A Role of Cytokine Gene Polymorphisms in Cognitive Functioning

Anastasiya G. Trenova1, Georgi S. Slavov1, Maria G. Manova1, Lyuba D. Miteva2, Spaska A. Stanilova2

1 Department of Neurology, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria
2 Department of Molecular Biology, Immunology and Medical Genetics, Faculty of Medicine, Trakia University, Stara Zagora, Bulgaria

Correspondence:
Anastasiya G. Trenova, Department of Neurology, Faculty of Medicine, Medical University of Plovdiv, 15A Vassil Aprili Blvd., 4002 Plovdiv, Bulgaria
E-mail: atrenova@yahoo.com
Tel: +359 32 602 279

Received: 27 Apr 2017
Accepted: 15 Aug 2017
Published Online: 05 Oct 2017
Published: 30 June 2018

Key words: cytokines, single nucleotide polymorphisms, cognition, dementia

Citation: Trenova AG, Slavov GS, Manova MG, Miteva LD. A role of cytokine gene polymorphisms in cognitive functioning. Folia Med (Plovdiv) 2018;60(2): 191-9. doi: 10.1515/folmed-2017-0094

INTRODUCTION

Amongst the highest brain functions cognition is a matter of growing interest mainly due to the increasing prevalence of socially significant diseases leading to cognitive decline in adults such as neurodegenerative dementias and cerebrovascular disorders. In addition, multiple sclerosis, an immune-mediated disease of the central nervous system, is associated with a high rate (40-70%) of cognitive impairment. In all these conditions genetic predisposition has been established as one of the important etiological factors. Gene polymorphisms are found in more than 1% of the healthy human population. Single nucleotide polymorphisms (SNPs) - deletions, insertions, substitutions - are the most commonly occurring polymorphisms. Depending on their position in the genome, SNPs can affect the gene expression or the functional activity of the encoded protein. The combination of inherited and acquired SNPs determines the individual genotypic characteristics of each person, affects phenotypic features and the risk for developing certain diseases.

Cytokine synthesis is under strict genetic control. Cytokine genes are known to be highly polymorphic genes, but primarily within their protein-non-coding, regulatory sequences. Some cytokine SNPs have no clinical significance but many of them are functional, i.e. changing the gene expression and synthesis of the immune protein. Functional SNPs in cytokine genes are regarded as a possible cause for imbalance in the cytokine production, contributing to various pathological conditions.1

There is a large amount of evidence for participation of immune mechanisms and especially cytokines in neurodevelopment and cognitive functioning in humans. Experimental studies suggest that neurogenesis and synaptic plasticity, which are the cellular mechanisms of cognition, are strongly influenced by various cytokines.2,3 The cytokine effects on these processes seem to be dependent on their concentrations: under physiological conditions interleukine (IL)-1b has maintained long-term...
potentiation (LTP), whereas, higher concentration of IL-1b, under pathological conditions, has inhibited LTP.\(^4,5\) Over-expression of IL-6 by astroglia has been associated with reduction in neurogenesis in the hippocampal dentate gyrus and with neural stem cell dysfunction.\(^6,7\) Endogenous glial-derived TNF-alpha is critical for homeostatic synaptic scaling but pathological levels of the cytokine inhibit LTP in the dentate gyrus of rat hippocampal slices.\(^8\) Limited amounts of IFN-gamma have been shown to enhance neurogenesis.\(^9\) On the other hand, cytokines have been implicated in neurodegenerative processes. TNF-alpha has been shown to alter mitochondrial dynamics, resulting in cell death and through activation of TNF-receptor I to trigger caspase 8 apoptotic pathways. IL-1b can mediate potentiation of the NMDA receptor function and glutamate excitotoxicity in hippocampal neurons.\(^10,11\) Taken together these data raise the question about the role of cytokine gene polymorphisms in cognitive processes in health and disease.

The aim of this review is to summarize the contemporary knowledge about the correlations between different genetic variants of SNPs in cytokine genes and cognitive status in humans.

Various SNPs in several cytokine genes have been investigated in relation to cognitive functions. The most studied in this context are polymorphisms in IL-1b, IL-6, IL-10, IL-17A, IL-18 and TNF-alpha genes. The data obtained from this research are highly divergent.

### EVIDENCE FOR ASSOCIATION BETWEEN SNPS IN CYTOKINE GENES AND DIFFERENT COGNITIVE DOMAINS

Some investigators find association between genetic variants of SNPs and a particular cognitive domain (Table 1). Studies of Beste et al. (2010) in young, healthy adults suggest that attentional processes are affected by the TNF-alpha-308 A/G SNP.\(^12,13\) The A allele has been associated with better attentional processes. The same authors explain these findings with the facilitating effect of TNF-alpha on glutamatergic neural transmission, which has been shown to boost attentional selection processes. Entirely different are the observations of Gadiewski et al. (2013) in elderly people – carriers of A allele of TNF-alpha-308 A/G have shown dysfunction in some aspects of attention.\(^14\) The same allele in the study of Baune et al. (2008) has been associated with better information processing speed.\(^15\) These observations were not confirmed by other authors.\(^16\) Correlation between SNPs in IL-1b gene and memory functions has also been observed. The CT/TT genotype of IL-1b-1418C/T (rs16944) has been significantly associated with poorer memory in the participants of MEMO (Memory and Morbidity in Augsburg Elderly) study.\(^15\) In accordance with this are the findings of Tsai et al. (2010).\(^17\) Significant associations between two other SNPs in IL-1b gene (rs1143634 and rs1143633) and the verbal intelligence quotient have been reported by Sasayama et al. (2011).\(^18\) A study of Marioni et al. (2010) has implicated IL-1a gene polymorphisms rs2856838 and rs3783654 in mental flexibility.\(^19\) SNPs (rs554344 and rs580253) in IL-1b-convertase enzyme (IL1bCE) gene have been reported to influence cytokine production and cognitive functions. Subjects carrying the variants 10643C and 5352A allele in this gene have had significantly lower IL-1b serum levels and homozygous carriers of the same alleles have performed better on all executive function tests in PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) study. In addition, the haplotype with two variants (10643C and 5352A) present has been associated with better executive functions compared to the haplotype without variants. The authors have observed the same trend for memory function.\(^20\)

### A ROLE OF CYTOKINE GENE POLYMORPHISMS FOR AGE-RELATED CHANGES IN COGNITION

Studies have found a link between SNPs and both current cognitive status and its change over time (Table 1). SNPs related to high pro-inflammatory or low anti-inflammatory activity have been revealed as independent risk factors of reduced cognitive function in octogenarians. Subjects homozygous for the IL-18-607G-137C haplotype have shown poorer results on Performance Intellectual Quotient (IQ) subtests of Wechsler Adult Intelligence Scale. The TNF-alpha-308GA genotype has been related to a lower Verbal IQ-score and the IL-10-592 CC genotype has been associated with better Verbal IQ at the age of 80. TNF-308GA heterozygotes have had a more marked decline in Full IQ score from age 80 to age 85 and the same tendency has been observed for Verbal IQ in IL-10-592CC homozygotes.\(^21\) The correlation between four polymorphisms in IL-10 gene and cognition has also been assessed in the participants of PROSPER study. Carriers of the 4259G and -2849A variants performed worse on all cognitive domains. The same tendency has been observed for -1082A and -592A carriers but no
Table 1. Studies investigating association between cytokine gene polymorphisms and cognitive performance

| Gene       | Polymorphism          | Study population                                                                 | Cognitive functions                                      | Presence of association | Author                  |
|------------|-----------------------|----------------------------------------------------------------------------------|----------------------------------------------------------|-------------------------|-------------------------|
| TNF-alpha  | -308 A/G rs1800629    | 369 Caucasian participants aged 65 years and older                               | Information processing speed                              | Yes                     | Baune et al., 2008     |
| TNF-alpha  | -308 A/G rs1800629    | 96 Caucasian healthy participants; mean age 23.7±4.9 yrs                         | Attention                                                | Yes                     | Beste et al., 2010     |
| TNF-alpha  | -308 A/G rs1800629    | 131 healthy participants; mean age 70.5±4.5 yrs                                   | Attention                                                | Yes                     | Gadjewski et al., 2013 |
| TNF-alpha  | -308 A/G rs1800629    | 125 Asian early-stage breast cancer patients; mean age 50.26±8.82 yrs             | Attention, Memory, Processing speed, Response speed       | No                      | Chae et al., 2016      |
| IL-6       | -174 G/C rs1800795    | 125 Asian early-stage breast cancer patients; mean age 50.26±8.82 yrs             | Attention, Memory, Processing speed, Response speed       | No                      | Chae et al., 2016      |
| IL-1b      | -1418C/T rs16944      | 369 Caucasian participants aged 65 years and older                               | Memory                                                  | Yes                     | Baune et al., 2008     |
| IL-1b      | -1418C/T rs16944      | 161 Han Chinese men mean age 78.7±4.3 yrs                                       | Global cognition Working memory                           | Yes                     | Tsai et al., 2010      |
| IL-1b      | rs1143634 rs1143633   | 99 elderly Japanese women; mean age 65.0±3.8 yrs                                  | Verbal intelligence quotient                              | Yes                     | Sasayama et al., 2011  |
| IL-1b      | rs2856838 rs3783654   | 2031 Scottish Caucasians (73% female); mean age 67.2±6.5 yrs                      | Mental flexibility                                       | Yes                     | Marioni et al., 2010   |
| IL1bCE     | rs554344 rs580253     | 5680 Caucasians; mean age 75.3±3.3 yrs.                                          | Executive functions                                      | Yes                     | Trompet et al., 2008   |
| TNF-alpha  | -308 A/G rs1800629    | 252 Danish participants 80- and 85-years of age                                   | Global cognition Verbal Intellectual Quotient            | Yes                     | Krabbe et al., 2009    |
| IL-10      | -1082 G/A rs1800896   | 5804 Caucasians; mean age 75.3±3.3 yrs.                                          | Global cognition                                        | No                      | Trompet et al., 2010   |
| IL-10      | -1082 G/A rs1800896   | 5804 Caucasians; mean age 75.3±3.3 yrs.                                          | Global cognition                                        | No                      | Trompet et al., 2010   |
| IL-10      | -1082 G/A rs1800896   | 5804 Caucasians; mean age 75.3±3.3 yrs.                                          | Global cognition                                        | No                      | Trompet et al., 2010   |
| IL-10      | -1082 GA rs1800896    | 5804 Caucasians; mean age 75.3±3.3 yrs.                                          | Global cognition                                        | Yes                     | Trompet et al., 2010   |
| IL-10      | rs2254514             | 1651 Danish Caucasian participants; mean age 93.1±0.3 yrs                         | General cognitive functioning                              | Yes                     | Dato et al., 2010      |
| IL-15      | rs2322262             |                                                                                 |                                                          |                         |                         |
| IL-18      | -137 G/C rs187238     |                                                                                 |                                                          |                         |                         |
significant interaction between time and genotypes for all cognitive domains has been found.22

Dato et al. (2010) have reported interesting, sex-specific associations for cytokine gene polymorphisms in relation to cognitive functioning. IL10-1082GG female carriers have had a significantly lower cognitive functioning compared with AA + AG carriers. Women carrying the C allele (CC + CT) of the IL15 rs2254514 have shown significantly lower cognitive abilities compared with TT carriers. In men, the IL18-137G carriers (GG + GC) have performed worse on cognitive tests compared with CC carriers. Another important finding of this study is the association between the low-producing inflammatory haplotype IL18-137CC/IL10-1082(AG + GG) and better cognitive functioning, indicating that the balance between pro-inflammatory and anti-inflammatory activity of IL-18 and IL-10 loci prevents age-related cognitive decline.23

**CLINICAL EVIDENCE FOR PARTICIPATION OF CYTOKINE SNPS IN COGNITIVE PROCESSES**

Alzheimer’s disease (AD) is a neurodegenerative disorder, occupying one of the leading positions among the causes for cognitive decline and dementia in the elderly. Association between cytokine SNPs and the risk for AD represents an indirect evidence for the role of these polymorphisms in cognitive functioning (Table 2). In one study, significantly higher frequency of AA variant of IL-10-1082A/G has been found in patients with amnestic mild cognitive impairment who progressed to AD, than that found in patients that remained clinically stable.24

Two meta-analyses on the role of IL-10-1082 A/G in AD have presented similar results: carriers of A allele, corresponding to lower production of IL-10 had higher risk for the disease than GG homozygotes.25,26 These correlations have not been confirmed for the Asian population, which suggests ethnic variations in the genetic background of cognition.26

Several SNPs in genes encoding pro-inflammatory cytokines have been implicated in the risk of developing AD. Studies performed on thousands of patients of different ages, genders, and ethnic origins have shown the T allele of IL-1a-889 C/T and T allele of IL-1b +3953 C/T as strong risk factors for disease development.27-31 Moreover, a synergic effect of these SNPs has been found. Homozygosity for both IL-1a-889 TT and IL-1b+3953 TT genotypes has conferred the greatest risk for AD29,30 and has been associated with the lowest age of onset.32

The two most studied SNPs in the promoter region of TNF-alpha gene in relation to AD are TNF-alpha-308G/A and TNF-alpha-850C/T. Earlier studies have reported contradictory results about the effect of each SNP alone, but in haplotype with other polymorphisms TNF-alpha-308A and TNF-alpha-850T have been shown to increase the risk of developing the disease.33-35 Later, Yang et al. (2009) and Ardebili et al. (2011) have reported significantly higher frequency of TNF-alpha-308A allele in Alzheimer population.36,37 As TNF-alpha-308A allele is associated with increased transcription of TNF-alpha38, it is supposed that prolonged impact of higher concentrations of this proinflammatory cytokine activates glutamatergic excitotoxicity and apoptosis and thus accelerates cortical atrophy.14

Promoter SNPs, relevant to increased production of another proinflammatory cytokine IL-18, have been shown to correlate with the risk for AD. Homozygous carriers of C allele at position-607 in the IL-18 gene have had a higher risk to develop AD.39 A significant correlation has been reported between the CC variant of this SNP, increased cytokine production and degree of cognitive decline.40

Similar results have been provided by a study in the Chinese population. C allele at -607IL-18 and G allele at -137IL-18, both individually and as a haplotype (-607C/-137G) have determined a higher risk for occurrence of late onset AD.41 In addition, homozygous CC genotype of IL-18-137 G/C has been strongly and specifically associated with faster progression of cognitive impairment in patients with AD regardless of the presence of the ApoE e4 allele.39

Association between IL-6−572C/G promoter polymorphism and the risk of developing AD has been found in Chinese population. The −572CC genotype has increased the risk for AD by more than three-fold among the carriers of ApoE e4 allele.42

Taken together, the data presented above suggest that genetic background predisposing to higher proinflammatory and reduced anti-inflammatory activity increases the risk for cognitive decline.

Parkinson’s disease (PD) is another neurodegenerative disorder leading to cognitive impairment in a considerable proportion of the patients. In contrast to the European population, where A allele of IL-10-1082A/G is a risk factor for cognitive deficit, AA genotype of this polymorphism in Chinese patients with PD has a protective effect against cognitive decline. Homozygous CC variant of IL-17A rs8193036 has increased the risk for cognitive impairment in the same patients’ group.43
Table 2. Clinical studies investigating the role of cytokine gene polymorphisms in disease related cognitive impairment

| Candidate gene | Polymorphism | Study population | Disease causing cognitive impairment | Association | Author |
|----------------|--------------|------------------|--------------------------------------|-------------|--------|
| IL-10          | -1082 GA     | 138 subjects with MCI; mean age 80.37±5.93 yrs 63 Controls Caucasian | Mild Cognitive Impairment | Yes | Arosio et al., 2010 |
|                | rs1800896    |                  |                                      |             |        |
| IL-1a          | -889 C/T     | 152 patients with AD, mean age, 74.8 yrs 136 controls, mean age, 69.3 yrs Caucasian | Alzheimer disease | Yes | Bosco et al., 2004 |
|                |              |                  |                                      |             |        |
| IL-1a          | -889 C/T     | 259 patients with AD 192 controls Caucasian | Alzheimer disease | Yes | Du et al., 2000 |
|                |              |                  |                                      |             |        |
| IL-1a          | -889C/T      | Australian patients with AD and age mach controls Caucasian | Alzheimer disease | Yes | Hedley et al., 2002 |
| IL-1b          | +3953 C/T    |                  |                                      |             |        |
| IL-1a          | -889C/T      | 233 British patients with AD, mean age 81.5±7.8 yrs 169 controls, mean age 74.4±9.6 yrs | Alzheimer disease | Yes | Nicoll et al., 2000 |
| IL-1b          | +3953 C/T    |                  |                                      |             |        |
| IL-1a          | -889C/T      | 361 patients with AD (from Italy and USA) 244 controls Caucasian | Alzheimer disease | Yes | Sepira et al., 2005 |
|                |              |                  |                                      |             |        |
| TNF-alpha      | -308 A/G     | 235 patients with AD, mean age 80.3 yrs 130 controls, mean age 77 yrs | Alzheimer disease | No | Culpan et al., 2003 |
|                | rs1800629    |                  |                                      |             |        |
| TNF-alpha      | -850 C/T     | 256 patients with AD, mean age 76.4±7.5 yrs 73 patients with vascular dementia, mean age 83.5±6.6 yrs 200 controls, mean age 70.5±11.3 yrs | Alzheimer disease | No | Terreni et al., 2003 |
|                | rs1799724    |                  |                                      |             |        |
| Gene          | SNP      | Study Details                                                                 | AD         | PD          | References       |
|--------------|----------|-------------------------------------------------------------------------------|------------|------------|-----------------|
| TNF-alpha    | -308 A/G | 506 patients with AD, mean age, 71.5±10.0 yrs                                | No         | Yes        | Laws et al., 2005 |
|              | -850 C/T | 277 controls, mean age, 65.3±12.5 yrs                                        | Yes        |            |                 |
|              | rs1799724| Caucasian                                                                      |            |            |                 |
| TNF-alpha    | -308 A/G | 112 Chinese patients with AD, mean age, 73.2±2.5 yrs                          | Yes        |            | Yang et al., 2009|
|              | rs1800629| 121 controls, mean age, 74.3±2.8 yrs                                         |            |            |                 |
|              |          | Caucasian                                                                      |            |            |                 |
| TNF-alpha    | -308 A/G | 160 patients with AD, mean age, 76.06±7.75 yrs                               | Yes        |            | Ardebili et al., 2011|
|              | rs1800629| 163 controls, mean age, 75.29±6.75 yrs                                       |            |            |                 |
|              |          | Caucasian                                                                      |            |            |                 |
| Il-18        | -607 C/A | 338 patients with AD, mean age, 74.3±7.5 yrs                                 | Yes        |            | Bossù et al., 2007|
|              | rs187238 | 139 controls, mean age, 69.4±6.4 yrs                                         |            |            |                 |
| IL-18        | -137 G/C | 109 Chinese patients with AD, mean age, 74.2±4.1 yrs                          | Yes        |            | Yu et al., 2009  |
|              | rs187238 | 109 controls, mean age, 74.2±4.1 yrs                                         |            |            |                 |
|              | -607 C/A | rs1946518                                                                     |            |            |                 |
| IL-6         | -572C/G  | 341 Chinese patients with AD, mean age, 74.8±9.3 yrs                          | Yes        |            | Wang et al., 2010|
|              | rs1800796| 421 controls, mean age, 75.2±8.5 yrs                                         |            |            |                 |
| IL-10        | -1082 A/G| 302 Chinese patients with PD, mean age, 64.96±9.96 yrs and 93 cases without CI, mean age, 60.72±11.26 yrs | Yes        |            | Nie et al., 2013 |
| Il-17A       | rs8193036|                                                                             |            |            |                 |
| IL-10        | rs1800871| 460 Chinese patients with PD, mean age, 62.15±9.76 yrs                       | No         |            | Liu et al., 2016 |
| IL-18        | rs1800872| 473 controls, mean age, 58.38±12.03 yrs                                      |            |            |                 |
|              | rs1946518|                                                                             |            |            |                 |
|              | rs187238 |                                                                             |            |            |                 |
| Lymphotoxin  | rs2857713| 351 patients with schizophrenia, mean age, 42.2±10.0 yrs                     | Yes        |            | Dickerson et al., 2007|
|              |          | 122 patients with BD, mean age, 40.8±12.4 yrs                                |            |            |                 |
|              |          | 160 controls, mean age, 34.4±12.1 yrs                                         |            |            |                 |
| TGF-beta     | +869 T/C | 158 patients with schizophrenia, mean age, 38.0±11.9 yr.                      | Yes        |            | Frydecka et al., 2015|
|              | rs1800470| 279 controls, mean age, 38.7±8.8 yrs                                         |            |            |                 |

AD - Alzheimer disease; PD - Parkinson’s disease; CI – cognitive impairment; BD - bipolar disorder
Completely different are the results reported by Liu et al. in 2016. The authors found no associations between promoter polymorphisms in IL-10 (rs1800871 and rs1800872) and IL-18 (rs1946518 and rs187238) genes and cognitive impairment in Chinese PD patients.44

Cognitive impairments are well recognized in schizophrenia and bipolar disorder (BD). Two studies have investigated the association between cytokine gene polymorphisms and cognitive functioning in these patients.45 Dickerson et al. (2007) have found a correlation between Repeatable Battery for the Assessment of Neuropsychological Status score and polymorphism in lymphotoxin gene (rs2857713) in schizophrenia but not in BD patients.46 In a group of 158 schizophrenia patients carriers of +869T allele in TGF-beta gene have shown lower performance on cognitive tests in comparison with +869CC homozygotes.47

In summary, the majority of the data accumulated to date support the hypothesis that various SNPs in cytokine genes could modify the risk for cognitive impairment in humans. In different conditions they may act as either protective or risk factors for cognitive decline. On the other hand, it has been suggested that polymorphisms do not implement this effect alone but in large interactions between each other, as well as with many other factors, some of which still wait to be identified. Further research is needed to reveal the precise role and the molecular mechanisms of action of the SNPs in cognitive processes. Comprehensive data obtained from large-scale studies on various populations and patients with different diseases should help to identify subgroups at higher risk for cognitive decline requiring close observation. Elucidation of the relationship between SNPs and certain cognitive domain will help for more effective intervention with selective programs for prevention and rehabilitation of cognitive decline.

REFERENCES

1. Stanilova S. Cytokine Gene Polymorphisms in Colorectal Cancer. In: Ettarh R, ed. Colorectal Cancer Biology - From Genes to Tumor. 1st ed. Rijeka: InTech; 2012:59-78.
2. Marin I, Kipnis J. Learning and memory ... and the immune system. Learn Mem 2013;20(10):601-6.
3. McAfoose J, Baune BT. Evidence for a cytokine model of cognitive function. Neurosci Biobehav Rev 2009;33:355-366.
4. Coogan AN, O’Neill LA, O’Connor JJ. The P38 mitogen-activated protein kinase inhibitor SB203580 antagonizes the inhibitory effects of interleukin-1beta on long-term potentiation in the rat dentate gyrus in vitro. Neuroscience 1999;93(1):57-69.
5. Ross FM, Allan SM, Rothwell NJ, et al. A dual role for interleukin-1 in LTP in mouse hippocampal slices. J Neuroimmunol 2003;144(1-2):61-7.
6. Vallières L, Campbell IL, Gage FH, et al. Reduced hippocampal neurogenesis in adult transgenic mice with chronic astrocytic production of interleukin-6. J Neurosci 2002;22(2):486-92.
7. Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. Science 2003;302(5651):1760-5.
8. Stellwagen D, Malenka RC. Synaptic scaling mediated by glial TNF-alpha. Nature 2006;440(7087):1054-9.
9. Baron R, Nemirovsky A, Harpaz I, et al. IFN-gamma enhances neurogenesis in wildtype mice and in a mouse model of Alzheimer’s disease. FASEB J 2008;22(8):2843-52.
10. van Horssen J, van Schaik P, Witte M. Inflammation and mitochondrial dysfunction: a vicious circle in neurodegenerative disorders? Neurosci Lett 2017;pii: S0304-3940(17)30542-6.
11. Viviani B, Bartesaghi S, Corsini E, et al. Cytokines role in neurodegenerative events. Toxicol Lett 2004;149(1-3):85-9.
12. Beste C, Baune BT, Falkenstein M, et al. Variations in the TNF-a gene (TNF-a -308G >A) affect attention and action selection mechanisms in a dissociated fashion. J Neurophysiol 2010a;104(5):2523-31.
13. Beste C, Heil M, Domschke K, et al. Associations between the tumor necrosis factor alpha gene (-308G-A) and event-related potential indices of attention and mental rotation. Neuroscience 2010b;170(3):742-8.
14. Gadjewski P, Hengstler J, Golkka K, et al. The functional tumor necrosis factor-α (308A/G) polymorphism modulates attentional selection in elderly individuals. Neurobiol Aging 2013;34(11):2694.e1-2694.e12.
15. Baune B, Ponath G, Rothermundt M, et al. Association between genetic variants of IL-1b, IL-6 and TNF-alpha cytokines and cognitive performance in the elderly general population of the MEMO-study. Psychoneuroendocrinology 2008;33:68-76.
16. Chae JW, Ng T, Yeo HL, et al. Polymorphisms on cognitive impairment in Asian breast cancer patients. PLoS One 2016;11(10):e0164204.
17. Tsai SJ, Hong CJ, Liu ME, et al. Interleukin-1 beta (C-511T) genetic polymorphism is associated with cognitive performance in elderly males without dementia. Neurobiol Aging 2010;31(11):1950-5.
18. Sasayama D, Hori H, Teraishi T, et al. Association of interleukin-1β genetic polymorphisms with cognitive performance in elderly females without
dementia. J Hum Genet 2011;56(8):613-6.
19. Marioni RE, Deary IJ, Murray GD, et al. Associations between polymorphisms in five inflammation related genes and cognitive ability in older persons. Genes Brain Behav 2010;9(3):348-52.
20. Trompet S, de Craen AJ, Slagboom P, et al; PROSPER Group. Genetic variation in the interleukin-1 beta-converting enzyme associates with cognitive function. The PROSPER study. Brain 2008;131(Pt 4):1069-77.
21. Krabbe KS, Mortensen EL, Avlund K, et al. Genetic priming of a proinflammatory profile predicts low IQ in octogenarians. Neurobiol Aging 2009;30(5):769-81.
22. Trompet S, de Craen AJ, Slagboom PE, et al. Variation in the IL-10 gene is a marker for risk prediction of cognitive function. Genes, inflammation, and age-related diseases 2010:69.
23. Dato S, Krabbe KS, Thinggaard M, et al. Commonly studied polymorphisms in inflammatory cytokine genes show only minor effects on mortality and related risk factors in nonagenarians. J Gerontol A Biol Sci Med Sci 2010;65(3):225-35.
24. Arosio B, Mastronardi L, Vergani C, et al. Interleukin-10 promoter polymorphism in mild cognitive impairment and in its clinical evolution. Int J Alzheimers Dis 2010;2010 pii: 854527.
25. Candore G, Balistreri CR, Grimaldi MP, et al. Polymorphisms of pro-inflammatory genes and Alzheimer’s disease risk: a pharmacogenomic approach. Mech Ageing Dev 2007;128(1):67-75.
26. Zhang Y, Zhang J, Tian C, et al. The -1082G/A polymorphism in IL-10 gene is associated with risk of Alzheimer’s disease: a meta-analysis. J Neurol Sci 2011;303(1-2):133-8.
27. Bosco P, Gueant-Rodriguez RM, Anello G, et al. Association of IL-1 R5*2 allele and methionine synthase, 2756 AA genotype with dementia severity of sporadic Alzheimer’s disease. J Neurol Neurosurg Psychiatry 2004;75(7):1036-38.
28. Du Y, Dodel RC, Eastwood BJ, et al. Association of an interleukin-1-alpha polymorphism with Alzheimer’s disease. Neurology 2000;55(4):480-3.
29. Hedley R, Hallmayer J, Groth DM, et al. Association of interleukin-1 polymorphisms with Alzheimer’s disease in Australia. Ann Neurol 2002;5(6):795-7.
30. Nicoll JA, Mrak RE, Graham DJ, et al. Association of interleukin-1 gene polymorphisms with Alzheimer’s disease. Ann Neurol 2000;47(3):365-8.
31. Seripa D, Matera MG, Dal Forno G, et al. Genotypes and haplotypes in the IL-1 gene cluster: analysis of two genetically and diagnostically distinct groups of Alzheimer patients. Neurobiol Aging 2005;26(4):455-64.
32. Sciacca FL, Ferri C, Licastro F, et al. Interleukin-1b polymorphism is associated with age at onset of Alzheimer’s disease. Neurobiol Aging 2003;24(7):927-31.
33. Culpan D, MacGowan SH, Ford JM, et al. Tumour necrosis factor-alpha gene polymorphisms and Alzheimer’s disease. Neurosci Lett 2003;350(1):61-5.
34. Terreni L, Fogliarino S, Quadri P, et al. Tumor necrosis factor alpha polymorphism C–850T is not associated with Alzheimer’s disease and vascular dementia in an Italian population. Neurosci Lett 2003;344(2):135-7.
35. Laws SM, Perneckzy R, Wagenpfel S, et al. TNF polymorphisms in Alzheimer disease and functional implications on CSF beta-amyloid levels. Hum Mutat 2005;26(1):29-35.
36. Yang L, Lu R, Jiang L, et al. Expression and genetic analysis of tumor necrosis factor-alpha (TNF-alpha) G-308A polymorphism in sporadic Alzheimer’s disease in a Southern China population. Brain Res 2009;1247:178-81.
37. Ardebili SM, Yeghaneh T, Gharesouran J, et al. Genetic association of TNF-α-308 G/A and -863 C/A polymorphisms with late onset Alzheimer’s disease in Azeri Turk population of Iran. J Res Med Sci 2011;16(8):1006-13.
38. Wilson AG, Symons JA, McDowell TL, et al. Effects of a polymorphism in the human tumour necrosis factor alpha promoter on transcriptional activation. Proc Natl Acad Sci USA 1997;94(7):3195-9.
39. Bossù P, Ciaramella A, Moro ML, et al. Interleukin 18 gene polymorphisms predict risk and outcome of Alzheimer’s disease. J Neurol Neurosurg Psychiatry 2007;78(8):807-11.
40. Bossù P, Ciaramella A, Salani F, et al. Interleukin-18 produced by peripheral blood cells is increased in Alzheimer’s disease and correlates with cognitive impairment. Brain Behav Immun 2008;22(4):487-92.
41. Yu JT, Tan L, Song JH, et al. Interleukin-18 promoter polymorphisms and risk of late onset Alzheimer’s disease. Brain Res 2009;1253:169-75.
42. Wang M, Jia J. The interleukin-6 gene -572C/G promoter polymorphism modifies Alzheimer’s risk in APOE epsilon 4 carriers. Neurosci Lett 2010;482(3):260-3.
43. Nie K, Zhang Y, Gan R, et al. Polymorphisms in immune/inflammatory cytokine genes are related to Parkinson’s disease with cognitive impairment in the Han Chinese population. Neurosci Lett 2013;541:111-5.
44. Liu Z, Guo J, Wang Y, et al. Lack of association between IL-10 and IL-18 gene promoter polymorphisms and Parkinson’s disease with cognitive impairment in a Chinese population. Sci Rep 2016;6:19021.
45. Misiak B, Stańczykiewicz B, Kotowicz K, et al.
Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: A systematic review. Schizophr Res 2017; pii: S0920-9964(17)30202-5.
46. Dickerson F, Boronow J, Stallings C, et al. The lymphotixin Cys13Arg polymorphism and cognitive functioning in individuals with schizophrenia. Schizophr Res 2007;89(1-3):173-6.
47. Frydecka D, Misiak B, Pawlak-Adamska E, et al. Sex differences in TGFB-β signaling with respect to age of onset and cognitive functioning in schizophrenia. Neuropsychiatr Dis Treat 2015;1:575-84.

Роль полиморфизмов генов цитокинов при когнитивных функциях

Анастасия Г. Тренова1, Георги С. Славов1, Мария Г. Манова1, Люба Д. Митева2, Спаска А. Станилова2

1 Кафедра неврологии, Факультет медицины, Медицинский университет - Пловдив, Пловдив, Болгария
2 Кафедра молекулярной биологии, иммунологии и медицинской генетики, Факультет медицины, Тракийский университет, Стара Загора, Болгария

Адрес для корреспонденции:
Анастасия Г. Тренова, Кафедра неврологии, Факультет медицины, Медицинский университет - Пловдив, бул. „Васил Априлов” № 15А, 4002, Пловдив, Болгария
E-mail: atrenova@yahoo.com
Tel: +359 32 602 279

Дата получения: 27 апреля 2017
Дата приемки: 15 августа 2017
Дата онлайн публикации: 05 октября 2017
Дата публикации: 30 июня 2018

Ключевые слова: цитокины, одиночные нуклеотидные полиморфизмы, познавательная способность, деменция

Образец цитирования:
Trenova AG, Slavov GS, Manova MG, Miteva LD. A role of cytokine gene polymorphisms in cognitive functioning. Folia Med (Plovdiv) 2018;60(2):191-9.
doi: 10.1515/folmed-2017-0094

Изменения в когнитивных функциях в процессе старения и при различных патологических состояниях являются предметом растущего интереса. Экспериментальные и клинические данные подкрепляют гипотезу о влиянии иммунной системы на когнитивные процессы. Установлено, что, баланс между провоспалительными и противовоспалительными цитокинами является необходимым фактором для нормальной когнитивной функции. Производство цитокинов находится под строгим генетическим контролем и описаны различные одиночные нуклеотидные полиморфизмы (ОНП) в генах цитокинов. Поскольку было доказано, что ОНП цитокина могут повлиять на экспрессию гена или функциональную активность иммунного белка, это логически привело к предположению о роли этих полиморфизмов в когнитивной функции. Исследования на предмет установления связи между различными генетическими вариантами полиморфизмов гена цитокинов и когнитивными способностями у здоровых субъектов и у пациентов с деменцией, показывают разные результаты. Обзор научной литературы показывает, что ОНП реализуют свое влияние на познавательную способность при больших взаимодействиях друг с другом, а также в комбинации с множеством других факторов, некоторые из которых всё ещё предстоит идентифицировать. В этой статье обобщены современные знания о взаимодействии между ОНП в генах цитокинов и когнитивном статусе у людей. Дальнейшие исследования необходимы для определения точной роли и молекулярных механизмов действия ОНП в когнитивных процессах.