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Genetic and Clinical Studies in 13 Patients with the Wolf-Hirschhorn Syndrome [del(4p)]

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Summary. Clinical and cytogenetic studies are reported on 13 patients with Wolf-Hirschhorn syndrome. The oldest of the living twelve probands is 24 years of age. Three of these patients had a translocation involving the short arm of chromosome 4, and in one of these the anomalous chromosome was inherited from the father. Another three patients were believed, on the basis of GTG-staining, to have a translocation although the origin of the translocated chromatin could not be identified. In the remaining seven patients the anomalous chromosome appeared to be a simple deletion, although in two cases a translocation could not be ruled out. Cytogenetic studies in these patients suggest that the critical deletion involved in Wolf-Hirschhorn syndrome is within 4p16.

In 1965 Wolf et al. and Hirschhorn et al. described the syndrome of delayed growth and development and congenital anomalies associated with partial deletion of the short arm of chromosome 4. At the present time the literature includes about 60 documented cases of Wolf-Hirschhorn syndrome, which is now accepted as a clinically recognizable entity.

When Giemsa-banding studies became available, attempts were made to localize the deletion involved in Wolf-Hirschhorn syndrome. Generally the deleted segment has been reported to involve bands 4p15 or 4p16, although to date there have not been sufficiently detailed cytogenetic studies to be sure about the critical deletion.

The purpose of this paper is to present clinical and cytogenetic findings from 13 patients with Wolf-Hirschhorn syndrome, and to localize the deleted segment in chromosome 4 typically associated with it.

Ten of these patients are described for the first time. Three were reported previously; two of these (SMA and GW) were described initially as having a new syndrome (Coffin 1968), and were later found to have del(4p) (Coffin and Wilson 1971). Patient DW showed an unusual abnormality of chromosome 4, most likely representing an unbalanced translocation in which translocated chromatin obscured the deletion of the short arm (Wilson et al. 1970). Banding cytogenetic studies from these 13 patients are reported in this paper for the first time.

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Clinical Data

These patients are eight females and five males, ranging in age from newly born to 24 years, eleven Caucasian and two Oriental. Family and birth data are listed in Table 1. All infants had remarkably low birth weights for their gestational ages. Four infants were premature (G.A. < 37 weeks) by reported dates, and five were post-term (G.A. 42 or more weeks). The mean birth weight of all 13 infants was 1,872 g; the mean birth weight of the nine infants who were term or post-term was 2,062 g.

The mean maternal age was 27 years, and the mean paternal age was 31 years. These ages are similar to the average parental ages in the general population. The mothers of the probands reported various abnormalities during pregnancy, particularly inadequate weight gain or actual weight loss. Prior obstetrical history was not remarkable. A balanced translocation was segregating in the family of EC (Fig. 1). In that family four paternal relatives who had died in infancy showed multiple congenital anomalies, including craniofacial defects. The family histories of other probands were not remarkable.

All the patients in this report were first identified in infancy or early childhood. Seven of the patients were ascertained in a state hospital for the mentally retarded. One patient (ME) died in the neonatal period. The others are still surviving, and the oldest, a male, is now 24 years of age. All the surviving patients have developed convulsions, which have often been difficult to control. The onset of convulsions varied from shortly after birth to 2 years of age. All these patients have severe or profound mental retardation.

The patients showed a characteristic craniofacial appearance consisting of microcephaly, prominent glabella, highly arched eyebrows, hypertelorism, slanted palpebral fissures—usually slanting downwards, strabismus, iris defects (coloboma or ectopic pupil), a broad malformed nose, large and simple low-set ears, a carp-shaped mouth with downturned corners, often a cleft lip or cleft palate, and micrognathia (Fig. 2). Hemangioma, scalp defects, preauricular skin tags or pits, and skin dimpling elsewhere on the body (including deep sacral dimples), and hypoplastic or inverted nipples were often seen. Congenital lesions of the heart (with various anomalies) were found in fewer than half of the patients. Most of the males had anomalous genitalia, primarily cryptorchidism and hypospadias. The one patient (ME) examined at autopsy showed a number of internal genital abnormalities, although generally the external genitalia in the

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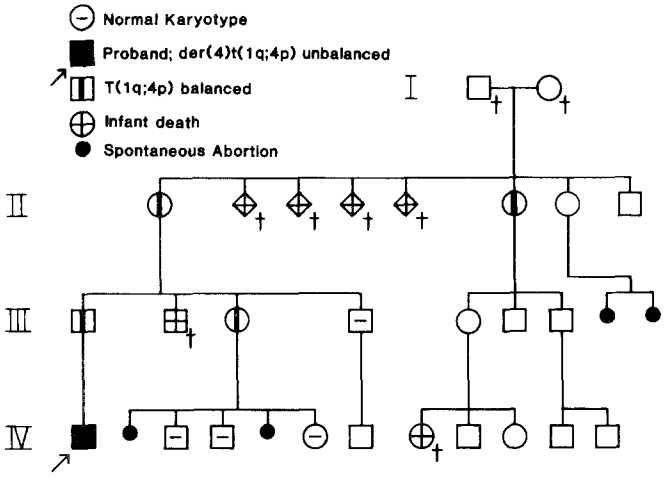
Table 1. Family and birth history of 13 persons with Wolf-Hirschhorn syndrome

	BP	*RE*	*ML*	*KK*	*SMA*	*SS*	*PR*	*EE*	*GW*	*MH*	*ME*	*DW*	*EC*
Birth weight (g)	1,050	2,350	1,820	1,970	1,700	1,000	1,670	2,100	1,670	2,300	1,900	2,060	2,750
Gestation (weeks)	32	43	38	40	46	38	41	43	30	40	42	36	43
Maternal age	21	18	31	27	26	Unknown	16	29	27	34	22	39	30
Paternal age	32	20	28	31	32	Unknown	20	36	36	34	26	41	33
Birth order	2	1	1	3	2	Unknown	1	3	2	2	4	1	4
Abnormal pregnancy history (with the proband)	Placenta praevia	None	Threatened Ab	Asthma; Flu syndrome, 1st trimester; Breech presentation	Anorectics; Exposure to paint and insecticide; Face presentation	Meconium in amniotic fluid	Pyelonephritis	Threatened Ab	Excess vomiting; Anorectics	Hyperemesis gravidarum	None	Oral contraceptive in first 2 months	Breech presentation
Maternal wt change in this pregnancy	2 kg gain			11 kg gain	6.3 kg gain		2 kg loss	6.5 kg gain					
Previous abnormal pregnancy history of mother	None	None	1st pregnancy	None	None	Unknown	1st pregnancy	Spon. Ab (1)	None	Caesarean section (uterine inertia); Hyperemesis gravidarum	None	Spont. Ab (2)	None
Family history of retardation or congenital defects	Negative	Negative	Down's syndrome in paternal uncle	Ureteral obstruction by renal artery in father	Negative	Unknown	Mental retardation in paternal 2nd cousin	Negative	Mental retardation in maternal cousin	Negative	Negative	Negative	See family pedigree (Fig. 1)



females were normal. A variety of skeletal anomalies was found in the majority of the cases, primarily clinodactyly, equinovarus deformities of the feet, malformed toes, scoliosis, and kyphosis. Roentgen examination showed small, delicate bone structure and severely retarded bone age. Delayed closure of the anterior fontanel was sometimes noted. Detailed clinical findings are summarized in Table 2.

Fig. 1. Family pedigree of EC. Carriers for the balanced translocation (1q;4p) are the father of the proband, the paternal aunt, paternal grandmother, and paternal great aunt. One person in generation I is presumed to be a carrier. In generation II, the 4 children who died in infancy were said to have abnormal facial features

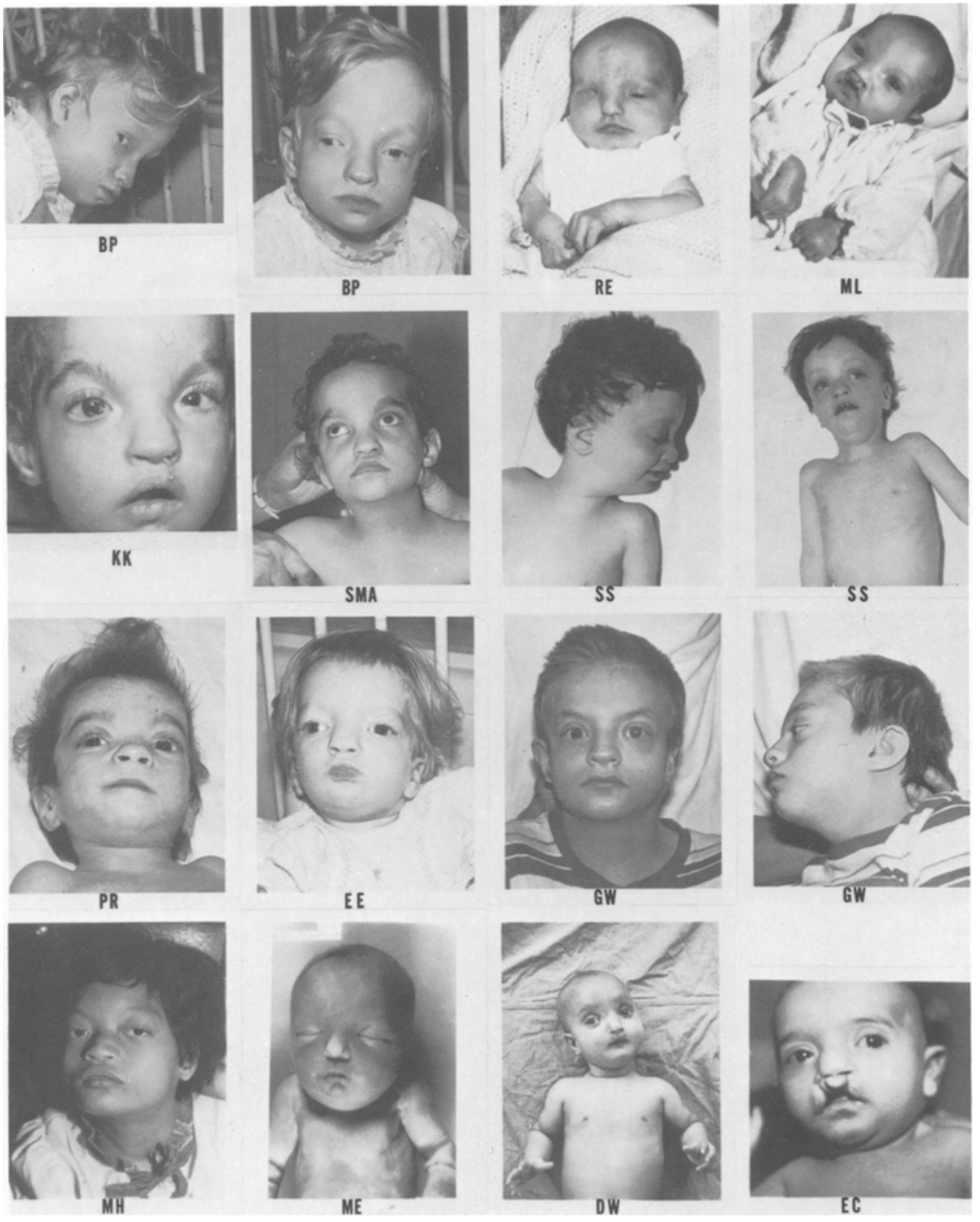


Fig. 2. Photographs of the 13 patients, illustrating features of the Wolf-Hirschhorn syndrome

Table 2. Clinical findings in 13 persons with Wolf-Hirschhorn syndrome

	BP	RE	ML	KK	SMA	SS	PR	EE	GW	MH	ME	DW	EC	Total
Present age (years)	17	8	2	12	17	5	14	14	24	13	Died at 3 days	14	2	
Sex	F	M	M	F	F	F	F	F	M	F	F	M	M	8F 5M
Ethnicity	Cauc.	Cauc.	Oriental	Cauc.	Cauc.	Cauc.	Cauc.	Cauc.	Cauc.	Oriental	Cauc.	Cauc.	Cauc.	11 Cauc./ 2 Oriental
Growth retardation, post-natal	+	+	+	+	+	+	+	+	+	+	Unknown	+	+	12/12
Mental retardation	+	+	+	+	+	+	+	+	+	+	Unknown	+	+	12/12
(I.Q. or D.Q.)	10	< 8	10–20	28	28	5	5	6	< 20	4	Unknown	< 20	25	
Microcephaly	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Prominent glabella	+	+	+	+	+	+	+	+	+	–	+	+	+	12/13
Craniofacial asymmetry	+	+	+	+	+	+	+	+	+	–	–	+	+	11/13
Hemangiomas	+	+	–	+	+	+	+	+	–	+	–	+	–	9/13
Hypertelorism	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Highly-arched eyebrows, sparse medially	+	+	+	+	+	+	+	+	+	+	Very sparse, not high	+	–	11/13
Slanted palpebral fissures	+ (up)	+ (down)	–	+ (down)	–	–	–	+ (down)	–	+ (up)	+ (down)	+ (down)	+ (down)	8/13
Strabismus	+	+	+	+	+	+	–	+	+	–	Unknown	+	+	10/12
Ptosis	+	+	–	–	–	–	–	–	–	–	–	+	–	3/13
Epicanthal folds	+	+	+	–	+	+	–	+	–	+	+	–	–	8/13
Microphthalmia	–	+	–	–	–	–	–	–	–	–	–	–	+ (micro-cornea)	2/13
Iris defect	+ (hetero-chromia) (ectopic pupil)	+	–	+ (colo-boma)	–	–	–	+ (colo-boma)	+ (speck-led)	–	–	+ (speck-led)	+ (ectopic pupil)	7/13
Cataract	–	+	–	+	–	–	–	–	+	–	–	–	–	3/13
Simple ears (lobeless)	+	+	+	+	+	+	+	+	+	+	+	+	–	12/13
Preauricular pits or skin tag	+	+	+	+	+	–	+	+	+	+	–	+	+	11/13
Narrow ear canals	+	–	+	+	–	–		–	+	+	–	+	–	6/13
Broad, malformed nose	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Carp mouth or down-turned corners	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13

Cleft lip	–	–	+	–	–	–	–	–	–	–	–	+	+	3/13
Cleft palate	–	–	+	–	+	–	–	–	– (bifid uvula)	–	–	+	–	3/13
Other palate deformity	–	+ (high)	–	+ (high)	+	–	–	+	–	–	–	–	–	4/13
Micrognathia	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Hypoplastic nipples	+							+			+	+	+	5/13
Heart defect	+ (pul. stenosis)	+ (systolic murmur)	–	–	+ (tetralogy of Fallot)	–	–	–	–		+ (PDA, patent f. ovale, abn origin of inom. art., hypoplastic lt iliac art., single umb. art.)	–	–	4/13
Cryptorchidism	F	+ (bilat)	– (gonads in labial scrotal folds)	F	F	F	F	F	+ (1°)	F	F	–	–	2/5
Hypospadias	F	+ (2°)	+ (3°)	F	F	F	F	F	+ (2°)	F	F	+ (1°)	–	4/5
Scoliosis (post-natal)	+ (and kyphosis)	–	–	–	–	–	–	–	+	+	–	–	–	3/13
Sacral dimple	+	+	+	+	+	+	+	+	+	+ (2)	+	+	+	13/13
Other dimples	+ (elbows)	–	–	–	+ (subacromial, elbows)	+ (subacromial)	+ (subacromial, elbows)	+ (elbows)	–	–	–	+ (subacromial, elbows, knuckles)	–	6/13
Flexion deformity of fingers	+	+	+	+	–	–	+	–	+	+	+	+	+	10/13
Contractures of feet (Equinovarus, Pes Cavus)	+	+	–	–	+	–	+	+	+	–	+	–	–	7/13
Malformed toes	+	–	–	–	–	–	–	+	+	+	–	+	+	6/13
Hypertonic deep tendon reflexes	–	+	+	–	+	+	+	+	+	–	–	+	–	8/13
Convulsions	+	+	+	+	+	+	+	+	+	+	–	+	+	12/13
Hypotonia in infancy	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Other			Incomplete masculinization of genitalia			Hypoplastic umbilicus. Ulnar deviation of hands					Abnormal labia minora. Autopsy: Hypoplastic corpus callosum, absent lt ovary, renal cystic disease			

Table 3. Dermatoglyphics

Patient	Sex	TFRC	Fingers										Axial triradius (%)		atd angle		a-b count	
			L5	L4	L3	L2	L1	R1	R2	R3	R4	R5	R	L	R	L	R	L
BP	F	128	U	U	A	U	U	U	A	U	U	U	15	45	42°	70°	37	41
RE	M	?	?	A	A	?	?U	?	A	U	U	U						
ML	M	144	U	W^{dl}	U	W^{dl}	U	W^{dl}	W^{dl}	U	W^{dl}	U	27	19	59°	52°	37	37
KK	F	123	U	U	A	R	R	W^{s}	U	A	U	U	16	13	47°	43°	43	41
SMA	F	176	U	U	W^{dl}	R	W^{dl}	W^{dl}	R	W^{dl}	W^{dl}	U	22	25	56°	54°	40	36
SS	F	164	U	W^{dl}	W^{dl}	W^{dl}	W^{dl}	W^{dl}	W	W^{dl}	W^{dl}	U	39	47	73°	103°	38	53
PR	F	41	U	A	A	A	W^{dl}	W^{dl}	A	A	U	U	28	30	65°	63°	40	41
EE	F	151	U	W^{dl}	U	W^{dl}	U	U	R	U	W^{cp}	U	23	25	55°	71°	40	49
GW	M	188	U	U	U	W^{cp}	W^{dl}	W	R	U	W	U	12	13	49°	52°	49	60
MH	F	170	U	W	U	W	W	W	W	U	U	U	8	14	36°	47°	38	38
DW	M	82	U	U	U	A	W^{dl}	W	A	U	U	U	18	18	52°	53°	35	41
EC	M	107	U	W^{dl}	U	U	U	W	A	U	W	U	19	18	50°	50°	41	42

Dermatoglyphics

Dermatoglyphics of 12 patients were analyzed (Table 3). Digital arches were slightly increased although the mean total finger ridge count (TFRC) was only slightly low for the males (130, excluding patient RE who had incomplete data), and very slightly above average for the females (136). This latter finding is contrary to the findings of other published cases which show a low TFRC. Nine patients showed at least one axial triradius displaced distally.

Of the 24 palms of the 12 patients, six showed a Sydney crease, seven showed bridged transverse creases (described by Alter 1970 as a thenar slanting connection), and only two showed simian creases. Published reports emphasize the presence of simian creases in Wolf-Hirschhorn syndrome.

The most marked feature in patients with Wolf-Hirschhorn syndrome is ridge dissociation, seen in ten of twelve patients reported here. Ridge dissociation is sometimes so extreme that a complete analysis is impossible, as in patient RE.

Genetic Studies

Giemsa-banding (GTG) was done using a modification of the method described by Seabright (1971, 1972). The banding patterns were examined to localize the breakpoints in the abnormal chromosome 4.

Quinacrine fluorescence studies with the use of quinacrine dihydrochloride, modified from the method described by Caspersson and associates (1971), verified that the anomalous chromosome was 4, but were not informative regarding the position of the breakpoints.

Chromosome analyses from eleven patients (BP, RE, ML, KK, SMA, SS, PR, EE, GW, MH, EC) showed a shortened 4p (Figs. 3 and 4). The other two patients (ME, DW) showed an elongated 4p presumably due to translocated chromatin. The proximal breakpoint in the short arm of chromosome 4 occurred usually within p14, possibly in p15 in two patients, and once in p16.

In SS and PR the determination of the proximal breakpoint could not be made with certainty. Two interpretations are as follows: either an interstitial deletion of a segment 4p15.2 to p16, or a deletion of p14 to the termination. In the latter instance the GTG stain of the termination of the short arm of the anomalous chromosome resembled the short arm of the anomalous chromosome in the known translocation der(4) of EC. On the basis of this morphological evidence, a translocation of nonidentified chromatin to the short arm of 4 could not be ruled out. The distal end of the short arm of the anomalous chromosome 4 in EE, GW, and MH was more intensely stained than is typical for the p16 region of normal 4, suggesting a translocation rather than a simple deletion. The anomalous 4 in EE, GW, and MH was strikingly similar to the der(4) of the carrier paternal aunt of EC (Fig. 3).

A translocation was thought to be present in the anomalous chromosome in three patients (ME, DW, EC). The origin of the chromatin translocated to 4p could not be identified in ME or DW. In ME the breakpoint in the short arm of 4 was at p16, thus indicating that the deletion responsible for the Wolf-Hirschhorn syndrome is within the segment of 4p16 to the termination. The parents of ME were unavailable for study, so in this instance it was not known whether the presumed translocation was sporadic or inherited. More complex rearrangements possible in this instance of ME include a segmental duplication of a portion of 4p, i.e., a mirror duplication of the segment 4p12→p16,—an interpretation consistent with the cytogenetics. In this regard, the appearance of the patient did not resemble the reported phenotype for partial trisomy of 4p (Wilson et al. 1970; Rethoré et al. 1974). Karyotypes from parents of DW were normal, thus the translocation was *de novo.*

Patient EC had inherited a deleted chromosome 4 from his carrier father, who had a reciprocal translocation between the long arm of 1 and the short arm of 4. Presumably the proband was partially trisomic for the distal portion of the long arm of 1 (from q42 to the termination) as well as monosomic for 4p14 to the end of the short arm of 4. The phenotype was consistent with Wolf-Hirschhorn syndrome. The family pedigree of proband EC is illustrated in Fig. 1.

Except for the chromosome anomalies stated above, the karyotypes from these 13 probands were normal and conformed to the phenotypic sex. Results from chromosome analyses are summarized in Table 4.

Palmar formula		Palmar creases		Ridge dissociation
Right	Left	R	L	
11.7.7.3-t'-A^u.0.0.0.L/0	11.7.7.5'-t',t''-,L^u.0.0.0.L/0	Sydney	Bridged	–
		Simian	Simian	+
9.7.5'.1-t'-A^u/A^c.0.0.0.L	11.X.7.1-t'-A^u.0.0.0.0	Sydney	Normal	+
11.0.7.3-t'-A^u.0.0.0.0	9.7.5''.3-t-A^u.0.0.0.L	Normal	Normal	+
9.7.5''.3-t'-A^u.V.0.0.L/0	8.6.5'.1-t'-A^u/A^c.V.0.0.L	Normal	Bridged	+
11.11.9.3-t'-L^u.0.0.W.0	11.9.7.1-t,t''-L^u.0.0.L.0	Normal	Normal	+
11.9.7.5'-t'-A^u/A^c.0.0.L.L^c	11.10.8.5'-t'A^u/A^c.0.0.L.0	Bridged	Bridged	+
11.9.7.1-t'-A^u/A^c.L^c/L^r.0.L.0	11.9.7.1-t'-A^c.0.0.0/L.0	Normal	Normal	+
11/10.X.6.1-t-A^u.0.0.0.0	7.5''.3.1-t-A^u.0.0.0.L	Normal	Bridged	+
11.7.7.3-t-A^u.0.0.0.L	9/9.0.5''.1-t-A^u.0.0.0.D	Sydney	Sydney	+
9.7.5''.3-t'-A^u.0.0.0.L	7.5''.5''.3-t'-A^u.0.0.0.L	Sydney	Sydney	–
7.5'.5'.3-t'-0.0.0.0.L	7.5'.5'.1-t'-?.?V.0.0.L	Bridged	Bridged	+

Chromosome Measurements

In the 11 patients with shortened 4p, the short arm was about 58–89% of the length of the short arm of the normal chromosome 4 (Table 5). In patient EE, the shortened arm (estimated as 89% of its normal length) was detected in only about one-half of the cells examined. As a check on the accuracy of the visual identification in this instance, selection of the shortened chromosome was made from a karyotype employing only standard stains, and was always found to be 4 as identified by tritiated thymidine labeling; in no instance was 5 selected. This finding supported the validity of visual selection of a short arm 4 of about 89% of its normal length.

The centromeric index (C.I.), representing the ratio of the short arm to the total length of the chromosome, was determined for the anomalous chromosome in the eleven patients with shortened 4p. The C.I. for the shortened chromosome 4 ranged from 0.18 to 0.26, as compared to a range of 0.27 to 0.29 for the normal 4 (Table 6).

Gene Marker Studies

A battery of tests of blood cell types, serum types, and blood cell enzyme activity was done from patients BP, KK, SMA, PR, EE, GW, and DW. No evidence for gene deletion was found from the informative child-parent combinations. Heterozygosity in the proband was demonstrated for the following: red blood cell antigens of Rhesus, MNSs, Kidd, and Duffy; red blood cell acid phosphatase; and Gc and Gm serum types. Consequently, those genetic loci are presumed not to be within the deleted segment.

Discussion

In 1976 Johnson et al. found 42 cases of Wolf-Hirschhorn syndrome in the literature and reported an additional case. The authors noted that all cases were *de novo* occurrences. Since 1975 there have been at least 15 new cases in the literature (Bernstein et al. 1978; Chavin-Colin et al. 1977; del Mazo et al. 1978; Fraisse et al. 1977; Fryns et al. 1979; Hedner et al. 1977; Lambert et al. 1979; Levy et al. 1976; Mortimer et al. 1978; Neu et al. 1975; Nielsen et al. 1977; Perez-Castillo and Abrisqueta 1977; Stoll et al. 1981; Taillemite et al. 1977; Zizka et al. 1975). At this time the clinical findings are well delineated, although more data are needed regarding internal anomalies and findings at autopsy.

In a recent review of the cytogenetics of Wolf-Hirschhorn syndrome, Lurie et al. (1980) found that 14 patients, of approximately 100 cases of the syndrome (accumulated through personal communication as well as literature reports) had rings, translocations, mosaicism, or other unusual cytogenetic findings. When deletions occurred, most cases showed a deletion of about one-half of the short arm. Other chromosome anomalies or variants in proband or parent have occasionally been reported, such as translocation(13q14q) (Lambert et al. 1979; Fryns et al. 1979).

In instances of Wolf-Hirschhorn syndrome due to an inherited translocation, Lurie et al. (1980) found that the mother was the carrier in about half of the cases, and the father in the other half. The authors suggested that about 13% of all instances of Wolf-Hirschhorn syndrome are due to translocations, corresponding to an estimated 15% translocations in other deletion syndromes.

Other chromosomes involved in inherited translocations with chromosome 4, resulting in Wolf-Hirschhorn syndrome, include the following: long arm 1 (Patyutko et al. 1978; Stoll et al. 1981); long arm 2 (Ohdo et al. 1976); short arm 9 (Aurias et al. 1978); short arm 10 (Rolland et al. 1977); long arm 10 (Hedner et al. 1977); short arm 12 (Mortimer et al. 1978; Johnson et al. 1978; Carlin and Norman 1978); long arm 12 (Levy et al. 1976); short arm or long arm 19 (Neu et al. 1975); short arm 20 (Lejeune et al. 1975); short arm 22 (Lurie et al. 1980); arm unspecified of 22 (Schwanitz and Grosse 1973); arm unspecified of G (François et al. 1975).

Reports of del(4p) associated with Wolf-Hirschhorn syndrome in which the investigators specified the breakpoints are as follows. Levy et al. (1976) reported monozygotic twins, both affected by the syndrome, who inherited del(4p)mat. Their mother had a translocation between the short arm of 4 and the long arm of 12. She had mild retardation but no somatic abnormalities. The deletion of the short arm was described as juxtacentromeric.

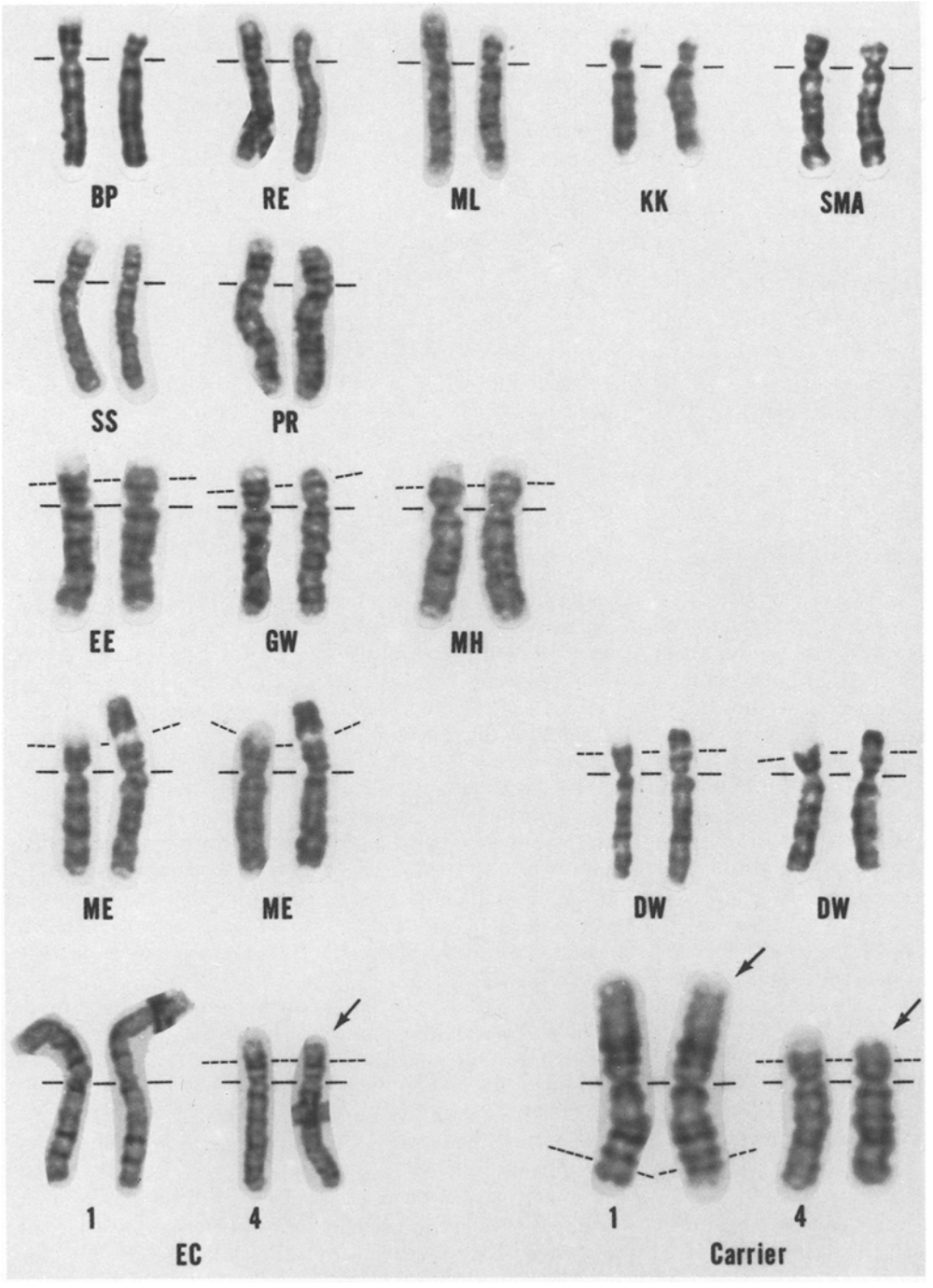


Fig. 3. GTG-banded No. 4 chromosomes of 13 patients and a balanced translocation(1;4) from a carrier paternal aunt of EC. The anomalous chromosome is on the right side of each pair, except for EC that has a normal 1 pair. In ME and DW the No. 4 chromosomes from 2 cells each are shown. The aberrations in the first row are simple deletions. The aberrations in SS and PR are either interstitial deletions or unbalanced translocations; note the similarity to der(4) in EC. All other patients have unbalanced translocations with breakpoints indicated by dashed lines. Origin of the translocated chromatin on der(4) is known only in EC

Mortimer et al. (1978) described a family with an inherited translocation between the short arm of 4 and the short arm of 12. Balanced carriers and persons with unbalanced translocation products were found in the family. One severely retarded person with somatic abnormalities had a partial trisomy for the short arm of chromosome 4, and an infant with Wolf-Hirschhorn syndrome showed deletion of bands 4p15 and 4p16.

Francke (1980) described a girl with the Wolf-Hirschhorn syndrome who had a deletion of the distal band 4p16 detectable in high resolution banding of premetaphase chromosomes. No report was given of the parents' karyotypes.

Stoll et al. (1981) described an affected girl who had inherited an unbalanced chromosome constitution from her mother. The mother had a translocation t(1;4)(q11;p16). The karyotypes of mother and child were similar except that band

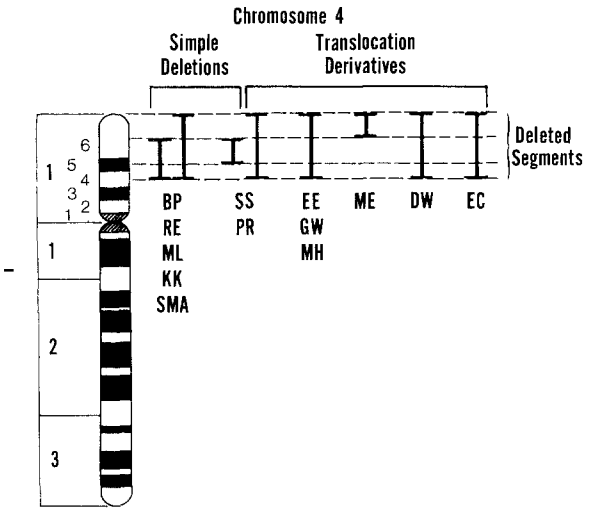


Fig. 4. Diagram of the segments deleted from chromosome 4 in 13 patients. The deletions of BP, RE, ML, KK, and SMA may be interpreted as either interstitial or terminal. The anomalous No. 4 in SS and PR may be interpreted as interstitial deletion or translocation. All others are interpreted as unbalanced translocation derivatives

4p16 (translocated to the long arm of 1) was not evident in the child's karyotype. The deficiency was explained on the basis of unequal crossing-over occurring between two homologues that have not paired exactly. A similar explanation presumably accounted for the case of Wolf-Hirschhorn syndrome reported by Neu et al. (1975) in which an infant had inherited an unbalanced translocation resulting in del(4p). The mother had a balanced translocation between the short arm of 4 and the short or long arm of 19.

Zizka et al. (1975) reported that the deletion in Wolf-Hirschhorn syndrome involved 4p15 or 4p16, and Lejeune et al. (1975) described a deletion of 4p16 and part of 4p15.

Additional studies reporting the localization of the deletion include the following. Nielsen et al. (1977) described a 13-year-old girl with Wolf-Hirschhorn syndrome and deletion of bands 4p12 to 4p15 by R-banding. Breg et al. (1977) reported that the patient first described by Wolf et al. (1965) had a deletion of segment 4pter to p14. Fryns et al. (1979) described an affected patient who had a deletion of the terminal band 4p16. Hedner et al. (1977) reported an affected girl who had a translocation between the short arm of 4 and the short arm of 10. The short arm distal to 4p13 appeared to be deleted. A typical patient described by Centerwall et al. (1975) had chromatin from the long arm of 22 translocated to 4p. The authors interpreted approximately 50 percent of the distal short arm to be deleted.

Del Mazo et al. (1978) described a female with Wolf-Hirschhorn syndrome who had a ring chromosome 4. By means of the GTG-banding technique, the ring was believed to have a portion of p16 and q35 deleted. The authors concluded that loss of the distal part of the 4p16 band may produce Wolf-Hirschhorn syndrome.

Table 4. Chromosome analyses

Patient	Tissue	No. cells	Stain	Analysis[a]
BP	Blood only	45	GTG	46,XX,del(4)(p14p16) or (p14)
RE	Blood only	30	GTG	46,XY,del(4)(p14p16) or (p14)
ML	Blood only	35	GTG	46,XY,del(4)(p14p16) or (p14)
KK	Blood	46	GTG	46,XX,del(4)(p14p16) or (p14)
	Skin	3	Unbanded	46,XX,Bp–
SMA	Blood	36	^{3}HT[b]	46,XX,del(4p)
	Skin	15	GTG	46,XX,del(4)(p14p16) or (p14)
SS	Blood only	15	GTG	46,XX,del(4)(p15.2p16) or 46,XX,–4,+der(4),t(4;?)(p14;?)
PR	Blood	90	GTG	46,XX,del(4)(p15.2p16) or 46,XX,–4,+der(4),t(4;?)(p14;?)
	Skin	5	Unbanded	46,XX,Bp–
EE	Blood only	89	GTG	46,XX,–4,+der(4);t(4;?)(p14;?)
GW	Blood	68	GTG	46,XY,–4,+der(4);t(4;?)(p14;?)
	Skin	4	Unbanded	46,XY,Bp–
MH	Blood	35	GTG	46,XX,–4,+der(4),t(4;?)(p14;?)
	Skin	5	Unbanded	46,XX,Bp–
ME	Blood	12	GTG	46,XX,–4+der(4),t(4;?)(p16;?)
	Skin	18	GTG	46,XX,–4,+der(4),t(4;?)(p16;?)
DW	Blood	94	^{3}HT	46,XY,4p+
	Skin	35	GTG	46,XY,–4,+der(4),t(4;?)(p14;?)
EC	Blood	20	GTG	46,XY,–4,+der(4),t(1;4)(q42;p14)pat
	Skin	5	Unbanded	46,XY,Bp–
Father	Blood	5	GTG	46,XY,t(1;4)(q42;p14)
Pat. Aunt	Blood	25	GTG	46,XX,t(1;4)(q42;p14)
Pat. Grandmother	Blood	10	GTG	46,XX,t(1:4)(q42;p14)
Pat. Great Aunt	Blood	10	GTG	46,XX,t(1;4)(q42;p14)

[a] When two interpretations are shown, the first is preferred
[b] Tritiated thymidine
Note: The karyotypes from blood cultures of all parents showed normal results with three exceptions: the parents of SS and ME were not available, and the father of EC had abnormal results as shown above

Table 5. Length of the short arm of the anomalous 4 compared to normal 4p

Patient	No. cells	%[a]
BP	4	58
RE	10	59
ML	10	62
KK	4	65
SMA	4	61
SS	10	82
PR	4	80
EE	4	89
GW	4	81
MH	10	80
EC	10	89

[a] Length of the anomalous 4p as a percent of normal 4p

Table 6. Mean centromeric index (short arm/total length)

Patient	No. cells	Anomalous 4p	Normal 4p
BP	4	0.18	0.28
RE	10	0.19	0.28
ML	9	0.20	0.28
KK	4	0.20	0.28
SMA	4	0.19	0.29
SS	10	0.24	0.28
PR	4	0.23	0.27
EE	4	0.26	0.28
GW	4	0.24	0.28
MH	10	0.24	0.28
EC	10	0.26	0.29

In three other instances of ring chromosome 4 and the Wolf-Hirschhorn syndrome (Perez-Castillo and Abrisqueta 1977; Fraisse et al. 1977; Chavin-Colin et al. 1977), the investigators believed that banding studies showed that 4p16 was deleted.

Francke et al. (1977) reported a patient with a proximal deletion of the short arm of 4 who had different and less marked clinical findings from Wolf-Hirschhorn syndrome. The patient had an interstitial deletion from p11 to p15.2. The authors concluded that the deletion responsible for Wolf-Hirschhorn syndrome was distal to p15.2.

The cytogenetic findings reported in this paper suggest that the localization of the deleted segment in Wolf-Hirschhorn syndrome is within 4p16. The usual site for the proximal breakpoint was within 4p14, resulting in deletion of about one-half of the short arm. These variations in deletions of the short arm did not result in detectable differences in the phenotype.

Various cytogenetic mechanisms involved in the production of Wolf-Hirschhorn syndrome were found in these patients. Simple deletions, either interstitial or terminal, and translocations were found. Moreover, some patients in whom a simple deletion appeared to be present on first evaluation were found on closer examination to have translocated chromatin on the end of the aberrant short arm. For example, in patients EE, GW, and MH, neither an interstitial nor terminal deletion could account for the GTG-staining of the shortened short arm.

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