Journal of Human Genetics (2011) 56, 613–616

www.nature.com/jhg

SHORT COMMUNICATION

# Association of interleukin-1β genetic polymorphisms with cognitive performance in elderly females without dementia

Daimei Sasayama[1,2], Hiroaki Hori[1], Toshiya Teraishi[1], Kotaro Hattori[1], Miho Ota[1], Junko Matsuo[1], Yumiko Kawamoto[1], Yukiko Kinoshita[1], Teruhiko Higuchi[3], Naoji Amano[2] and Hiroshi Kunugi[1,4]

**Interleukin-1β (IL-1β) is considered to have a role in age-related cognitive decline. A recent study has shown that a promoter polymorphism of the *IL-1β* gene (rs16944) is associated with cognitive performance in elderly males without dementia. In this study, we examined whether polymorphisms of the *IL-1β* gene also influence cognitive functions in elderly females. Cognitive functions were assessed by the Wechsler adult intelligence scale-revised (WAIS-R) in 99 elderly (⩾60 years) females without dementia. We selected five tagging polymorphisms from the *IL-1β* gene and examined the associations with the WAIS-R scores. Significant associations were found between verbal intelligence quotient (IQ) and the genotypes of rs1143634 and rs1143633 (*P*=0.0037 and *P*=0.010, respectively). No significant associations of rs16944 genotype were found with verbal or performance IQ. However, individuals homozygous for the G allele of rs16944 achieved higher scores in digit span compared with their counterpart, which is consistent with the previous findings in males. These results suggest that *IL-1β* gene variation may have a role in cognitive functions in aging females as well as males.**
*Journal of Human Genetics* (2011) **56,** 613–616; doi:10.1038/jhg.2011.56; published online 26 May 2011

**Keywords:** cognitive function; genetic polymorphism; interleukin-1β; intelligence

## INTRODUCTION

Interleukin-1β (IL-1β) has a significant role in age-related impairment in long-term potentiation in the hippocampus.[1] Some genetic studies support this evidence by demonstrating associations between gene variations and cognitive decline in an elderly population. One study[2] reported that genetic variation in the IL-1β-converting enzyme gene is associated with better performance on cognitive function and lower IL-1β production levels. Studies investigating the associations between *IL-1β* gene polymorphisms and cognitive functioning in elderly subjects have shown that a G>A polymorphism of the IL-1β promoter variant rs16944 had detrimental effects on memory performance,[3] while rs1143643 and rs1143634 of the *IL-1β* gene had no significant influence on cognitive performance.[4,5] Consistent with the findings by Baune *et al.*,[3] a recent study by Tsai *et al.*[6] has shown that rs16944 is associated with cognitive performance in elderly males without dementia; those individuals who had the G/G genotype of rs16944 performed better in digit span backward test compared with their counterpart. In this study, following the work by Tsai *et al.*,[6] we examined whether polymorphisms of the *IL-1β* gene also influence the cognitive functions in elderly females.

## MATERIALS AND METHODS

### Subjects

Subjects were 99 female healthy volunteers with age 60 years or older recruited from the community through advertisements in free local information magazines and by our website announcement. All subjects were biologically unrelated Japanese, and were screened using the Japanese version of the Mini International Neuropsychiatric Interview[7,8] by a research psychiatrist to rule out any axis I psychiatric disorders. Participants were excluded if they had a prior medical history of psychiatric treatment, central nervous system disease or severe head injury, or if they met Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria[9] for substance abuse or dependence, dementia or mental retardation. Although none of the participants had a systemic infection, eight were under treatment for major systemic illnesses (two with anti-hypertensive agents, one with a diabetes drug, one with an anti-coagulant agent, one with anti-thyroid agents and three with anti-lipidemic agents). All participants were administered the Japanese version of Wechsler adult intelligence scale-revised (WAIS-R)[10] by a research psychologist. The study protocol was approved by the ethics committee at the National Center of Neurology and Psychiatry, Japan. After description of the study, written informed consent was obtained from every subject.

[1]Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan; [2]Department of Psychiatry, Shinshu University School of Medicine, Matsumoto, Japan; [3]National Center of Neurology and Psychiatry, Kodaira, Japan and [4]Core Research of Evolutional Science & Technology (CREST), Japan Science and Technology Agency (JST), Tokyo, Japan
Correspondence: Dr D Sasayama, Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, 4-1-1, Ogawahigashi, Kodaira, Tokyo 187-8502, Japan.
E-mail: sasayama@shinshu-u.ac.jp
Received 28 March 2011; revised 26 April 2011; accepted 5 May 2011; published online 26 May 2011

**Table 1 Subjects characteristics and WAIS-R scores**

| | *Mean* | *Standard deviation* | *Range* |
|---|---|---|---|
| Age (years) | 65.0 | 3.8 | 60–74 |
| Education (years) | 12.9 | 2.0 | 9–20 |
| *WAIS-R scores* | | | |
| Verbal subtests (scaled scores) | | | |
| Information | 12.1 | 2.5 | 5–16 |
| Digit span | 11.4 | 2.5 | 7–19 |
| Vocabulary | 11.6 | 2.5 | 5–17 |
| Arithmetic | 10.7 | 2.6 | 6–16 |
| Comprehension | 11.8 | 2.6 | 4–18 |
| Similarities | 12.5 | 2.6 | 6–18 |
| *Performance subtests (scaled scores)* | | | |
| Picture completion | 11.0 | 2.3 | 4–16 |
| Picture arrangement | 11.6 | 2.9 | 5–17 |
| Block design | 11.1 | 2.4 | 6–16 |
| Object assembly | 10.4 | 2.5 | 5–17 |
| Digit symbol | 13.6 | 2.3 | 8–19 |
| Verbal IQ | 111.0 | 11.5 | 82–137 |
| Performance IQ | 109.4 | 11.2 | 86–142 |
| Full scale IQ | 111.1 | 10.5 | 87–133 |

Abbreviations: IQ, intelligence quotient; WAIS-R, Wechsler adult intelligence scale-revised.

## Genotyping

Five tagging single nucleotide polymorphisms (SNPs) of the *IL-1β* gene (rs2853550, rs1143634, rs1143633, rs1143630 and rs16944) were selected by Haploview 4.2[11] using Japanese and Chinese population in the HapMap SNP data set release 22 (International HapMap Project, http://hapmap.ncbi.nlm.nih.gov/), at an $r^2$ threshold of 0.80 with a minor allele frequency greater than 0.1. Genomic DNA was prepared from the venous blood according to standard procedures. The SNPs were genotyped using the TaqMan 5′-exonuclease allelic discrimination assay (Applied Biosystems, Foster City, CA, USA). Thermal cycling conditions for PCR were one cycle at 95 °C for 10 min followed by 50 cycles of 92 °C for 15 s and 60 °C for 1 min. The allele-specific fluorescence was measured with ABI PRISM 7900 Sequence Detection Systems (Applied Biosystems, Foster City, CA, USA). Genotype data were read blind to the WAIS-R scores. Ambiguous genotype data were not included in the analysis.

## Statistical analysis

Mean differences between groups were assessed by analysis of variance. Differences in the WAIS-R scores between the genotypes were tested using analysis of covariance, with age and years of education as covariates. Bonferroni method was used to correct for multiple comparisons among the five SNPs. However, as the subtest scores and the intelligence quotient (IQ) scales of WAIS-R are intercorrelated and thus are not completely independent measures, we did not apply the Bonferroni method for the number of WAIS-R subtests and IQ scales. Statistical analyses were performed using the statistical package for the social sciences (SPSS) version 11.0 (SPSS, Tokyo, Japan). Statistical tests were two tailed and statistical significance was considered when $P<0.05$.

**Table 2 Comparison of WAIS-R scores between genotypes**

| | | | *Mean (standard deviation)* | | | | |
|---|---|---|---|---|---|---|---|
| *SNP* | *Bp position on chromosome 2* | | A/A (*N*=0) | A/G (*N*=21) | G/G (*N*=75) | F *value* | *Adjusted* P value[a] |
| rs2853550 | 113 303 592 | Age (years) | — | 64.8 (3.9) | 65.0 (3.8) | 0.077 | 0.78 |
| | | Education (years) | — | 12.6 (2.0) | 13.0 (2.0) | 0.50 | 0.48 |
| | | VIQ | — | 110.6 (11.7) | 110.9 (11.5) | 0.037 | 0.85 |
| | | PIQ | — | 110.7 (11.2) | 109.2 (11.4) | 0.48 | 0.49 |
| | | | G/G (*N*=87) | G/A (*N*=11) | A/A (*N*=0) | | |
| rs1143634 | 113 306 861 | Age (years) | 65.1 (3.9) | 64.7 (3.3) | — | 0.098 | 0.75 |
| | | Education (years) | 12.9 (2.0) | 12.3 (1.6) | — | 1.1 | 0.29 |
| | | VIQ | 112.2 (11.2) | 101.0 (9.3) | — | 8.9 | **0.0037** |
| | | PIQ | 109.9 (11.1) | 105.5 (12.1) | — | 1.2 | 0.28 |
| | | | C/C (N=14) | C/T (N=41) | T/T (N=42) | | |
| rs1143633 | 113 306 938 | Age (years) | 63.4 (3.6) | 65.9 (3.7) | 64.7 (3.9) | 2.6 | 0.078 |
| | | Education (years) | 12.9 (2.2) | 12.7 (2.0) | 13.0 (1.9) | 0.27 | 0.77 |
| | | VIQ | 105.2 (10.6) | 108.8 (10.6) | 114.4 (11.6) | 4.8 | **0.010** |
| | | PIQ | 106.4 (10.7) | 108.5 (11.5) | 111.3 (11.2) | 1.2 | 0.29 |
| | | | G/G (*N*=72) | G/T (*N*=23) and T/T (*N*=1)[b] | | | |
| rs1143630 | 113 308 126 | Age (years) | 65.1 (3.8) | 64.8 (3.7) | | 0.16 | 0.69 |
| | | Education (years) | 12.9 (1.9) | 12.9 (2.3) | | 0.0080 | 0.93 |
| | | VIQ | 110.0 (11.9) | 113.1 (9.3) | | 1.5 | 0.23 |
| | | PIQ | 108.3 (11.4) | 112.7 (10.1) | | 2.7 | 0.10 |
| | | | G/G (*N*=37) | G/A (*N*=40) | A/A (N=19) | | |
| rs16944 | 113 311 338 | Age (years) | 65.7 (3.9) | 65.1 (4.0) | 63.9 (3.5) | 1.4 | 0.26 |
| | | Education (years) | 13.0 (1.8) | 12.7 (2.1) | 13.2 (1.9) | 0.56 | 0.57 |
| | | VIQ | 112.6 (11.4) | 108.7 (11.7) | 112.5 (11.0) | 0.96 | 0.39 |
| | | PIQ | 108.5 (12.3) | 110.8 (9.3) | 109.4 (13.0) | 0.67 | 0.52 |

Abbreviations: Bp position, base pair position; PIQ, performance intelligence quotient; SNP, single-nucleotide polymorphism; VIQ, verbal intelligence quotient.
*P*-values<0.05 are shown in bold face.
[a]*P* values for VIQ and PIQ were adjusted for age and years of education.
[b]Since only one subject was homozygous for T allele of rs1143630, the G/T and T/T genotype groups were combined into a T carrier group and contrasted with those homozygous for G allele.

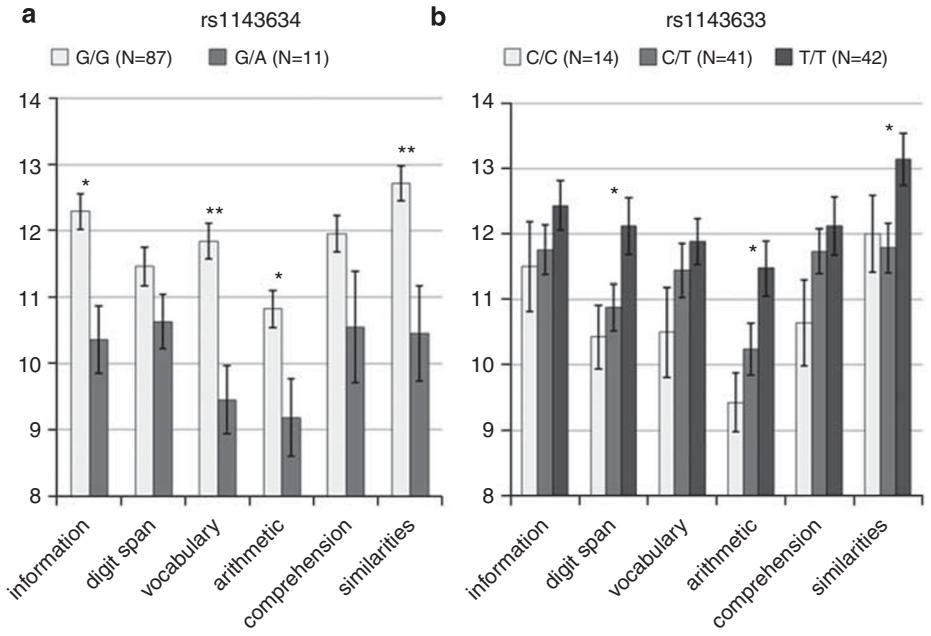


**Figure 1** Scaled scores of the verbal subtests. The mean scaled scores of the verbal subtests are shown for each genotype of rs1143634 and rs1143633 (**a**, **b**, respectively). Error bars indicate standard error of the means. $^{*}P<0.05$, $^{**}P<0.01$.

## RESULTS

The characteristics of the subjects and their WAIS-R scores are shown in Table 1. None of the SNPs were found to deviate significantly from Hardy–Weinberg equilibrium. The WAIS-R full scale IQ, verbal IQ (VIQ) and performance IQ (PIQ) were in normal distribution (all $P>0.05$, Shapiro–Wilk test). The VIQ and PIQ for each genotype of the examined SNPs are presented in Table 2. Significant differences in VIQ were found between the genotypes of rs1143634 and between the genotypes of rs1143633. The association between rs1143634 and VIQ remained significant after multiple test correction (Bonferroni-corrected $P=0.018$). The association of rs1143633 with VIQ was also significant after multiple test correction when individuals homozygous for T allele were compared with the C allele carriers (Bonferroni-corrected $P=0.031$). Figure 1 shows the mean scaled scores of the verbal subtests for each genotype of rs1143634 and rs1143633. No significant associations of rs16944 genotype were found with VIQ or PIQ. However, individuals homozygous for the G allele of rs16944 achieved higher scores in the digit span subtest compared with A allele carriers ($F=6.24$, $P=0.014$, adjusted for age and years of education).

## DISCUSSION

The results indicate that *IL-1β* gene polymorphisms rs1143634 and rs1143633 may be associated with verbal cognitive function in elderly female subjects. Furthermore, those homozygous for the G allele of rs16944 performed better in digit span test compared with A allele carriers, which was consistent with the findings in the previous study in males.[6] Despite the significant associations between VIQ and the genotypes of rs1143634 and rs1143633, the years of education were not significantly affected by the polymorphisms. This suggests that these polymorphisms influenced the cognitive function in old age, but did not have impact on educational attainment during school years. Thus, our findings lend support to the possibility that *IL-1β* gene variation may have a role in the cognitive deficit in the elderly.

A limitation of this study is that the cross-sectional design did not allow us to compare the time course of the cognitive decline between different genotypes. A prospective study is necessary to determine whether the *IL-1β* gene polymorphisms affect the cognitive function *per se* or cognitive decline in the elderly. Further study is still needed to explore the effect of the *IL-1β* gene variations on cognitive function in various age, gender and ethnic groups.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

This study was supported by Health and Labor Sciences Research Grants (Comprehensive Research on Disability, Health, and Welfare), Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS), Core Research of Evolutional Science & Technology (CREST), Japan Science and Technology Agency (JST), the Strategic Research Program for Brain Sciences by the Ministry of Education, Culture, Sports, Science and Technology of Japan (Understanding of molecular and environmental bases for brain health), and Intramural Research Grant for Neurological and Psychiatric Disorders of NCNP (HK).

1 Murray, C. A. & Lynch, M. A. Evidence that increased hippocampal expression of the cytokine interleukin-1 beta is a common trigger for age- and stress-induced impairments in long-term potentiation. *J. Neurosci.* **18,** 2974–2981 (1998).
2 Trompet, S., de Craen, A. J., Slagboom, P., Shepherd, J., Blauw, G. J., Murphy, M. B. *et al.* Genetic variation in the interleukin-1 beta-converting enzyme associates with cognitive function. The PROSPER study. *Brain* **131,** 1069–1077 (2008).
3 Baune, B. T., Ponath, G., Rothermundt, M., Riess, O., Funke, H. & Berger, K. Association between genetic variants of IL-1beta, IL-6 and TNF-alpha cytokines and cognitive performance in the elderly general population of the MEMO-study. *Psychoneuroendocrinology* **33,** 68–76 (2008).
4 Marioni, R. E., Deary, I. J., Murray, G. D., Fowkes, F. G. & Price, J. F. Associations between polymorphisms in five inflammation-related genes and cognitive ability in older persons. *Genes Brain Behav.* **9,** 348–352 (2010).
5 Lau, S., Bates, K. A., Sohrabi, H. R., Rodrigues, M., Martins, G., Dhaliwal, S. S. *et al.* Functional effects of genetic polymorphism in inflammatory genes in subjective memory complainers. *Neurobiol. Aging* doi:10.1016/j.neurobiolaging.2010.09.003 (in press).

6 Tsai, S. J., Hong, C. J., Liu, M. E., Hou, S. J., Yen, F. C., Hsieh, C. H. *et al.* Interleukin-1 beta (C-511T) genetic polymorphism is associated with cognitive performance in elderly males without dementia. *Neurobiol. Aging* **31,** 1950–1955 (2010).
7 Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E. *et al.* The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J. Clin. Psychiatry* **59** (Suppl 20), 22–33; quiz 34–57 (1998).
8 Otsubo, T., Tanaka, K., Koda, R., Shinoda, J., Sano, N., Tanaka, S. *et al.* Reliability and validity of Japanese version of the mini-international neuropsychiatric interview. *Psychiatry. Clin. Neurosci.* **59,** 517–526 (2005).
9 American Psychiatric Association. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders* 4th edn, (American Psychiatric Press, Washington D.C., 1994).
10 Wechsler, D. *The Wechsler Adult Intelligence Scale-Revised* (The Psychological Corporation, San Antonio, 1981).
11 Barrett, J. C., Fry, B., Maller, J. & Daly, M. J. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* **21,** 263–265 (2005).