Applying Systems Biology Methodology To Identify Genetic Factors Possibly Associated with Recovery after Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality worldwide. It is linked with a number of medical, neurological, cognitive, and behavioral sequelae. The influence of genetic factors on the biology and related recovery after TBI is poorly understood. Studies that seek to elucidate the impact of genetic influences on neurorecovery after TBI will lead to better individualization of prognosis and inform development of novel treatments, which are considerably lacking. Current genetic studies related to TBI have focused on specific candidate genes. The objectives of this study were to use a system biology–based approach to identify biologic processes over-represented with genetic variants previously implicated in clinical outcomes after TBI and identify unique genes potentially related to recovery after TBI. After performing a systematic review to identify genes in the literature associated with clinical outcomes, we used the genes identified to perform a systems biology-based integrative computational analysis to ascertain the interactions between molecular components and to develop models for regulation and function of genes involved in TBI recovery. The analysis identified over-representation of genetic variants primarily in two biologic processes: response to injury (cell proliferation, cell death, inflammatory response, and cellular metabolism) and neurocognitive and behavioral reserve (brain development, cognition, and behavior). Overall, this study demonstrates the use of a systems biology–based approach to identify unique/novel genes or sets of genes important to the recovery process. Findings from this systems biology–based approach provide additional insight into the potential impact of genetic variants on the underlying complex biological processes important to TBI recovery and may inform the development of empirical genetic-related studies for TBI. Future studies that combine systems biology methodology and genomic, proteomic, and epigenetic approaches are needed in TBI.

Keywords: genetic factors; recovery; rehabilitation; traumatic brain injury

Introduction

THE CENTERS FOR DISEASE CONTROL AND PREVENTION estimates that at least 5.3 million Americans have a lifelong or long-term need as a result of a prior traumatic brain injury (TBI).¹ The estimated economic cost of TBI, including direct and indirect costs, likely exceeds \$76.5 billion currently.² Childhood TBI results in approximately 2685 deaths, 37,000 hospitalizations, and 435,000 emergency department visits yearly in the United States, making it one of the leading causes of morbidity and mortality in children^{1,3}; however, the meager amount of scientific evidence available for prognosis, management, and treatment of TBI is disproportionate to the large societal and medical impact of this condition. Recovery after injury is related to multiple factors, in-

cluding age of injury, severity of injury, and time post-injury; however, there is often differential recovery in individuals with similar brain injuries.^{4–6} This differential recovery, in part, is likely a result of variation in individual (i.e., genetic) factors. Studies that seek to elucidate the impact of genetic influences on neurorecovery after TBI will lead to better individualization of prognosis and facilitate discovery and development of novel precision treatments, which are considerably lacking for this population.

The pathophysiology of TBI is complex and involves multiple biologic processes.^{7–9} After brain injuries, both focal and diffuse injury-related processes ensue, including diffuse axonal injury, cortical contusions, and hemorrhage.^{7,9–11} Secondary injury involves biologic processes that occur in response to injury and typically includes delayed neuronal injury, diffuse brain swelling,

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ischemic injury, hypoxic injury, and metabolic dysfunction.^{7,10,11} After the initial response to injury, biologic processes involved in repair and recovery become more critical. These processes include neuroplasticity of intact neural networks, repair of damaged neuronal circuitry, and replacement of lost neurons.⁷ Later in recovery, processes involved in cognitive and behavioral functioning become salient. Medical and rehabilitation interventions attempt to target several of these processes to maximize recovery. Acutely, clinical indicators (e.g., cerebral perfusion pressure) of more optimal early medical management are associated with better functional outcomes after severe TBI.¹² Later after injury, optimization of medical and rehabilitation therapies that focus on neuroplasticity become important.¹³ Further, genetic and environmental factors likely influence these biologic processes in differing manners and at various times post-injury to affect recovery.^{14–24}

Elucidation of the genetic contributions to recovery from TBI would transform our understanding of potential mechanisms of recovery and result in identification of novel targets for interventions to improve recovery.^{16,25–27} Genes related to the response to trauma (inflammatory cascade, calcium signaling, apoptosis, and vascular response), repair and plasticity, and cognitive and neuro-behavioral capacity/reserve are postulated to play a role in recovery.¹⁴ To date, there is a paucity of prior work evaluating the association of genetics with recovery after TBI in general and there are even fewer studies involving pediatric samples. Various studies in adults suggest that a number of genes may affect recovery²⁸, however, these studies are restricted primarily to one or a few candidate genes, limited by relatively small sample sizes, and lack consideration of gene–gene, gene–pathway, or gene–environment interactions.

The variety and breadth of candidate variants analyzed in prior adult studies highlight the potential for different genes to be important in recovery at various stages after TBI. For example, the interleukin genes, which are involved in cellular proliferation, seem to be important in survival and global outcomes,^{29–33} while dopamine-related genes may be more important for longer-term recovery of higher level cognitive and behavioral functioning.^{34–36} A better understanding of how genes influence biologic processes related to recovery after TBI is critically needed to advance the field of neurogenetics related to recovery after TBI.

The complex and multifactorial nature of TBI presents unique challenges to conventional, unimodal biological methodologies that integrative systems biology–based, approaches may enlighten.³⁷ To date, genetic association studies in TBI have primarily used narrow genetic approaches where a pre-determined, single, or small set of candidate genes or variants are evaluated. These narrow approaches are often inefficient and may be misleading because other genes or variants important to the recovery process are not considered. Alternatively, an unbiased genome-wide association study (GWAS) considers all genetic possibilities but requires large sample sizes, is limited by multiple testing concerns, and there is often the risk of identifying spurious associations.

A TBI systems medicine approach—integrating systems biology of TBI with clinical information—provides a strategy for identifying diagnostic and prognostic markers for medical management of TBI. Systems biology–based computational approaches, which integrate gene-level data with biologic processes, pathways, and networks, are not only successful in extracting novel biological insights,^{37–40} but also facilitate biomarker discovery and identify and prioritize novel testable disease candidate genes.^{41–44} Prior work has described the potential use of system biology approaches for biomarker discovery for TBI,^{37,45,46} but an examination of the

use of system biology approaches applied to genetic associations with clinical outcomes after TBI is lacking. A systems biology–based approach would inform selection of genes and require less multiple testing than a GWAS, but is more inclusive than focusing on a limited number of candidate genes or variants.

The objectives of this study were to use system biology–based approaches to identify biologic processes over-represented with genetic variants previously implicated in clinical outcomes after TBI and identify unique genes potentially related to recovery after TBI. Using these TBI-related biological processes, we identified and prioritized candidate genes in biologic processes likely important for recovery after TBI. The use of these system biology approaches provide a novel, biologically based method to better inform the evaluation of the association of genetics with recovery after TBI and has the potential to greatly advance the understanding of neurogenetics related to TBI recovery.

Methods

TBI gene list compilation

To generate a list of genes previously associated with clinical outcomes after TBI, we conducted a PubMed review using the following search terms: (“brain injury” OR “brain injuries” OR “concussion” OR “brain concussion” OR “head injuries” OR “head injury”) AND (“genetic” OR “genetics” OR “gene” OR “genes” OR “polymorphism” OR “DNA” OR “genetic polymorphism” OR “genetic variation” OR “genetic variability” OR “genotype”). In addition, the search was limited to English language articles, human studies, clinical research, and non-review articles using PubMed filters. The search was conducted from January 1, 1995, through September, 15, 2016. Inclusion criteria for articles required that each article evaluate the association of genetic variation (e.g., single nucleotide polymorphisms or other measure of genetic variation) with clinical or functional outcomes after traumatic brain injury. Genes were included only if a significant association was found. Articles evaluating the association of genetics with non-clinical outcomes (e.g., pathology post-mortem) or evaluating the association of gene expression or protein/biomarker levels with outcomes were excluded. Review articles and case reports also were excluded. Initially, 1269 articles were identified. After review of titles and abstracts, 1109 were excluded. After review of full manuscripts, 55 were excluded and the final number of studies included was 105. We then manually compiled a list of genetic loci that demonstrated a significant association with clinical or functional outcomes after TBI. Outcomes were grouped into Survival/Global functioning (e.g., Glasgow Outcome Scale), Cognitive (e.g., neuropsychological/intelligence measures), Behavioral/Emotional (e.g., Child Behavioral Checklist, anxiety, depression), and Medical Sequelae (e.g., seizures, dementia).

Functional enrichment analysis

We used ToppGene Suite⁴⁷ to systematically analyze this list of compiled TBI genetic loci. ToppGene Suite is a comprehensive platform for gene set enrichment analyses and machine learning-based candidate gene ranking. It is widely used, principally for linking biological states to observations of transcriptome or exome analyses.^{48–53} The current backend knowledgebase for ToppGene Suite is a comprehensive collection (more than 12 million gene annotations) of diverse gene set libraries compiled from a variety of publically available gene annotation databases and resources. ToppGene detects functional similarities or enrichment of a given gene list based on ontologies, pathways, phenotypes, and drug–gene association. Although there are several enrichment analyses tools available, the strength of ToppGene is its extensive collection of functional annotations compared to other system biology

tools.^{54,55} Biologic processes demonstrating enrichment at a p value of 0.05 (Bonferroni corrected) were considered to be significantly associated with the manually compiled gene list.

TBI candidate gene discovery and prioritization. After identifying genetically influenced biologic processes associated with TBI outcomes using information from previous genetic and TBI studies, we sought to identify additional TBI candidate genes and variants among these biologic processes likely to have the greatest impact on recovery after TBI. Using the theoretical basis that genes common among several processes would be more likely to have the greatest influence on recovery, the first approach we took was to identify genes common among these processes. Because it is possible that genes not common among several or more processes may also have a substantial impact on recovery, we took another systems biology-based approach to identify other candidate genes. In this second approach, we ranked all known genes associated with each of the enriched TBI-relevant biological processes using ToppGene⁴⁷ with default parameters.⁵⁶ ToppGene ranks candidate genes based on functional similarity to a user supplied training set (known TBI associated genes in this case). Functional similarity is computed using a variety of gene annotations (pathways, biological processes, phenotype, literature, protein

interactions, and co-expression) in an integrative systems biology-based machine learning approach. Using this second approach, *a priori*, we considered genes ranked in the top 5% likely to be significantly associated with recovery from TBI.

Results

Table 1^{29,32–36,57–135} includes the list of genes that were identified based on the search criteria and associated clinical and functional outcome categories. Thirty-three genes were identified, with apolipoprotein E (APOE) being the most commonly reported in the prior TBI literature. Figure 1 depicts the interrelationship among genes identified in Table 1 and clinical outcomes. Several genes identified were associated with multiple functional outcomes, with APOE, adenosine A1 receptor, brain-derived neurotrophic factor (BDNF), and glutamate decarboxylase 1 genes being associated with the all four outcomes. Other genes were associated with only one functional outcome category.

Using ToppGene Suite and the manually compiled list of genes from prior TBI genetic association studies, we found significant enrichment (p value 0.05; Bonferroni correction) for biologic processes, including behavior or cognition, cell death, cell proliferation,

TABLE 1. COMPILED LIST OF GENES WITH GENETIC VARIANTS ASSOCIATED WITH OUTCOMES AFTER TBI

Gene	Citation	Type of Outcome(s)
5'-Nucleotidase ecto (NT5E)	57	Medical sequelae
Adenosine kinase (ADK)	57	Medical sequelae
Adenosine A1 receptor (ADORA1)	58	Survival/global functioning; cognitive; behavioral/emotional
Angiotensin I converting enzyme (ACE)	59–61	Survival/global functioning; cognitive
Ankyrin repeat and kinase domain containing 1 (ANKK1)	35,36,62,63	Survival/global functioning; cognitive
Apolipoprotein E (APOE)	64–105	Survival/global functioning; cognitive; behavioral/emotional; medical sequelae
ATP-binding cassette B1(ABCB1)	106	Survival/global functioning
Aquaporin 4 (AQP4)	107	Survival/global functioning
ATP binding cassette subfamily B member 1 (ABCB1)	108	Survival/global functioning
B-cell lymphoma 2 (BCL2)	109	Survival/global functioning; behavioral/emotional
BMX non-receptor tyrosine kinase (BMX)	110	Behavioral/emotional; medical sequelae
Brain-derived neurotrophic factor (BDNF)	111–115	Survival/global functioning; cognitive; medical sequelae
Catechol-O-methyltransferase (COMT)	34,116,117	Cognitive
Cytochrome P450 family 19 subfamily A member 1 (CYP19A1)	118	Survival/global functioning
Dopamine beta-hydroxylase (DBH)	117	Cognitive
Fatty acid amide hydrolase (FAAH)	119	Behavioral/emotional
Glutamate decarboxylase 1 (GAD1)	117,120	Survival/global functioning; cognitive; medical sequelae
Glutamate ionotropic receptor NMDA type subunit 2A (GRIN2A)	117	Cognitive
Interleukin (IL)	29	Survival/global functioning
Interleukin 1 beta (IL-1B)	33,121	Survival/global functioning; medical sequelae
Interleukin 1 receptor antagonist (IL-1RN)	32	Survival/global functioning
Methylenetetrahydrofolate reductase (NAD(P)H) [MTHFR]	122	Medical sequelae
Monoamine oxidase A (MAO-A)	123	Behavioral/emotional
NADH: ubiquinone reductase (H+-translocating) (NADH)	124	Survival/global functioning; behavioral/emotional
Neuroglobin (NGB)	125	Survival/global functioning; behavioral/emotional
Nitric oxide synthase 3 (NOS3)	126	Survival/global functioning
Poly(ADP-ribose) polymerase 1 (PARP-1)	127	Survival/global functioning
RNA binding motif single stranded interacting protein 3 (RBMS3)	128	Medical sequelae
Solute carrier family 6 member 4 (SLC6A4)	129,130	Behavioral/emotional; survival/global functioning
Synuclein alpha (SNCA)	131,132	Medical sequelae
Tumor necrosis factor (TNFA)	133	Survival/global functioning; medical sequelae
Tumor protein P53 (TP53)	134	Survival/global functioning
WW and C2 domain containing 1 (WWC1)	135	Survival/global functioning; cognitive

TBI, traumatic brain injury.

FIG. 1. Known traumatic brain injury gene network and relationship with clinical outcomes. The relationship of known traumatic brain injury genes (green circles) with clinical outcomes (orange rectangles) is depicted. Black lines depict the interrelationship of genes with each other and clinical outcomes.

FIG. 2. Known traumatic brain injury gene network relationship with clinical outcomes and enriched biologic processes. The relationship of known traumatic brain injury genes (blue circles) with clinical outcomes (orange hexagons) and biological processes (green rectangle) is depicted. Black lines represent the interrelationship of genes with clinical outcomes and biologic processes.

FIG. 3. Comparison of gene sets known to be associated with various biological processes relevant to traumatic brain injury. Venn diagram on the left shows a comparison between known gene sets related to cell death, cell proliferation, and inflammation biologic process with 144 common genes. Venn diagram on the right side displays a comparison between genes associated with behavior/cognition and brain developmental process with 145 common genes.

inflammatory response, glucose metabolic process, and brain development. Figure 2 demonstrates the interrelationship of the compiled gene list, clinical outcomes, and biologic processes.

When evaluating genes common across these processes, we identified 144 genes common to cell proliferation, cell death, and inflammatory processes (Fig. 3), and 145 genes common to brain development, cognition, and behavior (Fig. 3). When ranking the genes using ToppGene associated with biological processes relevant to TBI (cell proliferation, cell death, inflammatory response, glucose metabolic processes, brain development, and cognition and behavior) and selecting the top 5% of the ranked genes from each of the six TBI-relevant biological processes, 155 unique genes were identified. When combining the 155 ranked genes with 144 and 145 genes identified using the common biological processes approach, there were 377 candidate genes identified (Fig. 4 and Supplementary Material; see online supplementary material at www.liebertpub.com). Approximately 21% (78/377) of these genes have been associated with brain injury previously in the literature (Supplementary Material). Genes identified were over-represented primarily in two biologic processes: response to injury (cell proliferation, cell death, inflammatory response, and cellular metabolism) and neurocognitive and behavioral reserve (brain development, cognition, and behavior).

Discussion

Using information from the prior literature in combination with a systems biology approach, we identified 377 genes associated with biologic processes important to TBI outcomes and recovery, with 299 of these genes representing novel candidates. Many of the previous TBI and genetic studies have evaluated the association of only one or a few genetic variants with outcomes after injury.²⁸ The findings from this study further highlight the complexity of genetic

influences related to TBI recovery. There are likely multiple genetic influences on recovery and narrow genetic approaches may not be ideal to evaluate genetic influences on recovery after TBI. Using systems biology methodology to inform approaches that more broadly considers genetic variants would allow identification of genes related to biologic systems important to recovery and inform future studies. These findings provide a framework for consideration of a modified genomics approach that is a compromise between genome-wide association and candidate-gene or polymorphism studies for understanding the influence of genetics on recovery after TBI.

Genetic influences may, in part, provide an explanation as to why there is significant variability in recovery after seemingly similar TBIs. However, due to the complex nature of recovery after TBI, one gene or a few variants are unlikely to account for a significant amount of variability in outcomes. It has been postulated that candidate genes associated with various biologic processes may modulate recovery after TBI.¹⁴ Candidate genes involved in neurologic injury and inflammatory processes may be more important soon after injury, whereas candidate genes involved in cognitive and behavioral processes become more salient later during recovery, when neuroplasticity is critical. Many candidate genes have functions that span several biologic processes; therefore, instead of evaluating individual genes, it may be more informative to evaluate information about the association of candidate gene sets with outcomes after injury to determine which genetically influenced biologic processes are most critical to recovery or specific outcomes.

Gene-enrichment analyses, which focuses on evaluating the association of groups of genes that share a common biologic function, chromosomal location, or regulation with outcomes, have been used to study other disease processes,¹³⁶ but have not been applied to recovery after TBI. Gene-enrichment analysis is a

FIG. 4. Novel candidate genes for traumatic brain injury outcome identified using system biology-based approaches. Green nodes represent biologic process important to traumatic brain injury outcomes. Blue nodes represent novel candidate genes identified using system biology methodology likely to be associated with biologic process important to traumatic brain injury outcomes. The red nodes represent genes previously associated with brain injury in the literature.

pathway-based statistical genetics approach to test for the over-representation of associated genetic variants.¹³⁶ It reduces multiple testing burden by focusing on overall effects of genes or processes rather than individual variants. A set of genes that cluster together in biologic processes hypothesized to be associated with an outcome can be selected based on prior knowledge. “Enrichment” of genes is tested by examining whether genes associated with outcomes in a sample are significantly over-represented in biologic processes hypothesized to be associated with outcomes relative to biologic processes hypothesized not to be associated with outcomes. Gene-enrichment analysis assists in assigning biologic meaning to groups of genes that emerge from analyses. Such an approach may provide better insight into recovery than limited candidate gene approaches previously used.

Genetic factors also are likely to interact with environmental and other factors to influence recovery. It is well known that environment may moderate the effect that one particular gene has in expression of a particular phenotype.¹³⁷ Consequently, it is essential to consider environmental factors in genetic studies. Genetic and environmental influences are both implicated in recovery after TBI; however, there is a lack of an understanding of how genes and environment interact to influence outcomes after TBI. Adverse effects of a given genotype may be negated by a favorable environment and/or exacerbated by a poor environment. A number of genetic variants implicated in recovery after TBI also interact with home and family environmental factors to influence outcomes in pediatric populations. For example, dopamine-receptor, dopamine pathway, serotonin transporter, and catechol-O-methyltransferase genetic variants interact with environmental factors to influence cognitive and behavioral functioning in various childhood popu-

lations.^{139–149} The influence brain injury and environmental factors have on genetic modifications (i.e., epigenetics) is just beginning to be explored in brain injury.¹⁵⁰ Additionally, work within the field of pharmacogenomics has demonstrated that genetic factors may explain variability in response among individuals receiving similar treatments.^{151–156} This previous work suggests that there is likely a complex interplay between genetic and environmental factors that ultimately influences recovery from TBI and that to fully understand genetic influences on recovery after TBI, gene-environmental interactions need to be considered in the future.

In line with recent precision medicine initiatives,¹⁵⁷ a better understanding of the association of variability in individual (e.g., genetic), environmental, clinical, and other factors with outcomes after TBI will critically inform prognosis and management strategies. Further, a more comprehensive understanding of the biologic processes important to recovery would allow development of biologically informed treatment strategies. Future studies that combine systems biology methodology and genomic, proteomic, and epigenetic approaches are needed.^{14,45,46,150} An improved understanding of the biology of recovery related to genetics in combination with an understanding of how environmental and genetic factors interact to determine recovery could transform management strategies for TBI.

Limitations

The primary limitation to the system biology approach used in this study is that the findings are biased based on previously published studies of the association of candidate genes or variants with outcomes after TBI. There may be other genes or variants important

to recovery, but they are unstudied currently. As other candidate genes are identified, the system biology models should be modified to reflect this new information.

Our original gene list included genes that demonstrated an association with outcomes after brain injury; however, we did not apply a weighted approach. For instance, certain genes or variants may be more influential in recovery than others, but an accurate assessment of the relative weight was not possible; therefore, weighted associations were not included in the analysis. In addition to potentially enriching positive findings in prior literature, the systems biology approach used is also at risk for increasing or magnifying spurious findings due to limitations of the underpinning studies. Prior work is most notably limited by low sample sizes combined with multiple comparisons and paucity of independently replicated findings. Further, our approach did not account for variation in primary outcomes. For instance, certain biologic processes may be more critical for survival, whereas other processes may be more important for long-term cognitive and behavioral functioning. The feasibility of doing sub-analyses based on outcome domain is limited because of the overall limited number of genetic studies performed to date in TBI. It is unclear if the same biologic processes are equally significant for recovery after milder and more severe injuries. Further, because of the limited number of genetic studies evaluating the pediatric population, it is unclear if the biologic processes important in recovery after adult TBI are the same for pediatrics.

Conclusion

The influence of genetics on recovery after TBI is incompletely understood. Narrow genetic approaches primarily used to evaluate the association of genetics with recovery after TBI. Unbiased whole genome approaches are limited by the need for large sample sizes, multiple testing concerns, and risk of identifying spurious associations. Using system biology methodology to inform genetic association studies provides a compromise between narrow and unbiased whole genome approaches. Systems biology methodology may help identify novel genes not previously considered. Additionally, using systems biology approaches that seek to identify genes or variants over-represented in biologic processes associated with recovery after TBI may provide valuable insight into the physiology of recovery and inform the development of future precision treatments. Future studies that combine systems biology methodology and genomic, proteomic, and epigenetic approaches are needed in TBI.

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