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Research report

KIAA0319 promoter DNA methylation predicts dichotic listening performance in forced-attention conditions

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ABSTRACT

Language lateralization is one of the most prominent examples of functional hemispheric asymmetries. Previous studies indicate a significant contribution of factors not related to DNA sequence variation on the development of language lateralization, but the molecular processes underlying this relation are unclear. The Brandler-Paracchini model of hemispheric asymmetries assumes that genes involved in the establishment of ciliogenesis and bodily asymmetries also affect functional hemispheric asymmetries. Thus, genes implicated in this model represent a key target for epigenetic modulation of language lateralization. Here, we analyzed DNA methylation in the *KIAA0319* (a gene involved in dyslexia and ciliogenesis) promoter region to investigate whether epigenetic markers of language lateralization can be identified in non-neuronal tissue. We found sex-specific effects of DNA methylation in single CpG sites on language lateralization in the forced-left (FL) and the forced-right (FR), but not on language lateralization in the non-forced (NF) condition of the dichotic listening task. These findings suggest that DNA methylation patterns in the *KIAA0319* promoter region might be associated with cognitive control processes that are necessary to perform well in the forced-attention conditions. Furthermore, the assumption of an association between genes involved in ciliogenesis and the ontogenesis of functional hemispheric asymmetries is supported.

1. Introduction

The vertebrate brain is divided into two hemispheres on the neuroanatomical level, which has wide implications on the functional level. Functional hemispheric asymmetries, i.e. performance differences between the left and right hemisphere, were initially thought to be uniquely human and determined by a single gene [1,2]. However, recent research indicates that hemispheric asymmetries are present in a large variety of species [3] and are influenced by multiple genetic [4] as well as multiple non-genetic factors [5]. Diverse aspects of hemispheric asymmetries have been shown to relate to a number of important aspects of cognitive neuroscience like language, perception, and emotional processing [6]. One of the most prominent examples of functional hemispheric asymmetries is language lateralization, the fact that there is a left-hemispheric dominance for language processing in 96% of strong right-handers (but only 73% of strong left-handers) [7]. Several studies have shown associations of language lateralization with genetic variants, for example in *KIAA0319* [8], *GRIN2B* [9], *CCKAR* [10], and *FOXP2* [11]. However, each of these candidates explains only a small fraction of interindividual variance. This is in line with a genetic linkage study indicating moderate heritability ($h^2 = 0.31$) of the trait [12]. For the dichotic listening task, the most widely used paradigm measuring language lateralization, it has been shown that cognitive control processes display moderate heritability whereas language lateralization itself shows low heritability at best [13]. These findings are in line with a significant contribution of non-genetic factors on language lateralization, but the molecular determinants are not well understood.

On the molecular level, environmental factors can affect cellular or behavioral phenotypes via epigenetic modifications modulating gene expression without changing the DNA sequence [14]. Among epigenetic modifications, DNA methylation is by far the best-characterized: The transfer of a methyl group to the C5 position of cytosine guanine (CpG) dinucleotides in a gene promoter typically results in reduced transcription of this gene [15]. DNA methylation has been shown to play a critical role in neurogenesis [16], synaptic transmission [17], learning and memory [18], but also in neurodegeneration [19] and mental disorders [20]. It has been proposed that DNA methylation in neuronal, but also in peripheral tissue reflects environmental influences and represents an informative biomarker for CNS-related traits [21]. As

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findings from genetic studies suggest a strong influence of non-genetic factors in the development of language lateralization, investigating promoter regions of relevant genes is promising to yield insights into its molecular determinants.

The Brandler-Paracchini model of hemispheric asymmetries assumes that genes involved in the establishment of ciliogenesis and bodily asymmetries also influence the early development of brain midline structures such as the *corpus callosum*, which then affects the development of reading ability or language lateralization [22,23]. In contrast to early single gene models of hemispheric asymmetries [1,2] the Brandler-Paracchini model is supported by molecular genetic evidence. Genes associated with handedness in subjects with and without dyslexia – a condition accompanied by reduced gray [24] and white matter asymmetries [25] – cause ciliopathies, heterotaxia, and situs inversus in knock-out mice [26]. Ciliopathies on the other hand result not only in altered bodily asymmetries but also in hypoplasia or agenesis of the *corpus callosum* [27]. These findings suggest that among the genes determining functional hemispheric asymmetries, some are also involved in the development of bodily asymmetries [26]. Moreover, candidate genes for dyslexia susceptibility like *DCDC2* [28,29], *DYX1C1* [30], and *KIAA0319* [31–34] are co-expressed in cilia [35]. A 77 kb spanning region on chromosome 6p22 including *ACOT13* and *TDP2* (formerly known as *THEM2* and *TTRAP*) and the first four exons of *KIAA0319* has repeatedly been associated with dyslexia [32] and reading ability in the general population [36,37]. More importantly, this chromosomal region has been directly associated with language dominance in healthy adults. Within the *KIAA0319/TDP2/ACOT13* region, a single nucleotide polymorphism (SNP; rs17243157 G/A; see Fig. 1) was significantly associated with left-lateralized activation of the posterior superior temporal sulcus (pSTS) during a reading and a speech listening task. Interestingly, those subjects bearing the gene variants associated with an elevated risk of dyslexia showed reduced pSTS asymmetry. The authors concluded that *KIAA0319* might be important for asymmetrical language processing in the pSTS [8].

Gene expression studies revealed that a risk haplotype for dyslexia within the *KIAA0319/TDP2/ACOT13* region (major allele of rs4504469 and rs2038137, minor allele of rs2143340, see Fig. 1) reduces *KIAA0319* gene expression by about 40% [33]. It was further shown that the minor allele (dyslexia risk allele) of rs9461045 in the region immediately upstream of *KIAA0319* (see Fig. 1) likely reduces *KIAA0319* gene expression [38]. *Kiaa0319* gene expression is essential for neocortex development in rats, as suppressed gene expression leads to impaired neuronal migration [33], reduced midsagittal corpus callosum volume [39], and impaired processing of complex auditory stimuli [40,41]. *KIAA0319* gene expression could thus represent an important step in the ontogenesis of dyslexia and altered hemispheric asymmetries.

KIAA0319 gene expression is not only regulated by DNA variations, but also by DNA methylation [42]. Recent studies have revealed some evidence for influences of DNA methylation on hemispheric asymmetries. For example, expression of numerous genes is considerably stronger in the right compared to the left fetal spinal cord at the starting point of rightward asymmetries in arm movements. Interestingly, asymmetries in gene expression coincided with opposed asymmetries in DNA methylation and miRNA expression [43]. The investigation of DNA methylation from buccal cells of healthy adults revealed that elevated DNA methylation in CpG stretches within the promoter region of *LRRTM1*, a promising candidate gene for handedness ontogenesis, is related to mixed-handedness, especially in females [44]. Taken together, these results strongly argue for a role of epigenetic processes in the development of hemispheric asymmetries.

We therefore investigated whether DNA methylation in the *KIAA0319* promoter region predicts language lateralization in healthy adults. The original dichotic listening task consists of consonant-vowel syllables presented to the left and right ear in homonym and dichotic stimulus pairs. As the subject is instructed to report the syllable he or she heard best in each trial, hemispheric dominance is assumed for the hemisphere contralateral to the more frequently reported – typically the right – ear. In later studies, two forced-attention conditions have been added in which the subject is instructed to only attend to input from the left ear and from the right ear, respectively. These additional conditions allow for the investigation of top-down attentional modulation [45]. The forced-left (FL) condition is suggested to induce a cognitive conflict, as bottom-up processing favors the more salient right ear, while top-down processing favors the left ear [46]. This makes the FL condition the most cognitively demanding, which also manifests in distinct activations in the left inferior prefrontal gyrus and caudate nucleus as revealed by fMRI [47]. In contrast, in the forced-right (FR) condition both bottom-up and top-down processing favor the more salient right ear. Thus, the two processing strategies are congruent, which reduces the need for cognitive control strategies compared to the FL condition [46].

In the context of the Brandler-Paracchini model of hemispheric asymmetries, we hypothesized that DNA methylation in the *KIAA0319* promoter region predicts language lateralization in the non-forced (NF) dichotic listening condition. However, *KIAA0319* is not only associated with language lateralization per se, but has been found to affect language-related cognitive skills [48,49] and executive functions [50]. Therefore, an involvement of DNA methylation in the *KIAA0319* promoter region in language lateralization in the forced-attention conditions (FL and FR) was also hypothesized.

2. Material and methods

2.1. Participants

59 healthy participants of Caucasian descent and free from neurological or psychiatric diseases took part in the study. The sample was

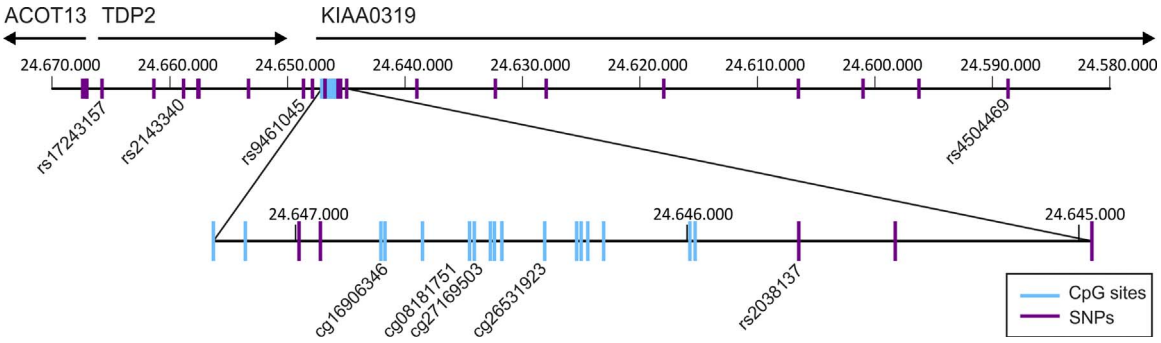

Fig. 1. The 77 kb *KIAA0319/TDP2/ACOT13* region associated with dyslexia by Francks et al. [32]. Depicted are all CpG sites analyzed in this study (turquoise) and SNPs associated with dyslexia in the studies by Dennis et al. [38], Francks et al. [32], Paracchini et al. [33], and Pinel et al. [8] (magenta). CpG sites and SNPs mentioned in the text are depicted with their corresponding names. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)