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Mandibulofacial Dysostosis in a Patient with a *de novo* 2;17 Translocation that Disrupts the *HOXD* Gene Cluster

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Abstract

Treacher Collins syndrome is the prototypical mandibulofacial dysostosis syndrome, but other mandibulofacial dysostosis syndromes have been described. We report an infant with mandibulofacial dysostosis and an apparently balanced *de novo* 2;17 translocation. She presented with severe lower eyelid colobomas requiring skin grafting, malar and mandibular hypoplasia, bilateral microtia with external auditory canal atreasia, dysplastic ossicles, hearing loss, bilateral choanal stenosis, cleft palate without cleft lip, several oral frenula of the upper lip/gum, and micrognathia requiring tracheostomy. Her limbs were normal. Chromosome analysis at the 600-band level showed a 46,XX,t(2;17)(q24.3;q23) karyotype. Sequencing of the entire *TCOF1* coding region did not show evidence of a sequence variation. High-resolution genomic microarray analysis did not identify a cryptic imbalance. FISH mapping refined the breakpoints to 2q31.1 and 17q24.3–25.1 and showed the 2q31.1 breakpoint likely affects the *HOXD* gene cluster.

Several atypical findings and lack of an identifiable *TCOF1* mutation suggest that this child has a provisionally unique mandibulofacial dysostosis syndrome. The apparently balanced *de novo* translocation provides candidate loci for atypical and *TCOF1* mutation negative cases of Treacher Collins syndrome. Based on the agreement of our findings with one previous case of mandibulofacial dysostosis with a 2q31.1 transocation, we hypothesize that misexpression of genes in the *HOXD* gene cluster produced the described phenotype in this patient.

Keywords

mandibulofacial dysostosis; translocation; syndrome; *TCOF1*; *HOXD*

INTRODUCTION

Treacher Collins syndrome (TCS) is the prototypical mandibulofacial dysostosis syndrome. The key features of TCS include malformed ears, malar and mandibular hypoplasia, lower lid coloboma, cleft palate, and conductive hearing loss. Individuals with mutations in *TCOF1*, located in chromosome band 5q32 encoding for the protein treacle, have been shown to have TCS [The Treacher Collins Collaborative Group, 1996]. Although the majority of individuals with TCS will have an identifiable mutation in *TCOF1*, this is not universal, suggesting genetic heterogeneity. One study reported 8/36 (22%) of patients with the clinical diagnosis of Treacher Collins syndrome did not have an identifiable mutation

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[Teber et al., 2004]. Another study reported that 2/28 (7%) did not have an identifiable mutation [Splendore et al., 2000]. In addition, TCS is thought to be inherited in an autosomal dominant pattern, but autosomal recessive inheritance has been reported [Lowry et al., 1985; Richieri-Costa et al., 1993] adding support to the possibility of genetic heterogeneity.

Although mandibulofacial dysostosis is a key feature in TCS, other syndromes including Nager syndrome, Miller syndrome, and Reynolds syndrome include mandibulofacial dysostosis as a primary finding. There have also been several reports documenting other unique mandibulofacial dysostoses syndromes separate from TCS [Verloes and Lesenfants, 1997; Delb et al., 2001; Hedera et al., 2002; Hing et al., 2006]. We report on a child with a provisionally unique mandibulofacial dysostosis and an apparently balanced *de novo* translocation involving chromosomes 2q and 17q.

MATERIALS AND METHODS

Chromosome, FISH, and Array CGH analysis

High-resolution karyotype analysis was performed on PHA-stimulated peripheral blood using standard procedures. Bacterial artificial chromosomes (BACs) used to generate home-brewed fluorescence *in situ* hybridization (FISH) probes were identified using the March 2006 assembly of the UCSC Genome Browser (http://www.genome.ucsc.edu/). The methods used to generate and hybridize these FISH probes have been described [South et al., 2006]. Array comparative genomic hybridization (CGH) analysis was performed using the Spectral Chip 2600 from Spectral Genomics (Houston, TX) and following the manufacturer's protocol with the exception that the Cy3-dCTP and Cy5-dCTP were purchased from Amersham Biosciences (Buckingamshire, England). Scanning was performed with Axon's GenePix 4000B microarray scanner and the images were analyzed with SpectralWare 2.2 for preparation of ratio plots. For higher-resolution array CGH, chip 8 of the 8-array Set with an average of 713 bp probe spacing was performed by the manufacturer and relative ratios were determined using the SignalMap software package, version 1.8 (NimbleGen Systems, Maddison, WI).

CLINICAL REPORT AND RESULTS

The patient was conceived through intracytoplasmic sperm injection due to reversal of a vasectomy without a previous history of infertility. She was a diamniotic, dichorionic twin, and her gestation was complicated by polyhydramnios. The twins were delivered at 34-weeks gestation by Cesarian section. Growth parameters for both were appropriate for gestational age. One twin presented with mandibulofacial dysostosis (Fig. 1A) while the other twin was unaffected. Our patient presented with cleft palate, lower lid ablepharon, microtia, prominent nasolabial folds, oral frenulae, microretrognathia, choanal atresia, conductive hearing loss, and normal limbs and genitalia. She required a tracheostomy at 1 week and had poor oral intake with gastroesophageal reflux which required gastrostomy tube placement and fundoplication at 1 month. She had significant lower lid ablepharon that resulted in corneal ulcerations and required lower eyelid reconstruction at 3 months (Fig. 1B). A release of her oral frenulae was performed (Fig. 1C). At 8 months she was re-evaluated and found to have normal development.

Computed tomography (CT) images revealed bilateral choanal stenosis and maxillary hypoplasia, osseous external canal atresia, hypoplasia of the middle ear cavity with dysplastic ossicles and an anteriorly displaced facial nerve. No pyriform aperture stenosis was detected. A bone conduction auditory brain stem response test revealed a 30 db hearing loss. CT imaging of the neck and plain films of the chest showed no overt vertebral

abnormalities. Images from an echocardiogram, renal ultrasound, and pelvic ultrasound were unremarkable.

A karyotype identified a balanced translocation reported as 46,XX,t(2;17)(q24.3;q23) at the 600 band level (Fig. 1D). Both parents had normal karyotypes. Array CGH analysis using a 1 Mb human BAC array did not identify an imbalance. To asses the possibility of a cryptic copy number change at either breakpoint at higher resolution, an additional whole-genome isothermal CGH array tiled with a median spacing of 6 kb was performed. Again, no copy number changes were found in or around the affected chromosomal band (Fig. 2). Finally, to test the idea that this patient has an atypical presentation of TCS with an unrelated balanced translocation, sequencing of the entire *TCOF1* coding region was performed clinically (The Johns Hopkins DNA Diagnostic Lab, Baltimore, Maryland) and no mutations were detected.

For a higher-resolution breakpoint mapping analysis and to identify potential genes affected by the translocation breakpoints, FISH with home-brewed BAC probes was performed on metaphase chromosomes (Table 1). By FISH, the 2q breakpoint was mapped to 2q31.1 with a single 176 kb BAC (RP11-387A1) that spans the breakpoint (Fig. 3A,B) and contains the *HOXD* gene cluster and the *EVX2* gene. FISH also refined the 17q breakpoint to a 2.5 Mb region between 17q24.3 and 17q25.1 (Fig. 3C).

DISCUSSION

Our patient represents a provisionally unique mandibulofacial dysostosis syndrome. The features that are atypical of TCS include multiple oral frenulae, more severe lower lid ablepharon, and a distinctive nasal configuration. In addition, no mutation in *TCOF1* was identified. We hypothesize that the translocation disrupts or deregulates the expression of a gene or genes in the 2q31.1 and/or 17q24.3–17q25.1 breakpoint regions producing the described phenotype in our patient.

Individuals with TCS in association with cytogenetic abnormalities have been reported. Arn et al. [1993] reported a child with a 3p24 deletion, and Sawada et al. [2002] reported a child with a pericentric inversion of chromosome 2 with breakpoints at p11.2 and q21. It is unknown whether or not these chromosome abnormalities were *de novo*. Jabs et al. [1991] reported an individual with TCS and a *de novo* 4p deletion. Balestrazzi et al. [1983] described a TCS patient with a de novo 5;13 balanced translocation. All of these cases were reported to have typical TCS and do not involve the chromosomal regions of the breakpoints in our patient.

In 1994, Nucci et al. reported a patient with a form of mandibulofacial dysostosis that had a balanced *de novo* translocation between 2q and 10p. This child had mild abnormalities similar to mandibulofacial dysostosis including cleft palate, pseudocoloboma of the lower lids with atresia of the lacrimal punctae. They found that the breakpoint in this patient interrupted the *HOXD* gene cluster at 2q31.1 occurring near the centromeric end of the cluster between the *HOXD11* and *HOXD12* genes. Based on roughly equal hybridization signal seen with FISH using the breakpoint spanning clone in our patient (Figure 3A) and on the position of the *HOXD* cluster within this BAC (Figure 3B), the breakpoint in our patient also likely disrupts the *HOXD* cluster near the centromeric end or in the flanking regulatory region.

Genes in the *HOXD* cluster are not known to be expressed in the anterior pharyngeal arches and specific deficiencies in these genes have not been shown to affect facial development in mice [Condie and Capecchi, 1993; Favier and Dollé, 1997; Mark et al., 1997; Spitz et al., 2005]. However, large interstitial deletions of chromosome 2q31.3 have been associated with craniofacial dysmorphism [Ramer et al., 1989; Ramer et al., 1990; Slavotinek et al.,

1999] and one patient with a 2q31.1–q32.2 deletion removing the *HOXD* gene cluster was reported to have cleft palate, low set ears, hypertelorism, and microphthalmia [Del Campo et al., 1999]. Deficiency of *Hoxd3* in mice leads to defects of the skull base and cervical vertebrae [Condie and Capecchi, 1993]. Mutations in the more posteriorly expressed members of the *HOXD* gene cluster, including the *EVX2* gene, cause patterning defects of the trunk and hindlimbs including synpolydactyly [Akarsu et al., 1996; Mugaraki et al., 1996; Goodman and Scambler, 2001], brachydactyly [Johnson et al., 2003], and hand-foot-genital syndrome [Mortlock and Innes, 1997].

A large block of synteny between mouse and human spanning 4 Mb surrounding the *HOXD* locus has been given as evidence of very long-range regulation of these genes [Lee et al., 2006] and these regulatory elements are being delineated in mice with experimentally induced rearrangements of the region [Kmita et al., 2000; Spitz et al., 2001; Kmita et al., 2002]. This is exemplified in a report of three patients with apparently balanced chromosomal rearrangements involving 2q31 occurring at distances greater than 390 kb on either side of the *HOXD* cluster who all had limb anomalies similar to those seen with mutations of the posterior genes of the *HOXD* complex [Dlugaszewska et al., 2006]. Another translocation reported by Spitz et al. [2002] demonstrated a translocation breakpoint 60 kb telomeric to the *HOXD* cluster in association with mesomelic dysplasia and vertebral defects.

The lack of limb, vertebral, and genital phenotypes in our patient and in the patient reported by Nucci et al. [1994] suggests that a generalized loss of function of the *HOXD* genes is not the mechanism causing anterior pharyngeal arch abnormalities in these cases. Agreement in the localization of the two breakpoints leads us to hypothesize that mandibulofacial dysostosis in these patients is due to misexpression of *HOXD* genes. We speculate that the observed translocations separates the *HOXD* gene cluster from negative regulatory elements (repressors) in the centromeric end of the cluster or brings HOXD genes into apposition with inappropriate regulatory elements on chromosome 17 allowing abnormal expression of *HOXD* genes in the pharyngeal arches. How inappropriate expression of *HOXD* genes causes the mandibulofacial phenotype, however, is not clear.

Aside from the possibility that *HOXD* misexpressioin is involved in the craniofacial defects in these cases, we considered what is known about the causes of TCS to search the relevant breakpoint regions for genes plausibly involved in the development of mandibulofacial dysostosis. TCS is caused by mutations in *TCOF1*, which encodes the Treacle protein. Treacle is a nucleolar phosphoprotein thought to function in ribosomal DNA gene transcription, and down-regulation of treacle results in reduced ribosomal DNA transcription and cell growth [Valdez et al., 2004]. Treacle function requires interaction with the upstream binding transcription factor (UBTF) [Valdez et al., 2004] making UBTF a candidate for mandibulofacial dysostosis. The gene encoding UBTF is found at chromosome 17q21, more than 25 Mb from the breakpoint in our patient, and is unlikely to be affected by this translocation. Examination of the 17q24.3–17q25.1 region shows that it spans 2.5 Mb and contains approximately 34 genes including multiple genes with known function in embryonic development (Figure 3C).

Genes encoding for LisH motif-containing proteins also represent potential candidates for the phenotype of our patient. Emes and Ponting identified sequence motifs, which possess a LIS1 homology in the products of genes mutated in TCS and oral-facial-digital type1 syndrome [2001]. There are functional similarities between these nucleolar proteins and it is suggested that they contribute to the regulation of microtubule dynamics. Given the co-occurrence of TCS features and the oral frenulae seen in our patient, it is possible that the causative gene or genes in our patient is/are associated with a similar sequence motif that

causes aberrant microtubule dynamics and defects of cell migration. However, examination of the genomic intervals near the breakpoints in this patient did not reveal any genes with known LIS1 homology.

Our case represents a provisionally unique mandibulofacial dysostosis syndrome highlighting the fact that mandibulofacial dysostosis is a primary feature of a number of syndromes. In addition, our case, combined with the report of Nucci et al. [1994], provides further evidence for the *HOXD* cluster as a candidate locus in patients with atypical TCS and without *TCOF1* mutations.

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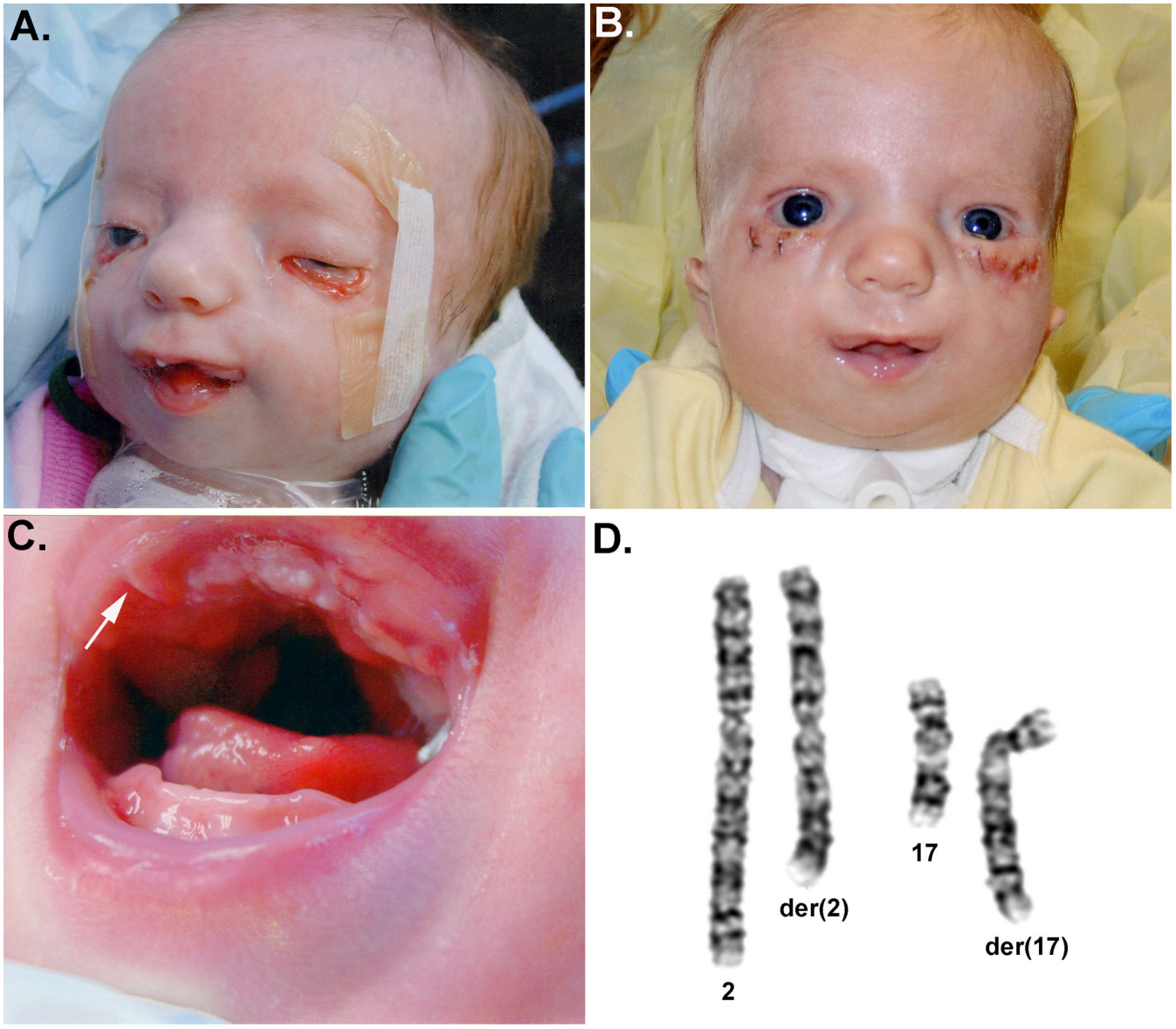

Figure 1.
Photographs of patient: (A) in infancy; (B) after lower eyelid reconstruction; (C) after oral frenulae release also showing cleft palate (arrow points to one remnant of oral frenulae). (D) Partial karyogram of normal and derivative chromosomes 2 and 17.

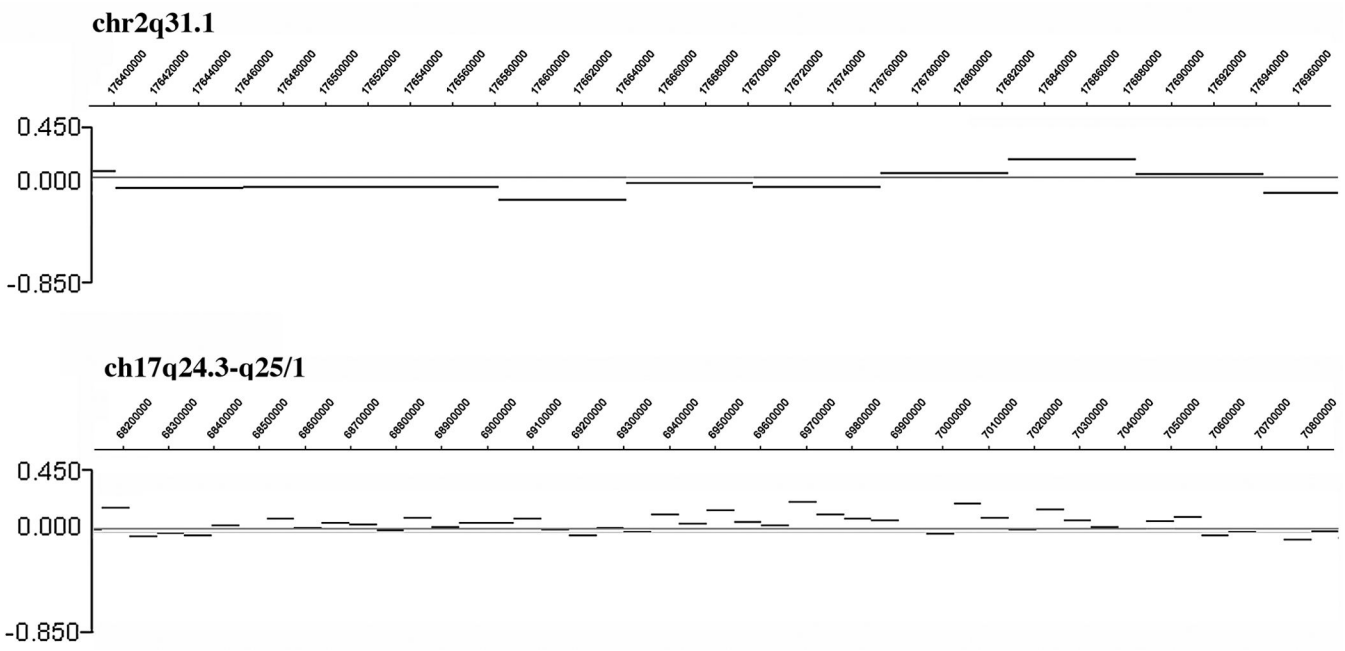

Figure 2.

High resolution CGH of the breakpoint intervals. Ratio plots for the 2q31.1 (top) and 17q24.3–25.1 (bottom) regions. No gains (relative ratio > 0.45) or losses (relative ratio < 0.85) of genetic material were detected across these intervals.

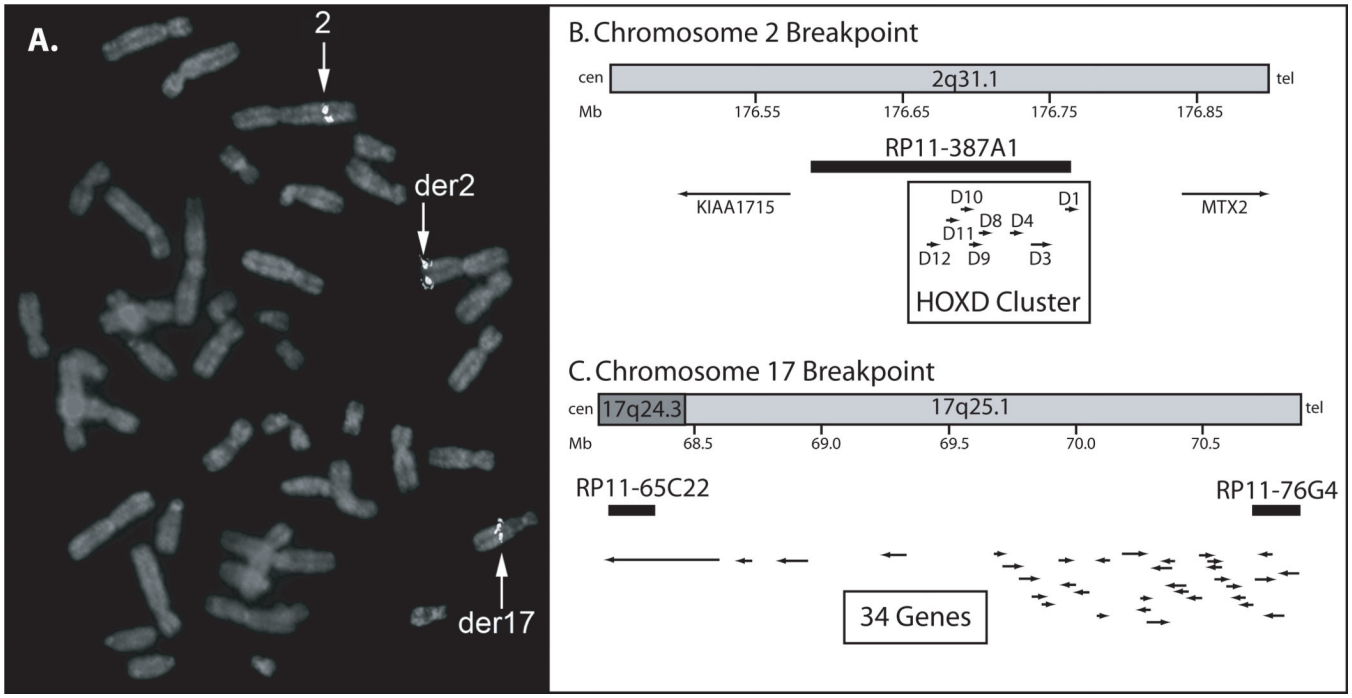

Figure 3.

(A) Metaphase FISH using BAC probe RP11-387A1 shows that this clone spans the 2q31.1 breakpoint with signals on the normal chromosome 2 and on both the der2 and der17 chromosomes. (B) Map of the 2q31.1 breakpoint (chr2:176,450,000–176,900,000) shows that the disrupted BAC (RP11-387A1) spans a 176 Kb region that includes most of the *HOXD* gene cluster and *EVX2* gene (shown boxed) as well as approximately 50 Kb of upstream sequence. Two other genes in the region (shown as labeled arrows) lie outside the disrupted BAC. (C) Map of the 17q24.3–25.1 breakpoint (chr17:68,165,340–70,882,076). FISH mapping of a proximal BAC (RP11-65C22) and distal BAC (RP11-76G4) maps the breakpoint to a 2.5 Mb interval that contains approximately 34 genes (shown as unlabeled arrows).

Table 1

Mapping of translocation breakpoints by FISH

BAC	RP11-79E23	RP11-91L3	RP11-91L23	RP11-12N7	RP11-387A1 (AC009336)	RP11-279N12
chromosome band	2q31.1	2q31.1	2q31.1	2q31.1	2q31.1	2q31.1
Mb location[a]	169,756,626–169,904,658	171,754,594–171,913,716	173,464,862–173,621,749	175,733,151–175,905,868	176,588,986–176,764,652	177,405,181–177,556,198
2	+	+	+	+	+	+
der2	+	+	+	+	+	–
der17	–	–	–	–	+	+
relative to breakpoint	proximal	proximal	proximal	proximal	spans	distal

BAC	RP11-81D7	RP11-89L7	RP11-79K13	RP11-90L11	RP11-65C22	RP11-76G4
chromosome band	17q23.3–24.1	17q24.1–24.2	17q24.2	17q24.3	17q24.3	17q25.1
Mb location[a]	59,885,663–60,066,618	61,469,372–61,644,232	64,421,495–64,592,701	:65,981,810–66,144,564	:68,165,340–68,348,074	70,695,485–70,882,076
17	+	+	+	+	+	+
der17	+	+	+	+	+	–
der2	–	–	–	–	–	+
relative to breakpoint	proximal	proximal	proximal	proximal	proximal	distal

+ signal present on chromosome,

– signal absent on chromosome

[a] location according to the March 2006 assembly of the UCSC Genome Browser (http://www.genome.ucsc.edu/).