Absent IgA and Deletions of Chromosome 18*

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Since extra chromosomal material in humans was first described by LeJeune, Turpin, and Gautier (1959) in association with Down's syndrome, patients with trisomic and partial monosomic conditions have been studied in an attempt to locate specific genetic loci upon specific chromosomes. An individual with a deletion of part of an autosome is hemizygous for genes on the homologue of the deleted fragment. As a result, recessive genes may be uncovered which, in the absence of a deletion, may have been masked by their dominant alleles. This type of 'deletion mapping' may be important in locating genes on autosomes. We here present studies on 4 patients with deletions involving chromosome 18 and discuss the possible relation between this chromosomal aberration and the locus for immunoglobulin A (IgA).

Wang *et al.* (1962) described a boy with multiple congenital anomalies including atretic ear canals, with secondary deafness and mental retardation. Chromosomal analysis revealed a ring 18 chromosome (18r)† in all cells counted. This was the first reported case of a deletion of a portion of chromosome 18. There have been numerous subsequent reports of similar deletions, both as rings (Grouchy, 1965; Genest, Leclerc, and Auger, 1963; Gripenberg, 1967; Gropp, Jussen, and Oftringer, 1964; Jeune *et al.*, 1967; Lucas *et al.*, 1963; Mikelsaar, Talvik, and Sitska, 1967; Palmer, Fareed, and Merritt, 1967) and as partial deletions of the long arm of chromosome 18 (18q-) (Day *et al.*, 1967; Grouchy, 1965; Insley, 1967; Law and Masterson, 1966; Nance *et al.*, 1968; Wertelecki, Schindler, and Gerald, 1966; Wolf *et al.*, 1967).

The clinical features of these patients are summarized in Table I. Deletion of the short arm of 18 (18p-) was first described by Bühler, Bühler, and Stalder (1964), and many subsequent reports have followed (Grouchy, 1965; Gorlin, Yunis, and Anderson, 1968; Kasahara and Reisman, 1967; McDermott *et al.*, 1968; Migeon, 1966; Nitowsky *et al.*, 1966; Reinwein, Ritter, and Wolf, 1967; Summitt, 1964; Uchida *et al.*, 1965; Van Dyke, Valdmanis, and Mann, 1964). The clinical picture has varied considerably from minimal physical abnormalities to severe central nervous system anomalies such as arrhinencephaly.

The more recent reports of deletions of chromosome 18 have mentioned the absence of serum and salivary IgA (Feingold *et al.*, 1969). This has resulted in speculation concerning a possible direct relation between the deleted chromosomal fragment and a gene involving the production of IgA. Serum and salivary immunoglobulin status has been investigated in our 4 patients with partial deletions of chromosome 18.

Case Reports

Case 1. A 4-year-old Caucasian girl was first seen at 2½ years of age because of a hearing loss. The mother and father were 23 and 26 years of age, respectively, at the time of her birth. There had been two previous spontaneous abortions at 3 and 2 months. For this reason, norethisterone acetate was taken throughout this pregnancy which was also complicated by a rubella exposure at 4 months and by intermittent glycosuria. There was no history of excessive irradiation in either parent. The pregnancy was 38 weeks long, and labour and delivery were uncomplicated. Birthweight was 2325 g. and length was 46 cm.

Development was consistently delayed, with Developmental Quotients* on two occasions being 42 and 55.

The child had frequent upper respiratory infections during the first 18 months of life, but has had few since then. She also had recurrent urinary tract infections associated with bilateral reflux and a hypotonic bladder.

* Revised Yale Developmental Schedules.

Received 1 October 1969.

* This article is contribution No. 366 from the Florence R. Sabin Research Laboratories of the Department of Biophysics, University of Colorado Medical Center.

These studies were aided by Public Health Service grant FR 69, a grant from the National Foundation-March of Dimes, and a grant from the Genetics Foundation.

† According to the *Chicago Conference*: Standardization in Human Cytogenetics, published by the National Foundation-March of Dimes, 1966.

TABLE I
COMPARISON OF PHYSICAL SIGNS IN CASE 1 AND
CASE 2

	Case 1 (46, XX, 18q -)	Case 2 (46, XY/46, XY, 18r)
Mental retardation	+	+
Short stature	+	-
Microcephaly	-	+
Atretic ear canals	+	-
Prominent anti-helix and/or anti-tragus	+	+
Maxillary hypoplasia	+	±
Hypertelorism	+	+
Epicanthic folds	-	+
Strabismus	+	+
Nystagmus	+	-
Carp mouth	-	+
Congenital heart disease	-	+
Hypotonia	+	+
Excessive whorls (> 6)	+	+

There have been no bladder infections since a bilateral ureteral implantation procedure was performed at 19 months of age.

The patient's father has a hearing loss secondary to a chronic otitis media which resulted in a mastoidectomy. Deafness occurring in several members of the mother's family is distributed in a manner suggesting dominant inheritance and otosclerosis. There is no family history of retardation, collagen diseases, or other neurological disorders. The mother has subsequently had two normal pregnancies and a third miscarriage.

At the time of the most recent evaluation (Table I), height and weight were both below the 3rd percentile; head circumference was at the 3rd percentile. The patient (Fig. 1a) had frontal bossing, thin, sparse hair, and vitiligo over the back, chest, and abdomen. Dimples were present over the elbows and the metacarpals. The eyes appeared sunken; there was a right esotropia, mild

bilateral ptosis, and slight nystagmus. Fundi appeared normal. Her low-set ears each had a prominent anti-helix and stenotic external auditory canals (Fig. 1b). There was conspicuous maxillary hypoplasia and the nose was small. Muscle tone was generally poor.

The following laboratory tests were within normal limits: complete blood count, blood urea nitrogen, creatinine, serum sodium, potassium, chloride, and total carbon dioxide, amino acid, and mucopolysaccharide screening, electrocardiogram, and x-rays of skull and chest, and bone age. Temporal bone tomograms confirmed the presence of hypoplastic auditory canals, but middle and inner ear structures appeared normal. On audiogram she had a conductive loss of 65 decibels. There were 10 digital whorls and no other dermatoglyphic abnormalities.

Blood group determinations were performed on the patient and her parents (Table II) and will be discussed below.

Case 2. A 22-month-old Caucasian boy was first evaluated at 9 months of age because of slow development. He was the product of a 40-week gestation which was essentially uncomplicated. The mother and father, 24 and 26 respectively at the time of his birth, had had two normal girls before this conception. Neither parent had had excessive irradiation. At birth, there was a nuchal cord, the baby was cyanotic, and multiple congenital anomalies (Table I) were noted including a single umbilical artery. At 1 month of age, severe respiratory distress developed, and a subsequent cardiac catheterization showed a mild pulmonary valvular stenosis. There has been no history of excessive infections.

His development has been slow and a Developmental Quotient at 15 months was 43.

A maternal aunt was a hydrocephalic stillborn (Fig. 2,

FIG. 1 a and b. Case 1 (46,XX,18q -) at 2 8/12 years. Note particularly the maxillary hypoplasia.

TABLE II
BLOOD GROUP DETERMINATIONS

Blood Group		Case 1	Father	Mother	Case 2	Father	Mother
C	C	—	—	—	+(Cc)	—	+(CC)
E	c	+(cc)	+(cc)	+(cc)	—	+(cc)	—
	e	—	—	—	—	—	—
MN	M	+(e—)	+(ee)	+(ee)	+(ee)	+(ee)	+(ee)
	n	+(MM)	+(MN)	+(MM)	+(MN)	+(MN)	+(MN)
Ss	S	—	—	—	—	—	—
	s	+(ss)	+(ss)	+(Ss)	—	—	—
Le	Le ^a	—	—	—	+(ss)	+(ss)	+(ss)
	Le ^b	—	—	—	—	—	—
		—	—	—	+(Le ^a Le ^b)	—	+(Le ^a Le ^b)
		—	—	—	—	—	—
D		—	—	—	—	—	—
P		—	—	—	—	—	—
K		—	—	—	—	—	—
Fy ^a		—	—	—	—	—	—
Jk ^a		—	—	—	—	—	—
Haptoglobins		—	—	—	—	—	—
ABO		2-1	2-1	2-1	2-1	1-1	2-2
		A ₂ B	A ₂	A ₁ B	O	O	B

II.7), and a child of the paternal grandfather by a second marriage has Down's syndrome (Fig. 2, II.1). The mother of this latter child was 41 years of age at the time of her birth.

The most recent physical examination showed a height at the 10th percentile and a weight and head circumference below the 3rd percentile. The head was dolichocephalic (Fig. 3a). There was hypertelorism, epicanthic folds, a slight mongoloid slant, and an alternating strabismus. Bilateral small posterior, polar axial cataracts were present, and the fundi were normal. The ears were large and low set, with a prominent anti-helix (Fig. 3b). The nose was upturned, the mouth was carp-shaped, and the palate was high arched. There was a thick roll of skin at the nape of the neck. A grade 2/6 systolic murmur was audible along the left sternal border. The phallus and scrotum were both small, and gonads were palpable in the inguinal canal. Slight clinodactyly of the fourth and fifth fingers and bilateral transverse

palmar creases were noted. Overlapping toes were noted on the puffy feet which were held in calcaneovalgus. The child had marked hypotonia.

The following laboratory studies were within normal limits: complete blood count, blood urea nitrogen, fasting blood sugar, creatinine, protein electrophoresis, ¹³¹I-labelled triiodothyronine uptake, serum sodium, potassium, chloride, total carbon dioxide, pH, and PCO₂, calcium, phosphorus, and alkaline phosphatase, amino acid and mucopolysaccharide screening. Skull films, intravenous pyelogram, bone age, and lumbosacral spine films were also normal. Early chest films showed cardiomegaly which had disappeared at 15 months of age, and an electrocardiogram revealed right ventricular hypertrophy. There were low and borderline low (6 and 16 mg./24 hr.) urinary hydroxyproline values on two occasions. Galactokinase, galactosepimerase, and uridine diphosphogalactose transferase enzymes displayed normal activity in the patient's red blood cells. An

FIG. 2. Pedigree of Case 2.

FIG. 3 a and b. Case 2 (46,XY/46,XY,18r) at 15 months. Note the carp-shaped mouth.

audiogram was normal. Dermatoglyphic analysis revealed 10 digital whorls, a left hypothenar, bilateral thenar, and a right hallucal whorl. Both triradii were distal.

Blood typing was done on the proband and his parents (Table II), and will be discussed below.

Case 3. This is an 18-year-old Caucasian girl who gave birth to a male infant with congenital absence of the abdominal musculature, cryptorchidism, and hydronephrosis. She was seen as part of the evaluation of this child. She had had some problems in school but was not grossly retarded.

Physical examination revealed partial syndactyly of toes two and three, laxity of the joints, and recurrent dislocation of the patellae. The examination was otherwise within normal limits.

Dermatoglyphs were normal, with no whorls.

Case 4. This is the 50-year-old mother of Case 3. She is of normal intelligence, and physical abnormalities were limited to those seen in her daughter.

Blood typing was impossible in this family because of the unavailability of certain family members. This family will be reported in detail elsewhere at a later date.

Cytogenetic Studies

Lymphocyte and fibroblast cultures were performed by a modification of standard techniques (Moorhead *et al.*, 1960; Tjio and Puck, 1958). In addition, a direct bone-marrow preparation was

studied in Case 2 by the method of Tjio and Whang (1962).

At the present time, the differentiation between chromosomes 17 and 18 in our cases is based upon morphology, the 17 being longer and more metacentric. Differentiation is also said to be possible by autoradiography, since chromosome 17 is one of the earliest chromosomes to terminate replication and 18 is relatively late (Giannelli and Howlett, 1967). Our autoradiographic studies to date have not been unequivocal.

Case 1. The proband (Case 1) showed a deletion of the long arm of chromosome 18 (46,XX,18q-) in 100% of the lymphocytes, and fibroblast culture revealed the abnormality in 18 of 19 cells examined (Table III, Fig. 4). Chromosomal analysis of both parents was normal.

Case 2. Karyotyping of lymphocytes, bone-marrow cells, and fibroblasts all revealed mosaicism for a ring 18 (46,XY/46,XY,18r), with only the fibroblast cultures having less than 50% of the cells affected (Table III, Fig. 4).

The father of Case 2 had 4 of 60 cells with an acentric fragment; the significance of this is not known. All other family members were normal, with the exception of the child of the paternal grandfather (Fig. 2, II.1) who had 47,XX,21+ in all cells examined (Table III).

TABLE III
CYTOGENETIC STUDIES

	Tissue	No. of Mitoses Examined	< 45	45	46	47	> 47
Case 1	Blood (25/25 had 18q-)	25	0	1	24	0	0
	Skin (19/20 had 18q-)	20	1	1	18	0	0
	Father Blood	25	0	1	23	1	0
	Mother Blood	20	0	0	15	0	0
	Brother Blood	10	0	0	10	0	0
	Brother Blood	20	0	0	20	0	0
Case 2	Blood (33/60 had 18r)	60	2	6	52	0	0
	Bone-marrow (14/20 had 18r)	20	0	0	20	0	0
	Skin (3/44 had 18r)	44	3	4	37	0	0
	Father Blood (4/60 had acentric fragment)	60	0	0	60	0	0
	Mother Blood	20	0	1	19	0	0
	Sister (III.1) Blood	20	0	0	20	0	0
	Sister (III.2) Blood	20	0	2	18	0	0
	Paternal grandfather (I.2) Blood	20	0	0	19	0	1(49)
	Child of paternal grandfather (II.1) Blood	20	0	0	0	20	0
	(47,XX,21+)						
Case 3	Blood (20/20 had 18q- and metacentric C)	20	0	1	19	0	0
	Skin (20/20 had 18q- and metacentric C)	20	1(40)	1	17	0	1(49)
	Son of Case 3 Blood	30	0	0	29	1	0
	Son of Case 3 Skin	14	1(42)	0	12	0	1(49)
Case 4	Blood (20/20 had 18q- and metacentric C)	20	0	0	20	0	0

Case 3. There was a deletion of the long arm of 18 and a metacentric C in 100% of the lymphocytes (Table III, Fig. 4).

Case 4. Karyotype revealed 18q- and a metacentric C in all of the lymphocytes (Table III).

It is of interest that the child with absent abdominal musculature, the son of Case 3, had a normal karyotype and no metacentric C.

It is recognized that autoradiographic studies may be helpful as evidence for which of the E chromosomes is involved in the deletion. Examination at this time, however, is highly suggestive of chromosome 18. The absence of physical abnormalities in Cases 3 and 4 is unusual, though the possibility of a balanced translocation involving a chromosome in the C group and the long arm of 18 cannot be excluded in these two patients. If true, then the abnormal child of Case 3, who appears to have a normal karyotype, might in fact have a hidden partial trisomy.

Immunoglobulins

Serum immunoglobulins were quantified by the method of radial diffusion described by Mancini, Carbonara, and Heremans (1965). Parotid fluid IgA was measured by the technique of electro-immunodiffusion (Merrill, Hartley, and Claman, 1967). The lower limits of accurate quantification

FIG. 4. Partial karyotypes of the E group from each of the three patients showing abnormalities of chromosome 18.

of serum and parotid fluid IgA by these methods in our laboratory are 10 and 1.5 mg./100 ml., respectively. Lesser concentrations are detectable but cannot be accurately measured.

Case 1. There were no detectable levels of IgA in serum or parotid fluid of the propositus (Table IV). Serum IgM and IgG were normal. Immunoglobulin levels were normal in the parents and the younger sib. Adequate diphtheria and tetanus antibody titres were demonstrated by a passive haemagglutination technique. Schick test was negative indicating a normal functional capacity to neutralize diphtheria toxin. Normal delayed hypersensitivity responses were elicited with monilia, vaccinia, and mumps skin test antigens; intermediate strength Purified Protein Derivative was negative. Lymphocytes responded normally to phytohaemagglutinin stimulation.

Cases 2, 3, and 4. Serum and salivary immunoglobulins were normal in the propositi and all family members tested (Table IV).

TABLE IV

IMMUNOGLOBULIN VALUES (mg./100 ml.)

	Age (yr.)	Serum†			Parotid IgA*
		IgG	IgA	IgM	
Case 1	3½	1000	0	155	0
Father	30	1000	330	140	12.0
Mother	27	1250	250	170	11.0
Brother	2	620	86	74	—
Case 2	1½	520	70	45	3.5
Father	27	770	220	65	6.6
Mother	25	960	265	80	11.0
Sister	6½	570	94	140	6.5
Sister	4½	465	54	26	6.5
Case 3	17	1100	240	36	—
Son	14/12	560	59	34	—
Case 4	50	1020	240	52	—

* Normal values: mean $\pm$ 1 SD: 8.1 ± 4.4 mg./100 ml.

† Allansmith *et al.* (1968), Buckley, Dees, and O'Fallon (1968), Fulginiti *et al.* (1966).

TABLE V

BLOOD GROUP DETERMINATIONS*

		D	C	E	c	e	Probable Genotype
Father	A	O	O	O	+	O	dce/dce
Mother	AB	+	O	+	+	+	DcE/D — — or DcE/Dc —
Pro-							
positus	AB	+	O	O	+	+	D — —/dce or Dc — /dce
Brother	AB	+	O	O	+	+	
Brother	A	+	O	O	+	+	

* Blood grouping kindly performed by Dr. Philip Levine of the Ortho Research Foundation.

Blood Groups

Complete blood typing and haptoglobin studies were carried out in families 1 and 2. This was impossible in Cases 3 and 4 because of the unavailability of certain family members.

The findings are summarized in Table II. It is of interest that there is a discrepancy in the E blood group in the family of Case 1. Blood specimens from all family members were sent to Dr. Philip Levine of the Ortho Research Foundation who kindly performed additional blood grouping. His findings are summarized in Table V. The mother of the propositus carries only a single dose of E and each of the three children, a single dose of e. Dr. Levine has indicated that this is an unusual but probably an independent finding and not related to the chromosomal deletion.

Haptoglobins, the ABO, C, MN, and Lewis blood groups can be excluded from the deleted fragment.

Discussion

In contrast to the X chromosome, little progress has been made in the location of autosomal markers. The possible location of the locus for leucocyte alkaline phosphatase activity upon the 21 chromosome has been discussed by several investigators (Alter *et al.*, 1962; King, Gillis, and Baikie, 1962; Trubowitz, Kirman, and Masek, 1962). Gerald *et al.* (1967) and Bloom, Gerald, and Reisman (1967) have proposed that the location of the haptoglobin locus may be on the D chromosome. The gene for the Duffy blood group has been variably located on chromosomes 16 and 1 by two groups of investigators (Crawford, Punnett, and Carpenter, 1967; Donahue *et al.*, 1968), and the gene for cystic fibrosis has been postulated to be on the short arm of chromosome 5 (Smith *et al.*, 1968). More recent reports (Dallaire and Destin, 1969) have questioned this latter localization. Human-mouse cell hybrids have provided evidence that the gene for thymidine kinase may be located on a chromosome of the E group (Migeon and Miller, 1968).

Recently attention has been focused upon IgA and chromosome 18. Finley *et al.* (1968) reported the absence of serum and salivary IgA in a girl with 18r who had no history of repeated infections. This has been followed by numerous studies of IgA in patients with abnormalities of the 18 chromosome (Borgaonkar *et al.*, 1969; Daentle and Smith, 1968; Feingold *et al.*, 1969; Haddad *et al.*, 1969; Holmes, 1969; Richards and Hobbs, 1968; Thuline and Ruvalcaba, 1968) (Table VI) which reveal a striking variability of levels. This variability is under-

TABLE VI
REPORTED IgA VALUES IN CASES WITH ABNORMALITIES OF
CHROMOSOME 18

Investigator	Chromosomal Abnormality	Immunological A		Infections
		Serum	Saliva	
Feingold <i>et al.</i> (1969)	18r	Absent	—	Increased
Finley <i>et al.</i> (1968)	18r	Absent	Absent	No increase
Holmes (1969)	18r	Normal	—	—
Richards and Hobbs (1968)	18r	Normal	?Normal	Increased
Borgaonkar <i>et al.</i> (1969)	18r	Normal	—	—
Haddad <i>et al.</i> (1969)	18q—	?Normal	—	—
	18q—	Normal	—	—
	18q—	Normal	—	—
Rudd, May, and La Marche (1969)	18q—	Increased	—	—
Daentle and Smith (1968)	18p—	Absent	Absent	No increase
	18p—	Normal	—	—
	18p—	Normal	—	—
	18p—	Normal	—	—
Thuline and Ruvalcaba (1968)	18p—	Absent	—	Some increase
Hecht (1969)	18+	Decreased	—	Increased
Case 1	18q—	Absent	Absent	Some increase
Case 2	18r	Normal	Normal	No increase
Case 3	18q—	Normal	—	No increase
Case 4	18q—	Normal	—	No increase

scored by the reports by Rudd, May, and LaMarche (1969) of a boy with 18q— and persistently raised IgA, and by Hecht (1969) of a child with trisomy 18 and low IgA.

Tomasi (1968) has summarized present knowledge of the nature of the formation and action of serum and salivary IgA. It is the predominant immunoglobulin in saliva, and nasal and tracheo-bronchial secretions (Keimowitz, 1964). Evidence is rapidly accumulating that secretory antibody levels are a better indicator of resistance to certain infections, e.g. viral respiratory, and that such antibodies are of the IgA class (Bellanti, 1968; Smith *et al.*, 1966). Susceptibility to recurrent or chronic infections has been attributed to a deficiency of secretory IgA (Buser, Büttler, and Du Pan, 1968). However, in those patients with chromosome 18 abnormalities, summarized in Table VI, there is no correlation between IgA levels and a history of recurrent respiratory infections. Furthermore, in other patients we have studied there has been no evidence of such a relation.

The exact incidence and clinical significance of IgA deficiency remains uncertain. Though IgA is usually absent from cord blood, it normally appears in low concentrations in the serum and saliva by 2–3 weeks of age, and then slowly rises until the adult range is reached by late childhood or puberty (West, Hong, and Holland, 1962). These levels are characterized by considerable variability and by an absence of a discernible relation between serum and salivary concentrations.

Bachmann (1965) screened the sera of almost 7,000 Swedish adults and found low IgA (3–10% of

normal) in 5 and non-detectable levels in 10. The frequency of absent IgA in this series was 0.14% (1:700). Johansson (1968) has cited frequencies ranging from 0.25% to 0.42%. Other studies have reported the absence of IgA in normal individuals (Rockey *et al.*, 1964) and in persons with a variety of abnormalities but no consistent history of increased susceptibility to infections (Levin *et al.*, 1963; West *et al.*, 1962). Stocker, Ammann, and Rossi (1968) recently reported a family with selective IgA deficiency present in 5 members in two generations with a postulated autosomal dominant mode of inheritance. Absent IgA has also been documented in a variety of disease states, including ataxia telangiectasia (Peterson, Kelly, and Good, 1964), steatorrhoea (Crabbé and Heremans, 1966), lupus erythematosus (Bachmann, Laurell, and Svenonius, 1965), and dysgammaglobulinaemia Type IV of Hobbs (1968).

Lack of knowledge of the precise incidence of isolated IgA deficiency in the general population makes difficult a definitive interpretation of the finding of absent IgA in 6 of 19 patients with a deletion of chromosome 18. However, the frequency of association of the two abnormalities, if substantiated by further studies, far exceeds even the highest of presently available incidence figures for IgA deficiency in the general population at any age beyond the first month of life. Furthermore, 15 patients with abnormalities of other chromosomes, including ring formations and partial deletions, have been investigated and normal values of IgA reported (Daentle and Smith, 1968; Feingold and Schwartz, 1968; Haddad *et al.*, 1969).

It has been proposed that a gene involving IgA may reside on chromosome 18 (Feingold *et al.*, 1968). The absence of IgA in association with both isolated long and short arm deletions makes this explanation less likely, though a minor deletion of the long arm cannot be excluded in the latter cases. Normal levels of IgA in cases with deletions of 18 might be explained either by mosaicism (as in Case 2) or by variation in the amount of chromosomal material lost. On the other hand, one assumes that a patient with a deleted fragment and hemizyosity for homologous loci would have diminished but not absent levels of IgA if normal gene dosage effects were operating. It may be, however, that only one of the pair of alleles is necessary to maintain normal levels of IgA and, if this were true, that the heterozygote would be normal. Such a situation might exist if the gene concerned functioned as a regulator gene. In the hemizygote, therefore, the presence or absence of normal amounts of IgA would depend upon whether the mutant or wild type allele was manifested. This might explain the unpredictability of IgA levels in patients with deletions of chromosome 18.

Alternatively, the entire effect of the deletion may be non-specific. Multiple genes may be important in determining immunoglobulin levels, and the deletion of a portion of chromosome 18, combined with other unknown factors, may lead to a deficiency of IgA. The physical abnormalities seen in chromosome 18 deletions have been described in other chromosomal abnormalities as well as in individuals with normal karyotypes, and are hence relatively non-specific. The absence of IgA may be another non-specific finding, the result of a chromosomal imbalance acting upon other unknown factors.

Summary

Four patients are reported with a deletion of chromosome 18. One of these has absent serum and salivary IgA. Three possibilities for the association of absent IgA and deletions of chromosome 18 are entertained: (1) the loss has a non-specific effect; (2) if a locus important in the production of IgA is present on chromosome 18 and only one of the alleles is necessary to maintain normal levels, IgA might be absent in a heterozygote who had lost the normal allele; (3) the association is coincidental.

Grateful appreciation is expressed to Dr. Eleanor Eller for the developmental evaluations, and David Peakman, A.I.M.L.T., and other members of the technical staff of the Cytogenetics Laboratory.

REFERENCES

- Allansmith, M., McClellan, B. H., Butterworth, M., and Maloney, J. R. (1968). The development of immunoglobulin levels in man. *Journal of Pediatrics*, **72**, 276-290.
- Alter, A. A., Lee, S. L., Pourfar, M., and Dobkin, G. (1962). Leukocyte alkaline phosphatase in mongolism; a possible chromosome marker. *Journal of Clinical Investigation*, **41**, 1341.
- Bachmann, R. (1965). Studies on the serum γ A-globulin level, III. The frequency of A- γ A-globulinemia. *Scandinavian Journal of Clinical and Laboratory Investigation*, **17**, 316-320.
- , Laurell, C. B., and Svenonius, E. (1965). Studies on the serum γ A-globulin level, II. γ A deficiency in a case of systemic lupus erythematosus. *ibid.*, **17**, 46-50.
- Bellanti, J. A. (1968). Role of local gamma-A-immunoglobulins in immunity. *American Journal of Diseases of Children*, **115**, 239-246.
- Bloom, G. E., Gerald, P. S., and Reisman, L. E. (1967). Ring D chromosome: A second case associated with anomalous haptoglobin inheritance. *Science*, **158**, 1746-1748.
- Borgaonkar, D. S., Bias, W. B., Scott, C. I., Wadia, R. S., and Borkowf, S. P. (1969). IgA and abnormal chromosome 18. *Lancet*, **1**, 206-207.
- Buckley, R. H., Dees, S. C., and O'Fallon, W. M. (1968). Serum immunoglobulins: 1. Levels in normal children and in uncomplicated childhood allergy. *Pediatrics*, **41**, 600-611.
- Bühler, E. M., Bühler, U. K., and Stalder, G. R. (1964). Partial monosomy 18 and anomaly of thyroxine synthesis. *Lancet*, **1**, 170-171.
- Buser, F., Büttler, R., and Du Pan, R. M. (1968). Susceptibility to infection and IgA deficiency in the infant. *Journal of Pediatrics*, **72**, 29-33.
- Crabbé, P. A., and Heremans, J. F. (1966). Lack of gamma A-immunoglobulin in serum of patients with steatorrhea. *Gut*, **7**, 119-127.
- Crawford, M. N., Punnett, H. H., and Carpenter, G. G. (1967). Deletion of the long arm of chromosome 16 and an unexpected Duffy blood group phenotype reveal a possible autosomal linkage. *Nature (London)*, **215**, 1075-1076.
- Daentle, D., and Smith, D. (1968). Personal communication to Stewart, J. M., Go, S., Ellis, E., and Robinson, A. *Lancet*, **2**, 779.
- Dallaire, L., and Destiné, M. L. (1969). Localisation of the cystic-fibrosis gene. *ibid.*, **1**, 419-420.
- Day, E. J., Marshall, R., MacDonald, P. A. C., and Davidson, W. M. (1967). Deleted chromosome 18 with paternal mosaicism. *ibid.*, **2**, 1307.
- Donahue, R. P., Bias, W. B., Renwick, J. H., and McKusick, V. A. (1968). Probable assignment of the Duffy blood group locus to chromosome 1 in man. *Proceedings of the National Academy of Sciences of the United States of America*, **61**, 949-955.
- Feingold, M., and Schwartz, R. S. (1968). IgA and partial deletions of chromosome 18. *Lancet*, **2**, 1086.
- , —, Atkins, L., Anderson, R., Bartsocas, C. S., Page, D. L., and Littlefield, J. W. (1968). IgA deficiency associated with partial deletion of chromosome 18. *Journal of Clinical Investigation*, **47**, 34a.
- , —, —, —, —, —, and — (1969). IgA deficiency associated with partial deletion of chromosome 18. *American Journal of Diseases of Children*, **117**, 129-136.
- Finley, S. C., Finley, W. H., Noto, T. A., Uchida, I. A., and Roddam, R. F. (1968). IgA absence associated with a ring-18 chromosome. *Lancet*, **1**, 1095-1096.
- Fulginiti, V. A., Sieber, O. F., Claman, H. N., and Merrill, D. (1966). Serum immunoglobulin measurement during the first year of life and in immunoglobulin-deficiency states. *Journal of Pediatrics*, **68**, 723-730.
- Genest, P., Leclerc, R., and Auger, C. (1963). Ring chromosome and partial translocation in the same cell. *Lancet*, **1**, 1426-1427.
- Gerald, P. S., Warner, S., Singer, J. D., Corcoran, P. A., and Umansky, I. (1967). A ring D chromosome and anomalous inheritance of haptoglobin type. *Journal of Pediatrics*, **70**, 172-179.
- Giannelli, F., and Howlett, R. M. (1967). The identification of the chromosomes of the E group (16-18 Denver): An autoradiographic and measurement study. *Cytogenetics*, **6**, 420-435.
- Gorlin, R. J., Yunis, J., and Anderson, V. E. (1968). Short arm deletion of chromosome 18 in cebocephaly. *American Journal of Diseases of Children*, **115**, 473-476.
- Gripenberg, U. (1967). The cytological behaviour of a human ring-chromosome. *Chromosoma*, **20**, 284-289.

- Gropp, A., Jussen, A., and Ofteringer, K. (1964). Multiple congenital anomalies associated with a partially ring-shaped chromosome probably derived from chromosome No. 18 in man. *Nature (London)*, **202**, 829-830.
- Grouchy, J. de (1965). Chromosome 18: A topologic approach. *Journal of Pediatrics*, **66**, 414-431.
- Haddad, Z. H., Allen, R. F., Towner, J. W., and Wilson, M. G. (1969). IgA, IgM, and partial deletion of chromosome 18. *Lancet*, **1**, 678.
- Hecht, F. (1969). IgA and partial deletions of chromosome 18. *ibid.*, **1**, 100-101.
- Hobbs, J. R. (1968). Immune imbalance in dysgammaglobulinaemia type IV. *ibid.*, **1**, 110-114.
- Holmes, L. (1969). Personal communication to Feingold, M. *American Journal of Diseases of Children*, **117**, 129.
- Innsley, J. (1967). Syndrome associated with a deficiency of part of the long arm of chromosome No. 18. *Archives of Disease in Childhood*, **42**, 140-146.
- Jeune, M., Lamit, J., Michel, M., Fournier, P., Laurent, C., and Nivelon, A. (1967). Un cas de chromosome 18 en anneau. *Pediatric*, **22**, 845-846.
- Johansson, S. G. O. (1968). Unpublished data cited by Hanson, L. A., 'Aspects of the absence of the IgA system' in Immunologic Deficiency Diseases in Man. Birth Defects: Original Article Series, Vol. IV, No. 1.
- Kasahara, S., and Reisman, L. E. (1967). Short arm deletion of chromosome 18. *Tohoku Journal of Experimental Medicine*, **93**, 291-300.
- Keimowitz, R. I. (1964). Immunoglobulins in normal human tracheobronchial washings. A qualitative and quantitative study. *Journal of Laboratory and Clinical Medicine*, **63**, 54-59.
- King, M. J., Gillis, E. M., and Baikie, A. G. (1962). The polymorph alkaline phosphatase in mongolism. *Lancet*, **2**, 661.
- Law, E. M., and Masterson, J. G. (1966). Partial deletion of chromosome 18. *Lancet*, **2**, 1137.
- LeJeune, J., Turpin, R., and Gautier, M. (1959). Le mongolisme, premier exemple d'aberration autosomique humaine. *Annales de Génétique*, **1**, 41-49.
- Levin, W. C., Ritzmann, S. E., Haggard, M. E., Gregory, R. F., and Reinarz, J. A. (1963). Selective α -beta-2A globulinemia. *Clinical Research*, **11**, 294.
- Lucas, M., Kemp, N. H., Ellis, J. R., and Marshall, R. (1963). A small autosomal ring chromosome in a female infant with congenital malformations. *Annals of Human Genetics*, **27**, 189-195.
- McDermott, A., Innsley, J., Barton, M. E., Rowe, P., Edwards, J. H., and Cameron, A. H. (1968). Arrhinencephaly associated with a deficiency involving chromosome 18. *Journal of Medical Genetics*, **5**, 60-67.
- Mancini, G., Carbonara, A. O., and Heremans, J. F. (1965). Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry*, **2**, 235-254.
- Merrill, D., Hartley, T. F., and Claman, H. N. (1967). Electriomuno diffusion (EID): A simple, rapid method for quantitation of immunoglobulins in dilute biological fluids. *Journal of Laboratory and Clinical Medicine*, **69**, 151-159.
- Migeon, B. R. (1966). Short arm deletions in group E and chromosomal 'deletion' syndromes. *Journal of Pediatrics*, **69**, 432-438.
- , and Miller, C. S. (1968). Human-mouse somatic cell hybrids with single human chromosome (group E): Link with thymidine kinase activity. *Science*, **162**, 1005-1006.
- Mikelsaar, A. V. N., Talvik, T. A., and Sitska, M. E. (1967). A ring-shaped chromosome (presumably No. 18) and its bearing on multiple congenital anomalies in man. *Genetika*, **5**, 63-66.
- Moorhead, P. S., Nowell, P. C., Mellman, W. J., Battips, D. M., and Hungerford, D. A. (1960). Chromosome preparations of leukocytes cultured from human peripheral blood. *Experimental Cell Research*, **20**, 613-616.
- Nance, W. E., Higdon, S. H., Chown, B., and Engel, E. (1968). Partial E-18 long-arm deletion. *Lancet*, **1**, 303.
- Nitowsky, H. M., Sindhvananda, N., Konigsberg, U. R., and Weinberg, T. (1966). Partial 18 monosomy in the cyclops malformation. *Pediatrics*, **37**, 260-269.
- Palmer, C. G., Fareed, N., and Merritt, A. D. (1967). Ring chromosome 18 in a patient with multiple anomalies. *Journal of Medical Genetics*, **4**, 117-123.
- Peterson, R. D. A., Kelly, W. D., and Good, R. A. (1964). Ataxia-telangiectasia. Its association with a defective thymus, immunological-deficiency disease, and malignancy. *Lancet*, **1**, 1189-1193.
- Reinwein, H., Ritter, H., and Wolf, U. (1967). Deletion of short arm of a chromosome 18 (46,XX,18p-). *Humangenetik*, **5**, 72-73.
- Richards, B. W., and Hobbs, J. R. (1968). IgA and ring-18 chromosome. *Lancet*, **1**, 1426-1427.
- Rockey, J. H., Hanson, L. A., Heremans, J. F., and Kunkel, H. G. (1964). Beta-2A aglobulinemia in two healthy men. *Journal of Laboratory and Clinical Medicine*, **63**, 205-212.
- Rudd, N. L., May, J. B., and LaMarche, P. H. (1969). IgA and partial deletions of chromosome 18. *Lancet*, **1**, 100.
- Smith, C. B., Purcell, R. H., Bellanti, J. A., and Chanock, R. M. (1966). Protective effect of antibody to parainfluenza type 1 virus. *New England Journal of Medicine*, **275**, 1145-1152.
- Smith, D. W., Docter, J. M., Ferrier, P. E., Frias, J. L., and Spock, A. (1968). Possible localisation of the gene for cystic fibrosis of the pancreas to the short arm of chromosome 5. *Lancet*, **2**, 309-312.
- Stocker, F., Ammann, P., and Rossi, E. (1968). Selective γ -A-globulin deficiency, with dominant autosomal inheritance in a Swiss family. *Archives of Disease in Childhood*, **43**, 585-588.
- Summitt, R. L. (1964). Deletion of the short arm of chromosome 18. *Cytogenetics*, **3**, 201-206.
- Thuline, H. C., and Ruvalcaba, R. H. A. (1968). Deletion of the short arm of a pair-18 chromosomes associated with serum IgA deficiency. Presented at Western Society for Pediatric Research, 25th-26th November, Denver, Colorado.
- Tjio, J. H., and Puck, T. T. (1958). Genetics of somatic mammalian cells. II. Chromosomal constitution of cells in tissue culture. *Journal of Experimental Medicine*, **108**, 259-268.
- , and Whang, J. (1962). Chromosome preparations of bone marrow cells without prior *in vitro* culture or *in vivo* colchicine administration. *Stain Technology*, **37**, 17-20.
- Tomasi, T. B. (1968). Human immunoglobulin A. *New England Journal of Medicine*, **279**, 1327-1330.
- Trubowitz, S., Kirman, D., and Masek, B. (1962). The leucocyte alkaline phosphatase in mongolism. *Lancet*, **2**, 486-487.
- Uchida, I. A., McRae, K. N., Wang, H. C., and Ray, M. (1965). Familial short arm deficiency of chromosome 18 concomitant with arhinencephaly and alopecia congenita. *American Journal of Human Genetics*, **17**, 410-419.
- Van Dyke, H. E., Valdmann, A., and Mann, J. D. (1964). Probable deletion of the short arm of chromosome 18. *ibid.*, **16**, 364-374.
- Wang, H. C., Melnyk, J., McDonald, L. T., Uchida, I. A., Carr, D. H., and Goldberg, B. (1962). Ring chromosomes in human beings. *Nature (London)*, **195**, 733-734.
- Wertelecki, W., Schindler, A. M., and Gerald, P. S. (1966). Partial deletion of chromosome 18. *Lancet*, **2**, 641.
- West, C. D., Hong, R., and Holland, N. H. (1962). Immunoglobulin levels from the newborn period to adulthood and in immunoglobulin deficiency states. *Journal of Clinical Investigation*, **41**, 2054-2064.
- Wolf, U., Reinwein, H., Gorman, L. Z., and Künzer, W. (1967). Deletion on long arm of a chromosome 18 (46,XX,18q-). *Humangenetik*, **5**, 70-71.