

Polymorphisms of the brain-derived neurotrophic factor and cognitive impairment in patients with Alzheimer's disease and mild cognitive impairment

Matea Nikolac Perkovic (1), Fran Brovecki (2), Natasa Klepac (3), Sanja Hajsek (3), Dorotea Muck-Seler (1), Nela Pivac (1)

(1) Division of Molecular Medicine, Rudjer Boskovic Institute, Bijenicka cesta 54, 10 000 Zagreb, Croatia

(2) Department for Functional Genomics, Center for Translational and Clinical Research, University of Zagreb School of Medicine, and University Hospital Center Zagreb, Zagreb, Croatia

(3) Department of Neurology, University Clinical Hospital Center Zagreb, Zagreb University School of Medicine, Zagreb, Croatia.

Introduction

Brain derived neurotrophic factor (BDNF) is a neurotrophin found in different brain areas like hippocampus, neocortex, amygdala, cerebellum and hypothalamus. It affects neurogenesis and synaptic plasticity, neurotransmission mediated by different neurotransmitters, cognition, learning and memory. BDNF modulates dopaminergic, cholinergic and serotonergic neurotransmitter system, regulates food intake, pain sensation, mood, behavior and response to stress. The reduction of the BDNF concentration in different brain areas has been associated with dementia and cognitive decline indicating an important role of this neurotrophin in the development of dementia which is characterized by progressive deterioration of intellectual functioning. Alzheimer disease (AD) is a most common type of dementia characterized by progressive loss of cognitive function. Since there is no cure for AD, the studies of the early phases of AD, that are trying to find new biological markers that could serve as early diagnostic indicators, have pointed out the potential importance of early detection of mild cognitive impairment (MCI). MCI is a disorder that has been associated with risk for AD since it represents a transitional state between normal and pathological aging (characterized with cognitive impairments that lead to dementia).

The aim of this study was to define the role of BDNF in the development of cognitive symptoms of dementia by analyzing five different BDNF polymorphisms, rs6265 (Val66Met), rs11030104, rs7934165, rs1519480 and rs56164415 (C270T) (Figure 1).

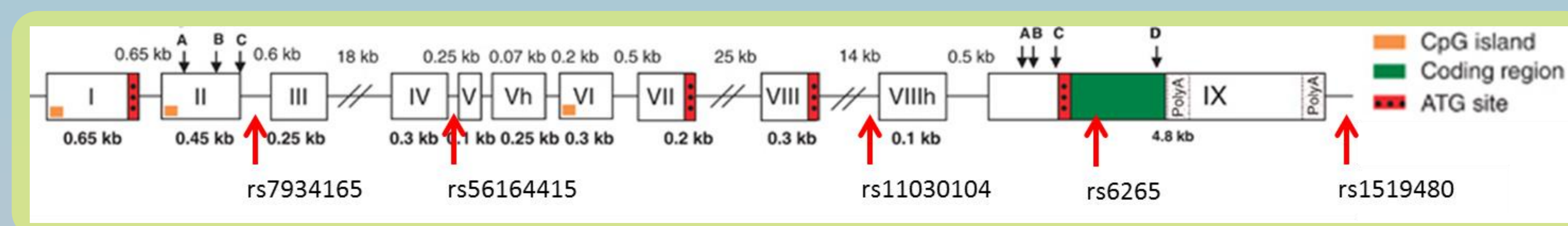


Figure 1. Structure of the human BDNF gene

Methods & Materials

The study investigated the association of the five BDNF polymorphisms, rs6265 (Val66Met), rs11030104, rs7934165, rs1519480 and rs56164415 (C270T), with cognitive impairment. Eighty-two patients with Alzheimer's disease (AD) and 49 patients with mild cognitive impairment (MCI), which presents a high risk condition for AD, were included. Diagnosis of AD was done according to the NINCDS-ADRDA and DSM-IV criteria. Cognitive impairment was evaluated using Mini-Mental Status Examination (MMSE) and Clock Drawing Test (CDT). Genomic DNA was extracted from peripheral blood using the salting out method. SNPs were genotyped with the ABI Prism 7000 Sequencing Detection System apparatus (ABI) using the TaqMan® Pre-designed and Custom TaqMan® SNP Genotyping Assay (Figure 2). The association of these five polymorphisms with cognitive decline in patients with AD or MCI was evaluated using one-way analysis of variance (ANOVA) in Sigma Stat 3.5.

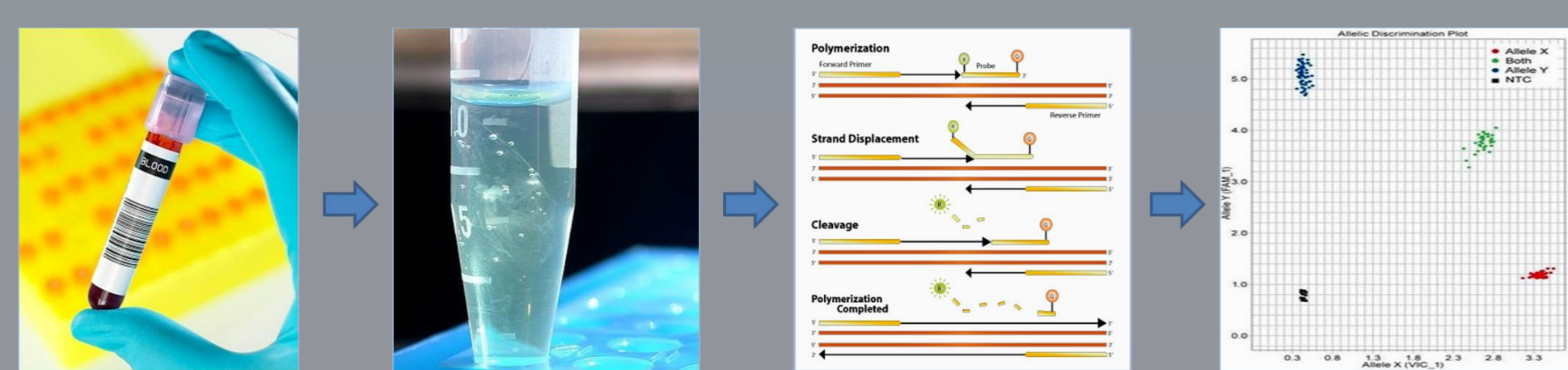


Figure 2. Genotyping procedure

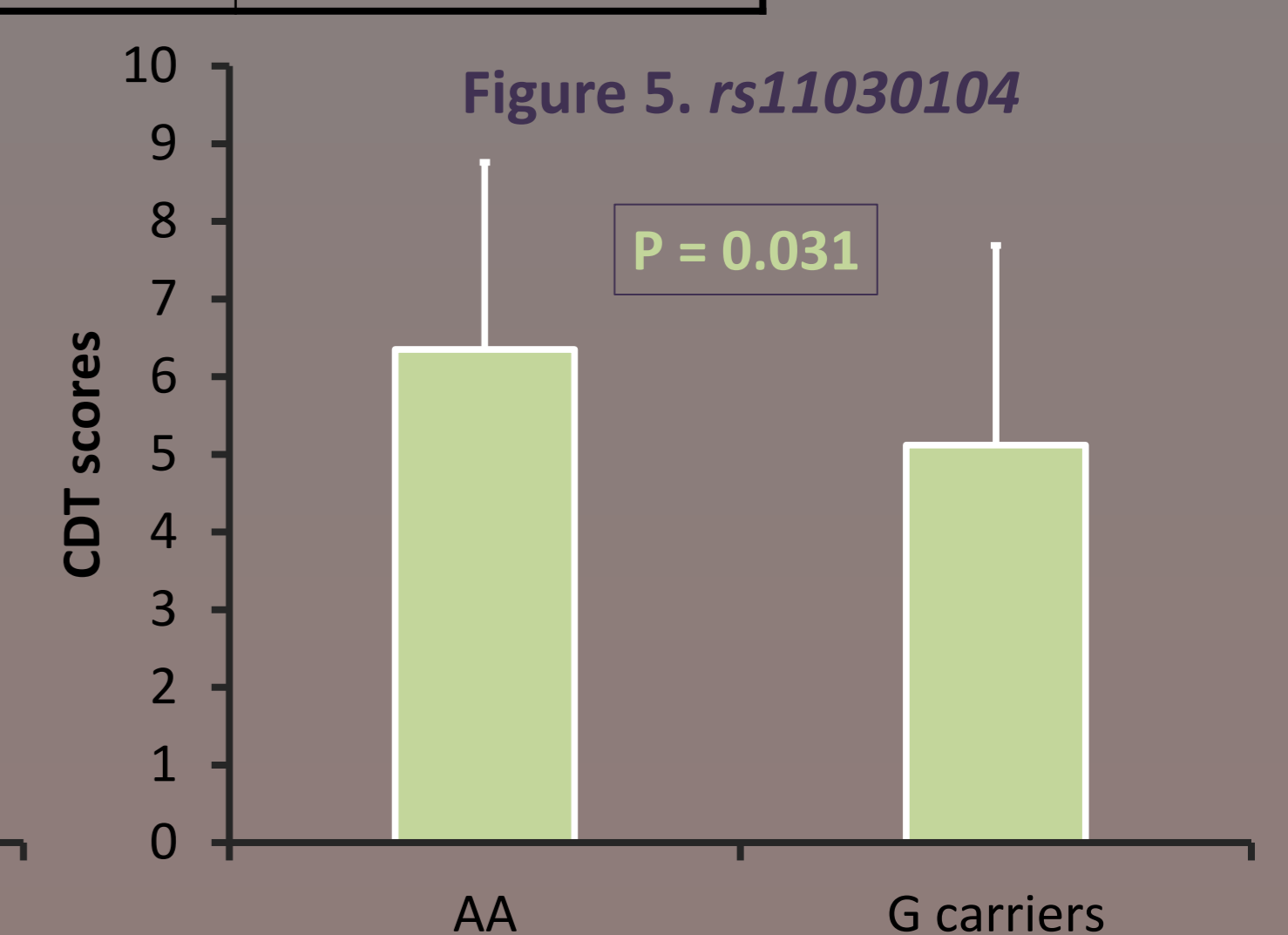
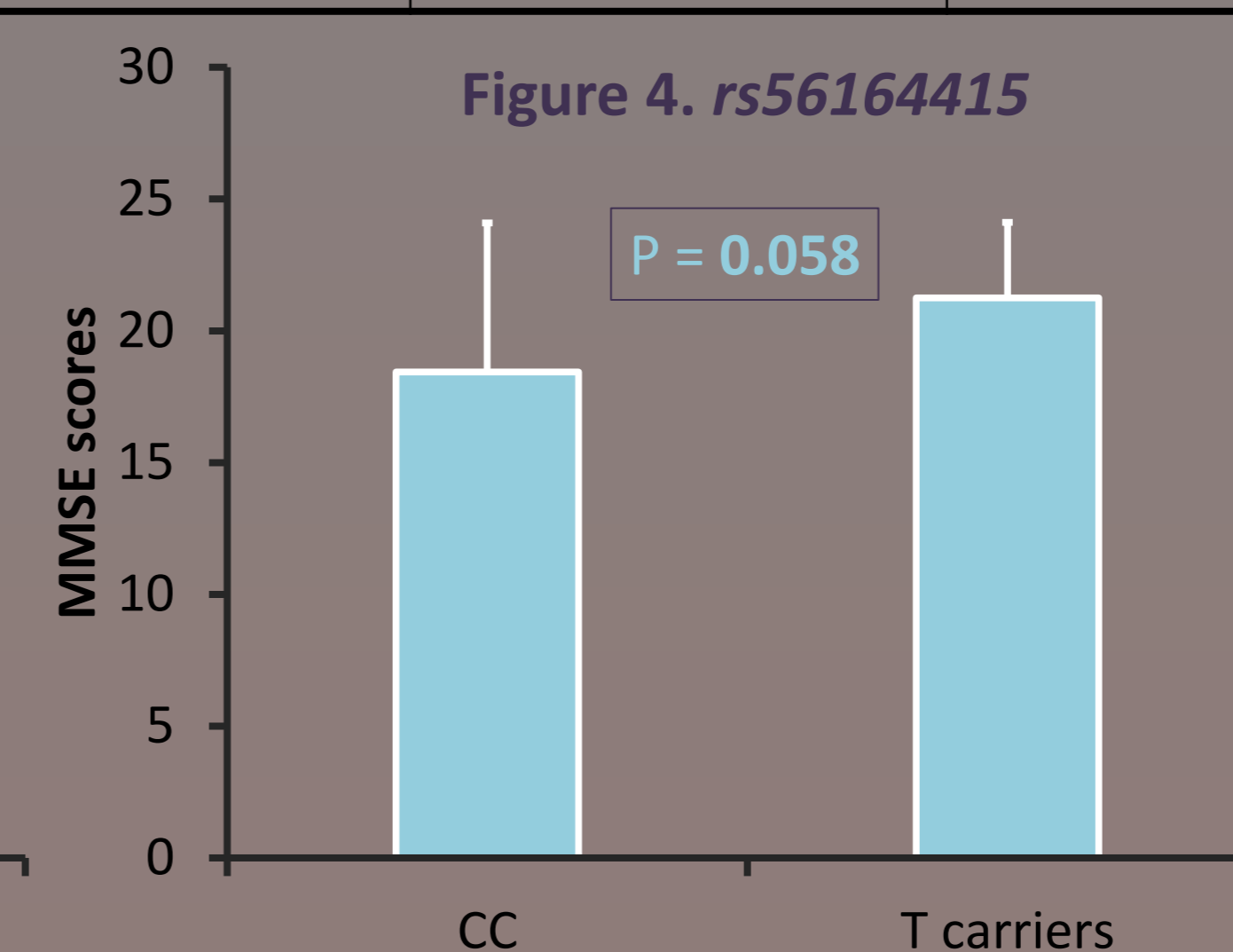
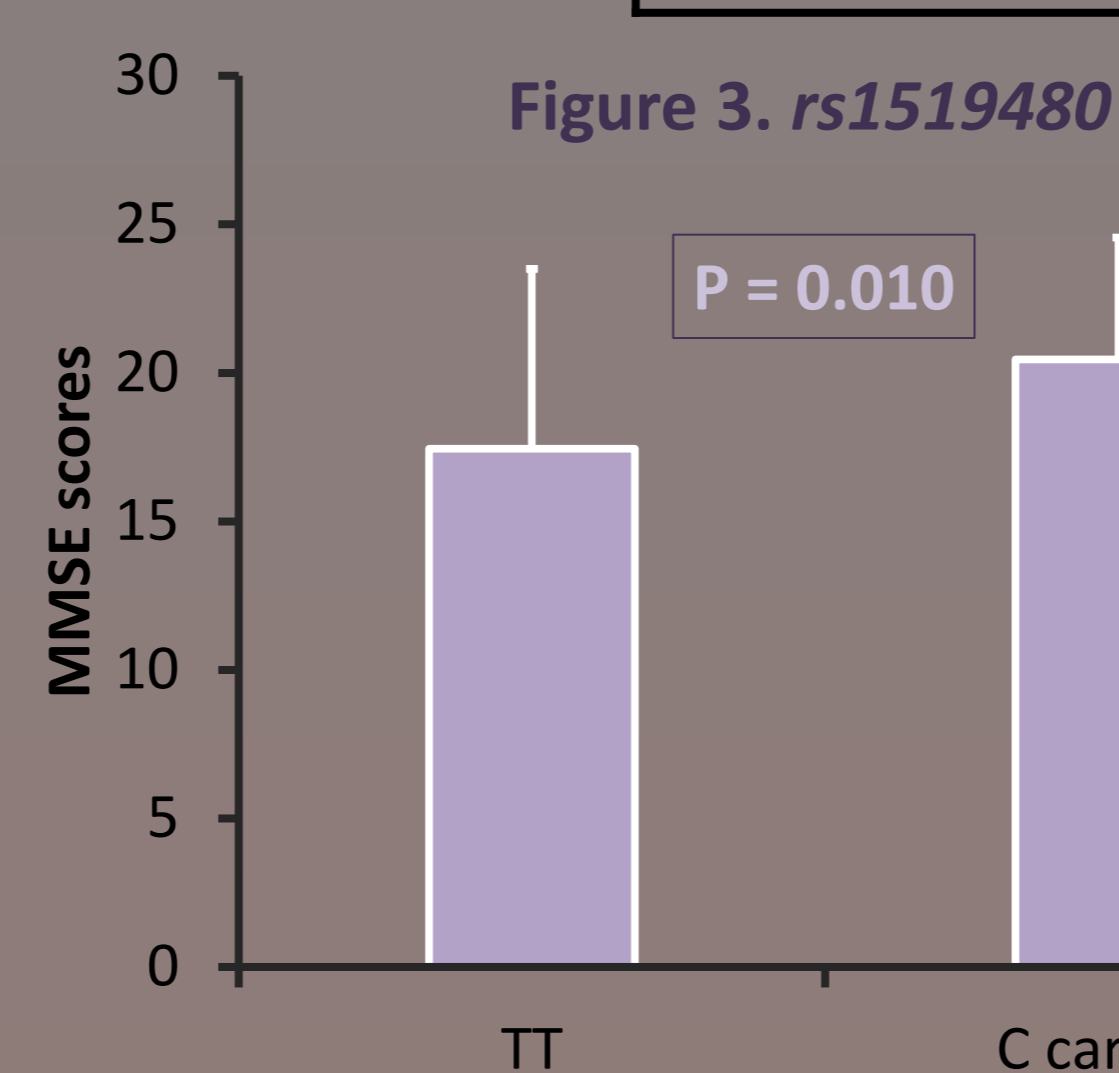
Results

Alzheimer's disease (AD)

Our results showed an association between rs1519480 and MMSE scores in patients with AD (Table 1), and these results were confirmed after dividing the subjects into TT homozygotes and C allele carriers according to the rs1519480 genotype (Figure 3). A marginal association was detected between MMSE scores and rs56164415 (C270T) polymorphism in patients with AD (Table 1), but this association proved to be significant after dividing the subjects into CC homozygotes and T allele carriers (Figure 4). Our results also indicated a significant association between CDT scores and rs11030104 polymorphism (Figure 5).

Table 1. The association of MMSE and CDT scores with BDNF polymorphisms in AD

SNP	MMSE		CDT	
	ANOVA			
	F	P	F	P
rs6265	0.385	0.681	1.502	0.229
rs11030104	0.438	0.647	2.858	0.063
rs7934165	2.070	0.133	0.861	0.427
rs1519480	3.856	0.025	1.496	0.231
rs56164415	3.676	0.059	1.583	0.212

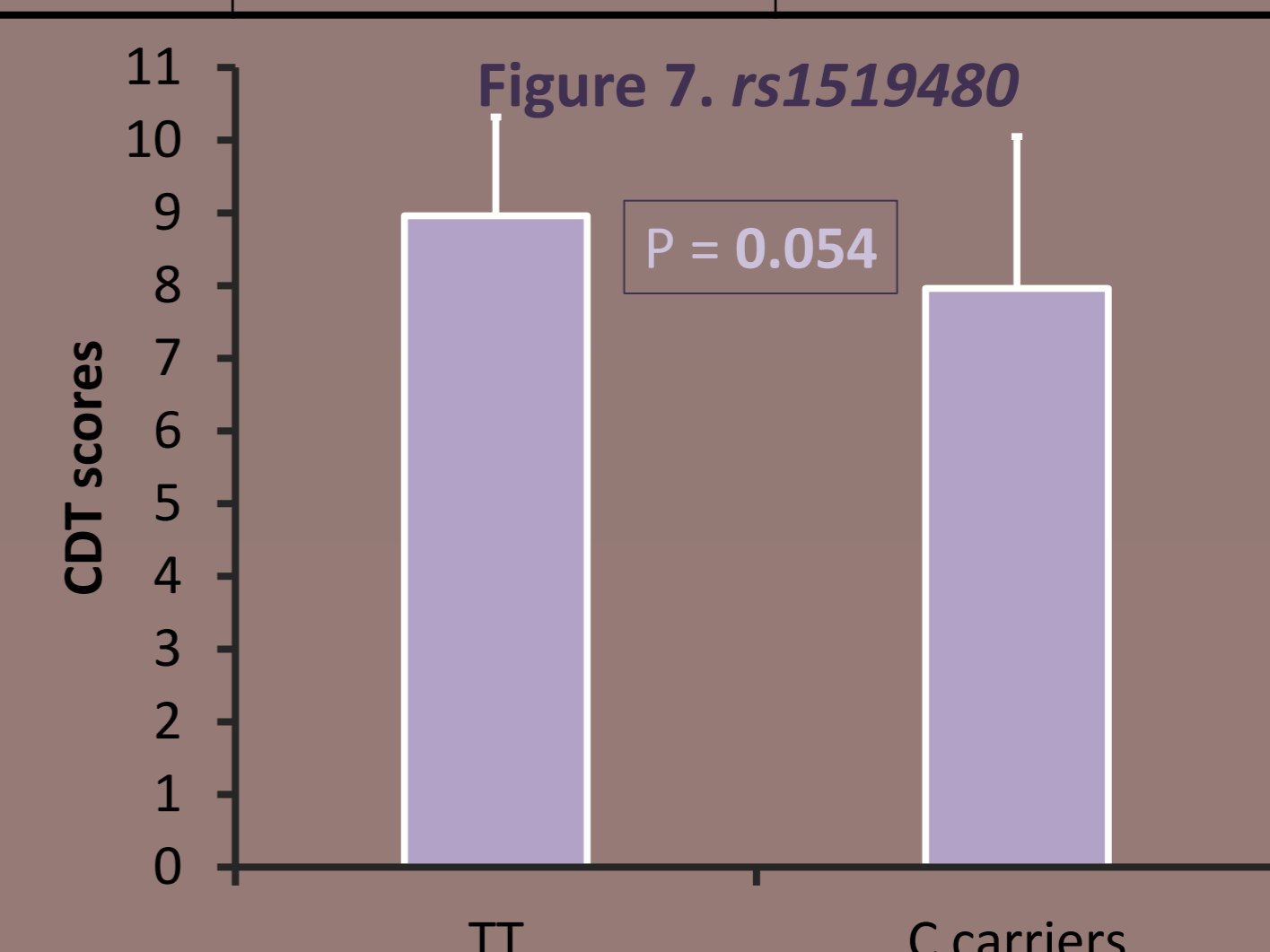
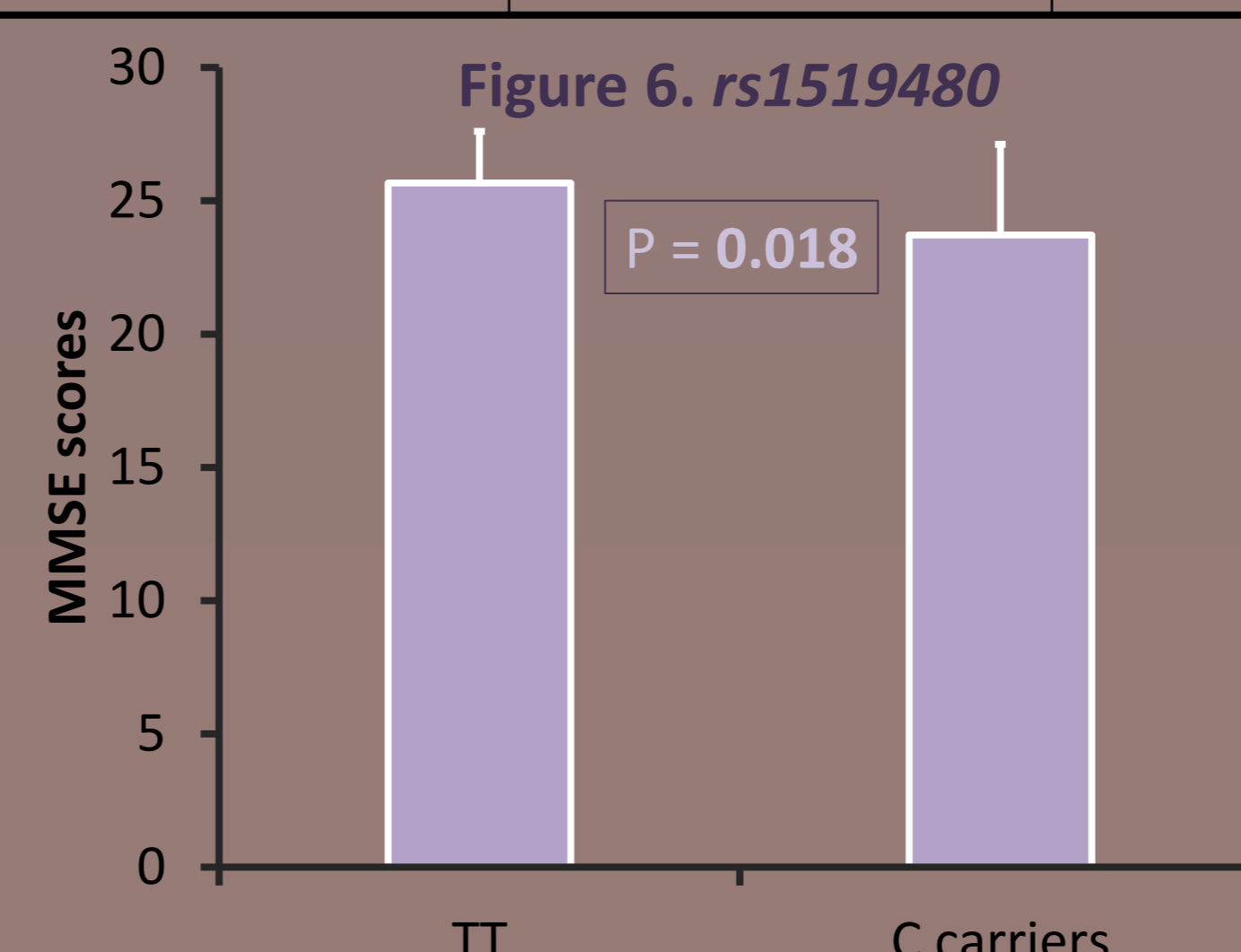


Mild cognitive impairment (MCI)

Our results showed an association between rs1519480 and MMSE and CDT scores in patients with MCI (Table 2). These results were confirmed after dividing the subjects according to the rs1519480 polymorphism into TT homozygotes and C allele carriers (Figure 6 and Figure 7).

Table 2. The association of MMSE and CDT scores with BDNF polymorphisms in MCI

SNP	MMSE		CDT	
	ANOVA			
	F	P	F	P
rs6265	0.860	0.358	0.985	0.326
rs11030104	2.252	0.140	1.039	0.313
rs7934165	0.577	0.566	1.615	0.210
rs1519480	3.270	0.047	5.453	0.007
rs56164415	1.358	0.250	0.242	0.625



Conclusions

The present findings confirmed a major role of BDNF in AD, and revealed a potential role of two selected BDNF polymorphisms (rs1519480 and rs11030104) in cognitive decline that is characteristic for patients with AD and MCI. The rs1519480 might influence BDNF mRNA expression in the prefrontal cortex and contribute to inter-individual variation in cognitive performance, as well as contributing to the risk for developing psychiatric and neurological conditions.