



FOXP2 gene deletion and infant feeding difficulties: a case report

Emily Zimmerman¹ and Jill L. Maron²

¹Northeastern University, Department of Communication Sciences & Disorders, Boston, Massachusetts 02115, USA; ²Mother Infant Research Institute, Tufts Medical Center, Boston, Massachusetts 02111, USA

Abstract Forkhead box protein P2 (*FOXP2*) is a well-studied gene known to play an essential role in normal speech development. Deletions in the gene have been shown to result in developmental speech disorders and regulatory disruption of downstream gene targets associated with common forms of language impairments. Despite similarities in motor planning and execution between speech development and oral feeding competence, there have been no reports to date linking deletions within the *FOXP2* gene to oral feeding impairments in the newborn. The patient was a nondysmorphic, appropriately and symmetrically grown male infant born at 35-wk gestational age. He had a prolonged neonatal intensive care unit stay because of persistent oral feeding incoordination requiring gastrostomy tube placement. Cardiac and neurological imagings were within normal limits. A microarray analysis found an ~9-kb loss within chromosome band 7q3.1 that contains exon 2 of *FOXP2*, demonstrating a single copy of this region instead of the normal two copies per diploid gene. This case study expands our current understanding of the role *FOXP2* exerts on motor planning and coordination necessary for both oral feeding success and speech–language development. This case report has important consequences for future diagnosis and treatment for infants with *FOXP2* deletions, mutations, and varying levels of gene expression.

Corresponding author:
e.zimmerman@neu.edu

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Ontology terms: oral–pharyngeal dysphagia, poor suck

Published by Cold Spring Harbor Laboratory Press

doi: 10.1101/mcs.a000547

INTRODUCTION

Oral feeding competency and speech–language emergence relies on shared physiological pathways of oral motor coordination, planning, and execution. In fact, the act of feeding and speech production relies on five shared cranial nerve innervations and 26 pairs of muscles (Matsuo and Palmer 2008; Travers 2009). Despite these similarities, to our knowledge there are no reports linking known genetic mutations associated with speech delays with impaired oral feeding skills in the newborn. Further, although there are several published reports of genetic mutations resulting in a variety of speech impairments, single-gene defects associated with impaired oral feeding in the newborn are largely unknown. Expanding our knowledge of the genetic basis for neonatal oral feeding deficits, particularly as it relates to speech development, could significantly advance the field.

RESULTS

Clinical Presentation

The male patient was born at 35-wk gestation to a 26-yr-old gravida 1, para 1 mother via a C-section because of failure to progress. Pregnancy complications included maternal

gestational diabetes treated with glyburide and preeclampsia. The patient had a birth weight of 5 lb, 13 oz (2636.50 g) and Apgar scores of 6 and 9, at 1 and 5 min, respectively. The patient required resuscitation with positive pressure mask ventilation at birth; cord blood pH was 7.3. He was transferred to the neonatal intensive care unit (NICU) within hours of birth because of hypoglycemia and hypothermia.

Genomic Analyses

Although the patient was born 5 weeks prematurely, his feeding-related issues exceeded those normally associated with late preterm birth, precipitating a genetic workup to determine the cause for his persistent feeding difficulties. A comparative genomic microarray was performed and analyzed with the purpose of identifying gains and/or losses of DNA copy number associated with chromosomal imbalances. Microarray analysis revealed an ~9-kb loss within chromosome band 7q3.1 that contains exon 2 of the forkhead box protein 2 (*FOXP2*). The patient has a single copy of this region instead of the normal two copies per diploid gene.

Phenotypic Analyses

On physical examination, the patient had no abnormal facial or physical features. Ears, nose, mouth, neck, chest, lungs, heart, abdomen, anus, genitalia, hips, extremities, back, and skin were all reported to be normally developed for his age. He did not have any significant respiratory distress or disease. The patient required continuous positive airway pressure (CPAP) for <2 min in the delivery room and remained on room air for the remainder of his NICU stay. The patient was noted to have hypertonic joints, occasional cortical thumbing, and diffusely increased tone. However, neurologic imaging, which included a head ultrasound and MRI, were within normal limits. In addition, the patient had a normal echocardiogram for his age.

Functional Feeding Analyses

Shortly after birth, the patient had a brief period of all per oral (PO) feeds. However, with an age-appropriate increase in daily feeding volumes, he demonstrated an inability to regulate suck–swallow–breath. Formula was found to pool in his cheeks resulting in increased desaturation events during oral feeding trials and increasing weight loss. Twenty-eight days after birth, the patient was trialed on PO feeds on demand with nasogastric (NG) supplementation to ensure appropriate weight gain. With feeding skills impaired, the patient was placed on thickened, honey-nectar liquids, which minimally improved organization of feeding and limited his feeding-associated desaturations. By 30 days of life, he was described as having a dysfunctional suck pattern characterized by fluctuation of jaw excursions with no consistency of movement and poor efficiency of the liquid bolus transfer. The patient was transferred to an outlying hospital for convalescent care while continuing to be fed with thickened PO feeds with NG supplementation.

In the outlying hospital, the patient's oral motor skills were characterized by his speech therapist as quickly latching to a pacifier with active and strong nonnutritive suck. He responded well to oral stimulation with increased tongue and jaw movements, as well as active sucking on the pacifier. When the patient was fed, he demonstrated poor oral transit of the liquid bolus and had difficulty coordinating suck and respiration, resulting in a substantial loss of the bolus at the lips. The patient received a modified barium swallow study, which revealed penetration of thin and thickened liquids into the airway, but no frank aspiration. He was noted to have nasopharyngeal reflux. Because of feeding issues, the patient had a gastrostomy tube placed at the age of 1 mo, 6 d. In total, he spent 42 d in the NICU because

of his inability to coordinate suck–swallow–breathe patterns necessary for oral feeding and went home at a postmenstrual age of 41 wk.

Medication List

During the patient’s NICU stay, the following medications were prescribed: acetaminophen and morphine postsurgical gastrostomy tube insertion, glycerin suppositories, and a multivitamin with iron. The patient was discharged from the NICU with no prescribed medications.

DISCUSSION

To our knowledge, this is the first case report linking a deletion in *FOXP2* to oral feeding incompetency in a human newborn. Benign copy number losses of this region have been reported in the Database of Genomic Variants (DGV; <http://dgv.tcag.ca/dgv/app/home>). However, hemizygous deletions and point mutations of *FOXP2*, as well as interruptions of *FOXP2* by chromosome translocation, have been associated with developmental verbal apraxia, a motor programming speech deficit. In fact, *FOXP2* has traditionally been considered the “speech and language gene.” It was the first gene to be implicated in a developmental disorder of speech and language (Lai et al. 2001) and is now known to play an essential role in normal speech development. Located on Chromosome 7 (Fisher et al. 1998; Lai et al. 2000, 2001), *FOXP2* regulates a large number of downstream target genes associated with common forms of language impairment (Vernes et al. 2008). Heterozygous mutations of *FOXP2* in humans cause severe speech–language delays (Lai et al. 2001, 2003; Liegeois et al. 2003; MacDermot et al. 2005; Fisher and Scharff 2009), specifically verbal apraxia (dyspraxia). Animal studies have demonstrated that functional knock-down of *Foxp2* in young zebra finches leads to incomplete and inaccurate vocal imitations during song learning (Middleton and Strick 2000; Fisher and Scharff 2009). Knockout mice with mutations in two copies of *Foxp2* have impaired vocalizations, as well as lung and brain development; mutations in one copy cause reduced vocalizations (Shu et al. 2007) (Table 1).

Given the shared developmental pathways responsible for oral feeding and speech, the potential role *FOXP2* plays in oral feeding is both biologically and developmentally plausible. Neurons that express *FOXP2* are found in deep cortical layers, the basal ganglia, parts of the thalamus, and the Purkinje cells of the cerebellum, suggesting that *FOXP2* is required for proper brain development (Ferland et al. 2003; Lai et al. 2003; Liegeois et al. 2003; Teramitsu et al. 2004; Spiteri et al. 2007; Takahashi et al. 2008; Campbell et al. 2009; Enard et al. 2009; Reimers-Kipping et al. 2011). In the mammalian brain, these areas belong to a distributed network of circuits that are involved in motor coordination, learning, and acquisition of sensorimotor skills, all essential developmental components for oral feeding (Ullman 2001; Watkins et al. 2002; Liegeois et al. 2003; Haesler et al. 2007; Ackermann 2008; Groszer et al. 2008; Campbell et al. 2009; Enard et al. 2009). We speculate that, given the patient’s clinical presentation, combined with the known expression pattern and function

Table 1. Variant table

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Deletion breakpoints	Predicted effect	Genotype
<i>FOXP2</i>	7	NM_001172766	NP_001166237	Deletion	113,925,160– 113,934,427	Apraxia of speech	Heterozygous

HGVS, Human Genome Variation Society.

of *FOXP2*, the ~9-kb deletion in the gene is likely responsible for oral feeding inability in this infant.

The patient was born preterm and is an infant of a diabetic mother, both of which can hinder feeding abilities. However, the patient's feeding issues were above and beyond what is considered typical for preterm infants with a history of diabetes—so much so that genetic testing was requested and a gastrostomy tube was placed. This case report is based on one subject and is a first indication that oral feeding incompetence has occurred with a single mutation of the *FOXP2* gene. Additional studies are needed to confirm the hypothesis that a *FOXP2* mutation may be associated with oral feeding dysfunction, much like the rigorous studies that have been completed with *FOXP2* and speech impairments, and those that have shown genetic alterations during development may be associated with oral feeding competence (Dietz et al. 2012; Maron 2012; Maron et al. 2012a,b, 2015).

Although more research needs to be conducted examining the role of *FOXP2* in neonatal oral feeding, this case report nevertheless lays the foundation for an improved understanding of a single-gene deletion in oral feeding delays in the newborn and emphasizes the importance of considering a genetic basis for poor oral feeding skills in otherwise healthy, nondysmorphic infants. The findings of this case report have clinical significance, as *FOXP2* may represent a novel gene required for oral feeding competence that could serve as a source of assessment in those infants with feeding difficulties. Timely identification of *FOXP2* deletions, mutations, or reduced expression levels of the gene may not only allow for targeted treatment strategies to improve oral feeding in the neonatal period but may also allow for anticipatory developmental strategies to optimize speech outcomes later in childhood.

METHODS

Information regarding the patient was obtained retrospectively by reviewing his medical files. The microarray was completed with a blood sample. The protocol used for this microarray test employed Affymetrix Cytoscan HD reagents. The array procedure was performed according to the manufacturer's recommendation. The microarray data were processed and analyzed using Affymetrix Chromosome Analysis Suite (ChAS 2.0) in combination with a Referenced Model provided by the manufacturer. This case was analyzed using human genome build GRCh37 (hg19).

ADDITIONAL INFORMATION

Ethics Statement

Written informed consent was obtained from the patient's parents for publication of this case report. Northeastern University's institutional review board reviewed and approved the case study materials.

Database Deposition and Access

The *FOXP2* deletion has been deposited in ClinVar (<http://www.ncbi.nlm.nih.gov/clinvar/>) under accession number SCV000245840. Data on the patient is not publicly available because consent could not be obtained.

Acknowledgments

We would like to thank the parents of the patient for their willingness to publish their child's case report.

Competing Interest Statement

The authors have declared no competing interest.

Referees

Chantal Lau
Anonymous

Received July 2, 2015; accepted
in revised form October 16, 2015.

Author Contributions

E.Z. and J.L.M. had contact with the parents of the patient. E.Z. attained the necessary medical records and wrote the paper. J.L.M. wrote and edited the paper.

Funding

No funding was used to complete this case report.

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