

## The Prader-Willi syndrome with a 15/15 translocation

### Case report and review of the literature

**Summary.** A case, diagnosed clinically as the Prader-Willi syndrome, was shown by Giemsa banding, to have a 15/15 chromosome translocation. A review of the literature indicates that such a translocation has only been described once before, in a normal woman, but that chromosome abnormalities in the Prader-Willi syndrome most commonly involve the D group. The significance of this would be clarified by specific chromosome identification in these patients.

The syndrome, originally described in 9 Swiss children by Prader, Labhart, and Willi (1956) is not uncommon, with over 170 cases described to date (Hall and Smith, 1972; Anand, Kogut, and Lieberman, 1972; Parra, Cervantes, and Schultz, 1973; Pipes and Horm, 1973; Haberfeilner, Giatzi, and Unterkircher, 1974; Morgner *et al*, 1974; Stolecke, Huerne, and Tiling, 1974). Indeed, it is possible that the dwarf Maribarbola in Velasquez's Las Meninas may be a case of this syndrome rather than achondroplasia, as is commonly assumed.

Chromosome studies, when performed, have been normal in most cases of the Prader-Willi syndrome though a variety of different karyotypes have been found in a few such patients. In this paper we describe an individual who has the clinical features of the Prader-Willi syndrome and who has been shown to have a 45,XY chromosome complement with a centric-fusion 15/15 translocation. Such a translocation has been described only once before—in a normal woman who repeatedly miscarried (Lucas, 1969).

#### Case report

The patient was the second son of 4 children born to

unrelated Caucasian parents in 1936. At the time of his birth the mother was 23 and the father 29. Neither earlier nor subsequently did his mother miscarry. His sibs were normal.

The pregnancy was uneventful, but the mother recalls very little intrauterine activity. Delivery was full term, with a breech presentation. Records are not available, but there were no obvious abnormalities of appearance, weight (about 2700 g), or head size at birth. However, the child failed to cry, became blue, and was kept in an incubator for three weeks. He was floppy and weak and, being unable to suck, he was fed with a dropper for six months.

There were no spontaneous limb movements until 15 months (when he raised his hand to bright objects). All his milestones were delayed; he did not sit unaided until 2½ years of age, did not talk before 3½, and walked only at 4½. He became obese from the age of 5 years. His milk teeth were discoloured on eruption and rapidly decayed. He was moderately retarded and from the age of seven to fourteen he attended a special school. Between 1937 and 1966 he was taken to six hospitals; the notes from one are available and record a tentative diagnosis of Fröhlich's syndrome. In 1972 at the age of 36, he was sent to a chest clinic because of breathlessness and from there he was referred, in 1974, to the Clinical Research Centre on account of gross and refractory obesity.

**Examination.** On examination (Fig. 1 and 2) he had the facial appearance of the Prader-Willi syndrome, with almond eyes and a fish shaped mouth. His teeth were carious. He was very obese (height 1.56 m, weight 104 kg), with brawny oedema of the legs. He had a severe kyphoscoliosis, and diminutive hands and feet, but his proportions were normal. His secondary sexual development was poor: his voice was unbroken, he did not shave, and there was little virilization. His testes were not palpable and the scrotum was rudimentary. The phallus was small (Fig. 3) but complete fusion had taken place. There was no true gynaecomastia. He was retarded and on formal testing was found to be functioning in the borderline area of subnormality (Wechsler Adult Intelligence scale IQ77; verbal subtest 71, performance 83).

**Laboratory investigations.** Routine investigations were without exception unremarkable, with normal blood count, urea and electrolytes, liver function tests, calcium, and phosphate. A fasting and a 2-hour post-prandial blood sugar were normal (both 3.3 mmol/l). Thyroid

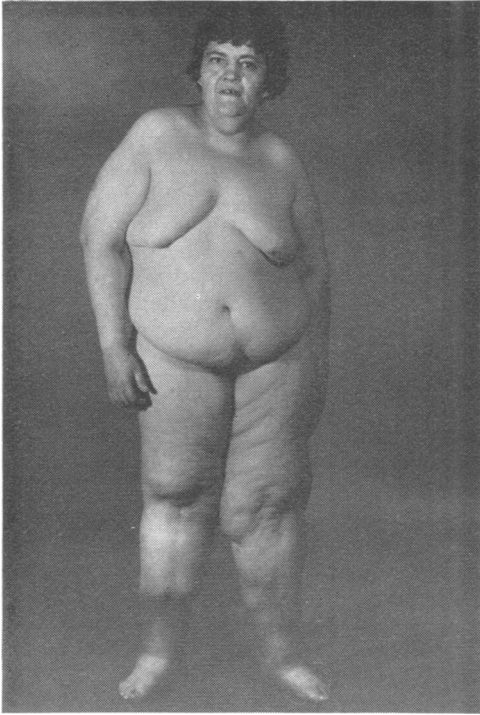


FIG. 1. The patient.



FIG. 2. Typical facial appearance.

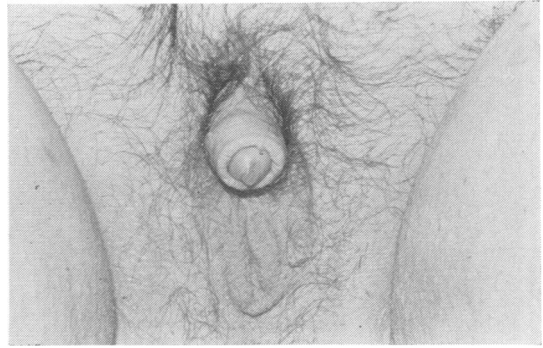


FIG. 3. External genitalia.

and adrenal function, were both normal. Plasma levels of testosterone-like substances were low (1.6 ng/ml—normal 5–19 ng/ml) and were associated with a low urinary output of gonadotrophins measured by bioassay (less than the equivalent of 3 mg first International Reference Preparation 24 hours). Amino acids were absent from the urine. Radiographic examination showed a normal chest x-ray, a small pituitary fossa, a bone age in excess of 19 years (Greulich and Pyle, 1959), and an obvious kyphoscoliosis, with prominent osteophytes (Fig. 4). Lung function tests were normal. Striated muscle, obtained by biopsy, appeared normal when examined by conventional microscopy and histochemically; there were, however, minor abnormalities on electron microscopy. An excess of glycogen and mitochondria lay between the myofibrils. Beneath the plasma membrane, membranous bodies, were seen near to mitochondria in the midst of large collections of glycogen.

**Cytogenetic findings.** Chromosome preparations were made from peripheral blood culture. Fifty cells were examined and the chromosome complement was 45 in every one. Analysis of the mitoses showed that only 4 large acrocentric group D chromosomes were present. There was one large metacentric chromosome slightly smaller than a No. 3. The remaining chromosomes were those of a normal male.

The large metacentric chromosome suggested a centric fusion between 2 members of the D group. Giemsa banding (Seabright, 1971) identified the metacentric chromosome as a translocation between the members of pair No. 15. The karyotype was therefore 45,XYt(15q15q) (Fig. 5).

The karyotype of the patient's mother and father were normal. Analyses of blood groups and other genetic markers are shown in Table I.

### Discussion

Table II lists the five cardinal features originally

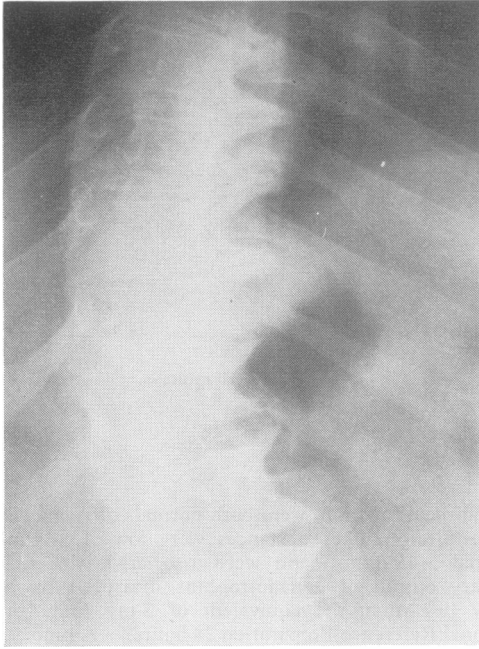


FIG. 4. Gross spinal osteophytes.

stressed by Prader and his colleagues (1956), along with those characteristics regularly reported by

subsequent reviewing authors (Laurence, 1967; Landwirth, Schwartz, and Grunt, 1968; Zellweger and Schneider, 1968; Dunn, 1968; Cohen and Gorlin, 1969; Hall and Smith, 1972). The figures in parentheses refer to the percentage occurrence in the largest single series of 32 cases (Hall and Smith, 1972). The diagnosis of this syndrome is based entirely on clinical observation. The patient we have described displays all of the original (and commonest) and many of the other characteristics of the condition. He had strikingly small dainty hands and feet, and the typical facies. The more recently described features of obvious dental caries in both milk and permanent teeth (Foster, 1971) and scoliosis (Pearson, Steinbach, and Bier, 1971) were also present. He is the second oldest case to be diagnosed, Juul and Dupont (1967) having described a patient of 43 years.

As in 40% of Smith and Hall's cases, there was a breech presentation at birth. This, presumably, reflects the reduced intrauterine activity consequent upon the muscular hypotonia. A number of papers (Laurence, 1967; Dunn *et al*, 1961; Dunn, 1968; Afifi and Zellweger, 1969) have attempted to define its nature histologically or histochemically. Surprisingly, there was a conspicuous lack of agreement and, in the majority of cases, muscle biopsy was normal. Afifi and Zellweger (1969) described the electron microscopical appearance of muscle biopsies from 7 cases. As in the present case there

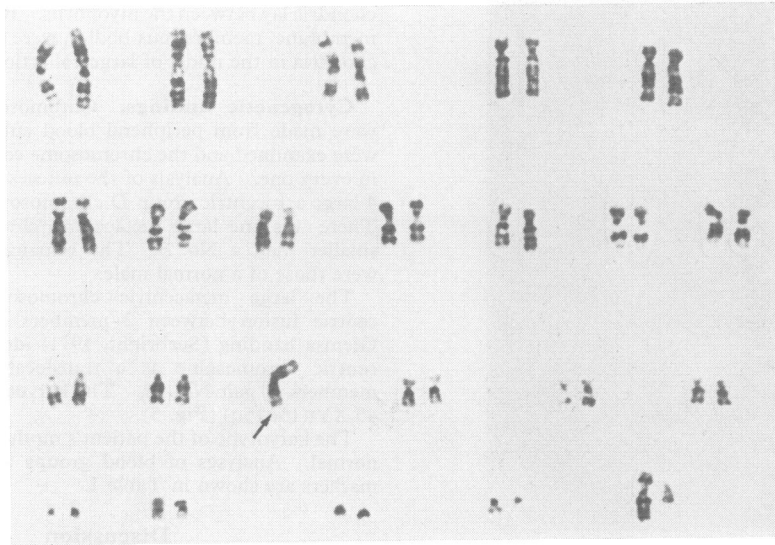


Fig. 5. Karyotype. 45,XY,t(15q;15q). Abnormal meta centric chromosome is arrowed.

TABLE I  
BLOOD GROUPS AND GENETIC MARKERS OF PATIENT AND PARENTS

						Hp	Tf	PGD	PGM	AK	ADA	GPT	Pi	Gm	Inv	ES-D	SGOT	PHI
Patient	A <sub>1</sub> NSNS	P <sub>1</sub>	r <sup>r</sup>	K-k <sup>+</sup>	Fy (a+b-)	2-1	C	A	1	1	1	1	M	-1 -2 +10	-1	1	1	1
Father	O M <sub>s</sub> NS	P <sub>1</sub>	R <sub>2</sub> r <sup>r</sup>	K-k <sup>+</sup>	Fy (a+b+)	2-1	C	A	1	1	2.1	2-1	M	-1 -2 +10	-1	1	1	1
Mother	A <sub>1</sub> MSNS	P <sub>2</sub>	R <sub>1</sub> r	K-k <sup>+</sup>	Fy (a+b+)	2-1	C	A	1	1	1	2-1	M	-1 -2 +10	-1	1	1	1

was no clear single abnormality. Abnormal features have included massive sarcolemmal aggregates of mitochondria, tortuous irregular Z lines which sometimes lay obliquely across the myofilaments, and limited areas of myofilament disarray, with loss of recognizable contractile elements. To what extent these changes were primary, or secondary to disuse could not be determined. Several of these cases, however, showed mitochondrial disarray, as in our patient, but no excess of glycogen.

Muscular hypotonia is more characteristic of infancy. All of the cases described by Zellweger and Schneider (1968) learned to walk between the ages of 2 and 4. Other authors (Forsman and Hagberg, 1964; Roget *et al*, 1965) have reported cases, like ours, where motor development was more severely delayed. When the children become active enough to forage for food, the main clinical problem becomes obesity and its consequences. Thus, in the absence of understanding of the basic aetiology of the Prader-Willi syndrome, control of obesity remains the most important therapeutic measure.

Skeletal collapse and kyphoscolioses are quite common (Pearson *et al*, 1971) but severe cardio-respiratory consequences of obesity have not been reported regularly. However, Jenab *et al* (1959) describe a child not actually identified as the Prader-Willi syndrome but very reminiscent of it (suggestive features included neonatal hypotonia with breech delivery, retardation, hyperphagia, and obesity after the age of 3, hypogonadism, dwarfism, and the published photograph of the child). Vigorous dieting failed to control his obesity and he died at the age of 6 of a Pickwickian cardiorespiratory syndrome. Many authors (Pipes and Horm, 1973; Evans, 1965; Laurence, 1967) have stressed the difficulties of achieving weight reduction in these patients. The present patient's obesity seems less refractory than usual, and he has so far lost 16 kg on a simple 800 calorie diet at home.

Mental retardation is a universal finding. Our

TABLE II  
FEATURES OF PRADER-WILLI SYNDROME

Cardinal	{ Neonatal hypotonia (100%) with feeding problems (100%), blue spells, diminished spontaneous movement and weak or absent cry Hypogonadism (100%) and cryptorchidism (84%) Mental retardation (97%) with delayed milestones (100%) Obesity (100%) with hyperphagia Short stature (94%)
Gestation	{ Diminished intrauterine movement (74%) Breech delivery (40%) Non-term delivery (43%)
CNS	{ Epilepsy (16%) 'Personality problems' (71%)
Facies	{ Narrow bifrontal diameter (40%) Strabismus (40%) Almond shaped eyes (19%) Fish shaped mouth
Skeletal	{ Small hands and feet (Acromicria) (79%) Enamel hypoplasia (12%) with dental caries Kyphoscoliosis
Metabolic	{ Diabetic glucose tolerance test (30%) Abnormal urinary gonadotrophins (usually low)

patient scored better on IQ testing than most reported cases, where intelligence quotients have ranged from 20 to 87 (Zellweger and Schneider, 1968). Most previous studies, however, have used the W.I.S.C. or Stanford Binet scales. A variety of personality problems has been reported. Descriptions range from 'vicious' to 'friendly co-operative natures' leading to their becoming 'pets of the ward'. Whether this is related to intelligence quotient is not known. The patient here described was, like the majority, affable, and well adjusted within the limits of his—relatively high—intelligence quotient.

**Cytogenetics.** Of the 170 published cases of the Prader-Willi syndrome 61 have had chromosome analyses. Ten of the 61 cases have been considered to have karyotype abnormalities (Table III). This is much higher than expected in the normal population (Court Brown, 1967). Three of the 10 cases had karyotype abnormalities associated with a

TABLE III  
ABNORMAL KARYOTYPES IN 10 CASES OF  
PRADER-WILLI SYNDROME

Buhler <i>et al</i> (1963)	45,XYt(D/D)
Roget <i>et al</i> (1965)	47,XY + D/46,XY,
Dubowitz (1967)	46,XY + m16
Dunn (1968)	46,XY long Y
	46,XY long Y
Schneider and Zellweger (1968)	46,XY
	46,XYt(D/E)
Cohen and Gorlin (1969)	46,XY/45,XY,t(G/G)
	46,XYt(G/G) + C
Ridler <i>et al</i> (1971)	47,XY + t(G/G)
Haberfeilner <i>et al</i> (1974)	47,XX + G or D
	46,XY 16q +

chromosome in the D group, and 2 were translocations, but in none of these previous cases was the number of the chromosome identified. Buhler *et al* (1963) describe a case of D/D translocation. Though not diagnosed as the Prader-Willi syndrome, the description of the patient strongly suggests that this was the diagnosis and the case has been included in reviews of the syndrome (Dunn, 1968; Schneider and Zellweger, 1968). A fifth case (Ridler, Garrod, and Berg, 1971) had a chromosome complement of 47,XX: the extra chromosome was slightly smaller and more metacentric than a G chromosome, but, as it was frequently found in satellite association, it was considered to be either an extra G chromosome or a fragment of a D chromosome. The case described here appears to be yet another instance of the Prader-Willi syndrome with a karyotype abnormality involving the D group. Furthermore, the use of Giemsa banding has allowed, for the first time, the specific demonstration of an abnormality in pair number 15.

The only previous case of a translocation involving both members of pair number 15 (Lucas, 1969) was a phenotypically normal woman who repeatedly miscarried. Chromosomal analysis of one conceptus revealed a trisomy D. In neither this woman nor in our own case was there evidence of mosaicism which suggests that the chromosomal rearrangement occurred very early in the development of the zygote. It is possible that the loss of genetic material in our case was greater than in that of Lucas. Alternatively, either case could have been a number 15 isochromosome. Though 15/15 translocations are so rare, Robertsonian exchanges in man are, in general, common compared with other types of translocation. They may not be of pathological significance, as their distribution is non-random and their occurrence unrelated to exposure to irradiation or mutagens (Hecht and Kimberling, 1971).

In view of the apparent prevalence of D group abnormalities associated with the Prader-Willi

syndrome, it would be tempting to speculate that the number 15 chromosome is involved in its pathogenesis. However, as the great majority of cases had normal karyotypes it may be that the chromosomal abnormality in our patient was unrelated to his clinical condition.

It would nevertheless be valuable if the previously described cases of the Prader-Willi syndrome with abnormal karyotypes were submitted to further analysis with banding or auto-radiography.

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C. J. HAWKEY\* and ALISON SMITHIES†

*From Northwick Park Hospital and  
Clinical Research Centre, Harrow,  
Middlesex, England*

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\* Present address: Radcliffe Infirmary, Oxford, OX2 6HE.

† Present address: Department of Health and Social Security, Hannibal House, Elephant and Castle, London SE1 6TE.

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There is no cytogenetic evidence available for mosaicism in the propositus or her parents.

The patient's salient clinical features are: profound mental and motor retardation; microcephaly with trigonocephaly; ear malformations; small, sunken eyes; unusual eyebrows; cleft lip and palate; bulbar nose; coloboma iris; polydactyly; unusual dermatoglyphic patterns; large adductor thumbs; enlarged great toes; multiple capillary haemangiomas; club feet; inguinal and umbilical hernias; hyperconvexed fingernails; and seizure disorder.

As with many other genetic disorders, it is constantly necessary to redefine specific disease entities in the light of newly available evidence. This is particularly true in the case of chromosomal disorders. Numerous advances in analytical cytogenetic techniques (Casperson, Zech, and Johansson, 1970; Moorhead *et al*, 1960; Seabright, 1971; Sumner, Evans, and Buckland, 1971) have revolutionized our ability to identify individual chromosomes reliably and rearrangements thereof. These important developments are comparatively recent; and, as a consequence, much of the literature detailing the various clinical features of different chromosomal syndromes was written without the benefit of these techniques of establishing unquestionable chromosomal diagnoses.

This is particularly true in the case of trisomy 13, which has been variously referred to as Patau's syndrome, trisomy D (13-15), or D1 trisomy syndrome. Most of the cases of D-group trisomy reported were discovered before the advent of G and Q banding, making accurate identification of the additional D-group chromosome impossible in most instances. As a consequence, clinical characteristics of patients who may have had complete trisomy 14 or 15, if either of these is a viable condition, could have been confused with those directly attributable to trisomy 13. It is the purpose of this study to furnish information which may facilitate distinction of trisomy 13 from the other D-group trisomic conditions and to report extended survival and development beyond that previously reported in cases of complete trisomy 13.

### Case study

We should like first to report the clinical findings in our patient. The propositus is a 5-year and 3-month-

## Trisomy 13 in a female over 5 years of age\*

**Summary.** A case of simple trisomy 13, confirmed by G-banded chromosome analysis, is reported in a Caucasian female over 5 years of age.

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