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The 11q Terminal Deletion Disorder:
A Prospective Study of 110 Cases

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We performed a prospective study of 110 patients (75 not previously published) with the 11q terminal deletion disorder (previously called Jacobsen syndrome), diagnosed by karyotype. All the patients have multiple dysmorphic features. Nearly all the patients (94%) have Paris-Trousseau syndrome characterized by thrombocytopenia and platelet dysfunction. In total, 56% of the patients have serious congenital heart defects. Cognitive function ranged from normal intelligence to moderate mental retardation. Nearly half of the patients have mild mental retardation with a characteristic neuropsychiatric profile demonstrating near normal receptive language ability, but mild to moderate impairment in expressive language. Ophthalmologic, gastrointestinal, and genitourinary problems were common, as were gross and fine motor delays. Infections of the upper respiratory system were common, but no life-threatening infections were reported. We include a molecular analysis of the deletion breakpoints in 65 patients, from which genetic "critical regions" for 14 clinical phenotypes are defined, as well as for the neuropsychiatric profiles. Based on these findings, we provide a comprehensive set of recommendations for the clinical management of patients with the 11q terminal deletion disorder.

KEY WORDS: 11q terminal deletion disorder; Jacobsen syndrome; partial 11q monosomy; neurocognitive profile; Paris-Trousseau syndrome; thrombocytopenia; hypoplastic left heart syndrome; candidate gene; FRA11B; CCG trinucleotide repeat

INTRODUCTION

The 11q terminal deletion disorder (previously called Jacobsen syndrome) is a recognized pattern of malformation caused by terminal deletion of the long (q) arm of chromosome 11. Based on karyotype analysis, the breakpoints arise typically in sub-band 11q23.3 with deletions extending to the telomere [Penny et al., 1995]. Since the first report in 1973 by Dr. Petrea Jacobsen [Jacobsen et al., 1973], a Danish geneticist, ~90 cases have been reported in the English literature [Schinzel et al., 1977; Reddy et al., 1984; Kuster et al., 1985; Reddy et al., 1986; Fryns et al., 1987; Obregon et al., 1992; van Hemel et al., 1992; Neavel and Soukup, 1994; Ono et al., 1994; Hertz et al., 1995; Lewanda et al., 1995; Penny et al., 1995; Somani et al., 1995; Gangarossa et al., 1996; Ono et al., 1996; Pivnick et al., 1996; Clang and La Baere, 1998; Lin et al., 1998; McClelland et al., 1998; Michaelis et al., 1998; Sirvent et al., 1998; Aalfs et al., 1999; Matheisel et al., 2000; Krishnamurti et al., 2001; Puvabanditsin et al., 2001; Ounap et al., 2002] presenting a wide range of phenotypes of varying severity. The previously described clinical findings, most of which have been described retrospectively as case reports, include developmental delay, short stature, congenital heart defects, thrombocytopenia, genitourinary anomalies, pyloric stenosis, and ophthalmologic problems.

Previous molecular analyses of chromosome 11q deletions have been performed on a small number of cases. Penny et al. [1995] characterized the deletions of 17 patients by analysis of polymorphic microsatellite markers in patients and their parents and suggested that critical regions of deletion might correlate with specific clinical phenotypes. More recently, Tunnacliffe et al. [1999], integrated their own and all previously published mapping data with the physical map of the region, using a 40 Mbp YAC map spanning 11q23-qter. The improved accuracy and resolution of this physical map clearly demonstrated both the variation of deletion sizes in patients with the 11q terminal deletion syndrome, and evidence of the clustering of deletion breakpoints.

To correlate the clinical, cytogenetic, and molecular findings of the 11q terminal deletion syndrome, we embarked on a multidisciplinary study of the 11q terminal deletion disorder, which included 110 patients diagnosed by karyotype. The purpose of this study is to define the clinical spectrum and to provide recommendations for the medical management of individuals affected with this disorder. In addition, based on the detailed molecular analysis of the chromosome deletions of 65 patients, genetic critical regions containing putative disease-causing genes for 14 individual phenotypes have been

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identified. We also performed a neuropsychiatric assessment of 13 patients. This led to the identification of a neuropsychiatric profile in which 12 correlated with the deletion size.

MATERIALS AND METHODS

Patient Ascertainment

Patients with terminal deletions in 11q diagnosed by karyotype were ascertained through the European (European Chromosome 11q Network: http://www.11q.org) and American (11q Research and Resource Group: http://web.ukonline.co.uk/c.jones/11q/contents.htm) 11q family support groups, physician referral, or directly by parental contact made available through the internet. All studies on human subjects were performed in compliance with the standards established by the Institutional Review Board at the University of California, San Diego. Clinical information for the majority of patients (91) was obtained from a 30-min questionnaire performed with the parents, either by telephone (36) or in person (55). For the remaining 19 patients, information was obtained by direct contact with the patients' primary care and/or subspecialty physicians, or by medical records provided by the parents. Not all clinical information was obtained from all patients, resulting in different numbers of patients reported for individual phenotypes. Patients whose karyotypes indicate an interstitial deletion in 11q were excluded from this study.

Clinical Analyses

Patient assessments were performed as specified below by general pediatricians and pediatric sub specialists in their respective areas of expertise. A comprehensive dysmorphologic assessment was conducted on 36 patients. Nine patients had insulin growth factor-1 (IGF-1) levels measured by a commercial laboratory (Quest Diagnostics, San Juan Capistrano, California). Thirteen patients underwent neuropsychiatric evaluations including total intelligence quotient, receptive and expressive language quotients, and spacial and recognition quotients. The parents of 11 patients also completed a short survey assessing behavioral habits. A total of 17 patients underwent a comprehensive transthoracic echocardiogram, including two-dimensional, color, and spectral Doppler imaging using either an Acuson 128XP or an ATL Apogee CFM portable echo machine. In total, 14 patients had complete blood counts. Platelet counts were obtained by a clinical laboratory automated platelet counter, and platelet morphology was analyzed in a double-blinded fashion, independently by two pediatric hematologists with significant experience studying Paris-Trousseau syndrome. Ten patients underwent ophthalmologic evaluations in a private office setting, which included pupil dilation. A total of 13 patients had serum IgA levels measured by a commercially available assay at the UCSD Medical Center clinical chemistry laboratory. In total, 15 patients had screening orthopedic assessments. Three patients had urine metabolic screens performed. Plasma concentrations of amino acids were determined with a Beckman automated amino acid analyzer. Organic acid analysis was performed by gas chromatography/mass spectrometry as described previously [Hoffmann et al., 1989]. Carboxylase activity in lymphocytes and cultured fibroblasts was measured as described previously [Weyler et al., 1977].

Molecular Analyses

Deletion breakpoints of 41 new patients were mapped by either fluorescence in situ hybridization (FISH) analysis of metaphase chromosomes (37 patients) or a combination of FISH and polymorphic marker analysis (4 patients). In addition, limited FISH analysis was performed on chromosomes from four other patients whose deletions had been previously mapped by other studies (see Fig. 2).

FISH Analysis

Metaphase chromosomes were prepared from a short-term culture of peripheral blood lymphocytes using previously described techniques. FISH-probes were prepared from genomic DNA clones obtained from a variety of sources. PAC clones from the de Jong (RP1) PAC library [Woon et al., 1998] were isolated in our laboratories by PCR of library pools with STS markers and/or hybridization of high-density filters with specific probes, all library resources being provided by the HGMP-Resource Centre (Hinxton, Cambridge). Most of these PAC clones have been previously published [Tunnacliffe et al., 1999; Jones et al., 2000]; cosmid clones from the ICRF c107 chromosome 11 cosmid library [Nizetic et al., 1994] were identified by hybridization of high-density filters with specific probes, and subsequently confirmed by PCR analysis of STS or probe content; BAC clones from the RP11 library [Osoegawa et al., 2001] were identified by BLAST analysis of the high throughput genome sequencing database (HTGS) and subsequently confirmed by PCR analysis of STS content; and YAC clones from the CEPH YAC library were previously published [Tunnacliffe et al., 1999]. Probes were labeled with biotin by nick-translation and hybridized to metaphase chromosomes together with a commercial chromosome 11 centromere probe (VYSIS) using previously described techniques [Jones et al., 1994]. Fluorescent signals were analyzed using a Nikon Opti Phot 2 fluorescent microscope.

Polymorphic Marker Analysis

Polymorphic marker analysis for chromosome 11q was performed on family triads using the Généthon polymorphic microsatellite $(AC)_n$ repeat primer pairs (Généthon, Evry, France), as described previously [Penny et al., 1995]. Briefly, 50 ng of DNA was amplified in a standard 10 μl PCR reaction, with 1 μCi of either α^{32}P-dCTP or α^{32}P-dATP (Amersham, Piscataway, New Jersey). The reaction was diluted with 100 μl of a formamide loading buffer, denatured and 3 μl loaded and run on a 6% denaturing poly-acrylamide gel. The gel was dried and exposed to X-OMAT AR X-Ray film (Kodak, Rochester, New York). Comparison of parental and patient alleles identifies hemizygous loci in the patient, as well as indicating the parental origin of the chromosome deletion by interpretation of haplotypes.

Details of all markers used in this study (whether for microsatellite analysis or for clone isolation) can be found online in the relevant genomic databases, principally; Genbank (http://www.ncbi.nih.gov/Genbank/index.html), CEPH-Généthon (http://www.cephb.fr/ceph-genethon-map.html) and the Genome Database (GDB; http://www.gdb.org/gdb/).

RESULTS

A total 110 patients were studied, three are shown in Figure 1. The clinical findings are summarized in Tables I–IV. The sex ratio was 0.53 (38 males, 72 females), with ages ranging from newborn to 30 years. Most (103) of the patients studied were less than age 18 years at the time of study. Not all clinical information was obtained from all patients, resulting in different numbers of patients reported for the clinical features.

Chromosome 11q deletions in our cohort are most frequently de novo in origin, with the majority of parents displaying a normal karyotype. Out of 73 cases, 6 (8%) were due to the unbalanced inheritance derived from a parent carrying a balanced translocation, and among these there was not a predilection for a specific reciprocal chromosome. From our cohort of 66 families in which the deletion was de novo in origin there was one case of recurrence.

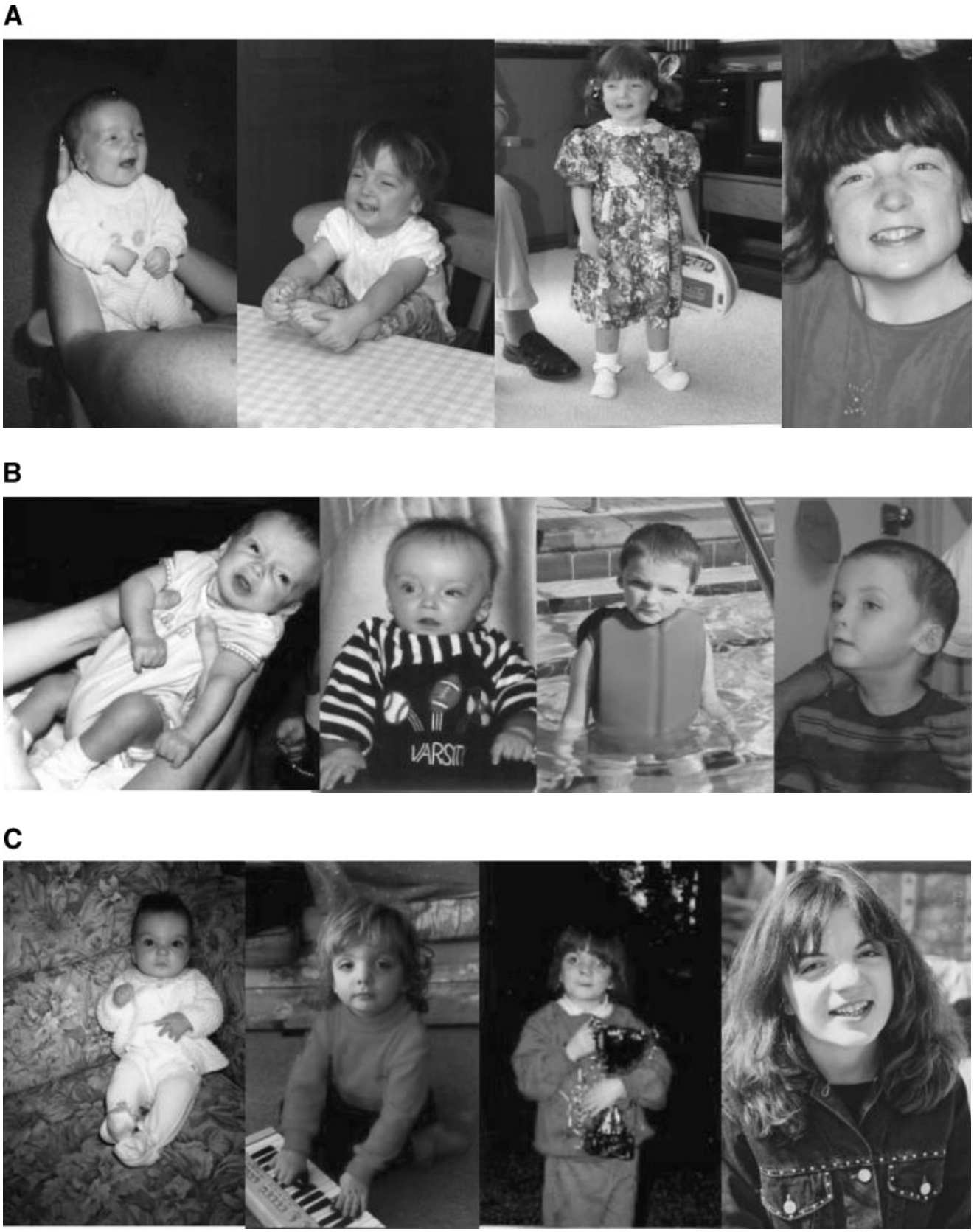


Fig. 1. Serial photographs of three patients with the 11q terminal deletion disorder. **A**: Ages 3 months, 2 years , 4 years, and 10 years; (**B**) ages 5 weeks, 7 months, 5 years, and 5 years; (**C**): ages 9 months, 2 years, 6 years, and 14 years.

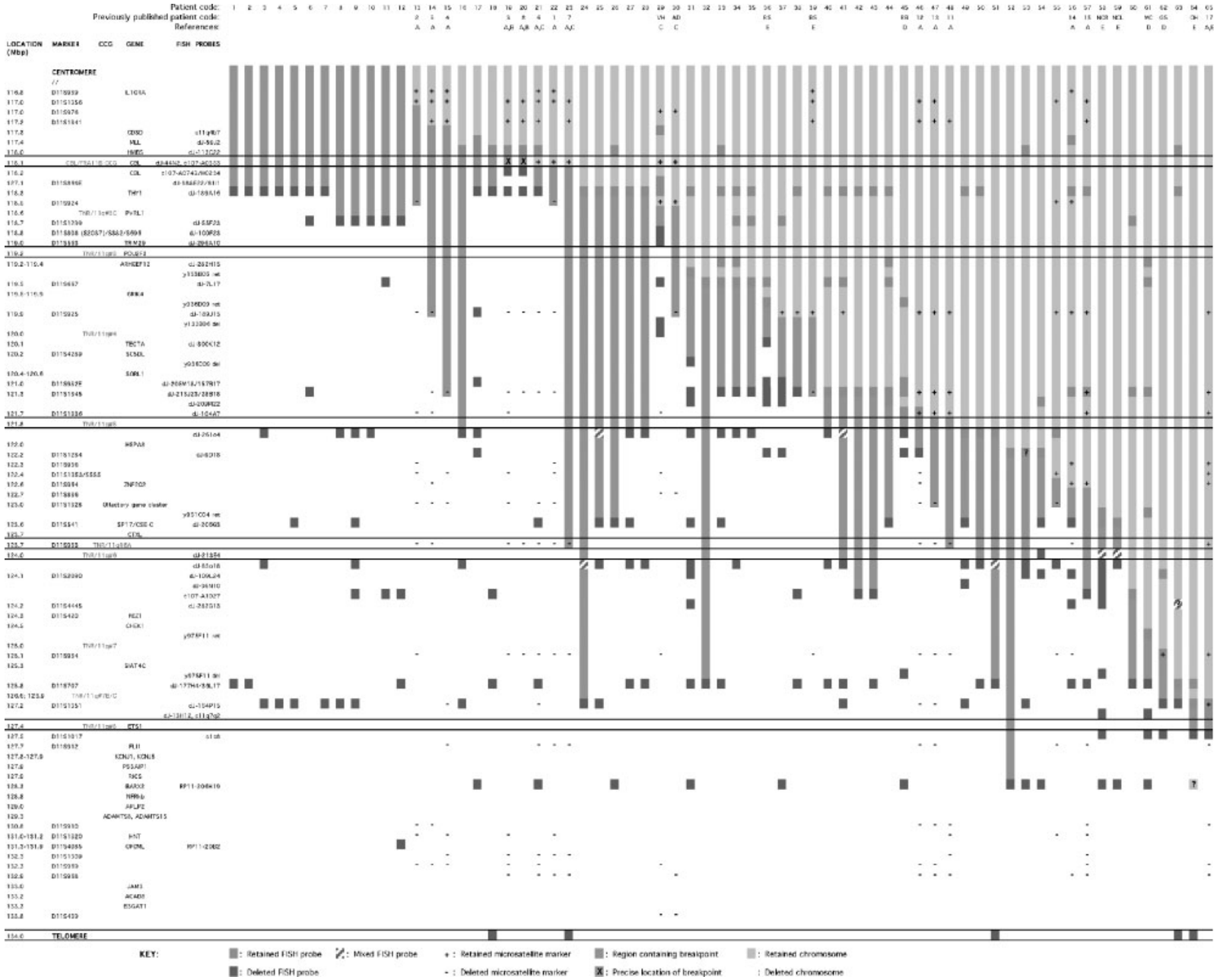

Patient code:
Previously published patient code:
References:
LOCATION (Mbp)
MARKER
CCG
GENE
FISH PROBES
CENTROMERE
TELOMERE
KEY:
: Retained FISH probe
: Deleted FISH probe
: Mixed FISH probe
: Retained microsatellite marker
: Deleted microsatellite marker
: Region containing breakpoint
: Precise location of breakpoint
: Retained chromosome
: Deleted chromosome

Fig. 2.

TABLE I. Common Clinical Findings in the 11q Terminal Deletion Disorder

Problem	Frequency	Percentage
Thrombocytopenia	64/68	94
Paris-Trousseau	13/14	93
Developmental delay	11/13	85
Congenital heart disease	52/93	56
Short stature	25/37	68
Undescended testes	18/31	58
Recurrent infections	42/78	54
IGF-1 deficiency*	4/8	50
Abnormal brain imaging study	24/47	51
Chronic constipation	30/72	42
Eczema	15/69	22
Pyloric stenosis	13/87	15
Male	7/31	23
Female	6/56	11
Structural kidney defects	7/90	8

*Measured only in patients with height <5th percentile.

TABLE II. Common Dysmorphic Features

Phenotype	Percentage
a: Common dysmorphic features (>49%)	
Eyes	
Ocular hypertelorism	92
Down slanting palpebral fissures	83
Strabismus	67
Ptosis	58
Sparse eyebrows	50
Nose	
Broad nasal bridge	91
Short nose	69
Anteverted nares	64
Mouth	
Thin upper lip	84
V-shaped mouth	67
High-arched palate	64
Long philtrum	58
Dental anomalies	50
Hands	
Syndactyly	72
Finger pad anomalies	56
Low-set thumb	56
Hand anomalies	53
5th finger clinodactyly	53
Dermatoglyphic anomalies	53
Feet	
Toe anomalies	83
2–3 syndactyly	58
Ears	
Low-set, malformed	81
Other	
Prominent forehead	62
Short neck	50
b: Abnormalities occurring in <50% of patients (n=29–36)	
Flat nasal bridge	47
Prominent nasal bridge	42
Epicanthal folds	42
Retrognathia	36
Sacral dimple/angioma	36
Brachydactyly of feet	36
Pes planus	31
Prominent glabella	31
Trigonocephaly	29
Inguinal hernia	25
Short philtrum	22
Iris coloboma	11
Eyelid coloboma	11
Cataract	3

Dysmorphic and Craniofacial Features

In total, 36 patients underwent a comprehensive dysmorphic assessment, a summary of the results is shown in Table II.

Growth/Endocrine

In total, 25 of 37 (68%) patients had short stature (defined as below the 5th percentile for sex and age). Serum IGF-1 levels were measured in eight of those patients with short stature and four patients (50%) were found to have IGF-1 deficiency.

Cognitive and Behavioral

Neurocognitive assessments were performed on 13 patients with 11q- (Table III). The Kaufman brief intelligence test scores ranged from 40 to 98 (mean = 49, n = 13). Five (38%) had moderate mental retardation (IQ < 50), six (46%) had mild mental retardation (IQ, 50–79), and two (15%) were normal (IQ, 92 and 98). Receptive language scores ranged from 40 to 99 (mean 64, n = 13), and expressive language score ranged from 40 to 107 (mean 57, n = 12). Five of the six patients who had mild mental retardation (IQ, 50–76) had receptive language scores one standard deviation higher than expressive language (74 vs. 55). Spacial ability scores ranged from 45 to 107 (mean = 60, n = 13). Facial recognition scores ranged from 33 to 78% (mean = 56%, n = 9), without any apparent pattern among individual patients.

Cardiac

In total, 56% (52/93) of patients had serious cardiac defects, most of which required surgical intervention (Table IV). Two thirds of the patients with heart defects had, at about equal frequencies, either a hemodynamically significant ventricular septal defect or a left-sided obstructive lesion including abnormalities of the mitral and aortic valves, aorta and left ventricle. There were no cases of subaortic stenosis. Our cohort included only two children with hypoplastic left heart

Fig. 2. Molecular mapping of chromosome 11q deletions of 65 patients with the 11q terminal deletion disorder. The extent of chromosome 11q deletions of 65 patients with the 11q terminal deletion disorder are shown, 41 of which are newly identified cases from this study, together with previously published analyses from a further 24 cases. Individual patients are attributed a patient code unique to this article in the first row, and previously published codes together with their relevant references below [A: Penny et al., 1995; B: Jones et al., 1995; C: Michaelis et al., 1998; D: Tunnacliffe et al., 1999; E: Jones et al., 2000]. Most of the patients whose deletions have been previously characterized have not been further analyzed in this study (the exceptions are patients 21, 23, and 59). Each column in the main body of the figure represents an individual patient's chromosome 11q deletion. Green-shaded bars indicate the region of the chromosome that is intact (retained); the un-shaded areas indicate the region that is deleted; and red-shaded bars represent ambiguity in the locations of deletion breakpoints as defined by the resolution of this study. Chromosome markers (D11S) and known genes, together with the locations of $(CCG)_n$ trinucleotide-repeats of $n > 3$, are listed at the left of the figure (centromeric at the top, telomeric at the bottom). The order of all map elements is based on the collation of the completed genomic sequence (Contig Accession; NT_033899) and our own high-density BAC map, and their locations on chromosome 11 are indicated in the far left column "Location" (in Mbp, from pter = 0). Where a+ or a− appear in the body of the figure, this refers to the presence or absence of the microsatellite marker at that location (in the column "Marker") as defined by polymorphism analyses. Solid green or red boxes indicate the presence or absence of the relevant probe at that location (in the column "FISH probe") as defined by FISH analysis. A variety of probes were used for FISH analysis, distinguished by their library-specific prefixes (see methods for references); RP11 = BAC, dJ = PAC, c107 = cosmid, y = YAC (ret, retained; del, deleted).

TABLE III. Cognitive Assessments on 13 Patients With the 11q Terminal Deletion Disorder (in Order of Total IQ)

Patient	Age	Sex	Total IQ	Expressive	Receptive	Spacial	Facial recognition
63	2	F	98	79	57	107	ND
33	4	M	92	107	92	89	58
41	11	F	76	68	99	61	67
61	16	M	67	62	71	58	67
43	10	F	64	40	76	70	63
57	12	F	53	45	67	58	52
44	4	F	51	58	56	45	ND
40	20	F	50	57	55	46	63
35	18	F	48	40	40	45	48
42	21	F	43	42	55	45	56
34	10	M	41	ND	54	52	ND
6	9	F	40	41	55	45	33
38	6	F	40	40	40	58	ND

syndrome, one underwent heart transplantation as a neonate, and the other had a Norwood procedure as a neonate. The other one third of children with congenital heart disease had a variety of heart defects, each occurring less commonly, including double outlet right ventricle, d-transposition of the great arteries, secundum atrial septal defects, dextrocardia, aberrant right subclavian artery, patent ductus arteriosus, and a left-sided superior vena cava. In addition, atrioventricular canal defects have been reported.

We also performed echocardiograms on 17 children. One patient with a history of a heart murmur who had not been evaluated for over 10 years was found to have severe aortic stenosis.

Hematology (Paris-Trousseau Syndrome)

Based on clinical questionnaire, 94% (64/68) of patients with 11q- had a history of thrombocytopenia. We studied prospectively 14 patients with 11q-, 13 had either thrombocytopenia and/or abnormal platelet morphology indicative of Paris-Trousseau syndrome [Favier et al., 1993; Breton-Gorius et al., 1995]. Specifically, these patients were found to have thrombocytopenia at birth, with counts as low as 10–20,000. Over time (years), we have found that the platelet counts tend to increase to near or low normal levels. Most recently, several adolescent age patients with 11q- with normal platelet counts were found to have markedly prolonged bleeding times, indicating persistence of abnormal platelet function despite resolution of the thrombocytopenia.

TABLE IV. Heart Defects in 11q-

Left-sided/flow lesions
Hypoplastic left heart syndrome
Shone's complex
Coarctation
Bicuspid aortic valve
Aortic valve stenosis
Mitral valve stenosis
Membranous ventricular septal defect
Miscellaneous Lesions
Secundum atrial septal defect
Double outlet right ventricle
Aberrant right subclavian artery
Atrioventricular septal canal defect
d-transposition of the great arteries
Dextrocardia
Left-sided superior vena cava
Tricuspid atresia
Type B interruption of the aortic arch/truncus arteriosus
Pulmonary stenosis

Gastrointestinal

A total of 11 of 74 (15%) patients had pyloric stenosis, including 6/56 females (11%) and 6/33 males (18%). Thus, pyloric stenosis occurred at >116× and >45× the frequency in females and males in the general population, respectively [Schechter et al., 1997]. Chronic constipation requiring medical treatment was common, occurring in 30/72 (42%) patients. Three of these patients had rectal biopsies to rule out Hirschsprung disease, and all demonstrated the presence of ganglion cells. Two females had rectal abnormalities, one with an imperforate anus and the other with anal stenosis requiring surgery. Feeding difficulties, usually the result of poor tone and oral motor coordination, were common and accounted for one of the most common reasons for prolonged hospitalization during the newborn period. Gastric feeding tubes have been used commonly temporarily until neurologic maturity is achieved.

Genitourinary and Renal Anomalies

In total, 18 of 31 (58%) males had undescended testes, all but one of whom underwent surgical correction. One male had hypospadias and one female had a posteriorly shifted vagina.

Structural defects of the kidney were common. Of 90 patients surveyed, 5 had a duplicated ureter, 1 had a single kidney and 1 had a severely dysplastic kidney that required surgical removal, 4 had hydronephrosis, and 1 each had a narrowed ureter and a "distorted" bladder.

Immune/Allergy

There was no evidence of immunodeficiency detected in our cohort and no life threatening or opportunistic infections were reported. However, recurrent episodes of otitis media and/or sinusitis were frequent, occurring in 42 of 78 subjects (54%). Serum IgA levels were measured in 13 subjects, all of which were normal or low normal for age. Total neutrophil counts and total lymphocyte counts were also normal. Pressure equalization tubes were utilized commonly. Eczema was reported in 15 of 67 subjects (22%), and all of the cases were mild to moderate in severity (the incidence of eczema in the general population is estimated to be 10–20%) [Daniels and Harper, 2002]. There was no apparent increase in the frequency of respiratory, food, or medication allergy in our cohort.

Metabolic

Quantitative assays of the concentrations of urine amino acids and organic acids were measured in three patients (two males and one female), all levels were normal.

Neurologic

Most patients have fine and gross motor impairments. Seizures were uncommon, only three patients had a history of atypical seizures. One patient had suffered a stroke of unknown etiology and was wheelchair-bound. All other patients beyond toddler age were ambulatory.

Ophthalmologic and Otolaryngologic

We performed a comprehensive ophthalmologic evaluation in ten 11q- patients [Lee et al., 2004]. All ten had exotropia, seven had refractive error, three had ptosis, two had amblyopia. Three had tortuosity of the retinal vessels, an extremely rare finding whose clinical significance is unknown. Based on the questionnaire, hearing deficits occur, including the need for hearing aids. The frequency of hearing impairments is unknown due to a limited number of patients that had formal, standardized hearing testing. The etiology of the hearing impairment is most likely multifactorial.

Orthopedic

In total, 15 patients underwent screening assessments of gait, joint range of motion, and there were no obvious musculoskeletal abnormalities. Fourteen of the children were ambulatory, one was wheelchair-bound after suffering a stroke.

Mapping of Deletion Breakpoints and Identification of Minimal Regions

The locations of chromosome deletion breakpoints in 41 patients who have not previously been published were mapped by either polymorphism analysis of microsatellite markers or FISH analysis of metaphase chromosomes. These results, together with previously published data from a further 24 cases, were collated with the recently completed sequence of the distal 38.5 Mbp of chromosome 11q (April 2003, contig accession; NT_033899) and with a BAC contig of the same region, assembled by analysis of the Human Genome Sequencing Project. This latter resource includes the locations of 559 STS markers, 154 EST clones and 129 genes, providing a highly redundant overlapping panel of 349 sequenced BAC clones and a total of 1,190 resolvable loci. Integration of all map elements and BAC end locations from our contig, together with the completed genomic sequence, enabled the accurate interpretation of deletion breakpoint mapping data performed by our laboratories and also those previously published. These data are summarized in Figure 2.

Molecular analysis of the deletion breakpoints demonstrates significant heterogeneity in the sizes of deletions (including between patients with the same breakpoints based on karyotype analysis). Nineteen (26%) had deletions whose breakpoints extended to or were centromeric to FRA11B; six (8%) had the smallest deletions, extending only as far as D11S420, and the remainder of the breakpoints were intermediate in size. To date, we have not found any interstitial deletions in patients determined to have a terminal 11q deletion by karyotype analysis.

Critical regions were defined as the region that is hemizygous in all patients for an individual phenotype. Specifically, the critical region was defined as the region spanning from the most distally located probe that is retained, to the telomere. Towards this end, we have identified critical regions for 14 phenotypes, as well as for cognitive functions (Fig. 3A,B). The smallest critical region (6.8 Mbp) extends from D11S1351 to the telomere and was associated with four of the phenotypes, including Paris-Trousseau platelet disorder, undescended testes, pyloric stenosis, and mental retardation (defined as a total IQ < 80). Ocular coloboma had the largest critical region, extending from D11S1299 to the telomere (15.3 Mbp). The remaining critical regions are intermediate in size.

There are $\sim$40 known genes that map to the 15.3 Mbp region from D11S1299 to the telomere, with a variety of functions including transcription factors, metabolism, and cell adhesion molecules. Figure 3C shows the chromosomal locations of these genes, the tissues in which they are expressed, and their known or proposed functions. In addition, there are more than 150 other anonymous cDNA clones or predicted transcription units that map to this region, for which little or no homology to known genes is apparent.

DISCUSSION

We performed a prospective analysis of 110 patients with the 11q terminal deletion disorder. Although there was a significant degree of phenotypic variability between individuals, there were several unique and interesting features identified. The first observation is of a male to female ratio of 0.53, although the basis for this is unknown.

Our data demonstrate high penetrance for cognitive dysfunction in these patients, with 12 of the 13 patients' neurocognitive profiles correlating with deletion size (Fig. 3A). All six patients with intermediate intelligence test scores had intermediate size deletions, whereas the five patients with the lowest total intelligence scores, including global language impairment, had deletions that were among the largest detected. In contrast, patients with intermediate size deletions (originating between D11S1345 and D11S420) had intermediate total intelligence quotients, with a predilection for near normal receptive language, but mild to moderately impaired expressive language. Two patients had normal intelligence: One had among the smallest deletions detected, originating telomeric to D11S707, and the other patient had an intermediate size deletion, originating telomeric to D11S667. Thus, there appears to be a strong, although not complete, correlation between cognitive function and deletion size.

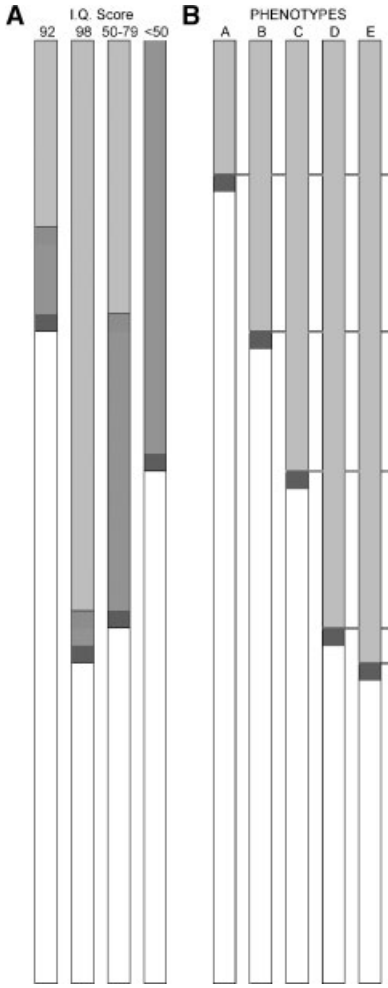
Almost all patients have the Paris-Trousseau syndrome, a defect in platelet development characterized by neonatal thrombocytopenia and persistent platelet dysfunction [Favier et al., 1993; Breton-Gorius et al., 1995]. The very high penetrance of Paris-Trousseau syndrome in the 11q deletion disorder, and its exclusive association with 11q deletions, suggest this bleeding disorder may be pathognomonic for the 11q terminal deletion disorder.

Although only two patients in our cohort had hypoplastic left heart syndrome (HLHS), a review of the literature as well as of other unpublished cases of HLHS suggest a frequency of between 5 and 10% in the 11q terminal deletion disorder. This represents a frequency that is 1,000–2,000 times that of the general population, which is unprecedented for any dysmorphic disorder.

Ophthalmologic assessments revealed a high frequency of a very unusual vascular disorder, retinal artery tortuosity. The clinical significance of this abnormality is unknown, but may be indicative of a defect in retinal vascular development.

Pyloric stenosis occurs at a very high rate (15%), and shows a predominance in males as it does in the general population. However, the frequency in females is increased relatively higher in patients with 11q terminal deletions.

Based on our clinical findings, we have formulated a comprehensive set of clinical recommendations for the clinical management of the 11q terminal deletion disorder (Table V). Some questions remain regarding the clinical management and natural history of these patients. For example, although half of the patients with short stature had IGF-1 deficiency, it is unknown whether these patients would benefit from growth hormone replacement therapy.



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LOCUS	LOCATION (Mbp)	GENE	EXPRESSION	FUNCTION	RELATED DISEASE
(Centromere)					
FRA11B	118.1	*CBL2*	Lymphocyte	RTK adaptor; regulates RTK ubiquitination	
	118.2	*MCAM*	Prostate tumour, melanoma	Cell adhesion molecule	
	118.3	*USP2*	(Widespread)	Ubiquitin specific protease	
	118.3	*THY1*	T-cell	Cell adhesion molecule	
	118.7	*PVRL1*		Cell adhesion molecule; herpesvirus receptor	Cleft lip/palate-ectodermal dysplasia syndrome (CLPED1)
D11S1299	118.7				
	119.0	*TRIM29*	(Widespread)	Transcription factor	Ataxia telangiectasia, Group C
	119.1	*POU2F3*	Keratinocytes	POU/homeobox domain transcription factor	
	119.3	*ARHGEF12*	Ubiquitous	Guanine nucleotide exchange factor	
dJ-7L17	119.5				
	119.5	*GRIK4*	CNS	Kainate-preferring ionic channel	
	120.0	*TECTA*	Inner ear	Tectorial membrane component	Recessive sensorineural deafness
	120.2	*SC5DL*	Ubiquitous	Sterol C-5 dehydrogenase	
	120.4	*SORL1*	Brain, spinal cord, testis	Sortilin-related receptor; protein sorting?	
D11S1345	121.3				
dJ-261o4	121.9				
	122.0	*HSPA8*	Pancreatic gastrinoma	Heat shock protein/protein folding	
	122.7	*ZNF202*	Testis	Transcription factor; tumor susceptibility	
	122.6	*CSE-C*	?	Sialic acid acetylesterase	
	123.6	*SPA17*	Sperm	Binding to oocyte; cell adhesion?	
	123.7	*NRGN*	Brain (telencephalic neurons)	Mediator of thyroid hormone	
	123.7	*CTXL*	Ubiquitous	Ig Superfamily	
D11S2090	124.2				
	124.4	*FEZ1*	Brain	Axonal development	
	124.5	*EI24*	Colorectal cancer	P53-induced immediate early response gene	
	124.5	*ITM1*	Ovary, testis	Transmembrane protein	
	124.5	*CHEK1*	Ubiquitous	Kinase/Cell cycle	
	124.6	*ACRV1*	Testis	Sperm binding?	
	124.8	*DDX25*	Testis	RNA Helicase	
	125.3	*DCPS*	?	Pyrophospatase/mRNA decapping enzyme	
	125.3	*SIAT4C*	Placenta, testis, ovary	Acetyl neuraminyltransferase	
D11S707	125.7				
D11S1351	127.2				
	127.4	*ETS1*	Endothelium	Transcription factor/hematopoiesis	
	127.6	*FLI1*	Neuroepithelium	Transcription factor/hematopoiesis	
	127.8	*KCNJ1*	Kidneys	K+ channel	Bartter syndrome
	127.8	*KCNJ5*	Heart	K+ channel	
	127.9	*P53AIP1*	?	Mediator of p53-dependent apoptotis	
	127.9	*RICS*	?	RhoGTPase activator/organization of cytoskeletal networks	
	128.3	*BARX2*	CNS, craniofacial, lung, limbs	Homeobox transcription factor	Ovarian Cancer?
	128.8	*NFRKB*	?	Transcription factor	
	129.0	*APLP2*	Sperm	Cell cycle	
	129.3	*ADAMTS8*	Ubiquitous	Disintegrin-like/metalloprotease; angiogenesis inhibitor	
	129.4	*ADAMTS15*	Fetal kidney and liver	Disintegrin-like/metalloprotease	
	130.8	*HNT*	Brain	Cell adhesion molecule	
	131.9	*OPCML*	Brain	Cell adhesion molecule	Ovarian Cancer
	133.0	*JAM3*	Heart	Cell adhesion molecule	
	133.2	*ACAD8*	Ubiquitous	Fatty acid beta-oxidation	
	133.3	*B3GAT1*	Brain	Glucoranyltransferase	
(Telomere)	134.0				

Fig. 3. Critical regions of deletion for 11q- syndrome phenotypes, and candidate gene locations. The critical regions of chromosome 11q deletion associated with specific phenotypes are represented at the left of the figure, and the locations of known genes are shown on the right. **A**: Deletions from 13 patients for whom IQ scores were obtained are represented according to the convention of Figure 1. The deletions of two patients with normal IQ are shown separately from the deletions of other patients, which are grouped in IQ ranges of 50–79 (six patients) and <50 (five patients). For these patients, the most proximal and distal breakpoints amongst their deletions are used to represent the range of potential deletion sizes. **B**: The most distal breakpoints of other phenotypes are shown together in the following five groups (total number of patients in brackets); A: ocular coloboma (4); B: high palate (21), chronic constipation (10), and ptosis (12); C: eczema (7), abnormal brain imaging (10), carp mouth (20), short stature/IGF1 deficiency (4), and recurrent infections (17); D: heart defects (32); E: mental retardation (14), platelet disorder (38), undescended testes (9), and pyloric stenosis (6).

Note: Phenotypes are grouped together based on the location of the critical region of deletion, and not necessarily because they are clinically associated. **C**: Known genes in the 11q deletion syndrome disorder (starting from *FRA11B*, the most proximal breakpoint reported) are ordered according to their location in contig NT_033899, and their distance from 11pter is shown in Mbp (calculated backwards from a total chromosome 11 length, or 11qter location, of 134 Mbp). Genetic markers and FISH probes are shown in the column "LOCUS" above a red line that delineates the breakpoint location. Anonymous cDNA clones and predicted transcripts are omitted from this list, as are other genes for which there is no significant published data. Expression pattern and evidence of gene function are collated from Locus Link (http://www.ncbi.nlm.nih.gov/LocusLink) and papers cited therein. Citations regarding previously identified disease genes on 11q are (order as figure): [Kapp et al., 1992; Simon et al., 1996; Verhoeven et al., 1998; Suzuki et al., 2000; Sellar et al., 2001; Sellar et al., 2003].

Longevity

The normal life expectancy of these children is unknown. Historically, the two most common causes of morbidity and mortality have been congenital heart defects and bleeding. With improved outcomes in children with most forms of congenital heart disease, outcomes of patients with 11q- with congenital heart defects should continue to improve. Most, if not all cases of bleeding complications resulted from an unawareness of the underlying bleeding propensity that these children have. Hence, proactive platelet transfusions and possibly ddAVP should minimize bleeding risks.

Although there is no apparent increased risk of pediatric neoplasms in our cohort, malignancies are a potential concern as these children reach adulthood. The majority of patients with the 11q terminal deletion syndrome reported to date are of a young age, and consequently their risk for developing malignancies in adulthood is unknown.

11q deletions are often found in a variety of adult-onset malignancies, including malignant melanoma, epithelial cancers of the cervix, colon, ovary, lung, breast, stomach and nasopharynx, neuroblastoma, and lung carcinoids [Keldysh et al., 1993; Negrini et al., 1995; Rasio et al., 1995; Davis et al., 1996; Gabra et al., 1996; Hui et al., 1996; Koreth et al., 1997; Launonen et al., 1998; Connolly et al., 1999; Guo et al., 1999; Skomedal et al., 1999; Goldberg et al., 2000; Pulido et al., 2000; Petzmann et al., 2001]; and at least three tumor suppressor genes, *CHK1* [Bertoni et al., 1999; Menoyo et al., 2001], *BARX2* [Sellar et al., 2001], and *OPCML* [Sellar et al., 2003] are commonly deleted in patients with 11q terminal deletions. Of

TABLE V. Clinical Recommendations for 11q Terminal Deletion

Genetic
Karyotype analysis of parents
Cardiac
Baseline evaluation by a pediatric cardiologist, including an echocardiogram, and then as needed (e.g., new murmur)
Bleeding
Monthly CBC, first 3 months, then once/year
Platelet function studies, once platelet count normalizes
Platelet transfusion and/or ddAVP for bleeding/high risk procedures
Avoidance of medications that interfere with platelet function
? oral contraceptive therapy for heavy menses
Neurocognitive/behavioral
Baseline evaluation by a neuropsychologist/behavioral specialist, and then yearly, or more often (as needed, e.g., prior to school entry)
Behavioral pediatrician/pediatric psychologist, as needed (e.g., for ADHD)
Baseline brain imaging, and as needed
Ophthalmologic
Baseline (age 6 weeks), age 3 months, 6 months, then every 6 months until age 3 years, and then yearly thereafter
Endocrine
Baseline growth hormone (IGF-1) and hypothalamic/pituitary, and as needed based on clinical course (e.g., short stature). Risks/benefits of human growth hormone replacement therapy unknown.
Gastrointestinal
Upper GI series/abdominal ultrasound to rule out pyloric stenosis (if clinically indicated)
Rectal mannometry and/or Rectal biopsy for chronic constipation
Swallowing studies, if clinically indicated, for failure to thrive
Genitourinary
Baseline renal ultrasound
Referral to a pediatric urologist for undescended testes or any other anomalies
Otolaryngology (ear, nose, and throat)
Imaging study for bifid uvula to rule out midline defects
ENT referral for chronic/recurrent ear infections, sinusitis
Age-appropriate formal hearing testing, beginning in infancy
Allergy/immune
No contraindications for routine immunizations
Treat eczema symptomatically; dermatology referral for refractory cases
Neurologic
Baseline brain imaging
Vision/hearing testing (see above)
Referral to a pediatric neurologist for seizures
Neurosurgical
Early referral to a pediatric neurosurgeon for craniosynostosis, as indicated
Orthopedic
Baseline physical/occupational therapy evaluation
Referral to a pediatric orthopedic surgeon as needed
Metabolic
Metabolic evaluation only as indicated on an individual basis
Health maintenance
No contraindications to normal immunization schedule

these, the role of the gene *OPMCL* in causing ovarian cancer [Sellar et al., 2003] presents the most significant risk. OPCML is located close to the 11q telomere and is deleted in all 11q- patients, raising the significant possibility that female patients might be at increased risk of developing ovarian cancer in late adulthood. It is worth noting that the absence of chromosome 11q might be involved mainly in tumor progression rather than in the early steps of the neoplastic transformation. Thus, for many of the tumors mentioned above, we might not observe an increased risk but possibly tumors with a more aggressive course.

At the time of this writing, the original index case of the 11q terminal deletion disorder [Jacobsen et al., 1973] is 43 years-old and healthy. It is most likely that older living patients exist, but have not been diagnosed because karyotype analysis was not available at the time of their birth.

Mechanism of Deletion

Previous analysis of the deletion breakpoints led to the identification of one mechanism responsible for causing at least a subset of 11q terminal deletions [Jones et al., 1995]. In this case, the deletion was caused by expansion of a CCG-trinucleotide repeat at the site of the deletion breakpoint, and consequent expression of the folate-sensitive fragile site in 11q23.3, FRA11B. Breakpoints distal to FRA11B have also been shown to co-localize with other CCG-trinucleotide repeats [Jones et al., 2000]. Evidence of breakpoint clustering is maintained even in this large number of cases in our cohort, and this raised the possibility that the CCG-trinucleotide repeats telomeric to FRA11B might be the locations of other (as yet unidentified) folate-sensitive fragile sites. To test this hypothesis, we performed fragile site analyses on metaphase chromosomes from ten parents of five patients, at least four of whom had breakpoints that were telomeric to FRA11B. No additional folate-sensitive fragile sites in 11q were detected, suggesting a different mechanism may be responsible for the generation of deletions with breakpoints telomeric to FRA11B.

Of possible relevance, Penny et al. [1995], found that in cases where the deletion breakpoint was relatively small, originating telomeric to the marker D11S925, these chromosomes were always derived from the father. Thus, parental imprinting may

be involved in the mechanism of the generation of smaller 11q terminal deletions. To date, we know of two exceptions to this: in the first case, the deletion was inherited from the mother, who also had the deletion. The second was the result of uniparental disomy (Dr. John Johnson, personal communication). Thus, all de novo deletion breakpoints arising distal to D11S925 are inherited from the father.

Interestingly, two patients in our cohort were found to be mosaic for the deletion in an analysis of peripheral blood lymphocytes, suggesting that mosaicism may occur in other tissues as well, and may contribute to phenotypic variability.

Identification of Critical Regions and Disease-Causing Genes

The 11q terminal deletion disorder appears to be a contiguous gene disorder. The delineation of the critical regions will facilitate the identification of candidate disease-causing genes for the individual phenotypes, based on their known functions and expression patterns. For example, the critical region for Paris-Trousseau contains about 20 known genes. One such gene, *Fli1*, has previously been shown to be involved in hematopoeisis. Generation of a Fli1-knockout led to a phenotype reminiscent of Paris-Trousseau syndrome, implicating a role for Fli1 in platelet development and function, and in causing Paris-Trousseau syndrome [Hart et al., 2000].

Limitations

We have employed a comprehensive and conservative approach in our assessments of patients with the 11q terminal deletion disorder. Nonetheless, certain limitations exist. For example, all the patients we studied were living at the time of our assessment. Thus, it is possible that we may underestimate the frequency of life-threatening problems in these children. For example, the frequency of HLHS is much greater, based on case reports in the literature and other cases identified from other geneticists, than that of our cohort, indicating a selection bias for patients with non-fatal congenital heart defects. Similarly, the numbers of cases clustering at specific regions appears to decrease for smaller deletion sizes. This may be indicative of a selection bias that would over-represent patients with a more serious clinical phenotype caused by larger deletions. Secondly, the majority of clinical information was obtained through a parental questionnaire, which could possibly lead to inaccuracies. In most cases, information obtained by the parents indicative of serious medical problems, e.g., congenital heart disease, was documented independently through records obtained by physicians. Finally, the age of the child at the time of assessment might affect the reporting frequency. One obvious example could be the frequency of malignancies, given the fact that many of the malignancies whose genetic loci have been associated to regions that are deleted in the 11q terminal deletion disorder are of adult onset.

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REFERENCES

Aalfs CM, Hoovers JM, Wijberg FA. 1999. Molecular analysis of a translocation (6;11)(p21;q25) in a girl with Jacobsen syndrome [letter]. Am J Med Genet 86:398–400.

Bertoni F, Codegoni AM, Furlan D, Tibiletti MG, Capella C, Broggini M. 1999. CHK1 frameshift mutations in genetically unstable colorectal and endometrial cancers. Genes Chromosomes Cancer 26(2):176–180.

Breton-Gorius J, Favier R, Guichard J, Cherif D, Berger R, Debili N, Vainchenker W, Douay L. 1995. A new congenital dysmegakaryopoietic thrombocytopenia (Paris-Trousseau) associated with giant platelet alpha-granules and chromosome 11 deletion at 11q23. Blood 85(7): 1805–1814.

Clang DR, La Baere RJ. 1998. Jacobsen syndrome: Chromosome deletion at 11q23. J Am Osteopath Assoc 98(10):551–554.

Connolly KC, Gabra H, Millwater CJ, Taylor KJ, Rabiasz GJ, Watson JE, Smyth JF, Wyllie AH, Jodrell DI. 1999. Identification of a region of frequent loss of heterozygosity at 11q24 in colorectal cancer. Cancer Res 59(12):2806–2809.

Daniels J, Harper J. 2002. The epidemiology of atopic dermatitis. Hosp Med 63(11):649–652.

Davis M, Hitchcock A, Foulkes WD, Campbell IG. 1996. Refinement of two chromosome 11q regions of loss of heterozygosity in ovarian cancer. Cancer Res 56(4):741–744.

Favier R, Douay L, Esteva B, Portnoi MF, Gaulard P, Lecompte T, Perot C, Adam M, Lecrubier C, van den Akker J, et al. 1993. A novel genetic thrombocytopenia (Paris-Trousseau) associated with platelet inclusions, dysmegakaryopoiesis and chromosome deletion at 11q23. Acad Sci 316:698–701.

Fryns JP, Kleczkowska A, Smeets E, van den Berghe H. 1987. Distal 11q deletion: A specific clinical entity. Helv Paediatr Acta 42:191–194.

Gabra H, Watson JE, Taylor KJ, Mackay J, Leonard RC, Steel CM, Porteous DJ, Smyth JF. 1996. Definition and refinement of a region of loss of heterozygosity at 11q23.3-q24.3 in epithelial ovarian cancer associated with poor prognosis. Cancer Res 56(5):950–954.

Gangarossa S, Mattina T, Romano V, Milana G, Mollica F, Schiliro G. 1996. Micromegakaryocytes in a patient with partial deletion of the long arm of chromosome 11 [del(11)(q24.2qter)] and chronic thrombocytopenic purpura. Am J Med Genet 62(2):120–123.

Goldberg EK, Glendening JM, Karanjawala Z, Sridhar A, Walker GJ, Hayward NK, Rice AJ, Kurera D, Tebha Y, Fountain JW. 2000. Localization of multiple melanoma tumor-suppressor genes on chromosome 11 by use of homozygosity mapping-of-deletions analysis. Am J Hum Genet 67(2):417–431.

Guo C, White PS, Weiss MJ, Hogarty MD, Thompson PM, Stram DO, Gerbing R, Matthay KK, Seeger RC, Brodeur GM, et al. 1999. Allelic deletion at 11q23 is common in MYCN single copy neuroblastomas. Oncogene 18(35):4948–4957.

Hart A, Melet F, Grossfeld P, Chien K, Jones C, Tunnacliffe A, Favier R, Bernstein A. 2000. Fli-1 is required for murine vascular and megakaryocytic development and is hemizygously deleted in patients with thrombocytopenia. Immunity 13:167–177.

Hertz JM, Tommerup N, Sorensen FB, Henriques UV, Nielsen A, Therkelsen AJ. 1995. Partial deletion 11q: Report of a case with a large terminal deletion 11q21-qter without loss of telomeric sequences, and review of the literature. Clin Genet 47:231–235.

Hoffmann G, Aramaki S, Blum-Hoffmann E, Nyhan WL, Sweetman L. 1989. Quantitative analysis for organic acids in biological samples: Batch isolation followed by gas chromatographic-mass spectrometric analysis. Clin Chem 35:587–595.

Hui AB, Lo KW, Leung SF, Choi PH, Fong Y, Lee JC, Huang DP. 1996. Loss of heterozygosity on the long arm of chromosome 11 in nasopharyngeal carcinoma. Cancer Res 56(14):3225–3229.

Jacobsen P, Hauge M, Henningsen K, Hobolth N, Mikkelsen M, Philip J. 1973. An (11;21) translocation in four generations with chromosome 11 abnormalities in the offspring. Hum Hered 23:568–585.

Jones C, Slijepcevic P, Marsh S, Baker E, Langdon WY, Richards RI, Tunnacliffe A. 1994. Physical linkage of the fragile site FRA11B and a Jacobsen syndrome chromosome deletion breakpoint in 11q23.3. Hum Mol Genet 3:2123–2130.

Jones C, Penny L, Mattina T, Yu S, Baker E, Voullaire L, Langdon WY, Sutherland GR, Richards RI, Tunnacliffe A. 1995. Association of a chromosome deletion syndrome with a fragile site within the proto-oncogene CBL2. Nature 376(6536):145–149.

Jones C, Müllenbach R, Grossfeld P, Auer R, Favier R, Chien K, James M, Tunnacliffe A, Cotter F. 2000. Co-localisation of CCG-repeats and chromosome deletion breakpoints in Jacobsen syndrome: Evidence for a common mechanism of chromosome breakage. Hum Mol Genet 9(8):1201–1208.

Kapp LN, Painter RB, Yu LC, van Loon N, Richard CW III, James MR, Cox DR, Murnane JP. 1992. Cloning of a candidate gene for ataxia-telangiectasia group D. Am J Hum Genet 51(1):45–54.

Keldysh PL, Dragani TA, Fleischman EW, Konstantinova LN, Perevoschikov AG, Pierotti MA, Della Porta G, Kopnin BP. 1993. 11q deletions in human colorectal carcinomas: Cytogenetics and restriction fragment length polymorphism analysis. Genes Chromosomes Cancer 6(1):45–50.

Koreth J, Bakkenist CJ, McGee JO. 1997. Allelic deletions at chromosome 11q22-q23.1 and 11q25-qterm are frequent in sporadic breast but not colorectal cancers. Oncogene 14(4):431–437.

Krishnamurti L, Neglia JP, Nagarajan R, Berry SA, Lohr J, Hirsch B, White JG. 2001. Paris-Trousseau syndrome platelets in a child with Jacobsen syndrome. Am J Hematol 66(4):295–299.

Kuster W, Gebauer HJ, Majewski F, Lenard HG. 1985. Report of a deletion 11 (qter-q23.3) and short review of the literature. Eur J Pediatr 144(3): 286–288.

Launonen V, Stenback F, Puistola U, Bloigu R, Huusko P, Kytola S, Kauppila A, Winqvist R. 1998. Chromosome 11q22.3-q25 LOH in ovarian cancer: Association with a more aggressive disease course and involved subregions. Gynecol Oncol 71(2):299–304.

Lee WB, O'Halloran HS, Grossfeld PD, Scher C, Jockin YM, Jones C. 2004. Ocular findings in Jacobsen syndrome. J AAPOS 8(2):141–145.

Lewanda AF, Morsey S, Reid CS, Jabs EW. 1995. Two craniosynostotic patients with 11q deletions, and review of 48 cases. Am J Med Genet 59(2):193–198.

Lin JH, Hou JW, Teng RJ, Tien HF, Lin KH. 1998. Jacobsen distal 11q deletion syndrome with a myelodysplastic change of hemopoietic cells. Am J Med Genet 75(4):341–344.

Matheisel A, Babinska M, Wierzba J, Wozniak A, Nedoszytko B, Balcerska A, Limon J. 2000. A case with 47,XXY,del(11)(q23) karotype-coexistence of Jacobsen and Klinefelter syndromes. Genet Couns 11(3):267–271.

McClelland SM, Smith AP, Smith NC, Gray ES, Diack JS, Dean JC. 1998. Nuchal thickening in Jacobsen syndrome. Ultrasound Obstet Gynecol 12(4):280–282.

Menoyo A, Alazzouzi H, Espin E, Armengol M, Yamamoto H, Schwartz S Jr. 2001. Somatic mutations in the DNA damage-response genes *ATR* and *CHK1* in sporadic stomach tumors with microsatellite instability. Cancer Res 61(21):7727–7730.

Michaelis R, Velagaleti GVN, Jones C, Pivnick EK, Phelan MC, Boyd E, Tarleton J, Wilroy RS, Tunnacliffe A, Tharapel AT. 1998. Most Jacobsen syndrome deletion breakpoints occur distal to FRA11B. Am J Med Genet 76:222–228.

Neavel CB, Soukup S. 1994. Deletion of (11)(q24.2) in a mother and daughter with similar phenotypes. Am J Med Genet 53(4):321–324.

Negrini M, Rasio D, Hampton GM, Sabbioni S, Rattan S, Carter SL, Rosenberg AL, Schwartz GF, Shiloh Y, Cavenee WK, et al. 1995. Definition and refinement of chromosome 11 regions of loss of heterozygosity in breast cancer: Identification of a new region at 11q23.3. Cancer Res 55(14):3003–3007.

Nizetic D, Monard S, Young B, Cotter F, Zehetner G, Lehrach H. 1994. Contruction of cosmid libraries from flow-sorted human chromosomes 1, 6, 7, 11, 13, and 18 for reference library resources. Mamm Genome 5(12):801–802.

Obregon MG, Mingarelli R, Digilio MC, Zelante L, Giannotti A, Sabatino G, Dallapiccola B. 1992. Deletion 11q23-qter (Jacobsen syndrome). Report of three new patients. Ann Genet 35(4):208–212.

Ono J, Harada K, Hasegawa T, Sakurai K, Kodaka R, Tanabe Y, Tanaka J, Igarashi T, Nagai T, Okada S. 1994. Central nervous system abnormalities in chromosome deletion at 11q23. Clin Genet 45:325–329.

Ono J, Hasegawa T, Sugama S, Sagehashi N, Hase Y, Oku K, Endo Y, Ohdo S, Ishikiriyama S, Tsukamoto H, et al. 1996. Partial deletion of the long arm of chromosome 11: Ten Japanese children. Clin Genet 50(6): 474–478.

Osoegawa K, Mammoser AG, Wu C, Frengen E, Zeng C, Catanese JJ, de Jong PJ. 2001. A bacterial artificial chromosome library for sequencing the complete human genome. Genome Res 11(3):483–496.

Ounap K, Bartsch O, Uibo O, Laidre P. 2002. Girl with combined cellular immunodeficiency, pancytopenia, malformations, deletion 11q23.3 → qter, and trisomy 8q24.3-qter. Am J Med Genet 108(4):322–326.

Penny LA, del Aquila M, Jones MC, Bergoffen JA, Cunniff C, Fryns JP, Grace E, Graham JM, Kousseff B, Mattina T, et al. 1995. Clinical and molecular characterization of patients with distal 11q deletions. Am J Hum Genet 56(3):676–683.

Petzmann S, Ullmann R, Klemen H, Renner H, Popper HH. 2001. Loss of heterozygosity on chromosome arm 11q in lung carcinoids. Hum Pathol 32(3):333–338.

Pivnick EK, Velagaleti GV, Wilroy RS, Smith ME, Rose SR, Tipton RE, Tharapel AT. 1996. Jacobsen syndrome: Report of a patient with severe eye anomalies, growth hormone deficiency, and hypothyroidism associated with deletion 11 (q23q25) and review of 52 cases. J Med Genet 33:772–778.

Pulido HA, Fakruddin MJ, Chatterjee A, Esplin ED, Beleno N, Martinez G, Posso H, Evans GA, Murty VV. 2000. Identification of a 6-cM minimal deletion at 11q23.1-23.2 and exclusion of *PPP2R1B* gene as a deletion target in cervical cancer. Cancer Res 60(23):6677–6682.

Puvabanditsin S, Garrow E, Zia-Ullah MO, Supavekin S, Lianthanasarn P, Denev KI. 2001. Monosomy 11Q: Report of new phenotypic manifestations. Genet Couns 12(3):283–286.

Rasio D, Negrini M, Manenti G, Dragani TA, Croce CM. 1995. Loss of heterozygosity at chromosome 11q in lung adenocarcinoma: Identification of three independent regions. Cancer Res 55(18):3988–3991.

Reddy KS, Thomas IM, Narayanan HS. 1984. Partial deletion of the long arm of chromosome 11 the Jacobsen syndrome. Indian J Pediatr 51:359–362.

Reddy KS, Thomas IM, Narayanan HS. 1986. Partial deletion of the long arm chromosome 11 in Jacobsen syndrome. Indian J Pediatr 53(1):123–126.

Schechter R, Torfs CP, Bateson TF. 1997. The epidemiology of infantile hypertrophic pyloric stenosis. Paediatr Perinat Epidemiol 11(4):407–427.

Schinzel A, auf der Maur P, Moser H. 1977. Partial deletion of long arm of chromosome 11[del(11)(q23)]: Jacobsen syndrome. Two new cases and review of the clinical findings. J Med Genet 14:438–444.

Sellar GC, Li L, Watt KP, Nelkin BD, Rabiasz GJ, Stronach EA, Miller EP, Porteous DJ, Smyth JF, Gabra H. 2001. BARX2 induces cadherin 6 expression and is a functional suppressor of ovarian cancer progression. Cancer Res 61(19):6977–6981.

Sellar GC, Watt KP, Rabiasz GJ, Stronach EA, Li L, Miller EP, Massie CE, Miller J, Contreras-Moreira B, Scott D, et al. 2003. OPCML at 11q25 is epigenetically inactivated and has tumor-suppressor function in epithelial ovarian cancer. Nat Genet 34(3):337–343.

Simon DB, Karet FE, Rodriguez-Soriano J, Hamdan JH, DiPietro A, Trachtman H, Sanjad SA, Lifton RP. 1996. Genetic heterogeneity of Bartter's syndrome revealed by mutations in the K+ channel, ROMK. Nat Genet 14(2):152–156.

Sirvent N, Monpoux F, Pedeutour F, Fraye M, Philip P, Ticchioni M, Turc-Carel C, Mariani R. 1998. Jacobsen syndrome, thrombopenia, and humoral immunodeficiency. Arch Pediatr 5(12):1338–1340.

Skomedal H, Helland A, Kristensen GB, Holm R, Borresen-Dale AL. 1999. Allelic imbalance at chromosome region 11q23 in cervical carcinomas. Eur J Cancer 35(4):659–663.

Somani S, Levin A, Nowaczyk M, Feigenbaum A, Davidson R, Costa T. 1995. Ocular manifestations of Jacobsen syndrome (11Q-). Am J Hum Genet 57(4 SS):572.

Suzuki K, Hu D, Bustos T, Zlotogora J, Richieri-Costa A, Helms JA, Spritz RA. 2000. Mutations of PVRL1, encoding a cell-cell adhesion molecule/herpesvirus receptor, in cleft lip/palate-ectodermal dysplasia. Nat Genet 25:427–430.

Tunnacliffe A, Jones C, Le Paslier D, Todd R, Cherif D, Birdsall M, Devenish L, Yousry C, Cotter FE, James MR. 1999. Localisation of Jacobsen syndrome breakpoints on a 40-Mb physical map of distal chromosome 11q. Genome Res 9:44–52.

van Hemel JO, Eussen B, Wesby-van Swaay E, Oostra BA. 1992. Molecular detection of a translocation (Y;11) (q11.2;q24) in a 45,X male with signs of Jacobsen syndrome. Hum Genet 88:661–667.

Verhoeven K, Van Laer L, Kirschhofer K, Legan PK, Hughes DC, Schatteman I, Verstreken M, Van Hauwe P, Coucke P, Chen A, et al. 1998. Mutations in the human alpha-tectorin gene cause autosomal dominant non- syndromic hearing impairment. [see comments] Nat Genet 19(1):60–62.

Weyler W, Sweetman L, Maggio DC, Nyhan WL. 1977. Deficiency of propionyl-Co A carboxylase and methylcrotonyl-Co A carboxylase in a patient with methylcrotonylglycinuria. Clin Chim Acta 76(3):321–328.

Woon PY, Osoegawa K, Kaisaki PJ, Zhao B, Catanese JJ, Gauguier D, Cox R, Levy ER, Lathrop GM, Monaco AP, et al. 1998. Construction and characterization of a 10-fold genome equivalent rat P1-derived artificial chromosome library. Genomics 50(3):306–316.