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Dyslexia risk gene relates to representation of sound in the auditory brainstem

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ABSTRACT

Dyslexia is a reading disorder with strong associations with *KIAA0319* and *DCDC2*. Both genes play a functional role in spike time precision of neurons. Strikingly, poor readers show an imprecise encoding of fast transients of speech in the auditory brainstem. Whether dyslexia risk genes are related to the quality of sound encoding in the auditory brainstem remains to be investigated. Here, we quantified the response consistency of speech-evoked brainstem responses to the acoustically presented syllable [da] in 159 genotyped, literate and preliterate children. When controlling for age, sex, familial risk and intelligence, partial correlation analyses associated a higher dyslexia risk loading with *KIAA0319* with noisier responses. In contrast, a higher risk loading with *DCDC2* was associated with a trend towards more stable responses. These results suggest that unstable representation of sound, and thus, reduced neural discrimination ability of stop consonants, occurred in genotypes carrying a higher amount of *KIAA0319* risk alleles. Current data provide the first evidence that the dyslexia-associated gene *KIAA0319* can alter brainstem responses and impair phoneme processing in the auditory brainstem. This brain-gene relationship provides insight into the complex relationships between phenotype and genotype thereby improving the understanding of the dyslexia-inherent complex multifactorial condition.

1. Introduction

Dyslexia is characterized by poor reading, writing, and spelling skills despite typical intelligence, no visual acuity problems, and appropriate education (ICD-10-CM, http://www.icd10data.com/ICD10CM/Codes/F01-F99/F80-F89/F81-/F81.0). Boys are 2–3 times more likely to be affected than girls, and cumulative incidence rates vary from 5–12% (Shaywitz et al., 1990). Dyslexia persists in 4–6% of adults (Schulte-Körne and Remschmidt, 2003) disadvantaging employment, and compromising participation in public life. Prevention requires early sensitive screenings and successful remediation, which are both still desirable.

Various cognitive domains support literacy acquisition. Thus, heterogeneous cognitive fingerprints of dyslexia phenotypes exist (Heim and Grande, 2012; Ramus and Ahissar, 2012) and multiple subtypes of dyslexia have been suggested (Bosse et al., 2007), but *a bona* fide theory of the underlying mechanisms has not been established yet. A widely accepted rationale bases dyslexia on an impairment of phonological representations (Snowling, 2001). Others advocate auditory processing deficits such as an impaired oscillatory phase locking for low frequency temporal coding in auditory cortex (Goswami, 2011), or a decreased sensitivity to rapidly changing phonological features (Benasich et al., 2002; Tallal, 1980). Auditory processing deficits might cause an impoverished

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distinction between speech sounds (Vandermosten et al., 2010), a deficient access to otherwise intact phonetic representations (Boets et al., 2013), or a deficient match between memory representations and auditory sensations (Díaz et al., 2012; Jaffe-Dax et al., 2015). Alternatively or additionally, visual attention, visual-magnocellular processing, or visual-auditory integration compose further cognitive problems (Heim et al., 2010; Stein and Walsh, 1997; Valdois et al., 2014; Widmann et al., 2012).

Dyslexia is moderately to highly heritable (Schumacher et al., 2007) with a multifactorial etiology (Fisher and DeFries, 2002) and a complex underlying genetic architecture. Evidence exists for multiple genes to contribute to the phenotype, with considerable genetic heterogeneity across individuals (Carrion-Castillo et al., 2013). Dyslexia is linked to several risk loci including nine so-called *DYX*-regions (*DYX1-DYX9*) (Carrion-Castillo et al., 2013; Giraud and Ramus, 2013; Peterson and Pennington, 2012; Poelmans et al., 2011), but a consistent genome-wide association is still missing. However, *DYX2* on chromosome 6 is the best replicated susceptibility locus (Gabel et al., 2010), with *DCDC2* (Lind et al., 2010; Ludwig et al., 2008; Meng et al., 2005; Newbury et al., 2011; Scerri et al., 2011; Schumacher et al., 2006; Wilcke et al., 2009) as well as *KIAA0319* (Cope et al., 2005; Francks et al., 2004; Harold et al., 2006; Kaplan et al., 2002; Luciano et al., 2007; Meng et al., 2005; Paracchini et al., 2008; Scerri et al., 2011) as strongest candidate genes of this locus. Numerous studies evaluate the genetic origin of dyslexia, excellently compiled in recent reviews (Carrion-Castillo et al., 2013; Giraud and Ramus, 2013).

Despite considerable progress, complex gene-brain relations of *KIAA0319* and *DCDC2* are far from comprehensive, because studies elucidating the genes' impact on cell anatomy and systems physiology are scarce. Animal experiments associate the functional role of both genes with neuronal migration (Burbridge et al., 2008; Meng et al., 2005; Paracchini et al., 2006; Peschansky et al., 2010) and, thus, a role in the formation of the neuronal cell assemblies during brain development. Furthermore, both genes are expressed in mature neurons after migration and contribute to protein binding.

More specifically, *KIAA0319* encodes an integral transmembrane protein (Velayos-Baeza et al., 2010), and is a component in the early endosome, its membrane and the plasma membrane, possibly supporting a broader spectrum of signaling functions. In addition to neuronal migration, *KIAA0319* is associated with a negative regulation of dendrite development. It regulates processes that stop, prevent or reduce the frequency, rate or extent of dendrite development (http://www.ncbi.nlm.nih.gov/gene/9856; Gene ID: 9856, updated on 6-Mar-2016). Animal studies indicated that in utero RNA interference (RNAi) targeting *Kiaa0319* in male Wistar rats affected acoustic discrimination abilities of complex stimuli, which was associated with formation of heterotopias in white matter (Szalkowski et al., 2013). Electrophysiologically, a downregulation of *Kiaa0319* expression was followed by a decreased response consistency to sound stimuli as measured from neurons in the primary auditory cortex, resulting in a reduced neuronal discrimination ability (Centanni et al., 2014a,b).

At the cellular level *DCDC2* is involved in processes such as cellular defense response, dendrite morphogenesis, intracellular signal transduction, regulation of smoothened signaling pathway, regulation of Wnt signaling pathway, and regulation of cilium assembly. At the systems level, *DCDC2* is correlated with visual learning and sensory perception of sound. *DCDC2* is a component of axoneme, cytoplasm, cytoskeleton, kinocilium, nucleus and primary cilium. The doublecortin domain, to which *DCDC2* belongs, has been shown to bind tubulin and enhance microtubule polymerization. Its function may affect the signaling of primary cilia (http://www.ncbi.nlm.nih.gov/gene/51473; Gene ID: 51473, updated on 6-Mar-2016). *DCDC2* has been reported to be a deafness gene in a Tunisian family motivated by the considerations that hair cell kinocilia and cell primary cilia length regulation is likely influenced by *DCDC2's* role in microtubule formation and stabilization (Szalkowski et al., 2012). *Dcdc2* knockout mice showed a deficit in rapid auditory processing (Truong et al., 2014), which is consistent with the observation of degraded neural spike timing and, thus, difficulties in the encoding of rapid sequential sensory input as measured in the somatosensory cortex in the same mutants (Che et al., 2014).

Taken together, auditory processing deficits have been linked to gene homologues for both genes (Centanni et al., 2014a,b; Szalkowski et al., 2012; Truong et al., 2014). The physiological consequence of altered functions of *KIAA0319* and *DCDC2* is linked to imprecise neuronal temporal coding. It is plausible to assume that an imprecise encoding of acoustic input leads to processing deficits of ascending speech signals challenging the formation of robust phoneme representations in long-term memory. Thus, a temporal processing deficit might prevent the uncomplicated acquisition and consolidation of literacy skills as suggested by dominating theories (Goswami, 2011; Tallal, 2012).

A huge body of brain-behavior association studies report altered structural and functional correlates pointing to irregular auditory and phonological processes in dyslexia (Banai et al., 2005; Díaz et al., 2012; Hämäläinen et al., 2013; Hornickel and Kraus, 2013; Kujala et al., 2006; Paulesu et al., 2014; Schulte-Körne and Bruder, 2010). Several brain-gene studies considered *KIAA0319* and *DCDC2* in the context of literacy. Late electrophysiological responses to speech sounds (300–700 ms) are affected in rare variants in a region between *KIAA0319* and *DCDC2* (Czamara et al., 2010). A *KIAA0319/TTRAP/THEM2* locus was associated with a reduced left-hemispheric functional asymmetry of posterior superior temporal sulcus during reading (Pinel et al., 2012). The *KIAA0319* single nucleotide polymorphism rs2143340 was related to activation in the bilateral supramarginal gyri during a word rhyming task (Cope et al., 2012). In the same study, alleles of a *DCDC2* complex tandem repeat were related to activation in the right lateral occipital temporal gyrus and the left supramarginal gyrus. These gene-related abnormal functional activations in the parietal lobes are consistent with the *DCDC2*-related reduced white matter volume, and a degraded cortical thickness in the same region (Darki et al., 2014).

The impact of dyslexia risk genes on early auditory processing is currently unknown. Interestingly, the sensation related processing of speech sounds has been found to be noisy at a very early stage in the auditory pathway of poor readers. Speech evoked brainstem responses (cABRs) were unstable and indistinctive in poor readers and in children with poor phonological skills (Banai et al., 2005; Chandrasekaran et al., 2009; Hornickel et al., 2009; Hornickel and Kraus, 2013; Strait et al., 2011; White-Schwoch and Kraus, 2013). Particularly striking is the sensitivity of cABRs in the phase of the formant transition of a given stimulus (Hornickel and Kraus, 2013). Formant transitions are fast changes of frequency bands that constitute important phonetic features because a correct encoding of formant transitions enables us to distinguish between stop consonants. Ultimately, we investigated how the two prominent dyslexia susceptible genes *DCDC2* and *KIAA0319* relate to the stability of speech-evoked brainstem responses in the phase of the formant transition of the syllable [da], which has been reported to be an electrophysiological marker of dyslexia in the early auditory pathway (Hornickel and Kraus, 2013). Here, we provide the first evidence that the dyslexia-associated gene *KIAA0319* affects response consistency in the auditory brainstem and, thus, impairs phoneme encoding at a very early stage in the auditory pathway.