BISATELLITED DERIVATIVES OF CHROMOSOME 15: CYTOGENETIC AND CLINICAL STUDIES

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ABSTRACT

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Extra de novo bisatellited chromosomes in five unrelated patients were identified as inv dup(15)(pter -- q1:p1 or q1 -- pter) by QFQ, GTG, RHG, and anti-5-methylcytidine banding. Clinical studies on these patients, and 12 probable and 7 confirmed cases in the literature, indicated an association between inv dup(15) and a mildly dysmorphic syndrome. Features present in virtually all cases included mental and developmental retardation, hypotonia, and behavioral disturbances. 60% - 80% had strabismus, short stature, seizures, and nonspecific dermatoglyphic abnormalities. 20% - 60% had mild facial and limb dysmorphisms, and vertebral anomalies. Parental ages were distinctly elevated.

Inv dup(15) is likely to have arisen via the meiotic mechanisms of translocation, U-type exchange, or parental paracentric inversion heterozygosity. Proximal and distal QFQ polymorphism asymmetry in all five patients ruled out an origin via sister chromatid exchange. An analysis of the theoretical segregation behavior of the derivative suggested the occurrence of second division nondisjunction in four of our cases and one in the literature.

A sixth patient with an extra bisatellited chromosome was also evaluated. The errcr in this case was tentatively identified as t(15;15)(p11;q14). The phenotypic findings were similar to those of inv dup(15).

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INTRODUCTION

The delineation of syndromes associated with mildly dysmorphic autosomal errors is a relatively difficult process. Many affected patients lack compelling indications for chromosome analysis, and are overlooked. In other instances, technical limitations hamper interpretation and comparison of cytological data.

These problems are evident in previous studies of bisatellited chromosomes believed to represent errors of chromosome 15. The cytological nature of these derivatives, and the associated phenotype, are not well understood. This paper attempts to clarify some of the characteristics of this disorder.

Six patients with mental retardation and minimal phenotypic findings were evaluated over a two year period. Each had a small acrocentric bisatellited supernumerary, with banding chracteristics similar to the proximal portion of chromosome 15. The clinical findings in these patients suggested an association between the bisatellited chromosomes and a mildly dysmorphic syndrome. Data supporting the delineation of this syndrome, and data bearing upon the identity, origin, and structure of the extra chromosomes, are reported here.

Literature Review

1a. Small supernumerary chromosomes in man.

Prior to 1970, cytogenetic techniques lacked the resolution necessary for precise identification of most marker[1] chromosomes. Small supernumeraries were particularly troublesome, in that they resembled many normal chromosomes or their derivatives, but were not associated with consistent phenotypes. Small supernumeraries of a de novo origin were usually accompanied by mental retardation and congenital anomalies; familial supernumeraries frequently occurred in phenotypically normal persons, and could not be related to clinical disorders. Phenotype-karyotype correlations eventually led to recognition of the XYY male (Sandberg et al., 1961), and the Cat-Eye syndrome (Schachenmann et al., 1965). Attempts to define full trisomy 22 (Hsu et al., 1971) and a "metacentric microchromosome" syndrome (Abbo and Zellweger, 1970), were less successful. Partial D group trisomies were occasionally suggested by certain somatic characteristics (Yunis and Hook, 1966), or translocation carrier parents (Bloom and Gerald, 1968).

The introduction of chromosome banding techniques in the early 1970's transformed the study of supernumerary chromosomes. A number of abnormalities were subsequently associated with specific phenotypes, and more data bearing on the origin of small supernumeraries

[1]By convention, unidentified chromosomes are frequently referred to as "markers" (Chicago Conference, 1966).

became available. These observations are reviewed below.

1b. Small supernumeraries derived from D and G group chromosomes other than chromosome 15.

Proximal trisomy 13 has been encountered in a limited number of cases, and is associated with low birth weight, microcephaly, small mouth, bulbous nose, micrognathia, ear deformities, clinodactyly, increased neutrophil projections, and mental retardation (Schinzel et al., 1976, Wilroy et al., 1977).

Proximal trisomy 14 is associated with a pattern of malformations that includes mental retardation, prominent nose, broad nasal bridge, hypotelorism, palate anomalies, long upper lip, poorly defined philtrum, characteristically shaped mouth, short neck, limb anomalies, and short stature (Simpson and Zellweger, 1977, de Grouchy and Turleu, 1977).

Proximal trisomy 21 is associated with mental retardation and few somatic anomalies (Williams et al., 1975, Hagemeijer and Smit, 1977). Studies on distal trisomy 21 have mapped the segment responsible for the Down syndrome phenotype to bands 21q21-22 (Aula et al., 1973, Williams et al., 1975, Wahrman et al., 1976, and Hagemeijer and Smit, 1977).

Proximal trisomy 22 is associated with mental retardation, antimongoloid slant, preauricular tags and sinuses, large or lowset ears, congenital heart disease, and minor skeletal anomalies (Garlinger et al., 1977).

Full trisomy 22 is associated with a syndrome of microcephaly, asymmetrical cranium, flat occiput, strabismus, epicanthus, short

beaked nose, ear deformities, long upper lip, long philtrum, cleft or high arched palate, micrognathia, preauricular tags and sinuses, dislocated hips, tapered fingers, hypoplastic male genitalia, congenital heart disease, mental and growth retardation, and hypotonia (de Grouchy and Turleau, 1977). Hsu and Hirschhorn (1977) also noted an antimongoloid slant and hypertelorism.

The marker chromosome associated with the Cat-Eye syndrome was recently identified as a bisatellited derivative of chromosome 22, with proximal and distal C bands. Phenotypic findings common to these cases include coloboma, micrognathia, depressed nasal bridge, hypertelorism, preauricular tags and sinuses, congenital heart disease, renal anomalies, anal stenosis and atresia, and mental retardation (Toomey et al., 1977).

1c. Small supernumeraries not derived from acrocentric autosomes.

Normal males with additional apparent deleted Y chromosomes have been reported by Nielsen et al. (1971), and Christensen and Nielsen (1971). Wisniewski and Higgins (1977) described a mentally retarded boy with multiple anomalies and an extra deleted Y as the result of nondisjunction following a de novo Y/autosome translocation. 3 to 1 meiotic disjunctions in carriers of balanced autosomal translocations have produced a number of probands with various 47 + marker karyotypes (Lindenbaum and Bobrow, 1975). 18p isochromosomes represent still another form of small marker (Ogata et al., 1977, Tangheroni et al., 1973, Nielsen et al., 1974, Taylor et al., 1975, Balicek et al., 1976). Condron et al. (1974) described psychomotor retardation, small head, lowset ears, small mouth, narrow high arched palate,

frail habitus, and upper motor neuron lesions as features associated with this syndrome. Paluthke et al. (1976) identified a small metacentric marker as an extra deleted number 17. A few rare cases of centric fission in man have also been described (Archidiacono et al., 1978, Sinha et al., 1972, Hansen, 1975, Dallopiccola et al., 1976).

In some cases, the morphological characteristics of small metacentric supernumeraries led investigators to conclude that they were fused acrocentric short arms, the products of balanced reciprocal Robertsonian translocations (Palmer et al., 1969, Friedrich and Nielsen, 1974). Family and newborn studies have suggested that these presumptive t(p;p) chromosomes function as benign familial traits (Friedrich and Nielsen, 1974, Palmer et al., 1969, Soudek et al., 1973).

C banding has been applied to estimate the heterochromatic content of some unidentified small chromosomes. Soudek and Sroka (1977) found that small markers varied in their C banding properties. Some were entirely heterochromatic, and presumably benign, while others possessed variable amounts of nonstaining euchromatin. The presence of more than one C band was noted in some patients, along with a bisatellited appearance (Soudek and Sroka, 1977, de Gutierrez et al., 1975).

1d. Population studies on supernumerary chromosomes.

The incidence of supernumeraries in newborns and institutional popualations has been estimated by a number of investigators. Pooling the newborn studies, Jacobs (1974) placed the frequency of unidentified supernumeraries at .02%. Friedrich and Nielsen (1974) reported

an incidence of .6 per 1000 liveborn, and Gerald and Walzer (1970) reported an incidence of .8 per 1000. As expected, studies on retarded populations gave higher frequencies. Jacobs et al. (1972) reported a frequency of .28% in a mentally retarded group. Speed et al. (1976) found .32% in a complete survey of the mentally retarded in Northeast Scotland.

2a. Supernumerary chromosomes derived from chromosome 15.

According to Lauritsen (1977), full trisomy 15 occurs in 5% of all karyotypically abnormal spontaneous abortions. In contrast, a liveborn with full trisomy 15 has never been described. Partial trisomies have been observed in living individuals, and those related to this report fall into three morphological categories: 1) de novo presumed proximal trisomy 15 without confirming evidence, 2) proximal trisomy 15 confirmed through a balanced carrier parent, 3) de novo bisatellited acrocentrics believed to represent either proximal trisomy or tetrasomy of chromosome 15.

The term proximal refers to portions of chromosome 15 bordered by 15pter and the landmark band, 15q21. This includes the short arm and approximately one half of the long arm. The short arm of chromosome 15 is believed heterochromatic, and is not known to contain genetic material necessary for normal development. Excess long arm euchromatin is presumed the cause of clinical defects in these patients.

Specific syndromes associated with these errors are poorly defined. Earlier attempts to delineate them made use of patients

in all three categories without regard for cytogenetic heterogeneity (Centerwall and Morris, 1975, Castel et al., 1976). The results were confusing and equivocal. The following review covers patients in categories 1 and 2 separately from those in category 3. (Case summaries for all patients in these categories are appended. The cases are numbered according to their appearance in the appendix.)

2b. Patients with proximal trisomy 15.

Fourteen previous cases with proximal trisomy 15 fit categories 1 and 2. Phenotypic findings present in at least three of the 14 patients are summarized in Table 1. Mental retardation was the only uniform finding. More than half the patients had strabismus, micrognathia, arched or cleft palate, and abnormal dermatoglyphics. Approximately half also had lowset malformed ears, growth retardation, and genital anomalies (males).

Heterogeneity was evident; half of the patients were trisomic for 15pter → q15 or less, and the other half for 15pter → q21-22. The latter group did not have unique findings associated with bands q21-22, with the possible exception of hyperactivity[2], and appeared less malformed than the pter → q15 trisomies. Malsegregating familial translocations are considered a less reliable source of

[2]Hyperactive patients occur in category 1; it is interesting to compare their histories (see Appendix) with those of the inv dup(15) cases (Table III). Cases 1, 2, and 4 resemble the inv dup(15) patients. Case 3 does not, and is the only one with cytogenetic evidence firmly excluding it from the inv dup(15) category (C banding). The other three may have modified inv dup(15) chromosomes, and this point is covered later in the discussion.

Table 1. Phenotypic findings in 14 patients with proximal trisomy 15.*

Case #	5	6	13	14	12	3	10	7	8	9	1	2	4	11	
Partial trisomy	a	a	a	a	a	a	a	b	b	b	b	b	b	b	
Additional Error	c	c	d	d	e	-	-	f	f	f	-	-	-	-	
Sex	F	M	M	M	F	F	M	M	F	M	F	F	F	F	8F/6M
Age	14	5	12		21	5	13	8	14	31	8	12	10	4	
Birth Weight (Kg.)	2.6	2.4	2.5	3.0		2.1	2.4				3.0		1.9	2.8	
Oval Facies	+	+	-	-	+	-	-				-	-	-	-	3/11
High Forehead	+	+	-	-	+	-	-				-	-	-	-	3/11
Enopthalmia	+	+	-	-	+	-	-				-	-	-	-	3/11
Hypertelorism	-	-	+	+	+		-				-	-	+	-	4/10
Strabismus	+	+	+	+	-	-	-	-	+	+	-	+	+	-	8/14
Epicanthus	-	-	-	-	+	-	-	-	-	-	+	+	-	-	3/14
Malocclusion	-	-	-	-	+	+	-				-	+	-	+	4/11
Receding Chin	+	+	+	+	-	+	+				-	-	-	-	6/11
Palate	-	A	C	C	-	C	A	A	C	A	A	A	A	A	12/14
Short Neck	+	+	-	-	-	-	-				-	-	-	+	3/11
Lowset Ears	+	+	-	+	-	+	+	+	+	-	-	-	-	-	7/14
Malformed Ears	+	-	-	+	+		-				-		-	+	4/9
Chest Deformity	-	+	+	+	-	-	-				-	-	-	-	3/11
Kyphosis	+	+	-	-	+	-	-				-	+	-	-	4/11
Clinodactyly	-	-	-	-	-	+	+				-	-	+	-	3/11
Webbing Toes 2 & 3	+	+	-	-	-	-	+	-	-	-	+	-	-	-	4/14
Genital Abnormality	-	+	+	-	-	-	+				-	-	-	-	3/6 males
Hypotonia	-	-	+	+	-	+	-	+	+	-	-	-	-	-	5/14
Growth Retardation	-	-	-	-						-	-	-	-	-	6/14
Mental Retardation	+	+	+	+	+	+	-	+	+	+	+	+	+	+	13/13
Dermatoglyphics	+	+	+	+	-	+			+		-	+	-	-	7/11

Table 1 (continued).

a = 15pter → q13 to q15
b = 15pter → q21 to q22
c = monosomy 21q22ter
d = trisomy 8q24ter
e = trisomy 7q35ter
f = monosomy 11qter ?
A = arched
C = cleft

* Cases are arranged in order of increasing amounts of chromosome 15 present in the error. Cases 1, 2, 3, and 4 belong in category 1.

data for syndrome delineation, because a complicating abnormality involving a second chromosome is usually present. Familial translocations were responsible in five of the seven 15pter → q15 cases, and three of the seven 15pter → q21-22 cases. This alone may account for the impression that 15pter → q15 trisomies are more damaging.

2c. Bisatellited derivatives of chromosome 15 in category 3.

Bisatellited chromosomes known to represent errors of chromosome 15 have very distinctive characteristics (Schreck et al., 1977, Van Dyke et al., 1977). 1) They are approximately the same size as 15pter → q21-22, and have G and Q banding patterns matching this area. 2) The G technique produces a distinctive dark band on the marker coinciding in position with the chromosome 15 landmark band 15q21 (see Figure 10). Later studies revealed that this band was not 15q21, but composed of C band positive heterochromatin (Schreck et al., 1977, Van Dyke et al., 1977, Pfieffer and Kessel, 1976). 3) A definitive characteristic was demonstrated by Schreck et al. (1977) using a technique originally described by Miller et al. (1974). Miller et al. demonstrated the preferential binding of antibodies against the nucleotide 5-methylcytidine by indirect immunofluorescence following slide exposure to ultraviolet irradiation. The areas of banding were confined to the heterochromatic regions of chromosomes 1, 9, 15, 16, and mid Yq, giving a powerful technique for differentiating chromosome 15 abnormalities from those involving other acrocentrics. The technique was first used to confirm chromosome 15 translocations in two families (Breg et al., 1974). Later, Schreck

et al. (1977) applied it to a number of patients with extra G like chromosomes. Among these cases were three with bisatellited chromosomes previously interpreted as chromosome 15 derivatives (Breg et al., 1971, Parker and Alfi, 1972, Bucher et al., 1973[3]). Anti-5-methylcytidine banding demonstrated two intensely staining areas corresponding to the proximal and distal C bands on these markers. The results clearly revealed that the bisatellited chromosomes were composed of a small segment of euchromatin bordered on either end by material derived from the short arms of number 15. The euchromatin presumably represents either trisomy or tetrasomy of proximal 15q. Schreck et al. described the rearrangement as inv dup(15) (pter → q1:p1 or q1 → pter). (This designation is adapted for the remainder of this report.)

Previous reports of chromosomes with characteristics like those above were located in the literature. Seven cases of inv dup(15) confirmed by anti-5-methylcytidine banding were available (Schreck et al., 1977, Van Dyke et al., 1977). These were compared to 15 other patients with bisatellited supernumerary acrocentrics of G group size or slightly larger. Twelve of the unconfirmed cases had 1) G and/or Q patterns identical to 15pter → q21, or 2) a distal G band resembling 15q21 that was C band positive. These 12 cases were considered as probable inv dup(15). A summary of the cytogenetic data on the 12 probable and 7 confirmed examples is given in Table

[3]The case briefly described by Breg et al. (1971) is one of the two patients described by Crandall et al. (1973).

2.[4] Original studies suggested or, in one case, confirmed with polymorphisms, a chromosome 15 origin in all but three of the probable cases. Rasmussen et al. (1976) and Kakati and Sinha (1973) interpreted chromosome 13 as the origin in their reports due to similarities in C band polymorphisms.[5] We questioned this evaluation, and felt that other cytogenetic data presented favored a chromosome 15 origin. Jacobs et al. (1978) made no attempt to identify the marker in their patient, but presented G banded material consistent with 15pter → q21.

All total, 19 cases were considered confirmed or probable examples of inv dup(15). Phenotypic findings in 16 of the 19 are summarized in Table 3.[6] Mental retardation, varying from profound to mild, was present in all cases. Common features included strabismus, abnormal dermatoglyphics, hypotonia, developmental and growth retardation. Seizures were present in eight cases, hyperactivity in four, and autism in three. Extensive physical malformations were generally

[4]The three remaining patients with bisatellited supernumerary acrocentrics are briefly described here. The first case was reported by Unis and Hook (1966). The patient was a seven year old male with severe mental retardation, a convulsive disorder, but no other major malformations. Autoradiography suggested that the extra chromosome was derived from a number 13. This diagnosis was supported by the demonstration of increased neutrophil projections, a characteristic of full trisomy 13. The next case was described as an example of Rubinstein-Taybi syndrome by Padfield et al. (1968), and was evaluated by Simpson (1973). Simpson identified a supernumerary bisatellited chromosome, and considered it a deleted 14 with G banding. This case is again mentioned in the discussion. The last patient, a child with Cat Eye syndrome, has been previously discussed (Toomey et al., 1977).

[5]In both of these reports, it was suggested that chromosome 13 usually had the largest C bands in the D group. This is contradictory to our experience; chromosome 15 C bands are usually the largest, and chromosome 13, the smallest, with our Q to C method.

[6]Case 24 (Speed et al., 1976) was not included because no clinical data had been published with the report. Case 26 (Power et al., 1977) was a phenotypically normal female mosaic. Case 33 (Jacobs et al., 1978) had to be excluded because of septic meningitis at age 1.

Table 2. Cytogenetic findings in 19 cases with presumed or confirmed inv dup(15).

Case #	15	16	19	17	18	20	21	22	23	25	27	28	29	30	31	32	26	24	33
Satellites on p and q	+	+	+		+	+	+		+	+	+	+	+		+	+	+	+	+
Satellites on q only								+						+					
Q bands = 15pter --q21	+	+	+						+	+				+	+	+			
G bands = 15pter --q21		+	+	+	+	+	+	+	+	+	+	+	+				+	+	+
C bands on p and q	+	+	+	+					+	+			+	+	+				+
Anti-5-methylcytodine	+	+	+										+	+	+	+			
Q and C polymorphisms = chrom. 15									+				+						

Table 3. Phenotypic findings in 16 cases of presumed or confirmed inv dup(15).

Case #	15	16	17	18	19	20	21	22	23	25	28	27	29	30	31	32	
Age		10	1.3	11	11	1	30	5	12	14	7	.5	7				
Sex	M	F	M	M	M	F	M	F	M	F	F	M	M	M	M	F	6F/11M
Birth Weight (Kg.)				3.2	2.6	3.4		3.8	2.5	3.2	3.0	3.6	2.9				
Microcephaly		-		-	-	-	-	+	-			+					2/8
Strabismus	+	+	+	-	+	+	-	+		+	+		+	-	-	+	10/14
Epicanthus		-	+	+	-	-	-	-			+	+					4/9
Arched Palate		-		-	+	-	+	-									2/6
Scoliosis		-		-	-		-	-			+				+		2/7
Dermatoglyphics		+		-	-		+	+	-	+	+	+					6/9
Webbing Toes		-		-	+			-				+					2/5
Hypotonia		-	+	+	+	+		+	+	+	+			+			9/10
Developmental Retard.			+	+	-	+	+	+	+	+	+						8/9
Growth Retardation		-		-	-		+	-	+	+	+	+					5/9
Mental Retardation	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	15/15
Autism	+								+	+							3
Hyperactivity		+		+	+			-					+				4
Seizures		-		+	+	+	+	+	+			+			+		8/9
Abnormal EEG				+	+	+		+	+	+		+	+				8
Maternal Age	39	23		28	34	33	43	30	36	39	30	36	38	42	36	34	
Paternal Age	33					38	42	30	37	35	27	33		45	42	53	

absent. A very provocative elevation in mean parental ages was evident.

2d. Comparison of features in categories 1 and 2 with those in category 3.

Although the published data are incomplete, certain differentiating trends are suggested in the comparison of phenotypic findings of categories 1 and 2 with category 3 (Table 4). In general, physical malformations were more common in the partial trisomies. Micrognathia, severe palate anomalies, and ear abnormalities were most frequent in categories 1 and 2, while convulsive disorders and behavioral aberrations appeared to characterize the inv dup(15) patients. The incidence of strabismus, epicanthus, dermatoglyphic errors, growth and mental retardation were relatively similar in both.

3a. Dicentric chromosomes in man.

Recent studies have suggested that two centromeres may be included in the structure of inv dup(15) chromosomes (Schreck et al., 1977, Van Dyke et al., 1977).

Two types of dicentric chromosomes are known to occur in man. Type 1 is functionally dicentric, and forms two primary constrictions prior to anaphase. Type 2 has only a single functioning centromere. It forms a single primary constriction prior to anaphase, and is initially indistinguishable from a normal monocentric chromosome.

3b. Functionally dicentric chromosomes (type 1).

Type 1 dicentrics are associated with chromosome breakage

Table 4. A comparison of phenotypic findings in patients from Tables 1 and 3.

	Partial Trisomy	Presumed inv dup(15)
Strabismus	8/14	10/14
Micrognathia	6/11	0
Epicanthus	3/14	4/9
Palate Anomaly	12/14	2/6
Lowset Ears	7/14	1/7
Malformed Ears	4/9	0
Abnormal Dermatoglyphics	7/11	6/9
Hypotonia	5/14	9/10
Mental Retardation	13/13	15/15
Growth Retardation	6/14	5/9
Hyperactivity	3*	4*
Seizures	0	8/9
Autism	0	3*

* Positive findings only for these features were scored, since negative findings were difficult to determine from the published descriptions.

syndromes (German, 1972), induced chromosome damage (Bloom, 1972), and fibroblast senescence (Benn, 1976). Inherited type 1 dicentrics have been rarely observed. Jacobs et al. (1972) described only a single type 1 dicentric out of 24,000 individuals karyotyped for various reasons, and Hamerton et al. (1975) did not observe any in 46,000 newborns. 16 patients with problems of sexual differentiation and type 1 dicentric Y chromosomes were reviewed by Cohen et al. (1973).

The rarity of inherited type 1 dicentrics can be attributed to their instability over many generations. Since both centromeres remain functional, an opposing orientation on the spindle apparatus eventually occurs. This results in breakage or complete loss of the dicentric due to anaphase bridging (Mather and Stone, 1933, Evans, 1962). In corn, anaphase bridging may result in the classic bridge-breakage-fusion cycle of McClintock (1951). Evidence for a similar process in man was reported by Van Dyke et al. (1977).

Exceptionally stable type 1 dicentrics have been reported (Sears and Camara, 1952, Niebuhr, 1972, Cohen et al., 1973, Hair, 1953, in Warburton et al., 1973). Niebuhr (1972), Cohen et al. (1973), and Hair (Warburton et al., 1973) suggested that the stability of these rearrangements might be due to the closeness of their two centromeres.

3c. Functionally monocentric dicentrics (type 2).

Sears and Camara (1952) proposed that the inactivation of one centromere of a dicentric could produce stability. Centromeric deactivation results from functional dominance of one centromere over

the other; the weaker centromere retains its ability to orient on the spindle, but can do so only in the absence of the dominant centromere. This theory is currently accepted as an explanation for type 2 dicentrics in man.

Type 2 dicentrics initially appear monocentric. All centromeres in the human karyotype are marked by adjacent C banding heterochromatin, and an inactive centromere is suggested when C banding material occurs at a position expected for a second centromere as determined by other banding techniques. Further examination of the area in question usually reveals additional morphological data consistent with this assumption.

Inactive centromeres were first described on X chromosome derivatives (Disteche et al., 1972), Robertsonian translocations (Niebuhr, 1972), and autosomal translocations (Warburton et al., 1973). Since these reports, many other cases involving X chromosomes (Valenta et al., 1977), and fewer cases involving autosomes, have been described (Soudek and Sroka, 1977, Van Dyke et al., 1977, Roberts et al., 1977, Nakagome et al., 1976, Schreck et al., 1977, Pallister et al., 1974, Wisniewski et al., 1978).

Characteristics common to most type 2 dicentrics are:

1) A minority of cells usually have some structural peculiarity localized near the deactivated centromere. This included a tendency for the chromatids to oppose each other in a semi-constricted manner, to form constriction-like notches, or to overlap suggestively (Pallister et al., 1974, Disteche et al., 1972, Nakagome et al., 1976, Wisniewski et al., 1978). Unusual modifications of the

condensation process in distal regions of these rearrangements were mentioned by Wisniewski et al. (1978) and Pallister et al. (1974).

2) Centromeric deactivation may be incomplete in some cells. Type 2 chromosomes with two primary constrictions were noted by Niebuhr (1972), Therman et al. (1974), Warburton et al. (1973), Pallister et al. (1974) and Wisniewski et al. (1978). In general, the frequency of true dicentrics was only a few percent, and some observers failed to note any (Disteche et al., 1972, Nakagome et al., 1976). Mosaicism in many cases of type 2 isodicentric X chromosomes can be explained by the loss of the chromosome in some cells early in development (Valenta et al., 1977). Technical difficulties generally limit the study of human mitosis, but Therman et al. (1974) produced photographs showing anaphase lag or bridging in a case of a type 2 isodicentric X. A mosaicism suggestive of a bridge-breakage-fusion cycle was described by Van Dyke et al. (1977).

3) The relative activity of both centromeres can be estimated from the morphology and banding of asymmetrical type 2 rearrangements. In cases where this was possible, a specific centromere was always seen to dominate the other, a relationship that apparently never changed (Warburton et al., 1973, Pallister et al., 1974, Nakagome et al., 1976, Robert et al., 1977, Wisniewski et al., 1978).

Centromeric deactivation is the most popular hypothesis explaining type 2 dicentrics in man, but other interpretations are possible. One theory held that the second centromere was submicroscopically deleted. Therman et al. (1974) briefly discussed this possibility and offered strong arguments against it. Hsu (1976)

pointed out that centromeric heterochromatin is not necessary for centromere functioning, and only marks the position of these structures. Like all markers, absolute linkage cannot be assumed. Soudek and Sroka (1977) felt that no factual basis existed for interpreting two C bands as an indication of dicentric structure. While this position may be valid in some cases, the majority of reported rearrangements compel a dicentric interpretation on morphological grounds.

3d. Evidence suggesting a type 2 structure for inv dup(15) chromosomes.

The presence of two C bands on the inv dup(15) chromosomes suggests a type 2 dicentric structure. Supporting evidence is scant; only the patient of Van Dyke et al. (1977) was studied in an attempt to confirm this hypothesis. Morphological peculiarities on the distal long arm have not been described by any of the investigators. Asymmetry of the polymorphism effectively marked both ends of the bisatellited chromosome in the patients of Rasmussen et al. (1976), Pfieffer and Kessel (1976), and in four patients of Schreck et al. (1977). No shifts in the site of the primary constriction were noted in any of these cases. This might be explained by the general rule of centromeric dominance in type 2 rearrangements, but may also indicate absence of a distal centromere.

4a. Cytological mechanisms related to inv dup(15).

Several earlier observers suggested an origin by simple translocation and abnormal meiotic disjunction (Pfieffer and Kessel, 1976,

Rasmussen et al., 1976, Crandall et al., 1973, Watson and Gordon, 1974, Power et al., 1977). According to Watson and Gordon (1974), if both sets of satellites arose from different acrocentric chromosomes (nonhomologs), a chain four tetravalent and 3:1 disjunction could have occurred. Rasmussen et al. (1976) commented that a dicentric arising from nonhomologous acrocentrics might undergo "centromeric noncoordination" in meiosis, resulting in an aneuploid gamete.

Van Dyke et al. (1977) and Schreck et al. (1977) introduced mechanisms consistent with the anti-5-methylcytidine banding data. Van Dyke et al. dismissed the possibility of centric fusion or parental inversion heterozygosity, and proposed a mechanism involving non-sister chromatid exchange. According to this model, an abnormal exchange between two homologous, but nonsister chromatids, connected the two number 15 centromeres in meiosis I. At anaphase I, the attached number 15 chromosomes were pulled entirely to one pole; one daughter cell was formed without any chromosome 15 material, while the other received two normal non-sister chromatids and the dicentric. The second division then yielded a normal gamete and a dicentric bearing gamete.

Schreck et al. presented five mechanisms, all involving a meiotic exchange and nondisjunction. 1) A recently broken chromosome 15 could have undergone sister strand reunion, and then nondisjoined with its normal homolog. This mechanism would have produced dicentrics with symmetrical polymorphisms, a prediction not consistent with some patients (Schreck et al., 1977). 2) An incomplete reciprocal translocation between two number 15's could have produced a monocentric

bisatellited derivative, a number 15 with a deleted short arm, and an acentric long arm fragment. Given a chromosomal exchange of this type, patients would have inherited a number 15 with a deleted short arm, as well as the bisatellited derivative. A chromatid exchange would have allowed the patients to inherit a normal 15, as well as the bisatellited chromosome. The second alternative is consistent with the patients' karyotypes (Schreck et al., 1977). 3) A U-type nonsister chromatid exchange, similar to that proposed by Van Dyke et al. (1977) could have occurred. U-type exchanges are thought to arise from errors in crossing over, and have been documented in plants by Jones and Brumpton (1971), and Brandham (1975). 4) Crossing over within the loop of a paracentric inversion in a heterozygous parent could have produced a bisatellited dicentric. 5) Crossing over within the loop of a pericentric inversion could have produced a bisatellited monocentric. If mechanism 5 were responsible, a pericentric inversion should have been detected due to an alteration in its arm ratio. This has not been the case (Schreck et al., 1977). A paracentric inversion, on the other hand, could go undetected because of the unremarkable metaphase banding pattern present on the proximal portion of chromosome 15. Van Dyke et al. (1977) were unable to detect such an inversion in the parents of their case.

Mechanisms 2, 3, and 4 seem the most consistent with the cases reported. It would seem attractive to relate the nondisjunction required by all mechanisms to centromeric deactivation in meiosis. However, there is no data available on this point.

Materials and Methods

1. Ascertainment.

Cases III and IV were ascertained during a dermatoglyphic study of an institutionalized, idiopathically retarded population in Michigan (Hassold, 1977). The population consisted of 868 individuals, 77 of whom had an arch or radial loop on at least one thumb. 47 of these individuals were karyotyped at the Cytogenetics Laboratory, Hawthorne Center, and 4 were subsequently referred to this laboratory for further study. Two patients presented with bisatellited supernumerary acrocentrics, and were briefly described in Hassold (1977). Cases II and V were not part of the study population, but were referred by the Hawthorne Center Laboratory because of similar findings. Case I was referred to this laboratory in 1972 because previous studies had suggested trisomy 22, a diagnosis inconsistent with her clinical findings. She was reevaluated in 1977 due to her resemblence to cases II through V. Case VI was ascertained for similar reasons. He was initially seen in our clinic in 1974, and cytogenetic studies suggested partial trisomy 22. Again, his clinical findings were not consistent with this syndrome.

2. Clinical Evaluation

Data on the prenatal, perinatal, developmental, and medical histories of all patients were initially obtained from institutional and physicians' records, and in cases I and VI, our own clinic charts. This information was reviewed and updated during interviews

with the parents. A sister of case V served as informant since both parents were deceased. Biochemical, radiological, psychometric, and EEG evaluations were conducted by the various physicians or institutions caring for the patients. Red cell and serum polymorphism data were supplied by the laboratory of Dr. Everett Lovrien, University of Oregon. Dermatoglyphic data were obtained from the study of Hassold (1977), and by the author. Recent clinical findings reported below were observed during a 1977 physical evaluation of all patients performed by Dr. John Heffelfinger, Coldwater State Home, Dr. James Higgins, Michigan State University, and the author.

To clarify the data available on published cases, authors were contacted by letter and asked to review their patients with a clinical checklist we provided. This list was constructed using our patients as a model, but included a number of unrelated findings. A copy of this checklist is enclosed in the Appendix.

3. Cytogenetics

Short term peripheral blood culture were processed according to the standard method of Moorhead et al. (1960). Modal karyotype numbers were established by a routine count of 30 cells stained with conventional 2% giemsa. Mosaicism studies were conducted on a variable number of metaphases stained with 2% giemsa, or with one of the banding techniques. The exclusion of mosaicism was calculated according to the tables of Hook (1977).

Techniques for the induction of CBG, GTG, and QFQ[7] bands were modified after Salamanca and Armendares (1974), Sun et al. (1974), and Caspersson et al. (1970), and are described below.

For GTG banding, flame dried slides were incubated overnight at 60°C, and then treated in a .025 M potassium phosphate buffer with a pH of 6.8, for 1 to 10 minutes. A .1% trypsin solution was freshly prepared in distilled H_2O; slides were placed in this solution for 0.5 to 2 minutes, and then stained with 2% giemsa for 10 minutes. Metaphase spreads were photographed on Pan-X film at ASA 400, and printed on Kodabromide #4 paper.

For CBG bands, flamed dried slides were first treated in a .2N HCl bath at room temperature for 30 minutes. They were then placed in a 0.07N barium hydroxide solution at 40°C for 12 minutes. The HCl treatment was repeated for 15 minutes after rinsing. Slides were placed in a 2X SSC (pH = 7.0) saturated environment at 60°C for 14 to 20 hours. After rinsing, slides were stained in 2% giemsa for 15 minutes, photographed on Pan-X film at ASA 800, and printed on Kodabromide paper.

For QFQ bands, flame dried slides were stained in a 0.5% atabrine solution supplemented with 0.05 gm. quinacrine mustard for 8 to 12 minutes. Slides were briefly rinsed in distilled H_2O for 15 seconds, and then placed in a citric acid/sodium phosphate buffer

[7]The 1975 supplement to the 1971 Paris Conference on nomenclature in human cytogenetics established symbols for the various banding techniques then available. According to this nomenclature: QFQ = Q bands by fluorescence using quinacrine; GTG = G bands by trypsin using giemsa; RHG = R bands by heating using giemsa; CBG = C bands by barium hydroxide using giemsa.

(pH = 5.6) for 1 minute. A coverslip was mounted with the same buffer, and the slide photographed under UV illumination on Tri-X film. Metaphases were printed on Kodak Contrast 4 paper.

A technique suggested by Hassold (personal communication) was modified to produce RHG bands. Slides were prepared by airdrying, and aged approximately 10 days prior to treatment. A citric acid/sodium phosphate buffer with a pH of 5.05 was heated to 87°C. in a water bath. Slides were immersed in the heated solution for 25 minutes, and immediately stained with 2% giemsa. Metaphase spreads were photographsed on Pan-X film at ASA 800, and printed on Kodabromide paper.

A sequential QFQ → CBG technique was improvised. After standard preparation and microscopy, QFQ slides were destained in a 100% xylene → 70% EtOH → EtOH sequence. They were then treated with the CBG technique, and metaphases were relocated using stage coordinates. Anti-5-methylcytidine banding was performed at Columbia University, New York, through the courtesy of Dr. O.J. Miller. The procedure is described in Schreck et al. (1977).

QFQ and CBG polymorphisms were demonstrated with the above sequential technique. A conservative procedure for scoring acrocentric short arm and satellite polymorphisms was adapted. QFQ polymorphisms were scored in five cells from each individual according to the following criteria:

1 = not visible to dull

2 = bright

3 = intense

A greater degree of subjectivity complicated the scoring of CBG

polymorphisms. This was in part due to artifacts induced by the prerequisite sequential banding technique, and the limited number of cells in which acceptable results were produced. Three cells from each person were scored according to two criteria:

S = small to medium

L = medium to large.

Results

1. Cases Reports

Case I (DD)

DD is a 15 year old caucasian female. She was born to a 26 year old father and a para 3, gravida 2, 30 year old mother. During the course of the pregnancy, her mother suffered a chronic low grade viral infection. She also experienced severe emotional trauma at the death of her father in the 4th month of gestation, and was prescribed Milprem for a period of one week. The delivery was at full term and uncomplicated. The birth weight was 7 lb. 3 oz., and the length 19". The infant experienced choking spells after birth and became cyanotic on the second day due to aspiration of milk.

Her early infancy was chracterized by poor development. She was hypotonic, inactive, and prone to ear infections; 22 were reported in the first year. Her sucking reflex and growth were poor. She sat at 8 months, crept at 15 months, spoke single words at 2 1/2 years, and walked at 8 years. Mental retardation was diagnosed at age 2 1/2.

DD's behavior grew increasing hyperactive during early childhood. She was prone to withdrawal, loss of contact, rapid mood changes,

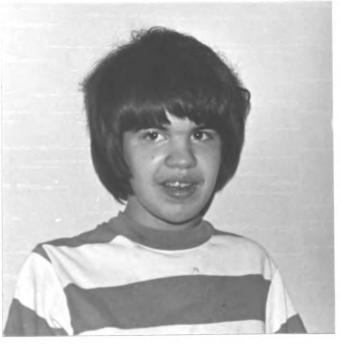


Figure 1. Case I, DD.

disturbed mannerisms, and frequent aggressive spells. Her gait was clumsy and characterized by toe walking. Hearing was normal and speech clear, but with marked perseveration and echolalia. An EEG at age 5 suggested right side brain damage and a possible seizure pattern. Her first grand mal seizure occurred at age 11. Anti-convulsant therapy included Dilantin and Phenobarbital, but the seizures continued: she has averaged 1 every 2 months. Her most recent EEG was mildly abnormal and suggested a mild seizure tendency. Sleep pattern was fairly well organized, but showed a number of low amplitude minor theta and sharp wave transients in the left temporal region, with some anterior temporal emphasis. The waking record showed a slight enhancement of fast activity.

Physical examination at age 15 revealed the following: flat occiput, external strabismus, slightly depressed nasal bridge, short philtrum, lowset ears with a slight posterior rotation, minimal prognathism, slight proximal placement of the thumbs, increased carrying angle, webbing of toes 2 and 3 bilaterally, lordosis, dark pigmentation, and a strange gait. Reflexes, menstrual history, and breast development were normal. Her height was 142.3 cm. (less than 3 s.d.), and head circumference 50.5 cm. (less than 2 s.d.). SMA-12, CBC, and urinalysis evaluations were normal. Her IQ was estimated as 35 on the Stanford-Binet scale.

Her dermatoglyphics were as follows:

left					right				
1	2	3	4	5	1	2	3	4	5
U	W	U	U	U	U	W	U	U	U

thenar/I	open/loop	open/open
II	open	open
III	open	open
IV	loop	loop
atd	t	t
creases	normal	normal

DD's family history was negative for consanguinity, mental retardation, and congenital malformations. She has 3 normal sibs, and her mother did not experience any miscarriages.

Case II (CL)

CL is a 26 year old caucasian male. He was born to a 38 year old father and a gravida 5, para 3, abortus 1, 36 year old mother. The pregnancy was full term with an unremarkable delivery. The birth weight was 9 lb. 8 oz., and no abnormalities were noted. His sucking reflex and appetite were good, although frequent enemas were required during the first two years for bulky stools.

An an infant, he failed to make eye contact, and had infrequent spontaneous movements. He was hypotonic, rolled over at one year, walked normally at two years, spoke recognizable words at four years, and has never been toilet trained. In early childhood, he became increasingly hyperactive and aggressive, and was committed to an institution for the mentally retarded at age 5. The following features were noted upon admission: height, weight and head circumference values all above the 25th percentile, enopthalmos, a soft systolic murmur in the mitral valve area, cryptorchidism, a voice

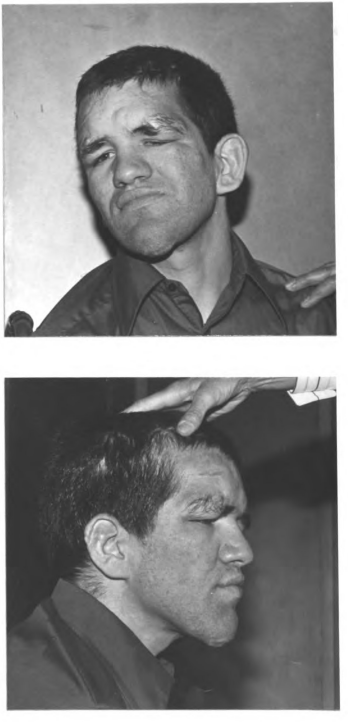


Figure 2. Case II, CL.

but no speech, and hyperactivity. The heart murmur and cryptorchidism were not detected in later exams.

Shortly after commitment, he experienced his first grand mal seizure. Isolated seizures occurred throughout late childhood, and became very frequent in adolescence. An EEG at 17 showed poor organization and background fast activity. Seizure discharges and sharp waves were noted. He was given Dilantin and Mellaril, but would not tolerate Phenobarbital. In October, 1969, brain damage associated with repeated daily seizures confined him to a wheelchair. Afterwards, the frequency of seizures diminished, with the last reported in October, 1976. His behavior is now subdued, and his condition described as stable.

Physical examination at age 26 revealed the following: prominent forehead with heavily scarred supraorbital ridges, antimongoloid slant, enopthalmos, recessed short upper lip, short philtrum, prolonged chin, increased carrying angle, mild intention tremor of the right hand, minimal flexion contractures of the knees, webbing between toes 2 and 3 bilaterally, and small scrotal cysts. An excessive breath and body odor was also noted. His height was 164 cm. (less than 3rd percentile), and his head circumference was 60.3 cm. (50th percentile). Skull and chest X-rays were normal. His IQ was established as 16 on the Stanford Binet scale.

His dermatoglyphics are summarized below.

	left					right				
	1	2	3	4	5	1	2	3	4	5
	A	R	U	U	U	U	U	U	U	U

thenar/I	open/open	open/open
hypothenar	open	open
II	open	open
III	open	open
IV	open	open
atd	t	t
creases	normal	normal

CL's family history is negative for congenital malformations, mental retardation, and consanguinity. He has 3 normal sibs. His mother's first pregnancy ended in a first trimester spontaneous abortion.

Case III (ML)

ML is a 17 year old caucasian male. He was born to a 38 year old father and a gravida 4, para 2, aobrtus 1, 38 year old mother. The pregnancy was complicated by an episode of bleeding lasting for one week in the third month. The delivery was at full term and uncomplicated. The birth weight was 7 lb. 4 oz., and no abnormalities other than a shrill cry were noted. He sucked well and had no feeding problems.

ML was described as a hypotonic, irritable infant who disliked being touched. He sat at 10 months, walked at 15 months, and had poor speech development. His gait was clumsy and he fell frequently. A diagnosis of cerebral palsy was offered at age 4. He became increasingly self abusive, aggressive, and hyperactive, and was unable to attend special education classes because of behavioral problems.

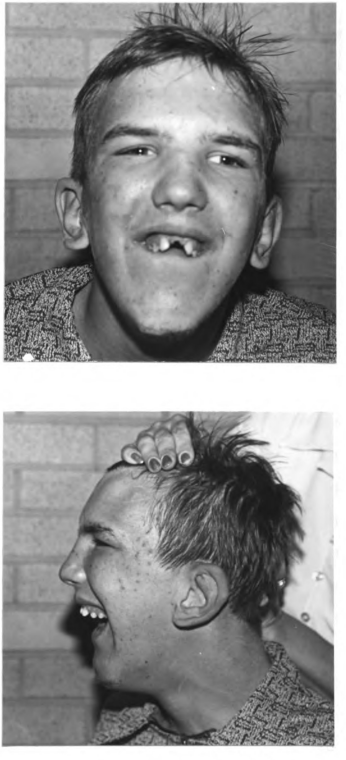


Figure 3. Case III, ML.

He was placed in an institution for the mentally retarded at age 9.

He experienced his first grand mal seizure at the age of 10 following a blow to the head. He was hospitalized for observation, but an EEG showed no abnormalities. More seizures occurred in early adolescence; an EEG at age 15 was slightly abnormal, and suggestive of a diffuse disturbance of brain function. At age 16, he underwent psychiatric evaluation because of frequent seizures. His last reported seizure occurred in September, 1977, but it is unclear whether the frequency is diminishing. His present medications consist of Valium, Phenobarbital, and Malox for a duodenol ulcer.

Physical examination at age 17 revealed enopthalmos, epicanthal folds, minimal antimongoloid slant, external strabismus, short philtrum, a high arched palate, pointed overbite, prolonged chin, thickened asymmetrically placed ears, facial asymmetry due to hemiparesis, arched placement of the digits into the palms, increased carrying angle, and clinodactyly. Hemiparesis was present with the greatest muscle tone on the right side. Scoliosis was suggested, but likely due to a pelvic tilt and a definite size difference between the legs. Slight spasticity in the legs was also noted. Hearing and sight were normal, and speech was clear, but for the most part parroted. He was hyperactive, self abusive, and frequently aggressive. Urinalysis, CBC, and radiological evaluations were normal. His IQ was estimated as 25 on the Stanford-Binet scale. His height was 170.2 cm (25th percentile), and head circumference 54.6 (greater than 2 s.d.). His dermatoglyphics are summarized below:

	left					right				
	1	2	3	4	5	1	2	3	4	5
	U	A	A	U	U	R	A	A	U	U
thenar/1st			open/open			open/open				
II			open			B and C triradii displaced medially with a loop inbetween				
III			open							
IV			open			open				
atd			t			t				
creases			normal			normal				

ML's family history is negative for mental retardation, congenital malformations, and consanguinity. His mother's first pregnancy ended in first trimester spontaneous abortion. He has 2 normal sibs.

Case IV (RF)

RF is a 49 year old caucasian female. She was born to a 34 year old father and a gravida 3, para 1, abortus 1, 34 year old mother. The pregnancy was complicated by two instances of first trimester hemorrhaging, an acute gall bladder infection accompanied by bronchitis in the 7th month. The birth was one month premature, with an uncomplicated delivery. The birth weight was 6 1/2 lb., and no unusual features were noted. Her sucking reflex and appetite were good. Early infancy was unremarkable until the 10th week, when RF developed influenza and an ear infection. Convulsions occurred for two days, followed by a temporary paralysis. Her recovery was slow, and the convulsions did not recur.

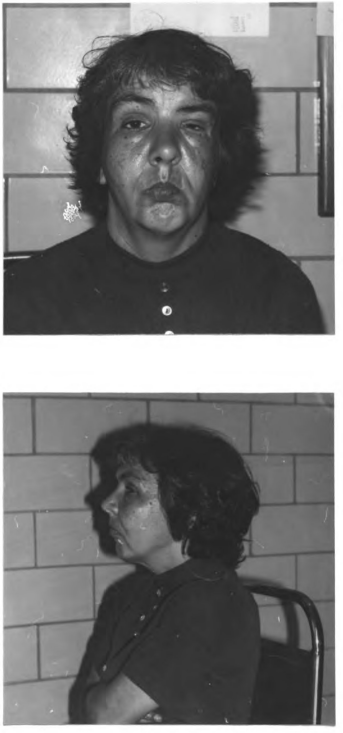


Figure 4. Case IV, RF.

RF was an inactive, hypotonic infant. She sat alone at 13 months, walked at 2 years, and spoke single words at 3 years. Her gait was awkward, and characterized by toe walking. Speech was infrequent, usually unintelligible, and softly spoken. Early childhood was dominated by hyperactivity and unpredictable aggressive episodes. She was placed in an institution for the mentally retarded at the age of 6.

RF suffered grand mal seizures for a period of 12 years, beginning at age 18. They were most frequent at age 20-21, and occurred at intervals of 2 to 3 weeks. Her last reported seizure was at age 31. An EEG at age 39 showed short bursts of spiked discharges and bifrontal abnormalities or seizure discharges. She had been treated with Dilantin and Phenobarbital since age 19. RF's first 20 years of institutionalization were dominated by behavioral problems, principly hyperactivity and aggression. In the last two decades however, her behavior has become subdued and she is presently considered nonaggressive, cheerful, and cooperative. She is a self feeder, completely toilet trained, has normal mobility, but little recognizable speech.

Physical examination at age 48 revealed the following: small palpebral fissures, minimal antimongoloid slant, slightly lowset ears, a high arched palate, hypoplasia of the left side of the face, a low posterior hairline, increased carrying angle, proximally placed thumbs, proximally placed 5th toes, webbing between toes 2 and 3 bilaterally, and a high instep. Her reflexes were depressed at the knee and ankle, but otherwise normal. There were multiple pigmented nevi on the face and trunk, and a dark complexion. Her height was

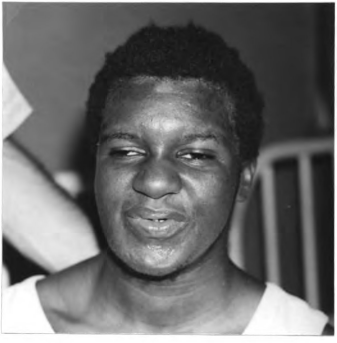
155 cm. and head circumference 55.2 cm. Urinalysis, CBC, and radiological evaluations were normal. She has had normal menses since age 14. Her IQ was estimated as 24 on the Stanford-Binet Scale. Her dermatoglyphics are summarized below:

	left					right				
	1	2	3	4	5	1	2	3	4	5
	A	A	U	U	U	U	A	U	U	U
thenar/1st	pattern/open					open/open				
II	open					open				
III	open					open				
IV	pattern					pattern				
atd	t					t				
creases	normal					normal				

RF's family history is negative for mental retardation, congenital malformations, and consanguinity. A cousin of the maternal grandmother had epilepsy. RF has two normal sibs. Her mother's second pregnancy ended in first trimester spontaneous abortion.

Case V (EL)

EL is a 27 year old black female. She was born to a 40 year old father and a gravida 4, para 3, 35 year old mother. The pregnancy was full term with an unremarkable delivery. The birth weight was 6 lb. No abnormalities were noted in early infancy. She was not hypotonic, but was considered slow by family members. At the age of 1, she suffered a high fever. No convulsions occurred, but it was reported that her right hand was held at an odd angle afterwards. She recognized her parents at 1 1/2 years, sat alone at 2 years,



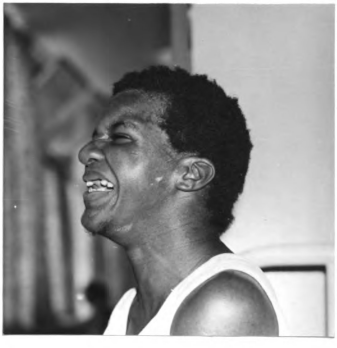


Figure 5. Case V, EL.

walked at 4 years, was toilet trained at 8 years, and spoke single words at 10. Menses began at 10 1/2. Her gait was initially abnormal, and characterized by toe walking. In late childhood, her behavior grew increasingly hyperactive and aggressive, and she was institutionalized at the age of 12.

Upon admission, her weight was 38 kg., height 146 cm., and head circumference 52.7 cm. The only physical abnormality noted was irregular dentition. Her height at age 17 was 147 cm. (less than 2 s.d.), and head circumference 54.6 cm. (50th percentile).

Physical examination at age 27 revealed the following: small forehead, flat occiput, periodic nystagmus, external strabismus, short philtrum, lowset small posteriorly rotated ears, malocclusion, hair growth on the chin, lack of breast development, increased carrying angle, clinodactyly, camptodactyly, arched placement of digits into the palms, proximally placed 5th toes, webbing between toes 2 and 3 bilaterally, lordosis, and an awkward "tin soldier" gait. Her menstrual history was normal. Speech development was restricted to a few words. She was chronically abusive, hyperactive, and destructive. The results of SMA-12, CBC, urinalysis and radiological evaluations were normal. There was no indication of seizures in her history, and her EEG's were normal. Her IQ was estimated as 8 on the Stanford-Binet scale. Her dermatoglyphics are summarized below:

left					right				
1	2	3	4	5	1	2	3	4	5
U	U	U	U	U	U	U	U	U	U

thenar/1st	open/open	open/open
II	open	open
III	pattern	open
IV	pattern	pattern
atd	60°	60°
creases	normal	normal

EL's family history is negative for mental retardation, congenital malformations, and consanguinity. She had a total of 5 sibs. The first died at age 3 months of unknown causes. Two were twins of unknown zygosity; one twin, although fully formed, was stillborn. The remaining sibs are normal. No spontaneous abortions were noted.

Case VI (TM)

TM is a 3 1/2 year old caucasian male. He was born to a 24 year old father and a gravida 5 para 4, 28 year old mother. During the pregnancy, his mother experienced frequent heartburn and headaches, for which she took approximately 4 1/2 teaspoons of baking soda a day, and approximately 24 aspirins a week. A fever of 104° in the 3rd month was treated with Nyquil. TM was born at full term. Respiration was immediate and spontaneous, and no abnormalities were noted. He weighed 10 lb. 12 oz., with a length of 55.9 cm. (3 s.d. above norm), and a head circumference of 36.8 cm. (50th percentile).

Feeding was difficult for the first 3 months due to a poor sucking reflex. He reacted poorly to sight and sound, and was inactive and hypotonic. Physical examination at 5 months revealed no obvious malformations. He had weak muscle tone, hyperactive deep tendon reflexes, and was unable to support his head or roll over. An EEG

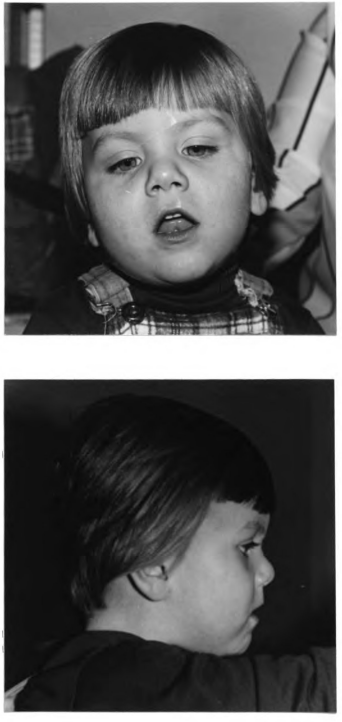


Figure 6. Case VI, TM.

showed generalized slowness and excessive beta and fast activity.

Hyperactivity, gross delay of developmental milestones, and probable profound mental retardation were evident upon reexamination at age 3 1/2. Sight and hearing appeared normal. The following features were noted: minimal epicanthal folds, external strabismus, high cheek bones, antiverted nostrils, posteriorly rotated ears, clinodactyly, slight proximal placement of the thumbs, tapered thumbs and big toes, slightly increased carrying angle, and webbing between toes 2 and 3 bilaterally. His length was 88.9 cm. (less than 10th percentile), and head circumference 47 cm. (less than s.d.). Fasting blood and electrolytes, Multi-20, fundoscopy, Torch, and radiological evaluations were within normal limits. His dermatoglyphics are summarized below:

	left					right				
	1	2	3	4	5	1	2	3	4	5
	U	W	A	U	U	U	R	U	U	U
Thenar/1st			open/open					open/open		
II			open					open		
III			loop					loop		
IV			open					open		
atd			t					t		
creases			normal					normal		

TM's family history is negative for congenital malformations, consanguinity, and mental retardation. His mother had four normal children by her first marriage, and one normal child, in addition to TM by her second marriage. She has had no miscarriages.

2. Summary of phenotypic findings.

The clinical findings in cases I-V are presented in Table 5. Case VI is not included because his chromosomal abnormality differs from the others.

3. Linkage studies.

Data on red cell and serum polymorphisms were obtained from patients and their parents. This information is summarized in Table 6.

No segregational anomalies were observed in these families. Biochemical studies were not performed in cases IV and V because one or both parents were unavailable.

4a. Cytogenetics of cases I-V.

A preliminary evaluation of 30 cells from each patient revealed a modal count of 47 + acrocentric marker, and no evidence of mosaicism. The extra chromosomes had terminal satellites on both arms, and were somewhat larger than a number 22 (Figure 7). Both arms were observed in satellite association, but rarely at the same time (Figure 8).

QFQ, GTG, and RHG patterns in the medial portion of the extra chromosomes were identical in all five patients (Figures 9-11). The QFQ pattern was consistent with proximal 13q and 15q, less consistent with 14q, and inconsistent with chromosomes 21 and 22. RHG produced a moderately dark medial band consistent with proximal 13q and 15q, but none of the other acrocentrics. The GTG pattern resembled 15pter → 15q21, and a faint band similar to 15q14 was present at the midpoint of the markers in early metaphase preparations.

Table 5. Phenotypic findings in cases I-V.

Case	I	II	III	IV	V	
Sex	F	M	M	F	F	3F/2M
Age	15	26	17	49	27	
Birth Weight (Kg.)	2.7	3.6	2.7	2.5	2.2	
Flat Occiput	+	-	-	-	+	2/5
Low Posterior Hairline	+	-	-	+	-	2/5
Facial Asymmetry	-	-	+	+	-	2/5
Antimongoloid Slant	-	+	+	+	-	3/5
Enopthalmos	-	+	+	-	-	2/5
Strabismus	+	-	+	-	+	3/5
Nystagmus	-	-	-	-	+	1/5
Short Philtrum	+	+	+	-	+	4/5
Malocclusion	-	-	-	-	+	1/5
High Arched Palate	-	-	+	+	-	2/5
Prolonged Chin	-	+	+	-	-	2/5
Lowset Ears	+	-	+	+	+	4/5
Malformed Ears	-	-	+	-	-	1/5
Rotated Ears	+	-	+	-	+	3/5
Increased Carrying Angle	+	+	+	+	+	5/5
Clinodactyly	-	-	+	-	+	2/5
Proximally Placed Thumbs	+	-	-	+	-	2/5
Ab. Dermatoglyphics	-	+	+	+	+	4/5
Webbing Toes 2 and 3	+	+	-	+	+	4/5
Lordosis	+	-	-	-	+	2/5
Normal Menses	+			+	+	3/3
Normal Breasts	+			+	-	2/3
Dark Pigmentation	+	-	-	+	-	2/5
Short Stature	+	+	-	-	+	3/5
Mental Retardation	+	+	+	+	+	5/5
Hypotonia	+	+	+	+	-	4/5
Aggressive Behavior	+	+	+	+	+	5/5
Seizures	+	+	+	+	-	4/5
Abnormal EEG	+	+	+	+	-	4/5
Abnormal Gait	+	-	+	+	+	4/5
Toe Walking	+	-	-	+	+	3/5
Maternal Age	30	36	38	34	35	34.6
Paternal Age	26	38	38	34	40	35.2
Hyperactivity	+	+	+	+	+	5/5
Developmental Retardation	+	+	+	+	+	5/5

Table 6. Linkage data.

Case I (DD)

	Father	Mother	DD
ABO	AA_1	AA_1	A
Rh	DCce	DEce	ce
MN	MS	NSs	MNS
Kell	k	Kk	k
Fy	B	B	B
Jk	A+	A+	A+
P	-	-	-
Le A	-	-	-
Tf	C	C	C
Hp	2-1	2	2
E_1	U	U	U
Gc	1	1	1
ACP	A	A	A
Ak	1	1	1
6PDG	A	A	A
PGM	1	1	1
ADA	1	1	1
GPT	2-1	2-1	2-1
AMY_2	A	A	A
ESD	1	1	1
C3	FS	FS	S

Case II (CL)	Father	Mother	CL
ABO	AA_1	B	AA_1B
Rh	DCe	DCEce	DCEce
MN	MNs	MNSs	NSs
Kell	Kk	k	k
Fy	B	B	B
Jk	AB	AB	A
P	-	+	+
Le A	-	-	-
Tf	C	C	C
Hp	2-1	2-1	2-1
E_1	U	U	U
Gc	2-1	1	1
ACP	CA	BA	A
Ak	1	1	1
6PGD	A	A	A
PGM	2-1	2-1	1
ADA	1	1	1
GPT	2-1	2-1	1
AMY_2	A	A	A
ESD	1	2-1	1
C_3	S	FS	S

Table 6 (continued)

Case III (ML)

	Father	Mother	ML
ABO	0	AA_1	O
Rh	ce	DCe	Cce
MN	MNs	NSs	MNSs
Kell	k	k	k
Fy	B	A	AB
Jk	AB	A	A
P	+	+	+
Le A	-	-	-
E_1	U	A	U
ACP	CA	BA	CA
Ak	1	1	1
6PGD	A	A	A
PGM	1	2	2-1
ADA	1	1	1
GPT	1	1	1
ESD	1	1	1

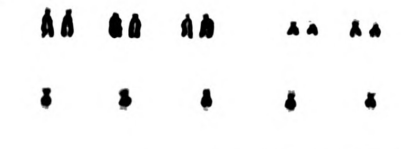


Figure 7. Conventional giemsa staining. Top: normal D and G group autosomes. Bottom: inv dup(15) from cases I-V.

Figure 8. Inv dup(15) in satellite association.

Figure 9. QFQ staining. Top: normal D and G group autosomes. Bottom: inv dup(15) from cases I-V.

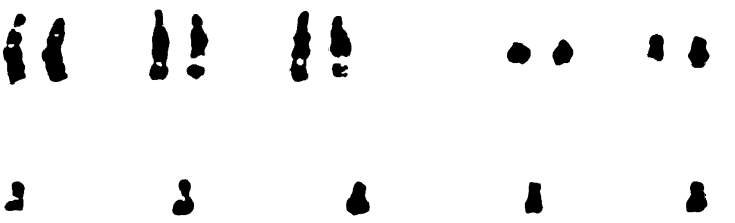


Figure 10. GTG staining. Top: normal D and G group autosomes. Bottom: inv dup(15) from cases I-V.

Figure 11. RHG staining. Top: normal D and G group autosomes. Bottom: inv dup(15) from cases I-V.

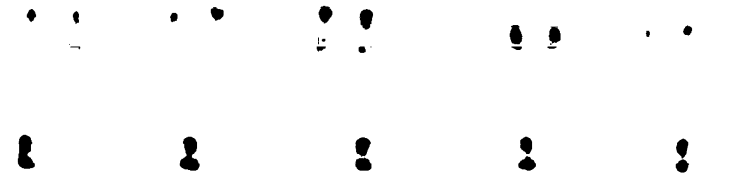


Figure 12. CBG staining. Top: normal D and G group autosomes. Bottom: inv dup(15) from cases I-V.

CBG banding revealed two heterochromatic regions, one corresponding to the short arm, and a second located proximal to the satellites on the long arm (Figure 12). The distal CBG band corresponded to the distal GTG band resembling 15q21 (Figure 10).

The distal CBG band varied in size within the same individual. In early metaphase, proximal and distal bands were visually equivalent. In many late metaphases, the distal band was smaller than the proximal band. A similar pattern was also observed in the distal satellites, although these structures are less amendable to quantification. A difference between the condensation rates of the proximal and distal regions is the most likely explanation for these observations.

We tentatively concluded that the bisatellited chromosomes represented abnormalities of 13q or 15q. Interpretation of the rearrangements was complicated by the CBG results. Three possible structures were postulated:

1) A deleted acrocentric monocentric with an acrocentric short arm translocated to its distal end.

2) An asymmetrical dicentric formed from an end to end translocation of two deleted acrocentrics.

3) A symmetrical dicentric formed by a U-type exchange.

The identity of the bisatellited chromosomes was clarified by anti-5-methylcytidine banding, and an analysis of polymorphisms. Anti-5-methylcytidine banding produced two regions of intense staining corresponding to the CBG bands on each marker. This indicated that both regions were composed of chromosome 15 short arm material, and by interence, that the medial portion contained chromosome 15 long arm

euchromatin (Miller et al., 1974, Schreck et al., 1977).

In all five cases, proximal and distal QFQ satellite polymorphisms were asymmetrical, and therefore inconsistent with an origin by sister chromatid exchange. Since these polymorphisms also marked the opposing ends of each chromosome, it was possible to detect any shifts in the location of the primary constrictions. None were observed.

QFQ and CBG polymorphisms were then analyzed for information bearing upon the identity and origin of the markers. In cases I-III, normal acrocentric polymorphisms were compared to those of the bi-satellited chromosomes. A number of normal acrocentrics were excluded as possible contributors on the basis of visible dissimilarities. The results of this comparison are given in Table 7. The order of the parental chromosomes corresponds to the order of their appearance in the partial karyotypes (Figures 13-15).[8]

A similar procedure was applied in cases IV and V, although only the patients' normal acrocentrics were available for comparison. The results are given in Table 8. Again, the order of the normal acrocentric corresponds to their appearance in the partial karyotypes (Figure 16).

The data in Tables 7 and 8 were then used to determine which pairs of acrocentrics could have contributed the polymorphisms observed on each of the bisatellited chromosomes. This process is illustrated by the following example. In case I, polymorphisms on a maternal 14, 15 and 21 were similar to the proximal polymorphism on

[8]Scores assigned to each chromosome are listed in the Appendix.

Table 7. Normal acrocentrics not excluded as contributors in cases I-III.

		13				14				15				21				22			
		P	P	M	M	P	P	M	M	P	P	M	M	P	P	M	M	P	P	M	M
Case I	p								+'				+'						+		+
	q										+'	+	+								
Case II	p						+'		+		+'	+			+'						
	q												+								
Case III	p							+'	+'	+		+'	+			+'			+		
	q												+								

M = maternal, P = paternal, p = supernumerary short arm polymorphism, q = supernumerary long arm polymorphism, + = not excluded, +' = not excluded and also inherited by proband.

Table 8. Normal acrocentrics not excluded as contributors in cases IV and V.

		13a	13b	14a	14b	15a	15b	21a	21b	22a	22b
Case IV	p			+		+	+	+	+		+
	q				+						
Case V	p										
	q	+		+	+	+	+	+	+	+	+

p = supernumary short arm polymorphism, q = supernumerary long arm polymorphism, + = not excluded.

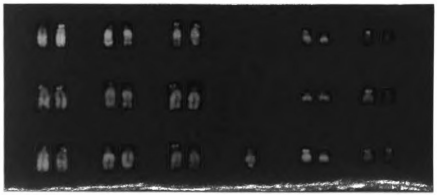


Figure 13. QFQ polymorphisms in family of DD. Top: paternal. Middle: maternal. Bottom: DD.

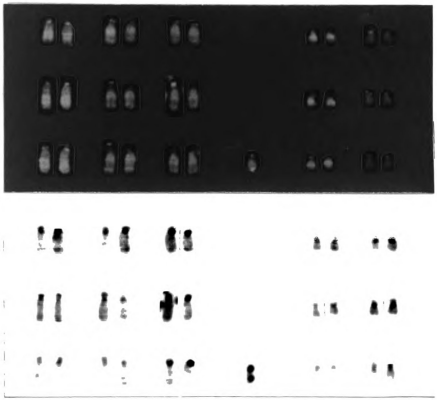


Figure 14. QFQ - CBG polymorphisms in family of CL. Upper photo, QFQ. Top: paternal. Middle: maternal. Bottom: CL. Lower Photo: same chromosomes with CBG staining.

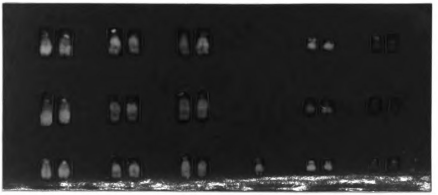


Figure 15. QFQ polymorphisms in family of ML. Top: paternal. Middle: maternal. Bottom: ML.

Figure 16. QFQ polymorphisms in cases IV and V. Top: RF. Bottom: EL.

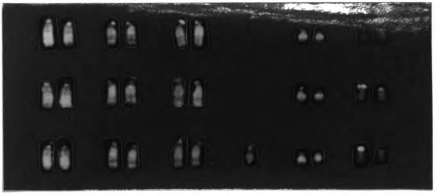


Figure 17. QFQ polymorphisms in family of TM. Top: paternal. Middle: maternal. Bottom: TM.

the proband's bisatellited chromosome. The only maternal acrocentric with a polymorphism similar to the distal polymorphism on the bisatellited chromosome, was a number 15. Therefore, maternal 14/15, 15/15, or 21/15 rearrangements could have given rise to the marker. The same reasoning was applied to each person analyzed, and the results are given in Table 9.

In case II, involvement of at least one number 15 was indisputable. The distal end of the bisatellited chromosome was marked by a brilliant satellite present only on a maternal 15. Polymorphisms in cases I and III also indicated involvement of at least one number 15. In all three, a 15/15 rearrangement was one of the possibilities consistent with the data. In cases II and III, only maternal chromosomes were likely to have participated in the rearrangement.

In cases IV and V, involvement of number 15 could not be determined from the limited data. Both patients inherited normal 15's with polymorphisms similar to those on their bisatellited chromosomes, an observation not inconsistent with the anti-5-methylcytidine results. In case V, the proximal polymorphism of the bisatellited chromosome did not match any of those present on normal acrocentrics. This indicated a meiotic origin.

The exclusion of mosaicism, according to the calculations of Hook (1977), is given in Table 10. No dicentric chromosomes, or fragments of a possible anaphase bridge origin were observed. Although the long arm chromatids of the bisatellited chromosomes were generally held in a characteristic parallel position (Figure 7), constriction-like abnormalities were not observed at their distal ends. As previously noted, the primary constriction in each did not vary in

Table 9. Possible rearrangements giving rise to supernumeraries as determined from tables 6 and 7.

	Maternal	Paternal	Mitotic
Case I	14/15 15/15 15/22	15/22	14/15 15/15
Case II	14/15 15/15	None	None
Case III	14/15 15/15 15/21 15/22	None	None
Case IV	?	?	14/14 14/15 14/21 14/22
Case V	?	?	None

Table 10. The highest level of mosaicism excluded in patients with .95 and .99 confidence levels.

	Cells	.95	.99
Parents (all)	50	6%	9%
Case I	350	1%	2%
Case II	206	2%	3%
Case III	279	2%	2%
Case IV	330	1%	1%
Case V	100	3%	5%

Table 11. Possible rearrangements giving rise to the supernumerary in case VI as determined by familial polymorphisms.

Maternal	Paternal	Mitotic
14/14	14/15	14/14
14/15	14/22	14/15
14/21	15/22	14/22
15/15		15/15
15/21		15/22

position.

There was no evidence of paracentric or pericentric inversion of chromosome 15 in standard metaphase preparations from any of the parents or patients. Parental karyotypes in all cases were normal.

4b. Cytogenetics, case VI.

A preliminary evaluation of 30 cells from case VI revealed a modal count of 47 chromosomes with no evidence of mosaicism. The extra chromosome was an acrocentric somewhat smaller than a number 21, and characterized by terminal satellites on both arms (Figure 18). Either end of the marker participated in satellite association; both ends were never observed in association at the same time.

CBG banding revealed only a single large proximal heterochromatic region, even in prometaphase spreads.

The intensity of the QFQ long arm pattern was most consistent with the proximal portions of 13q and 15q. It was less consistent with 14q, and inconsistent with chromosomes 21 and 22 (Figure 17). The GTG technique produced relatively poor banding even with repeated trials; observed patterns were essentially devoid of landmarks. The entire long arm was lightly stained, with intense banding only at the centromere and short arm. The overall pattern was consistent with all the acrocentrics except number 21. The RHG technique produced moderately dark staining on the entire long arm, and was consistent with the proximal portion of 15q. Anti-5-methylcytidine banding produced intense staining on the marker's short arm. A trace amount of banding was observed at the distal tip of the long arm (O.J. Miller, personal communication).

Figure 18. Extra chromosome in case VI shown with a normal G group for size comparison. Top: conventional giemsa. Bottom: RHG staining.

An analysis of polymorphisms was conducted using the same format established in cases I-V. Unlike these cases, the terminal satellites were stained with equal intensity, and did not exclude a sister chromatid exchange as a possible mechanism.

A comparison of familial QFQ and CBG polymorphisms can be found in the appendix. The results were ambiguous, but did exclude chromosome 13 from the rearrangement. Possible rearrangements consistent with the polymorphism data are listed in Table 11.

An evaluation of 50 cells from each parent, and 100 cells from the patient did not reveal evidence for additional cell lines or inversion heterozygosity.

The evidence obtained on this patient is consistent with the following interpretation: t(15;15)(p11;q14 or 15), but others may be proposed.

Discussion

1a. Identification of the bisatellited chromosomes.

Six patients with de novo bisatellited acrocentric supernumeraries were evaluated with a combination of five banding techniques. QFQ, GTG, RHG, and CBG procedures produced identical findings in cases I-V. Each bisatellited chromosome had a single primary constriction and two terminal CBG positive regions, presumably composed of acrocentric short arm material. The medial euchromatin bordered by these regions had GTG, QFQ, and RHG patterns consistent with 15q11 → 15, and to a lesser extent, proximal 13q. The marker in the sixth patient did not have a distal CBG band and was somewhat smaller, but in other respects,

resembled the first five. Anti-5-methylcytidine banding was performed in all cases because of its ability to differentiate chromosome 15 material from other acrocentrics. Both CBG positive regions in the first five patients banded with this technique, indicating a complex origin from chromosome 15. The sixth marker stained on its short arm, and also at the tip of its distal long arm, suggesting that it might represent a variant form of the larger bisatellited chromosomes.

Chromosome polymorphism studies confirmed much of the anti-5-methylcytidine data in cases I-III. Asymmetrical QFQ polymorphisms on each supernumerary ruled out an origin by sister chromatid exchange. QFQ and CBG preparations indicated that at least one chromosome 15 had contributed to the bisatellited derivatives, but did not establish the specific identity of the second chromosome involved. Anti-5-methylcytidine studies had indicated that a 15/15 rearrangement was present, and the polymorphism data were consistent with this interpretation. In cases IV-VI, polymorphism data were limited. However, no inconsistencies with the anti-5-methylcytidine results were evident, and a sister chromatid exchange was ruled out by asymmetrical QFQ polymorphisms in cases IV and V.

From these observations we concluded that the extra chromosomes in cases I-V were identical with markers studied in six patients by Schreck et al. (1977). Following their nomenclature, the bisatellited derivatives are designated inv dup(15)(pter → q1:p1 or q1 → pter). To our knowledge, the extra chromosome in case VI has not been previously reported. It is tentatively described here as t(15;15)(p11; q14 or 15).

1b. Further characterization of the inv dup(15) chromosome.

Three alternative structures can be proposed (see Figure 19).

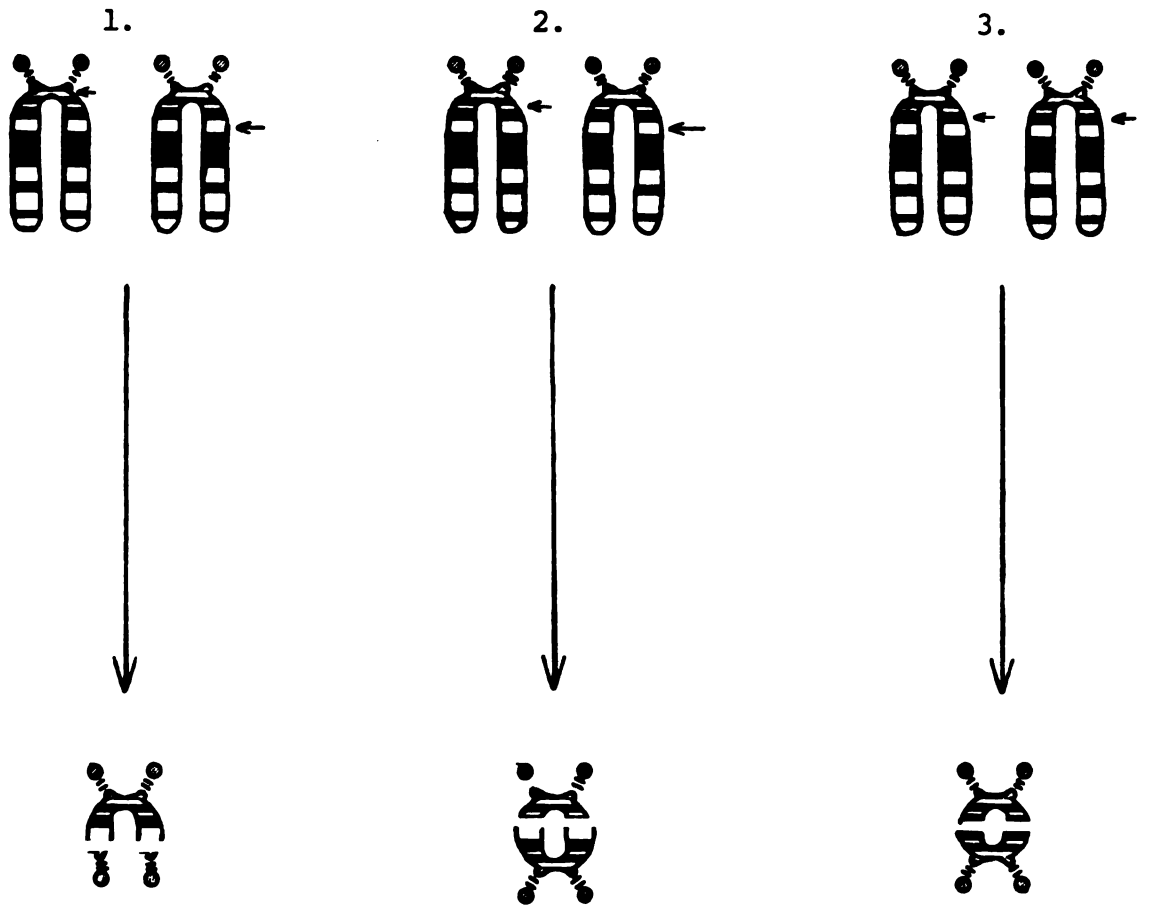
1) t(15;15)(p11;q15): a monocentric derivative produced by translocation of short arm material from one number 15 to a breakpoint at q15 on the long arm of the second number 15. This represents a proximal trisomy of 15q, and a partial tetrasomy of 15p.

2) tdic(15;15)(q;q): a dicentric derivative produced by translocation of the short arm, centromere, and proximal long arm from one number 15 to a breakpoint on the proximal long arm of a second number 15. The breakpoint on the first number 15 would lie proximal to band 15q14, and on the second number 15, distal to this band. The rearrangement would represent a proximal trisomy/tetrasomy of 15q, and a full tetrasomy of 15p.

3) tdic(15;15)(q14;q14): a dicentric derivative produced by a U type exchange or symmetrical translocation involving two number 15's. It represents a tetrasomy for 15pter → 15q14.

Current metaphase banding techniques lack sufficient resolution to distinguish between these alternatives. Of bands 15q11 → 15q15, only 15q14 is consistently reproduced in RHG and GTG preparations. A similar band is present on the inv dup(15), but none of the proposed structures require a change in its position or appearance. Prometaphase banding techniques may be useful in solving this problem, once they are adequately developed.

The demonstration of a second centromere would eliminate option 1. Dicentric studies have been reported in one previous case (Van Dyke et al., 1977). An additional fragment was interpreted as the



t(15;15)(p11;q15) tdic(15;15)(q;q) tdic(15;15)(q14;q14)

Figure 19. Alternative structures for inv dup(15).

product of a bridge-breakage-fusion cycle due to reactivation of the inv dup(15)'s second centromere. In our patients, semi-constricted long arms, distal primary constrictions, or other morphological abnormalities were not observed. Furthermore, there was no indication of the mosaicism described by Van Dyke et al. (1977).

Certain characteristics were noteworthy. Satellite polymorphisms marked the opposing ends of each inv dup(15), making it possible to observe any shift in the position of the primary constriction. None were noted. Asymmetrical QFQ and CBG polymorphisms were also described in seven previous cases (Schreck et al., 1977, Pfieffer and Kessel, 1976, Rasmussen et al., 1976, Centerwall and Morris, 1975), and no inconsistencies were noted. In our patients, inv dup(15) long arm chromatids were held in a characteristic parallel attitude, whereas similar sized G group chromosomes tended to have widely separated chromatids. In early metaphase, the size of the inv dup(15) proximal and distal CBG bands were generally equivalent. However, the distal band seemed to decrease in size more rapidly than the proximal band as metaphase progressed. This was also true of the distal satellites; they became increasingly more difficult to resolve in later periods of metaphase, when compared to the proximal satellites. This phenomena seems to reflect an abnormal change in the rate of condensation of the distal-most regions, a characteristic also observed in a previous case of a type 2 autosomal dicentric (Wisniewski et al., 1978).

Premature condensation of the distal-most regions may be related to a mechanism allowing maintenance of inactive centromeres. However, this point must be confirmed in later studies. All five inv dup(15) chromosomes described in this report did not display morphological

characteristics associated with type 2 dicentrics, with the possible exception of centromeric dominance. We must conclude that current data is insufficient to resolve the number of centromeres on these rearrangements.

2a. The inv dup(15) phenotype, cases I-V.

The developmental histories of our patients were remarkably similar, and perhaps the most characteristic aspect of this disorder. Four of the five pregnancies were full term, and all birth weights were appropriate for gestational age. No abnormalities of any significance were noted at birth or in the neonatal period, although two infants experienced feeding problems due to a poor sucking reflex. Hypotonia and/or developmental retardation were noticeable in the first year. As infants and young children, our patients were generally inactive and lethargic. In two cases, indifference to external stimuli prompted questions of possible sensory impairment.

Developmental milestones were grossly delayed in all five children. Speech and toilet training were never achieved in two. Four walked with an awkward gait, and three were toe walkers. Between the ages of 4 and 6, each of our patients grew increasingly hyperactive, aggressive, and unpredictable. Mental retardation was obvious; all five were eventually too difficult to manage in the home environment, and were institutionalized. Because of past medical histories, gait abnormalities, and the absence of congenital malformations, diagnostic workups tended to favor disorders related to postnatal insult.

Four of the five patients developed a convulsive disorder in the institutional environment. The age of onset ranged from 5 to 18,

and the frequency of seizures tended to increase with age throughout adolescence. In the two older patients, the disorder gradually disappeared, and recent EEG's were interpreted as normal. A reduction in hyperactivity also roughly followed the abatement of seizures. The remaining two cases with seizures appear to be following the same general course. The patient who never developed a convulsive disorder has remained chronically hyperactive and abusive.

All five patients are mentally retarded, two profoundly, and three severely. The behavior of our least retarded case (Case I) resembles that of the patient of Rasmussen et al. (1976) who was diagnosed with infantile autism.

All five patients are free of major life threatening defects, and enjoy generally good health.

It is important to note that the mildly dysmorphic features in these patients were recognized only after careful examination. The facies was not strikingly dysmorphic. The head shape was suggestive of a mild dolicocephaly, with the visual impression of bitemporal narrowing. A flat occiput was noted in two patients. Facial abnormalities often included strabismus, slight antimongoloid slant, short philtrum, and slightly lowset ears. Enopthalmia, facial asymmetry, high arched palate, prolonged chin, malocclusion, and malformed ears were seen in one or two cases. Neck and trunk deformities were absent except for low hairlines and lordosis in two patients. Urogenital anomalies were completely absent, as were heart defects. Certain minor limb malformations were noted. The carrying angle in all our patients was increased. Proximal placement of thumbs, and

clinodactyly were occasionally seen. In two patients, the placement of digits into the palm appeared more arched than usual. Dermatoglyphic abnormalities were present, but in a nonspecific fashion. Arches or radial loops were observed on digits other than number 2, and case V had elevated atd angles. The legs and feet were generally unremarkable. One patient had a high instep (probably familial), and two had proximally placed fifth toes. Four of the five had webbing between the second and third toes bilaterally. Short stature was observed in three patients, but true microcephaly was not. Neurological findings were essentially normal, as were the results of SMA-12, CBC, urinalysis, and radiological studies.

A few unusual features were noted. Two patients had dark skin pigmentation, a trait recognized by, but not in, their families. One had a normal menstrual history, but lacked breast development. One patient had a mild hemiparesis, while another had a peculiar persistent breath and body odor.

2b. The inv dup(15) syndrome.

A total of 19 cases likely to have the same inv dup(15) chromosome as our patients were ascertained in the literature. Seven of these have been confirmed by anti-5-methylcytidine banding (Schreck et al., 1977, Van Dyke et al., 1977). The remaining 12 (see Table 2) compare well with the GTG, QFQ, and CBG findings in our five cases, and the seven previously confirmed. We feel that there is little uncertainty in considering all as examples of the same chromosome abnormality, an assumption strengthened by phenotypic considerations

Table 12. Phenotypic findings of inv dup(15) syndrome in previously reported cases.

Case #	15	16	17	18	19	20	21	22	23	25	27	28	29	30	31	32	
Sex	M	F	M	M	M	F	M	F	M	F	M	F	M	M	M	F	6F/10M
Birthweight				3.2	3.6	3.4		3.8	2.5	3.2	3.6	3.0	2.9				
Maternal Age	39	23		28	34	33	43	30	36	39			38	42	36	34	35 (13)
Paternal Age	33			33		38	42	30	37	35			36	45	42	53	38.5 (11)
Full Term				+	+	+		+	-	+	+	+	+				8/9
Brachycephaly				-	-						+		-				1/4
Dolicocephaly				-	-								-				0/3
Flat Occiput				-	-						+		-				1/4
Microcephaly		-		-	-	-	-	+	-		+		-				2/9
Facial Asymmetry					-									+			1/2
Low Hairline				-	-			-					-				0/4
Antimongoloid Slant				+	-	-	-	-					-				1/6
Enopthalmos				-	+	-	-	-					-				1/6
Epicanthus		-	+	+	-	-	-	-			+	+	-				4/10
Strabismus	+	+	+	-	+	+	-	+		+		+	+	-	-	+	10/14
Nystagmus				-	-	-	-	-					-				0/6
Short Philtrum				-	-	-		-					-				0/5
Malocclusion	+			-	-	-		-					+				2/6
Lowset Ears				-	-	-	+	-			-		-				1/7
Rotated Ears				-	-	-	-	-			-		-				0/7
Arched Palate		-		-	+	-	+	-					-				2/7
Camptodactyly		-		-	-			-				+	-				1/6
Clinodactyly		-		-	-		+	-					-				1/6
Proximal Thumbs		-		-	-			-					-				0/5
Proximal Toes		-		-	-			-					-				0/5
Webbing Toes 2 & 3		-		-	+			-			+		-				2/6
Carrying Angle		-		-	-			-					-				0/5
Short Stature		-		-	-		+	-	+	+	+	+	-				5/10
Scoliosis		-		-	-		-	-				+	-		+		2/8

Table 12 (continued)

Case #	15	16	17	18	19	20	21	22	23	25	27	28	29	30	31	32	
Lordosis				-	-		-						-				0/4
Kyphosis	+			-	-		-						-				1/5
Hypospadius				-	-		-						-	+			1/5
Normal Menses										+							1/1
Normal Breasts										+							1/1
Heart Defect		-		-	-			+	-	-			-				1/7
Mental Retardation	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	15/15
Developmental Retard.			+	+	-	+	+	+	+	+		+					8/9
Hyperactivity		+		+	+			-					+				4/5
Autism	+		-	+					+	+			-				4/6
Hypotonia		-	+	+	+	+		+	+	+		+	-	+			9/11
Abnormal Gait				-	-				+	+			-				2/5
Toe Walking				-	-								-				0/3
Aggression				-	+								-				1/3
Seizures		-		+	+	+	+	+	+		+				+		8/9
Abnormal EEG				+	+	+		+	+	+	+		+				8
Dermatoglyphics		+		-	-		+	+	-	+	+	+	+				7/10

discussed in this section.

Three of the published cases were excluded from phenotypic comparison for reasons previously given (see literature review). The data available on the remaining 16 ranged from complete to minimal. When reviewing these cases, it was often difficult to determine the normal features of each patient, and statements made by several authors regarding an overall absence of malformations in their patients were not reassuring. Patients were scored normal, or lacking a feature, if it was specifically stated that an examination for the feature had been attempted, if a specific anatomical area had been evaluated and found normal, or if the feature was mentioned in a comparison with other patients. Published photographs were in general not acceptable sources of data. Even with these precautions, biases could not be avoided. To help overcome this problem, authors were contacted by letter, and additional data was obtained on three cases (Van Dyke, Crandall, personal communication).

A summary of the findings in these 16 patients appears in Table 12. The results are compared with our cases in Table 13. There was good agreement on the range of phenotypic features in both groups. Data on birth weights, pregnancy duration, and parental ages were in close agreement, as were the frequencies of the most common abnormalities. With the exception of a short philtrum, the same facial features were present in both groups. Limb anomalies were less frequent in the published cases. In particular, there were no previous reports of increased carrying angles, or proximally placed digits. The vertebral column was involved in both groups; lordosis was seen in our cases,

Table 13. Comparison of findings in previously reported cases with those in cases I-V.

Sex	6F/10M	3F/2M
Maternal Age	35 (13)	34.6 (5)
Paternal Age	38.5 (11)	35.2 (5)
Full Term	8/9	4/5
Brachycephaly	1/4	0/5
Flat Occiput	1/4	2/5
Microcephaly	2/9	0/5
Facial Asymmetry	1/2	2/5
Low Hairline	0/4	2/5
Antimongoloid Slant	1/6	3/5
Enopthalmos	1/6	2/5
Epicanthus	4/10	1/5
Strabismus	10/14	3/5
Nystagmus	0/6	1/5
Short Philtrum	0/5	4/5
Malocclusion	2/6	1/5
Lowset Ears	1/7	4/5
Rotated Ears	0/7	3/5
Arched Palate	1/7	2/5
Camptodactyly	1/6	1/5
Clinodactyly	1/6	2/5
Proximal Thumbs	0/5	2/5
Webbing Toes 2 & 3	2/6	4/5
Carrying Angle	0/5	5/5
Short Stature	6/10	3/5
Scoliosis	2/8	0/5
Lordosis	0/4	2/5
Kyphosis	1/5	0/5
Hypospadius	1/5	0/2
Normal Menses	1/1	3/3
Normal Breasts	1/1	2/3
Heart Defect	1/7	0/5
Mental Retardation	15/15	5/5
Developmental Retardation	8/9	5/5
Hyperactivity	4/5	5/5
Austism	4/6	1/5
Hypotonia	9/11	4/5
Abnormal Gait	2/5	4/5
Toe Walking	0/3	3/5
Aggression	1/3	5/5
Seizures	8/9	4/5
Abnormal EEG	8	4/5
Dermatoglyphics	7/10	4/5

while scoliosis and kyphosis were described in the others. Only a single instance of a heart defect or urogenital anomaly was evident. The behavioral abnormalities in our patients were also reported in some of the previously described cases. Of particular interest was the diagnosis of autism in four cases. Mental retardation was the common denominator of both groups. Our patients were severely and profoundly retarded; examples of mild and moderate retardation were present in the published group. Convulsive disorders were common in the reported cases. The age of onset of seizures was earlier, and the frequency more erratic in the patients of Power et al., 1977, Watson and Gordon, 1974, Crandall et al., 1973, Centerwall and Morris, 1975. Two cases reportedly suffered grand mal seizures as early as age six months.

A syndrome may be defined from a composite of both groups. However, the frequency of certain features may later be amended. Features to be expected in 80 to 100% of the patients are: mental retardation, gross developmental retardation, hypotonia, and behavioral disorders (hyperactivity, autism, aggression). 60% to 80% of the cases can be expected to have strabismus, short stature, convulsive disorders, and nonspecific dermatoglyphic findings. From 20% to 60% should have mild facial dysmorphisms such as a flat occiput, epicanthus, antimongoloid slant, enopthalmos, short philtrum, and lowset ears. The same number should possess limb anomalies such as an abnormal carrying angle, clinodactyly, proximally placed digits, and webbing between toes 2 and 3. It should be emphasized that the expression of these traits is generally mild. Vertebral anomalies including

scoliosis, kyphosis, and lordosis occur in approximately 25% of the patients.

Abnormalities of the urogenital system or heart are very unlikely. Aside from strabismus and hypotonia, abnormal neurological signs may occur, but are infrequent and nonspecific. Contractures, tremor, absent and hyperactive reflexes were observed in isolated cases. The gait may or may not be abnormal. In at least two cases (Crandall, personal communication, and Case II), the patients' coordination and dexterity were especially good during childhood. Radiological, hematological, and biochemical findings are generally unremarkable. Virtually all patients were the products of full term pregnancies, and uncomplicated deliveries. Birth weights were appropriate for gestational age.

Two instances of mosaicism with contrasting phenotypes were reported. The mother of two cases described by Power et al. (1977), was herself a 46/47 mosaic. Only a single tissue was sampled, but from her reproductive history, it is safe to assume that gonadal tissue was also involved. She did not present with any abnormalities clearly related to the extra chromosome. The patient of Van Dyke et al. (1977) had an unusual 46/47/48 mosaicism, and was as severely affected as the other cases. It was more likely in his case that the normal cell line arose after conception.

The inv dup(15) phenotype is relatively unique among recognized autosomal syndromes. It is only mildly dysmorphic, and best characterized by mental and developmental retardation, seizures, and behavioral disorders.

2c. Unresolved cases similar to inv dup(15).

Phenotypically, case VI resembles the inv dup(15) syndrome. He was born at full term, and was inactive and hypotonic as an infant. Later examinations revealed an abnormal EEG, developmental retardation, hyperactivity, epicanthal folds, strabismus, rotated ears, clinodactyly, proximally placed thumbs, an increased carrying angle, webbing between toes 2 and 3, and abnormal dermatoglyphics. In addition, his growth rate has shown a gradual decline.

Certain cases in the literature may have inv dup(15) or a modified form. Padfield et al. (1968) described a case of Rubinstein-Taybi syndrome that Simpson (1973) later reported with an extra bi-satellited chromosome. The patient was the product of a full term pregnancy, with normal birth weight. Both parents were 39. She had an antimongoloid slant, epicanthus, strabismus, nystagmus, short philtrum, malocclusion, ear deformities, arched palate, broad thumbs and toes, seizures, toe walking, and profound mental retardation (Partington, personal communication). Simpson interpreted the error as a partial trisomy 14 with G banding. The original karyotypes left some doubt, and the phenotypic findings were not entirely consistent with proximal trisomy 14 (Simpson and Zellweger, 1972).

Three cases in category 1 of the proximal 15 trisomies share many features in common with the inv dup(15) patients, and have not received an exhaustive cytogenetic evaluation (Webb et al., 1967, Magenis et al., 1972, Howard-Pebbles et al., 1977. See Table 1 and appendix for further details.).

2d. Comparison of proximal trisomy 15 with the inv dup(15) syndrome.

Cytogenetic studies on the inv dup(15) rearrangement failed to clarify the nature of the euchromatic error. A recomparison of proximal trisomy 15 patients to those with inv dup(15) was performed with the hope of clarifying this problem. The results (excluding cases 1, 2, and 4 from the proximal trisomy group) are given in Table 14. A clear phenotypic distinction between the proximal trisomy and inv dup(15) patients is apparent. Proximal trisomy 15 is associated with more physical dysmorphisms, but not with seizures and behavior disturbances. This would seem to argue that the euchromatic errors are quantitatively different. Unfortunately, a number of reasonable objections can be raised against the significance of this comparison. The preponderance of physical malformations in the trisomy patients may be attributable to autosomal imbalances involving chromosomes other than number 15, since most of these cases resulted from malsegregating familial translocations. Furthermore, the exclusion of cases 1, 2, and 4 is not fully warranted; they may actually represent "pure" proximal trisomies.[9]

Additional banding studies on cases I, II and IV are certainly called for. Phenotypic similarities between these patients and those with inv dup(15) suggest that both groups may have the same euchromatic imbalance. A clear demonstration of this imbalance in

[9]The term "pure" is used in reference to a karyotypic aberration involving a well defined segment of <u>one</u> chromosome only. "Pure" proximal trisomies are especially valuable in phenotype - karyotype coorelations. Since there is no complicating input from a second chromosome (as in a translocation), phenotypic abnormalities can be attributed to the "pure" aberration without ambiguity.

Table 14. Comparison of phenotypic findings associated with proximal trisomy 15 and those in inv dup(15) syndrome.

	Partial Trisomy	inv dup(15)	
	(11)	Cases I-V	Literature (16)
Strabismus	6/11	3/5	10/14
Epicanthus	1/11	1/5	4/10
Enopthalmos	3/8	2/5	1/6
Hypertelorism	3/7	0	0
Lowset Ears	7/11	4/5	1/7
Malformed Ears	4/7	1/5	0
Malocclusion	3/8	1/5	2/6
Palate Anomaly	9/11	2/5	2/7
Micrognathia	6/8	0	0
Chest Deformity	3/8	0	1
Kyphosis	3/8	0	1/5
Webbing of Toes 2 & 3	3/11	4/5	2/6
Genital Anomaly	3/8	0	1
Short Stature	6/11	3/5	6/10
Mental Retardation	10/10	5/5	15/15
Hyperactivity	0	5/5	4/5
Autism	0	1/5	4
Seizures	0/6	4/5	8/9

cases I, II and IV may help to resolve the structural ambiguity of inv dup(15).

3a. Mechanisms in the origin of inv dup(15).

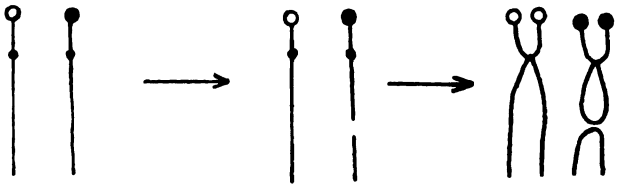
Data bearing upon the origin of inv dup(15) suggest a spontaneous meiotic rearrangement and nondisjunction. An analysis of polymorphisms revealed the following information on our patients (see Table 9).

Case	Origin
I	Maternal meiotic or post-meiotic
II	Maternal meiotic
III	Maternal meiotic
IV	Inconclusive
V	Meiotic, parent unknown

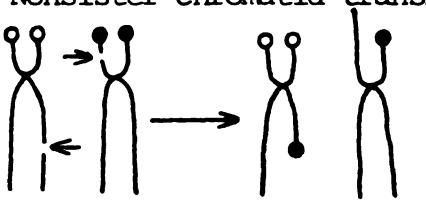
In previously reported cases only two were mosaics, and it was not or could not be determined when their normal cell lines arose.

The discussions of Van Dyke et al. (1977), and Schreck et al. (1977) also emphasized meiotic events. Five mechanisms possibly responsible for the rearrangements are summarized in Figure 20. Mechanism I produces a dicentric inv dup(15) with identical proximal and distal polymorphisms, and is inconsistent with seven previously reported patients and cases I-V. Mechanism II produces a monocentric inv dup(15) with dissimilar proximal and distal polymorphisms, and is consistent with the data. Mechanism III produces a dicentric inv dup(15) and is also consistent with the data. Mechanisms IV and V involve parental chromosome 15 inversion heterozygosity. Mechanism

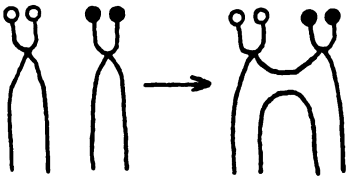
I. Sister strand reunion.



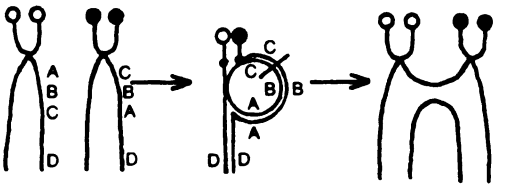
II. Nonsister chromatid translocation.



III. U-type nonsister chromatid exchange.



IV. Paracentric inversion.



V. Pericentric inversion.

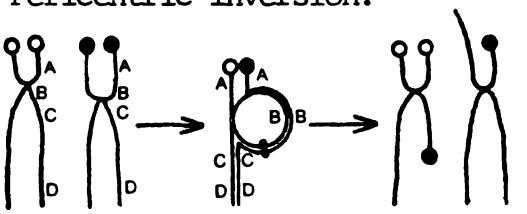


Figure 20. Five mechanisms in the origin of inv dup(15).

IV requires careful consideration. The derivative, a dicentric inv dup(15) with asymmetrical polymorphisms, is consistent with the data. A parental paracentric inversion of 15q11 → 15q15 would be difficult to detect with current metaphase banding techniques. Studies on the parents of our patients, and those of Van Dyke et al. (1977) were noninformative. A prometaphase study of these individuals is highly desirable since discovery of such an inversion would indicate a higher recurrence risk. Mechanism V, pericentric inversion heterozygosity, would be accompanied by a noticeable change in the arm ratio of the affected homolog. Such a chromosome has not been observed in our data, nor reported previously.

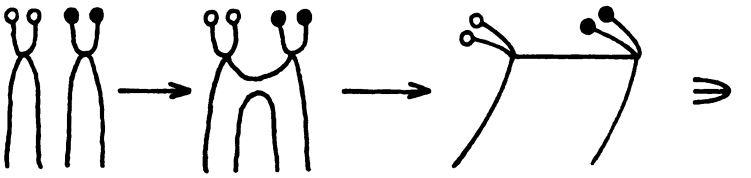
Mechanisms II, III, and IV are the most probable, and require a nondisjunction at some point in meiosis. The theoretical segregation behavior of these rearrangements is diagrammed in Figures 21 and 22.

In mechanism II, first and second division nondisjunctions produce the same findings as mechanisms III and IV: a first division error will result in the inheritance of an inv dup(15) and a normal 15 with <u>non-identical</u> proximal polymorphisms; a second division error will result in the inheritance of an inv dup(15) and a normal 15 with <u>identical</u> proximal polymorphisms.[10]

Chromosome 15 and inv dup(15) polymorphisms from cases I-V (see Tables 6 and 7), and the patient of Pfieffer and Kessel (1976) can be compared with these predictions. If all six cases are presumed to be

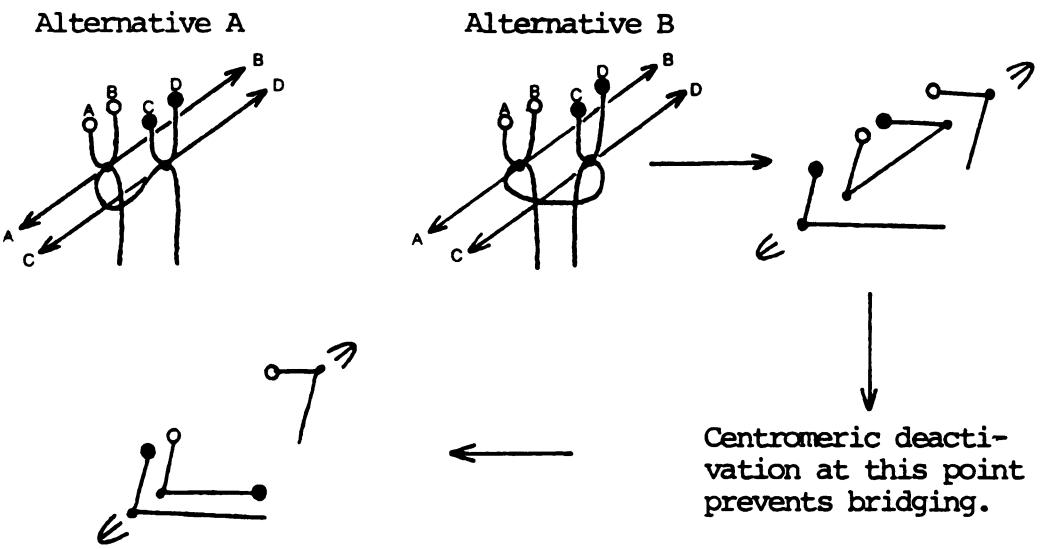
[10]Interpretations of meiotic errors based on the use of chromosomal polymorphisms only must take short arm crossing over into account. Chiasma on acrocentric short arms are difficult to resolve, but are believed rare (Hulten and Lindsten, 1970).

1) First division nondisjunction.

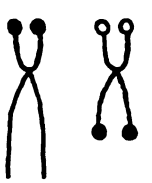


One gametocyte receives all chromosome 15 material. The second receives none.

2) Second division disjunction and centromeric deactivation. Two orientations on the spindle are possible. Alternative A is inconsistent with the data. Alternative B produces the appropriate gametes.



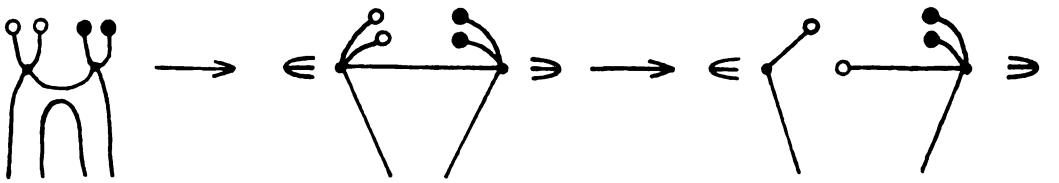
3) Result, a 24 + inv dup(15) gamete. Note that the proximal polymorphisms of the inv dup(15) and the normal 15 are not identical, and that the distal inv dup(15) polymorphism is identical to that of the inherited normal 15.



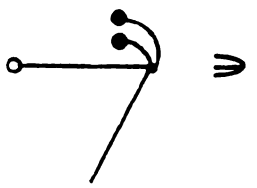
(Note that the chromosomes are single stranded at this stage, but are drawn double stranded for the sake of clarifying inv dup(15).)

Figure 21. First division nondisjunction and second division centromeric deactivation of inv dup(15) derived from either a paracentric inversion, or a U-type exchange.

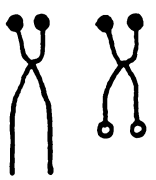
1) First division centromeric deactivation prevents bridging.



2) Second division nondisjunction of the normal 15/inv dup(15) dyad.



3) Result, a 24 + inv dup(15) gamete. Note that in this case, the proximal polymorphisms on the inv dup(15) and the normal 15 are identical.



(Note that the chromosomes are single stranded at this point, but are drawn double stranded to clarify inv dup(15).)

Figure 22. First division centromeric deactivation and second division nondisjunction of inv dup(15) derived from either a paracentric inversion or a U-type exchange.

meiotic in origin, the following conclusions regarding the division of nondisjunction can be drawn:

Case	First Division Nondisjunction	Second Division Nondisjunction
I		+
II		+
III		+
IV		+
V	+	
Pfieffer and Kessel		+

Five of the six cases apparently nondisjoined in the second meiotic division. If a dicentric structure is also assumed, then centromeric deactivation probably occurred in first division in five cases, and in second division in one case.

Studies on nondisjunction in Down syndrome have demonstrated its occurrence in both divisions, and both parents (Mikkelson et al., 1976, Wagenbichler et al., 1976). A relationship between advanced parental age and an increased likelihood of primary nondisjunction is well established in man. (Lilienfield and Benesch, 1969, Penrose and Smith, 1966). The data for inv dup(15) also suggest that the risk for offspring with this abnormality increases with parental age. The mean maternal age in 18 cases was 34.8; the mean paternal age in 16 cases was 37.5.

Although the timing of events in meiosis can be predicted from the theoretical behavior of inv dup(15), there is no evidence favoring one mechanism of rearrangement over the others. An additional complication must also be recognized. Two cases probably underwent further structural modification during, or following, the initial rearrangement. In the patient of Centerwall and Morris (1975), and in one patient of Schreck et al. (1977), proximal satellites were inexplicably

deleted. These variants suggest that the mechanism producing some inv dup(15)'s is more complex than those previously reviewed. The nature of this alternative mechanism is not apparent in the data.

3b. Additional etiological considerations.

Reproductive histories were incompletely reported in the literature. Data for the calculation of spontaneous abortion frequencies in families where consanguinity or mosaicism were not present, were obtained from cases I-V, and the reports of Crandall et al. (1973), Centerwall and Morris (1975), and Pfieffer and Kessel (1976). A total of 41 pregnancies and 34 live births gave an abortion frequency of .17, a figure consistent with the expected value, .15. The mosaic described by Power et al. (1977) had a total of two affected and three normal children, a first trimester spontaneous abortion, and a second trimester spontaneous abortion. Assuming that all of her gonadal tissue contained the inv dup(15), approximately one half of her pregnancies were at risk due to secondary nondisjunction.

The remaining families were ascertained through a single affected child. One patient (Kakati and Sinha, 1973) had a hyperactive sib, but no details were available. The patient of Van Dyke et al. (1977) had two sibs in special education classes. The parents were first cousins. The only sib of patient RD (Crandall et al., 1973) died of multiple congenital anomalies including absent thumbs and spina bifida. The remaining family histories were unremarkable.

No teratogenic exposure prior to conception was evident for any of our patients or those reviewed in the literature. Birth dates were

available in only six cases, and were insufficient to suggest any seasonal clustering. In parity, patients were always last, or second to the last, reflected in a high mean parental age. First cousin consanguinity was reported in the parents of two cases (Van Dyke et al., 1977, Watson and Gordon, 1974). The nationality of the consanguineous parents were Pakistani and Palastinian. In the remaining cases, racial background, where reported, was caucasian, except for case V, a black American female.

3c. Etiological conclusions.

It is concluded that inv dup(15) arises sporadically, is more likely in offspring of older parents, and cannot as yet be associated with a specific recurrence risk. A common mechanism of origin is likely, given the consistency of the rearrangement. Prophase banding studies are clearly indicated because of the unsolved question of paracentric inversion heterozygosity. The frequency of reported cases may suggest that an inverted variant 15 is segregating in certain populations, and may carry with it a definable risk for offspring affected with inv dup(15).

Summary

Extra bisatellited acrocentric chromosomes were detected in six unrelated patients with mental retardation and minimal somatic abnormalities. In five of the six, the supernumerary was larger than a number 22, and had GTG, RHG, and QFQ patterns similar to proximal 15q. Proximal and distal CBG bands were demonstrated, indicating a euchromatic segment bordered on either end by material derived from an

acrocentric short arm. A dicentric structure was suggested by these findings, but only a single primary constriction was evident. Anti-5-methylcytidine banding identified chromosome 15 as the origin of the CBG positive material. These results matched those of chromosome 15 derivatives described as inv dup(15)(pter → q1:p1 or q1→ pter) by Schreck et al. (1977).

Alternative structures for inv dup(15) can be proposed. The simplest interpretation is t(15;15)(p11;q15), a proximal long arm trisomy accompanied by a partial short arm tetrasomy. More complex interpretations involving two centromeres and a long arm tetrasomy, such as tdic(15;15)(q14;q14), can also be considered. Current metaphase techniques are unable to distinguish between these alternatives.

Data bearing upon the origin of inv dup(15) were obtained from CBG and QFQ polymorphism studies. Family studies in cases I-III were consistent with the anti-5-methylcytidine data. In cases II-III, QFQ inv dup(15) polymorphisms indicated a maternal meiotic origin. Data on cases IV and V were more limited, although no inconsistencies with the anti-5-methylcytidine results were noted. QFQ polymorphisms in case V supported a meiotic origin.

Inv dup(15) is likely to have arisen via the meiotic mechanisms of translocation, U-type exchange, or parental paracentric inversion hyeterozygosity, followed by a nondisjunction. Proximal and distal QFQ polymorphism asymmetry in all five patients ruled out an origin via sister chromatid exchange. An analysis of the theoretical segregation behavior of the derivative suggested the occurrence of second division nondisjunction in four of our cases, and one in the literature.

The extra chromosome in our sixth patient was smaller than inv dup(15). CBG studies failed to demonstrate a distal heterochromatic band. GTG, QFQ, and RHG results were similar to inv dup(15); anti-5-methylcytidine banding confirmed a chromosome 15 origin. The abberration was interpreted as t(15;15)(p11;q14 or 15). Polymorphism studies were non-informative.

Clinical studies on our cases suggested an association between inv dup(15) and a distinct syndrome. As many as 19 patients with this aberration have appeared in the literature. However, confusion over the identity of the derivative, and the isolated nature of the reports, prevented previous recognition of this syndrome. Comparison of our patients and 16 of the 19 in the literature revealed a consistent pattern of phenotypic abnormalities. Virtually all patients had mental and developmental retardation, hypotonia, and behavioral disturbances. 60% to 80% had seizures, short stature, and nonspecific dermatoglyphic abnormalities. 20% to 40% had mild facial and limb dysmorphisms, and vertebral anomalies. A de novo meiotic origin was indicated in almost all cases, and parental ages were distinctly elevated.

Available data suggests a sporadic occurrence, and are insufficient to propose a specific recurrence risk. Prometaphase banding studies are suggested, both to better define the structure of inv dup(15), and to explore the possibility of parental paracentric inversion heterozygosity.

APPENDICES

APPENDIX A

APPENDIX A

Case Summaries of Previously Reported Cases

Category 1

Case 1. Webb et al. (1967).

Partial D trisomy was reported in a profoundly retarded 8 year old girl. The supernumerary was described as 65% of the size of a normal D group, with a satellited short arm, and a "negatively heteropycnotic" area on the distal end of the long arm. Autoradiography was consistent with chromosome 15. Mosaicism was demonstrated in blood, marrow, and skin. The patient was born to a 46 year old father and a 38 year old mother. The family history was negative. The pregnancy was initially threatened by miscarriage. Birth weight was 3040 gm. Evaluation at 8 years revealed profound mental retardation, hyperactivity, epicanthal folds, mild microcephaly, and normal dermatoglyphics. The mother's pregnancy history included 7 liveborn children, and two first trimester spontaneous abortions.

Case 2. Magenis et al. (1972).

An extra 15q- chromosome with an apparent breakpoint of 15q21 was identified by G and Q banding in a 12 year old girl. The patient was born to a 30 year old mother, was 1 week premature, and weighed 6 lb. 6 oz. She was lethargic and inactive from birth, and difficult to feed. Developmental retardation was evident. At age 12, her height and weight were less than 10th percentile. She was profoundly

retarded, had epicanthal folds, a wide nasal bridge, strabismus, anti-mongoloid slant, large mouth, widely spaced teeth, full lips, retro-cessed large ears, mild kyphosis, spindle shaped fingers, brachy-dactyly of the 5th fingers, and cubitus valgus. Additional findings are available in Centerwall and Morris (1975).

Case 3. Mankinen et al. (1976).

Proximal trisomy 15pter → q15 was identified by Q, R, G, and C banding in a 5.75 year old female. The patient was born to a 36 year old father and a gravida 5, para 4, 34 year old mother. Little fetal activity was noted during the pregnancy. The birth was premature; the patient weighed 2100 gm. and the umbilical cord was wrapped once around the neck. Noted at birth were micrognathia, cleft palate, a hooked nose, and lowset ears. Cardiomegaly, absence of sucking and rooting reflexes, generalized hypotonia, and 50th percentile values for height and weight were mentioned in the first year. At 5.75 years, head circumference, height, and weight were all below the 3rd percentile. Additional findings were prominent philtrum, small mouth, irregular dentition, single palmar creases, clinodactyly, decreased subcutaneous tissue, and severe mental retardation.

Case 4. Howard-Peebles and Yarbrough (1977).

Proximal trisomy 15pter → q21 or 22 was identified by G banding in a 10 year old girl. The patient was born to a 31 year old father and a 30 year old mother. There was a negative family history, no evidence of pregnancy wastage, and 2 normal sibs. The patient's birth was 5 weeks premature, and she weighed 1956 gm. Walking occurred at

15-16 months. She had a severe language delay, poor gross and fine motor control, hyperactivity, and moderate mental retardation. Physical examination at age 10 revealed strabismus, slight hypertelorism, a slightly high arched palate, squared off feet, and bilateral clinodactyly. Her weight was 58th percentile, head circumference 50th percentile, and height 3rd percentile.

Category 2

Case 5. Rethore et al. (1973).

Proximal trisomy 15/partial monosomy 21 was described in a 14.75 year old female due to malsegregation of a maternal t(15;21)(q13;q22). The patient was the product of a normal pregnancy and weighed 2600 gm. at birth. Thrombocytopenia occurred at the age of 4 but later regressed. Examination at age 14.75 revealed the following: oval facies, a high flat forehead, retracted temporal regions, enopthalmos, strabismus, prominent nasal bridge, fleshy nose, short upper lip, prominent raphe of the philtrum, receding chin, short neck, low posterior hairline, lowset slightly malformed ears, narrow shoulders, kyphosis, long second phalanges on digits 3 and 4 bilaterally, limited limb extension, webbing between toes 2 and 3. She was hypotonic, a toe walker, and had an IQ of 17. Her height was 149 cm., weight 57 kg., and head circumference 54 cm. Her dermatoglyphics were abnormal.

Case 6. Rethore et al. (1973).

This is a male sib of case 5 and had the same chromosome abnormality. He was born after 8 months gestation and weighed 2400 gm.

The following were noted at age 5: oval facies, a high forehead, slightly prominent metopic suture, retracted temporal regions, enophthalmos, strabismus, prominent nasal bridge, short upper lip, receding chin, large lowset ears, arched palate, short neck, narrow shoulders, depressed sternum, kyphosis, an extra nipple, undescended testes, long second phalanges on digits 3 and 4 bilaterally, webbing between toes 2 and 3, hypertonia, incomplete limb extension, toe walking, abnormal dermatoglyphics, and an IQ of 20. He had no speech and was not toilet trained.

Cases 7, 8, and 9. Breg et al. (1974).

Two patients with proximal trisomy 15 were reported in this abstract. Castel et al. (1976) attributes a third case to these investigators, and briefly summarized the phenotypic findings in all three. A balanced t(11;15) was responsible in all cases. The breakpoints were not given, but proximal trisomy 15 involved slightly less than one half of the long arm. Castel et al. suggested that partial monosomy 11qter also occurred. Case 7, a male, had growth retardation, mental retardation, hypotonia, limb anomalies, lowset ears, microcephaly, strabismus, cleft palate, hip luxation, and hypotonia. Case 9, a male, had mental retardation, strabismus, and an arched palate. Additional data is available in Centerwall and Morris (1975).

Case 10. Bannister and Engle (1975).

A male with proximal trisomy 15 due to malsegregation of a maternal t(15;17) was described. Although the rearrangement was studied with G banding, breakpoints were not specified. Interpretations

of t(15;17)(q22;p13) or (q15;p12) are both possible, and it may be that a proximal trisomy for 17p also occurred. The patient was the product of a full term uncomplicated pregnancy with breech delivery, and weighed 2400 gm. Development was initially normal, but leveled off after three months. When examined at 16 months, the patient could neither speak nor sit, and his measurements were all below the 3rd percentile. He had lowset rounded and protruding ears, a high arched palate, micrognathia, a beaked nose, antiverted nostrils, bilateral inguinal hernias, a small penis and poorly developed scrotum, clinodactyly, syndactyly of toes 2 and 3 on the right and 3 and 4 on the left, and asymmetrical proximal femoral epiphyses preventing complete hip abduction. Pelvocaliectasis, ureterectasis, and a reflux of the low pressure type were also present.

Case 11. Cohen et al. (1975).

Partial trisomy 15 due to the malsegregation of a maternal t(4;15)(p16;q22) in a 4 year old girl was described. The patient was born after 36 weeks gestation, weighed 2780 gm., and was given an Apgar of 10. At the age of 1, severe myopia and bilateral retrolental opacities were diagnosed. She sat at 2 years and her development was considered very slow. Examination at age 4 revealed severe motor and mental retardation, no speech, blindness, flattened right side of the head, generalized hypertrichosis, microopthalmia, high arched palate, malocclusion, dysplastic posteriorly rotated ears, rocker bottom feet, short second metatarsi, marked spasticity, contractures of the left knee and elbow, frequent fisting, involuntary rhythmic movements, periodic athetotic movements, hypoactive deep tendon reflexes, and

normal dermatoglyphics. Her height and head circumference were both below the 3rd percentile.

Case 12. Castel et al. (1976).

Partial trisomy 15/partial trisomy 7 due to malsegregation of a maternal t(7;15)(q35;q14) was described in a 21 year old girl. Her mother had bilateral hip luxation and blindness in the left eye. The patient was born after 42 weeks gestation. She sat at 4 years, walked at 8, and menstruated at 18. At 21, her height, weight and head circumference were all below 3 s.d. Her IQ was 22, and she had no speech. She was described as quite and shy, with a decreased sensitivity to pain. Physical findings included oval facies, high forehead, thick eyebrows, epicanthal folds, hypertelorism, slight enopthalmos, antimongoloid slant, prominent cheek bones, antiverted nostrils, a small nose, thick lips, prominent raphe of the philtrum, malocclusion, slightly malformed ears, kyphosis, small hands, convex nails, camptodactyly of digits 4 and 5, small feet, bilateral hip luxation, and perception deafness.

Case 13. Pfieffer and Kessel (1976).

A 12 year old male with partial trisomy 15/partial trisomy 8 due to malsegregation of a maternal t(8;15)(q24;q13) was described. The boy was born at full term following a pregnancy complicated by hydramnios. He weighed 2500 gm. He sat at 1 year and walked at 18 months. Social adaptability was diminished because of perseveration and aggressive behavior. The following features were noted at 12 years: mental retardation, unilateral cleft lip and palate,

hypertelorism, strabismus, hyperopia, micrognathia, enopthalmos, deep set large ears, funnel chest, mild scoliosis, hypospadius, hypotonia, hyperactive reflexes, intentional tremor, abnormal dermatoglyphics, slight ventricular dilation, and a nonspecifically altered EEG.

Case 14. Pfieffer and Kessel (1976).

This is a 6 year old male sib of case 13, and had the same abnormal karyotype. He was born at full term following a pregnancy complicated by hydramnios. His birth weight was 3000 gm., and his developmental milestones were considered normal. His social adaptability was also described as inadequate. At 6, the following features were noted: mental retardation, unilateral cleft lip and palate, hypertelorism, strabismus, hyperopia, micrognathia, lowset large abnormal ears, funnel chest, hypotonia, hyperactive reflexes, moderately abnormal EEG, abnormal dermatoglyphics, and mild hydrocephaly suggested by echoencephalography.

Category 3

Case 15. Breg et al. (1971).

This patient was described as a 47, XY, gs+ nonmongoloid retarded male in the original report. Schreck et al. (1977) provided the following information. The patient had severe infantile autism, moderate retardation, ptosis, strabismus, malocclusion, and kyphosis. Both parents had normal karyotypes. Parental ages at birth were M = 39, F = 33. Schreck et al. identified the error as inv dup(15).

Case 16. Parker and Alfi (1972).

This patient was initially described as having partial trisomy 15. Her findings included mental retardation, 50th percentile growth, slender habitus, hyperactivity, immature speech, thin helices, strabismus, and otherwise normal features. Schreck et al. (1977) identified the error as inv dup(15) and mentioned that her retardation was mild. Additional data is available in Centerwall and Morris (1975).

Case 17. Kakati and Sinha (1973).

This patient was a 16 month old male. He was irritable, hypotonic, had a hoarse cry, slight strabismus, slightly depressed and widened nasal bridge, epicanthal folds, developmental and mental retardation. The authors suggested a D13 origin because the centromeric heterochromatin was similar to a D13.

Case 18. Crandall et al. (1973).

The chromosome error in this patient was described as a partial 15 trisomy with long arm satellites derived by translocation with an unidentified acrocentric. The patient was the product of a full term pregnancy complicated by bleeding in the first month. His mother had a total of 6 pregnancies; two ended in first trimester spontaneous abortions. The family history was otherwise unremarkable. The birth weight was 3232 gm., and the patient's development was considered slow. He talked at 2 years, walked at 22 months, and used sentences at 3 and 1/2 years. Grand mal seizures were reported at 3 and 1/2 and 7 years. An EEG at 7 showed spikes in both hemispheres; a later EEG was reported mildly abnormal due to diffuse slowing. The patient was hyperkinetic

with an IQ of 42. At age 11, measurements were at the 50th percentile. His speech was immature, but intelligible. There was a slight anti-mongoloid slant, epicanthal folds, and hypotonia. Dermatoglyphics were normal. Maternal age at birth was 28. Urine and amino acid screens were normal.

Case 19. Crandall et al. (1973).

This was an 11 year old boy with cytogenetic findings identical to the first patient presented in this paper. The patient was the only child of a 34 year old mother. Her first child died at 5 days with multiple anomalies including spina bifida and absent thumbs. Her second pregnancy ended in first trimester spontaneous abortion. The last pregnancy was full term and unremarkable. Birth weight was 3629 gm. The patient rolled over at 3-4 months, sat at 8 months, and walked at 15 months. Grand mal seizures began at age 1, and ceased at age 3. His first EEG was consistent with a seizure disorder, but later EEG's were normal. He was hyperactive with an IQ of 52. Physical examination at age 11 revealed 50th percentile growth, a mild articulatory speech defect, enopthalmia, strabismus, high arched palate, hypotonia, hyper-extension of the elbows, brachydactyly, and webbing between toes 2 and 3 bilaterally. His dermatoglyphics, urine, and amino acid screens were normal. This patient was also studied by Schreck et al. (1977).

Case 20. Watson and Gordon (1974).

Proximal trisomy 15q22 was identified in an 11 month old female. Long arm satellites were present, and the authors suggested a translocation from an unknown acrocentric. The patient was born after a full

term pregnancy and weighed 3400 gm. She had 6 normal sibs. The family history was unremarkable except that the parents were first cousins. Parental ages at birth were M = 33, F = 38. The patient presented at 11 months with developmental delay, abnormal limb movements convulsive in nature, and several daily minor seizures. An EEG showed spike and wave activity. Clinical findings included mild synophrys, strabismus, and hypotonia. The facies lacked other distinctive features. Her head circumference was 42.5 cm. (2 s.d.), and her weight was 8250 gm. (less than 10th percentile). There were not other abnormal neurological signs. Urine, amino acid, CBC, and radiological studies were normal.

Case 21. Wurster-Hill and Hoefnagel (1974).

The error in this patient was interpreted as trisomy 15pter -- q23. The long arm had satellite projections, but the authors contended that they really represented sticky ends. Hoefnagel et al. (1963) described the patient's phenotype. He was 30 years old, and had been institutionalized since age 10 because of profound mental retardation and a convulsive disorder. No family history was available except for the parents' ages at birth: M = 43, P = 42. The patient had never developed speech. His measurements were all at 3 s.d. He had a dull facial expression, broad base of the nose, large lowset ears, high arched palate, short first and fifth fingers, and mild clinodactyly. The eyes, musculature, external genitalia, and neurological findings were all unremarkable. Urinalysis was normal.

Case 22. Centerwall and Morris (1975).

The extra chromosome in this 4.5 year old girl was identified as proximal trisomy with a breakpoint of 15q22. Satellites were observed on the long arms but not on the short arms. The authors were not certain that short arm satellites were deleted and felt that the morphology might be consistent with an intrachromosomal ring origin in which the distal long arm was lost and the short arm satellites were transferred to the distal breakpoint. The patient was the product of an uneventful pregnancy and weighed 3864 gm. The mother had a total of 4 pregnancies, one of which ended in first trimester spontaneous abortion. The family history was unremarkable. Parental ages at birth were M = 30, P = 30. The patient was cyanotic at birth, but otherwise normal. She sat at 2 years and could not walk unassisted at age 4.5. An interventricular septal defect was diagnosed at 15 months. Daily myoclonic seizures began at 6 months and were under control by the age of 1. EEG's at 9 and 20 months were abnormal. At age 4.5, the following features were noted: severe mental retardation, no speech, height 103.5 cm (15th percentile), weight 13.6 kg (less than 1st percentile), head circumference 47 cm (less than 1st percentile), cyanosis, strabismus, Brushfield spots, a low finger ridge count, and elevated atd angles. No other congenital anomalies were noted. Her bone age was normal.

Case 23. Pfieffer and Kessel (1976).

The extra chromosome in this case was identified as der (15;22) (15pter → 15q21::22q11 → 22pter). The 15 portion carried brilliant satellites that clearly matched those on a maternal 15. The origin

of the distal short arm material was believed to be a maternal 22, but the evidence was not striking. The family history was unremarkable and the parental ages at birth were M = 36, P = 37. The patient was delivered 3 weeks premature after an uneventful pregnancy, and weighed 2500 gm. Developmental retardation was noted in early infancy. Spontaneous movements were infrequent and poor. At 11 months, he was hypotonic, and could not sit or stand. Reflexes of the abdominal wall were absent. Pneumocephalography suggested external hydrocephalus, and an EEG was normal. At the age of 5.5, he was hospitalized for grand mal seizures. Spike waves were seen upon EEG. These were eliminated with ACTH therapy, but a pattern of astatic propulsive seizures continued. His measurements were all below the 3rd percentile, and he was autistic and autoaggressive. At the age of 12, he was described as severely hypotrophic and hypotonic. His dermatoglyphics were normal, and the only dysmorphism noted was a mild funnel chest.

Case 24. Speed et al. (1976).

This patient, ascertained during a population study, was found to have a bisatellited proximal 15-like supernumerary with apparent breakpoints at 15q22. Clinical data were not presented, and the only feature noted was mental retardation.

Case 25. Rasmussen et al. (1976).

The authors of this report concluded that the supernumerary in their patient represented a translocation between the proximal portion of a number 13, and the short arms of a 14, 15, or 22. Number 13 was considered the principle component because of similarities in size of

the proximal heterochromatic regions. The patient was born following a normal pregnancy and weighed 3200 gm. Parental ages at birth were M = 39, P = 35. The family history was essentially negative. Bilateral hip luxation was noted in the patient; a sister also had unilateral hip luxation. The patient walked clumsily at 2 years, spoke at 4 years, and menstruated at 13. Early childhood autism was diagnosed, with poor relationship, many repetitive ritualistic activities, stereotyped motor behavior, echolalia, and self-mutilating habits. Petit mal seizures were suspected, but never actually diagnosed. An EEG showed well defined spike foci in the left parieto-tempero-occipital regions. Neurological exam at age 5 showed convergent strabismus and atypical plantar reflexes. Severe mental retardation was diagnosed. At age 14, the autism was described as receding. Her height was 148 cm (less than 2 s.d.). Neurological exam showed ataxia of the extremities, hypotonia of the legs, and dyskinetic movements. No other congenital malformations were noted. Urine, amino acid, and radiological evaluations were all negative. Here dermatoglyphics showed a reduced ridge count, and t' bilaterally associated with a pattern type of I^r IV e t'4.

Cases 26, 27, and 28. Power et al. (1977).

This paper describes the only examples of inheritance of the bisatellited marker. The mother, case 26, an essentially normal female, was found to have a 50% mosaicism in her peripheral blood. She had suffered from epilepsy since age 14, but her maternal grandmother was also an epileptic. Her pregnancy history included 4 normal children, 2 affected, and 2 spontaneous abortions at 3 and 5 months. In all

three cases, the acrocentric was identified as 15pter → q22 plus long arm satellites from an unknown source.

Case 27, a female, was the first affected child of case 27. She was born at full term and weighed 3000 gm. She was described as a quiet baby with developmental delay. She sat at 10 months, and walked at 2 1/2 years. At age 3, she was thin, hypotonic, with height and weight values below 3rd percentile. Strabismus and epicanthal folds were noted. At the age of 7, she had an IQ of 25, no speech, and severe dorsal scoliosis. Her total ridge count was 63; she had 3 radial loops, 2 arches, and elevated atd angles. Urine and amino acid screens were normal.

Case 28, a boy, was born at full term following a pregnancy complicated by several maternal seizures. His birth weight was 3630 gm. At 6 months, he was evaluated for a major epileptic seizure. His weight and height were both below 3rd percentile, and his head circumference was less than 3 s.d. The following features were noted: flat occiput, open fontanelle, epicanthal folds, large simple ears, webbing between toes 2 and 3, a sacrococcygeal pit, and probable severe mental retardation. An EEG showed epileptic features suggestive of a multiple cortical epileptic foci. Radiological, urine, and amino acid screens were all normal. He had a ridge count of 86, two arches, two radial loops, and elevated atd angles.

Parental ages at the time of the birth of Case 27 were M = 30, P = 27, and for case 28, M = 36, P = 33.

Case 29. Van Dyke et al. (1977).

An extensive mosaicism was described in this patient: 46,XY/47 +

idic(15)(pter → q15 → pter)/48, XY, + idic(15) + idic(15)(pter → q12 → pter). The authors proposed that the second small submetacentric marker arose mitotically from the first as the result of a bridge-breakage-fusion cycle initiated by functional dicentric activity in the first marker. Q and C band polymorphisms, as well as anti-5-methylcytidine banding, were consistent with a chromosome 15 origin for both ends of the larger supernumerary. The patient had 11 sibs, 2 of whom were in special education classes. The parents were first cousins. The mother was 38 at the time of the patient's birth. At age 7, he was described as hyperactive, severely retarded, with a normal physical appearance except for strabismus and a maxillary overbite. An EEG showed a diffuse disturbance of cerebral function. Urine and amino acid screens were normal.

Cases 30, 31, and 32. Schreck et al. (1977).

In addition to the 3 patients previously mentioned, 3 additional cases were briefly described in this report. All were identified as having an inv dup(15). Case 30, a male, was profoundly retarded, hypotonic, had facial asymmetry, and hypospadius. Parental ages at birth were M = 42, P = 45. Case 31, a male, was profoundly retarded with a convulsive disorder and slight scoliosis. Parental ages were M = 36, P = 42. Case 32, a female, was mildly retarded, had a personality disorder, and strabismus. Parental ages were M = 34, P = 53.

Case 33. Jacobs et al. (1978).

The authors in this case did not attempt to identify the extra chromosome, but presented the results of G and C banding uninterpreted.

The patient was a 29 year old female, with four other sibs. Parental ages at birth were M = 35, P = 32. The patient was the product of a normal pregnancy and weighed 6 lb. 6 oz. Her development was described as normal until the age of 1 when she developed acute septic spinal meningitis. She regressed to an infantile state, losing the ability to walk and talk. She was institutionalized in 1957. In 1965, her IQ was 20. Her clinical findings include hip luxation, seizures, hirsutism, small hands held in a silver fork attitude, tapered fingers with some clubbing, tapered toes, hypotonia, hyporeflexia, and spasticity.

APPENDIX B

APPENDIX B

Phenotypic Checklist Supplied to Previous Investigators

Case

Age

Birth weight

Duration of pregnancy

Age of mother at birth

Age of father at birth

PHYSICAL FINDINGS (At anytime in patient's history)

	Yes	No	Suggested	Not Evaluated
HEAD				
Brachycephaly				
Dolicocephaly				
Reduced Bitemporal Diameter				
Flat Occiput				
Microcephaly				

Other:

FACIES				
Low Posterior Hairline				
Antimongoloid Slant				
Enopthalmos				
Epicanthal Folds				
Hypertelorism				

	Yes	No	Suggested	Not Evaluated
Strabismus				
Nystagmus				
Flat Nasal Bridge				
Short Philtrum				
Thickened Lips				
Prognathism				
Downturned Mouth				
Malocclusion				
Lowset Ears				
Deformed Ears				
Rotated Ears				

Other:

EXTREMITIES

Increased Carrying Angle				
Camptodactyly				
Clinodactyly				
Proximally Placed Thumbs				
Hammer Toes				
Syndactyly of Toes 2 and 3				
Club Foot				

Other:

TRUNK

Short Stature				

	Yes	No	Suggested	Not Evaluated
Scoliosis				
Lordosis				
Kyphosis				
Sacral Dimples				
Hypospadius				
Cryptorchidism				
Normal Menses				
Normal Breasts				
Heart Defect				

Other:

NEUROLOGICAL

Mental Retardation (degree)				
Developmental Retardation				
Hyperactivity				
Autistic Behavior				
Aggressive Behavior				
Hypotonia				
Poor Sucking Reflex				
Abnormal Speech				
Abnormal Gait (not attributed to drugs or brain damage due to seizures)				
Toe Walking				

Other:

History of Seizures? Frequency?

Abnormal EEG? (brief interpretation)

Anticonvulsants? (describe)

Missing or Abnormal Reflexes? (describe)

Feeding or Digestive Problems? (describe)

Dermatoglyphic Abnormalities? (describe)

Current Status (change in EEG findings, etc.)

Other:

APPENDIX C

APPENDIX C

Analysis of Familial Polymorphisms - Cases I-V

Case I and Parents (DD)

A	B	C	D	E	F	Possible rearrangements
13 P	1-1	S	1-1S	-	-	mat t(14;15)
p	2-1	L		-	-	t(15;15)
M	2-1	L		-	-	t(15;22)
M	2-1	L	2-1L	-	-	pat t(15;22)
14 P	1-1	S		-	-	mitotic t(14;15)
P	1-1	S	1-1S	-	-	t(15;15)
M	1-1	S		-	-	
M	1-1	L	1-1L	+	1	
15 P	1-2	L	1-2L	-	+	
P	1-2	L		-	+	Marker:
M	1-2	L		-	+	p = 1-1L
M	1-1	L	1-1L	+	-	q = 1-2L
21 P	1-3	S	1-3S	-	-	
P	1-1	S				
M	1-1	S	1-1S	-	-	
M	1-1	S				
22 P	2-1	L	2-1L	-	-	
P	1-1	L		+	-	
M	2-1	L	2-1L	-	-	
M	1-1	L		+	1	

A = parental chromosomes
B = QFQ scores for parental chromosomes. First digit for short arm, second digit for satellites
C = CBG score for parental chromosomes
D = Normal Acrocentrics in Proband
E = +, similar to marker short arm polymorphisms, -, not similar
F = +, similar to marker long arm polymorphisms, -, not similar

Case II and parents (CL)

	A	B	C	D	E	F	Possible rearrangements
13	P	2-1	L	2-1L	-	-	mat t(14;15)
	P	2-1	L		-	-	t(15;15)
	M	1-1	L	1-1L	-	-	
	M	2-1	S		-	-	pat None
14	P	1-2	L	1-2L	+	-	Mitotic None
	P	1-1	L		-	-	
	M	1-2	L		+	-	
	M	1-1	S	1-1S	-	-	
15	P	1-2	L	1-2L	+	-	
	P	1-2	L		+	-	
	M	1-3	L		-	+	Marker:
	M	1-2	L	1-2L	+	-	p = 1-2L
							q = 1-3L
21	P	1-1	S	1-1S	-	-	
	P	1-1	S		-	-	
	M	1-2	S	1-2S	-	-	
	M	1-1	S		-	-	
22	P	2-1	S		-	-	
	P	1-1	L	1-1L	-	-	
	M	1-2	S		-	-	
	M	1-1	S	1-1S	-	-	

Case III and parents (ML)

	A	B	C	D	E	F	Possible rearrangements
13	P	1-1	S		-	-	mat t(14;15)
	P	2-1	S	2-1S	-	-	t(15;15)
	M	2-1	S	2-1S	-	-	t(15;21)
	M	2-1	L		-	-	t(15;22)
14	P	1-3	L		-	-	
	P	1-1	L	1-1L	+	-	pat None
	M	1-1	L	1-1L	+	-	
	M	1-1	L		+	-	Mitotic None
15	P	1-1	L	1-1L	+	-	
	P	1-1	L		+	-	
	M	1-2	L		-	+	
	M	1-1	L	1-1L	+	-	Marker:
							p = 1-1L
21	P	1-3	S	1-3S	-	-	q = 1-2L
	P	1-1	S		-	-	
	M	1-1	L		+	-	
	M	1-1	S	1-1S	-	-	

A	B	C	D	E	F	Possible rearrangements
22 P	2-2	L		-	-	
P	1-1	S	1-1S	-	-	
M	1-1	S	1-1S	-	-	
M	1-1	L		+	-	

Case IV (RF)

13	2-1	-	-	Parental ?
	2-1	-	-	Mitotic t(14;14)
				t(14;15)
14	1-1	+	-	t(14;21)
	1-2	-	+	t(14;22)
15	1-1	+	-	
	1-1	+	-	Marker:
				p = 1-1
21	1-1	+	-	q = 1-2
	1-1	+	-	
22	2-1	-	-	
	1-1	+	-	

Case V (EL)

13	1-1	-	+	Parental ?
	2-1	-	-	Mitotic None
14	1-1	-	+	
	1-1	-	+	
15	1-1	-	+	
	1-1	-	+	Marker:
				p = 1-2
21	1-1	-	+	q - 1-1
	1-1	-	+	
22	1-1	-	+	
	1-1	-	+	

A = Acrocentric chromosomes
B = QFQ scores of acrocentric chromosomes. First digit for short arm, second digit for satellites
C = +, similar to marker short arm polymorphisms, -, not similar
D = +, similar to marker long arm polymorphisms, -, not similar

Case VI (TM)

A	B	C	D	E	F	Possible rearrangements
13 p	2-1	S		-	-	Mat t(14;14)
p	2-1	S	2-1S	-	-	t(14;15)
m	2-1	S	2-1S	-	-	t(14;21)
m	2-1	S		-	-	t(15;21)
14 p	1-3	L		-	-	Pat t(14;15)
p	1-2	L	1-2L	+	+	t(14;22)
m	1-2	L	1-2L	+	+	t(15;22)
m	1-2	L		+	+	
15 p	1-3	L		-	-	Mitotic
p	1-2	L	1-2L	+	+	t(14;14)
m	1-2	L	1-2L	+	+	t(14;15)
m	1-2	L		+	+	t(14;22)
						t(15;15)
21 p	1-1	S		-	-	t(15;22)
p	1-1	S	1-1S	-	-	
m	1-2	S		-	+	
m	1-1	S	1-1S	-	-	
22 p	1-1	L		-	-	
p	1-2	L	1-2L	+	+	
m	1-3	S	1-3S	-	-	
m	2-1	S		-	-	Marker:
						p = 1-2L
						q = 1-2

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