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Original article

Polymorphic variation in the epigenetic gene *DNMT3B* modulates the environmental impact on cognitive ability: A twin study

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ABSTRACT

Background: Though cognitive abilities in adulthood are largely influenced by individual genetic background, they have also been shown to be importantly influenced by environmental factors. Some of these influences are mediated by epigenetic mechanisms. Accordingly, polymorphic variants in the epigenetic gene *DNMT3B* have been linked to neurocognitive performance. Since monozygotic (MZ) twins may show larger or smaller intrapair phenotypic differences depending on whether their genetic background is more or less sensitive to environmental factors, a twin design was implemented to determine if particular polymorphisms in the *DNMT3B* gene may be linked to a better (worse) response to enriched (deprived) environmental factors.
Methods: Applying the variability gene methodology in a sample of 54 healthy MZ twin pairs (108 individuals) with no lifetime history of psychopathology, two *DNMT3B* polymorphisms were analyzed in relation to their intrapair differences for either intellectual quotient (IQ) or working memory performance.
Results: MZ twin pairs with the CC genotype for rs406193 SNP showed statistically significant larger intrapair differences in IQ than CT pairs.
Conclusions: Results suggest that *DNMT3B* polymorphisms may explain variability in the IQ response to either enriched or impoverished environmental conditions. Accordingly, the applied methodology is shown as a potentially valuable tool for determining genetic markers of cognitive plasticity. Further research is needed to confirm this specific result and to expand on other putative genetic markers of environmental sensitivity.

1. Introduction

Interindividual differences in adult cognitive abilities are highly influenced by genetic background [19,21]. However, environmental influences and gene-environment interactions have also been suggested to play an important role in shaping cognition [30,38,47,62]. Of note, the popular concept of cognitive plasticity refers to changes in cognitive performance in response to experience, rising from either structured education/training or other environmental factors [31,44].

In this context, determining whether individuals with a given genetic background are more sensitive to external influences which modify cognitive traits can be achieved by the variability gene methodology. The concept of "variability gene" [8,9] was first

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introduced in the field of human genetics to label genes contributing to phenotypic variation (individual differences) rather than affecting the mean level of a trait in a population.

Variability genes as a proxy for cognitive plasticity may constitute an important issue in epidemiological research. Their study may allow not only identifying people with high capability of response to training or other interventions, but at the same time determining which individuals are particularly prone to cognitive deficits after potential environmental deprivation/insults. Also, research findings have been reported on the relationship between polymorphic genetic variants and response to cognitive training [5,61,76]. In this regard, the variability gene approach has (in principle) the additional advantage of testing gene-environment interactions through recognizing polymorphic variants which may be associated to either better or worse cognition depending on the environment. To the knowledge of authors, the use of this methodology in cognitive research is still lacking, even though similar genetically informative designs have shown a role for genetic variants in supporting cognitive plasticity and/or flexibility [29,46,77].

The main conceptual and methodological approach in variability gene studies is the assessment of intrapair differences in monozygotic (MZ) twins in relation to their genotype for a particular polymorphic variant. Since MZ twins of a pair have almost identical DNA sequences, this approach postulates that duos having a specific genetic background would display larger intrapair differences than other pairs with distinct genes: the environment would have a larger or smaller effect depending on the genes with which it interacts. In general, intrapair differences for a phenotype in a MZ twin are assumed to be caused by uniquely environmental influences and stochastic events [80].

The parallel concept of "phenotypic plasticity" has largely been used in disciplines like Biology or Ecology to explain the ability of a single genome/genotype to produce more than one phenotypical trait in response to environmental conditions and hence, give rise to interindividual differences [23,71,84]. The analogous "plasticity gene" term has similarly been underscored [6] in behavioral science since it posits a novel conceptual framework to study gene-environment interactions: rather than engendering susceptibility to deficit, a "plasticity gene" would be part of a genetic structure with high likelihood of either enrichment (from supportive experiences) or impoverishment (from adverse external inputs).

In particular, feasible candidate genetic loci for investigating variability genes in relation to cognitive plasticity may be at genes from the epigenetic machinery. Epigenetics can be defined as the study of heritable changes in gene expression occurring through modulation of the chromatin structure rather than by changes in the DNA sequence [2]. Despite their almost identical DNA sequence, epigenetic differences resulting from exposure to distinct environments can be found within members of a MZ twin pair [41,69]. One of the most widely studied epigenetic mechanisms is DNA methylation. In response to environmental clues, DNA (cytosine-5-)-methyltransferases (DNMT) enzymes catalyze the addition of methyl groups, typically in CpG dinucleotides of DNA regions, thus altering gene expression and cell function [45]. Importantly, there is consistent evidence linking epigenetic processes such as DNA methylation with brain and cognitive plasticity [4,10,39,48]. In this regard, DNA methyltransferase 3B (DNMT3B) is of particular significance, due to its active role in modulating global methylation dynamics and central nervous system development in mammals [24,40,60]. Accordingly, previous neuroscience research has suggested an important role for the DNMT3B protein activity in cognitive plasticity, mainly via covalent modifications to DNA leading to synaptic changes [53,56,78].

Since several reports have been published relating polymorphic variation in genes coding for proteins that regulate epigenetic processes and both neuropsychiatric and neurocognitive disruptions [57], the present study takes as starting point the likewise plausible hypothesis that DNA polymorphisms in the *DNMT3B* gene may contribute to cognitive differences between subjects in response to similar external experiences.

Of note, the *DNMT3B* gene has largely been studied in relation to psychopathology, neurocognition and associated epidemiological variables [16,17,15,34,35,58,64,73,86]. These studies provide some evidence linking *DNMT3B* polymorphisms and risk for cognitive performance deficits and mental health problems. Complementarily, the current work is aimed at determining whether some of these polymorphic variants are likely to cause more permeable cognitive performance (either intellectual quotient (IQ) or working memory (WM)) in healthy individuals. IQ and WM are particularly important in this setting, since both of them have been shown to be permeable to environmental influences such as training [43,50,55]; this is likely influenced by the genetic background [11,75]. It is worth noting that, despite the genetic link between IQ and WM [28], previous research indicates that stimulating better performance in one of them does not necessarily imply improvements in the other [68,74], probably indicating distinct plasticity pathways.

To evaluate the potential role of *DNMT3B* polymorphisms as modulators of the cognitive response to environmental factors, informative single nucleotide polymorphisms (SNPs) were genotyped for a group of 108 MZ twins (54 pairs) from the general population who did not show a lifetime history of (DSM-IV) mental disorders. Intrapair differences in neuropsychological test scores for either IQ or WM were estimated and studied in relation to *DNMT3B* genotypes of each pair.

2. Materials and methods

2.1. Sample description

Twins included in this study were drawn from a larger ongoing twin sample consisting of 242 Caucasian Spanish adult twins (UB Twin Registry) from the general population who gave permission to be contacted for research purposes. Exclusion criteria applied for that sample included age under 17 and over 65, a medical history of neurological disturbance, presence of sensory or motor alterations and current substance misuse or dependence. Written informed consent was obtained from all participants after a detailed description of the study aims and design, approved by the local Ethics Committee.

Peripheral blood or saliva samples were obtained, and zygosity of the pairs was determined by genotyping 16 highly polymorphic microsatellite loci from DNA samples (SSRs; PowerPlex® 16 System Promega Corporation). Identity on all the markers can be used to assign monozygosity with greater than 99% accuracy [33]. From this sample, 186 individuals were members of MZ twin pairs (i.e., there were 93 MZ pairs).

A battery of psychological and neurocognitive tests and medical records and were completed for all participants in face-to-face interviews by trained psychologists. The Structural Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [25] was administered in a face-to-face interview to screen for presence of any lifetime mental disorder. Twin pairs where one or both co-twins met diagnostic criteria for any current or past psychiatric disorder were excluded from the larger 186-MZ-subject sample. Accordingly, 108 healthy twins (54 MZ pairs) were included in all statistical analyses described below. Further recruiting and demographic details of this sample can be found elsewhere [1].

2.2. Neurocognitive assessment

Intelligence quotient (IQ) was estimated from five subtests (block design, digit span, matrix reasoning, information and