Familial mental retardation in a family with an inherited chromosome rearrangement*

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Summary. A family of three generations has been described with an insertional type of chromosome rearrangement involving chromosomes 11 and 18 [46,XX or XY, ins(11;18)(p15;q11q21)] detected by G-banding using a trypsin digestion method. Four members of this family with clinical features of 18q— have inherited the der(18) from their father and are thus deficient for (18)(q11q21). Three other family members have inherited the der(11) and thus have a duplication of the same segment [(18)(q11q21)]. Genetic marker studies on this family, show no significant segregation of any of the markers studied with either the der(11) or der(18). Eight family members had the *PepA*⁸ *PepA*¹ genotype and four of these were carrying the der(18), indicating that the *PepA* locus which had been previously assigned to chromosome 18, does not lie in the segment q11→q21.

Since the initial report by de Grouchy *et al* (1964) over 50 cases of 18q— have been described (Wertelecki and Gerald, 1971; Lurie and Lazjuk, 1972). Familial occurrences of 18q— have also been observed usually resulting from the segregation of a balanced chromosome rearrangement in one of the parents (Law and Masterson, 1966; Valdmanis *et al* 1967; Jacobsen *et al* 1971; Rudd and LaMarche, 1971; Gouw, Ten Kate, and Anders, 1973).

Previous cytogenetic studies of 18q— individuals were unable to distinguish terminal from interstitial deletions. With the advent of Q- and G-banding techniques (Caspersson, Zech, and Johansson, 1970; Seabright, 1971; Sumner, Evans, and Buckland, 1971; Wang and Federoff, 1972; Hamerton, Ray, and Douglas, 1973), specific areas of each chromosome can be readily identified (Paris Conference, 1971). We report here a family with an insertional type of chromosome rearrangement involving chromosomes 11 and 18 detected by G-banding. The rearrangement was shown to be

segregating through three generations and resulted in four subjects with an 18q— karyotype, of whom three were definitely mentally retarded and the fourth was too young for her mental status to be determined.

Materials and methods

Blood samples were collected from available family members and lymphocyte cultures established by standard methods. Air dried preparations were stained conventionally, using orcein, and for G-banding by the method described previously (Hamerton *et al*, 1973). White blood cells were analysed by the method of Lewis (1973) for their peptidase A (*PepA*) phenotypes. Red blood cells and plasma were analysed by standard procedures to determine the phenotypes of the other genetic markers listed in Appendix I (pp. 364–365). Quantitative levels of IgA, IgM, and IgG were determined by quantitative immunodiffusion. Dermatoglyphic analysis was carried out according to the methods of Holt (1968). The chromosome nomenclature used is that recommended by the Paris Conference (1971).

The pedigree of the family is given in Fig. 1 and the family data summarized in Appendix II (p. 366). Detailed clinical observations on certain family members are given below. Data on the other family members are given in Appendix II.

Case Reports

III.6. The proband (Fig. 2) presented at the age of

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FIG. 1. Pedigree of the family.

FIG. 2. Propositus (case III.6) at 28 months of age.

23 months for investigation of physical and mental retardation. He was the product of a full-term pregnancy, complicated by pre-eclampsia and antenatal haemorrhage; delivery was normal. The maternal age at his birth was 22 years. At birth his weight was 2825 g (<10th centile), length 50.5 cm (50th centile), and head circumference 33.5 cm (<10th centile); it was noted that he had bilateral clubbed feet.

At 23 months, his developmental milestones were reported to be retarded; he had not yet begun to speak and had only begun to pull himself up to standing position. His parents described him as a cold and unaffectionate child. On physical examination, head circumference was 45.2 cm, weight 10.2 kg, and length 82 cm, all of which were below the third centile. There was a periodic esophoria of the left eye; the fundi were normal. Neurological examination showed a mild degree of generalized hypotonicity associated with increased patellar tendon reflexes and extensor response on plantar stimulation. No other physical abnormalities were noted. Investigations done at this time showed a normal electroencephalogram, normal skull films and a negative complement fixation test for syphilis. Haematological and biochemical results were all within normal limits. Paper chromatography of amino acids in the urine revealed no abnormalities. At 23 months developmental performance was that of a 10-month-old child.

III.3 (Fig. 3). This subject was the 3300 g product of a full-term pregnancy which was complicated by pre-eclampsia; delivery was normal. To date, she has been healthy and has reached her expected developmental

FIG. 3. Case III.3 at the age of 3 years 9 months. She is phenotypically normal.

milestones. On examination at 45 months, she was a healthy, active girl. Head circumference was 48 cm (< 10th centile), weight 17.6 kg (75th centile), and height 96.5 cm (10th centile). Bilateral subacromial dimples were present. The remainder of the physical examination revealed no abnormalities.

III.10 (Fig. 4). This child was the product of a 40-week pregnancy complicated by pre-eclampsia and a urinary tract infection. Artificial rupture of membrane was carried out and delivery was by mid-forceps rotation. At birth, she weighed 3473 g (50th centile), length was 54.6 cm (< 97th centile), and head circumference 37.5 cm (< 97th centile). The child has been healthy and seems to be developing normally.

On examination at 8 months, she was lively and active with a head circumference of 41.5 cm (< third centile), a length of 72 cm (97th centile), and a weight of 8.27 kg (50th centile). Her head had a flat occiput and was brachycephalic. She had a flattened nasal bridge, bilateral epicanthic folds, upward slanting palpebral fissures, prominent antihelices, slight mid-facial retraction, a carp-shaped mouth, and a high arched palate. The

tip of the spleen was palpable 1 cm below the left costal margin. The remainder of the examination was normal.

II.4 (Fig. 5). This 42-year old paternal aunt of the propositus, was the third of 11 liveborn children, born at a maternal age of 22 years and a paternal age of 42 years. The mother died at the age of 63 from a post-operative pulmonary embolus. The father is suffering from Parkinson's disease. No details of the patient's birth could be obtained.

At the age of 9, the patient was admitted to the Manitoba School for the mentally retarded. At that time, a provisional diagnosis of 'cultural familial mental retardation' was made.

At the time of examination, the patient was severely retarded, spoke in an infantile manner, and showed ataxia. Her mental age was given as 2 years 8 months on the Stanford Binet intelligence scale. Height was 165 cm, sole-to-pubis measurement 78.8 cm, span 161 cm, and head circumference 51.7 cm. She weighed 65.6 kg. She had deep-set eyes, hypotelorism (interpupillary distance 58 mm), and mild mid-facial retraction. There was no discernible squint. Fundoscopic examination revealed an absent red reflex with bilateral diffuse lenticular cataracts. Prominent antihelices were present. The patient had a carp-shaped mouth. The hearing was grossly normal. The patient was obese with a protruberant abdomen; the remainder of the physical examination was within normal limits.

II.5. No details of the pregnancy or birth history are available. There was a history of convulsions in childhood, which have since subsided. An EEG carried out in 1955 showed abnormal patterns in the posterior areas. During late childhood, the patient was admitted to the Manitoba School for the Mentally Retarded and was known to be aggressive and violent.

On physical examination at 40 years of age, he was ataxic and showed frequent bouts of head-rolling. Height was 169 cm, sole-to-pubis distance 82 cm, arm span 160.5 cm, weight 66 kg, and head circumference was 50.5 cm. His occiput was noticeably flat and his face distorted by numerous scars. Slight hypotelorism was evident (interpupillary distance 58 mm). An opaque cataract was obvious in the left eye while the right eye appeared normal on fundoscopic examination. The patient's pinnae exhibited prominent antihelices and large antitragi. The external auditory canals did not appear narrowed, and hearing was not grossly impaired. The palate was strikingly high-arched and narrow. The right testis was small. The metacarpophalangeal joints on both hands showed abnormalities resulting from multiple trauma, and he had bilateral pes planus. The patient gave no scorable responses, on numerous psychological tests that were attempted.

II.6. This subject was admitted to the Manitoba School for the mentally retarded during late childhood. On examination at the age of 38 he was moderately obese, fairly well co-ordinated, but showed almost constant head rolling. Height was 166.4 cm, pubis-to-sole

FIG. 4a. Case III.10 at 8 months of age showing bilateral epicanthic folds, mongoloid slant and carp-shaped mouth.
FIG. 4b. Side view of case III.10 showing mild mid-facial retraction.

measurement 79 cm, arm span 169 cm, weight 74 kg, and head circumference 57 cm. The eyes were deep set and exhibited slight hypotelorism (interpupillary distance 57 mm). A slight esophoria was present in the left eye. Both the retina and disc appeared normal on fundoscopic examination. Both ears showed prominent antitragi, and a prominent antihelix was evident on the right pinna. The abdomen was protruberant. No other physical abnormalities were detected. The patient had a recent psychological evaluation which showed a verbal IQ of 44 and a performance IQ of 40.

Chromosome analysis

The proband (III.6), his father (II.9), three of his aunts (II.13, II.15, and II.17), his grandfather (I.16), and two cousins (III.14 and III.17) were all shown to have a balanced insertional type chromosome rearrangement involving chromosomes 18 and 11, in which the chromosome segment (18)(q11q21) had been inserted into band p15 of chromosome 11, [46,XX or XY,ins(11;18)(p15;q11q21)] (Fig. 6). Chromosome analysis of II.4, II.5, II.6, and III.10, showed that they had inherited the der(18) chro-

mosome from their respective fathers, but otherwise had a normal karyotype [46,XX or XY, -18, +der(18),ins(11;18)(p15;q11q21)pat]. Each of these individuals was thus deficient for the segment (18)(q11q21). Analysis of the chromosomes of II.7, III.3, and III.16, showed that they had each inherited the der(11) and had normal chromosomes 18 so that they each had a duplication of the (18)(q11q21) segment, [46,XX, -11, +der(11),ins(11;18)(p15;q11q21)pat] (Fig. 7).

Dermatoglyphics

Dermatoglyphic data on those family members studied are given in Table I, together with some relevant population data. Parker *et al* (1972) has reported that the 18q- syndrome is characterized by complex digital patterns which can best be described as double or multiple loops (W^a). These, like whorls, have two triradii and are characterized by high ridge counts.

The mean number of whorls in the four patients

FIG. 5a. Case II.4 at the age of 42 showing mild hypotelorism and a carp-shaped mouth.
FIG. 5b. Side view of case II.4 demonstrating mid-facial retraction.

who had inherited the der(18) chromosome only (II.4, II.5, II.6, and III.10) was 8.7 ± 1.5 (mean $\pm$ SD) which is significantly increased over the mean for the population ($t=8.2$, 3 df; $p<0.01$). The mean number of whorls for five patients carrying the balanced ins(11;18) was 4.6 ± 3.0 , which does not differ significantly from the normal ($t=1.46$, 4 df; $0.50 < p < 0.10$), or from the der(18) patients ($t=2.01$, 6 df; $0.10 < p < 0.05$). The mean total ridge count (TRC) was 170 ± 11 for der(18) and 197 ± 41 for ins(11;18), which are not significantly different ($t=1.30$, 5 df; $0.50 < p < 0.10$). However, both are significantly elevated over the population mean ($t=6.02$, 3 df; $p<0.01$ and $t=3.2$, 4 df; $0.01 < p < 0.05$, respectively).

Genetic markers

Quantitative studies. Levels of IgA, IgM, and IgG obtained for II.4, II.5, II.6, and II.9 are summarized in Table II. These show the immunoglobulin levels to be normal or increased in these individuals.

Qualitative studies. Phenotypes of a number

of red cell enzymes, serum proteins, and blood groups of the available family members were determined; these results have been summarized in the Appendix I. None of the alleles or haplotypes associated with any of the gene loci examined was found to segregate with either the der(11) or the der(18) chromosome. All individuals with the der(18) (II.4, II.5, II.6, and III.10) were found to have the Pep A 8-1 phenotype and, hence, the *Pep A⁸ Pep A¹* genotype (see below).

Discussion

Insertions which result from three chromosome breaks (Hamerton, 1971), are less common in human populations than reciprocal translocations which only require two breaks. In *Drosophila*, insertions have been induced but are relatively rare in comparison to reciprocal translocations (Lindsley and Grell, 1968). The introduction of chromosome banding techniques for the study of human chromosomes, will allow the different types of chromosome rearrangements to be distinguished in human populations. In a series of structural rearrangements ascertained in various ways, and in

FIG. 6. A karyotype (case II.17) showing balanced insertion between chromosome Nos. 11 and 18: 46,XX,ins(11;18)(p15;q11q21).

which break points had been determined by banding (Jacobs *et al*, 1974), 58 were Robertsonian translocations, 53 reciprocal translocations, and 10 inversions; none were insertions. In a smaller series ascertained in a newborn survey, J. L. Hamerton (unpublished data) observed two insertions in 26 balanced rearrangements. One of these was the present family and the other an ins(12;10). Thus, while two break rearrangements occur with a frequency of about 1 in 500 newborn infants, (J. L. Hamerton, unpublished data; Jacobs *et al* 1973/1974), insertions and other three break rearrangements are probably at least 10 times less frequent.

A few other families with this type of three break

rearrangement have been described. Gray *et al* (1972) described an ins(4;1), Grace, Sutherland, and Bain (1972) an ins(3;7), and Shapiro and Warburton (1972) an ins(2;12) in a mother of two mentally retarded children who had inherited the der(12). Recently, Rethoré *et al* (1972) described a family in which there were three malformed sibs in which an ins(7;3)(q31;p21p26) was segregating. The present family was ascertained through a retarded child with a balanced chromosome complement (III.6) who was referred to our department for genetic evaluation. At about this time III.10 was born and was studied routinely in a newborn chromosome survey and shown to have a 46,XX,18q—complement on orcein staining.

FIG. 7. Partial karyotypes showing chromosome 11 and 18. Balanced insertion (II.17 and 13), [ins(11;18)(p15;q11q21)]. der(18) (II.5 and 4), [der(18)ins(11;18)(p15;q11q21)pat]. der(11)(q11q21) (III.16 and II.7), [der(11)ins(11;18)(p15;q11q21)pat].

In the present family, a three break insertional type rearrangement has been shown to be segregating. This resulted from the deletion of an interstitial segment of chromosome 18(q11q21) and its insertion into a breakpoint at p15 of chromosome 11 (Fig. 8). The most likely meiotic configuration for such an insertion are two unequal bivalents which

would segregate at random and would result in equal numbers of gametes, carrying either the normal chromosomes 11 and 18, the der(11) and der(18), or either of the two derivative chromosomes along with the complementary normal chromosome (Fig. 8). In the unlikely event of crossing over within an interstitial inserted segment in a multivalent, all the gametes would be unbalanced; dicentric and acentric fragments would result, and might be one reason for the relatively high frequency of spontaneous abortions observed in some sibships.

At the present time, chromosome studies have not been possible on six subjects. Seventeen individuals have been studied. Eight of these had balanced heterozygous karyotypes; four had inherited the der(18), three the der(11), and two had normal karyotypes.

The four subjects (II.4, II.5, II.6, and III.10), who had inherited the der(18) and are deficient for an interstitial segment of chromosome 18, have some features of the 18q- syndrome (Lurie and Lazjuk, 1972). Table III lists the more frequent clinical features of this syndrome and compares these with the major clinical features shown by our der(18) patients. Examination of this table shows that the 18q- condition has a rather variable phenotype. The major clinical features of our subjects include mental retardation (3/4, one—III.10—too young to assess), microcephaly (3/4), abnormal ears (4/4), mid-face retraction (3/4), carp-shaped mouth (2/4), high arched palate (2/4), and a high frequency of whorls or complex digital patterns (4/4). The major reasons for the observed variability in the 'deletion' syndromes have been discussed (Hamerton, 1971) and include variability in the type of chromosome abnormality and the amount of chromosome material deleted. In the past, conventional staining methods have simply allowed the detection of an 18q-; the use of banding will allow the identification of the deleted region, and in many cases will allow a distinction to be made between a balanced and an unbalanced karyotype. In the present family this distinction was made by using G-banding, but could not be detected by conventional means.

The digital patterns are of interest in this family and are characterized by a high frequency of whorls and complex patterns and a high total ridge count (TRC). Examination of the data suggests that subjects with an apparently balanced karyotype [ins(11;18)] show a significant increase in TRC; however, only those patients who have inherited the der(18) chromosome, and thus have an interstitial deletion, have a significantly raised frequency of

TABLE I
DERMATOGLYPHIC FINDINGS IN THE PROPOSITUS AND HIS FAMILY

Case	Sex	Age at Examination (yr)	Digital Patterns										No. of Whorls*	Total Ridge Count†	atd Angles (combined left and right values)‡
			Left					Right							
			V	IV	III	II	I	I	II	III	IV	V			
III.6 (propositus)	M	2 yr 4 mth	L ^u	L ^u	L ^u	W ^d	L ^u	W ^d	W ^d	L ^u	L ^u	L ^u	3	193	97°
I.16	M	84	L ^u	L ^u	W ^d	W ^d	L ^u	W ^d	W ^d	L ^u	L ^u	L ^u	4	205	85°
II.4	F	42	W ^d	W ^o	W ^o	W ^o	W ^d	W ^d	W ^o	W ^o	W ^o	W ^o	10	161	90°
II.5	M	40	W ^d	W ^o	L ^u	W ^o	W ^o	W ^o	W ^s	L ^u	W ^o	W ^s	8	160	95°
II.6	M	38	W ^s	W ^o	W ^o	W ^o	W ^d	W ^o	W ^d	W ^o	W ^s	W ^o	10	177	80°
II.9	M	33	L ^u	W ^d	L ^u	W ^s	W ^d	W ^d	W ^d	L ^u	W ^d	L ^u	6	225	86°
II.15	F	26	L ^u	L ^u	L ^u	L ^u	L ^u	W ^d	L ^u	L ^u	L ^u	L ^u	1	125	79°
II.17	F	23	W ^s	W ^d	W ^d	W ^d	W ^s	W ^d	W ^d	W ^d	W ^o	L ^u	9	226	85°
II.10	F	24	L ^u	L ^u	W ^s	W ^s	L ^u	L ^u	W ^s	W ^o	W ^o	L ^u	5	173	100°
III.3	F	3 yr 9 mth	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	L ^u	0	154	104°
III.10	F	8 mth	L ^u	W ^s	W ^o	W ^o	W ^o	W ^d	W ^o	W ^o	W ^o	L ^u	7	182	93°

L^u = ulnar loop; W^d = double loop or 'complex pattern'; W^o = circular whorl; W^s = spiral whorl.

Normal values (Holt, 1968)

* Mean no. of whorls 2.6 (British population 1000 ♂ and ♀ pooled).

† Mean for British males 145.18; SD 50.49.

Mean for British females 126.97; SD 52.33.

Pooled estimate 136.07; SD 51.41.

‡ Mean atd° for males 92.5°; SD 14.2 (infants).

88.2°; SD 15.9 (school children).

85.0°; SD 15.3 (adults).

Mean atd° for females 97.5°; SD 19.6 (infants).

89.8°; SD 17.5 (school children).

85.9°; SD 15.7 (adults).

TABLE II
QUANTITATIVE VALUES OF IMMUNOGLOBULINS (mg%)

Case	Source	Age (yr)	IgG (N=600-1700)	IgA (N=70-400)	IgM (N=80-300)
II.4	Serum	42	1900	370	590
II.5	Serum	40	1750	500	340
II.6	Serum	37	1350	640	440
II.9	Serum	33	1100	280	340

N = Normal values.

TABLE III
CLINICAL FINDINGS IN PARTIAL 18 LONG-ARM DELETION

	Percent of Cases*	Present Cases			
		II.4	II.5	II.6	III.10
Mental retardation	100	+	+	+	Not yet evident
Microcephaly	76	+	+	-	+
Prominent antihelix and/or antitragus	65†	+	+	+	+
Narrow ear canals	38	-	-	-	-
Mid-face retraction	62	+	-	+	+
Carp-shaped mouth	50‡	+	-	-	+
Fundoscopic abnormalities	29	-	-	-	-
High (or cleft) palate	42	-	+	+	+
Many whorls (>5)	51†	+	+	+	+
Sub-acromial dimples	54‡	-	-	-	-
Genital anomalies	44	-	-	-	-
Fusiform fingers	100**	-	-	-	-
Abnormalities of foot	36	-	-	-	-

+ present; - not present.

* Adapted from Lurie and Lazjuk (1972).

† Data from Wertelecki and Gerald (1971).

‡ Data from de Grouchy (1969).

** Data from Rudd and LaMarche (1971).

'complex digital patterns'. One subject (III.3) who had inherited the der(11) and had therefore a triplication of the inserted region, had no whorls. These observations suggest that a high TRC and high number of whorls are at least partially independent of each other, contrary to the view of Parker *et al* (1972). Abnormal dermatoglyphics have been reported in other individuals with rearrangements involving chromosome 18 (Valdmanis *et al*, 1967; Hoehn, Sander, and Sander, 1971; Jacobsen *et al*, 1971; Rudd and LaMarche, 1971; Lurie and Lazjuk, 1972; Parker *et al*, 1972; Gouw *et al*, 1973). In particular others have reported an increase in whorls or complex patterns in the 18q- syndrome (Valdmanis *et al*, 1967; Hoehn *et al*, 1971; Jacobsen *et al*, 1971). High TRCs have also been recorded in a few subjects with a balanced rearrangement (Jacobsen *et al*, 1971), although in that family increased TRC's were also found in members who had normal chromosomes.

The significance of these observations is by no means clear. De Grouchy (1965) postulated that a distal part of 18q was involved in the determination of whorl count. It seems unlikely, however, that we are dealing with a specific chromosome region. Rather, the well-known effect of chromosome imbalance on dermatoglyphic patterns is the result of non-specific alterations in developmental processes which lead to these alterations in pattern. The most surprising observation is the increase in TRC

FIG. 8. Diagram to illustrate the nature of the rearrangement which has occurred in this family and the gametes which would result from the pairing of two unequal bivalents.

seen in the apparently balanced heterozygotes and further studies are required here, on both normal and balanced subjects, to determine whether this is a generalized heritable increase in these families, or if it is really due to the movement of a chromosome segment from one region of the genome to another.

There have been several reports of the absence of serum IgA in patients with an 18q- or an 18r. This had led to the suggestion that the long arm of chromosome 18 may be involved in the control of IgA synthesis (Feingold *et al.*, 1969; Finley *et al.*, 1969; Masterson and Law, 1969; Stewart *et al.*, 1970; Rudd and LaMarche, 1971). The finding of normal or raised IgA levels in three patients carrying the der(18) (II.4, II.5, II.6) and one subject with a balanced karyotype (II.9) neither supports nor refutes this hypothesis, but simply suggests that 'the IgA centre' if present on chromosome 18, does not lie in the (18)(q11q21) region.

The association of 18q- with a syndrome of severe mental retardation and a spectrum of clinical findings in II.4, II.5, and II.6 is clear, and patients with similar clinical findings have been reported previously (Wertelecki and Gerald, 1971; Lurie and Lazjuk, 1972). In the present family the deletion resulted from the segregation of derivative chromo-

somes, formed as the result of a balanced insertion between chromosomes 11 and 18. Three subjects (II.7, III.3, and III.16) have inherited the der(11) and so had a triplication of the inserted region from chromosome 18. Two of these appear mildly retarded (II.7 and III.16) while one (III.3) seems to be developing relatively normally; one subject (III.16) is a spastic quadriplegic, has frequent upper respiratory infections, slurring of speech, and a poor vocabulary for a child of four; whether any of these latter findings result from the chromosome abnormality is not certain. It is clear, however, that a deletion of this chromosome segment seems to have more deleterious consequences than its duplication.

Eight members of this family are carrying the balanced rearrangement; seven of these are mildly retarded or have low normal intelligence and one (III.6) is severely retarded. The significance of these findings is much less clear. This family comes from a poor environmental background and many members are still living in poor conditions and many of their children are emotionally deprived. It is impossible, therefore, to determine whether the low intelligence of most members of the family is due to 'position effect', resulting from the shift of a chromosome segment from one posi-

tion in the genome to another, to a hidden imbalance not detectable by means available to us, or largely to environmental factors. It is interesting to note that II.2, the only adult member of the family who has normal chromosomes, also has the highest intelligence, although of course no definite conclusions can be drawn from this observation.

Genetic marker studies in families in which a marker chromosome is segregating have been used to assign particular gene loci to specific chromosomes or chromosome regions either by linkage analysis or by deletion mapping. Three autosomal loci have been localized using this approach: the Duffy blood group gene locus to the centromeric region of chromosome 1 (Donahue *et al.* 1968; Ying and Ives, 1968), the α -haptoglobin gene locus to the long arm of chromosome 16 (Robson *et al.* 1969; Magenis, Hecht, and Lovrien, 1970) and the red cell acid phosphatase gene locus to the p23 $\rightarrow$ pter region of chromosome 2 (Ferguson-Smith *et al.* 1973). The assignment of a considerable number of gene loci to specific human chromosomes using somatic cell hybrids, combined with a precise identification of chromosomes (Ruddle, 1973), allows a greater use to be made of 'deletion mapping' to assign a gene locus to, or exclude it from, a specific chromosome region.

The previous assignment of the *PepA* locus to chromosome 18 (Creagan *et al.* 1973; McAlpine *et al.* 1974), allowed the use of 'deletion mapping' in the present family. Four individuals who were shown to be deficient for (18)(q11q21) were also shown to be heterozygous at the *PepA* locus and to have the genotype *PepA*⁸ *PepA*¹. This demonstration of heterozygosity for a locus known to be assigned to chromosome 18, indicates that each of these individuals has two *PepA* alleles so that the gene locus cannot be located in the deleted segment of chromosome 18, (18)(q11q21).

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SUMMARY OF PHENOTYPES OF GENETIC

Pedigree No.	Sex	Enzymes												
		Pep A	Pep B	Pep C	Pep D	PGM ₁	G6PD	6PGD	AK ₁	PHI	GPT	GOT ₁	AcP ₁	ADA
I.16	M	8-1	1	1	1	1	B	A	1	1	2	1	BA	1
II.4	F	8-1	1	1	1	1	B	A	1	1	2	1	B	1
II.5	M	8-1	1	1	NT	1	B	A	1	1	2	1	B	1
II.6	M	8-1	1	1	1	1	B	A	1	1	2	1	BA	1
II.7	F	1	1	1	1	1	B	A	1	1	NT	1	BA	1
II.9	M	8-1	1	1	1	1	B	A	1	1	2-1	1	B	1
II.10	F	1	1	1	1	2	NT	NT	1	1	NT	1	BA	1
II.13	F	NT	NT	NT	NT	1	B	A	1	NT	2-1	1	B	NT
II.14	M	NT	NT	NT	NT	1	B	A	1	NT	2	1	A	NT
II.15	F	1	1	1	1	1	B	A	1	1	2-1	1	BA	1
II.17	F	1	1	1	1	1	B	A	1	1	2	1	BA	1
III.3	F	8-1	1	1	1	2-1	B	A	1	1	2-1	1	BA	1
III.6	M	8-1	1	1	1	2-1	B	A	1	1	2-1	1	B	1
III.10	F	8-1	1	1	1	2-1	B	A	1	1	2-1	1	B	1
III.14	F	NT	NT	NT	NT	1	B	BA†	1	NT	2	1	B*	NT
III.16	M	NT	NT	NT	NT	1	B	A	1	NT	2-1	1	BA	NT

NT = Not tested.

* Samples were tested for Gm(1,2,3,5,6,13,14,17,21) and Inv(1).

† All samples were Lu(a-b+) and K-k+. A number of other blood groups were tested which were uninformative. These results are available on request.

‡ The AcP and 6PGD phenotypes of III.14 are inconsistent with those of her parents (II.13 and II.14). The cytological results suggest that these inconsistencies are probably paternal in origin as the patient has the same chromosome rearrangement as her mother (II.13).

I

MARKERS IN THE FAMILY

Serum Proteins							Blood Groups†										
Gc	Hp	Tf	C'3	Pi	Gm*	Inv	ABO	MNSs	Rh	Fy		Jk		Le	Co	Do	P
										a	b	a	b	a	b	a	
2-1	2	C	2	MM	1,3,5,13,14,17,21	-1	B	MSMS	R ₁ R ₂	+	+	-	+	-	NT	-	NT
1	2	C	2	MM	1,3,5,13,14,17,21	-1	A ₁ B	MSMS	R ₂ r	+	+	-	+	-	NT	NT	NT
1	2-1	C	2	MM	3,5,13,14	-1	A ₁ B	MSNS	R ₁ r	-	+	-	+	-	NT	NT	NT
2-1	2	C	2	MM	1,3,5,13,14,17,21	-1	B	MSNS	R ₂ r	+	+	-	+	-	NT	NT	NT
2-1	2-1	C	2	MM	1,3,5,13,14,17,21	-1	B	MSNS	R ₁ R ₁	+	+	+	+	+	NT	+	NT
1	2-1	C	2	MM	3,5,13,14	-1	B	MSMS	R ₁ R ₁	+	+	+	+	+	-	+	P ₁
1	2	C	1-2	MM	3,5,13,14	1	B	MSMS	R ₁ R ₂	-	+	+	+	+	-	+	P ₂
NT	NT	NT	NT	NT	NT	NT	A ₁ B	MSNS	R ₁ r	-	+	+	+	+	-	+	P ₁
NT	NT	NT	NT	NT	NT	NT	O	MSM ₅	R ₁ r	+	+	+	-	-	+	+	P ₁
1	2-1	C	2	MM	1,3,5,13,14,17,21	-1	B	MSNS	R ₁ r	+	+	+	+	-	NT	+	NT
1	2-1	C	2	MM	3,5,13,14	-1	A ₁ B	MSMS	R ₂ r	+	+	+	+	+	NT	+	NT
1	2	C	1-2	NT	3,5,13,14	1	O	MSNS	R ₁ R ₂	+	+	+	-	+	NT	+	P ₂
1	2	C	2	NT	3,5,13,14	1	B	MSNS	R ₁ R ₁	+	+	-	+	+	NT	+	P ₂
NT	NT	NT	NT	NT	3,5,13,14	NT	NT	MSNS	R ₁ R ₂	NT	NT	NT	NT	NT	NT	NT	P ₂
NT	NT	NT	NT	NT	NT	NT	A ₁	MSM ₅	R ₁ R ₁	-	+	+	-	NT	NT	NT	P ₁

Appendix II

SUMMARY OF FAMILY DATA

Pedigree No.	Date of birth	Date of death	Parents	Comments*	Karyotype
I.16	14 Jan. 1889	—	—	Ukrainian, at present suffering from Parkinson's disease; low-normal intelligence No data	46,XY,ins(11;18)(p15;q11q21)
I.17	—	Unknown	—	—	—
II.1	—	—	I.16; I.17	Stillborn female; no other data	—
II.2	1929	—	I.16; I.17	Normal phenotype; no children	46,XY
II.4	1931	—	I.16; I.17	Severely retarded; see text	46,XX, -18, + der(18),ins(11;18)(p15;q11q21)pat
II.5	1933	—	I.16; I.17	As II.4	46,XY, -18, + der(18),ins(11;18)(p15;q11q21)pat
II.6	1935	—	I.16; I.17	As II.4	46,XY, -18, + der(18),ins(11;18)(p15;q11q21)pat
II.7	1938	—	I.16; I.17	Mother of two normal children; apparently of low-normal intelligence; no further examination permitted	46,XX, -11, + der(11),ins(11;18)(p15;q11q21)pat
II.9	1940	—	I.16; I.17	Father of the propositus; no obvious stigmata; dull normal intelligence	46,XY,ins(11;18)(p15;q11q21)pat
II.10	1942	—	—	Mother of the propositus	46,XX
II.11	1943	—	I.16; I.17	No data	No karyotype
II.13	1945	—	I.16; I.17	Dull low-normal intelligence; emotional instability; otherwise normal phenotype	46,XX,ins(11;18)(p15;q11q21)pat
II.15	1947	—	I.16; I.17	Possible mild mental retardation; obtained grade 7 education	46,XX,ins(11;18)(p15;q11q21)pat
II.17	1950	—	I.16; I.17	Dull normal intelligence; obese and resembles other family members including II.4; deep set eyes; mild mid-face retraction	46,XX,ins(11;18)(p15;q11q21)pat
III.1	1962	—	II.7; II.8	These two girls are reported as normal by their mother and doing well in school; no studies possible	—
III.2	1964	—	II.9; II.10	Sister of propositus; see text	46,XX, -11, + der(11),ins(11;18)(p15;q11q21)pat
III.4	Dec. 1969	—	II.9; II.10	Two abortuses 10-week gestation	—
III.5	12 Nov. 1970	—	II.9; II.10	Propositus, see text	46,XY,ins(11;18)(p15;q11q21)pat
III.6	May 1971	—	II.9; II.10	Twin abortuses; no data	—
III.7	Sept. 1971	—	II.9; II.10	Spontaneous abortion; no data	—
III.8	21 July 1972	—	II.9; II.10	Sister of propositus; see text	46,XX, -18, + der(18),ins(11;18)(p15;q11q21)pat
III.9	—	—	II.11; II.12	No data	—
III.10	—	—	II.13; II.14	Infantile behaviour; aggressive; speech disorder; learning disability and emotional disturbance; IQ 83	46,XX,ins(11;18)(p15;q11q21)mat
III.11	—	—	II.13; II.14	Possible early spontaneous abortion; no data	—
III.12	7 Oct. 1969	—	II.13; II.14	Mild spastic quadriplegia; slurring of speech; poor vocabulary; recurrent upper respiratory infections; remainder of physical examination normal; IQ 85	46,XX, -11, + der(11),ins(11;18)(p15;q11q21)mat
III.13	—	—	II.15; II.16	Mild mid-face retraction; slow but no other abnormalities; able to repeat in 'parrot fashion' with little understanding	46,XY,ins(11;18)(p15;q11q21)mat
III.14	14 Nov. 1970	—	II.15; II.16	Cause of death—aspiration pneumonia; according to physician there were no congenital anomalies and child was generally normal; no necropsy	—
III.15	Dec. 1971	15 Jan. 1972	II.15; II.16	Clinically normal female infant	46,XX
III.16	31 Jan. 1973	—	II.15; II.16	Early miscarriage; poor maternal recall; no further data obtainable	—
III.17	14 Aug. 1971	—	II.17; II.18	—	—

* In generation II, there were several early abortions about which there are no data.