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Isochromosome 15q of Maternal Origin in a Prader-Willi Patient with Pituitary Adenoma

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Abstract. We report on a Prader-Willi syndrome (PWS) patient carrier of a balanced 15q15q translocation and affected by a prolactin-secreting pituitary adenoma. Evidence provided by molecular studies indicates that the structural rearrangement is an isochromosome of maternal origin. According to the identification of isodisomy as the basis of the association of rare disorders and the recent report on chromosome 15 monosomy and nullisomy in pituitary adenoma, we suggest that in our case PWS and pituitary adenoma might be related.

Key words: Prader-Willi syndrome, Uniparental disomy, Imprinting, 15q15q Robertsonian translocation, Isochromosome 15

INTRODUCTION

Prader-Willi syndrome (PWS) is a complex disorder frequently associated with chromosome 15 abnormalities [1]. Del(15)(q11-q13) on the paternally derived chromosome is the most frequent rearrangement, found in approximately 60-80% of cases [2-4]. Further molecular analyses showed that most non-deleted PWS patients had maternal uniparental disomy (UPD) for chromosome 15 [5]. These observations supported the hypothesis that the genes in the 15q11-q13 region are subjected to genetic imprinting, i.e. the epigenetic mechanism by which gene expression depends upon the sex of the transmitting parent.

De novo balanced t(15q; 15q) karyotypes are not an uncommon finding in PWS patients [6, 7] and some cases were found to be isochromosomes [3, 8].

We report on a PWS patient with a prolactin-producing pituitary adenoma carrier of a de novo t(15q; 15q).

PATIENT AND METHODS

The proband was a 26-year-old male referred with the clinical diagnosis of PWS. A prolactin-producing pituitary adenoma was first diagnosed when the patient was 14 years old and later successfully treated with bromocriptine.

Cytogenetic analysis was performed on peripheral blood lymphocytes from the patient and his parents using high-resolution chromosome techniques followed by GTG banding. Fluorescent in situ hybridization (FISH) analysis was carried out with the Oncor Prader-Willi cosmid (region A D15S11). Hybridization and fluorescent detection were performed according to the Oncor protocol.

Six microsatellite polymorphisms at loci D15S11, D15S128, GABRB3, CYP19, FES, and D15S87, were analysed by polymerase chain reaction (PCR) amplification using ^{33}P-labelled cytosine and subsequent 8% polyacrylamide gel electrophoresis. Primers obtained from PRIMM were designed as previously reported [9].

RESULTS

Cytogenetic study revealed the presence of a t(15q; 15q) in the patient and a normal karyotype in his parents. No mosaicism was detected in 100 metaphases examined. No interstitial deletion in the 15q11-q13 region could be detected either by cytogenetic investigation on prometaphases of the patient on FISH analysis with the proximal cosmid D15S11. Cytogenetic results have been published elsewhere [10]. Results from the DNA polymorphism analysis are shown in Figure 1. Non-paternal inheritance was observed at all loci examined. The patient was homozygous throughout the chromosome and his haplotype on 15q coincided with that of the mother at heterozygous loci D15S128, CYP19 and D15S87. These results indicate that the t(15q; 15q) in our patient is an isochromosome-5q-producing maternal disomy.

DISCUSSION

Robertsonian translocations may be an important cause of UPD. Several cases have been ascertained through the screening of PWS patients [3, 8, 11].

In our case, molecular results indicated that the t(15q; 15q) is an isochromosome of maternal origin in agreement with the hypothesis that all rob(15q; 15q) associated with PWS may represent i(15) leading to UPD [11].

As first suggested by Nicholls [12], isodisomy might be the basis of an association of rare genetic disorders through homozygosity of a mutant recessive allele at a second locus mapping on the same chromosome. Indeed, PWS has been occasionally observed in conjunction with a separate genetic disorder such as urticaria pigmentosa, septo-optic dysplasia and Bloom syndrome [13-15]. On this basis and because of a recent report on monosomy and nullisomy 15 in pituitary adenoma [16], we hypothezise that a tumor suppressor gene regulating proliferation and differentiation of pituitary cells may be localized on chromosome 15q. The observations on Prader-Willi-like patients with various types of brain damage such as craniopharyngiomas [17], and the pituitary deficiency observed in septo-optic dysplasia give credence to the supposition that hypothalamic

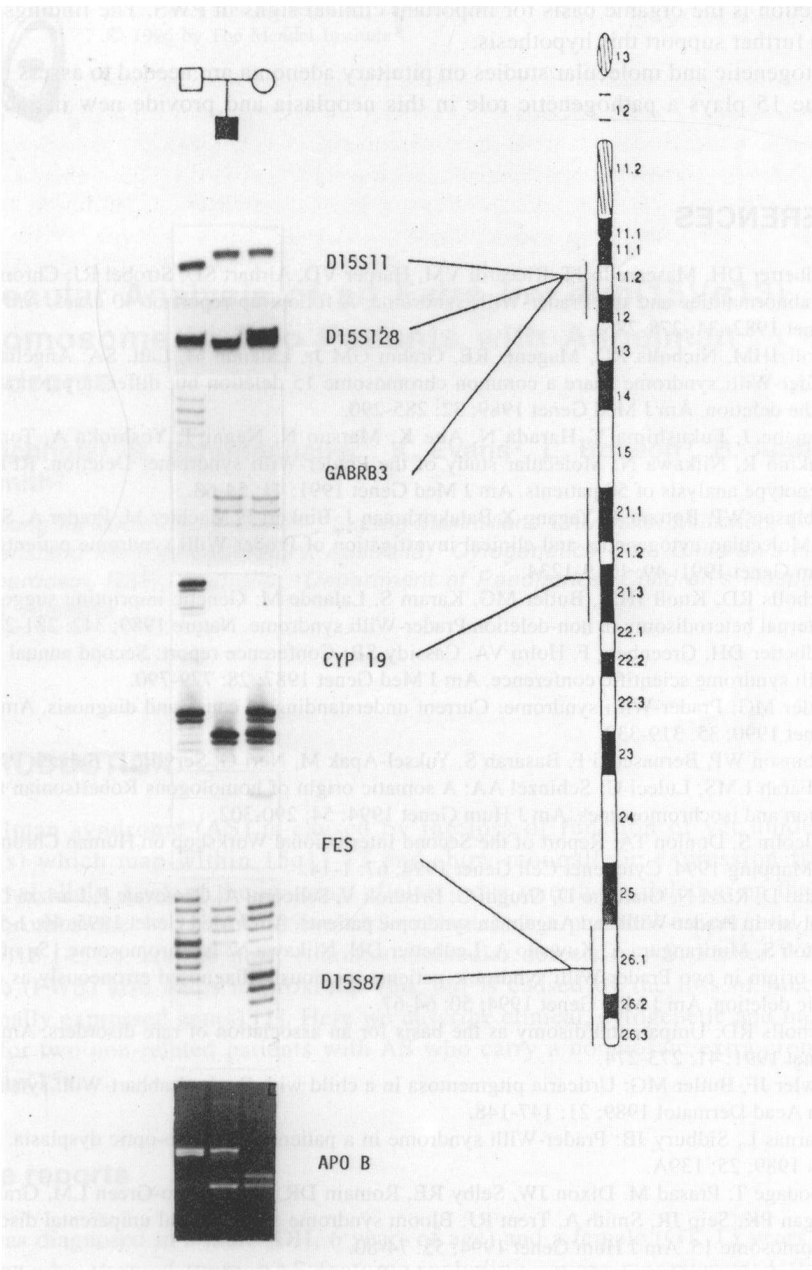

Fig. 1 - Ideogram of chromosome 15, indicating regional localization of the polymorphic markers used in this study and PCR-detected polymorphism patterns at six loci mapped to 15q and one locus (APOB) mapped to 2p. Non-paternal inheritance at all six loci was observed. The patient had a homozygous pattern consistent with one of the maternal alleles at D15S128, CYP19 and D15S87.

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dysfunction is the organic basis for important clinical signs in PWS. The findings in our patient further support this hypothesis.

Cytogenetic and molecular studies on pituitary adenoma are needed to assess if chromosome 15 plays a pathogenetic role in this neoplasia and provide new insights into PWS.

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