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Clinical Report

Interstitial Deletion of Chromosome 12q:
Genotype–Phenotype Correlation of Two Patients Utilizing Array Comparative Genomic Hybridization

Ophir D. Klein,[1] Philip D. Cotter,[1,2] Ann M. Schmidt,[3] David P. Bick,[3] William E. Tidyman,[4] Donna G. Albertson,[5,6] Daniel Pinkel,[5] and Katherine A. Rauen[1]*

[1]*Department of Pediatrics, Division of Medical Genetics, University of California San Francisco, San Francisco, California*
[2]*Department of Pathology, Children's Hospital and Research Center, Oakland, California*
[3]*Genetics Center, Children's Hospital of Wisconsin, Milwaukee, Wisconsin*
[4]*Department of Anatomy, University of California San Francisco, San Francisco, California*
[5]*Department of Laboratory Medicine, University of California San Francisco, San Francisco, California*
[6]*Cancer Research Institute, University of California San Francisco, San Francisco, California*

Interstitial deletions of chromosome 12q are rare, with only 11 reported cases in the literature. We recently described two cases with cytogenetically identical interstitial deletions of the long arm of chromosome 12. Here, we report on a third patient, a 26-month-old male with a cytogenetically-identical interstitial deletion: 46,XY,del(12)(q21.2q22). Phenotypic features of this male proband included craniofacial and ectodermal anomalies, genitourinary anomalies, minor cardiac abnormalities, mild ventriculomegaly on brain MRI, hyperopia, and developmental delay. To further define the extent of the chromosomal aberration, microarray-based comparative genomic hybridization (array CGH) analysis was performed and the array data was compared to one of our previously reported cases. Although cytogenetic analysis of the two patients was concordant, molecular analysis by array CGH revealed that the patients had discordant distal breakpoints. The determination of molecular breakpoints and phenotypic analyses in these two patients, in conjunction with previously reported cases, leads us to propose a 12q deletion phenotype and a possible genetic locus for hyperkeratosis pilaris/ulerythema ophryogenes.

KEY WORDS: **array CGH; array comparative genomic hybridization; cardio-facio-cutaneous syndrome; chromosome 12q; hyperkeratosis pilaris; interstitial deletion; genotype-phenotype correlation; ulerythema ophryogenes**

INTRODUCTION

Proximal and interstitial deletions of chromosome 12q are rare, with only 11 reported cases in the literature [Funderburk et al., 1984; Meinecke and Meinecke, 1987; Watson et al., 1989; Tonoki et al., 1998; Brady et al., 1999; Sathya et al., 1999; Gallego et al., 2000; Rauen et al., 2000, 2002; Rapley et al., 2001; Petek et al., 2003]. We recently described two cases with cytogenetically-identical interstitial deletions of the long arm of chromosome 12. The first case was that of a girl who presented with a phenotype consistent with cardio-facio-cutaneous (CFC) syndrome, including characteristic craniofacial features, sparse curly hair, scant eyebrows, hyperkeratosis pilaris, a muscular VSD, and developmental delay [Rauen et al., 2000; Carey and Opitz, 2001]. We proposed a possible locus for CFC syndrome based on her karyotype, 46,XX,del(12)(q21.2q22).

Subsequently, we reported a second patient who had the identical 12q deletion. Cytogenetic analysis demonstrated a male with a karyotype 47,XYY,del(12)(q21.2q22) [Rauen et al., 2002]. Phenotypic features of this male proband included craniofacial anomalies, ectodermal findings, genitourinary anomalies, minor cardiac abnormalities, and developmental delay. Although the patient did not have the classic composite phenotype for CFC syndrome, there were many features observed in this patient that are seen in CFC syndrome, including craniofacial anomalies, ectodermal findings, cardiac defects, and developmental delay. The patient's chromosomal aberration was further defined by the use of microarray-based comparative genomic hybridization (array CGH) analysis, a technology that measures copy number change across the entire genome and aids in refining chromosome breakpoints at the molecular level.

In this report, we describe a third patient with a cytogenetically identical interstitial 12q deletion. Array CGH, a genome scanning technique, which has a resolution significantly higher than conventional GTG-banding, was used to compare the extent of the interstitial deletion between the two patients. Examination of the molecular breakpoints and phenotypes of the two patients, in conjunction with previously reported cases, enables us to propose a 12q deletion phenotype and a possible genetic locus for the skin condition ulerythema ophryogenes.

CLINICAL REPORT

Clinical Description

The proband is the first child born to healthy, non-consanguineous parents. The family history is non-contributory. The

*Correspondence to: Katherine A. Rauen, Ph.D., M.D., Cancer Research Institute, UCSF Comprehensive Cancer Center, 2340 Sutter Street, Room S429, Box 0128, San Francisco, CA 94115. E-mail: rauen@itsa.ucsf.edu

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mother and father were 30 and 29 years old, respectively, at the time of birth. A sonogram at 20 weeks' gestation showed a single umbilical artery and duplication of the right renal collecting system. Amniocentesis revealed a normal male 46,XY karyotype. There were no teratogenic exposures noted. The infant was born by vacuum extraction at 37.5 weeks. Rapid breathing was noted at birth, and a chest X-ray was consistent with transient tachypnea of the newborn. At birth, he weighed 3,285 g (25th–50th centile) and measured 48 cm (10th–25th centile). Head circumference at 1 week was 35.5 cm (25th–50th centile). Neonatal examinations were notable for a large anterior fontanel, ears with overfolded helices, redundant nuchal skin, and bilateral hydroceles (Fig. 1). Extremities showed bilateral single palmar creases and 2–3 toe syndactyly. Neurological examination was normal.

An initial evaluation included a renal sonogram that showed moderate hydronephrosis of the right kidney and duplication of right renal collecting system; voiding cystourethrogram was normal. A neonatal echocardiogram, performed because of a murmur, demonstrated a small persistent patent ductus arteriosis and patent foramen ovale; the murmur resolved spontaneously. A head MRI performed at 4 months showed mild ventriculomegaly, and enlarged ventricles were seen on a second MRI done at 16 months. Two electroencephalograms, obtained at 2 months and 14 months for concern about staring spells, were normal; the patient has never had clinically evident seizures. Concern over tracking led to ophthalmologic evaluation at 8 months, which showed marked hyperopia, and the patient was treated with corrective lenses. At 7 months of age a dermatologic evaluation for xerosis revealed eczematous papules, excoriations and scaling on the extremities, trunk, and scalp, and he was diagnosed with atopic dermatitis (Fig. 2). Radiographs of the spine at 15 months of age showed persistent S-shaped scoliosis. Computed tomography of the skull at 2 years showed cranial asymmetry, with left ear posterior to the right ear. The patient was found to have bilateral conductive hearing loss at 2 years, despite having passed an earlier hearing test.

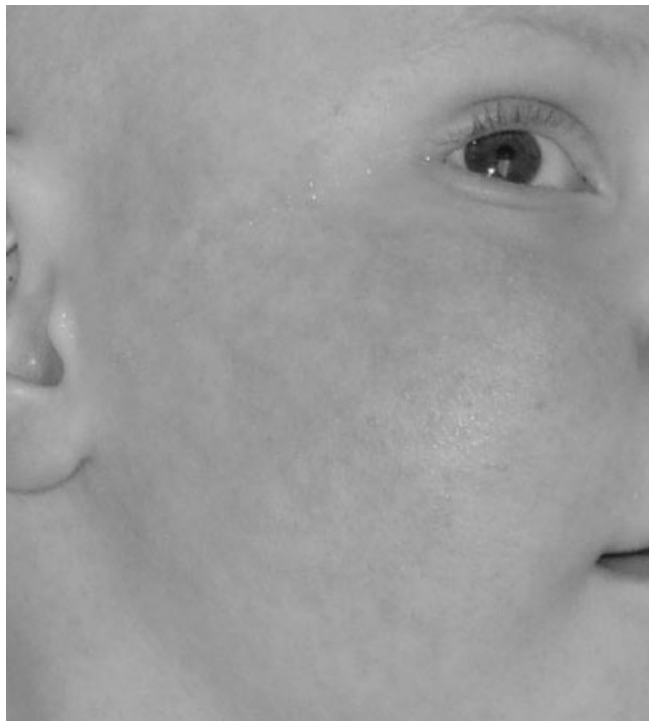

Fig. 2. Dermatitis. Disseminated keratotic papules on the patient's cheek.

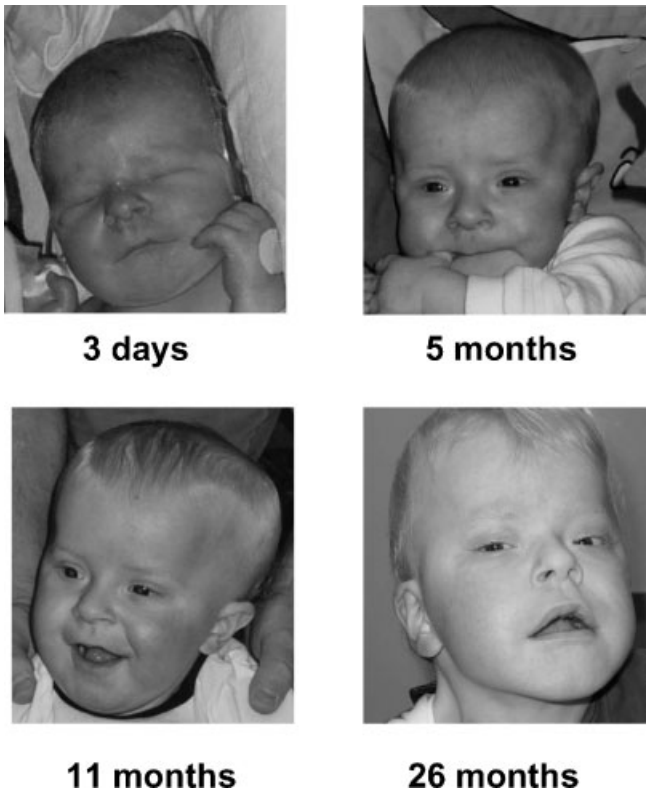

Fig. 1. Proband at indicated ages. Clinical details are provided in the text.

Because of feeding difficulties, the patient had a failure-to-thrive evaluation at 2 months, including several metabolic tests, which were normal. A karyotype showed 46,XY,del(12)(q22.q24.1). Persistent feeding problems led to poor weight gain and a gastrostomy tube was placed at 4 months of age. Since then, the patient's length has remained in the 25th–50th centile and his weight is maintained in the 10th–25th centile. Subsequent examinations have shown right occipitoparietal flattening with a large anterior fontanel, telecanthus with hypoplasia of the supraorbital ridges, low-set ears with thickened helices, a long philtrum and Cupid's bow upper lip, and an additional upper labial frenulum (Fig. 1). A supernumerary tooth in the anterior, upper-right quadrant was noted. Hair texture was fine with bitemporal alopecia and thinning of the lateral aspects of his eyebrows. He had a persistent hyperkeratotic papular rash over his eyebrows, cheeks, the extensor surface of the upper arms and thighs, chest, and abdomen.

Although initially within normal limits, psychomotor development was delayed by the 6-month visit, at which point the patient could not roll. At 8 months of age the patient was babbling and sitting with assistance. In addition, he demonstrated increased muscle tone, head lag when pulled to sit, and placing and stepping reflexes. At 26 months, the patient spoke no words and, although he was able to roll over, he was unable to sit or stand without support.

MATERIALS AND METHODS

Cytogenetic Analysis

Cytogenetic analysis and GTG-banding were performed using standard techniques on metaphases from peripheral blood lymphocytes.

Array CGH Analysis

In order to analyze the chromosome deletion at a higher resolution, array CGH analysis was performed using a microarray consisting of 2,464 BAC, PAC, and P1 clones printed in triplicate (HumArray2.0) as previously described [Snijders et al., 2001; Rauen et al., 2002]. In addition, DNA from a previous patient we reported with the same cytogenetic deletion was re-analyzed on HumArray2.0 and compared with the current case [Rauen et al., 2002]. In brief, DNA was isolated from peripheral blood lymphocytes using a QIAamp DNA Blood Midi kit (Qiagen, Valencia, CA), according to the manufacturer's instructions. The patient's DNA and normal male reference DNA were labeled by random priming with Cy3 or Cy5 labeled nucleotides and hybridized for 2 days to the array. Sixteen bit $1,024 \times 1,024$ pixel DAPI, Cy3, and Cy5 images were collected using a custom CCD camera system [Pinkel et al., 1998], and the data were analyzed using UCSF SPOT [Jain et al., 2002] to automatically segment the array spots and to calculate the $\log_2$ ratios of the total Cy3 and Cy5 intensities for each spot after background subtraction. A second custom program, SPROC, was used to calculate averaged ratios of the triplicate spots for each clone, standard deviations of the triplicates and plotting position for each clone on the array on the May 2004 freeze of the draft human genome sequence (http://genome.ucsc.edu). SPROC also implements a filtering procedure to reject data based on a number of criteria, including low reference/DAPI signal intensity and low correlation of the Cy3 and Cy5 intensities with a spot. The data files were edited to remove ratios on clones for which only one of the triplicates remained after SPROC analysis and/or the standard deviation of the $\log_2$ ratios of the triplicates was >0.2 [Snijders et al., 2001].

RESULTS

Cytogenetic analysis demonstrated an abnormal karyotype of 46,XY,del(12)(q21.2q22) in all 20 metaphases examined (Fig. 3). Parental karyotypes were normal, indicating that the deletion was de novo.

Microarray analysis of the case reported here (Patient 2), and of a previously reported case [Patient 1; Rauen et al., 2002] that had a cytogenetically identical deletion of chromosome 12, revealed a difference in the size of the deletion between these two patients. Microarray analysis of the current case (Patient 2) demonstrated an interstitial deletion of the long arm of one copy of chromosome 12 (Fig. 4). Both patients had similar proximal breakpoints which lie between the same two genomic clones annotated to cytogenetic bands 12q15 (RP11–15L3 nondeleted) and 12q21.1 (RP11–92P22 deleted). The distal molecular breakpoint of Patient 1 was within cytogenetic band 12q21.33 (CTD-2017D5 deleted; RP11–51M11 nondeleted). Based on the sequence position, Patient 1 had a minimum deletion of 14.3 Mb and a maximal deletion of 20.7 Mb as demonstrated by 4 BACs with a single copy loss. However, Patient 2 had a larger deletion as demonstrated by 11 genomic clones with a single copy loss. The distal molecular breakpoint was within band 12q22 (RP11–215G13 deleted; RP11–31A19 nondeleted) yielding a minimal deletion of 19.2 Mb and a maximal deletion of 25.5 Mb. In addition, there was one clone, RP11-82I16, within the deleted region which was present in two copies. Patient 2 also appeared have a single copy gain of genomic clone PR11–61P1 on 12q. It is possible that these clones represent a polymorphism, a misplacement of the clone designation on the array or an error in the genome sequence, which has yet to be resolved. We are currently investigating these possibilities. No other copy number alterations were detected. Thus, based on array analysis, the 12q breakpoints were distinct and refined at the molecular

Fig. 3. Partial karyotype and ideogram of the normal and deleted chromosomes 12 from the proband. Arrows indicate cytogenetic breakpoints.

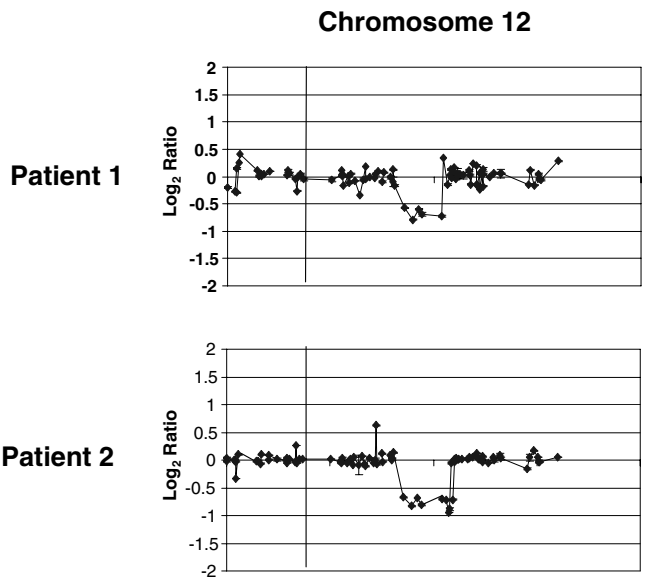

Fig. 4. Array CGH analysis. Microarray analysis of Patient 1 and Patient 2 demonstrated an interstitial deletion of the long arm of one copy of chromosome 12. Both patients have similar proximal breakpoints between the same two genomic clones (RP11-15L3 nondeleted and RP11-92P22 deleted) annotated to 12q15 and 12q21.1, respectively. The distal deleted clone in Patient 1 was CTD-2017D5 on 12q21.33, and this patient had a maximal deletion of approximately 20.7 Mb. The distal deleted clone in Patient 2 was RP11-215G13 on 12q22, and this patient had a maximal deletion of approximately 25.4 Mb.

level as follows: Patient 1 del(12)(q21.1q21.33) and Patient 2 del(12)(q21.1q22).

DISCUSSION

Interstitial deletions of the long arm of chromosome 12 are rare, with only four reported cases sharing common deleted regions on 12q with the patient reported here [Watson et al., 1989; Brady et al., 1999; Rauen et al., 2000, 2002]. Of the four cases in the literature, two were previously reported by our group [Rauen et al., 2000, 2002; Carey and Opitz, 2001] and the patient reported here represents the third case that has a cytogenetically detected interstitial deletion of chromosome 12, del(12)(q21.2q22). The proband had several phenotypic features in common with our previously reported cases and with other reported patients with overlapping 12q deletions. Concordant phenotypic features include craniofacial dysmorphology consisting of a prominent forehead and low-set ears, ectodermal anomalies, and developmental delay (Table I).

To better identify breakpoints at the molecular level and aid in genotype–phenotype correlation, array CGH analysis was performed on the present case and compared to the array analysis of a previously reported patient with an identical cytogenetic deletion on 12q [Rauen et al., 2002]. Both patients had similar proximal breakpoints by array analysis, which redefined the proximal breakpoint within band 12q21.1. However, the distal breakpoint was markedly discordant. The distal molecular breakpoint of Patient 1 was within cytogenetic band 12q21.33 yielding a maximal deleted region of 20.7 Mb. Patient 2 had a larger deletion with the distal molecular breakpoint within band 12q22 yielding a maximal deletion of 25.4 Mb. This discordance of cytogenetically similar deletions underscores the importance of accurately defining chromosomal aberrations at the molecular level.

TABLE I. Summary of Clinical Characteristics of Present Case Compared to Previously Reported Cases of 12q Deletion With Overlapping Deleted Regions

Clinical characteristic	Watson et al. [1989]	Brady et al. [1999]	Rauen et al. [2000]	Rauen et al. [2002]	Present case
Sex	F	F	F	M	M
Developmental delay	+	+	+	+	+
Growth retardation	−	+	+	−	−
Macrocephaly		−	+		
Facial dysmorphism	+	+	+	+	+
Prominent forehead	+	+	+	+	+
Hypotelorism	−	−	−	+	−
Telecanthus/hypertelorism	−	+	+	−	+
Downslanting palpebral fissures	−	−	+	+	−
Short, upturned nose	−	−	+	+	+
Low-set ears	+	+	+	+	+
Pterygium colli	−	+	−	−	+
Cardiac anomaly	−	−	+	+	+
2-3 toe syndactyly	+		−	+	+
Single palmar creases	− (Not reported)	− (Not reported)	−	+	+
GU anomalies	− (Not reported)	− (Not reported)	−	+	+
Pyloric stenosis	−	+	−	+	−
Ectodermal anomaly—hair	+	+	+	+	+
Ectodermal anomaly—skin	− (Not reported)	− (Not reported)	+	+	+
Asthma/reactive airway	− (Not reported)	− (Not reported)	− (Not reported)	+	−
Ocular abnormality	− (Not reported)	−	+	−	+
Head imaging—abnormal	− (Not reported)	− (Not reported)	+(Ventriculomegaly)	−	+ (Ventriculomegaly)
Cytogenetic karyotype	46,XX,del(12) (q15q21.2)	46,XX,del(12) (q21.2q23.2)	46,XX,del(12) (q21.2q22)	47,XYY,del (12) (q21.2q22)	46,XY, del(12) (q21.2q22)
Array CGH molecular karyotype	−	−	−	47,XYY,del (12) (q21.1q21.33)	46,XY, del(12) (q21.1q22)

In comparing the present case to reports we have previously published [Rauen et al., 2000, 2002] with overlapping deletions, there were several concordant phenotypic features (Table I). Based on these patients' features, we propose a 12q deletion phenotype comprising developmental delay, facial dysmorphology including a prominent forehead and short upturned nose, ectodermal abnormalities, such as sparse hair and hyperkeratosis pilaris/ulerythema ophryogenes, and possibly cardiac and renal malformations. Although several of these features may be seen in chromosome aberrations, ectodermal anomalies such as hyperkeratosis pilaris/ulerythema ophryogenes are rarer. Ulerythema ophryogenes (UO) is a form of follicular keratosis with a similar distribution to hyperkeratosis pilaris involving the lateral aspects of the upper arms, thighs, and buttocks. UO begins in early childhood, may be associated with alopecia and is typified by chronic erythematous hyperkeratotic papules that usually involve the lateral aspects of the eyebrows. Hyperkeratosis pilaris/ulerythema ophryogenes may be a cutaneous finding in CFC [Schepis et al., 1999; Drolet et al., 2000]. UO has also been reported in patients diagnosed with Cornelia de Lange [Florez et al., 2002] and Rubinstein-Taybi [Gomez Centeno et al., 1999] syndromes. In addition, hyperkeratosis pilaris/ulerythema ophryogenes has been associated with 18p- syndrome [Zouboulis et al., 1994; Horsley et al., 1998; Nazarenko et al., 1999]. It has been proposed that haploinsufficiency for *LAMA1* located on human chromosome 18p11.3 may have a possible role in the development of hyperkeratosis pilaris/ulerythema ophryogenes [Zouboulis et al., 2001]. All three of the patients we have reported with 12q deletions have had similar cutaneous findings of hyperkeratosis pilaris/ulerythema ophryogenes, indicating that haploinsufficiency for a gene(s) in the common deleted region 12q21.1 → q21.33 is likely responsible for the development of this skin condition. A possible candidate gene in the common deleted region of both patients analyzed by array CGH is stem-cell factor/kit ligand (*SCF*). This immunomodulatory gene is known to be involved in skin development and in the allergic response, and it may be involved in atopic dermatitis [Yoshida et al., 2001; Peters et al., 2003]. It is possible that haploinsufficiency for *SCF* in our patients contributes to the skin anomalies. *SCF*, along with interferon-γ and signal transducer and activator of transcription-6 (*STAT-6*) on 12q21 → q21.24, have been implicated in asthma susceptibility [Wills-Karp and Ewart, 2004]. Thus, this region of 12q may contain gene candidates involved in immunomodulation important for atopy.

In contrast to skin findings, an ectodermal anomaly seen in Patient 2 but not Patient 1 is a supernumerary tooth. One possible cause for the additional tooth may be haploinsufficiency for plexin C1 at 12q22, a finding that is unique to Patient 2. The plexin ligands, the semaphorins, have been implicated in tooth development [Loes et al., 2001; Lallier, 2004].

Chromosome 12q has been reported as a possible candidate region for CFC [Rauen et al., 2000; Carey and Opitz, 2001]. The patient described in this report had the identical cytogenetic deletion as a previously reported patient with a CFC phenotype [Rauen et al., 2000]. Concordant craniofacial anomalies include a high forehead with bitemporal narrowing, telecanthus with hypoplasia of the supraorbital ridges, short nose with a bulbous tip, and low-set ears. Ectodermal findings were similar as well and consisted of sparse hair with temporal alopecia, scant eyebrows and eyelashes, and hyperkeratosis pilaris. Both patients had ventriculomegaly and global developmental delays. The patient reported here does not have the classic composite phenotype for CFC syndrome, although, importantly, there are isolated craniofacial and ectodermal features observed in this patient which are seen in CFC syndrome. Lack of the classic phenotype of CFC may be due to several factors. Although both patients have the same region of chromosome 12q deleted as determined by standard cytogenetic methods, these two patients may have distinct deletions at the molecular level. Unfortunately, the initial patient we reported with the same 12q deletion and a CFC phenotype [Rauen et al., 2000; Carey and Opitz, 2001] is not available for array analysis, but we speculate that there may exist discordance at the molecular level among these two patients. Future analyses may yield a critical minimal region of deletion for CFC. In addition, patients with the clinical diagnosis of CFC fall along a phenotypic spectrum. This results in occasional diagnostic difficulties due to variable expressivity of the CFC phenotype. A final possibility is that a deletion in 12q results in a phenotype that has overlapping manifestations with CFC.

In summary, we report a third patient with an interstitial deletion of chromosome 12q. Array CGH analysis was used to refine the 12q molecular breakpoints of two patients who had cytogenetically identical deletions. Array analysis revealed that the deletions were molecularly distinct: the current case had del(12)(q21.1q22) and the previously reported case had del(12)(q21.1q21.33). The high resolution of array CGH allowed breakpoints to be localized at the molecular level and provided more accurate sizing of the chromosomal aberrations. Therefore, we were able to establish a finer mapping of candidate genes which may be implicated in specific malformations. Based on the features of three patients with similar deletions, we propose a 12q-deletion phenotype comprising developmental delay, facial dysmorphology, ectodermal abnormalities, and possible cardiac and renal malformations. All three patients we have reported had hyperkeratosis pilaris/ulerythema ophryogenes, an ectodermal disorder that has been seen in patients diagnosed with CFC and 18p- syndromes. We propose that hyperkeratosis pilaris/ulerythema ophryogenes has a genetically heterogeneous pathogenesis involving loci on 18p and 12q.

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