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Delineation of a Contiguous Gene Syndrome with Multiple Exostoses, Enlarged Parietal Foramina, Craniofacial Dysostosis, and Mental Retardation, Caused by Deletions on the Short Arm of Chromosome 11

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Summary

A contiguous gene syndrome due to deletions of the proximal short arm of chromosome 11 is described in eight patients belonging to four families. The main clinical features are multiple exostoses, enlarged parietal foramina, craniofacial dysostosis, and mental retardation. The patients have cytogenetic and/or molecular deletions of chromosome 11p11-p13. These deletions are located between the centromere and D11S914 in a region of ~20 cM. The present study confirms the presence of a multiple exostoses gene on chromosome 11p. Furthermore, it suggests that the gene for isolated foramina parietalia permagna and genes associated with craniofacial dysostosis and mental retardation reside in the same chromosomal region.

Introduction

Multiple exostoses (EXT) is a skeletal disorder characterized by the presence of multiple exostoses in the juxtaepiphyseal regions of many long bones (Solomon 1961). EXT can be inherited as an isolated autosomal dominant trait, and three different loci have been found for this genetically heterogeneous disease: EXT1 is located on 8q23-q24 (Cook et al. 1993; Lüdecke et al. 1995), EXT2 on 11p11-p12 (Wu et al. 1994; Wuyts et al. 1995), and EXT3 on 19p (Le Merrer et al. 1994). The majority of EXT families are linked to EXT1 or EXT2, with EXT3 being a minor locus. EXT can also be associated with mental retardation, bulbous nose, sparse hair, and cone-shaped epiphyses in patients with the tricho-rhino-phalangeal syndrome (TRP) type II, the Langer-Giedion syndrome (LGS). The latter three abnormalities are also found in patients with tricho-rhino-phalangeal syndrome type I (TRP I), but these patients are rarely mentally retarded and do not have multiple exostoses. Recent molecular studies have confirmed the longstanding suggestion that the LGS is a contiguous gene syndrome due to large deletions on 8q24 comprising both the EXT1 gene and the more proximal located TRPI gene (Lüdecke et al. 1995). A contiguous gene syndrome comprising the EXT2 gene has never been described. However, Shaffer et al. (1993) reported a familial interstitial deletion of chromosome 11p11.12-p12 in three patients, one of which developed multiple exostoses. As the authors thought the chromosome 11p deletion did not cosegregate with EXT in this family, the deletion was considered to be coincidental with EXT. Two of the three patients also had enlarged parietal foramina. Foramina parietalia permagna (FPP), or enlarged parietal foramina, consists of cranial defects in parietal bone mostly located symmetrically on both sides of the sagittal suture. FPP is also called the "Catlin mark," referring to the family name of one of the original families described by Goldsmith (1922). The size of the openings decreases with time, and considerable intrafamilial variability has been observed (Pendergrass and Pepper 1939; Murphy and Gooding 1970). The cranial ossification defect in FPP can be very extensive. It even has been proposed that FPP and hereditary cranium bifidum are the same entity, since neonates with hereditary cranium bifidum become adults with FPP (Murphy and Gooding 1970; Little et al. 1990). It is possible that FPP results from failure of mineralization of membranous bone in the region of the obelion (Currarino 1976). Whereas the parietal defects in FPP are large, small foramina of a few millimeter are very common and occur in more than

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half of the population (Currarino 1976). It is likely that the latter are merely normal variations in the diameter of the parietal emissary foramina, which may attain a diameter of several millimeters. In contrast, it is unclear whether the parietal ossification defects in FPP are defects around the parietal emissary foramina, since patients exist with FPP and normal parietal emissary foramina (Piersol 1902). FPP can occur as an isolated autosomal dominant trait, but the gene has not yet been localized (Lother 1959; Schmidt-Wittkamp and Christians 1970; Rasore-Quartino et al. 1985; Zabek 1987). We report here four families with multiple exostoses and/or FPP due to interstitial deletions of the short arm of chromosome 11 and suggest that this microdeletion is responsible for a contiguous gene syndrome.

Material and Methods

Cytogenetic Analysis

Chromosomes were obtained from phytohaemagglutinin blood cultures or fibroblasts with conventional techniques using trypsin-Giemsa (GTG) banding. In all four families the initial analysis at the 250-band resolution yielded normal results. Further analysis of prometaphase chromosomes at a higher resolution resulted in the identification of the chromosome abnormalities in families 1–3. In family 4, no cytogenetic abnormality could be detected even at the 525-band level.

Molecular Analysis

Molecular analysis of the patients and their parents was performed by PCR with polymorphic microsatellite markers of the pericentromeric region of chromosome 11, including D11S915, D11S914, D11S935, D11S871, D11S905, D11S1355, D11S903, D11S1361, D11S554, D11S1319, D11S1344, D11S1326, D11S956, and D11S916. PCR reactions were performed by standard methods. The determination of the deletion breakpoints was solely based on the presence or absence of parental alleles, without including results based on band signal density or Southern blots.

Results

Patients

Patient 1.—The proband, a boy, was described elsewhere as an unusual case of acrocephalosyndactyly (Lorenz et al. 1990). Examination at birth disclosed mild turricephaly, antimongoloid eye slants, and simian creases. At the age of 4 mo he was referred for craniosynostosis, brachy- and turricephaly, and bilateral encephalocele-like masses in the parietal region. At that time he had facial dysmorphism with a broad and high forehead, antimongoloid eye slants, blepharophimosis, strabism, broad nasal bridge, small upturned nose with hypoplastic alae nasi, and downturned mouth corners (fig. 1*A, B*). He also showed a short neck and short fingers, mild cutaneous syndactyly of fingers 2–5, micropenis, and muscular hypotonia. X-rays revealed very large foramina parietalia, brachycephaly, a lacunar skull, numerous wormian bones, and fused coronal suture (fig. 2*A, B*). Computed tomography (CT) of the skull showed that there were meningoencephaloceles herniated through the large foramina parietalia.

X-rays of the hands, made at age 4 1/2 years, showed cone-shaped epiphyses of the middle phalanges II and the left proximal phalanx III, and a pseudoepiphysis of the left metacarpal II. Radiographs of the knees at the age of 6 years revealed broad-based, hornlike exostoses in the juxtaepiphyseal regions of femur, tibia, and fibula (fig. 3*A*). When last seen at age 9 years, the meningoencephaloceles were still protruding through the foramina parietalia. He had severe psychomotor retardation, marked hypotonia, and nystagmus. He did not speak and had no comprehension of words. The boy could only crawl and walk a few steps with support and needed to be fed (table 1).

Patient 2.—This male patient was born in 1983 as the only child of healthy, nonconsanguineous parents from Yugoslavia. Pregnancy and birth were normal. Birth weight, length, and occipitofrontal circumference were within normal limits. At age 14 mo there were focal seizures, which developed later into epilepsy. Examination at this age disclosed a mild facial dysmorphism with a high and broad forehead, slight mongoloid eye slants, strabism, and a downturned mouth. He had a short neck, tapered fingers, micropenis, marked muscular hypotonia, and nystagmus (fig. 1*C*). Length and weight were normal for age. X-rays of the skull showed brachycephaly and Wormian bones, but notably no craniosynostosis and no parietal foramina (figs. 2*C, D*). He could not walk without support until the age of 4 years, and psychomotor retardation became evident. X-rays of the hands and knees obtained at the age of 7 years showed multiple large, broad-based exostoses (fig. 3*B*). Reevaluation of a thorax radiograph of age 2 years revealed fused 1st and 2d right ribs, very short 12th ribs, and atypically fused sternal ossification centers. The boy is now 11 years old and severely mentally retarded (table 1).

Family 3

Patients 3–5 have been reported by Shaffer et al. (1993) as patients III-1, III-2, and II-4, respectively. A summary of the most important abnormalities is given in table 1. All three patients showed multiple exostoses, craniofacial dysostosis, and severe mental retardation and two of the three patients had FPP. Figure 1*D* shows the face of patient 4 at age 3 years.

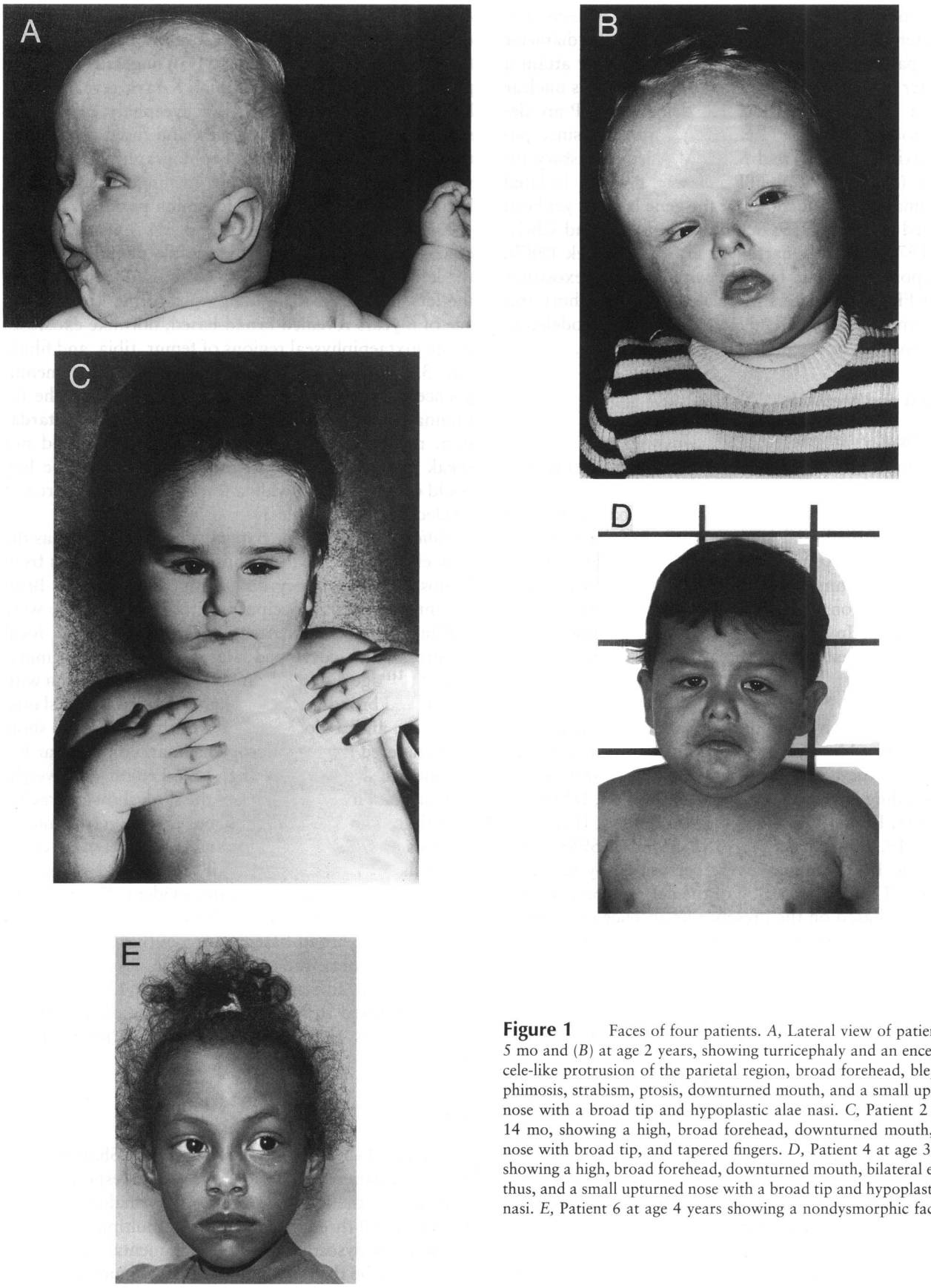

Figure 1 Faces of four patients. *A,* Lateral view of patient 1 at 5 mo and (*B*) at age 2 years, showing turricephaly and an encephalocele-like protrusion of the parietal region, broad forehead, blepharophimosis, strabism, ptosis, downturned mouth, and a small upturned nose with a broad tip and hypoplastic alae nasi. *C,* Patient 2 at age 14 mo, showing a high, broad forehead, downturned mouth, small nose with broad tip, and tapered fingers. *D,* Patient 4 at age 3 years, showing a high, broad forehead, downturned mouth, bilateral epicanthus, and a small upturned nose with a broad tip and hypoplastic alae nasi. *E,* Patient 6 at age 4 years showing a nondysmorphic face.

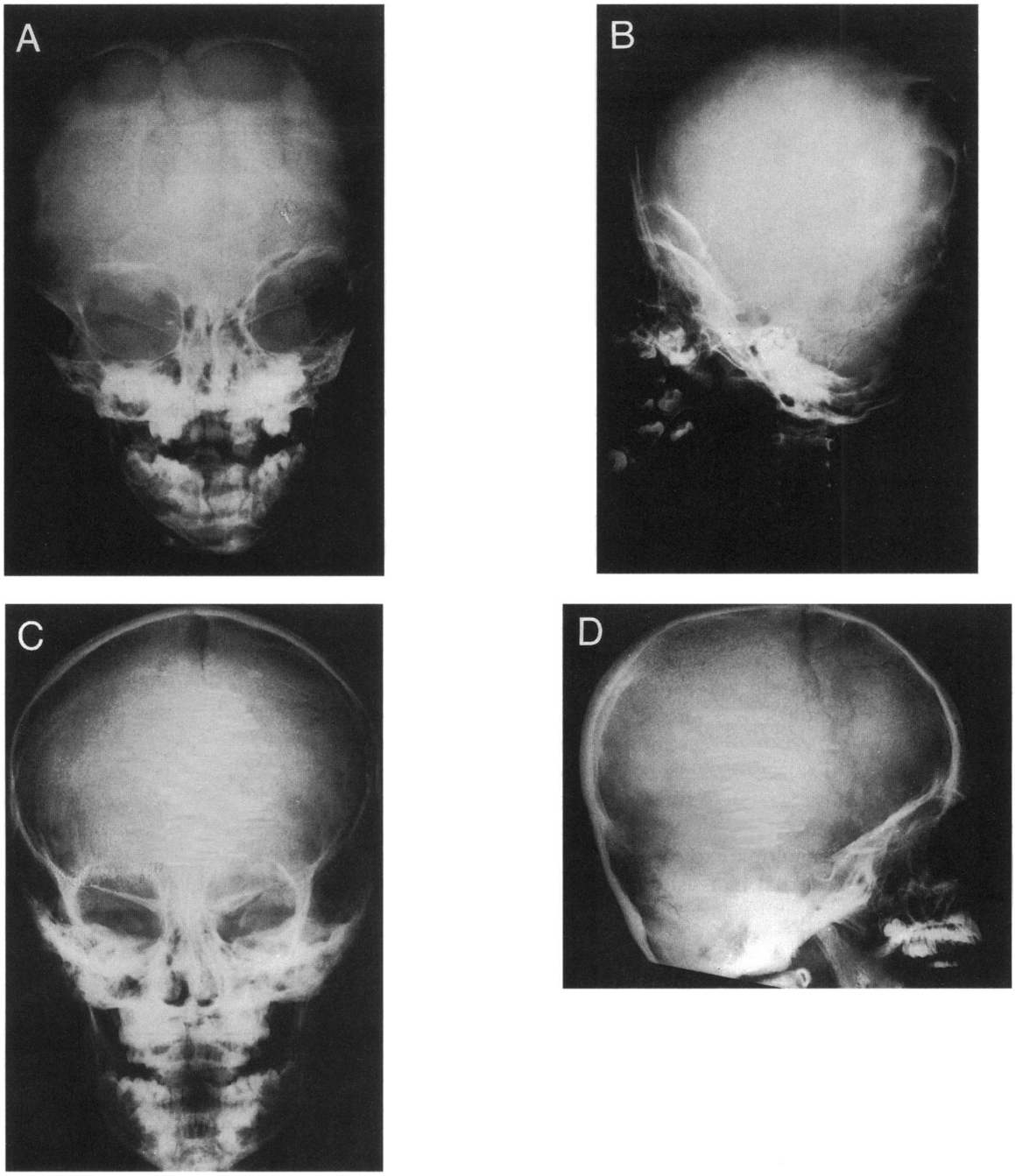

Figure 2 Anteroposterior and lateral skull radiographs showing parietal foramina, craniosynostosis, or brachycephaly. *A, B,* Patient 1 at age 6 years; note fused coronal suture, turri- and brachycephaly, lacunar skull, numerous sutural bones, and extensive parietal foramina. *C, D,* Patient 2 at age 10 years; note brachycephaly in the absence of parietal foramina.

Family 4.—The proband (patient 6) is a 4-year-old female of Caucasian/African-American background. She was the 3,200-g product of an uncomplicated term gestation. In the newborn period she was noted to have wide sagittal sutures with absent bone in the vertex of the skull. Skull radiographs at 1 d of age revealed 3-cm radiolucent defects in both posterior parietal bones near the posterior fontanel. She has a history of bony protuberances at the ends of her long bones. Her cognitive development has been normal, but she has a history of destructive and self-abusive behavior and hyperactivity.

On physical examination, the proband's height is at the 50th centile, weight is at the 10th centile, and head circumference is at the 10th centile. She has four 0.5-cm café-au-lait spots on the trunk and capillary hemangioma on the left shoulder. There are symmetrical 1-cm

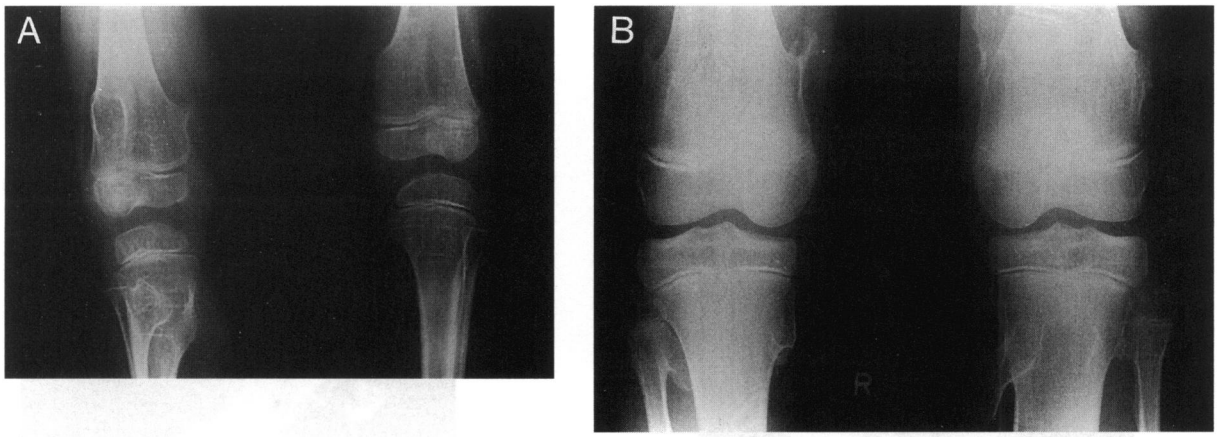

Figure 3 X-rays demonstrating multiple exostoses in the juxtaepiphyseal regions of femur, tibia, and fibula in patient 1 at 4 years (*A*) and in patient 2 at age 10 years (*B*).

round defects in the posterior parietal-occipital skull. The forehead is somewhat high but not broad (fig. 1*E*). The facial features are nondysmorphic. There is a mild bilateral fifth finger clinodactyly. Palmar creases are normal except for a slightly short distal crease on the left. There is a bony mass palpable on the distal right femur.

The family history is significant for the proband's mother, having parietal bone foramina and multiple osteocartilaginous exostoses of the right scapula, proximal humeri, and proximal tibia, which have been removed, with pathological study revealing osteochondromas. The maternal grandmother (patient 8) and maternal aunt (patient 7) also have multiple exostoses and parietal foramina. There is a maternal half-sister with parietal foramina but no obvious exostoses at age 2 years. None of these family members have mental retardation.

Cytogenetic Analysis

Patient 1

Standard chromosome analysis using cultured blood lymphocytes and GTG banding resulted in normal findings (Lorenz et al. 1990). Because the results had been obtained at the resolution of 250 bands, renewed chromosome analysis was carried out at the 550+ band level using a fibroblast cell culture and high-resolution GTG banding. This analysis revealed a deletion on the short arm of chromosome 11 of bands p11.2-p13 (fig. 4*A*), which was con-

Table 1

Radiological and Clinical Abnormalities in Patients with Chromosome 11p Deletions

	Our Patients (Sex)								Others' Patients (Sex)[a]		
Abnormality	1 (M)	2 (M)	3 (F)	4 (M)	5 (M)	6 (F)	7 (F)	8 (F)	A (M)	B (M)	C (F)
Multiple exostoses	+	+	+	+	+	+	+	+	NK	+	+
Parietal foramina	+	–	+	–	+	+	+	+	+	+	+
Craniosynostosis	+	–	–	–	–	–	–	–	–	–	–
Wormian bones	+	+	+	–	–	NK	NK	–	NK	NK	NK
Mental retardation	+	+	+	+	+	–	–	–	NK	+	+
Adipose appearance	+	+	–	+	+	–	–	+	NK	NK	–
Hypotonia	+	+	+	+	+	–	–	–	NK	NK	NK
Seizures	–	+	–	–	+	–	–	–	–	–	–
Brachycephaly	+	+	+	+	+	–	–	–	NK	NK	+
High and broad forehead	+	+	+	+	+	–	–	–	NK	NK	–
Telecanthus	+	–	+	+	+	–	–	–	NK	NK	NK
Epicanthus	+	–	+	+	+	–	–	–	NK	NK	NK
Simian creases	+	NK	+	+	+	NK	–	NK	+	NK	NK
Micropenis	+	+	NR	–	+	NR	NR	NR	+	+	NR

Note.—NR, not relevant; and NK, not known.

[a] A, Gustavson et al. (1984) (case 2); B, McGaughran et al. (1995); and C, Potocki et al. (1995).

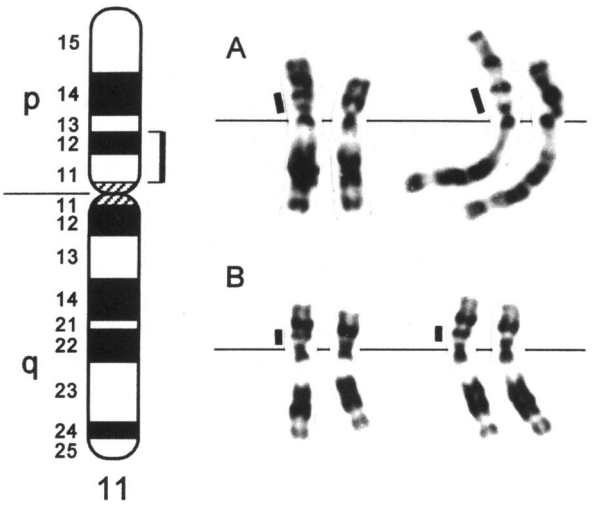

Figure 4 GTG-banded partial karyotypes. *Left,* normal chromosomes 11; *right,* abnormal chromosomes 11, showing very small interstitial deletions within the short arm. *A,* Case 1, del(11)(p11.12p13). *B,* Case 2, del(11)(p11.12p13).

firmed with GTG-banded prometaphases from cultured blood lymphocytes. Parental karyotypes were normal.

Patient 2.—Standard chromosome analysis in 1985 was normal. After the finding of multiple exostoses, chromosome analysis of cultured blood lymphocytes was repeated by high-resolution GTG banding. This showed a de novo deletion of chromosome 11p12 extending to bands p11.2 and p13 (fig. 4*B*).

Family 3.—Cytogenetic findings in this family have been reported by Shaffer et al. (1993). Patients 3–5 have an interstitial deletion of band p11.2-p12 of chromosome 11, resulting from the malsegregation of a familial balanced insertional translocation of band 11p11.2 into 13q14.1.

Family 4.—G-banded karyotype was normal at the 525-band level in the proband and at the 500-band level in the maternal grandmother. Other family members have not had chromosome analysis.

Molecular Analysis

Patient 1.—PCR analysis showed a de novo deletion of the paternal allele at loci D11S905, D11S1355, D11S903, D11S554, D11S1344, and D11S1326, whereas two alleles were present for markers D11S915, D11S914, D11S935, D11S956, and D11S916 (fig. 5). D11S1361 was not informative. The distal deletion breakpoint is located between D11S905 and D11S935. Marker D11S871, which maps between the latter two markers, was not informative. The deleted region extends to D11S1326, which is one of the most proximal markers on the short arm of chromosome 11 (James et al. 1994). Since the centromere has to be present in the rearranged chromosome, the proximal deletion breakpoint must be located close to the centromere on 11p (fig. 5).

Patient 2.—PCR results indicated a de novo interstitial deletion on the paternal chromosome 11p. D11S935, D11S905, D11S1355, D11S903, D11S554, and D11S1344 all map in the deleted region, whereas D11S915, D11S914, D11S1326, and D11S916 do not (fig. 5). D11S1361 and D11S956 were not informative. These results locate the breakpoints of the deletion in patient 2 between D11S914 and D11S935 (distal side) and between D11S1344 and D11S1326 (proximal side) (fig. 5).

Family 3.—PCR analysis in family 3 was performed with chromosome 11 markers D11S935, D11S905, D11S1355, D11S903, D11S1361, D11S554, D11S1319, D11S1344, D11S1326, and D11S916. Loci D11S1355, D11S903, D11S1361, D11S554, and D11S1319 were deleted from the maternal chromosome 11 in the three patients, whereas two copies were present from D11S935, D11S905, D11S1344, D11S1326, and D11S916 (fig. 5).

Family 4.—PCR analysis in family 4 revealed a deletion for markers D11S903, D11S554, and D11S1361, whereas markers D11S935, D11S905, D11S1355, D11S1319, D11S1344, D11S1326, and D11S916 were not deleted (fig. 5)

Discussion

We describe here a contiguous gene syndrome due to microdeletion of the proximal short arm of chromosome

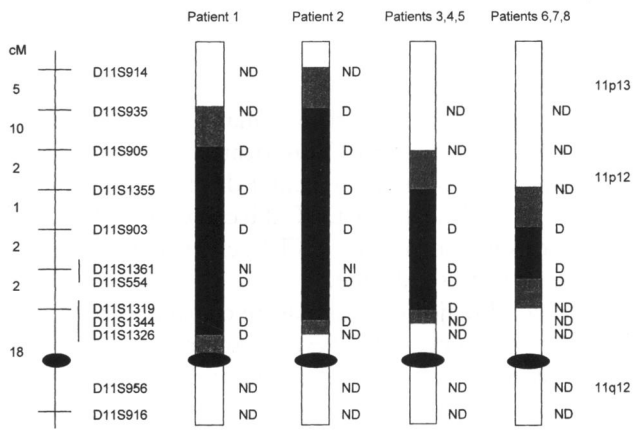

Figure 5 Molecular analysis using centromeric chromosome 11 markers in the three families. Blackened zones indicate the deleted regions, while the deletion breakpoints need to be in the gray zones. Patient 1 shows a deletion of D11S905 extending proximally to marker D11S1326. A deletion is present in patient 2, with D11S935 as the most distal and D11S1344 as the most proximal deleted markers. Patients in family 3 show a deletion of D11S1355 extending proximal of D11S1319. Markers D11S905, D11S1344, and D11S1326 are not deleted in this family. In family 4 the deletion includes markers D11S903, D11S1361, and D11S554 but not D11S1355, D11S1319, D11S1344, or D11S1326.

11. The most characteristic symptoms observed in eight patients from four unrelated families with this MCA/MR syndrome are multiple exostoses (EXT), enlarged parietal foramina (FPP), craniofacial dysostosis, and mental retardation. Therefore, we refer to this microdeletion syndrome with the acronym DEFECT 11 syndrome, for Deletion, Enlarged Foramina, Exostoses, Craniofacial dysostosis, and reTardation. Less frequent symptoms are micropenis, seizures, hypotonia, adipose appearance, simian creases, epicanthus, and telecanthus (table 1).

The interstitial deletions of the proximal short arm of chromosome 11 at 11p11-p13 were detected by high-resolution prometaphase banding in three of the four families and can be overlooked with conventional metaphase banding, as was the case in family 1 (Lorenz et al. 1990) and family 2. In family 3 (Shaffer et al. 1993) an insertional translocation of band 11p11.2 into 13q14.1 led to the discovery of the interstitial deletion of 11p11-p12. In this family, multiple exostoses were thought to segregate independently from the chromosomal abnormality, but further evaluation at an older age proved that both abnormalities cosegregated. In the fourth family, no cytogenetic chromosome 11p abnormality could be found, even at the 525-band level. Molecular studies showed that this family has the smallest deletion.

The deletions are located between D11S914 and the centromere, an interval of ~20–25 cM on the short arm of chromosome 11. This region (fig. 5) comprises the EXT2 gene, which was previously mapped by linkage analysis in families with isolated EXT to chromosome 11p, in a 3-cM region between D11S1355 and D11S1361/D11S554 (Wuyts et al. 1995). The EXT2 gene must be located in close proximity to D11S903, since no recombinants with this marker have been observed (Wuyts et al. 1995). This location is corroborated by the finding of a small molecular deletion of D11S903 in a family with isolated EXT (Hecht et al. 1995). All these data suggest that the EXT2 gene is deleted in this contiguous gene syndrome.

The second major clinical feature of patients with DEFECT 11 syndrome is FPP. Several arguments support the hypothesis that EXT and FPP in this syndrome result from a deletion of two neighboring genes and not from the deletion of one single gene with pleiotropic effects. In the extensive literature on EXT and FPP, both conditions have always been reported as separate entities and never in combination such as in this chromosome 11 contiguous gene syndrome. In none of the many EXT families with autosomal dominant inheritance, FPP has been reported. On the other hand, FPP without any evidence for multiple exostoses has been found in several families as an autosomal dominant trait (Goldsmith 1922; Lother 1959; Schmidt-Wittkamp and Christians 1970; Rasore-Quartino et al. 1985; Zabek 1987). Although the gene responsible for autosomal dominant FPP has not been mapped yet, it is likely that it is also located in chromosome 11p11-p13. Linkage analysis in these families could prove this. From this perspective, it is also interesting that Hecht et al. (1995) described an EXT family without FPP with a microdeletion around D11S903. It is probable that the deletion in this family includes the EXT2 gene but not the FPP gene. The absence of FPP in patient 4 illustrates nonpenetrance of FPP, as previously observed in families with autosomal dominant inheritance of isolated FPP (Goldsmith 1922). Reduced penetrance might also explain the absence of FPP in patient 2, since the deletion in this patient encompasses the deletions in patients 3 and 5–8, who have FPP.

Craniofacial dysostosis is another symptom in DEFECT 11 syndrome. Patients 1–5 show brachycephaly with a somewhat turricephalic skull shape. Patient 1 (Lorenz et al. 1990) and patient 3 (Shaffer et al. 1993) were reported in the original papers to have a Saethre-Chotzen-like phenotype. This diagnosis was based on the combination of brachycephaly, a high broad forehead, FPP, coronal synostosis, very wide anterior fontanel, cutaneous syndactyly between fingers 2 and 5 in patient 1, and brachycephaly and high and broad forehead and FPP in patient 3. However, we think it is inappropriate to speak of a true Saethre-Chotzen phenotype, because of the absence of facial asymmetry, syndactyly, ear abnormalities, and craniosynostosis in the majority of these patients. Furthermore, Saethre-Chotzen craniosynostosis is an ill-defined clinical entity with large clinical and genetic heterogeneity. Since FPP has been observed in other patients with Saethre-Chotzen craniosynostosis (Friedman et al. 1977; Thompson et al. 1984; Young and Swift 1985) and other craniofacial dysostosis syndromes (Dunn 1960; Hermann and Opitz 1969; Lehrer and Familiant 1969), it is possible that FPP and the craniofacial dysostosis in this syndrome represent pleiotropic manifestations of mutations in a single gene. However, the absence of craniofacial dysostosis in family 4 that shows FPP, and in families with autosomal dominant inheritance of isolated FPP, suggests that there is a specific 11p gene involved in craniofacial dysostosis. The 11p deletion in family 4 is smaller than in families 1–3 (fig. 5). Therefore, the putative craniofacial dysostosis gene might be located between D11S1355 and D11S903 or between D11S554 and D11S1319. Patients 1–5 are severely retarded, but the three patients from family 4 are mentally normal. Therefore, a specific mental retardation gene could be located in the same intervals, although mental retardation is a nonspecific feature in many deletion syndromes. Furthermore, contiguous gene syndromes in general are characterized by phenotypic variability (Fisher and Scambler 1994).

The deletions in patients 1 and 2 are of paternal origin, whereas those in patients 3–8 are of maternal origin, so that no evidence for imprinting in this region is presently available. The frequency of this new syndrome might be underestimated, since FPP can easily be overlooked and exostoses may only develop later during life. We already know of four additional patients with 11p deletions showing similar clinical features (Gustavson et al. 1984; McGaughran et al. 1995; Potocki et al. 1995; P. Meinecke, unpublished results).

The new syndrome is analogous to the LGS, which is caused by deletions of the 8q24 region (Lüdecke et al. 1995). Both are contiguous gene syndromes due to deletion of several genes including an EXT gene (EXT1 in the LGS and EXT2 in the DEFECT 11 syndrome). The presence of deletions in both syndromes indicates that hereditary multiple exostoses can be caused by loss-of-function mutations of the EXT1 or EXT2 gene leading to haploinsufficiency (Fisher and Scambler 1994). This is in line with the putative tumor-suppressor function of both genes in bone and cartilaginous tissue (Hecht et al. 1995; Raskind et al. 1995).

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