SIMPLIFIED GENETICS

APOE Discussions and Research

ApoE4 carriers of the "concussion gene" have been shown to have more severe concussions, longer recovery times and an increased likelihood of having problems six months out versus those without the gene. Carriers are found to be 10 times more likely to develop Alzheimer's disease after a concussion. Carriers with both copies of the gene (2% of population) are 19 times more likely to develop Alzheimer's.

Presence of ApoE ε4 has been shown to reduce the prospect of a favorable outcome in children and young adults. The influence of APOE genotype in younger patients after head injury can be expressed as, at age <15 years, carriage of ApoE ε4 being equivalent to ageing by 25 years. This finding is consistent with experimental data suggesting that the effect of APOE genotype on outcome after head injury may be expressed through the processes of repair and recovery.[18]

In 2013, the American Academy of Neurology published the article, "Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the Guideline Development Subcommittee of the American Academy of Neurology." In the article, they state that "ApoE epsilon 4 and concussion history is recognized as a risk factor for chronic neurobehavioral impairment.[23]*" and report the research as class II, data.*

They go on to publish, along with that article, the "Summary of Evidence-Based Guidelines: Evaluation and Management of Concussions in Sports", which under the heading "Clinical Context: Retirement from Play—Counseling" states that the presence of ApoE4 should be a consideration for retirement from play when counseling players with multiple concussions.

This statement is endorsed by:

- *NFL Players Association*
- *American Football Coaches Association*
- *Child Neurology Society*
- *National Academy of Neuropsychology*
- *National Association of Emergency Medical Service Physicians*
- *National Association of School Psychologists*
- *National Athletic Trainers Association*
- *Neurocritical Care Society*

Some people may not want to know this information and I expect it will be challenged initially. If you knew that three of your players, on each play, were using a helmet that, not only offered them less protection than the other players but also made them 10 times more likely to get Alzheimer's disease and twice as likely to develop CTE, you would want a way to identify those players. That is what research says about the presence of this gene. And we can now accurately identify those players.

Identifying these individuals will enable those responsible for their wellbeing to provide optimal care and offer better counseling to protect them as they age, particularly when the injuries are being sustained in a voluntary sport activity as opposed to accidental trauma. In those instances, genetic testing can identify athletes who need to be proactive in doing the proper things during and after contact sports to minimize the potential impact on their lives as they age, like increased protective mechanisms and practices and activities for the enhancement of cognitive reserve.

I think ***not*** performing this test may even confer liability to universities for not offering to provide student athletes with the answer to this risk factor and will eventually be required at the level of the sports physical for clearance to participate in a contact sport. E4/E4 carriers will eventually have to be cleared yearly by an entity like Cerebrum or a concussion specialist after undergoing specialized testing (eye tracking, speech pattern testing and neurocognitive assessment if for no reason other than to assess a baseline prior to beginning the sport).

Essentially, the test identifies which Apolipoprotein E Polymorphism an individual possesses. There are 3 common polymorphisms which are identified as ApoE ε2, ApoE ε3 and Apo E ***ε4.*** *Each person has 2 of these located on the 19th chromosome.*

Resulting genotype variations are:
ε2/ ε2 ε2/ ε3 ε2/ ***ε4 - Carrier***

ε3/ ε3 ε3/ ***ε4 - Carrier***

ε4/ ε4 – Homozygous

Approximately 75% of the U.S. population does not carry the Apo ***ε4*** *gene, but roughly 25% carry at least one copy and 2% of the population carries two copies.*

Apo E is involved in cholesterol metabolism and deposition, and is essential in the repair of damaged nerves by depositing lipids needed for repair of damaged cells. [1,2,3]

Apo E up-regulated with neuronal stress, like an inflammatory response protein, but each polymorphism is of different quality and is produced in different quantities. What we are testing for is to see if the athletes possess a version of the Apo E ε4 polymorphism.

Apo E ε4 = a bad version of a good protein. ApoE ε4 is associated with a decrease in the ability of the brain to respond and to repair neurons following injury.[4]

Why does ApoE ε4 lead to poor quality neuronal repair?

1. Abnormal deposition of β-Amyloid[5]

2. Impaired β-Amyloid Clearance[7]
3. NeuroFibrillary Tangle Formation[5]
4. Neural plaque formation.[6]
5. Altered Cerebrovascular Integrity[6]

What else do we know about ApoE ε4?

ApoE ε4 is also associated with higher incidences of coronary disease and dyslipidemias. Like with β-Amyloid deposition and poor clearance, the ApoE ε4 structure impairs its ability to hang on to cholesterol or to pick it back up again for clearance, hence the vascular deposition and coronary issues exemplified in this population of patients.

ApoE ε4 leaves debris behind that leads to dysfunction and increased likelihood of symptoms of impairment that are evident in longer healing times, increased susceptibility to recurrent concussive events and markedly increased likelihood of global neurologic dysfunction that often manifests as the behavioral changes associated with the progressive clinical stages CTE, dementia and Alzheimer's disease. ApoE ε4 is recognized as a major genetic risk factor for developing Alzheimer's disease. [8]

The presence of the ApoE ε4 allele is associated with dramatic blood-brain barrier defects following brain trauma.[6] ApoE ε4 influences the neurodegenerative cascade after TBI by affecting β-Amyloid deposition.

What evidence exists to support that the established poor healing qualities of ApoE ε4 create any measureable problems for those with this polymorphism who sustain a concussive event?

Research : Individual studies and my summaries of each

Several studies in the last 20 years have supported the idea that ApoE ε4 carriers have worse outcomes following TBI than non-carriers.[8]

Study A - 236 patients. Examined the risk of Alzheimer's disease following TBI and determined a 10-fold increase in Alzheimer's disease following head trauma in ApoE ε4 carriers.[19] Neurology, 1995.

Study B - 30 professional boxers (23-76 yo) with >12 bouts studied. Determined that ApoE ε4 carriers were found to have significantly greater scores on a clinical scale of chronic TBI than non-carriers.[10] JAMA, 1997.

Study C - Prospective study of 57 TBI patients. Significant negative outcome findings in *ApoE ε4 carriers vs. noncarriers when controls were placed for age, severity of initial injury and initial CT scan findings. Those with unfavorable outcomes at six*

months (severe disability, vegetative state or death) were more than twice as likely to carry the ApoE ε4 allele.[11] Lancet, 1997.

Study D - 87 adults with mild (GCS>13) to moderate (9-12) TBI. Patients positive for ApoE ε4 allele had adjusted lower mean scores on 12 of the 13 neuropsychological outcomes measured at three weeks and 11 of the 13 at six weeks following injury.[12] Neurology, 2002.

Study E - 325 patients, nine-year prospective study of fall-related TBI in the elderly. Determined that fall-related TBI in this group predicted earlier onset of dementia, particularly in carriers of ApoE ε4.[15] Eur J Neurology, 2005.

Study F - 648 patients referred for TBI rehabilitation. ApoE ε4 was not found to impact severity of initial injury, but was associated with worse chronic TBI measurement scores.[13] J Neurotrauma, 2011.

Study G - 53 professional football players studied. Older players with ApoE ε4 exhibited significantly lower cognitive test scores than those without the allele. Determined that cognitive status of professional athletes with repeated exposure to head trauma was influenced by age, presence of ApoE ε4 and cumulative exposure to contact.[14]

Study H - 396 patients with TBI, ages 2 to 70 with an initial neuropsychiatric testing done within six months of the original injury. Reassessed an average of 18 years following their injury. Statistically significant number of those without the ApoE ε4 allele had good late outcomes (31%) compared to carriers of the ApoE ε4 allele (22%).[16]J Neurol Neurosurg Psychiatry, 2003.

Study I - 110 veterans in Defense and Veterans Head Injury Center. Carriers of ApoE ε4 determined to display worse memory performance than those without the allele. No difference in demographics, injury variables or executive functions.[17] Neurology, 2002.

Study J - 1094 patients enrolled. Prospective cohort. Presence of ApoE ε4 reduced the prospect of a favorable outcome in children and young adults. The influence of APOE genotype in younger patients after head injury can be expressed as, at age <15 years, carriage of ApoE ε4 being equivalent to ageing by 25 years. This finding is consistent with experimental data suggesting that the effect of APOE genotype on outcome after head injury may be expressed through the processes of repair and recovery.[18]

Study K - 69 TBI patients. Carriers of ApoE ε4 were more likely to experience longer periods of being unconscious following TBI and were significantly less likely to have a good functional outcome (defined as no dysarthria, behavioral abnormalities, or dysphasia; no severe cognitive abnormalities; and the ability to live independently). [20] Neurology. 1999

Testing for this risk factor, in my opinion, should be mandatory before medical clearance in high impact sports, particularly in children less than 15 years of age. Studies have shown that concussions are anywhere from 50-70% underreported in high school and college athletes. [21,22]

Most common reasons cited for not reporting:

1. *Did not think injury was serious enough*
2. *Did not want to be taken out of the game*
3. *Did not recognize concussive symptoms*[21]

Identifying this risk factor can allow those affected to make better decisions to protect themselves now and in the future.

Cognitive reserve is thought to play a significant role in the development of CTE and is considered protective against clinical manifestations of other neurodegenerative processes such as Alzheimer's disease. This reserve is believed to be developed through occupation and education and can minimize the functional and cognitive impact of these neurodegenerative sequelae of TBI, particularly in those with increased susceptibility determined by identifying the ApoE polymorphism they possess.

The APOE ε4 allele and human traumatic brain injury outcome

It has been reported that head injury triggers amyloid β protein deposition in those with genetic susceptibility conferred by APOE ε4, and that amyloid β protein deposition is recorded in one third of severe head injury patients at necropsy.[38] *It has been postulated that head injury-related deposition of amyloid β protein in those who survive may be followed by the development of the full spectrum of Alzheimer's disease pathology later in life.*

The Glasgow group were the first to report in a clinical setting the influence of APOE ε4 and a poor outcome following traumatic brain injury. Since then, numerous clinical studies in all types of traumatic brain injury have supported the association of APOE ε4 allele possession with an unfavorable outcome. It was reported recently that the possession of the APOE ε4 allele predisposes a patient to a larger-sized intracerebral hematoma.

Similarly, possession of the APOE ε4 allele has also been shown to be associated with a poor outcome following spontaneous non-aneurysmal intracerebral hemorrhage, hemorrhage associated with amyloid angiopathy, subarachnoid hemorrhage and, more recently, an increased risk of developing cerebral amyloid angiopathy in patients recovering from traumatic brain injury.

It has been reported that head injury triggers amyloid β protein deposition in those with genetic susceptibility conferred by APOE ε4. Presently, very few reports are available documenting the effect of APOE ε4 status and human traumatic brain injury.

Previous reported studies were on small cohorts and are generally institutionally based, with very few studies looking at moderate to severe traumatic brain injury. Furthermore, most, if not all, studies reported to date were conducted in white population groups, with a predominance of males.

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