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Hard to swallow: Developmental biological insights into pediatric dysphagia

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ABSTRACT

Pediatric dysphagia—feeding and swallowing difficulties that begin at birth, last throughout childhood, and continue into maturity—is one of the most common, least understood complications in children with developmental disorders. We argue that a major cause of pediatric dysphagia is altered hindbrain patterning during pre-natal development. Such changes can compromise craniofacial structures including oropharyngeal muscles and skeletal elements as well as motor and sensory circuits necessary for normal feeding and swallowing. Animal models of developmental disorders that include pediatric dysphagia in their phenotypic spectrum can provide mechanistic insight into pathogenesis of feeding and swallowing difficulties. A fairly common human genetic developmental disorder, DiGeorge/22q11.2 Deletion Syndrome (22q11DS) includes a substantial incidence of pediatric dysphagia in its phenotypic spectrum. Infant mice carrying a parallel deletion to 22q11DS patients have feeding and swallowing difficulties that approximate those seen in pediatric dysphagia. Altered hindbrain patterning, craniofacial malformations, and changes in cranial nerve growth prefigure these difficulties. Thus, in addition to craniofacial and pharyngeal anomalies that arise independently of altered neural development, pediatric dysphagia may result from disrupted hindbrain patterning and its impact on peripheral and central neural circuit development critical for feeding and swallowing. The mechanisms that disrupt hindbrain patterning and circuitry may provide a foundation to develop novel therapeutic approaches for improved clinical management of pediatric dysphagia.

1. Introduction

Approximately 25% of all infants and children, and as many as 80% with neurodevelopmental disorders, have pediatric dysphagia (Fig. 1A)—extreme difficulties with feeding and swallowing that slow weight gain, disrupt nutrition, cause acute choking that can lead to life threatening aspiration-based infections of the nasal sinuses, middle ears, and lungs (Tutor and Gosa, 2012; Miller, 2009; Arvedson, 2008; Cooper-Brown et al., 2008; Lefton-Greif, 2008; Prasse and Kikano, 2009; Bingham, 2009; Arvedson et al., 1994; Karpinski et al., 2014; Durvasula et al., 2014). Dysphagia-related symptoms likely compromise many aspects of postnatal development including sensory experience, motor activity, cognitive exploration, language acquisition and social engagement. Perhaps due to a general increase in the incidence of neurodevelopmental disorders or enhanced diagnostic awareness, current data suggest that the frequency of pediatric dysphagia is increasing (Kakodkar and Schroeder, 2013). Nevertheless, our current understanding of this serious complication for many infants and children is based primarily upon descriptions of clinical phenomena. The basic underlying biology remains unknown, in large measure because of a lack of valid animal models of human neurodevelopmental disorders that include early post-natal feeding and swallowing dysfunction in their phenotypic spectrum.

22q11.2 Deletion Syndrome (22q11DS), also known as DiGeorge Syndrome, has become a "model" genetic disorder (Meechan et al., 2015) for understanding the relationship between complex behavioral disruptions and additional phenotypes that are often

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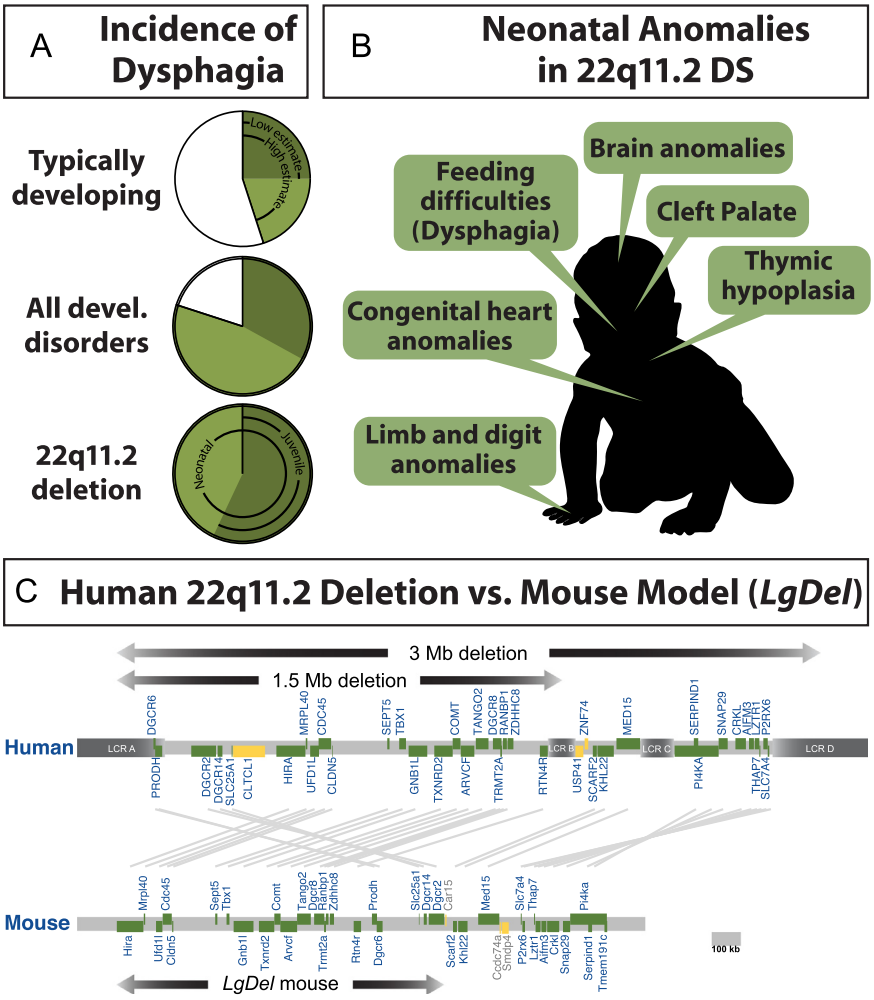

Fig. 1. A. Pediatric dysphagia is a frequent complication in early life. *Top:* Otherwise typically developing children with no diagnoses of known developmental or neurodevelopmental disorders. Current estimates suggest that as few as 25% and as many as 45% of typically developing children have dysphagia at some point during infancy or childhood (data from (Lefton-Greif, 2008)). *Middle*: Incidence of pediatric dysphagia in all developmental disorders, including neurodevelopmental disorders suggesting that approximately 80% of children with developmental disorders have pediatric dysphagia (data from (Lefton-Greif, 2008)). *Bottom*: Frequency of pediatric dysphagia in children with DiGeorge/22q11.2 Deletion Syndrome (22q11DS). Available estimates (Eicher et al., 2000) indicate that all of these children have dysphagia at birth, and 57% continue to have dysphagic symptoms from 4 years of age onward. B. A summary of clinically significant morphogenetic anomalies seen in infants with 22q11DS. As these infants grow, they will also encounter behavioral difficulties that identify 22q11DS as a neurodevelopmental disorder. C. The minimal critical deletion on human Chromosome 22, q11.2 that causes 22q11DS, and the parallel deletion in *LgDel* mice that model 22q11DS. In humans, low copy repeats (LCR) flank the deleted region, providing a potential mechanism for deletion during meiotic recombination. In mice, there are no LCRs that flank the orthologous region to 22q11.2 on mmChromosome 16. The deletion was engineered by placing lox-p sites at the 3' and 5' genes in the orthologous region followed by Cre recombination to recover heterozygous deleted mice (Merscher et al., 2001). Figure adapted from (Meechan et al. 2015).

coincident in a broad range of neurodevelopmental disorders (Fig. 1B,C). One of the most clinically relevant 22q11DS phenotypes, aside from cognitive and social impairment, is disrupted feeding and swallowing that defines pediatric dysphagia (Eicher et al., 2000). All 22q11DS patients have neonatal feeding and swallowing impairments, and nearly 60% continue to experience complications from 4 years of age onward (Eicher et al., 2000). In some patients, these difficulties likely result from craniofacial dysmorphology including cleft palate and other anomalies that often require surgical intervention. Unfortunately, current surgical treatments are only effective in approximately 25% of patients (Brandao et al., 2011; Widdershoven et al., 2008), suggesting mechanisms beyond oropharyngeal mechanics may contribute to pathology. Indeed, many cases of pediatric dysphagia in 22q11DS patients are not accompanied by overt craniofacial dysmorphology that requires surgical intervention (Eicher et al., 2000; Rommel et al., 2008). Nevertheless, these patients have the same nutritional and respiratory complications. Apparently, pediatric dysphagia can arise due to disruptions in developmental mechanisms other than those responsible for oropharyngeal morphogenesis.

The lack of foundational knowledge of pediatric dysphagia pathogenesis in 22q11DS or any other developmental disorder makes it difficult to predict clinical course, and design effective new therapies. Current therapies—often based upon approaches used for dysphagic adults—focus on oral motor interventions like non-nutritive sucking or oral stimulation (Arvedson et al., 2010; Pinelli and Symington, 2005), modified feeding schedules, altered food consistency (Vandenplas, 2009; Strowd et al., 2008; Dion et al., 2015; Stuart and Motz, 2009), and peripheral neuromuscular stimulation (Kakodkar and Schroeder, 2013; Huckabee and Doeltgen, 2007; Sharp et al., 2010). These approaches, however, are only marginally effective (Kakodkar and Schroeder, 2013; Christiaanse et al., 2011), and most have not been adequately evaluated in controlled clinical trials (Morgan et al., 2012). Moreover, while possibly helpful, these approaches do not define or ameliorate underlying pathology. In this review, we will address likely developmental biological foundations of pediatric dysphagia. We argue that key mechanisms for understanding the