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Research report

The *DCDC2*/intron 2 deletion and white matter disorganization: Focus on developmental dyslexia

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ABSTRACT

Introduction: The *DCDC2* gene is involved in neuronal migration. Heterotopias have been found within the white matter of *DCDC2*-knockdown rats. A deletion in *DCDC2*/intron 2 (*DCDC2*d), which encompasses a regulatory region named 'regulatory element associated with dyslexia 1' (READ1), increases the risk for dyslexia. We hypothesized that *DCDC2*d can be associated to alterations of the white matter structure in general and in dyslexic brains.
Methods: Based on a full-factorial ANCOVA model, we investigated voxel-based diffusion tensor imaging data of four groups of subjects: dyslexia with/without *DCDC2*d, and normal readers with/without *DCDC2*d. We also tested *DCDC2*d effects upon correlation patterns between fractional anisotropy (FA) and reading scores.
Results: We found that FA was reduced in the left arcuate fasciculus and splenium of the corpus callosum in subjects with *versus* without *DCDC2*d, irrespective of dyslexia. Subjects with dyslexia and *DCDC2*d showed reduced FA, mainly in the left hemisphere and in the corpus callosum; their counterpart without *DCDC2*d showed similar FA alterations. Noteworthy, a conjunction analysis in impaired readers revealed common regions with lower

Abbreviations: VB, voxel-based; DTI, diffusion tensor imaging; FA, fractional anisotropy; *DCDC2*d, *DCDC2*/intron 2 deletion; READ1, regulatory element associated with dyslexia 1; DYS+, subjects with dyslexia with *DCDC2*d; DYS−, subjects with dyslexia without *DCDC2*d; NR+, normal readers with *DCDC2*d; NR−, normal readers without *DCDC2*d

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FA mainly in the left hemisphere. When we compared subjects with dyslexia with *versus* without *DCDC2*d, we found lower FA in the inferior longitudinal fasciculus and genu of the corpus callosum, bilaterally. Normal readers with *versus* without *DCDC2*d had FA increases and decreases in both the right and left hemisphere.

Discussion: The major contribution of our study was to provide evidence relating genes, brain and behaviour. Overall, our findings support the hypothesis that *DCDC2*d is associated with altered FA. In normal readers, *DCDC2*-related anatomical patterns may mark some developmental cognitive vulnerability to learning disabilities. In subjects with dyslexia, *DCDC2*d accounted for both common – mainly located in the left hemisphere – and unique – a more severe and extended pattern – alterations of white matter fibre tracts.

1. Introduction

A disturbance in the genetically driven developmental mechanisms of early neuronal migration is at the basis of several neurodevelopment disorders, including developmental dyslexia (hereafter: dyslexia; Diaz & Gleeson, 2009). Dyslexia is an aetiologically heterogeneous condition, typically diagnosed in the first school years, characterized by an impaired reading acquisition in spite of adequate neurological and sensorial conditions, educational opportunities, and normal intelligence. Following earlier descriptions of high familial aggregation of the disorder, substantial heritability has been reported, with estimates across dyslexia and related quantitative traits (such as reading and spelling) ranging from .18 to .72 (Plomin & Kovas, 2005). A multifactorial threshold model of inheritance, whereby multiple genetic and environmental factors contribute to phenotypic variation, has been found as the most plausible mode of familial transmission of the disorder (Plomin & Kovas, 2005).

The *DCDC2* gene has been recognized as one of the leading risk genes in dyslexia (Brkanac et al., 2007; Cope et al., 2012; Deffenbacher et al., 2004; Harold et al., 2006; Marino et al., 2012; Meng et al., 2005; Newbury et al., 2011; Powers et al., 2013; Schumacher et al., 2006; Wilcke et al., 2009; Zhong et al., 2013), and in reading abilities in the normal range (Lind et al., 2010; Scerri et al., 2011), even though negative results have been also reported (Becker et al., 2014; Ludwig et al., 2008; Parracchini et al., 2011). Data show that the *DCDC2* gene is involved in neuronal migration and is most highly expressed in the entorhinal cortex, inferior and medial temporal cortex, hypothalamus, amygdala and hippocampus (Meng et al., 2005). The embryonic knockdown of the *DCDC2* function in rodent neocortical progenitor cells results in postnatal small and scattered heterotopias within the white matter (Burbridge et al., 2008). The specific function of the Dcdc2 protein in neuronal migration has yet to be elucidated, but analyses of its protein structure provide some clues. It was found that Dcdc2 exhibits the same functional features displayed by the Dclk and Dcx proteins, which have been found to have a role in the axonal growth across the corpus callosum, and in neuronal migration within the cerebral cortex (Coquelle et al., 2006; Deuel et al., 2006; Koizumi, Tanaka, & Gleeson, 2006). A highly polymorphic, short-tandem repeat (named BV677278) located in the intron 2 of the *DCDC2* gene was reported (Meng et al., 2005), for which a role as a regulatory region has been suggested (Meng et al., 2011). Recently, Powers et al. (2013) identified the BV677278-binding protein as the transcription factor ETV6, confirmed BV677278 as a regulatory element, and proposed a new name for BV677278, i.e., regulatory element associated with dyslexia 1 (READ1). As such, READ1 could substantially influence the function of the *DCDC2* gene in neuronal migration. Noteworthy, a rare *DCDC2* variant, i.e., a *DCDC2*/intron 2 deletion embedding READ1 (*DCDC2*d), was found to increase the risk of dyslexia by independent studies (Brkanac et al., 2007; Cope et al., 2012; Harold et al., 2006; Marino et al., 2012; Wilcke et al., 2009) although negative findings have also been reported (Ludwig et al., 2008; Powers et al., 2013). Interestingly, in healthy adult humans *DCDC2*d has been found associated with altered grey matter volumes in specific cortical regions (Meda et al., 2008), several of which correspond to those found altered by post-mortem studies of dyslexia (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985). Furthermore, in adult healthy humans allelic variation in the *DCDC2* gene has been associated with individual differences in fibre tracts – as those connecting the left medial temporal gyrus with the angular and supramarginal gyri, the superior longitudinal fasciculus as well as the corpus callosum (Darki, Peyrard-Janvid, Matsson, Kere, & Lingberg, 2012) – which are commonly found altered in neuroimaging studies of reading and dyslexia (Vandermosten, Boets, Wouters, & Ghesquière, 2012; Wandell & Yeatman, 2013; Fig. 1 and Table 1).

Neuroimaging studies have consistently revealed that dyslexia is linked to alterations of a left-hemispheric network, including the inferior frontal, temporo-parietal and occipito-temporal cortical regions (Brambati et al., 2004, 2006; Silani et al., 2005). The first two regions constitute a dorsal phonological route, whereas the occipito-temporal region hosts a ventral orthographical route. Furthermore, some studies suggest a role of the corpus callosum that drives the left lateralization of the reading network (Linkersdorfer, Lonnemann, Lindberg, Hasselhorn, & Fiebach, 2012; Richlan, Kronbichler, & Wimmer, 2013; Vandermosten et al., 2012; Wandell & Yeatman, 2013). The recent computational methods that allow the study of brain structural properties via magnetic resonance imaging (MRI), such as voxel-based diffusion tensor imaging (VB-DTI) techniques, have greatly

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