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Genetics and outcomes after traumatic brain injury (TBI): What do we know about pediatric TBI?

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Abstract

Human genetic association studies in individuals with traumatic brain injury (TBI) have increased rapidly over the past few years. Recently, several review articles evaluated the association of genetics with outcomes after TBI. However, almost all of the articles discussed in these reviews focused on adult TBI. The primary objective of this review is to gain a better understanding of which genes and/or genetic polymorphisms have been evaluated in pediatric TBI. Our initial search identified 113 articles. After review of these articles only 5 genetic association studies specific to pediatric TBI were identified. All five of these studies evaluated the apolipoprotein (APOE) gene. The study design and methods of these identified papers will be discussed. An additional search was then performed to evaluate genes beyond APOE that have been evaluated in adult TBI; findings from these studies are highlighted. Larger genetic studies will need to be performed in the future to better elucidate the association of APOE and other genes with outcomes after TBI in children. There is great potential to utilized genetic information to inform prognosis and management after TBI in children; however, we have much work ahead of us to reach the goal of individualized management.

Keywords

Brain injuries; child; genes; genetic polymorphism; epidemiology; pediatric; humans

1. Introduction

Traumatic brain injury (TBI) is a significant cause of morbidity and mortality. Approximately 1.7 million people in the US alone sustain a TBI annually [1]. However, individuals with seemingly very similar injuries often have vastly different outcomes. Genetic factors may explain, in part, differential recovery trajectories. As our genetic and genomic technologies have improved, genetic analysis has become more accessible for use in the study of outcomes after TBI.

Genetic association studies typically fall under two types of approaches; candidate gene approaches or genome-wide association studies (GWAS) [2]. In candidate gene studies,

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prior knowledge is required to form hypotheses related to specific functions of genes and the phenotype or outcome of interest [2]. Single Nucleotide Polymorphisms (SNPs) are genetic variants that correspond to a difference in a single base pair in deoxyribonucleic acid (DNA). SNPs may be located in critical areas in genes and may ultimately lead to changes in a protein hypothesized to be important in a disease specific pathway. Alternatively, in GWAS, prior knowledge about a disease specific gene is not required [2]. GWAS are more exploratory in nature and often consist of the screening of millions of SNPs for an association with an outcome of interest. GWAS are particularly useful in identifying groups of genetic variants or regions of interest within a specific gene that can be further analyzed to better characterize pathophysiologic pathways. However, a major limitation for GWAS is the large number (> 100,000 cases) of samples required to attain statistical significance.

To our knowledge, there have been no GWAS performed to evaluate outcomes after TBI likely in part due to the large sample size required. However, various review articles published recently have discussed specific genes potentially important to outcomes after TBI. Due to the complex nature of TBI, there are various pathophysiologic pathways that could be influenced by genetics and potentially contribute to varied outcomes after injury. A recent review by McAllister [3] postulated several domains that may be influenced by genetics and are important to the modulation of outcomes after neurotrauma, including pre-injury risk factors, response to neurotrauma, repair and plasticity, pre- and post-injury cognitive and neurobehavioral capacity/reserve, and epigenetic factors [3]. In particular, there has been an extensive study of the role of the apolipoprotein (APOE) gene in outcomes and recovery after TBI [4]. APOE is an attractive target because it is thought to play an important role in synaptic repair, remodeling, and neuron protection [5]. Three commonly reported alleles of the APOE gene include APOE e2, e3, and e4. The presence of the APOE e4 allele has been associated with poorer global functional outcomes after adult TBI; however, the association is small to modest in magnitude [6] and likely only explains a portion of the variation in recovery after TBI. Since brain injury is a complex process, multiple other molecular pathways may be related to outcomes or recovery after injury. Due to the oxidative stress, inflammatory processes, and cell death that occur after TBI, genes associated with these pathways are also attractive to evaluate. Several studies have identified an association between genes specific to cell regulation and outcomes after TBI in adults [7–10]. Additionally, because cognitive and behavioral sequelae are common after brain injury, catecholamine-related genes important to regulation of behavior, attention, and executive function may also be associated with outcomes after TBI. Several studies in adult TBI demonstrated an association among dopamine-related genes and cognitive and behavioral outcomes after TBI in adults [11–15]. Overall, the study of the association of genetics with outcomes after TBI is in the early stages. Multiple genes are likely to influence recovery; therefore, it will be important to continue to evaluate the influence of other genes beyond APOE in recovery after TBI.

To date, genetic association studies described in recent reviews have focused on the adult TBI population. TBIs in children occur when the brain is at a significantly different stage of development and maturation compared to TBI in adults; therefore, genes or polymorphisms important to outcomes or recovery after adult TBI may be significantly different for pediatric TBI. The aim of this article is to review human genetic association studies specific to TBI in children. This review will evaluate the methodology of these studies and discuss them in the context of genetic association studies performed in adult TBI. The potential future directions of genetic association studies after TBI in children will also be discussed.

2. Methods

An initial literature search was performed using Pub Med on February 21, 2012. The search terms included (gene or genotype or polymorphism) and traumatic brain injury (TBI) The search was limited to "Human" studies of children 0–18 years published in "English" using the Pub Med limits function. The overriding inclusion criterion for articles was that they had to evaluate the association of "genes", "genotypes", or "polymorphisms" with outcomes after pediatric TBI. Articles were excluded if the primary study population included non-traumatic brain injuries (e.g., perinatal brain injury, cerebral palsy, anoxic brain injury) or did not have a study population with an average age below 18 years.

A follow-up literature search was performed using The Human Genome Epidemiology Network (HuGE Net) (http://hugenavigator.net/HuGENavigator/startPagePhenoPedia.do) on March 12, 2012 [16,17]. HuGENet is a global collaborative effort coordinated by the US Centers for Disease Control and Prevention (CDC). The HuGE Navigator is a searchable online database of published data on human genetic associations and human genome epidemiology studies published since 2000. The database is updated weekly and is based on MeSH indexing of PubMed records. The HuGE Navigator uses a computerized literature search screening tool based on machine-learning techniques and has a sensitivity of 97.5% and specificity of 98.3% [18]. A curator then manually reviews to verify that the articles meet criteria for indexing on HuGENet.

The primary search term used in the navigator was "Brain Injuries". Articles specific to TBI were included, while articles that primarily evaluated other types of brain injuries were excluded (e.g., anoxic brain injury, stroke, etc). Additional MeSh search terms ("Brain Injury, Chronic"; "Cerebral Hemorrhage, Traumatic"; "Epilepsy, Post-Traumatic"; "Brain Concussion"; "Brain Hemorrhage, Traumatic") were also used in the HuGE Navigator to ensure that all articles specific to TBI were identified. All of the studies identified in our initial search for pediatric specific articles were also identified using the HuGE navigator and no new studies were identified.

3. Results

Our pediatric specific search initially identified 113 studies. Based on review of article titles, abstracts, and methods sections of the papers, 4 articles met the inclusion criteria. Articles were excluded for two primary reasons: (1) the mean age of the population was above 18 years of age and (2) TBI was not the focus of the study (e.g., perinatal or anoxic brain injury). All 4 articles evaluated the association of the APOE genotype with of outcomes after pediatric TBI. Additionally, one review article entitled "Apoliprotein and brain injury: implications for children" was identified. On review of the text, one unpublished study was described in the article that evaluated the association of Apoliprotein E and outcomes after pediatric TBI. After reviewing the references of the 5 articles identified, 1 additional paper was identified that included both adult and pediatric participants, but stratified analysis by age. A follow-up search with the HuGE Navigator did not reveal any additional articles. All of the studies included in this review evaluated the association of the APOE gene with outcomes after pediatric TBI. Given the limited number of studies examining genetic influences in pediatric TBI, we chose to include all of them despite considerable heterogeneity in study design and outcomes. Detailed descriptions of the studies' methodologies and findings are below.

3.1. Summary of genetic studies in pediatric TBI (Table 1)

Quinn et al. [19] evaluated the association of APOE e4 allele and post-traumatic brain swelling in children who died following TBI [19]. The study consisted of 165 cases from

1962–2000 of children between the ages of 2–19 years who survived 1 hour to 5 months (median 3 days) after injury. The median age was 13 years and 76% were male. Race or ethnicity of the study population was not described, but the study was conducted in Glasgow, Scotland and Southampton, UK. 78% of the injures were due to road traffic accident, 12% due to falls, 8% due to assault, and 2% were secondary to other causes. APOE genotyping was performed using postmortem tissue in 64% (106/165) of the cases Genotyping was performed "blind" to histological assessments. The primary outcome of presence of cerebral swelling (unilateral or bilateral) was determined by macroscopic and microscopic analysis of post-mortem brains. Twenty-five percent (27/106) possessed the APOE e4 allele. However, approximately equal proportions of individuals with (66%) and without the e4 allele (65%) had evidence of brain swelling on autopsy. Multiple other outcomes were measured in the study, including presence of skull fracture, raised intracranial pressure, ischemic damage, hematomas, contusion index, survival time, and microscopically graded diffuse axonal injury; however, the association of the e4 allele with these other outcomes was not reported. Overall, this study did not find an association of the APOE e4 allele with the presence or absence of cerebral swelling after pediatric TBI. One of the primary limitations of the study was that it only included post-mortem cases, thus biasing the study towards individuals that likely had more severe injuries and a greater likelihood of poor outcomes.

Moran et al. [20] evaluated whether APOE alleles were a predictor of outcomes in children after mild TBI [20]. The study included children ages 8–15 years that presented to the emergency department and were diagnosed with concussion. Inclusion criteria included loss of consciousness (LOC) or a Glasgow Coma Scale (GCS) score of 13 or 14, or two or more acute signs or symptoms of concussion noted by emergency department personnel. Exclusion criteria included LOC more than 30 minutes, any GCS below 13, delayed neurological decline, Abbreviated Injury Severity (AIS) score above 3, any surgical intervention, previous head injury requiring medical treatment, history of severe psychiatric illness resulting in hospitalization, premorbid neurological disorders or mental retardation, hypoxia, hypertension, shock during or following injury, injury resulting from child abuse or assault, or injuries that would interfere with neuropsychological testing. Outcomes were assessed in the emergency department and at 2 weeks, 3 months, and 12 months post-injury. Outcome measures included assessments of memory (California Verbal Learning Test, child version), development (Developmental Test of Visual-Motor Integration), neuropsychological functioning (Cambridge Neuropsychological Test Automated Battery), general intelligence (Wechsler Abbreviated Scale of Intelligence), and academic achievement (Wide Range Achievement Test). Post-concussive symptoms were also assessed with the Post-Concussive Symptom (PCS) Interview and the Health and Behavior Inventory (HBI). 387 children were initially eligible for the study, 186 agreed to participate, and 99 were genotyped. Of the 99 participants 28 had a least one APOE e4 allele and 71 did not have any APOE e4 alleles. The average age of the APOE e4 allele group was 11.73 years and the non-e4 allele group was 12.06 years. 71% and 69% of the e4 allele and non-e4 allele groups were male, respectively. Both groups were 82% Caucasian. The e4 allele carrier group was more likely to have presented with a GCS score below 15. Additionally, the e4 group performed better on the Developmental Test of Visual-Motor Integration than the non e4 group ($P < 0.05$). The groups did not differ on any of the other measures evaluated. The overall conclusion of the study was that presence of at least one APOE e4 allele was not significantly associated with differential outcomes on neuropsychological testing or post concussive ratings after mild TBI in children.

Lo et al. [21] evaluated the association of the APOE alleles with cerebral perfusion pressure (CPP) and global outcome in 65 critically ill children admitted to the intensive care unit after TBI [21]. Information specific to age and GCS scores was not reported for the participants

[21]. Additionally, participant ethnicity was not reported; however, the study was performed in the United Kingdom. Forty-five of 65 children had intracranial pressure monitoring performed. Outcome measures assessed included CPP, modified GCS, and modified Glasgow Outcome Scale (GOS). 21% were APOE e4 allele carriers and 78% were non-carriers. 27% of the APOE e4 carriers had a poor outcome versus 11% of the non-carriers, but this was not statistically significant ($p = 0.35$). However, increased CPP insult was associated with a poor outcome as measured by GOS (poor outcome = score of 1, 2, or 3). Poor outcomes 6 months after injury were more likely in carriers of the APOE 4 allele with less CPP insult compared to those without the e4 allele ($p = 0.03$). Overall, the Lo et al. [21] study suggests that individuals that are carriers of the APOE e4 allele may be less tolerant to increases in cerebral perfusion pressure compared to children that do not carry the e4 allele. Some limitations to the study include the lack of demographic information provided specific to age of injury, severity of injury, and ethnicity of the population, thus making it difficult to make inferences about the generalizability of the findings in the study. Additionally, the cohort in the study included a higher proportion of individuals with the e2 allele compared to the general population, which may have confounded the results.

Brichtova and Kozak [22] evaluated the association of the APOE alleles with outcomes after TBI in 70 children [22]. The cohort consisted of 48 boys (69%) and 22 girls (31%), ranging in age from 1 month to 17 years (mean age 9.47 years, SD: 4.87). Fifteen (21%) had mild TBI (GCS 13–15), 10 (14%) had moderate TBI (GCS 9–12), and 45 (64%) had severe TBI (GCS 3–8). Ethnicity was not reported in the study; however, the study was conducted in the Czech Republic. The primary outcome measure was GOS at 12 months post-injury. 27% of the APOE e4 carriers had a poor outcome based on GOS (scores of 1, 2, or 3) compared to 14% of the non-APOE e4 carriers. Specifically, the authors found that the APOE e4 genotype was associated with an unfavorable outcome when compared to e2/e3 and e3/e3 genotypes. Overall, this study found that the presence of the APOE e4 allele was associated with poor global outcomes as measured on the GOS.

Teasdale et al. [23] evaluated whether the APOE e4 allele was associated with poor global outcomes after TBI in individuals age 0–93 years (mean age 37 years) [23]. 1094 individuals were initially included in the study with 984 participants undergoing genotyping. Of the 984 participants, 81% were male, 28% had a mild TBI (GCS 13–15), 19% had a moderate TBI (GCS 9–12), and 54% had a severe TBI (GCS 3–8). Race and ethnicity were not described, but the study was performed in Southampton, UK. There was no overall association found between the APOE genotype and outcome after injury. 36% of APOE e4 carriers had an unfavorable outcome compared with 33% of non-carriers. However, an interaction between age and outcome was observed, with younger age being associated with a greater likelihood of a poor outcome. In children less than 16 years, there was a 3.06 (95% confidence interval: 1.22–7.65) greater odds of an unfavorable outcome for carriers of the APOE e4 allele compared to non-carriers. Of the 212 children less than 16 years in the study, 94% non-carriers of the APOE e4 allele and 83% of the carriers of the APOE e4 allele had a favorable outcome. Demographics specific to the child participants were not reported. Overall, this study indicated that there may be an age effect related to the presence of the APOE e4 genotype, with the presence of the APOE e4 allele in younger individuals being associated with a greater risk for an unfavorable outcome.

The final study identified was an unpublished study that was described in the context of a larger review article by Blackman et al. [5]. The study included 71 children with a TBI requiring inpatient rehabilitation admission. The mean age was 13 years and 2 months. Further demographic variables were not reported. The primary outcome was the Functional Improvement Measure for Children quotient (WeeFIM, version 5.01) on discharge from inpatient rehabilitation. The WeeFIM Quotient was better for APOE e4 carriers compared to

non-carriers. However, the e4 frequency in the population studied was only 4%, which may have limited the ability of the authors to make definitive conclusions.

3.2. Combined analysis of pediatric APOE studies

Because the Brichtova and Kozak [22], Lo et al. [21], and Teasdale et al. [23] articles all used GOS as an outcome measure, we were able to combine the data from these studies to assess to association of the APOE e4 allele on global outcomes 6–12 months post TBI in children. When combining the data from these papers, 77/95 carriers (81%) and 230/252 non-carriers (91%) of APOE e4 had a good outcome (GOS scores of 4 or 5) and 18/95 carriers (19%) and 22/252 (9%) non-carriers of APOE e4 had a poor outcome (GOS scores of 1, 2, or 3) 6 or 12 months after injury. Analysis of the combined data using SAS enterprise guide 4.3 revealed a 2.44 (95% confidence interval: 1.25–4.80) greater odds of having a poor outcome in children that are carriers of the APOE e4 allele compared to non-carriers.

4. Discussion

Our review indicates that there is a paucity of genetic association studies specific to TBI in children. The only gene evaluated to date is APOE and the findings are mixed. However, the combined data from 3 studies that used GOS as a common outcome measure suggests that the APOE e4 allele is associated with poor global outcomes 6–12 months after TBI in children. This is in agreement with a meta-analysis performed in adult TBI that found the APOE e4 allele to be significantly associated with poor outcomes assessed by GOS 6 months after injury (relative risk = 1.36; 95% confidence interval 1.04–1.78) [6]. Our combined analysis demonstrated a slightly larger association (odds ratio = 2.44); however, the individuals in our analysis likely consisted of children with more severe injuries, which may bias the results towards the more severe population. Future research is needed to determine if the association of the APOE e4 allele with poor outcomes holds true across all severities of injury. Additionally, future studies will need to evaluate if there are age effects within childhood TBI, especially because the brain is actively developing and changing throughout childhood and there may be differential genetic effects for younger children versus older children.

One study identified in our review failed to find an association between APOE and neuropsychological recovery and post-concussion symptoms after mild TBI in children. Several studies evaluating the association of APOE genotype with outcomes after mild to moderate brain injury in adults have been performed, and the results have been mixed. Several studies did not identify a significant association between APOE genotypes and neuropsychological outcomes after mild to moderate TBI in adults [24–26]. However, other studies have demonstrated an increased risk of problems after mild to moderate TBI in adults who are APOE e4 carriers. One study found an association between APOE e4 carriers and poorer neuropsychological outcomes at 3 weeks, but not at 6 weeks post-injury [27]; another study demonstrated that there was an increased risk of fatigue in APOE e4 carriers after mild TBI in adults [28]; a third study found head injury in combination with the APOE e4 genotype increases the risk of dementia [29]. Future studies will need to be performed to better elucidate the influence of APOE genotype on differing outcomes after varying severities of TBI.

Several studies have also evaluated the association of APOE with the risk of sustaining a concussion. Kristman et al. [30] performed a prospective evaluation in search for an association between the APOE e4 allele and concussion injuries in college athletes. They did not identify an association with a risk of sustaining a concussion between APOE e4 carriers and non-carriers [30]. Similarly, Terrel et al. [31] did not find an association between the

APOE e4 allele and self-reported history of multiple concussions in college athletes [31]. However, a polymorphism in another area of the APOE gene, the promoter region, was associated with a graded increase in self-reported history of concussion [31]. Most recently, Tierney et al. [32] demonstrated an association between the presence of both the APOE e4 allele and APOE promoter polymorphism with a history of at least one concussion injury [32]. The findings from this study indicate that multiple polymorphisms in the APOE gene may interact with each other to determine overall risk of concussion. In the future, studies evaluating the association of the APOE gene with outcomes after mild TBI in children should consider evaluating the influence of the polymorphism in the APOE promoter region used in the evaluation of concussion injuries in college athletes. Additionally, the Tierney et al. [32] study highlights the potential importance of evaluating the influence of a combination of genetic polymorphisms within or across genes on outcomes in future genetic association studies.

4.1. Beyond APOE in adult TBI

The association of APOE with outcomes after TBI in adults has been well studied; however, the pathophysiology of TBI is complex and multiple other genes likely influence outcomes. Genes that influence a range of pathways including cell-cycle regulation and cognitive processing may also be important to recovery after TBI. Because the genetic association studies in pediatric TBI have only evaluated APOE, we also used the HuGE navigator to identify genes beyond APOE that have been associated with outcomes after TBI in adults. Since the primary goal of this review articles was to focus on TBI in children, findings from the adult search are briefly summarized below, but detailed in a table in Appendix A.

Using the HuGE navigator, 74 publications were identified and included 29 genes. Eight publications were excluded as they did not evaluate TBI specifically as a diagnosis [33–39] or only included penetrating brain injuries in the population evaluated [40]. Forty-three of the publications were specific to the association of the APOE gene with outcomes after TBI [6,19–22, 24,25,28–30,32,41–72]; one was a meta-analysis [6]. Twenty-three of the studies evaluated the association of genes besides APOE alleles with outcomes after TBI in adults [7–12,15,31,73–83] (Appendix A). A wide variety of genes beyond APOE potentially associated with outcomes after TBI in adults have been evaluated. Outcomes measured in these studies varied widely and included survival, global disability outcomes, higher cognitive skills, and medication response. The studies are fairly recent as they have all been published in 2005 or more recently. These studies highlight the potential for different genes to be important at different stages after TBI. For example, the interleukin genes, which are involved in the cellular proliferation, seem to be important in survival and global outcomes after injury [7,9,76,81,84] while dopamine related genes may be more important for longer-term recovery of higher level cognitive and behavioral functioning [11,12,15]. Future studies should evaluate the association of genes beyond APOE with outcomes after TBI in children.

Preliminary data analysis from our group indicates that catecholamine-related genes may be associated with executive functioning 12 months after TBI in early childhood [85]. The studied consisted of 52 Caucasian children (16 with TBI and 36 with orthopedic injury) with a mean age of 5.44 years at the time injury. We found that polymorphisms in the catechol-O-methyl transferase gene and the dopamine receptor gene were associated with executive function outcomes 12 months after injury. Larger studies will need to be performed in the future to validate these findings; however, the results of this analysis indicate that catecholamine related genes may influence higher level cognitive and behavioral functioning after TBI in children.

4.2. Importance of common data elements

Our review also highlights the importance of using common data elements with genetic studies in TBI to enable combined analysis and direct comparison among studies [86–91]. In this review, we were able to perform a combined analysis to evaluate the overall association of the APOE e4 allele with global outcomes after pediatric TBI measured with the GOS. However, the generalizability of the results is limited as demographic variables (e.g., age, race, and gender) and injury severity variables (e.g., GCS) were not consistently reported across studies. The combined analysis used one study that only included "critically ill" patients (GCS not reported) [21], another that included approximately 65% severe injuries [22], and the severity in the third was not reported for the child sub-analysis [23]. Common data elements included in future studies will need to span across multiple domains, including global outcomes [91,92], neuropsychological [91,92], psychological and psychosocial [90–92], biospecimens and biomarkers [89], radiological imaging [86,87], and demographics and clinical assessment [88]. Having comparable demographic, phenotypic, and environmental measures across studies will potentially improve cross-study comparison in human genetic association studies of TBI [93], thus improving our understanding of the association of genetics with outcomes after TBI and the generalizability of the findings. Additionally, tailoring outcome measure to the specific function or biological process associated with the genes being studied may help to streamline the design of human genetic association studies to better elucidate the relationship of genetics with recovery and outcomes after TBI.

4.3. Limitations

The primary limitations of this review is that, to date, there have been very few studies that have addressed the association of genetics with outcomes after TBI in children; thus it is difficult to make definitive conclusions regarding the overall association of genetics with outcomes after pediatric TBI. However, this limitation is important to note because it highlights the need for more studies in this area in the future. Additionally, although the combined analysis reported in our review indicates that APOE may be associated with outcomes after pediatric TBI, the findings are limited because there was a lack of consistently reported demographic and injury-related information in the studies evaluated. Therefore, we were unable to account for potential confounders (e.g., age, race, gender, time since injury) and heterogeneity of the population in the analysis. Future studies are needed to confirm our findings, and should also attempt to clarify the role of potential confounding factors.

5. Conclusion

The evaluation of the association of genetics with outcomes after TBI in children is in the early stages. The literature related to genetic studies in children is currently very limited and has only assessed the influence of the APOE gene on outcomes after injury. APOE appears to be associated with global outcomes after TBI in children; however, larger studies should be performed to validate these findings.

5.1. Future directions

Future studies should also evaluate the association of genes beyond APOE with outcomes after TBI in children. Studies that consider common functional pathways or gene-gene interactions should be performed because it is unlikely that one gene or polymorphism will explain the majority of recovery, but rather quite likely that combinations of genes or polymorphisms are more influential. Gene-environment interactions also need to be considered since environment is known to be related to recovery after TBI in children. Additionally, longitudinal pediatric specific studies should be developed in order to improve our understanding of the combined effect of TBI and genetics on brain development.

Methodological challenges related to TBI and genetic research will need to be addressed in the future as well. The genetic effects of polymorphisms are often small-to-modest in magnitude [94], thus future studies may need to be multi-center in nature to allow for recruitment of large sample sizes. Additionally, TBI is a very heterogeneous phenotype and detailed data need to be collected that characterize injury severity and outcomes precisely. Collection of common data elements would potentially improve the ability to combine data across multiple studies. Widespread biobanking and electronic medical records also provide promise as tools for developing large clinical genetic studies [95] to elucidate the role of genetics in recovery after TBI in children. As our genetic technologies continue to improve, there is the great potential to utilize genetic information to individualize prognosis and management after TBI in children; however, we have much work ahead of us to reach the goal of using genetic information to individualize management.

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Appendix A. Genes Beyond APOE Evaluated in Adult Traumatic Brain Injury: Manuscripts organized by gene, polymorphism, design, population, race, outcome measure and findings

Article	Gene	Polymorphism	Design	Population	Race	Outcome measure	Findings
Ariza et al. 2006	Angiotensin converting enzyme (ACE)	17p23 insertion deletion polymorphism	Cohort	73 subjects (mean age 30) with a GCS score of < 13 (31 with GCS 9–12 and 42 with GCS <9)	Unclear, performed in Spain	Rey's Auditory Verbal learning Test (AVLT), Rey's Complex Figure (CFT), Word Fluency test, backward digit span, Trail Making Test (visual scanning, motor speed, attention, and mental flexibility), Symbol Digit Modalities Test (SDMT) and Grooved Pegboard Test	Carriers of the ACE Alu deletion polymorphism were associated with poorer performance in frontal lobe functions involving visual scanning, fine motor speed, attention, and mental flexibility compared to the Alu insertion homozygotes
Chan et al. 2008	Serotonin transporter	5-HTTLPR, rs25531	Case control	174 total subjects (mean age 38.2, 61.5% male) − 75 cases with TBI and depression (mean age 39.0, 54.7% male); 99 controls with TBI and no depression (mean age 37.7, 66.7% male). 136 had a GCS of 13–15, 16 with GCS 9–12, and 6 with GCS < 9. All individuals had a TBI within the past 12 months.	60.1% Caucasian, 12.6% Asian, 8.4% South Asian, 4.8% Hispanic, 3.6% Middle-Eastern, 3% African American	Presence of depression in individuals with TBI using the DSM-IV criteria for mood disorder and the Hamilton Depression Rating Scale (HAMD)	No association between the serotonin transporter gene polymorphism and depression following TBI
Chuang et al. 2010	Neuroglobin	rs3783988 and rs10133981	Cohort	196 subjects (mean age 33.4 years; 78.6% male), with GCS score < 9.	Caucasians	Glasgow Outcome Scale (GOS), Neurobehavioral Rating Scale-Revised (NRS-R), Disability Rating Scale (DRS)	Individuals with the TT genotype for rs3783988 were more likely to have better GOS and DRS scores 3, 6, 12, and 24 months post-injury. No significant relationship was identified with the rs10133981 genotype.
Hadjigeorgiou et al. 2005	Interleukin (IL)	Variable nucleotide tandem repeat (VNTR) polymorphism in second intron of IL-1RN and IL-1B −511 allele	Cohort	151 subjects (mean age 38.5, 84.8% men) with TBI (59 with GCS 3–8, 24 with GCS 9–12, and 68 with GCS 13–15)	Unclear – Greece study	Hemorrhagic event noted on CT scan, Glasgow Outcome Scale (GOS) and modified Rankin Scale (mRS) at 6 months	Individuals with the Il-1RN VNTR allele 2 genotype were more likely to have hemorrhagic events after TBI compared to other types of alleles. No significant relationship was found with genotypes from the IL-1B (−511) polymorphism that was also evaluated. No significant associations identified with GOS and mRS scores 6 months post-injury.
Hoh et al. 2010	B-cell CLL/lymphoma 2 (BCL2)	17 tagging polymorphisms used	Cohort	205 subjects (mean age 34.51, 79.5% male) with TBI (82 with GCS 3–5, 123 with GCS 6–8)	Unclear	Glasgow Outcome Scale (GOS), Disability Rating Scale (DRS), and Neurobehavioral Rating Scale-Revised (NRS-R)	Presence of the allele for rs17759659 was associated with poorer outcomes on the GOS, DRS, NRS-R, and higher mortality. The association with GOS was the only outcome that remained significant after Bonferroni correction. Other associations with BCL2 gene polymorphisms were also noted, but associations did not remain significant after Bonferroni correction.
Johnson et al. 2006	Interleukin-1(IL-1) APOE	ApoE alleles, IL-1A receptor allele 1 or 2, IL-1B allele 1 or 2.	Case Control, cross sectional	38 TBI cases (mean age 38, 82% male) with a survival period range of 7–576 hours (mean 36 hours); 37 controls (mean age 59 years, 32% male) who all died from non-neurological causes	Unclear all subjects from UK	Presence of programmed cell death on pathology (Tunnel Histochemistry)	No association was identified between ApoE4, IL-1alpha allele 2 and IL-1beta allele 2 and the amount of cell death measured on pathology specimens.
Johnson et al. 2009	Neprilysin	GT repeats in promoter region	Cohort	81 subjects (age range 0.15–79 years; mean age 33.2) who all survived < 25 days post-injury (range 4 h–25 days; mean 3.45 days)	European Caucasians	Presence of amyloid plaques on pathology specimen	There was an increased risk of early amyloid plaque formation in individuals with > 41 GT repeats in the neprilysin gene promoter
Lanctot et al. 2010	Serotonin transporters (5HT), methylene tetrahydrofolate reductase (MTHFR), brain-derived neurotrophic factor (BDNF), tryptophan hydroxylase-2 (TPH2)	rs25531, 5HT1AC-(1019)G, 5HT2A T-(102)C, MTHFR C-(677)T, BDNF val66met, TPH2 G-(703)T	Cohort	99 subjects (mean age 39.9, 50.5% male) with depression following TBI who were treated with citalopram. 44 mild TBI, 45 moderate TBI,	52.2% European Caucasian 13.3% Asian 34.4% other	Response of depression to treatment with citalopram based on Hamilton Depression (HAMD) change	MTHFR and BDNF polymorphisms predicted greater treatment response and the serotonin transporter gene polymorphism predicted a greater number of adverse events.

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Article	Gene	Polymorphism	Design	Population	Race	Outcome measure	Findings
				and 1 severe TBI based on GCS.			
Libera et al. 2011	Interleukin-6 (IL-6)	–174C/G	Cohort	77 males with severe TBI, mean age 37 years, mean GCS 5.6	Not reported, study performed in Brazil	Survival versus intensive care unit discharge	The carries of the G allele were more frequently in the survivor group (81%) compared to the non-survivor group (65%) ($p = 0.031$)
Lipsky et al. 2005	Catechol-O-methyltransferase (COMT)	COMT Val158Met polymorphism	Cohort	113 subjects (mean age 24.6, 93.8 = % male) with primarily moderate and severe TBI (24 with LOC < 1 hour, 14 with LOC > 1 hour; 27 with PTA < 7 days, 15 with PTA > 7 days)	Unclear	Executive function assessed by multiple tests, Wisconsin Card Sorting Test (WCST) or perseverative errors and responses; Stroop Color and Word trial score, Controlled Oral Word Association Test (COWA), animal naming test, and Trail Making test B total time.	Individuals with the val/val COMT genotype had more perseverative responses measured by the WCST than other genotypes
Martinez-Lucas et al. 2005	Tumor protein p53	Arg72Pro polymorphism	Cohort	90 Caucasian subjects (mean age 33.9) with severe TBI (GCS < 9).	Caucasian	Glasgow Outcome Scale (GOS) at discharge from ICU and GOS 6 months post-injury. Scores dichotomized into good (GOS of 4 or 5) and poor (GOS of 1, 2, or 3) outcomes.	The Arg/Arg genotype of the Arg72Pro polymorphism in p53 is associated with a 2.9 greater odds of an adverse outcome at time of discharge from the ICU. The relationship was not significant at 6 months post-injury.
McAllister et al. 2005	Dopamine D2 receptor (DRD2)	rs1800497	Case control	39 cases with mild to moderate TBI (mean age 31.8, 38.4 days post injury) and 27 healthy comparison (mean age 32.0) subjects.	99% Caucasian and European decent	Califomia Verbal Learning Test (CVLT) and Continuous Performance Test (CPT), Wide-Range Achievement test (WRAT-3) reading subtest, Wechsler Adult Intelligence scale III (WAIS-III) Block Design subtest.	The T allele (rs1800497) was associated with overall lower performance on the CVLT. Additionally, the T-allele was associated with impaired responses on the reaction time, vigilance, and distractibility scales of the CPT in individuals with mild TBI. No significant relationships were identified with the other measures.
McAllister et al. 2008	Dopamine D2 Receptor (DRD2) Neural cell adhesion molecule 1 (NCAM1) ankyrin repeat and kinase domain containing 1 (ANKK1)	rs1800497 plus an additional 31 polymorphisms	Case Control	93 cases (mean age 33.8 years) with mild to moderate TBI (GCS 9–15 and LOC < 24 hours), 1 month post-injury (mean 43.1 days) 48 healthy controls (mean age 30.4 years)	Caucasians of European descent	Califomia verbal leaming test (CVLT), Gordon Continuous Performance Test (CPT)	rs1800497 was associated with poorer performance on the CVLT in both TBI and control. A haploblock of 3 SNPs in ANKK1 (rs11604671, rs4938016, and rs1800497) demonstrated the greatest association with cognitive outcome measures.
McDevitt et al. 2011	Heavy neurofilament (NEFH)	rs165602	Matched case control	48 athletes (mean age 19.46 years) with self-reported history of concussion were matched to 48 controls (mean age 19.44 years) without a self-reported history of concussion	Not reported	Self-reported history of concussion	There was no significant association between the NEFH rs165602 polymorphism and self-reported history of concussion.
Robertson et al. (2011)	Endothelial Nitric Oxide Synthase (NOS3)Gene	−786 > C, 849G > T, variable nucleotide repeat in intron 4	Cohort	51 participants with a severe TBI (GCS motor score ≤5), mean age 35 years.	37% Caucasian, 35% African American, 8% Asian, 23% Hispanic	Cerebral blood flow	The NOS# 786T > C variant was significantly related to global cerebral blood flow and cerebral vascular resistance.
Romeiro et al. 2007	Aquaporin 4	rs3906956	Cohort	102 subjects with TBI (mean age 26.9, 100% male, mean GCS 12))	Unclear, performed in Brazil	Brain edema on CT scan	There was not sufficient variation in the AQP4 gene in exon 4 to evaluate for a genetic association, so positive or negative findings could not be reported.
Sarnaik et al. 2010	Poly(ADP-ribose) pomymerase-1 (PARP-1)	rs1109032, rs3219090, rs3219119, rs2271347,	Cohort	188 subjects(mean age 34.2) with severe TBI (GCS < 9)	94.1% Caucasian	CSF levels of PARP-1 modified protein and Glasgow Outcome Scale (GOS) score 6 months post-injury (Score of 1–3 = un-favorable outcome; score of 4–5 = favorable outcome.	rs3219119 AA genotype was associated with a favorable neurological outcome on GOS. rs2271347 correlated with CSF PARP-1 modified protein levels, but not outcome.
Scher et al. 2011	Methylene-tetrahydrofolate reductase (MTHFR)	C677T variant A1298C variant	Case Control	1600 individuals consisting of 800 randomly selected epilepsy cases and 800 matched controls. Mean age was 32 yeasrs. TBI severity	68% White, 19% African American, 13% other races	Documented history of adult onset epilepsy	C677T variant is associated with an increased risk of post-traumatic epilepsy, specifically the TT genotype is associated with a 1.57

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Article	Gene	Polymorphism	Design	Population	Race	Outcome measure	Findings
				was minor for both cases (69%) and controls (82%)			greater odds of developing epilepsy after adjusting for age, sex, race.
Tanriverdi et al. 2006	Interleukin-1 alpha (IL1A)	IL-1A allele 2 at position −889	Cohort	71 subjects (mean age 25.8) − 23 severe TBI (GCS 3–8), 40 moderate (GCS 9–12)TBI, 8 mild TBI (GCS 13–15)	Unclear	Glasgow Outcome Score (GOS) 6 months post-injury	No significant differences in outcome based on GOS 6 months post-injury between presence or absence of IL1A allele 2 at position −889
Terrell et al. 2008	Tau APOE	Tau His47Tyr and Ser53Pro; APOE alleles; APOE promoter G-219T polymorphism	Case control, cross-sectional,	195 subjects − 72 with a history of concussion (mean age 19.8, 95.8% male), 123 with no history of concussion (mean age 19.9, 87.8% male)	54.2% white, 40.3% black, 5.6% other	Reported history of concussion	Individuals with the Tau Ser53Pro genotype approached significant association with reported history of concussion (OR 2.1; 95% CI 0.3–14.5). A statistically significant increase in the association of the APOE promoter G– 219 TT genotype was associated with an increased reported history of concussion (OR 2.8; 95% CI 1.1–6.9)
Uzan et al. 2005	Interleukin (IL-1) beta	+3953 and −511 genotype polymorphisms	Cohort	69 subjects (mean age 23.9, 79.7% male) with TBI (22 with GCS 3–8, 39 with GCS 9–12, and 8 with GCS 13–15)	Unclear, done in Turkey	Glasgow Outcome Scale (GOS) at 6 months post-injury	Individuals with the IL-1Beta allele 2 present at position +3953 and −511 were more likely to have an unfavorable outcome (GOS 1,2, or 3) 6 months post-injury than individuals without allele 2 at these positions
Wagner et al. 2007	Dopamine transporter gene (DAT)	DAT variable nucleotide tandem repeat (VNTR)	Cohort	63 subjects (mean age 31.49) with severe TBI (GCS < 9)	Unclear	Dopamine and dopamine metabolite (homovanillic acid, 3,4-dihdroxypheny lacetic acid) CSF levels within 5 days after injury	Individuals who were homozygotes for the 10 repeat VNTR had higher CSF dopamine levels than individuals with the other VNTR genotypes.
Wagner et al. 2010	Adenosine A1 receptor	rs3766553, rs903361, rs10920573, rs6701725, rs17511192	Cohort	187 subjects with severe TBI (GCS < 9) (age range 18–75)	Caucasian	Time to first post-traumatic seizure, categorized as early, late, and delayed-onset.	rs3766553 was associated with early, late, and delayed-onset post-traumatic seizures. rs10920573 demonstrated an associated with CT genotype and late post-traumatic seizures. With both the rs3766553 and rs10920573 present there was a 46.7% chance of late post-traumatic seizures.

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Table 1

Gene Association Studies in Pediatric Traumatic Brain Injury. Studies organized by gene, polymorphism, design, population, race, outcome measure and findings

Article	Gene	Polymorphism	Design	Population	Race	Outcome measure	Findings
Blackman et al. 2005	APOE	APOE alleles	Cohort	70 children admitted for inpatient rehabilitation, mean age 13 years and 2 months.	Not reported	Functional Improvement Measure for Children (WeeFIM)	APOE e4 carriers had a better WeeFIM scores on discharge compared to non APOE e4 carriers.
Brichtova and Kozak 2008	APOE	APOE alleles	Cohort	70 children (68,6% boys) age 1 month to 17 years (mean age 9.47 years) with mild (21.4%), moderate (27.3%), and severe (64.3%) TBI.	Not reported, but study conducted in the Czech Republic	Glasgow Outcome Scale (GOS) one year post injury.	The presence of the APOE e4 allele was associated with a poorer outcome measured on the GOS compared to the absence of the APOE e4 allele.
Lo et al. 2009	APOE	APOE alleles	Cohort	Cases 65 critically ill children admitted to intensive care unit with brain trauma. GCS and age of injury were not reported.	Not reported. Study performed in the United Kingdom	Cerebral perfusion pressure (CPP) in patients with ICP monitoring (45/65 cases), modified GCS, and the modified Glasgow Outcome Scale (GOS).	CPP insult was lower in e4 allele carriers compared to non-e4 carriers; however, e4 allele carriers were more likely to have poor outcome on the GOS. Individuals homozygotic for the e3 allele had a good recovery despite having suffered more CPP insult compared to those not e3 homozygous. Overall conclusion was that different APOE alleles may affect cerebral ischemic tolerance differently.
Moran et al. 2009	APOE	APOE alleles	Cohort	99 children with mild TBI. 28 with the e4 allele (mean age 11.73 years). 71 without the e4 allele, mean age 12.06.	82% were Caucasian in each	California verbal learning test (CVLT), Developmental Test of Visual-Motor Integration (VMI), Cambridge Neuropsychological Test Automated Battery (CANTAB), Wechsler Abbreviated Scale of intelligence (WASI), Wide Range Achievement Test (WRAT-3), Post Concussive Symptom Interview (PCS), Health Behavior Inventory (HBI)	The e4 group was more likely to have a GCS score < 15. The e4 group performed better on the VMI than the non-e4 group. The groups did not significantly differ on any of the other measures. Overall, conclusion was that there was no significant difference between e4 carriers and non-e4 carriers.
Quin et al. 2004	APOE	APOE alleles	Cohort	165 cases of children between the ages of 2–19 years who survived 1 hour to 5 months (median 3 days) post injury. Median age was 13 years and 76% of the population was male.	Not reported. Study performed in Glasgow Scotland and Southampton, UK.	Presence of post-mortem swelling determined by macroscopic and microscopic evaluation of port-mortem brains.	No association between the presence of the APOE e4 allele and cerebral swelling measured by analyzing post-mortem tissue.
Teasdale et al. 2005	APOE	APOE alleles	Cohort	1094 patients with mild, moderate, and severe TBI, mean age of 37 years. Subgroup analysis of 215 children ages 0–15 was performed. Demographics of the child sub-group were not reported	Not reported	Glasgow Outcome Scale (GOS)	Children that were carriers of the APOE e4 allele had a 3.06 greater odds of an unfavorable outcome (GOS scores of 1, 2, or 3).