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Clinical and Molecular Characterization of Patients with Distal 11q Deletions

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Summary

Jacobsen syndrome is caused by segmental aneusomy for the distal end of the long arm of chromosome 11. Typical features include mild to moderate psychomotor retardation, trigonocephaly, facial dysmorphism, cardiac defects, and thrombocytopenia, though none of these features are invariably present. To define the critical regions responsible for these abnormalities, we studied 17 individuals with de novo terminal deletions of 11q. The patients were characterized in a loss-of-heterozygosity analysis using polymorphic dinucleotide repeats. The breakpoints in the complete two-generation families were localized with an average resolution of 3.9 cM. Eight patients with the largest deletions extending from 11q23.3 to 11qter have breakpoints, between D11S924 and D11S1341. This cytogenetic region accounts for the majority of $11q^-$ patients and may be related to the FRA11B fragile site in 11q23.3. One patient with a small terminal deletion distal to D11S1351 had facial dysmorphism, cardiac defects, and thrombocytopenia, suggesting that the genes responsible for these features may lie distal to D11S1351. Twelve of 15 patients with deletion breakpoints as far distal as D11S1345 had trigonocephaly, while patients with deletions distal to D11S912 did not, suggesting that, if hemizygosity for a single gene is responsible for this dysmorphic feature, the gene may lie distal to D11S1345 and proximal to D11S912.

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Introduction

The distal 11q deletion (Jacobsen) syndrome is caused by segmental aneusomy for the distal end of the long arm of chromosome 11. The incidence of distal 11q deletions is difficult to estimate, but is probably <1 in 100,000. Patients with this syndrome have lost portions of chromosomal bands 11q23, q24, and/or q25. These deletions result from either a de novo terminal deletion, the unbalanced segregation of a reciprocal translocation in offspring of balanced translocation carriers (Jacobsen et al. 1973), unbalanced segregation of de novo translocations (Van Hemel et al. 1992), or other chromosomal rearrangements, such as a ring 11 (Niikawa et al. 1981; Cousineau et al. 1983). Patients with more proximal interstitial deletions of 11q that remove various portions of the region between 11q14 and 11q23.1 have also been reported (Wakozano et al. 1992). These patients have a different clinical presentation and should be grouped into their own category.

Terminal deletions extending proximal to 11q23.3 generally are not observed. The exception to this is a case of an infant who was mosaic 46,XY/46,XY del(11)(q21qter) with holoprosencephaly, cyclopia, and arrhinencephaly, among other major malformations (Helmuth et al. 1989), who died several minutes after birth. Terminal deletions extending proximal to 11q23.3 may be lethal, and it is possible that this individual survived to 35 wk because of his mosaic status.

There is significant variability in the range of features observed in distal $11q^-$ patients. Commonly observed features include mild to moderate psychomotor retardation, postnatal growth retardation, trigonocephaly, dysmorphic facies, cardiac defects, digit anomalies, and thrombocytopenia or pancytopenia. Approximately 25% of patients die before the age of 2 years, mainly from the cardiac defects. Life expectancy for those who survive this period is unknown, though one patient in this report is in her late teens.

Though some of the variation among patients is likely to be due to the genetic background of the individual, a

significant percentage may be due to the varying size and location of the deletion. Until recently, the deletions exhibited by these patients have been characterized by karyotype analysis (for an exception, see Van Hemel et al. 1992), which has not provided sufficient resolution to precisely compare the extent of many deletions or to determine which genes may be encompassed by these deletions. In an effort to begin to localize the genes responsible for the abnormalities observed in distal $11q^-$ patients, we studied 17 individuals with de novo terminal deletions of 11q. In the present paper, we present a molecular analysis of these deletions and correlate this to the clinical presentations of the patients.

Subjects and Methods

This study was approved by the institutional review board of the Salk Institute, and informed consent was obtained from the families that participated. Patients with de novo terminal deletions of chromosome 11q and their parents donated whole blood, from which genomic DNA was prepared, using an Applied Biosystems automated DNA extractor or Gentra Puregene DNA extraction kit.

PCR primers for the Généthon microsatellite repeat polymorphisms were prepared by Genset. One primer was end-labeled with ^{33}P (Amersham) by using T4 polynucleotide kinase (New England Biolabs). PCR reactions were performed in 10 mM TRIS-HCl (pH 8.8), 50 mM KCl, 1.5 mM $MgCl_2$, 0.001% gelatin, 200 mM each dNTP, 1 mM each primer, 1 U *Taq* polymerase, and 100 mg genomic DNA, for 35 cycles of 94°C for 40 s and 55°C for 30 s in a 15-μl volume. PCR reactions were run on 5% polyacrylamide/5 M urea/32% formamide (J. T. Baker). The gels were dried unfixed and exposed to XAR film (Kodak) overnight.

For cytogenetic analysis of fragile sites, peripheral blood specimens were cultured for 72 h at 37°C in RPMI 1640 (Gibco BRL) supplemented with 10% fetal bovine serum and 4 mM phytohemagglutinin (Murex Diagnostics). During the incubation period, cells were exposed either to 5×10^{-7} M FUdR (Sigma) for the last 48 h or to 1 mM thymidine (Sigma) for the last 24 h. Cultures were harvested following a 25–40-min colcemid treatment (0.05 mg/ml) (Gibco BRL). Slides were prepared and G-banded. For each patient, 100 metaphases were analyzed and scored for expression of folate-sensitive fragile sites.

Results

DNA was prepared from whole blood from the patient and, where possible, from both parents. The extent of the deletion in each patient was mapped in a loss-of-heterozygosity analysis using a collection of polymorphic microsatellite $(AC)_n$ repeats along the length of the long arm of chromosome 11 (Gyapay et al. 1994). Primer pairs flanking each polymorphic region were used to PCR-amplify these regions in each family, and the number and sizes of alleles at a marker were examined for each individual. If two different alleles were apparent in the patient at a particular marker, that marker was scored as "retained" and was not included in the deleted region. If the patient clearly did not have either of the alleles present in one parent, the patient was scored as "deleted" for that marker, and that marker was included in the deleted region. If the sizes of the alleles in the parents and patient did not allow either of these two scenarios to be clearly distinguished, the marker was scored as "uninformative" for that patient. The results of the loss-of-heterozygosity analysis are summarized in figure 1.

For patients 9 and 10, DNA from only one parent was available. For all the markers examined, both patients had an allele that was the same size as one of the alleles present in the available parent. Given the heterozygosities of the markers used in the study, it is extremely unlikely that the available parent is the source of the deleted chromosome, and we have indicated in table 1 that the unavailable parent was the source of the chromosome that had suffered a deletion, though we note that this has not been demonstrated definitively. For patient 16, DNA from neither parent was available. For these three patients (9, 10, and 16), it was possible only to score the markers that were retained, in which two alleles were clearly distinguishable in the patient. Without the crucial parental DNA it was impossible to distinguish a marker that was deleted from one that was simply homozygous in size in the patient. Therefore, markers that were retained could be excluded from the area of deletion, but the area of deletion could not be positively defined. For these patients the cytogenetic diagnosis was used to help place them in figure 1.

Eight patients with cytogenetic breakpoints in 11q23.3 had a breakpoint in the interval defined proximally by D11S1356 or D11S1341 and distally by D11S924 or D11S925. One member of this group, patient 8, was unusual in that he was mosaic for the deleted chromosome and both his mother and brother expressed fragility at the rare, folate-sensitive fragile site, FRA11B, which maps cytogenetically to 11q23.3. The breakpoint in this patient has been characterized molecularly to lie within the same 100 kb as does FRA11B (Jones et al. 1994). The parents of patient 7 were examined for fragility at FRA11B and were found to be negative (data not shown).

The parental origin of the deletion could be definitively determined in 14 cases and is presumed in another 2 (see above). Of these, 6 showed deletion of the maternal chromosome, while 10 showed deletion of the paternal chromosome, suggesting that there is no bias in the parent of origin. Of the patients with deletions that cluster between D11S1356-1341 and D11S924-925, five of eight have a maternal origin of the deleted chromosome. Of the patients

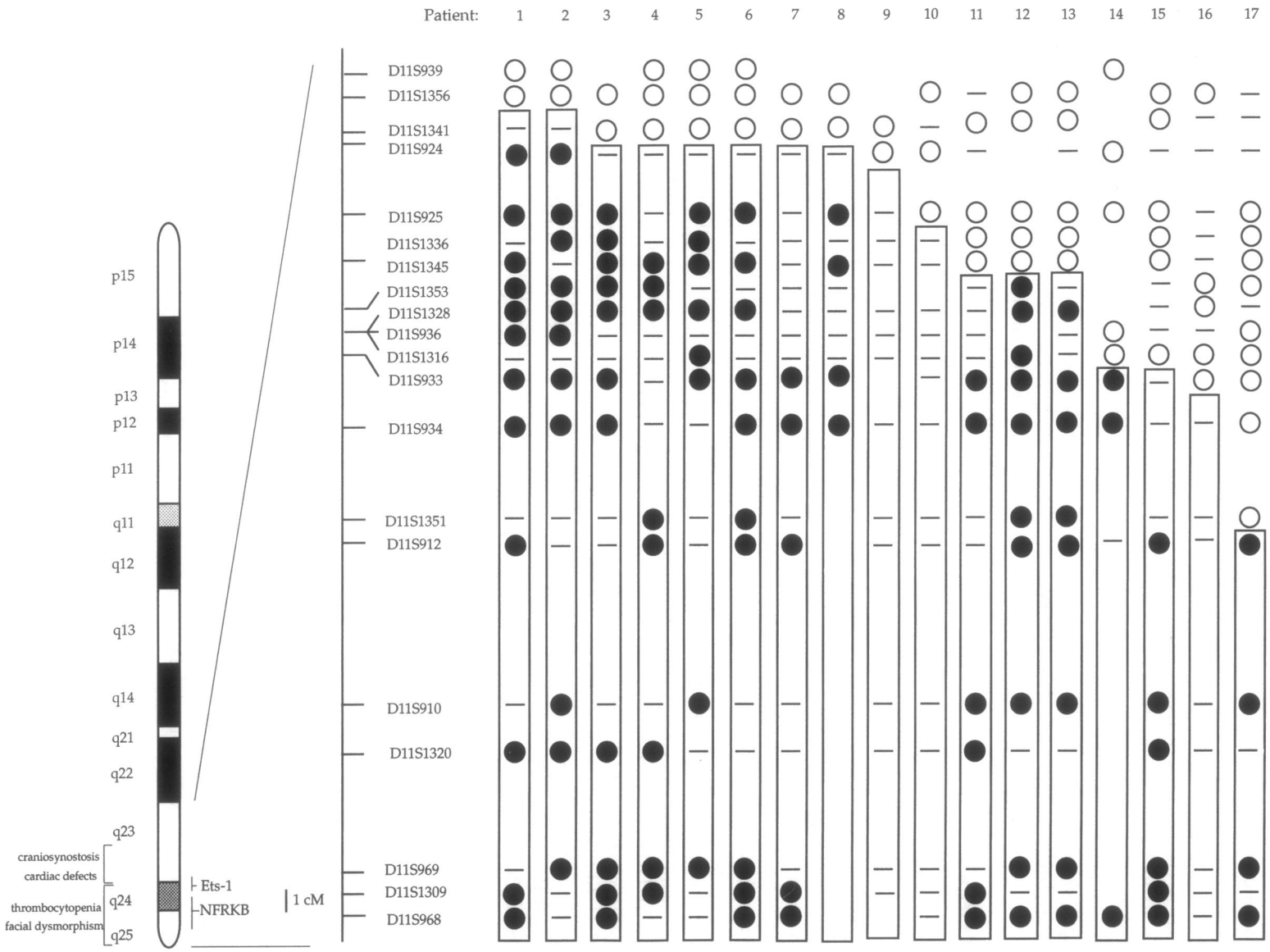

Figure 1 Molecular deletion analysis in patients with distal 11q deletion syndrome. An ideogram of chromosome 11 is shown on the left, with the region affected by the deletions expanded. The approximate positions of the regions that may influence several of the features seen in $11q^-$ patients are indicated to the left of the ideogram. The approximate positions of two potential candidate genes are indicated to the right of the ideogram. The names of the microsatellite markers are shown at their genetic position as shown in Gyapay et al. (1994). Each numbered column represents the results from one patient. Unblackened circles indicate retained markers; blackened circles represent deleted markers; and dashes represent uninformative markers. The parent from which the deleted chromosome was inherited was not available for patients 9, 10, and 16. The maximum extent of the deletion in each patient is boxed.

with more distal breakpoints whose parent of origin could be determined, five of six have paternal deletions.

Discussion

This report presents a molecular analysis of 17 patients with de novo terminal deletions of chromosome 11 and correlates this data to their clinical features. There is a broad phenotypic spectrum in patients with terminal deletions of 11q, and a number of the features associated with this disorder are fairly nonspecific and are associated with many chromosomal anomalies and syndromes. Though correlations with this small number of patients are tenuous, the data are sufficient to allow comment on several aspects of the phenotype of distal $11q^-$ patients with regard to regions of 11q that may contain candidate genes.

Patient 17, who has a small terminal deletion, did show some features of the facial dysmorphism, suggesting that a region influencing craniofacial development may be distal to D11S1351. Patients with larger deletions often have an increased number of dysmorphic facial features, which suggests that the deletion of additional regions may increase the degree of facial dysmorphism.

There was a general relationship between degree of psychomotor impairment and extent of deletion. Patients with larger deletions extending into 11q23 or q24.1 tended to have moderate psychomotor retardation with significant speech impairment, while the patients with small terminal deletions had mild (patient 16) or no (patient 17) psychomotor retardation. Three of the patients had imaged structural defects of the brain. Patient 1 had cerebral atrophy; patient 6 had cerebellar hypoplasia; and patient 9 had agenesis of the corpus callosum as well as asymmetric hemispherical atrophy or hypoplasia. Further investigation into the specific CNS abnormalities and cognitive impairments will be necessary to determine how this class of deletions disrupts neural development and function.

The cardiac defects reported for this group are fairly nonspecific and are associated with a wide variety of chromosomal anomalies and deletions. Patient 15, with the smallest deletion and a serious cardiac malformation, is deleted as far as D11S912 and perhaps as far as D11S933. Patient 17 had a minor cardiac defect, and her deletion extended to D11S912 but not to D11S1351. This suggests that a gene (or genes) that influences cardiac development may lie distal to either D11S933 or D11S912. However, only 10 of 16 patients who are deleted for this region have any cardiac defect, and only 5 of 16 had hemodynamically serious defects. This variability suggests that either the genetic background of the individual or some random aspect of the developmental process plays a significant role in the expression of this feature.

Two additional features often observed in distal $11q^-$ patients, the trigonocephaly and digit anomalies, may be caused by the deletion of separate regions, and the data are therefore discussed separately for each. However, craniosynostoses syndromes, of which several are known or presumed to be caused by single-gene defects, often include additional abnormalities, such as ear, limb, and cardiovascular malformations (Jabs et al. 1993). The presence of trigonocephaly and digit anomalies in distal $11q^-$ patients is not inconsistent with the hypothesis that a gene involved in the control of several developmental processes has been deleted.

Trigonocephaly resulting from premature metopic suture closure is reported in 95% of $11q^-$ deletion cases in the literature and 9 of 15 patients in this study with deletions extending beyond D11S912. An additional 2 patients had either dolichocephaly or scaphocephaly, for a total of 11 of 15 patients whose deletions extend beyond D11S912 with calvarial suture anomalies. Patients 14 and 15, who have deletions distal to D11S1316, had trigonocephaly. The two patients with the smallest terminal deletions, including patient 17 who has a deletion that extends to D11S912 but does not include D11S1351, did not have trigonocephaly. If hemizygosity for a single gene is responsible for the calvarial suture anomalies observed in these patients, this may indicate that a gene influencing calvarial suture closure lies between D11S1316 and D11S912. The absence of this feature in four patients (patient 8, who was mosaic for the deletion, and patients 4, 10, and 12) whose deletions clearly include this area may indicate that the genetic background of the individual influences the expression of this feature.

Twelve of the 15 patients with the largest deletions, a group that excludes the 2 patients with the smaller terminal deletions, had primary defects of the digits, such as cutaneous syndactyly, clinodactyly, short fingers with broad terminal phalanges, and toe abnormalities. Patient 16, who has a smaller terminal deletion, had fifth-finger clinodactyly, but because it was also observed in her mother, it may be unrelated to her chromosome 11 deletion. The presence of these primary defects in 12 of 15 patients whose deletions extend past D11S912 may indicate that a region influencing the development of the digits may lie proximal to D11S912. Eight of the 15 patients with the largest deletions also had secondary defects of the hands, digits, or feet—such as abnormal palmar creases, absent digit creases, and camptodactyly—that more likely reflect an underlying neurological deficit.

Taken together, the data localizing the trigonocephaly and digit anomalies define an interval distal to D11S933 and proximal to D11S912, an 8-cM region that probably corresponds to distal 11q23.3 and possibly proximal 11q24.1. This region may therefore be a starting place to search for developmental control genes that could play a role in a craniosynostoses syndrome.

Many craniosynostoses syndromes are monogenic and are inherited as autosomal dominant traits with high penetrance and variable expressivity. The mechanism underlying the dominant behavior of the mutations that cause these syndromes has not been definitively determined,

Table 1

Summary of Clinical Presentations

	Patient						
	1	2	3	4	5	6	7
Sex	F	M	F	F	F	M	F
Age at latest evaluation (years)	2 9/12	15	6/12	2	3 9/12	5	18
Karyotype diagnosis del(11)	q23	q23	q23.3	q23.3	q23.3	q23.3	q23.3
Parental origin of deletion	Maternal	Paternal	Maternal	Paternal	Paternal	Maternal	Maternal
Growth:							
Birthweight (% for gestational age)	50%	50%	<10%	3%–10%	10%		50%
Birthlength (% for gestational age)		50%	<10%	3%–10%	25%		
Head circumference (% for gestational age)				75%–90%			
Most recent height	<3%	<3%			<5%		
Most recent weight	<3%	10%			20%		
Most recent head circumference	25%	10%			15%		
CNS:							
Psychomotor retardation[c]	++	++	++	+	++	++	++
Imaged structural brain defect[d]	CA					CA, CH	
Occular coloboma	+	+					
Strabismus					+		+
Craniofacial:							
Trigonocephaly/suture anomaly	+	+	+		+	+	+
Hypertelorism				+			
Broad flat nasal bridge							+
Epicanthus	+	+	+				
Ptosis	+	+	+		+		
Ectropian of eyelid	+	+					
Abnormal palpebral fissure slant	+	+	+		+	+	
Short nose/long philtrum	+	+	+		+	+	+
Anteverted nares		+					
Carp mouth	+	+	+		+	+	
Retrognathia		+		+		+	
Dental anomalies							
High arched palate	+	+				+	+
Lowset/malformed ears	+			+	+		
Cardiac defects[e]			PFO*				VSD*
Thrombocytopenia/pancytopenia[f]			P			T	
Muscle tone	Hypo	Hypo	Hyper		Hypo		Hypo
Primary digit/hand/foot anomalies	+	+	+		+	+	
Secondary hand/foot anomalies		+	+		+	+	
Major joint contractures	+						+
Genitourinary anomalies[h]		DH, DIU	PK		DU	PK	
Cryptorchidism						+	
Pyloric stenosis							
Inguinal hernia							
Recurrent infections[i]		UTI			OM		+
Vertebral anomalies	+						
Reference	Obregon et al.	Obregon et al.	...	...	...	...	...

NOTE.—A blank space indicates that this feature was not mentioned.

[a] Patient's karyotype diagnosis was mosaic 46,XY/46,XY del (11) (q23.3qter).

[b] Parental origin of the deleted chromosome was inferred.

[c] Moderate psychomotor impairment is indicated by ++; and mild psychomotor impairment is indicated by +.

[d] CA = cerebral atrophy; CH = cerebellar hypoplasia; and ACC = agenesis of the corpus callosum and asymmetric hemispherical atrophy or hypoplasia.

[e] Defects marked with an asterisk (*) are not hemodynamically serious. PFO = patent foramen ovale; VSD = ventricular septal defect; HLH = hypoplastic left heart; PDA = patent ductus arteriosis; ASD = atrial septal defect; and AC = aortic coarctation.

[f] T = thrombocytopenia; and P = pancytopenia.

[g] Patient had pancytopenia until 6 mo of age and has subsequently had intermittent thrombocytopenia.

[h] DU = duplicated ureter; DH = distal hypospadias; PK = polycystic kidney; HK = hypoplastic kidney; SS = shawl scrotum; and DIU = dilated ureter.

[i] UTI = urinary tract infection; and OM = otitis media.

though both a gain-of-function of the protein product (Jabs et al. 1993, 1994; Muenke et al. 1994) and haploinsufficiency (Vortkamp et al. 1991, 1992) have been postulated. All of the distal $11q^-$ patients presumably have one functioning allele of the genes within the deleted region, on their normal chromosome, indicating that the observed defects do not result from recessively acting mutations or dominant gain-of-function mutations. This leaves haploinsufficiency for one or several genes as the most likely cause for the abnormalities. Characterization of the mutations associated with Pfeiffer syndrome (Muenke et al. 1994), Jackson-Weiss and Crouzon syndromes (Jabs et al. 1994),

Patient									
8	9	10	11	12	13	14	15	16	17
M	F	M	M	M	F	M	F	F	F
	6	1 8/12	1 6/12	2 5/12	1 6/12	3	5 5/12	15	3 9/12
q23[a]	q23	q23	q23	q24.2	q24.1	q23.2	q24.1	q24.2qs	q25
Maternal	Paternal[b]	Paternal[b]	Paternal	Paternal	Paternal	Maternal	Paternal		Paternal
25%	50%	25%		25%	25%	25%	10%–25%	<3%	50%
50%	90%					50%	10%–25%	10%	50%
	75%			>95%			10%	<10%	
	<5%	10%–25%	<5%	<3%	<10%	10%	<3%	3%	10%–25%
	<5%	50%	<10%	10%	<10%	10%		92%	10%–25%
		3%	<50%		50%		25%	97%	75%
NA	++	+	+	+	++	++	+	+	+
	ACC								
	+	+					+		
	+		+		+	+	+		
		+		+			+	+	+
	+	+	+	+					+
	+				+	+	+		+
	+					+			
		+							
+	+	+	+	+	+	+	+		+
	+	+	+	+	+	+	+		+
	+		+			+			+
		+	+	+	+	+			
+	+					+			
	+	+							
			+						
+	+	+	+	+		+		+	+
HLH	VSD		PDA, ASD	Murmur*	VSD*	AC	VSD		VSD*
T	T	T	T	P	P		T, P[s]	T	T
	Hypo	Hyper							
+	+	+	+	+		+	+	+	
+		+					+		
						+			
SS				DIU					HK
		+	+	+					
			+		+				
			+	+					
	+		+						
Voullaire et al.	...	...	...	...	O'Hare et al.	Fryns et al.	...	...	...

and the Boston type of craniosynostosis (Jabs et al. 1993) suggests that many craniosynostoses syndromes may behave in a dominant manner because the mutations confer a gain of function in the protein product. However, work on Greig cephalopolysyndactyly syndrome (Vortkamp et al. 1991, 1992; Hui and Joyner 1993), which is likely to be caused by a null mutation, suggests that haploinsufficiency for a developmental control gene, perhaps with DNA-binding function, is a plausible model for the generation of the craniosynostosis and perhaps other anomalies observed in distal $11q^-$ syndrome patients.

Thrombocytopenia was observed in 8 of 17 patients,

though this feature resolved in patients 10 and 11 and is intermittently observed in patient 15. Pancytopenia was observed in 4 of 17 patients, though it had resolved by 6 mo in patient 15. The size of the deletion did not predict whether thrombocytopenia or pancytopenia was observed. The data from patient 17, who had significant thrombocytopenia and a small terminal deletion with a breakpoint between D11S1351 and D11S912, may suggest that a gene (or genes) influencing platelet production lies distal to D11S1351. Patient 15, whose deletion extends to at least D11S912 and possibly to D11S933, indicates that a gene influencing hematopoiesis may lie distal to these markers. The fact that approximately only one-half of patients who are deleted for these regions have thrombocytopenia or pancytopenia indicates that the genetic background of the individual can influence the expression of this feature.

Potential candidate genes may be known for thrombocytopenia at this time. There are two genes known to map to this area that are likely to play some role in hematopoiesis. Ets-1 is a member of the ets family of DNA-binding proteins that maps to 11q24, close to D11S912 (Selleri et al. 1994). The members of this family of proteins bind to a variety of transcriptional enhancers and promoters and are thought to play roles in transcriptional regulation (MacLeod et al. 1992). Ets-1 is expressed only in hematopoietic tissues (Ben-David et al. 1991), and ets-binding sites are found in regulatory regions of the IL-2 gene, the stromolysin gene, the T-cell receptor α- and β-chain genes (MacLeod et al. 1992), and perhaps many other genes expressed in hematopoietic cells.

The nuclear-factor–related-κB (NFRKB) gene maps to 11q24-q25. This DNA-binding protein is expressed preferentially in T and B cells, as well as in brain and testes, and is proposed to play a role in the tissue-specific expression in these cell lineages (Adams et al. 1992). The product of this gene plays a role in IL-2–receptor-gene expression, which is a critical event in T-cell activation, and may have additional roles in hematopoietic differentiation. It is possible that one or both of these genes, when present in only one copy, are insufficient for normal hematopoietic differentiation or development and result in the thrombocytopenia or pancytopenia observed in $11q^-$ patients.

An intriguing finding is the group of eight patients with the largest deletions whose breakpoints map within the same interval, and the colocalization of this interval with a folate-sensitive fragile site (Jones et al. 1994). In the literature, this same cytogenetic breakpoint in 11q23.3 is reported in 70%–80% of $11q^-$ patients. Three folate-sensitive fragile sites—FRAXA (Verkerk et al. 1991), FRAXE (Knight et al. 1993), and FRA16A (Nancarrow et al. 1994)—have now been cloned, and all are associated with the expansion of a $(CCG)_n$ trinucleotide-repeat region. Expansion of these $(CCG)_n$ repeats to a very large size is associated with a cytogenetically visible fragile site. Expansion to a very large size typically occurs when a slightly enlarged repeat is inherited from the mother. A $(CCG)_n$ trinucleotide repeat and the FRA11B fragile site are known to map within the same 100 kb as does the deletion breakpoint in patient 8 (Jones et al. 1994), whose mother expresses fragility at FRA11B (Voullaire et al. 1987). It is possible that the fragile site was involved in the genesis of the deletion in this patient.

The parental origin of deletion could be determined in 14 of 17 cases, with 6 showing a maternal origin of deletion and 8 showing a paternal origin of deletion. It is interesting to note that, in relation to the possible mechanism for the generation of these deletions, five of eight patients with breakpoints clustered between D11S1356-1341 and D11S924-925 had a maternal origin for their deletion, while five of six patients with more distal breakpoints had a paternal origin of their deleted chromosome.

Folate-sensitive fragile sites appear as constrictions or, less frequently, as breaks, in metaphase-chromosome spreads after induction in culture by the use of low-folate media. The in vivo consequences of fragile sites for chromosome integrity remain to be determined. It has been suggested that fragile sites may predispose to chromosome breakage in vivo (Glover and Stein 1987, 1988). In addition, >50% of the breakpoints that have occurred during chromosome evolution in primates are reported to be at or close to fragile sites (Miro et al. 1987). The data of Jones et al. (1994) and those reported here suggest that breakage at FRA11B could be considered as a mechanism for the generation of the a portion of 11q terminal deletions. If this were the case, the very low frequency with which these patients are observed would suggest that this mechanism of mutation occurs at a much lower frequency than many other mechanisms for generating mutations. It is possible that analogous groups of patients with deletions resulting from fragile sites on other chromosomes, such as the X chromosome, are not observed, because these terminal deletions happen to delete genes that are required for viability. Further mapping experiments will resolve whether the other seven patients reported here with breakpoints in 11q23.3 are located at this same position.

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