Clinical Report

Speech and Language Impairment and Oromotor Dyspraxia Due to Deletion of 7q31 That Involves FOXP2

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We report detailed clinical, cytogenetic, and molecular findings in a girl with a deletion of chromosome 7q31-q32. This child has a severe communication disorder with evidence of oromotor dyspraxia, dysmorphic features, and mild developmental delay. She is unable to cough, sneeze, or laugh spontaneously. Her deletion is on the paternally inherited chromosome and includes the FOXP2 gene, which has recently been associated with speech and language impairment and a similar form of oromotor dyspraxia in at least three other published cases. We hypothesize that our patient’s communication disorder and oromotor deficiency are due to haploinsufficiency for FOXP2 and that her dysmorphism and developmental delay are a consequence of the absence of the other genes involved in the microdeletion. We propose that this patient, together with others reported in the literature, may define a new contiguous gene deletion syndrome encompassing the 7q31-FOXP2 region. Cytogenetic and molecular analysis of this region should be considered for other individuals displaying similar characteristics. © 2006 Wiley-Liss, Inc.

Key words: FOXP2; speech and language impairment; 7q31 deletion; oromotor dyspraxia

INTRODUCTION

There are 13 published case reports describing cytogenetically visible interstitial deletions of the long arm of chromosome 7 that involve band 7q31, excluding complex rearrangements. Eleven of the reports describe children with interstitial deletions of the long arm of chromosome 7 extending from bands 7q21 or q22 through to 7q31 or q32 [Ayraud et al., 1976; Higginson et al., 1976; Franceschini et al., 1978; Klep-de-Pater et al., 1979; Serup, 1980; Abuelo and Padre-Mendoza, 1982; Young et al., 1984; Martin-Pont et al., 1985; Fagan et al., 1989; Morey and Higgins, 1990; Montgomery et al., 2000]. There is one patient with a deletion of bands 7q31-q34 [Stallard and Jubel, 1981]. The smallest reported deletion involving the 7q31 region extends from 7q31.2 to 7q32.3 [Sarda et al., 1988].

We report the clinical, cytogenetic, and molecular findings in a 5-year-old female with a cytogenetically visible deletion of 7q31.2-q32.2 who has dysmorphic features, a severe communication disorder with speech and language impairment, and dyspraxia. She cannot cough, sneeze, or laugh spontaneously. Abnormalities in FOXP2, a gene which maps to 7q31, are associated with speech and language impairment.

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and oromotor dyspraxia, a severe form of speech and language disorder (SPCH1 [MIM 602081]) [Lai et al., 2001; MacDermot et al., 2005] and haploinsufficiency for FOXP2 is likely to be responsible for the speech and language disorder observed in this patient.

MATERIALS AND METHODS

Clinical Report

The proband was born at 39 weeks gestation to a 35-year-old G2P1 woman, following an uncomplicated pregnancy. There were no exposures to illicit or prescription drugs, cigarette smoke, or alcohol. Fetal activity was reported as normal. She was born by spontaneous vaginal vertex delivery weighing 3,118 g. With the exception of gagging episodes the parents reported no medical concerns with regard to her in the first year of life. At age 12 months she was noted to be developmentally delayed with low tone and microcephaly. At age 14 months her head circumference (OFC) was 42.5 (<3rd centile), weight was 11.9 kg (95th centile), and length was 77.7 cm (25–50th centile). She had bitemporal narrowing, brachycephaly, a small nose, a long philtrum, and down-turned corners of her mouth. Her anterior and posterior fontanelles were closed. She had simple ears with thick lobules. Her hair texture and distribution was normal. She had normal hands and feet with persistent fetal finger pads, and a normal chest and cardiac examination. Her abdomen was soft with no hepatosplenomegaly. Her external genitalia were normal female. She had a normal back and extremities.

She sat at 9 months of age and by age 14 months was developing some righting reactions. She did not crawl but would put herself into position on her hands and knees. She had a pincer grasp and was able to transfer objects from hand to hand. She was babbling with a few words (mama, dada, baba) with specific meaning. She was sociable and happy; she would play peek-a-boo, pat-a-cake, and wave bye-bye. Her parents reported that she would laugh by spontaneous speech was unintelligible. The findings were consistent with an oromotor and oral speech, and speech sound inventory revealed a significantly restricted repertoire consisting exclusively of vowels, stop consonants, and nasals. Her spontaneous speech was unintelligible. The findings were consistent with an oromotor and verbal dyspraxia.

She had some repetitive behaviors such as hand flapping and extended hand regard and some unusual sensory interests indicated by sniffing and squeezing. She did not meet criteria for autism on the Autism Diagnostic Observation Schedule (ADOS) Module One [Lord et al., 2000] and on Autism Diagnostic Interview—Revised [Lord et al., 1994], because of her strong social communication, which included spontaneous use of varied gestures to compensate for language difficulties. This was consistent with results of a semi-structured interview (Autism Diagnostic Interview) carried out with her mother.

Her cognitive abilities as assessed by the Stanford Binet [Thorndike et al., 1986] and Leiter [Roid and Miller, 1997] scales showed scattered abilities ranging from below average to average with strengths in nonverbal sequential ordering and identifying absurdities in pictures. The greatest challenge came from quantitative concepts and manipulating parts to make a whole.

The proband has an older sister and a younger brother who are well. A paternal first cousin has Williams-Beuren syndrome with the standard 7q11.23 microdeletion. A paternal first cousin once removed is mentally handicapped but not available for testing. The family is of Italian origin. The parents are not consanguineous.

Cytogenetic and Molecular Analyses

Lymphocyte cultures were established according to standard procedures. An interstitial deletion of the 7q31.2 to 7q32.2 region was found in a G-banded karyotype at 450–750 band resolution [Josiek et al., 1991]. By fluorescence in situ hybridization (FISH) using probes for loci D7S486 and D7S522 within 7q31 (control probe for William syndrome, Vysis, Downers Grove, IL) the karyotype was further defined as 46,XX,del(7)(q31.2q32.2)(D7S486-D7S522-) (Fig. 1). Parental karyotypes were normal.

To confirm the extent of the 7q31-q32 deletion and to refine the breakpoints, the proband's chromosomes were examined by FISH using multiple bacterial artificial chromosome (BAC) probes and the proband's DNA was examined using the Spectral Genomics CGH microarray, which contains clones uniformly distributed across the genome at an approximate 1 Mb resolution. Our combined data localized the centromeric boundary between BACs RPCI-11-150B23 and GIT-D-2023N18, which are separated by approximately 36 kb at 7q31.2 allowing...
the mapping of the proximal breakpoint of the deletion. The telomeric boundary could be positioned between RPCI-11-35B6 and D7S5530, which are separated by less than 100 kb at 7q32.2. Additional mapping information can be found at [http://www.chr7.org/](http://www.chr7.org/) and all FISH probes shown are available upon request for testing other cases. This analysis showed that the entire consensus FOXP2 gene would be hemizygoously deleted as would the majority or all of its longer alternatively spliced forms. The size of the proximal and distal breakpoints is between D7S471/D7S2554 and D7S461/D7S530 at 7q31.2 and 7q32.2, respectively. The size of the deletion is approximately 16 Mb and a total of 51 known genes (with HUGO approved names) reside in this interval in addition to FOXP2. Examples include CFTR, CORTBP2, KCND2, CADPS2, SPAM1, GRM8, and PAX4.

In addition to the deletion of 7q31-q32, the proband carried an inversion variant (called WBS-INVI) with the upper size of 1.7 Mb. We have recently shown that this variant can be associated with the Williams-Beuren phenotype [Scherer et al., 2003]. Using three-color interphase FISH we could refine the sites of the inversion breakpoints between the LIMK1 and CYCLN2 and the HIP1 and POR genes at 7q11.23 (Fig. 1). The proband’s phenotypically normal father appears to be mosaic for cells carrying combinations of normal chromosomes, the WBS-INVI variant, and a different 1.6 Mb inversion variant also previously shown to be associated with Williams-Beuren syndrome [Osborne et al., 2001]. We have, so far, not observed the WBS-INVI variant in non-Williams-Beuren syndrome families so it may be relevant to the phenotype of the proband from this study. For example, the strong social skills and problems with visuospatial reconstruction may reflect the expression of a component of the Williams-Beuren phenotype [Osborne, 1999].

**DISCUSSION**

Abnormalities of FOXP2, a gene which localizes to the 7q31 region, have been associated with speech and language impairment in three families; in one patient with a chromosomal translocation involving the 7q31.2 region, and in two multiplex families with FOXP2 point mutations which segregate with a severe speech and language disorder in an autosomal dominant fashion [Vargha-Khadem et al., 1995; Lai et al., 2001; MacDermot et al., 2005]. FOXP2 is a member of the forkhead class of transcription factors and is thought to be involved in the development of corticostriatal and olivocerebellar circuits involved in motor control [Lai et al., 2003]. The gene is expressed in several structures including the cortical plate, basal ganglia, thalamus, inferior olives, and cerebellum. It is thought that haploinsufficiency of FOXP2 underlies impairments in sequencing of movement and procedural learning leading to the FOXP2-related speech and language disorder and oromotor apraxia.

In a well-studied kindred with an autosomal dominant type of communication disorder (the KE family) (OMIM #602081), Lai et al. [2001] identified a pathogenic point mutation in FOXP2. In an unrelated child with speech and language impairment, verbal dyspraxia, and a de novo balanced reciprocal translocation t(5;7)(q22;q31.2), it was determined that the rearrangement breakpoint disrupted the FOXP2 gene itself [Lai et al., 2000, 2001]. A truncating mutation of FOXP2 was associated with a severe speech and language disorder in a multiplex two generation family [MacDermot et al., 2005].

The communication disorder in our patient consists of oromotor and verbal dyspraxia with inability to cough or sneeze and atypical resonance during running speech consistent with the diagnosis of oromotor dyspraxia and a significant oral language impairment. The child with the reciprocal translocation t(5;7) was diagnosed with oral dyspraxia at 3 years of age and also was unable to laugh or sneeze spontaneously [Lai et al., 2000]. Our patient has a global impairment affecting all aspects of language functioning, with more prominent difficulties in expressive (relative to receptive) language. The extent of her difficulties with the verbal expression of language is influenced by her restricted motor-speech skills; however, the presence of significant difficulties with the comprehension of spoken language suggest that expressive language functioning is an additional area of impairment, rather than secondary to her dyspraxia. Limitations in both receptive and expressive language with expressive language more severely impaired than receptive language have been described in all patients with FOXP2 mutations [Vargha-Khadem et al., 1995; Lai et al., 2001; Watkins et al., 2002; MacDermot et al., 2005].

Excluding those with complex rearrangements, there are 13 published case reports of children with chromosome 7 deletions that involve 7q31 [Ayraud et al., 1976; Higginson et al., 1976; Franceschini et al., 1978; Klep-de-Pater et al., 1979; Serup, 1980; Stallard and Juberg, 1981; Abuelo and Padre-Mendoza, 1982; Young et al., 1984; Martin-Pont et al., 1985; Sarda et al., 1988; Fagan et al., 1989; Morey and Higgins, 1990; Montgomery et al., 2000]. Our patient’s deletion is closest in size and position to that present in the child reported by Sarda et al. [1988], who was reported to have a deletion extending from 7q31.2 to 7q32.3. The band level appears to have been ~450, based on the R-banded chromosome 7 pairs depicted in the report. The clinical findings in this patient, who was 7 years of age at the time of the report, included dysmorphic facies similar to those observed in our patient, mild psychomotor delay, no physical malformations, hyperactivity, and
complete absence of language. It would appear that the patient described by Sarda et al. [1988] and our patient may serve to delineate the phenotype of a new contiguous gene deletion syndrome at 7q31-q32.

The patient described by Serup [1980] had poor vocalizations, moderate motor retardation, and swallowing difficulties at age 25 months. A dysfunction in pharyngeal and laryngeal musculature coordination was postulated as responsible for the swallowing difficulties. From the published photograph her face resembles that of our patient. She appeared to have a broad, short nose with short columella (giving a somewhat flattened appearance), a long and well-delineated philtrum, horizontal to downward slanting palpebral fissures, and large, low-set ears. Although this patient seems similar to our patient clinically, there is insufficient information about the speech and language disorder to conclude that it is the same as that in our patient. Moreover, while the karyotypic description of the deletion (7q22.1-7q31.2) would suggest FOXP2 would be deleted (it maps to 7q31.2), experiments would need to be performed to test this given inaccuracies sometimes associated with chromosome banding.

The remaining 11 reports of chromosome 7 deletions involving band q31 were reviewed for evidence of speech and language impairment. All of the deletions were larger than that noted in our patient. Most of the children had physical abnormalities and multiple medical problems. Four died in infancy [Ayraud et al., 1976; Franceschini et al., 1978; Martin-Pont et al., 1985; Morey and Higgins, 1990; Montgomery et al., 2000] and there was no information reported on the speech or vocalizations in the patients described by Young et al. [1984]; Fagan et al. [1989]; or Higginson et al. [1976]. Of the remaining three patients, one was reported to have an unusual cry at age 13 months [Stallard and Juber, 1981]. One patient had no speech at the age of 6 years [Klep-de-Pater et al., 1979] and another had abnormalities of speech initiation and a cry described as aphonic at 9 years of age [Abuelo and Padre-Mendoza, 1982]. A review of patients with distal 7q deletions noted that four of the seven reported patients had “an unusual cry” as infants [Abuelo and Padre-Mendoza, 1982]. Since the region of overlap for those four patients was 7q31, they hypothesized that the unusual cry might be correlated with the 7q31 segment. However, our patient did not have an abnormal cry as an infant and there is no mention of that finding in other individuals with documented abnormalities of FOXP2 reported to date [Sarda et al., 1988; Hurst et al., 1990; Lai et al., 2000; MacDermot et al., 2005].

Since FOXP2 has been shown to be responsible for orofacial dyspraxia and speech and language impairment in a number of patients, hemizygosity of this gene in our patient is likely the cause of her speech and language difficulties and oromotor apraxia. This is the second published report of a small deletion within 7q31-q32 associated with a severe communication disorder, oromotor dyspraxia, similar mild dysmorphic features, and mild developmental delay. We propose that these patients may define a new contiguous gene deletion syndrome encompassing the 7q31-FOXP2 region. The availability of high-resolution mapping reagents and techniques should facilitate assessment for this microdeletion in any clinical cytogenetics laboratory.

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