REVIEW

A Role of Cytokine Gene Polymorphisms in Cognitive Functioning

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The changes in cognitive functions that occur with aging and in various pathological conditions are a subject of growing interest. Experimental and clinical data justify the hypothesis about the influence the immune system exerts on cognitive processes. The balance between pro-inflammatory and anti-inflammatory cytokines has been established as a necessary factor for normal cognitive functioning. Cytokine production is under strong genetic control and various single nucleotide polymorphisms (SNPs) in cytokine genes have been described. As cytokine SNPs have been demonstrated to affect the gene expression or the functional activity of the immune protein this logically led to the suggestion about the role of these polymorphisms in cognitive functioning. Studies exploring the association between different genetic variants of cytokine gene polymorphisms and cognitive abilities in healthy subjects and in demented patients show divergent results. The review of relevant literature suggests that SNPs implement their effect on cognition in large interactions with each other, as well as with many other factors, some of which still remain to be identified. This article summarizes the contemporary knowledge about the correlations between SNPs in cytokine genes and cognitive status in humans. Further research is needed to determine the precise role and the molecular mechanisms of action of the SNPs in cognitive processes.

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 Gadjewski 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-converting 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 IL-6	-308 A/G rs1800629 -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 -592 C/A rs1800872 4259 A/G rs3024498 -2849 G/A rs6703630	5804 Caucasians; mean age 75.3±3.3 yrs	Global cognition	No No Yes Yes	Trompet et al., 2010
IL-10	-1082 GA rs1800896	1651 Danish Caucasian participants; mean age 93.1±0.3 yrs	General cognitive functioning	Yes (gender differentiated)	Dato et al., 2010
IL-15	rs2254514 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 IL18-137 G 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 amnesic 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 AD^{29,30} 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 pro-inflammatory 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 rs1800896	138 subjects with MCI; mean age 80.37±5.93 yrs 63 Controls Caucasian	Mild Cognitive Impairment	Yes	Arosio et al., 2010
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 IL-1b	-889C/T +3953 C/T	Australian patients with AD and age match controls Caucasian	Alzheimer disease	Yes	Hedley et al., 2002
IL-1a IL-1b	-889C/T +3953 C/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-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 rs1800629	235 patients with AD, mean age 80.3 yrs 130 controls, mean age 77 yrs	Alzheimer disease	No	Culpan et al., 2003
TNF-alpha	-850 C/T rs1799724	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 Vascular dementia	No	Terreni et al., 2003

TNF-alpha	-308 A/G rs1800629 -850 C/T rs1799724	506 patients with AD, mean age, 71.5±10.0 yrs 277 controls, mean age, 65.3±12.5 yrs Caucasian	Alzheimer disease	No Yes	Laws et al., 2005
TNF-alpha	-308 A/G rs1800629	112 Chinese patients with AD mean age, 73.2±2.5 yrs 121 controls, mean age, 74.3±2.8 yrs	Alzheimer disease	Yes	Yang et al., 2009
TNF-alpha	-308 A/G rs1800629	160 patients with AD, mean age, 76.06±7.75 yrs 163 controls, mean age, 75.29±6.75 yrs Caucasian	Alzheimer disease	Yes	Ardebili et al., 2011
IL-18	-607 C/A rs187238	338 patients with AD, mean age, 74.3±7.5 yrs 139 controls, mean age, 69.4±6.4 yrs Caucasian	Alzheimer disease	Yes	Bossù et al., 2007
IL-18	-137 G/C rs187238 -607 C/A rs1946518	109 Chinese patients with AD, mean age, 74.2±4.1 yrs 109 controls, mean age, 74.2±4.1 yrs	Alzheimer disease	Yes	Yu et al., 2009
IL-6	-572C/G rs1800796	341 Chinese patients with AD, mean age, 74.8±9.3 yrs 421 controls, mean age, 75.2±8.5 yrs	Alzheimer disease	Yes	Wang et al., 2010
IL-10 IL-17A	-1082 A/G rs8193036	302 Chinese patients with PD (209 cases with CI, mean age, 64.96±9.96 yrs and 93 cases without CI, mean age 60.72±11.26 yrs)	PD related cognitive impairment	Yes	Nie et al., 2013
IL-10 IL-18	rs1800871 rs1800872 rs1946518 rs187238	460 Chinese patients with PD, mean age, 62.15±9.76 yrs 473 controls, mean age, 58.38±12.03 yrs	PD related cognitive impairment	No	Liu et al., 2016
lymphotoxin	rs2857713	351 patients with schizophrenia, mean age, 42.2±10.0 yrs 122 patients with BD, mean age, 40.8±12.4 yrs 160 controls, mean age, 34.4±12.1 yrs Non-Caucasian	Schizophrenia Bipolar disorder	Yes No	Dickerson et al., 2007
	TGF-beta rs1800470	158 patients with schizophrenia, mean age, 38.0±11.9 yr. 279 controls, mean age, 38.7±8.8 yrs	Schizophrenia	Yes	Frydecka et al., 2015

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.

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Роль полиморфизмов генов цитокинов при когнитивных функциях

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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.