Unbalanced reciprocal translocations in cases of Prader-Willi syndrome

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Summary. A case of Prader-Willi syndrome (PWS) associated with a de novo unbalanced 15q;17q reciprocal translocation presumptively resulting from the tertiary monosomic form of 3:1 meiotic disjunction is described. Twenty-three similar unbalanced translocations have been identified from the literature. The 24 karyotypes are characterised by having 45 chromosomes, monosomy for the pericentromeric region of chromosome 15 (range pter→q11 to q21), and little monosomy of the recipient (non-15) chromosome. Two-thirds of the cases with these karyotypes have phenotypic features of PWS. It seems probable that (i) where unbalanced reciprocal translocations are associated with PWS, they will almost invariably be presumptive segregants of the tertiary monosomic form of 3:1 disjunction and (ii) the majority of cases found with this type of karyotype, particularly it appears when de novo in origin, will be associated with phenotypic features of PWS.

Introduction

Hawkey and Smithies (1976) first suggested that chromosome 15 may be involved in the pathogenesis of Prader-Willi syndrome (PWS). Subsequently, there have been a number of reports associating abnormalities of chromosome 15 with PWS (reviewed by Guanti 1980; Kousseff 1982; Ledbetter et al. 1982; Charrow et al. 1983). These abnormalities, which may be present in up to 50% of PWS patients, are heterogeneous but fall into three main categories: (i) deletion of chromosome 15, (ii) balanced rearrangements involving chromosome 15, including reciprocal and Robertsonian translocations, and (iii) the presence of an extra idic(15) (Ledbetter et al. 1982). Abnormalities in the first category, which are the most commonly reported, comprise interstitial deletions of the long arm, deletions in “balanced” Robertsonian translocations, and unbalanced reciprocal translocations. We report here a case of PWS involving an unbalanced reciprocal translocation (previously cited in Duckett and Roberts 1981, and Duckett 1982) with partial monosomy of chromosome 15 resulting from a presumptive 3:1 meiotic disjunction and discuss similar cases found in the literature.

Case report

The proposita was the second child of a 30-year-old mother and a 31-year-old father. Her 3-year-older brother is phenotypically normal. The pregnancy was uncomplicated up to 36 weeks gestation, when labour was induced as the baby was small for dates and there were falling levels of oestriol and human placental lactogen. Delivery was by Caesarian section because of a breech presentation with foetal distress. At birth, the infant’s weight, length, and head circumference were 2120 g, 49.5 cm, and 34 cm, respectively, and the Apgar score was 7 at 1 min and 9 at 5 min. The proposita made very slow progress and was very hypotonic. She was slow to feed, requiring a nasogastric tube. She was 26 days old before being able to take all her feeds by mouth. On discharge from hospital at 1 month, she weighed 2520 g.

At 4½ months, the proposita was still hypotonic and showed delayed milestones but had started to feed on solids. She had odd facial features and was queried as having PWS. Her subsequent development to age 3 was slow but steady, and she remained hypotonic. She started to sit unaided at 10 months and to walk at about 19 months. At 2 years, a full Ruth Griffiths’ mental development assessment showed a general quotient of 83 with speech being the poorest response. After the age of 2 the proposita gained weight rapidly through hypophagia and by 32 months was obese, her weight being well above the 97th percentile and her height below the 50th percentile. At this time a thyroid function test was normal, and her facial features included almond-shaped eyes and a fish-shaped mouth (Fig. 1). She was now clinically diagnosed as having PWS and was referred for cytogenetic investigation. By 3 years of age she spoke only five single meaningful words, and a restricted carbohydrate diet was not controlling her obesity.

Cytogenetics

Chromosome preparations were made and banded using standard techniques. Each metaphase from lymphocyte cultures of the proposita showed a count of 45 with the loss of a No. 15 and a No. 17 chromosome and the presence of an extra chromosome apparently derived from an unbalanced reciprocal translocation, in which most of the long arm of a chromosome 15 was translocated onto the distal end of the long arm of a chromosome 17. Investigation of lymphocyte cultures from the parents and brother of the proposita showed normal karyotypes. The karyotype of the proposita was interpreted as 45,XX,-15,-17,+der(17),t(15;17)(q13;q25) (ISCN 1978).
Fig. 1. The proposita aged 35 months

Fig. 2. Partial GTG-banded karyotype of the proposita. The derivative chromosome 17 is indicated by an arrow

(Fig. 2). The proposita was therefore monosomic for the short arm, centromere, and a proximal long arm segment of chromosome 15 (pter → q13) and probably monosomic for a very small segment of the distal long arm of chromosome 17 (q25 → qter).

Discussion

The aetiology of the association of chromosome abnormalities with PWS is apparently complex (Ledbetter et al. 1982). However, Guanti (1980) postulated that PWS results from breakage of chromosome 15 in the q11 region, whilst Ledbetter et al. (1981) proposed that deletion of 15q11 → 13 causes this syndrome. There is increasing evidence that loss of a "critical region", now assigned to band 15q11, is involved in the majority of cytogenetically abnormal cases of PWS (Ledbetter et al. 1982), with many cases of interstitial deletion of this critical region being reported (inter alia Ledbetter et al. 1982; Bonuccelli et al. 1982; Butler et al. 1982; Mattei et al. 1983).

In the 12 cases of PWS known to us, including the present one, which are associated with an apparently unbalanced reciprocal translocation, there is monosomy of the short arm, centromere, and a variable length of proximal long arm material of chromosome 15 which includes this critical band (Table 1, section 1). Duckett and Roberts (1981) in reviewing monosomy of chromosome 15 material suggested that loss of the segment approximating to 15q21 → 24 was lethal at a pre- or early postzygotic stage. If this hypothesis is correct, it would follow that loss of the critical band 15q11 could not occur simultaneously with loss of the more distal segment 15q21 → 24 in a live-born individual. Thus in cases of unbalanced reciprocal translocation, the loss of the critical band associated with PWS would most likely originate from a meiotic disjunction of a balanced translocation with a breakpoint on chromosome 15 between q11 and q21, in which neither No. 15 centromere passes to that secondary gametocyte producing the gamete eventually fertilized. This could only result from the tertiary monosomic form (Rieger et al. 1976) of 3:1 disjunction or adjacent 2 disjunction at anaphase I. Table 1 (section 1) shows that all cases of PWS associated with an unbalanced reciprocal translocation have a karyotype which is consistent with the tertiary monosomic form of 3:1 disjunction in a parent, where each offspring has received a single translocation derivative and neither of the non-translocated pair of chromosomes from the translocation heterozygote, although it is theoretically possible for this form of disjunction to be mimicked by non-disjunction at anaphase II following a 2:2 disjunction at anaphase I. However, in all cases of PWS (section 1) including the present one, where tested, the karyotypes of the parents of the proband were normal. Nevertheless, these segregants have been considered as examples of de novo 3:1 disjunction (after Lindenbaum and Bobrow 1975). This classification is supported by (i) the