



Symposium on Natural and Applied Sciences

Hosted Online from London, United Kingdom

Date: 5th June, 2026

Website: <https://econferencia.com>

APOE rs769452 (Leu28Pro) IN OPEN TRAUMATIC BRAIN INJURY: EXPLORATORY FINDINGS AND AN UNRESOLVED MINOR ALLELE FREQUENCY DISCREPANCY

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Background

Work on apolipoprotein E in traumatic brain injury has concentrated almost entirely on the epsilon 2, 3 and 4 haplotype system. Meta-analyses of the epsilon 4 allele have produced inconsistent estimates of its effect on outcome [1, 2], the association appears to differ between adults and children [3], and a separate line of evidence links the allele to late post-traumatic seizures [4]. The rs769452 variant is a different, far less studied coding substitution in the same gene, replacing leucine with proline at position 28. Most global reference panels report a minor allele frequency below one per cent for this variant, which has kept it out of clinical association studies. No data exist for populations of Central Asia.

Objective

To determine the frequency of APOE rs769452 in patients with open traumatic brain injury and in healthy controls, to test its association with complications, and to assess whether the available sample provides adequate statistical power for a variant of this frequency.



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Methods

A case-control comparison was performed in 101 patients with open traumatic brain injury and 80 healthy individuals matched for sex, age and ethnicity. Genomic DNA was extracted on a silica membrane, and rs769452 was genotyped by real-time polymerase chain reaction with allelic discrimination on a CFX96 Touch instrument (Bio-Rad Laboratories, USA); ten per cent of samples were genotyped in duplicate. Conformity to Hardy-Weinberg equilibrium was tested with the chi-square goodness of fit test, which is a standard requirement in association studies [5]. Frequencies were compared with the chi-square test with Yates correction, and the association with complications was assessed by logistic regression adjusted for injury severity, age and sex. Statistical power was calculated in G*Power 3.1.9.7.

Results

The minor Pro allele was found in 16.8% of patients and 10.6% of controls (chi-square 2.35; $p=0.13$; OR 1.68; 95% CI 0.91-3.11). Genotype counts were Leu/Leu 72 (71.3%) versus 65 (81.2%), Leu/Pro 24 (23.8%) versus 13 (16.2%) and Pro/Pro 5 (5.0%) versus 2 (2.5%). Genotype distributions conformed to Hardy-Weinberg equilibrium in both groups (chi-square 2.31, $p=0.13$ in patients; chi-square 1.67, $p=0.20$ in controls). Observed heterozygosity was 0.24 against an expected 0.28 in patients and 0.16 against 0.19 in controls.

Carriage of the Pro allele was associated with infectious and inflammatory complications at trend level only (OR 2.5; 95% CI 0.9-6.8; $p=0.06$). Discrimination was poor, with an area under the receiver operating characteristic curve of 0.55 (sensitivity 29%, specificity 81%). Power analysis confirmed that the study had at least 80% power to detect an odds ratio of 2.0 or greater for



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common variants at a two-sided alpha of 0.05, but was underpowered for a variant with the frequency of rs769452.

The frequency observed in the control group is an order of magnitude higher than the values reported for rs769452 in global reference panels. Two explanations are possible: a genuine population difference in a group for which no prior data exist, or misclassification arising from the genotyping assay. These cannot be separated without independent verification, and until such verification is available the frequency estimate and the association derived from it remain provisional [6].

Conclusions

1. The Pro allele of APOE rs769452 was more frequent in patients with open traumatic brain injury than in controls (16.8% versus 10.6%), but the difference did not reach statistical significance.
2. The association with infectious and inflammatory complications reached trend level only (OR 2.5; 95% CI 0.9-6.8; $p=0.06$), and discrimination was close to chance (AUC 0.55).
3. The observed minor allele frequency substantially exceeds published reference values, so confirmation by an independent method, such as Sanger sequencing of a subset of samples, is required before the marker is interpreted further.
4. The sample size is insufficient for a low-frequency variant, and rs769452 should therefore be reported as exploratory rather than as an established risk marker.



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