Evaluating the effect of APOE gene polymorphisms on injury severity after traumatic brain injury

S. Mayur[1], U. Adiga[2]*, S. Adiga[3], Ananthan R[4]

[1]Central Research Laboratory, KS Hegde Medical Academy, NITTE—Deemed to be University, Mangalore, Karnataka, India- 5750128; [2]Department of Biochemistry, Apollo Institute of Medical Sciences and Research, Chittoor, Andhra Pradesh, India- 517127; [3]Department of Pharmacology, Apollo Institute of Medical Sciences and Research, Chittoor, Andhra Pradesh, India-517127; [4]Department of Neurosurgery, Justice K S Hegde Charitable Hospital, Deralakatte, Mangalore, Karnataka, India- 5750128

*corresponding author Email: ushachidu@yahoo.com

Journal of Livestock Science (ISSN online 2277-6214) 15: 314-321
Received on 15/8/24; Accepted on 15/9/24; Published on 16/9/24
doi. 10.33259/JLivestSci.2024.314-321

Abstract

Traumatic Brain Injury (TBI) is a multifaceted form of acquired brain damage caused by external force, leading to both structural and functional alterations in the brain. This study investigates the relationship between APOE gene polymorphism and injury severity (GCS) following TBI. Conducted as a cross-sectional study over three years at a tertiary care hospital in Mangalore, the research included TBI patients and healthy controls. Ethical protocols and convenient sampling were followed, with blood samples collected within 48 hours for genetic polymorphism analysis. The study analysed the frequencies of APOE gene genotypes among TBI patients and healthy controls. The most common genotype in TBI patients was e3/e3 (71.8%), followed by e3/e4, e2/e3, e2/e4, e2/e2, and e4/e4. Among healthy controls, e3/e3 was also the most prevalent genotype (64.34%), with no e4/e4 genotype instances. APOE (p=0.77) gene polymorphisms showed no significant deviations from Hardy-Weinberg equilibrium, indicating genetic stability. APOE3 was identified as the common wild-type allele, while APOE2 and APOE4 were classified as mutant alleles. The study assessed the association between APOE gene polymorphism and Glasgow Coma Scale (GCS) scores on admission using various models, including additive, e2 vs. non-e2, e3 vs. non-e3, and e4 vs. non-e4. The findings revealed no significant association between APOE gene polymorphisms and injury severity as measured by GCS scores. The APOE gene polymorphism may not play a significant role in determining injury severity.

Keywords: APOE gene polymorphisms; Traumatic brain injury; Glasgow coma scale; injury severity

Introduction

Traumatic brain injury (TBI) is a broad term used to describe acquired brain damage caused by external forces that alter the brain's structure and function (NCBI Bookshelf, 2023). Often referred to as the "silent epidemic," TBI affects individuals across all ages, cultures, and genders and represents a significant global health issue. The unique nature of each TBI case stems from the wide variety of injury mechanisms, force dynamics, and patient characteristics (such as genetics and preventive measures), all of which contribute to different recovery outcomes. Consequently, ongoing research is essential, with an urgent need to develop effective prognostic models and treatment plans based on admission data.

According to the 2017 Commission, TBI will remain a major contributor to injury-related deaths and disabilities until 2030. The annual incidence of TBI is estimated to range from 27 to 69 million cases globally (A.I.R. Maas et al., 2017). In Europe, approximately 82,000 individuals die each year due to TBI, with over 2 million people requiring hospitalization. In the USA, TBI claims the lives of 153 people daily, with 2.8 million hospital admissions annually. In India, TBI is a significant issue, particularly among the young and productive population. Epidemiological data suggest that there are approximately 1.6 million TBIs annually in India, resulting in 200,000 deaths and around 1 million individuals requiring rehabilitation services.

TBI is classified into two stages of injury based on pathophysiology. The initial injury is defined as the mechanical damage caused by trauma immediately upon occurrence. In contrast, secondary brain injury develops over time due to the progressive physiological impairments resulting from the primary injury. This process involves a series of events, such as hypercapnia, which increases intracranial pressure, causes the displacement or herniation of oedematous brain tissue, and increases cerebral blood flow. These events, in turn, lead to further complications, including ischemia, excitotoxicity, metabolic acidosis, oxidative stress, inflammation, and apoptosis. Research on gene expression has identified numerous genes that play a crucial role in the pathogenesis of secondary brain damage.

The APOE gene plays a significant role in traumatic brain injury (TBI) outcomes (Zhou, W., et al 2008) as its polymorphisms influence cholesterol availability in the central nervous system, impacting neuronal repair, regeneration, and myelination (Papaioannou, I, et al 2012; Segrest et al., et al. 1992; Boyles et al., 1985; Basu et al., et al. 1982). These variations in APOE may contribute to the differences in cognitive and motor recovery among TBI patients, affecting long-term prognosis.

Exploring genetic factors influencing TBI's prognosis is an expanding field. The APOE gene has three isoforms—E2, E3, and E4—distinguished by a single amino acid and closely linked to cholesterol metabolism. APOE is primarily produced by astrocytes in the brain and is vital for maintaining neuronal health. While some studies have associated the APOE variant with poor outcomes following TBI, other research has not provided conclusive evidence of this link. The relationship between APOE gene polymorphism and TBI outcomes remains an area requiring further investigation, particularly given the limited data currently available from Indian studies. This study evaluated the association between APOE gene polymorphism and injury severity (GCS) score following traumatic brain injury.

Methodology

The study was conducted at the Neurosurgery Inpatient Department and the Casualty of Justice K.S. Hegde Charitable Hospital in Deralakatte, Mangalore. Laboratory analyses were performed at the Central Research Laboratory, K.S Hegde Medical Academy, NITTE (Deemed to be University). Designed as a cross-sectional study, the research was conducted from February 2019 to January 2022. Patients aged 18 to 70 years presenting to the hospital with traumatic brain injury (TBI) were included in the study. Age-matched healthy donors who were willing to participate were also included as controls. To qualify as cases, patients had to meet specific age criteria, present within 48 hours of injury, and consent to participate. The Glasgow Coma Scale (GCS) was used to classify patients into groups with mild, moderate, or severe TBI. Non-traumatized, healthy donors served as the control group. The exclusion criteria for both patients and controls included various neurological and mental health conditions.

To thoroughly investigate the impact of TBI, clinical examinations were conducted, which included demographic data, details of the injury, and a range of clinical aspects observed at admission, such as blood pressure, GCS score, and CT-Brain findings.

The study was approved by the Central Ethics Committee of NITTE (Deemed to be University) on specific dates, as indicated by the permission numbers NU/CEC/2019/0250, NU/CEC/2020/0338, and NU/CEC/2021/154, ensuring compliance with ethical standards. Subject selection was conducted using convenient sampling. For genotyping purposes, blood samples from TBI patients and healthy donors were collected upon admission to the hospital. Two millilitres of EDTA-treated whole blood were stored at -20°C for genetic polymorphism analysis. DNA was isolated from the blood using a modified Miller et al. technique and quantified with a NanoDrop spectrophotometer. The DNA samples were then stored at -20°C for further analysis.

Selection of SNPs and INSILICO Analysis

SNP IDs (rs numbers) for APOE gene were collected from the published works on neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, and Traumatic Brain Injury as follows: rs440446, rs769452, rs429358, rs769455, rs7412 (Woo D et al, 2005, Radwan ZH et al 2014, Kulminski AM et al 2021, Prada D et al 2014, Reuter Rice et al 2018). Amino acid and nucleotide substitutions for each SNP were noted from NCBI website.

Point mutations in APOE have been associated with Alzheimer's disease, apoptosis after TBI, and impaired cognitive functions. Here, we evaluated the effect of missense SNPs in APOE and TP53 using several computational prediction tools.

Sequence-based Tools

SIFT: (Sorting Intolerant from Tolerant)

This tool predicts whether an amino acid substitution affects protein function based on sequence homology and the physical properties of amino acids. SIFT can distinguish between functionally neutral and deleterious amino acid changes in human polymorphisms. It uses FASTA sequence for prediction and position of amino acid substitution.

SNPs & GO: (Single Nucleotide Polymorphism & Gene Ontology)

This bioinformatics tool classifies SNPs as disease-related or neutral. This tool uses information derived from the protein sequence database, protein 3D structure, the function of the protein and Gene Ontology annotation. A score>0.5 is considered a disease-related mutation.

Panther: (Protein Analysis Through Evolutionary Relationships)

This is a diversified software system for inferring the functions of genes based on their evolutionary relationships. Input information required are FASTA format of the protein of interest and SNP position along with amino acid substitution. The mutation is classified as disease-related (Disease) or polymorphism (Neutral) along with the output value ranging between 0 and 1. Value >0.5 is predicted Disease mutation.

Consensus based

Meta- SNP:

This random forest-based binary classifier discriminates between disease-related and polymorphic non-synonymous SNVs. The required inputs are protein sequence in FASTA format and mutation in XPOSY format where X and Y are wild type and substituted amino acids respectively, and POS is position of the same. Meta-SNP takes as input the output of the four predictors such as PANTHER, PhD-SNP, SIFT and SNAP. Meta-SNP predictor is made available through a docker container at the link https://hub.docker.com/r/biofold/meta-snp. Output value ranges between 0 and 1, where mutation >0.5 is considered disease-related.

Support Vector Machine (SVM) based

I – Mutant 2.0:

This is a support vector machine (SVM) based tool for the automatic prediction of protein stability changes upon single point mutations. Predictions are based on the protein sequence. The prediction also gives the Reliability Index (RI), which ranges from 0-10. The higher the number, the more reliable the protein structure.

MuPro:

The software uses sequence and structural information to predict whether a mutation will increase or decrease the stability of the protein structure.

PhD-SNP: (Predictor of Human Deleterious Single Nucleotide Polymorphisms)

This web-based tool predicts whether or not the new amino acid derived from a nonsense SNP is disease-related. It uses the UniProtKB number along with the new amino acid position. A score>0.5 is considered a disease-related mutation.

Structure-based Tools

PolyPhen-2:

This online bioinformatics tool prognosticates the consequence of an amino acid change on the structure and function of a protein. The prediction is based on gathering information on the 3D protein structure, multiple alignments of homologous sequences, and amino acid contact information in several protein structure databases to calculate position-specific independent count scores (PSIC) for each variant. The next step is to compute the difference between PSIC scores in the two variants. A higher PSIC score difference indicates a higher functional impact of that particular amino acid change. Prediction outcomes are classified as. ≥1.0 = probably damaging, ≥0.75= possibly damaging, and ≤0.5 is considered benign.

PCR-RFLP

PCR was carried out using the following set of primers, 5'ACTGACCCCGGTG GCGGAGGAGACGCG TGC3' (forward) and 5'TGTTCCACCAGGG GCCCCAGGCGCTGG CGG3' (reverse) with annealing temperature of 65°C. The PCR product length obtained was 318bp. The PCR products were double digested with *AflIII* and *HaeII* restriction enzymes. This procedure provides results within one day. The resulting genotype and respective band lengths are mentioned in Table 1.

Results

The baseline characteristics of TBI subjects on admission are summarised in Table 2. The age of participants ranged from 18 to 72 years. The study population was predominantly male, comprising 76.5%, while female subjects accounted for 23.5%.

Upon admission, the study subjects were categorised into three groups based on their Glasgow Coma Scale (GCS) severity scores. The largest group was Mild TBI (n = 39, 45.9%), followed by Moderate TBI (n = 25, 29.4%), and Severe TBI (n = 21, 24.7%).

The mean age of the participants was 39.05 ± 14.035 years, with an average GCS score on admission of 10.99 ± 4.0.

APOE Deleterious SNP Predicted

We filtered all the SNPs that were classified as deleterious by at least 4 tools, as listed in Table 3. Accordingly, we have rs769452 C>T, rs429358 T>C, rs769455 T>C, and rs7412 C>T missense variants with L46P, C130R, R163C, and R176C list of amino acid substitutions shortlisted as more deleterious. Frequency information was collected from the 'Allele Frequency Aggregator', the ALFA project, which provides aggregator allele frequency from dbGaP. In accordance with ALFA, we could finally select rs429358 T>C and rs7412 C>T SNPs for our study, which shows allele frequency as listed in Table 4.

The APOE genotype frequencies were analysed for both healthy controls and patients with traumatic brain injury (TBI). Among the TBI patients, the most prevalent genotype was e3/e3 (71.8%), followed by e3/e4, e2/e3, e2/e4, e2/e2, and e4/e4 (as shown in Table 5). In the healthy control group, the e3/e3 genotype was also the most common (64.34%), followed by e2/e3, e3/e4, e2/e4, and e2/e2. Notably, there were no e4/e4 genotype carriers among the healthy controls.

The APOE genotype frequencies were analysed for both healthy controls and patients with traumatic brain injury (TBI). Among the TBI patients, the most prevalent genotype was e3/e3 (71.8%), followed by e3/e4, e2/e3, e2/e4, e2/e2, and e4/e4 (as shown in Table 5). In the healthy control group, the e3/e3 genotype was also the most common (64.34%), followed by e2/e3, e3/e4, e2/e4, and e2/e2. Notably, there were no e4/e4 genotype carriers among the healthy controls.

Table 1: The table presenting the RFLP product lengths and respective genotypes.

SNP Id	**APOE genotype**	**Fragment size**		**Amino acid change**
rs429358 rs7412		***Afl III***	***Hae II***	
	ε2/ ε2	231bp	267bp	Cys112, Cys158
	ε3/ ε3	231bp	232bp	Cys112, Arg158
	ε4/ ε4	295bp	232bp	Arg112, Arg158
	ε2/ ε3	231bp	267bp 232bp	Cys112, Cys158, Arg158
	ε2/ ε4	295bp 231bp	267bp 232bp	Cys112, Cys158, Arg112, Arg158
	ε3/ ε4	295bp 231bp	232bp	Cys112, Arg112. Arg158

Table 2: Baseline characteristics of subjects with traumatic brain injury

Variable	N	Mean ±SD/ Median (IQR)	Minimum, Maximum
Age	85	39.05 ±14	16, 72
GCS	85	10.99±4	3, 15
systolic bp	83	128± 20.8	110, 140
diastolic bp	82	78.46 ±11.26	70, 90
pulse(bpm)	83	83±15.4	60, 140
Rotterdam CT Brain Total	85	2.5±0.92	1,6

Table 3: Results of deleterious predictions for SNPs of APOE gene analysed by 8 prediction tools classified in four groups.

SNP rs	Uniprot accession No.	Amino acid change	Sequence-Based			Consensus-Based	SVM based				Structure Based
			SIFT	SNP & GO	Panther SCORE	Meta SNP SCORE	I-Mutant 2.0 (RI) SCORE	MuPro		PhD-SNP	PolyPhen 2 SCORE
								SVM	NEUR NET		
rs440446 C>G	P02649	N14K	NT TOL	U	U	NEUT 0.192	DEC 2	DEC -1	DEC -0.97	NEUT 0.331	U
rs769452 C>T	P02649	L46P	TOL	DIS	NEUT 0.33	NEUT 0.484	DEC 5	DEC -1	DEC -0.96	DIS 0.712	D 0.99
	P02649	L72P	TOL	U	NEUT 0.33	NEUT 0.484	DEC 5	DEC -1	DEC -0.96	DIS 0.712	U
rs429358 T>C	P02649	C130R	NT TOL	DIS	NEUT 0.474	NEUT 0.193	DEC 4	DEC -0.091	DEC -0.81	NEUT 0.188	B 0
	P02649	C156R	TOL	U	NEUT 0.474	NEUT 0.193	DEC 4	DEC -0.091	DEC -0.81	NEUT 0.188	B 0
rs769455 T>C	P02649	R163C	TOL	DIS	DIS 0.865	DIS 0.601	DEC 6	DEC -1	DEC -0.81	NEUT 0.415	D 1
	P02649	R189C	NT TOL	U	DIS 0.865	NEUT 0.482	DEC 5	DEC -1	DEC -0.89	NEUT 0.314	D 1
rs7412 C>T	P02649	R176C	NT TOL	DIS	DIS 0.716	NEUT 0.433	DEC 5	DEC -0.2	DEC -0.8	NEUT 0.258	D 1
	P02649	R202C	NT TOL	U	DIS 0.716	NEUT 0.433	DEC 5	DEC -0.2	DEC -0.8	NEUT 0.258	D 1

NT TOL- Not Tolerated; **TOL**- Tolerated; **DIS**- Disease Related; **NEUT**- Neutral; **DEC**- Decrease Protein Structure Stability; **INC**- Increase Protein Structure Stability; **CS**-Confidence Score; **RI**- Reliability Index; **SVM**- Support Vector Machine; **NEUR NET**- Neural Network; **B**- Benign; **D**- Probably Damaging; **U** – Unknown.

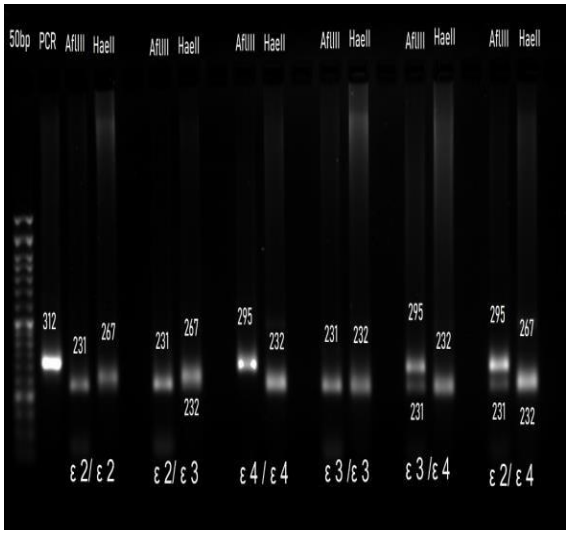

Fig 1: Agarose gel electrophoresis image presenting the patterns of APOE gene after digestion with AflIII and HaeII restriction enzymes.

Table 4: Allele frequency of APOE variants as listed in ALFA project of dbGaP.

SNP Id (rs)	Population	Sample size	Reference allele	Alternate allele
rs769452	Global	220104	T= 0.997	C= 0.0023
	South Asian	280	T= 1	C= 0.00
rs429358	Global	101010	T= 0.925	C= 0.0744
	South Asian	168	T= 952	C= 0.048
rs769455	Global	114288	C= 0.99	T= 0.0010
	South Asian	104	C= 1	T= 0.00
rs7412	Global	186114	C= 0.9168	T= 0.08316
	South Asian	146	C = 0.979	T= 0.021

Table 5: Pattern of APOE gene polymorphism among TBI patients and healthy control subjects.

APOE gene	Cases N=85		Control N=115	
polymorphism	N	%	N	**%**
e2/e2	1	1.2%	2	**1.73%**
e2/e3	8	9.4%	18	**15.65%**
e2/e4	2	2.4%	6	**5.21%**
e3/e3	61	71.8%	74	**64.34%**
e3/e4	12	14.1%	15	**13.04%**
e4/e4	**1**	**1.2%**	**0**	**0%**

Table 6: Hardy-Weinberg Equilibrium for APOE gene polymorphism**.**

		Cases	Allele frequency	Control	Allele frequency
e2/e2	Observed	1	p=0.07	2	p =0.122
	Expected	0	q=0.84	2	q= 0.787
			r=0.09		r =0.091
e2/e3	Observed	8		18	
	Expected	10		22	
e2/e4	Observed	2		6	
	Expected	1		3	
e3/e3	Observed	61		74	
	Expected	59		71	
e3/e4	Observed	12	$\chi 2$= 1.74	15	$\chi 2$= 2.49
	Expected	14		16	
e4/e4	Observed	1	p=0.88	0	p=0.77
	Expected	1		1	

There was no significant deviation from the expected gene frequencies for APOE (p=0.77) polymorphisms, as shown by Hardy-Weinberg Equilibrium (HWE) analysis among both TBI patients and healthy controls (Table 6), indicating that the alleles were in equilibrium.

The association between APOE gene polymorphisms and GCS scores upon admission was evaluated using various models (Table 7). The analysis revealed no significant correlation (p>0.05) between APOE gene.

Table 7: Association of injury severity (GCS) on admission with APOE gene polymorphism

APOE	Mild	Moderate	Severe	χ^2	p	Mild	Moderate - Severe	χ^2	p	Mild-Moderate	Severe	χ^2	p
e2/e2	0	0	1	f.e.t	0.824	0	1	f.e.t	0.81	0	1	f.e.t	0.52
e2/e3	4	2	2			4	4			6	2		
e2/e4	1	0	1			1	1			1	1		
e3/e3	27	20	14			27	34			47	14		
e3/e4	6	3	3			6	6			9	3		
e4/e4	1	0	0			1	0			1	0		
e2	5	2	4	1.237	0.539	5	6	0.001	0.97	7	4	0.923	0.33
Non e2	34	23	17			34	40			57	17		
e3	37	25	19	f.e.t	0.311	37	44	f.e.t	0.86	62	19	f.e.t	0.23
Non e3	2	0	2			2	2			2	2		
e4	8	3	4	0.797	0.671	8	7	0.407	0.52	11	4	0.038	0.84
Non e4	31	22	17			31	39			53	17		

polymorphisms and the severity of injury across the additive model, e2 vs. non-e2, e3 vs. non-e3, and e4 vs. non-e4 models

Discussion

It has been shown that Apolipoprotein E (Apo E), produced by macrophages, promotes nerve regeneration in rats following sciatic nerve transection (JK, B. et al., 1989). However, increasing evidence suggests a link between Apo E and poor outcomes after traumatic brain injury (TBI) (Teasdale, G.M. et al., 2005; Teasdale, G.M. et al., 1997; Baugh, C.M. et al., 2012). Most research indicates that the E4 variant has detrimental effects on head injury outcomes (Ariza, M. et al., 2006;), although Teasdale and colleagues did not find that E4 carriers had worse overall results (Teasdale, G.M. et al., 2005). The E4 allele has been associated with increased neurobehavioral disorders and compromised cognitive abilities (Diaz-Arrastia et al., 2003; Ariza, M. et al., 2006). It may also contribute to greater intracerebral hematomas, more severe contusions, and ischemic brain injury following TBI (Liaquat, I. et al., 2002; Smith, C. et al., 2006).

In our study, we examined three dichotomized groups (e2 vs. non-e2, e3 vs. non-e3, and e4 vs. non-e4) and six genotypes (e2/e2, e2/e3, e2/e4, e3/e3, and e4/e4) based on APOE gene polymorphism. The analysis revealed that none of the examined models of APOE gene polymorphism were statistically associated with the severity of injury as determined by the Glasgow Coma Scale (GCS) score at admission.

Numerous studies support the association between the ε4 allele and adverse neuropsychiatric outcomes, such as increased susceptibility to intracerebral hemorrhage and late-onset Alzheimer's disease (Verghese, P.B. et al., 2011). In contrast to E4, APOE2 may offer neuroprotective benefits, whereas the harmful effects of APOE4 are well-documented neurochemically (Mahley, R. et al., 2012; Corps, K.N. et al., 2015). Due to domain interaction, the distinct structure of the E4 isoform—which includes an arginine at position 112 instead of a cysteine—leads to abnormal cleavage and the release of neurotoxic fragments. APOE4 contributes to cellular apoptosis, suppresses neurite outgrowth, and increases the production of pro-inflammatory mediators from microglia. Given these pathological roles, it is hypothesized that TBI patients with the ε4 allele may experience more severe injuries, with higher subsequent damage and delayed recovery.

Subjects with the E4 isoform may be more vulnerable to injury severity post-TBI. This could be due to the cholesterol transported in CNS in the presence of E4 is VLDL due to structural compromise in E4 isoform. Whereas E3 and E2 are reported to transport LDL and HDL, respectively (Papaioannou et al. 2012; Segrest et al. et al. 1992). This variation may alter the myelination pattern ultimately altering the structure, and repair patterns in neurons. Thus, this knowledge may assist neurosurgeons with valuable prognostic information and help guide treatment strategy which may include, early rehabilitation to susceptible genotype carriers, as ApoE4 is associated with poorer outcomes and high incidences of neurodegenerative diseases post-TBI (Muza, P. et al., 2019) in those ethnic populations where ApoE4 is associated with poorer outcomes post-TBI.

Conclusion

The most common genotype among TBI patients in India was APOE3. The study found no significant association between APOE gene polymorphism and injury severity as assessed by the Glasgow Coma Scale.

Conflicts of interest

The authors do not have any conflicts of interest.

References

1) Ariza, M., Pueyo, R., del M Matarín, M., Junqué, C., Mataró, M., Clemente, I. & Sahuquillo, J. (2006). Influence of APOE polymorphism on cognitive and behavioural outcome in moderate and severe traumatic brain injury. Journal of Neurology, Neurosurgery & Psychiatry, 77(10), 1191-1193.
2) Baugh, C. M., Stamm, J. M., Riley, D. O., Gavett, B. E., Shenton, M. E., Lin, A. & Stern, R. A. (2012). Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma. Brain imaging and behavior, 6, 244-254.
3) Basu, S. K., Ho, Y. K., Brown, M. S., Bilheimer, D. W., Anderson, R. G., & Goldstein, J. L. (1982). Biochemical and genetic studies of the apoprotein E secreted by mouse macrophages and human monocytes. Journal of Biological Chemistry, 257(16), 9788-9795.
4) Boyles, J. K., Pitas, R. E., Wilson, E., Mahley, R. W., & Taylor, J. (1985). Apolipoprotein E associated with astrocytic glia of the central nervous system and with nonmyelinating glia of the peripheral nervous system. The Journal of clinical investigation, 76(4), 1501-1513.
5) Chiang, M. F., Chang, J. G., & Hu, C. J. (2003). Association between apolipoprotein E genotype and outcome of traumatic brain injury. Acta neurochirurgica, 145, 649-654.
6) Corps, K. N., Roth, T. L., & McGavern, D. B. (2015). Inflammation and neuroprotection in traumatic brain injury. JAMA neurology, 72(3), 355-362.
7) Diaz-Arrastia, R., Gong, Y., Fair, S., Scott, K. D., Garcia, M. C., Carlile, M. C., ... & Van Ness, P. C. (2003). Increased risk of late posttraumatic seizures associated with inheritance of APOE ϵ4 allele. Archives of neurology, 60(6), 818-822.
8) JK, B. (1989). A role for apolipoprotein E, apolipoprotein A-1, and low density lipoprotein receptors in cholesterol transport during regeneration and remyelination of the rat sciatic nerve. J Clin Invest, 83, 1015-1031
9) Kulminski, A. M., Philipp, I., Loika, Y., He, L., & Culminskaya, I. (2021). Protective association of the ε2/ε3 heterozygote with Alzheimer's disease is strengthened by TOMM40–APOE variants in men. Alzheimer's & Dementia, 17(11), 1779-1787.
10) Liaquat, I., Dunn, L. T., Nicoll, J. A., Teasdale, G. M., & Norrie, J. D. (2002). Effect of apolipoprotein E genotype on hematoma volume after trauma. Journal of neurosurgery, 96(1), 90-96.
11) Maas, A. I., Menon, D. K., Adelson, P. D., Andelic, N., Bell, M. J., Belli, A., ... & Francony, G. (2017). Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. The Lancet Neurology, 16(12), 987-1048.
12) Mahley, R. W., & Huang, Y. (2012). Apolipoprotein e sets the stage: response to injury triggers neuropathology. Neuron, 76(5), 871-885.
13) Muza, P., Bachmeier, C., Mouzon, B., Algamal, M., Rafi, N. G., Lungmus, C. & Ojo, J. O. (2019). APOE genotype specific effects on the early neurodegenerative sequelae following chronic repeated mild traumatic brain injury. Neuroscience, 404, 297-313.
14) NCBI Bookshelf. (2023). Traumatic Brain Injury: Definition, Epidemiology, Pathophysiology - StatPearls. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK554376/
15) Olivecrona, Z., & Koskinen, L. O. D. (2017). APOE ε4 positive patients suffering severe traumatic head injury are more prone to undergo decompressive hemicraniectomy. Journal of clinical neuroscience, 42, 139-142.
16) Papaioannou, I., Simons, J. P., & Owen, J. S. (2012). Targeted in situ gene correction of dysfunctional APOE alleles to produce atheroprotective plasma ApoE3 protein. Cardiology research and practice, 2012(1), 148796.
17) Prada, D., Colicino, E., Power, M. C., Cox, D. G., Weisskopf, M. G., Hou, L. & Baccarelli, A. A. (2014). Influence of multiple APOE genetic variants on cognitive function in a cohort of older men–results from the Normative Aging Study. BMC psychiatry, 14, 1-9.
18) Radwan, Z. H., Wang, X., Waqar, F., Pirim, D., Niemsiri, V., Hokanson, J. E. & Kamboh, M. I. (2014). Comprehensive evaluation of the association of APOE genetic variation with plasma lipoprotein traits in US whites and African blacks. PLoS One, 9(12), e114618.
19) Reuter-Rice, K., Regier, M., Bennett, E., & Laskowitz, D. (2018). The effect of the relationship of APOE polymorphisms and cerebral vasospasm on functional outcomes in children with traumatic brain injury. Biological Research for Nursing, 20(5), 566-576.
20) Segrest, J. P., Jones, M. K., De Loof, H., Brouillette, C. G., Venkatachalapathi, Y.V., & Anantharamaiah, G. M. (1992). The amphipathic helix in the exchangeable apolipoproteins: a review of secondary structure and function. Journal of lipid research, 33(2), 141-166.
21) Smith, C., Graham, D. I., Murray, L. S., Stewart, J., & Nicoll, J. A. R. (2006). Association of APOE e4 and cerebrovascular pathology in traumatic brain injury. Journal of Neurology, Neurosurgery & Psychiatry, 77(3), 363-366.
22) Teasdale, G. M., Murray, G. D., & Nicoll, J. A. R. (2005). The association between APOE ε4, age and outcome after head injury: a prospective cohort study. Brain, 128(11), 2556-2561.
23) Teasdale, G. M., Nicoll, J. A., Murray, G., & Fiddes, M. (1997). Association of apolipoprotein E polymorphism with outcome after head injury. The Lancet, 350(9084), 1069-1071.
24) Verghese, P. B., Castellano, J. M., & Holtzman, D. M. (2011). Apolipoprotein E in Alzheimer's disease and other neurological disorders. The Lancet Neurology, 10(3), 241-252.
25) Woo, D., Kaushal, R., Chakraborty, R., Woo, J., Haverbusch, M., Sekar, P., & Broderick, J. (2005). Association of apolipoprotein E4 and haplotypes of the apolipoprotein E gene with lobar intracerebral hemorrhage. Stroke, 36(9), 1874-1879.