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A Molecular Deletion of Distal Chromosome 4p in Two Families with a Satellited Chromosome 4 Lacking the Wolf-Hirschhorn Syndrome Phenotype

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Summary

We report two families with a satellited chromosome 4 short arm (4ps). Satellites and stalks normally occur on the short arms of acrocentric chromosomes; however, the literature cites several reports of satellited nonacrocentric chromosomes, which presumably result from a translocation with an acrocentric chromosome. This is the first report of 4ps chromosomes. Our families are remarkable in that both unaffected and affected individuals carry the 4ps chromosome. The phenotypes observed in affected individuals, although dissimilar, were sufficient to encourage a search for a deletion of chromosome 4p. By Southern blot analysis and fluorescence in situ hybridization, a deletion of material mapping approximately 150 kb from chromosome 4pter was discovered. This deletion is notable because it does not result in the Wolf-Hirschhorn syndrome and can result in an apparently normal phenotype. We speculate that homology between subterminal repeat sequences on 4p and sequences on the acrocentric short arms may explain the origin of the rearrangement and that position effect may play a role in the expression of the abnormal phenotype.

Introduction

Several reports of satellited nonacrocentric human chromosomes exist in the literature (table 1). These unique chromosomes presumably occur secondary to a translocation with an acrocentric chromosome. Generally, balanced carriers of translocations are not affected, but individuals with unbalanced segregants manifest anomalies because of partial trisomies or monosomies. Males with a Yqs chromosome are not affected by the secondary deletion of Yq13, because this region of the Y does not appear to contain expressed genes. There are four additional reports of satellited nonacrocentrics (2ps, 2qs, and two cases involving 4qs) in which carriers are not adversely affected even though the reciprocal translocation chromosome is absent (table 1) (Bauld and Ellis 1984; Mihelick et al. 1984; Babu et al. 1987; Elliott and Barnes 1992). In these cases, the satellites may have been translocated into the telomere so that no phenotypically important genetic material was lost. In one 4qs family a de novo interstitial deletion of 4q35 apparently occurred in the 4qs chromosome, resulting in a child with developmental delay (Babu et al. 1987).

The second report of a 4qs family involves an unaffected father with a 4qs and no apparent reciprocal chromosome who has a son with craniorachischisis and the same 4qs (Mihelick et al. 1984). This case is especially intriguing since, although both the father and son apparently have the same 4qs and thus similar regions of 4q deleted, yet their phenotypes differ remarkably.

We have identified two families with a satellited chromosome 4 short arm (4ps). In these families, individuals who carry the 4ps chromosome without the

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Table 1

Satellited Chromosomes

Satellited Chromosome	Acrocentric Chromosome Involved	Inheritance	Abnormal Phenotype[a]	Reference
1q11	13	De novo	Unknown	Mikkelsen et al. 1980
1q11	13	Familial	None (B)	Lucas et al. 1972
2pter	Unknown	Familial	None (U)	Elliott and Barnes 1992
2qter	Unknown	Familial	None (U)	Bauld and Ellis 1984
3q	15	Familial	None (B)	Hansmann et al. 1977
4qter	Unknown	Familial	None (U)	Babu et al. 1987
4q35	Unknown	De novo[b]	Yes (U)	Babu et al. 1987
4q35	Unknown	Familial	None (U)	Mihelick et al. 1984
	Unknown	Familial	Yes (U)	Mihelick et al. 1984
5p	13	Familial	Yes (U)	Dev et al. 1979
9p11	13	Familial	None (B)	Varley et al. 1981
9q	13	Familial	None (B)	Hansmann et al. 1977
12p11	21	Familial	None (B)	Parslow et al. 1979
12q24	21	Familial	Unknown	Mikkelsen et al. 1980
18p	13	Familial	None (B)	van Tuinen et al. 1983
Xp	21	De novo	Yes (U)	Stetten et al. 1986
Xp21	21	De novo	Yes (B)	Verellen-Dumoulin et al. 1984
Yq				Review in Schmid et al. 1984

NOTE.—A list of previously reported nonacrocentric satellited chromosomes is given along with the acrocentric involved in the translocation, the inheritance pattern, and the phenotypic status of balanced and unbalanced carriers.

[a] U = unbalanced translocation carrier with only the satellited nonacrocentric chromosome; and B = balanced translocation carrier.

[b] Affected patient had de novo interstitial deletion in the inherited 4qs chromosome.

reciprocal derivative acrocentric should have both a duplication of the nucleolus-organizer region, which presumably would not have a phenotypic effect, and a deletion of some portion of chromosome 4p. A deletion of the distal band of chromosome 4p is often associated with the Wolf-Hirschhorn syndrome (WHS) (Wilson et al. 1981). None of the relatives had WHS, and only a few of the 4ps individuals had phenotypic anomalies. We were interested in determining which region, if any, of chromosome 4 was deleted, in order to better understand the array of observed phenotypes.

Subjects and Methods

Case Reports

Two apparently unrelated families (A and B) were ascertained through the University of North Carolina Genetic Counseling Program (fig. 1). Family A (fig. 1, *left*) came to our attention through II-1, who presented with intrauterine growth retardation and eventually died in utero. An autopsy revealed no malformations. The second pregnancy (II-2) was electively terminated after anencephaly was detected on ultrasound.

The father (I-2) of these fetuses had a live-born son (II-4) by another woman (I-3). This boy appears normal intellectually and morphologically but has growth retardation. At approximately 2 years of age, his height was at the 10th percentile, his weight fell well below the 5th percentile, and his head circumference was less than the 2d percentile (although when adjusted for weight it was at the 5th percentile). The same father (I-2) was involved in two late-pregnancy losses (II-5 and II-6), one with the mother of the previously described son and the other with a third woman (I-4). Additional information on these pregnancies was not available. The remainder of the family history is unremarkable, including no reports of Huntington disease.

Family B (fig. 1, *right*) was ascertained through the proband (III-8), who was diagnosed in infancy as having Turner syndrome. Clinical findings in the first 2 years of life included lymphedema of the hands and feet, bilateral epicanthal folds, ptosis, a high-arched palate, webbing of the neck, widely spaced nipples,

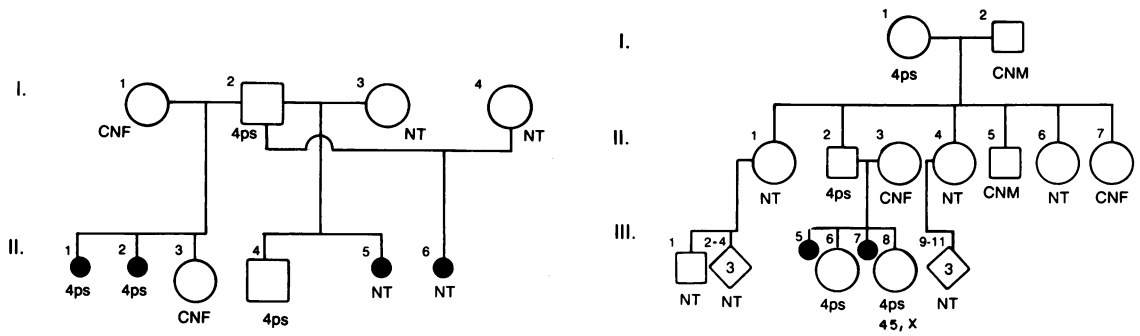

Figure 1 Pedigrees of the 4ps families. The pedigrees of family A (*left*) and family B (*right*) are given. Results of cytogenetic evaluation are noted; for phenotype description, refer to text. 4ps = presence of satellited chromosome 4; CNF = chromosomally normal female; CNM = chromosomally normal male; and NT = not tested.

coarctation of the aorta, a single kidney, ambiguous genitalia (clitoromegaly and no uterus), and growth retardation (height less than the 5th percentile and weight in the 7th percentile). Her head circumference was normal (slightly less than 50th percentile). She was also noted to be developmentally delayed. At 8 years of age her height and weight continued to be below normal (below and at the 5th percentile, respectively), while her head circumference remained normal (above the 50th percentile). Further developmental evaluation placed her in the mild mental retardation range.

Her sister (III-6) was evaluated and assessed as having borderline/mild developmental delay. She appeared otherwise normal.

Individuals II-5 and II-7 are both institutionalized. II-5 is reported to be schizophrenic and to have learning problems; II-7 is described as having emotional problems complicated by learning difficulties. I-2 reportedly suffers from Parkinson disease. There is no family history of Huntington disease, and all other family members are reportedly normal.

These two families are not aware of being related to one another; however, they do reside in neighboring counties and are of the same race. We cannot exclude an unknown common ancestor.

Cytogenetics

Giemsa-banded chromosome studies were performed either on cultured amniotic fluid cells (II-1, II-2, and II-3 in family A) or on peripheral blood lymphocytes (all others), according to standard techniques. Standard AgNOR staining was also performed on some samples (I-2, II-1, and II-4 in family A and II-2 and III-6 in family B) (Barch 1991).

Preparation of Genomic DNA and Probes

DNA was obtained from Epstein-Barr virus–transformed lymphoblastoid cell lines by using standard techniques (Berger and Kimmel 1987) on three patients (I-2 in family A and II-2 and III-8 in family B). Plasmids containing probes used in the Southern blot analyses (table 2) and fluorescence in situ hybridization (FISH) were transformed into competent HB101 cells (BRL, Gaithersburg, MD), followed by minipreparation of the plasmid DNA (Ausubel et al. 1988). Inserts from the Southern blot probes were removed from their vectors by using the appropriate restriction enzymes, were separated by gel electrophoresis using low-melt agarose, were purified using a Gene Clean kit (Bio 101, La Jolla, CA), and were labeled with ^{32}P-dATP by random primers (Boehringer-Mannheim, Indianapolis). The FISH probe inserts were not removed from their vectors before purification. Approximately 25–50 ng of the purified product were labeled with biotin-dATP by using a nick-translation kit (BioNick; BRL, Gaithersburg, MD) and were further purified with a Quick Spin column (Boehringer-Mannheim, Indianapolis).

Southern Blots

Human genomic DNA (4 μg/lane) was digested with restriction enzymes (table 2), was separated by size by using electrophoresis in 1% agarose gels, and was analyzed using Southern blot hybridization based on standard protocols (Sambrook et al. 1989). Autoradiograph signals were interpreted using RFLPs or densitometry readings from a Shimadzu scanning densitometer. The chromosome 7 probe KM-19 was used as a control probe in densitometric analysis.

Table 2

Southern Blot Results

Locus	Probe	Restriction Enzyme	Status[a] (method[b])		
				Family B	
			Family A, I-2	II-2	III-8
D4S141	2R3	*Hin*dIII	Not del (R)	Not del (D)	Not del (D)
D4S115	p252-3	*Pst*I	Not del (R)	Not del (R)	NT
D4S126	p309	*Sac*I	NT	NT	Not del (R)
D4S10	pCos5.52	*Msp*I	Not del (R)	NT	Not del (R)
D4S62	p8	*Hin*cII	Not del (R)	NT	Not del (R)
Raf2.....	Raf2	*Msp*I	Not del (R)	NT	Not del (R)

Note.—The results of qualitative and quantitative Southern blot analysis are given. No chromosome 4p deletions were found in the 4ps chromosomes, by any of these probes.

[a] del = deleted; NT = not tested; (D) = densitometry analysis; and (R) = RFLP.

FISH

The acrocentric beta-satellite probe and chromosome 4 centromeric alpha-satellite (D4Z1) probe labeled with biotin were obtained from Oncor (Gaithersburg, MD). A biotin-labeled chromosome 4 paint probe was acquired from Imagenetics (Naperville, IL). The pC847.351 cosmid probe and 847E-C repeat probe were provided by Dr. Michael R. Altherr in Dr. John J. Wasmuth's laboratory at UC Irvine. The B31 cosmid probe was provided by Dr. Marcy E. McDonald in Dr. James F. Gusella's laboratory at Harvard Medical School. The acrocentric beta-satellite probe is known to hybridize to beta-satellite sequences in the cytological satellites and in pericentromeric sequences in the short arm of acrocentric chromosomes; D4Z1 is known to hybridize to repeats found at the chromosome 4 centromere; and the chromosome 4 paint probe is known to hybridize to unique sequences located throughout the length of chromosome 4. The pC847.351 probe is a 38-kb cosmid probe which is part of the D4F26 locus and maps 150 kb from the p terminus of chromosome 4 (Altherr et al. 1991). The 847E-C probe hybridizes to a mildly repetitive sequence found repeated 10 times over the distal region of chromosome 4p; a single copy of the 847E-C repetitive sequence is also found on the short arms of acrocentric chromosomes (Altherr et al. 1989). Probe B31 maps to locus D4S142, which is located approximately 100 kb from the chromosome 4p terminus (Bates et al. 1990).

FISH was performed according to protocols provided by Oncor (Gaithersburg, MD) and Imagenetics (Naperville, IL). Slides hybridized with the pC847.351 and B31 cosmid probes received an additional round of amplification, in order to maximize the signal.

Results

Cytogenetics

A 4ps chromosome was observed in the indicated family members (fig. 1). Examples of the 4ps chromosomes are shown in figure 2. The substantial amount of G-negative material observed at the tip of the 4ps chromosome 4 led to assignment of the 4p breakpoint in the distal 4p16.3 band in both families.

Evidence of a reciprocal derivative acrocentric chromosome was not found in any individual examined in either pedigree by using G-banding or AgNOR staining. Positive silver staining of the 4ps chromosome

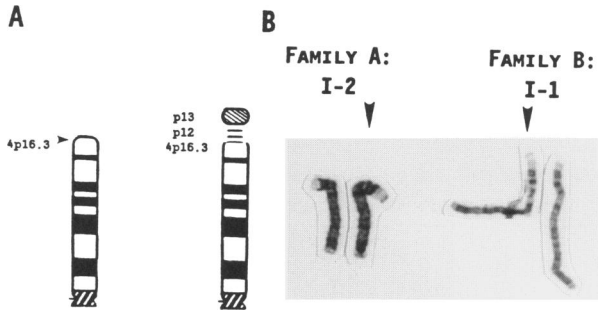

Figure 2 Examples of the satellited chromosome 4. *A*, Ideogram of chromosome 4p, illustrating the cytogenetic breakpoint in distal 4p16.3. A model of the rearrangement is also given, using the stalk (p12) and satellite (p13) regions from an acrocentric ideogram (850-band level; Harnden and Klinger 1985). *B*, Partial karyotypes of chromosome 4 pairs from both families. The 4ps chromosome is indicated by the arrowhead.

in at least some of the cells examined from each 4ps individual revealed activity of the ribosomal genes in the lymphocytes or amniocytes. Karyotypes from blood samples of II-5 and II-7 from family B did not reveal a 4ps chromosome or a candidate derivative acrocentric.

Southern Blot

Qualitative and quantitative Southern blot analyses were employed to detect deletions of chromosome 4p. None of the probes revealed deletions in the three patients studied (table 2). These data place the breakpoint distal to approximately 300 kb from the telomere.

FISH

FISH with the 847E-C repetitive probe demonstrated signals on both chromosome 4's in all three of the 4ps patients investigated (I-2 in family A and II-2 and III-8 family B). An 847E-C signal is not usually visible on the acrocentric chromosome short arms, because of the stringency routinely used in the FISH technique, but, if a number of 847E-C repeats from the chromosome 4 short arm were translocated to the derivative acrocentric, a signal might be detectable. There was no signal seen on any acrocentric chromosome, suggesting that the derivative acrocentric chromosome is not present in any of the family members examined (data not shown).

The beta-satellite probe hybridized to the short arms of the acrocentrics, as well as to the tip of the short arm of one chromosome 4 (data not shown); and the chromosome 4 paint probe displayed signals only along both chromosome 4 pairs (data not shown). The presence of a beta-satellite signal on all 10 acrocentric chromosomes and the lack of any exogenous chromosome 4 paint-probe signal argue against the presence of a derivative acrocentric chromosome in the 4ps individuals investigated.

Hybridization of the pC847.351 cosmid probe was consistently seen on only one chromosome 4 (table 3) and was not observed on any acrocentric short arms (fig. 3). We later confirmed by sequential banding (G-banding followed by FISH) that the pC847.351 signal was always seen on the normal chromosome 4 and never on the 4ps chromosome (table 3). All observations are statistically significant, with P values less than .0001 by a one-tailed t-test.

FISH with the probe B31 confirmed our observations with the pC847.351 probe. The probe only hybridized to one chromosome 4p in a total of 11, 9, and 22 metaphases in individuals I-2 (family A), II-2 (family B), and III-8 (family B), respectively.

Table 3

FISH Results

	No. of pC847.351 Cosmid Probe Signals/Total No. of Metaphases	
	On 4ps Chromosome	On Normal Chromosome 4
Family A:		
I-2	0/21	21/21
Family B:		
II-2	0/20	20/20
III-8	0/16	16/16

Note.—The chromosome 4 centromere probe (D4Z1) was observed on both sets of chromosome 4, but the pC847.351 signal was repeatedly observed on only one chromosome 4. Differentiation between the normal and satellited chromosome 4 was established by sequential G-banding followed by FISH (not shown). All of these observations are statistically significant ($P < .0001$) by a one-tailed t-test.

Discussion

We have presented two families, each with a 4ps chromosome which presumably occurred secondary to a translocation between chromosome 4 and an acrocentric chromosome. No deletion of chromosome 4p material could be detected by using Southern blot hybridization, but FISH with the cosmid probes pC847.351 and B31 revealed a deletion of material mapping approximately 150 and 100 kb from chromosome 4pter.

Deletions of the distal 2 Mb of chromosome 4p have been associated with WHS (Gandelman et al. 1991), but none of these individuals with the distal 150-kb material deleted have features of WHS. This implies that this most distal 150-kb area of 4p16.3 is not responsible for the WHS phenotype. Probes representing this area (i.e., pC847.351 and B31) should not be used to rule out the WHS deletion, as interstitial deletions of 4p16 could occur that result in WHS, leaving this most distal region intact (Roulston et al. 1991).

The 847E-C probe repeats are located along the distal chromosome 4p (fig. 4). Although the majority of the 847E-C repeats are on chromosome 4, single copies are found on the short arms of almost all acrocentric chromosomes (Altherr et al. 1989). The 4ps chromosome breakpoint appears to occur amid these

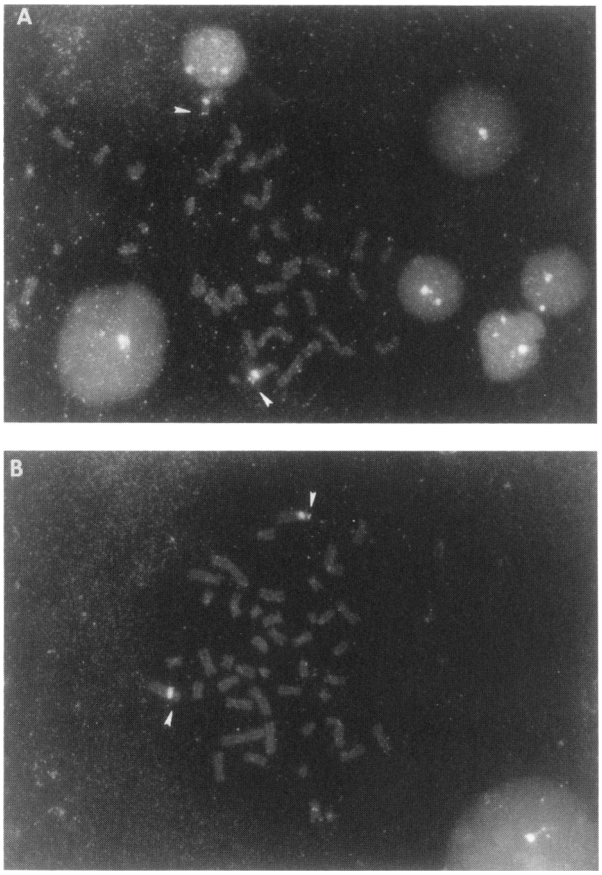

Figure 3 4ps Chromosome deletion demonstrated by FISH. *A*, Normal individual (control) with both copies of the cosmid probe pC847.351, at the distal tip of chromosome 4p (arrows). *B*, Example of a 4ps chromosome patient with a single pC847.351 signal on one chromosome 4p (arrows). A chromosome 4 centromere probe (D4Z1) was used for identification. These results imply a deletion of the distal 150 kb of chromosome 4p.

repeats, suggesting a mechanism for the formation of the 4ps chromosome; the repeats could supply the homology sufficient for recombination leading to a translocation.

The single copy of the 847E-C repeat on the acrocentric short arms is not usually visible by using the described FISH techniques, but, if a number of the 847E-C repeats from chromosome 4p translocated to the reciprocal acrocentric, then one might observe a signal. No signals were seen on any acrocentric chromosomes (data not shown), implying either that the breakpoint on chromosome 4 occurred in the distal region of the repeats or that the acrocentric chromosome involved in the original translocation is not present in the family members investigated. The derivative acrocentric chromosome was unidentifiable with G-banding, AgNOR staining, and FISH using the beta-satellite probe, the pC847.351 cosmid probe, the B31 cosmid probe, and chromosome 4 paint probes. These data support the hypothesis that the derivative acrocentric chromosome is not present in any of these individuals.

It is curious that both affected and unaffected individuals carry the same 4ps chromosome—and hence the same deletion. The search for the Huntington disease gene has demonstrated that expressed genes are located within 325 kb of the telomere, possibly within the region deleted in the 4ps chromosomes (Doggett et al. 1989). There are at least two potential explanations for these inconsistent observations. All affected individuals received their 4ps chromosome from their father. In one family (family B), the unaffected father (II-2) received his 4ps chromosome from his mother (I-1). This may suggest that genes in this deleted region

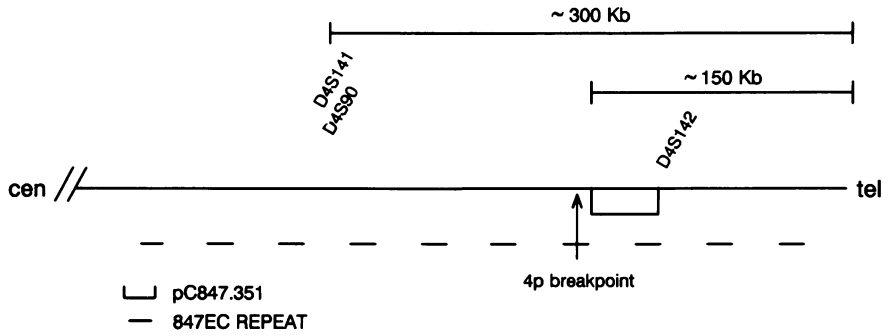

Figure 4 Approximate position of breakpoint in 4ps chromosome. A map of distal 4p16.3 demonstrates the approximate position of the pC847.351 and 847E-C probes used in FISH. The approximate position of the breakpoint in the 4ps chromosomes is given in respect to the FISH probes, one of the Southern blot probes (D4S141), and the most distal loci (D4S90 and D4S142). D4S90 and D4S141 are approximately 300 kb from the 4p telomere, and D4S142 is approximately 100 kb (Cox et al. 1989). The 4ps individuals appear to be deleted for approximately 150 kb of the most distal region of 4p16.3.

are susceptible to imprinting. There may be no detectable phenotype unless the 4ps chromosome is inherited from the father, because the genes in this region are normally active when paternally inherited and are normally inactive when maternally inherited. The varying severity and manifestation of phenotype could reflect an influence of environmental factors, interactions with other genes in the patient's genome, or a combination of both.

Another possible explanation for different phenotypes appearing with the same deletion could be the influence of the translocated ribosomal genes on the expression of neighboring 4p genes. Ribosomal genes are activated and inactivated in clusters. The mechanisms determining which ribosomal gene cluster will be active in a given cell are currently unclear; however, this decision is clonally transmitted (Ferraro et al. 1981). Ribosomal gene activation and inactivation states are thought to characterize different cell lineages and maturation states (Reeves et al. 1984; Smetana and Likovský 1984; Haaf et al. 1991), and experimental evidence suggests that methylation is the method of inactivation (Ferraro and Lavia 1983). If inactivation of the ribosomal gene cluster on the 4ps influences the expression of neighboring genes, then one might expect to see a range of phenotypes, depending on the time and the cell lineage in which the ribosomal genes became inactivated. If the ribosomal genes on the 4ps were never inactivated or were inactivated in tissues that did not rely on the expression of neighboring 4p genes for normal development, one would expect to see normal individuals. If the inactivation occurred early in a cell lineage which required the expression of the neighboring 4p genes, then one would expect to see severely affected individuals or nonviability. Individuals mildly to moderately affected with differing phenotypes would also be expected, again depending on the timing and type of cell lineage in which the ribosomal genes were inactivated. This is precisely the pattern of phenotypes seen in these two families.

A similar scenario could be described if activation, rather than inactivation, of the ribosomal genes were affecting neighboring chromosome 4p genes. This prospect is supported by the reported observation of an in vitro oncogene activation secondary to a translocation that placed a c-abl oncogene into active ribosomal DNA repeats (Takahashi et al. 1986).

There are other case reports in the literature which may support a position effect by ribosomal genes. The report of a 4qs chromosome family with one 4qs child affected with craniorachischisis and several unaffected 4qs carriers may represent an example similar to our case (Mihelick et al. 1984). The infertility in this family may suggest a position effect either at critical times in development or in tissues dependent on normal expression of the neighboring 4q genes. There are also two reports of families with a nucleolus-organizer region inserted into a chromosome (6q15 and 12p), with no apparent loss of chromosomal material (Watt et al. 1984; Prieto et al. 1989). In both of these reports there are several normal family members with the rearrangement, but each family has a case of a dysmorphic infant.

Although we cannot exclude the possibility that all of these observations may reflect ascertainment bias, a more likely explanation is that ectopic placement of ribosomal genes can result in both normal and abnormal phenotypes, as a result of variable influence on neighboring gene expression. On the basis of our observations and these reports, it appears that ribosomal gene position effects may exist, and we encourage careful evaluation of families with rearrangements involving the translocation of ribosomal genes into euchromatic regions of the genome.

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