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Alpha-synuclein (*SNCA*) polymorphisms exert protective effects on memory after mild traumatic brain injury

Kevin Shee[1,#,*], **Alexandra Lucas**[1,*], **Laura A. Flashman**[2], **Kwangsik Nho**[4], **Gregory J. Tsongalis**[5], **Brenna C. McDonald**[4], **Andrew J. Saykin**[4], **Thomas W. McAllister**[3], and **C. Harker Rhodes**[5]

[1]Geisel School of Medicine, Hanover, NH

[2]Department of Psychiatry, Geisel School of Medicine, Hanover, NH

[3]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN

[4]Departments of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN

[5]Human Brain Collection Core, NIMH, Bethesda, MD

Abstract

Problems with attention and short-term learning and memory are commonly reported after mild traumatic brain injury (mTBI). Due to the known relationships between α-synuclein (*SNCA*), dopaminergic transmission, and neurologic deficits, we hypothesized that *SNCA* polymorphisms might be associated with cognitive outcome after mTBI. A cohort of 91 mTBI patients one month after injury and 86 healthy controls completed a series of cognitive tests assessing baseline intellectual function, attentional function, and memory, and was genotyped at 13 common single nucleotide polymorphisms (SNPs) in the SNCA gene. Significant differences in two memory measures ($p = 0.001$ and 0.002), but not baseline intellectual function or attentional function tasks, were found between the mTBI group and controls. A highly significant protective association between memory performance and SNCA promoter SNP rs1372525 was observed in the mTBI patients ($p = 0.006$ and 0.029 for the long and short delay conditions of the California Verbal Learning Tests, respectively), where the presence of at least one copy of the A (minor) allele was protective after mTBI. These results may help elucidate the pathophysiology of cognitive alterations after mTBI, and thus warrant further investigation.

[#]**Corresponding author**, Kevin Shee, MD-PhD candidate, Geisel School of Medicine at Dartmouth, 61 Drake Lane, West Lebanon, NH 03784, Phone: (916) 294-5316, Kevin.Shee.MED@dartmouth.edu.

[*]These authors contributed equally to this manuscript

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Keywords

Traumatic Brain Injury; Parkinson's Disease; Alpha-Synuclein; Memory; Neuropsychiatry

Introduction

Mild traumatic brain injury (mTBI) is a major public health problem affecting over 1.27 million Americans every year [1]. While many mTBI patients recover without significant long-term consequences, some individuals continue to have persistent symptoms, including problems with memory, attention, processing speed, and executive function [2]. Patients with seemingly similar degrees of injury often display differing severity of deficits, leading our group and others to postulate that polymorphisms in genes modulating the neural response to trauma may influence clinical outcome after mTBI [3, 4].

Alterations in dopaminergic and other catecholaminergic signaling systems have been hypothesized to play a role in persistent cognitive complaints and deficits after TBI: striatal dopamine levels have been shown to decrease post-injury, and the clinical treatment of TBI involves increasing dopaminergic neurotransmission [5, 6]. Studies in both mice and humans have demonstrated abnormal dopamine transport and D2 receptor binding in response to varying severities of TBI [7, 8]. Furthermore, it has been recently shown that mTBI patients performing working memory tasks have an altered response to the dopamine D2 receptor agonist bromocriptine as compared to healthy controls [9].

Because of this putative role of dopaminergic pathways in mTBI, genes that influence dopaminergic function are attractive candidates for study. One candidate of interest is the gene for α-synuclein (*SNCA*), a member of the synuclein family of proteins that has been implicated in the pathogenesis of multiple neurologic diseases including Parkinson's disease (PD), multiple system atrophy, and Lewy body dementia [10]. In early functional studies by Abeliovich et al., α-synuclein knockout-mice showed a reduction in striatal dopamine and attenuated dopamine-dependent response to amphetamine without neuronal degeneration, suggesting a regulatory role of α-synuclein in dopaminergic neurotransmission [11]. α-Synuclein has since been further implicated as a regulator of dopamine biosynthesis and availability through interactions with tyrosine hydroxylase [12]; as a determinant of the density of dopaminergic neurons in the substantia nigra [13]; and as a mediator of long-lasting increase in neurotransmitter release [14]. Polymorphisms in the *SNCA* gene are well-documented genetic risk factors for PD [15], a disease pathologically characterized by loss of midbrain dopaminergic neurons, and whose clinical features include not only extrapyramidal motor symptoms, but often also impairment of memory and executive functions as is commonly seen in traumatic brain injury. Outside of PD, *SNCA* polymorphism associations have not been well elucidated.

Given the relationships between dopamine, mTBI, and SNCA, we hypothesized that polymorphisms in SNCA might influence cognitive performance in mTBI patients.

Methods

Participants

A cohort of 91 consecutive patients with mTBI was recruited from a Level 1 trauma center emergency department using American Congress of Rehabilitation Medicine criteria for mild TBI [16]. Specifically, mTBI was defined as an initial Glasgow Coma Scale (GCS) score of 13–15 when available and/or duration of loss of consciousness not exceeding 30 minutes. mTBI participants were studied approximately one month after injury. A total of 86 normal controls were evaluated. One cohort of healthy control subjects (n=38) was recruited specifically for this study through advertisements. Demographic, cognitive, and genotype data from additional healthy control subjects (n=48) studied by our group as part of previously published breast cancer and aging studies [17, 18] were obtained. Exclusion criteria of a history of other neurological disorders, substantial systemic medical illness, or current DSM-IV axis I psychiatric diagnosis disorder with the exception of substance abuse based on the Structured Clinical Interview for DSM-IV [19] resulted in the elimination of four mTBI subjects. The study protocol and informed consent were approved by the Dartmouth College Committee for the Protection of Human Subjects. Written informed consent was obtained from all participating subjects. Over 95% of the TBI and control groups were Caucasians of European descent.

Cognitive measures

All cognitive tests were determined prior to analyzing the data. The Wide-Range Achievement Test (WRAT) reading subtest [20] was used to estimate baseline level of general intellectual function. Simple Reaction Time, Vigilance, and Distractibility conditions of the Continuous Performance Test (CPT) were used as measures of attentional function [21]. The Short Delay (SD) and Long Delay (LD) conditions of the California Verbal Learning Test (CVLT) were selected as the primary outcome measures of memory [22].

Genotyping and characterizing the SNCA locus

DNA was purified from peripheral blood using QIAGEN's blood mini kit (QIAGEN, Alameda, CA). Genotyping was done using a custom made 3600 SNP microarray gene chip (Affymetrix, Inc., Santa Clara, CA) as previously described [4]. This study is based on the 13 SNCA polymorphisms included in that array.

Haploview [23] and the NCBI Homo sapiens Annotation Release 105 were used to characterize and study SNCA polymorphisms. P-values for Hardy-Weinberg equilibrium (HWE) and minor allele frequency were obtained based on both chi-squared and exact test analysis. In addition, linkage disequilibrium (r^2) was analyzed for all combinations of SNPs.

Statistical analyses

Between-group differences in demographic characteristics were examined by t-tests or chi-square tests for continuous or categorical variables, respectively. Each of the allele variables was summarized as a factor variable with two levels assuming a dominant genetic model (at least one copy of the minor allele vs no copies of the minor allele). Genetic group differences for cognitive measures were analyzed by analysis of covariance (ANCOVA) with

diagnosis, the allele variable, and the interaction between allele and diagnosis included in the model, covarying for age and gender; education was not included in the final model because of a significant correlation with both the independent variable and other covariates. Significance tests were examined for the main effects of diagnosis and allele status, and for the interaction between allele and diagnosis. Significant p-values for polymorphisms and cognitive measures were adjusted for multiple comparisons using the Benjamini and Hochberg false discovery rate (FDR) method, using an FDR of 0.10 [24]. All analysis was performed and repeated using Excel Data Analysis Toolkit, SPSS, and Stata.

Polymorphism comparison between mTBI and PD

PDGene contains a comprehensive, unbiased and regularly updated synopsis of genetic association studies performed in PD [15]. Meta-analyses were obtained for all characterized polymorphisms in the SNCA gene, and odds ratios and confidence intervals were averaged between all studies available. This data was downloaded on 1/10/2015 and compared to the results from our mTBI study.

Results

Demographics

The population characteristics of the healthy control and mTBI groups are summarized in Table 1. Due to the nature of the control cohorts (38 subjects recruited specifically for this study, 27 subjects from an aging study, and 21 subjects from a breast cancer study), there were significant differences in age, education, and sex between control and mTBI groups: all additional statistical analysis was therefore done co-varying for these three factors. However, the mTBI patients and the control subjects recruited specifically for this study and the mTBI patients were balanced for age, education and sex, and there were no substantive differences in the results of this study when only those control subjects were considered ($p>0.05$). The mTBI group had a mean (SD) GCS score of 14.8 (0.550), a post-traumatic amnesia duration of 5.36 (7.18) hours, and loss of consciousness of 5.13 (7.58) minutes, a cognitive profile consistent with mTBI. The mean injury-to-testing time was 39.5 (15.8) days.

Cognitive measures

Cognitive results are included in Table 1. There was no significant difference in baseline intellectual function as estimated by the WRAT reading score, or attentional function as measured by the Continuous Performance Tasks (CPT): Simple Reaction Time, Vigilance, and Distractibility. Significant performance differences were found between the two groups on the California Verbal Learning Test (CVLT) Short Delay and Long Delay free recall conditions ($p=0.001$ and $p=0.002$, respectively). Therefore, all further analyses were performed using both CVLT (SD and LD) conditions. These findings are consistent with previous studies, which confirm no difference in the WRAT reading scores of mTBI patients and controls [3, 25] but a significant difference in both CVLT-SD and LD[3, 4, 26]. Additionally, no significant differences were found between memory performance (CVLT-LD and CVLT-SD) of the volunteer, breast cancer study, and aging study control groups ($p>0.05$).

Genetic analysis

Based on the chi-square and exact test analyses, the analyzed SNPs were all in Hardy-Weinberg equilibrium ($p > 0.356$), with minor allele frequencies greater than 0.17. The default setting in Haploview showed strong linkage disequilibrium between some of the SNPs (data not shown).

Effects of genotype on memory performance

The effects of genotype on memory performance on the CVLT SD and LD trials are summarized in Table 2. Using an autosomal dominant inheritance model for analysis, the most significant association was of the promoter polymorphism rs1372525 in mTBI patients with the CVLT SD and LD trials ($p = 0.029$ and 0.006, respectively). The G/G genotype was associated with poorer memory performance phenotype in mTBI patients (n=30), while having at least one copy of the A allele was shown to exert a protective effect (n=61) (Figure 1a). In contrast, no similar relationship was found when comparing attentional function scores (e.g. CPT: Simple Reaction Time and Vigilance) with genotype (Figure 1b), suggesting a memory-specific effect. A similar pattern was observed in subjects with the polymorphism rs356219 (SD and LD), rs1023777 (SD and LD), and rs2301134 (SD only) (Table 2).

Because of the high degree of linkage disequilibrium between the polymorphisms studied, the analyses were repeated covarying for the most significant SNP, rs1372525. The previously noted significant associations for rs356219 and rs102377 and CVLT LD were no longer significant in the new model ($p = 0.195$ and 0.882, respectively), and their association with CVLT is presumably due to linkage disequilibrium with rs1372525. Similar results were obtained for the CVLT SD.

In order to be sure that the differences between the G/G subjects and A allele subjects were not due to chance differences in injury severity, the analyses were repeated across polymorphism groups for duration of loss of consciousness (LOC), duration of post-traumatic amnesia (PTA), and GCS score. For rs1372525, no significant differences were found between the two groups for LOC ($p = 0.710$), PTA ($p = 0.624$), and GCS ($p = 0.733$), thus ruling out the impact of injury severity on our findings.

Comparison of SNPs associated with PD and those associated with memory difficulties after mTBI

Because of the importance of SNCA in PD, we evaluated whether or not those polymorphisms found to have protective effects on memory after mTBI are also implicated in PD pathophysiology. Each of the polymorphisms examined in this study has been included in four or more PD genetic association studies, and meta-analysis of those studies is available in PDgene. Combining PDGene data downloaded on 1/10/2015 with our own polymorphism data, we found that there was no significant relationship between the polymorphisms most significantly associated with improved cognitive performance after mTBI and the polymorphisms associated with PD ($p>0.05$; Table 2). Specifically, rs1372525, the most significant polymorphism in the mTBI study, has not been associated with the risk of PD (OR ~1; Table 2).

Discussion

The specific pathophysiology responsible for problems with cognitive outcomes after mTBI is not well understood, although substantial evidence suggests a role for altered dopaminergic neurotransmission. SNCA is an attractive candidate for study in this context because of its role in PD, a disease caused by death of dopaminergic neurons. We hypothesized that polymorphisms in SNCA might also be associated with measures of cognitive outcome following mTBI.

Utilizing a cohort of 95 mTBI patients and 86 normal controls, we found that there are SNCA polymorphisms associated with cognitive outcomes related to memory function after mTBI. Specifically, we observed a strong association between the promoter polymorphism rs1372525 and a protective memory phenotype after mTBI, such that patients having at least one copy of the A allele performed significantly better for free memory recall as measured by the CVLT-SD and LD trials. All other polymorphism associations could be accounted for by linkage disequilibrium with rs1372525. We note with interest that this polymorphism is not associated with the risk of PD, and polymorphisms which are associated with risk of PD were not associated with a better or worse cognitive outcome in this mTBI cohort. This lack of association is supported by a recent study by Guella et al., who show that *SNCA* polymorphisms associated with cognitive defects in PD spectrum disorders are unrelated to those associated with risk for PD [27].

There are multiple potential mechanisms for the protective effect of rs1372525 and other *SNCA* promoter polymorphisms on memory. The first mechanism is through altered dopaminergic neurotransmission mediated by polymorphism-mediated changes in gene expression. It is well described that learning and memory are strongly dependent on dopamine neurotransmitter activity, particularly in the prefrontal cortex [28], hippocampus [29], and striatum [30]. Furthermore, *SNCA* promoter polymorphisms have been previously linked to altered α-synuclein expression in humans [31]. It is therefore possible that the protective mechanism of rs1372525 and other *SNCA* promoter polymorphisms involves regulation of α-synuclein expression, which could alter dopamine release and downstream activity to levels optimal for memory functions. An alternative possible mechanism by which specific *SNCA* polymorphisms may exert a protective effect on memory after mTBI involves decreasing α-synuclein aggregation. It has been shown that brain injury impairs axonal transport and induces inflammatory cascades, leading to the accumulation of α-synuclein and subsequent impairment of neurological and behavioral functions [32]. Interestingly, it has been shown that ‘risk’ polymorphisms in the 3’ region of SNCA leads to alternative splicing with increased relative levels of splice variant SNCA112-mRNA, resulting in enhanced α-synuclein aggregation [33]. Therefore, rs1372525 and other SNCA polymorphisms could exert neuroprotective effects post-mTBI by decreasing α-synuclein accumulation through alternative splicing or other means.

There are a few limitations to this study. First, cognitive change after mTBI is a complex, multifactorial process. Our significant results did not account for other factors that may play a role in cognitive recovery, such as post-injury treatment and psychosocial factors. Second, the subjects in this study are mostly of northern European Caucasian descent, and the study

needs to be repeated with other populations. Third, the control and mTBI populations were significantly different in their age, gender, and education levels. Although their estimated baseline intellectual function did not demonstrate a significant difference and these variables were covaried for in analyses, this study should ideally be repeated with mTBI cohorts with a larger female population. Finally, the sample size used in this study was limited and should be repeated in other mTBI cohorts.

Despite these limitations, our study provides novel evidence for a role of SNCA in memory performance post-mTBI. To our knowledge, this is the first report describing a direct link between α-synuclein and cognitive outcome after mTBI. Our significant results warrant future analysis, such as study in more severe cases of traumatic brain injury, interaction with post-injury treatment and psychosocial factors, and generalizability to other population cohorts.

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Highlights

- Patients with mTBI have significantly decreased memory performance one month after injury
- Protective association between memory performance and SNCA promoter polymorphism rs1372525
- Less significant SNCA polymorphisms attributed to linkage disequilibrium with rs1372525
- Protective effect of rs1372525 not related to risk for Parkinson's Disease

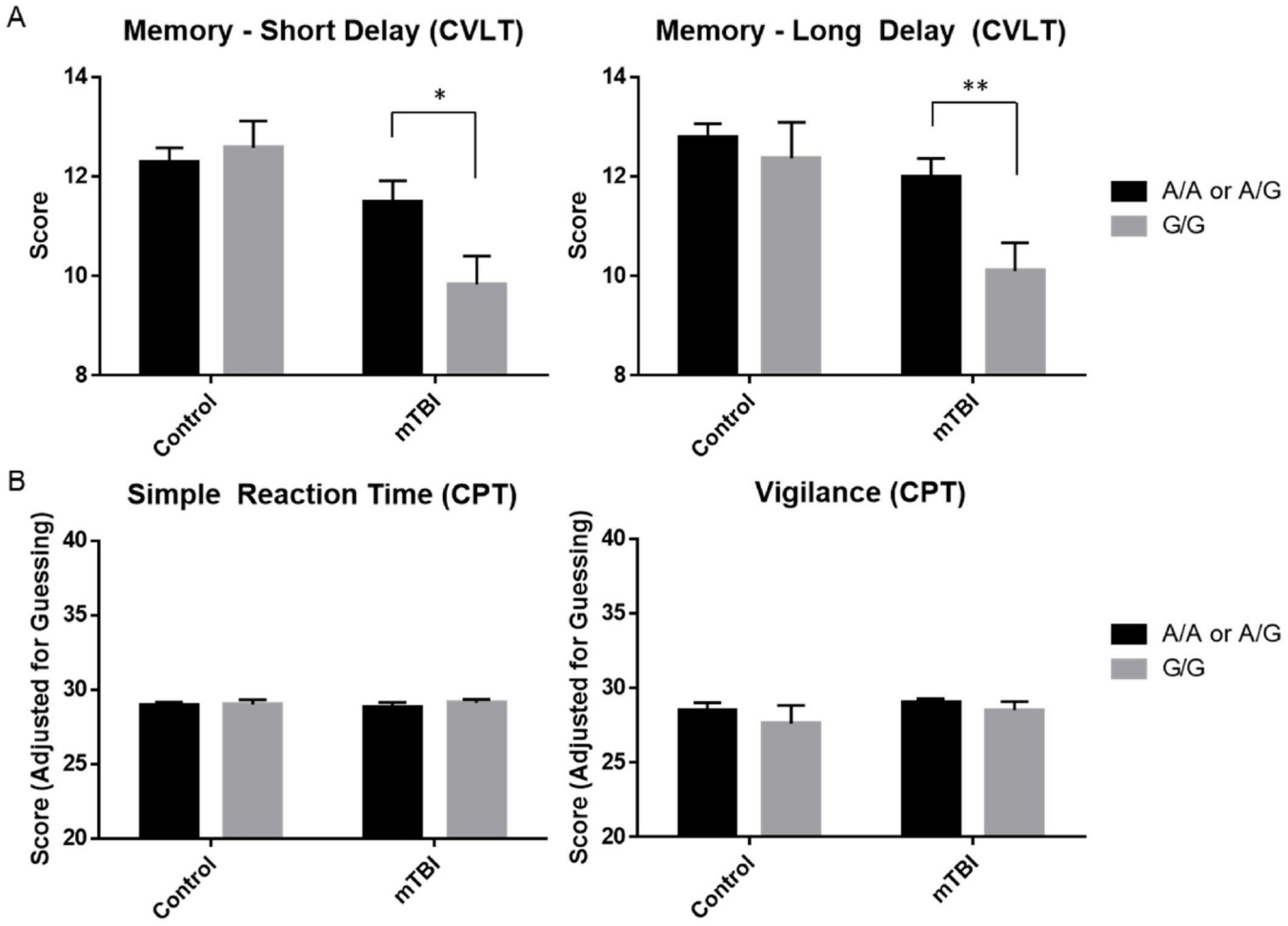

Figure 1. Effect of rs1372525 allele status on cognitive outcomes

A. Memory measures. Effect of rs1372525 genotype on the number of words recalled (Short and Long Delay free recall measures of the California Verbal Learning Test) in the mild traumatic brain injury (mTBI) group and the control group. Higher values indicate better memory performance. Statistically significant differences were found in the mTBI group between the G/G homozygotes (n = 61) and the groups with an A allele (n = 30). Error bars represent standard error. *p=0.029 **p=0.006

B. Attentional function measures. Effect of rs1372525 genotype as measured by CPT Simple Reaction Time and Vigilance Accuracy in the mild traumatic brain injury (mTBI) group and the control group. No statistically significant changes were detected (p>0.05). Error bars represent standard error.

Table 1

Study population demographics and cognitive performance measures

Demographic characteristics (Age, Gender, Education, Mother's education, and Father's education) of the mTBI patients and healthy controls. Cognitive performance measures (WRAT, Simple Reaction Time, Vigilance, and Distractibility conditions of the CPT, and Short and Long Delay Free Recall conditions of the CVLT) of the mTBI patients and healthy controls.

n	91	86	
Age, years	33.7 (13.7)	47.9 (10.2)	**<0.001**
Male, gender	56 (61.5%)	27 (31.8%)	**<0.001**
Education years	14.3 (2.63)	15.9 (2.38)	**<0.001**
Mother's education, years	13.7 (2.55)	13.4 (2.94)	0.367
Father's education, years	14.5 (3.52)	13.8 (3.64)	0.254
WRAT Reading Standard Score	106.8 (9.84)	105.9 (9.04) *	0.595
Simple Reaction Time Number Correct (CPT)	28.9 (2.23)	28.9 (1.20) **	0.931
Vigilance Number Correct (CPT)	28.9 (2.32)	28.4 (2.94) **	0.308
Distractability Number Correct (CPT)	26.0 (6.30)	27.4 (2.94) **	0.193
Short Delay Free Recall (CVLT)	10.9 (3.30)	12.7 (2.21)	**0.001**
Long Delay Free Recall (CVLT)	11.4 (3.14)	13.2 (2.33)	**0.002**

* n=58

** n=38

Table 2

Summary of the association of SNPs with memory outcome measures and relationship to PD

Differences in CVLT Short and Long Delay Free Recall measures between polymorphism changes were analyzed for mTBI patients using an analysis of covariance (ANCOVA). Bolded p-values ($p < 0.05$) indicate significant interactions of allele type with CVLT performance, covarying for sex and age, after correction for multiple comparisons at a Benjamini and Hochberg false discovery rate (FDR) of 0.10. Red text indicates the most significant polymorphism association. PD risk odds ratios were obtained from the PDGene database downloaded 1/10/2015 (www.pdgene.org).

rs2736994 (A→G)	Promoter region	0.661	0.479	NS	**0.85 (5e-15)**	Protective
rs1372525 (G→A)	Promoter region	**0.029**	**0.006**	Protective	~1 (>0.05)	NS
rs1023777 (C→T)	Promoter region	0.031	0.026	NS	**0.92 (1.29e-6)**	Protective
rs2583988 (T→C)	Promoter region	0.114	0.233	NS	**1.15 (2e-15)**	Increased risk
rs2619364 (G→A)	Promoter region	0.579	0.233	NS	**1.15 (2e-15)**	Increased risk
rs2301134 (A→G)	Promoter region	**0.023**	0.074	Protective/NS	~1 (>0.05)	NS
rs2301135 (C→G)	Promoter region	0.522	0.480	NS	~1 (>0.05)	NS
rs10005233 (T→C)	Intron 4	0.528	0.480	NS	~1 (>0.05)	NS
rs1812923 (A→C)	Intron 4	0.143	0.082	NS	~1 (>0.05)	NS
rs2737029 (C→T)	Intron 4	0.080	0.160	NS	**1.25 (3.12e-42)**	Increased risk
rs356188 (C→T)	Intron 4	0.579	0.957	NS	**0.82 (6.21e-21)**	Protective
rs7684318 (C→T)	Intron 4	0.117	0.290	NS	**1.37 (1.02e-25)**	Increased risk
rs356219 (G→A)	3' UTR	**0.020**	**0.016**	Protective	**1.32 (1.98e-63)**	Increased risk

NS = not significant.