstream or downstream of the melanocortin 4 receptor in the paraventricular nuclei of the hypothalamus, could be responsible for obesity in their subject. Indeed, it has been shown in the mouse that the *Sim1* gene is expressed in the central nervous system where it has an important role in the development of the supraoptic and the paraventricular nuclei of the hypothalamus.[7] In addition, there is good evidence from anatomical and pharmacological studies that these nuclei are involved in the regulation of body weight as these neurones express the melanocortin-4 receptor[8] and appear to be a target of alpha melanocyte stimulating hormone, which inhibits food intake.[9] Interestingly, the *SIM1* gene is also deleted in our patient. Therefore, this observation provides further support for the hypothesis that haploinsufficiency of the *SIM1* gene might be responsible for the obesity observed in our patient.

There is also some evidence in published reports that other chromosome 6q loci might carry obesity related genes, namely: (1) a patient reported by Stein *et al*[4] with a Prader-Willi-like phenotype and a deletion distal to the subband 6q16.2 as well as patients with distal deletion of chromosome 6q and obesity alone[10]; (2) the observation of patients with 6q duplication and obesity[11 12]; and (3) the discovery of a major locus for fasting insulin concentrations and insulin resistance with strong pleiotropic effects on obesity related phenotypes on distal chromosome 6q[13] (fig 3).

Finally, there is good evidence that some chromosome 6q genes are submitted to genomic imprinting (http://www.geneimprint.com). For example, transient neonatal diabetes mellitus is associated with paternal uniparental disomy for chromosome 6 or paternal duplication of chromosome 6q24.[14] In our report, the deletion was of paternal origin, as was the duplication of chromosome 6q24.3-q27 in the patient reported by Smith *et al*.[11] However, the relationship between imprinting and obesity in chromosome 6q deletion remains unknown. Further molecular studies of similar cases might help to resolve the possible causal relationship between imprinting and obesity.

In conclusion, this observation suggests that in patients with a Prader-Willi phenotype and a normal cytogenetic/molecular study of the 15q11-q12 region, deletion of the 6q16.2 region and the *SIM1* gene in particular should be looked for.

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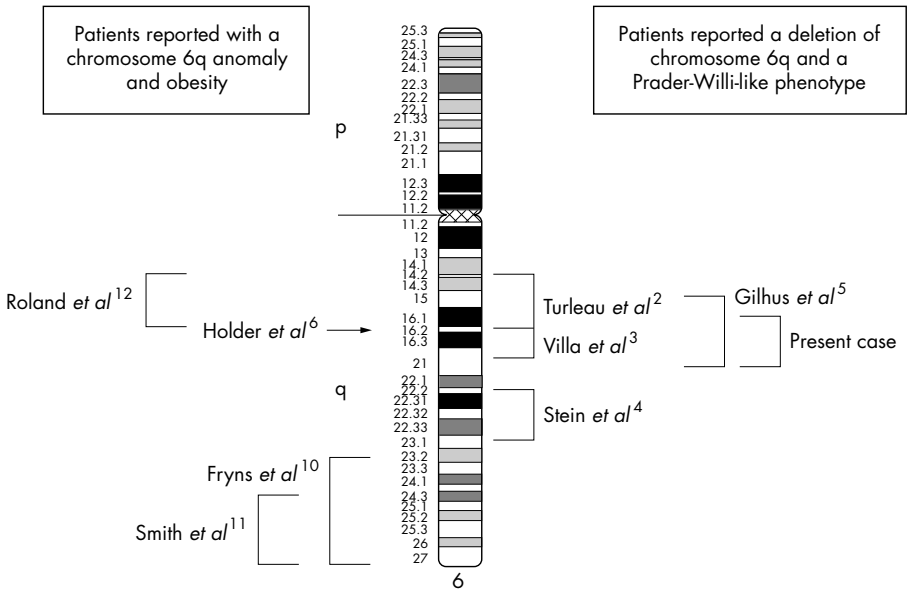

Figure 3 Ideogram of chromosome 6 showing the extent of the deletions in children with Prader-Willi-like phenotype as well as other chromosome anomalies of chromosome 6 and obesity.

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