# Genetic Influences on Patient-Oriented Outcomes in Traumatic Brain Injury: A Living Systematic Review of Non-Apolipoprotein E Single-Nucleotide Polymorphisms

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## Abstract

There is a growing literature on the impact of genetic variation on outcome in traumatic brain injury (TBI). Whereas a substantial proportion of these publications have focused on the apolipoprotein E (APOE) gene, several have explored the influence of other polymorphisms. We undertook a systematic review of the impact of single-nucleotide polymorphisms (SNPs) in non–apolipoprotein E (non-APOE) genes associated with patient outcomes in adult TBI). We searched EMBASE, MED-LINE, CINAHL, and gray literature from inception to the beginning of August 2017 for studies of genetic variance in relation to patient outcomes in adult TBI. Sixty-eight articles were deemed eligible for inclusion into the systematic review. The SNPs described were in the following categories: neurotransmitter (NT) in 23, cytokine in nine, brain-derived neurotrophic factor (BDNF) in 12, mitochondrial genes in three, and miscellaneous SNPs in 21. All studies were based on small patient cohorts and suffered from potential bias. A range of SNPs associated with genes coding for monoamine NTs, BDNF, cytokines, and mitochondrial proteins have been reported to be associated with variation in global, neuropsychiatric, and behavioral outcomes. An analysis of the tissue, cellular, and subcellular location of the genes that harbored the SNPs studied showed that they could be clustered into blood–brain barrier associated, neuroprotective/regulatory, and neuropsychiatric/degenerative groups. Several small studies report that various NT, cytokine, and BDNF-related SNPs are associated with variations in global outcome at 6–12 months post-TBI. The association of these SNPs with neuropsychiatric and behavioral outcomes is less clear. A definitive

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assessment of role and effect size of genetic variation in these genes on outcome remains uncertain, but could be clarified by an adequately powered genome-wide association study with appropriate recording of outcomes.

**Keywords:** genetics; living systematic review; outcome; prognosis; traumatic brain injury

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## Introduction

**O**UTCOME PREDICTION in severe traumatic brain injury (TBI) can be improved. Numerous research groups have produced prognostic models in an effort to predict outcome based on acute-phase patient demographics and clinical parameters.[1–3] The International Mission for Prognosis and Clinical Trials in Traumatic Brain Injury (IMPACT) model is a typical (and probably the best known) exemplar of such a prognostic model.[1–3] However, none of the available prognostic models include genetic variation as a variable.

Current implementations of the IMPACT model can predict outcome with an area under the receiver operating curve between 0.60 and 0.80,[1,3] with partial $R^2$ values that approach 0.35, suggesting that well over half of the variance in outcome is not accounted for by injury severity or type, age, or physiological or biochemical compromise immediately post-injury. This large unexplained outcome variance suggests that there may be other potential factors that contribute to outcome.[4]

One key contributor in this context may be genetic variation, which could impact outcome by modulating pre-injury reserve, secondary injury mechanisms, neural repair, and/or the activation of neurodegenerative processes.[5] The largest body of literature in this context focuses on the impact of genetic variations in apolipoprotein-E (APOE) on patient outcome post-TBI and provides evidence of a potentially significant, but inconsistent, impact of APOE polymorphisms on outcome.[7,8,10,11] Whereas these relationships are interesting and relevant, they do not form the focus of this systematic review. APOE polymorphisms will be covered in a separate living systematic review by our group.

We chose instead, in this article, to focus on single-nucleotide polymorphisms (SNPs) in genes other than those related to APOE, which have also been reported to have an impact on patient outcome. Although this body of literature is substantial and steadily growing, it has never been subjected to rigorous review, and no single publication provides a comprehensive summary of the available data in this area. Thus, the goal of this article is to provide a rigorous assessment of studies reporting the impact of non-APOE SNPs on patient outcome post-TBI. Given the continuing accumulation of new studies on this topic, this article is designed to be a living systematic review,[12] with periodic updates on the available literature to be published as new evidence becomes available. The question of interest for this systematic review was: What non-APOE SNPs are associated with patient outcome post-TBI?

## Methods

This review was conducted and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[13] A protocol was registered on June 10, 2014 with the University of York's International Prospective Register of Systematic Reviews (PROSPERO) database (registration number CRD42014013623; available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014013623).

This review is being prepared as a "living systematic review" as part of the CENTER-TBI project (www.center-tbi.eu).[14] A living systematic review is a high-quality, up-to-date online summary of health research that is updated as new research becomes available.[12] In practice, this means that the searches will be rerun frequently and any new studies incorporated into the review. We will seek to publish regular updates. In this context, we would see this article as part of a knowledge commons, which would provide a basis for ongoing update of the available literature in this area, could be revised and updated by collaboration between both current and new contributors.

### Inclusion/exclusion criteria

We included all studies of five or more adult patients (over 16 years of age) with TBI of all severities, which reported a global functional outcome measure of any type, reported by patient genotype (including mortality, Glasgow Outcome Scale [GOS], GOS-extended [GOSE], and Disability Rating Scale [DRS]). We also included studies that reported neuropsychological outcome. We only included studies in the English language.

We excluded studies that included non-TBI or pediatric patients, and those that did not report outcome data separately for the adult TBI cohort. Studies reporting nonfunctional outcome measures, such as histological findings at post-mortem, were also excluded. We elected to exclude studies with less than 5 patients given that such small patient numbers would not likely add to our review. Conversely, we did not restrict ourselves only to studies with a larger number of patients because this would have excluded several of the publications in this field. Finally, any studies reporting APOE as the genetic association of interest were not included within this systematic review. A separate living systematic review on APOE, and its association with patient outcome in adult TBI, is currently underway by our group. This was conducted as a separate living systematic review given the large volume of APOE studies available, warranting a separate review dedicated to this gene in adult TBI.

### Search strategy

At the beginning of August 2017, EMBASE, MEDLINE, and CINAHL (all through National Institute for Health and Clinical Excellence [NICE] Healthcare Databases) and Google Scholar were searched for published studies, and conference abstracts from inception to the start of August 2017 inclusive. Developed with search experts at Monash University's National Trauma Research Institute (NTRI), search strategies used a combination of keywords and MeSH terms (see Supplementary Appendix 1). Reference lists of included studies were manually reviewed to identify relevant publications not identified by the search strategy. Wherever conference abstracts were found, a further PubMed search was performed to discover whether the data had subsequently been published in full.

*Study selection*

Citations were downloaded into EndNote (Thomson Reuters) and duplicates removed. Titles and abstracts were screened against the eligibility criteria in EndNote by one author (C.A.M.), to remove irrelevant studies, and the remaining citations were reviewed in full text independently by two authors (C.A.M., with either V.F.J.N. or F.A.Z.) to assess them for eligibility. Disagreements regarding eligibility were resolved by consensus, and referral to a third reviewer (D.K.M.) was not required.

*Data extraction*

Citations and full-text files for all included studies were uploaded to Covidence (www.covidence.org), an online systematic review workflow tool, to undertake quality assessment and data extraction. Two authors (C.A.M., with either F.A.Z. or V.F.J.N.) independently extracted data, resolving disagreements through consensus. The following characteristics were extracted from all studies, where available:

1. Inclusion/exclusion criteria
2. Baseline characteristics, where possible, for each genotype within the cohort:
   a. Cohort sex composition
   b. Age (mean ± standard deviation [SD] if available)
   c. TBI severity (wherever possible as mean Glasgow Coma Sclae [GCS] ± SD, or GCS grouped according to existing practice as mild, moderate, or severe TBI)
3. Outcome data (see below)
4. Funding source(s)

For studies reporting global functional outcomes (e.g., GOS/GOSE, modified Rankin, numerical rating scale [NRS], DRS, and mortality), scores were extracted at all available time points for each genotype. Where possible, the total numbers of patients assessed at each time point was extracted and used to calculate the number of patients with a "favorable" outcome. Categorical scales were dichotomized in line with previously recognized methods for defining "favorable" outcomes (i.e., GOS 4–5, GOSE 5–8). If the reported data simply included author-defined favorable or unfavorable outcomes, without a breakdown of the underlying raw categorical data, then this was extracted instead. If ordinal data were not available, the mean scores and SDs (or standard errors/95% confidence intervals [CIs]) were extracted. In studies dealing with neuropsychological scales or other outcomes (e.g., measures of fatigue), reports of statistically significant differences between genotype results (at the alpha level selected by the study's authors) were extracted, with a narrative note made of nonsignificant results. In the case of no significant results being reported, results of the study were assumed to show no positive results, and the study was reported as negative for the SNP in question.

*Risk of bias assessment*

Risk of bias was assessed using the Quality In Prognostic Studies (QuIPS) risk of bias criteria, a validated domain-based tool for quality assessment of prognostic studies.[15] QuIPS addresses six important areas to consider when evaluating validity and bias in studies of prognostic factors: participation, attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis and reporting. The rating system for QuIPs is trichotomous, with a range from low risk, medium risk and high risk of bias. The lowest risk of bias that a study may receive in any given category is low risk. Two authors (C.A.M., with either F.A.Z. or

V.F.J.N.) independently completed the QuIPS for each study and then reached a final judgement on each of the six domains by consensus. The results of this process are presented for each study, as well as tabulated for the study overall (Supplementary Appendix 11). In line with the guidance provided by the team who developed QuIPS, we did not calculate a summated score for overall study quality.

*Data synthesis*

Many of the publications reviewed included results on outcome association for more than one SNP, and individual cohorts were sometimes used to explore the effect of more than one SNP in separate publications, though this was not always explicitly stated. Consequently, the results in the text of this article primarily relates to analysis with references to specific SNPs. The tables in the Supplementary Materials tabulate individual publications under summaries for each SNP, or class of SNPs. Where a study was used to explore more than one SNP or class of SNP, it was cited separately in the table that addressed results for that SNP. Studies were grouped by gene, where multiple mutations within a gene were studied. Within each group of genes, studies were subdivided for analysis by TBI severity/patient characteristics, or by outcome measures. Given the large number of heterogeneous studies with mixed patient cohorts and varied SNPs analyzed, a meta-analysis was not performed, and the results were synthesized narratively. Simple descriptive statistics can be found in the summary of patient cohorts for the various SNPs analyzed (Supplementary Appendix 4).

**Results**

*Search results*

A total of 4549 citations were identified through database searches (Fig. 1). After removing duplicates, 4429 were screened on citation and abstract, with 4166 excluded. We obtained 263 citations in full text, of which 105 were excluded (along with 92 review articles). Two articles were added from the reference sections of the included articles. The reasons for exclusion included non-TBI study populations and ineligible outcome measures (see Supplementary Appendix 3).

*Patient and study demographics*

We included 68 publications, reporting on the outcome impact of SNPs in over 10,000 patients.[16–29] It is difficult to be certain of the actual number of individual patients included in these studies, given that many originated from a small number of centers that published several articles on different SNPs in possibly identical, or at least overlapping, patient populations. Thus, the number of patients quoted across all of the studies is likely to be inflated secondary to counting individual patients more than once across the various studies described. The true number of unique individual patients studied across all of the included articles is likely substantially smaller. These 68 publications that described the outcome impact of various SNPs, including 23 on neurotransmitter (NT) SNPs,[16–36,74,75] nine on cytokine SNPs.[37–45] 12 on brain-derived neurotrophic factor (BDNF) SNPs,[46–53,76–79] and three articles on mitochondrial polymorphisms and patient outcome.[54–55] A further 21 studies reported on varied miscellaneous SNPs that did not fall into any of the previous groupings.[57–73,80–83]

Study design varied. Fifty-four publications described prospective cohort studies[16,17,19–24,26–31,34,35,37,38,40–44,46–53,55,57–64,66–69,71,73–80,83] Fourteen studies were retrospective cohort studies on banked DNA samples[18,25,32,33,36,39,45,54,56,65,70,72,82,83] Study location also varied
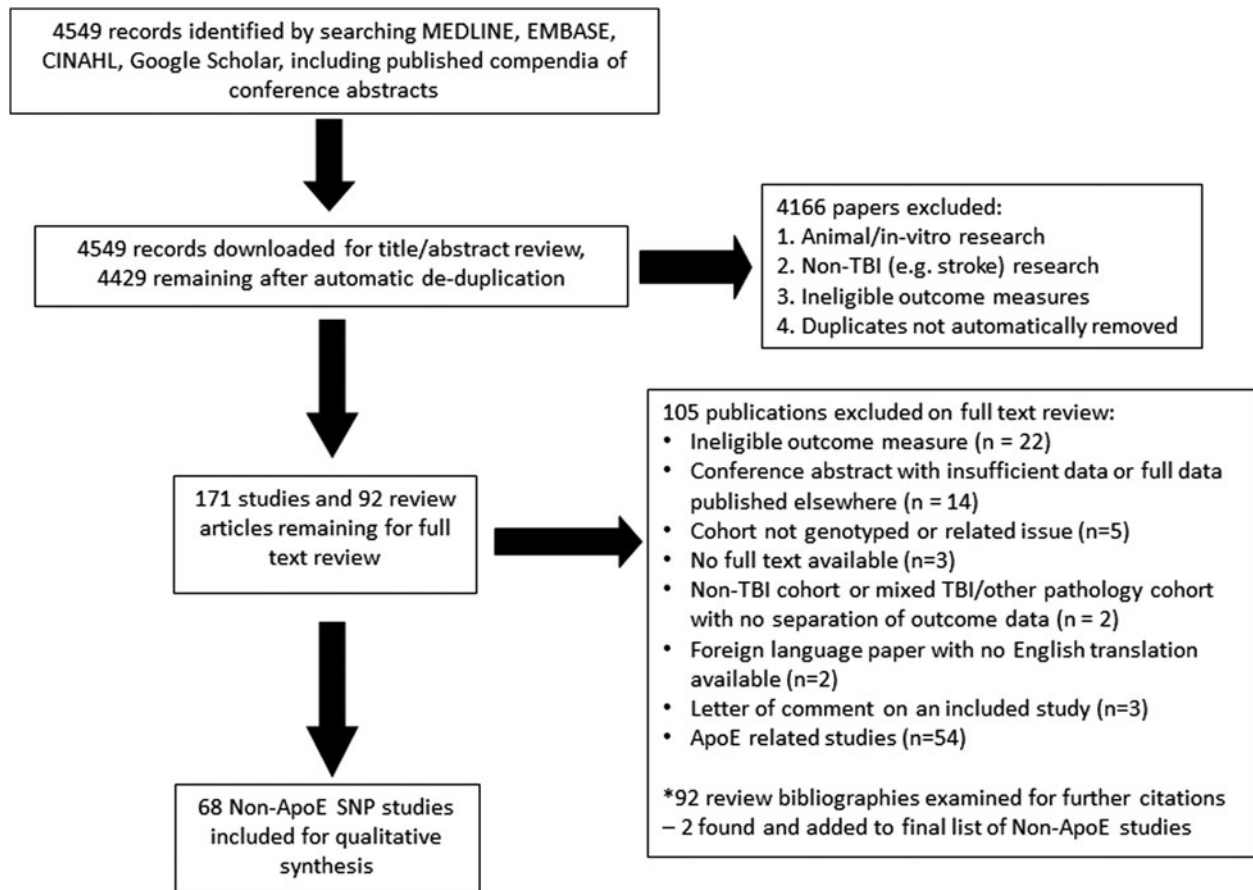
**FIG. 1.** PRISMA flowchart. ApoE, apolipoprotein E; SNP, single-nucleotide polymorphism; TBI, traumatic brain injury.

significantly, with the most commonly reported country of origin being the United States ($n = 43$). Twenty-six studies included fewer than 100 patients[17,19,24,26,27,32,35,37,40,42–44,47,50–53,57,67–69,71,74,76,78,80] Seven studies were published conference abstracts.[25,44,62,66,74,76,78] The diversity and number of studies make it difficult to provide summary tables in the body of the article, and all of these data are therefore provided as Supplementary Materials. A summary of all study design and patient characteristics can be seen in Supplementary Appendix 4. Brief descriptions of the various SNPs detailed below can be seen in Supplementary Appendix 2.

*Global patient outcome*

The relationship between various non-APOE SNPs and global/general patient outcome is described in the subsections below. A tabulated summary of all SNPs as they related to various measures of global/general patient outcome can be seen in Supplementary Appendix 5. A synthesis of these results (to the extent that was practicable) is provided later in this section.

Neurotransmitter single-nucleotide polymorphisms. Four studies on NTs assessed the association between various SNPs and general patient outcome as assessed by GOS[24] or GOSE,[18,19,75] although the SNP analyzed, TBI severity of the cohort, and outcome used varied between studies. The first study failed to find an association between the catechol-O-methyltransferase (COMT) valine (Val) to methionine (Met) SNP and GOSE at 1 or 2 years post-injury in mainly severe TBI patients.[18] The second study as-

sessed the same COMT mutation and found that Met allele carriers (i.e., Met/Met, Met/Val, or Val/Met) displayed better GOSE at 6 months in mild TBI patients (odds ratio [OR], 2.87; 95% CI, 1.20–6.86).[19] The third study evaluated the dopamine receptor D2 (DRD2)/ANKK1 SNPs, finding the ANKK1 rs1800497 heterozygotes to be associated with GOS at 6 months post-injury in severe TBI patients.[24] This study failed to document any association between DRD2 SNPs and outcome. The final study again evaluated various NT SNPs (ANKK1 rs116046/rs493801, DRD2 rs6277, and COMT rs4680), in addition to various others.[75] This study used complex statistical modeling and found an association between all of the above NT SNPs with patient outcome as assessed by GOSE at 3 to 6 months post-injury.

Cytokine single-nucleotide polymorphisms. Eight studies reported cytokine SNPs and their association with general patient outcome across the spectrum of TBI severity.[37,38,40,41,42–45] Four studies addressed various interleukin (IL)-1 SNPs.[37,38,40,41] Two of these studies reported on the impact of IL-1A SNPs,[37,38] with one study documenting worse outcome for IL-1ra-889 allele carriers[37] and the other study failing to document an association between the SNP and outcome.[38] One study documented an association between the IL-1B-3953 SNP and poor GOS.[40] Finally, the last IL-1 study found a weak association between IL-1 receptor antagonist (IL-1RN) SNP and worse outcomes.[41]

Three studies addressed the IL-6-174 SNP, with contradictory conclusions regarding its outcome impact. One study failed

to document any association between the IL-6-174 SNP and 6-month mortality.[43] The remaining two studies reported significant, but inconsistent, associations between the IL-6 polymorphisms and general patient outcome. One study documented better GOS in homozygote G allele carriers,[42] whereas the other study documented better outcomes with C-allele carriers (homozygotes or heterozygotes).[44]

Finally, one study assessed the tumor necrosis factor alpha (TNFA)-308 SNP. The results of this analysis displayed worse GOS at 6 months for the TNF-308*2$^+$ carriers (OR, 1.63; 95% CI, 1.14–2.34).[45]

### Brain-derived neurotrophic factor single-nucleotide polymorphisms.

Three studies, in severe TBI patients, addressed the association between BDNF SNPs and global patient outcome.[48,77,79] The first study failed to document any association between BDNF rs6265 or rs71244 SNPs and mortality within the first 7 days post-TBI. However, BNDF rs6265 V homozygotes and rs71244 T homozygotes displayed higher survival at 1 year.[48] Further, Failla and colleagues[48] developed a genetic risk score (GRS) based on the presence of ''risk'' BDNF SNPs, which, when included in a multi-variate Cox model (after adjusting for other admission patient characteristics and complication profiles), displayed a positive association with survival at both 1 week and 1 year in older patients, with the opposite trend observed in younger patients. For further details regarding this GRS and Cox modeling, we refer the reader to the parent article.[48]

The second study evaluated the interactions of CSF BDNF levels and BDNF GRS (rs6265, rs7124442) in modifying global outcomes.[79] CSF BDNF levels were associated with time until death ($p = 0.042$; hazard ratio [HR] = 10.973). BDNF-GRS and serum BDNF interactions were predictive of mortality through multi-variate modeling ($p = 0.047$; HR = 0.987).

The final study evaluated the interaction of CSF cortisol levels with BDNF GRS (rs6265, rs7124442) in modifying global outcome, as assessed by GOS at 6 months post-injury.[77] It was found that models including both CSF cortisol and BDNF GRS predicted mortality in younger patients (age, <48 years; $p = 0.004$). This study demonstrated some definitive links between CSF BDNF levels and mortality, though the associated risk of mortality appeared to be mediated by CSF cortisol, at least in part.

### Mitochondrial single-nucleotide polymorphisms coding for mitochondrial proteins.

Three studies documented the association between mitochondrial SNPs, coding for mitochondrial proteins, and patient outcome.[54–56] These studies included SNPs both in mitochondrial DNA (mtDNA) and in nuclear SNPs coding for mitochondrial proteins. The first study assessed a B-cell lymphoma 2 (BCL2) SNP and found that variant allele carriers (i.e., variant/ variant or wild-type/variant) displayed worse 3-month GOS, in mainly mild TBI patients.[56] The second study assessed various mtDNA haplotypes, and found that haplotypes H, J, T, and U were all associated with worse 6-month outcomes in mild-to-moderate TBI patients.[54] The last study evaluated various mtDNA SNPs as they related to 3-, 6-, and 12-month GOS and DRS. This study found the mtDNA 10398 G carriers to have lower DRS at 6 and 12 months post-TBI ($p < 0.02$).[55]

### Miscellaneous single-nucleotide polymorphisms.

Ten studies explored the outcome impact of miscellaneous SNPs (which did not fit into the previously mentioned categories) across the spectrum of TBI severity.[58–61,63–65,68,70,80,81] The SNPs studied were related to genes coding for p53,[68] angiotensin-converting enzyme (ACE),[58] neuroglobulin,[63] adenosine triphosphate (ATP) binding cassette,[59,61] aquaporin (AQP)-4,[64] aromatase rs2470144/rs4646/ rs2470152,[65] poly adenosine diphosphate-ribose polymerase-1 (PARP-1) rs3219119/rs3219090,[70] mannose binding lectin-2 (MBL2)/ficolin-2 (FCN2; rs1800451, rs1800450, rs5050737, rs7096206; rs3124953, rs17514136, rs17549193, and rs7851696),[80] and calcineurin (PPP3CC; rs2443504, rs2461491, rs2469749, and rs10108011).[81]

Several SNPs were found to be associated with variations in a range of outcomes: p53 arginine homozygotes were found to have a worse GOS at intensive care unit (ICU) discharge;[68] three ACE-related SNPs (C minor allele carriers for rs4461142, C minor allele carriers for rs7221780, and T minor allele carriers for rs8066276)[58] were associated with worse 6-month GOS; neuroglobulin rs3783988 C allele carriers were associated with poor GOS at 3/6/12/24 months[63]; ATP binding cassette C3435T C allele carriers were associated with worse 6-month GOS[61]; AQP-4 rs3763043 T homozygotes were associated with worse GOS at 6 months[64]; aromatase rs2470144 A allele carriers were associated with worse outcome at 6 months;[65] PARP-1 rs3219090 A allele/rs3219119 T allele carriers were associated with poor GOS at 6 months[70]; and calcineurin PPP3CC rs2443504 AA carriers had increased risk of mortality at 12 months.[81] Finally, no association with global outcome was observed for SNPs in MBL2 or FCN2.[80]

### "Other" outcomes: Neuropsychiatric, behavioral, miscellaneous

The multiple studies that contributed to this section of the review were varied in terms of SNPs addressed, the endpoints used, and the sample sizes in individual studies. The following description of the results of the review reflects this heterogeneity, which makes summary difficult; we have therefore classified these primarily by the target group in which the SNPs occurred.

### Neurotransmitter single-nucleotide polymorphisms.

Twenty-one studies documented the association between SNPs in a range of NT genes and neuropsychiatric/behavioral outcome post-TBI.[16,17,19–36,74] The full spectrum of TBI severity was described in the included studies. The NT based SNPs described included: ANKK1 TAQ1a,[74] COMT,[16,17,19,20] monoamine oxidase type A (MAO-A),[21] DRD2/ANKK1,[22–28] vesicular monoamine transporter type 2 (VMAT2),[29] combination of monoamine SNPs (COMT/DRD2/ANKK1/VMAT),[30] 5-HTTLPR,[31,32] glutamic acid decarboxylase (GAD),[33] vesicular glutamate transporter type 1 (VGLUT1),[34] and GRIN2A.[35,36] Full details of various neuropsychiatric and behavioral outcomes related to SNPs in NT genes can be seen in Supplementary Appendix 6.

Four studies focused on COMT SNPs and their association with neuropsychiatric/behavioral outcome.[16,17,19,20] The mutation evaluated in every study was the Val-158-Met SNP. Conflicting results were observed regarding the impact of this polymorphism on outcome. One study documented Val/Val homozygotes to have worse perseverance post-TBI,[16] a second (in contrast) reported worse post-traumatic behavior and cognition in Met allele carriers,[17] whereas a third study documented no difference in attention/ cognitive performance on both univariate and multi-variate regression.[18] Finally, a fourth study documented improved nonverbal processing skills in Met allele carriers.[20]

Eight studies documented the association between various DRD2/ANKK1 SNPs and neuropsychiatric/behavioral outcomes.

The DRD2 SNPs and the linked behavioral effects were: rs686 A allele carriers had less aggression,[22] C95T T allele carriers were found to have improved California Verbal Learning Test -II (CVLT-II) scores at 6 months,[23] and the rs2724838 SNP was associated with worse depression at 12 month post-injury.[24] In addition, DRD2 rs6279 C-homozygotes displayed improved cognition at 6 months; and executive function ($p = 0.013$), attention ($p = 0.006$), and language fluency at 6 months ($p = 0.003$).[24] Similarly, the ANKK1 SNPs and associated outcomes were: ANKK1 A2 allele carriers had worse depression and behavioral issues,[17] ANKK1 rs1800497 homozygotes had worse cognition[17,74] and executive functioning at 6 months post injury ($p = 0.048$),[24] and ANKK1/ TAQ1A T allele carriers were found to have worse CVLT scores in four studies.[25–28]

Mutations in VMAT2 were documented in two studies.[29,30] The first study found the rs363226 SNP to be associated with worse cognition at 6 months post-injury ($p = 0.006$).[29] The second study evaluated a panel of monoamine-based SNPs (COMT/DRD2/ ANKK1/VMAT), finding independent associations between: ANKK1 rs1800497, COMT rs4680, DRD2 rs6279, and VMAT rs363226 with cognition at 6 months post-injury.[30]

Polymorphisms in the serotonin transporter gene were assessed in two studies; both failed to demonstrate a statistically significant association between these SNPs of the 5-HTTLPR region and depression post-TBI.[31,32]

Finally, SNPs related to glutamate neurotransmission were evaluated in three studies.[34–36] One study addressed polymorphisms associated with the VGLUT1 gene, and found that G allele carriers had longer recovery times post-concussion.[24] Two studies addressed SNPs in the GRIN2A gene associated with N-methyl D-aspartate receptor subunits.[35,36] One study found L homozygotes to have a 6 times increased chance of prolonged recovery from their concussive symptoms ($p = 0.043$).[35] The second study documented the rs968301 GRIN2A SNP to be associated with a statistically significant decrease in intelligence post-TBI ($p = 0.025$).

*Cytokine single-nucleotide polymorphisms.* Two studies documented the association between cytokine based SNPs and "other" patient outcomes.[39,41] One study assessed SNPs in the IL-1B gene and found the rs1143634 CT genotype to be associated with post-traumatic epilepsy (PTE; OR, 2.85; $p = 0.005$).[39] The second study assessed the IL-1RN*2 SNP and found that the carriers displayed increased risks of poor outcomes (OR, 0.375; 95% CI, 0.155–0.901; $p = 0.028$) and hemorrhagic events.[41] Full details on these studies and the outcomes studied can be observed in Supplementary Appendix 7.

*Brain-derived neurotrophic factor single-nucleotide polymorphisms.* Nine studies documented the association between BDNF-based SNPs and neuropsychiatric/behavioral outcomes.[46,47,49–53,76,78] Six studies evaluated the BDNF Val-66-Met SNP as it related to these various outcomes.[46,47,49–52,76,78] One study assessed the relation of BDNF SNPs at rs71 24442 to cognitive outcome.[53] Full details can be seen in Supplementary Appendix 8.

BDNF Val-66-Met SNPs displayed varied and inconsistent effects across the studies identified. The BDNF Val-66-Met SNP was found to have the following documented associations post-TBI: Met allele carriers showed improved Wechsler Adult Intelligence Scale (WAIS) scores ($p < 0.01$),[46] Met allele carriers displayed improved executive functioning,[49] Met allele carriers had reduced treatment response to citalopram for depression post-TBI,[50] and

Met allele carriers had both worse reaction times ($p = 0.0003$)[51] and memory ($p = 0.05$) at 6 months post-TBI.[52] Further, one study found Met carriers were also found to have worse capacity in all domains of neurocognitive functioning, except visuospatial.[77,79] Finally, one study failed to document any difference in BDNF Val-66-Met SNP status and emergence from vegetative state at 3, 6, or 12 months post-injury.[47]

One study evaluated various SNPs of the BDNF gene, finding the rs7124442 CC homozygotes to display the largest decline in intelligence (as assessed by intelligence quotient [IQ]).[53]

*Miscellaneous single-nucleotide polymorphisms.* Ten studies documented the relationship between various SNPs and nonglobal patient outcomes (i.e., neuropsychiatric, behavioral, and other).[57,60,66,67,69,71–73,82,83] The targets for these polymorphisms included: ACE,[57] various oxytocin SNPs,[66] PERIOD3,[67] ATP binding cassette,[60] nitric oxide synthase-3 (NOS3),[69] alpha synuclein (SNCA),[71] kidney and brain expressed protein (KIBRA),[72] BMX,[73] methyenetetrahydrofolate reductase (MTHFR),[82] and adenosine A1 receptor.[83] Full details can be found in Supplementary Appendix 9. A full explanation of all abbreviations used in the other appendices can be found in Supplementary Appendix 10.

### Synthesis of data

The substantial variation that we encountered in study design, outcome metrics and timing, and SNPs targeted made it impossible to undertake a meta-analysis of these data. The details of individual studies are provided in the Supplementary Material that has been cited throughout the Results section. However, Table 1 provides a summary of those studies that examined the impact of target polymorphisms on global outcome. Similarly, whereas Appendix 2 in the Supplementary Materials provides a brief description of background biology, Figure 2 provides a more accessible summary of the cellular and subcellular location of the different genetic targets addressed by these candidate gene studies, in order to provide a pathophysiological context for the processes that these polymorphisms might be influencing.

### Risk of bias

In general, risk of bias was variable in all domains for most studies. Given the observational nature of all studies, methodological weaknesses were frequent. These most commonly involved failure to address potential confounders in patient selection or analysis, and selective outcome reporting. Only one of the 68 association analyses that we reviewed had low risk of bias in all of the areas assessed, and 14 studies had one or more fields within the QuIPS assessment graded as "high" risk of bias, with this most commonly attributed to either study attrition or issues surrounding confounding. A tabulated summary of the QuIPS grading can be seen in Supplementary Appendix 11.

### Discussion

This review summarizes the current literature on the impact of SNPs in non-APOE genes on patient outcomes post-TBI. Integrating these results is a complex task because of the diversity of biology addressed in these articles. Further, the scientific and clinical inferences that can be drawn from these data are limited by the small sample sizes in most studies, biases identified, and lack of

Table 1. Non-APOE Candidate Gene Studies Which Used Global Outcome as Phenotype of Interest

| Gene | Study | Total n | Outcome assessed | SNPs explored | Findings |
|---|---|---|---|---|---|
| DRD2/ANKK1 | Fallia and colleagues 2015[24] | 160 | GOSE at 6–12 months | ANKK1: rs1800497<br>DRD2: rs6279; rs2734838; rs17529477; rs4245147; rs7131056; rs4630328 | ANKK1 rs1800497 Taq1A polymorphism modifies outcome (better 6-month GOSE for heterozygotes, but no impact for either homozygotes. Did not survive FDR correction).<br>No impact from DRD2 SNPs on global outcome |
| | Neilson and colleagues 2017[75] | | GOSE 3/6 months | ANKK1: rs1800497; rs4938016; rs11604671<br>DRD2: rs6277 | Complex topological analysis. Different outcomes depending on CT findings:<br>In CT-negative patients: better outcomes with ANKK1 TAQ1ars11604671 A/A genotype and ANKK1 Taq1A C/G genotype and DRD2 rs6277 T/T genotype<br>In CT-positive patients: better outcomes with ANKK1 TAQ1ars11604671 A/G genotype and ANKK1 Taq1A C/C genotype and DRD2 rs6277 C/C genotype associated with better outcome in CT-positive patients |
| COMT | Wilmott and colleagues 2014[18] | 211 | GOSE at 1–2 years | COMT Val158Met: rs4680 | No impact of polymorphisms on global outcome |
| | Winkler and colleagues 2016[19] | 93 | GOSE at 6 months | COMT Val158Met: rs4680 | Met allele carriers have better outcomes at 6 months. |
| | Neilson and colleagues 2017[75] | 586 | GOSE 3/6 months | COMT Val158Met: rs4680 | Complex topological analysis with multiple genes. COMT rs4680 M/V genotype associated with better GOSE in CT-negative patients; M/M genotype associated with better outcomes in CT-positive patients |
| 5HT2AR | Neilson and colleagues 2017[75] | 586 | GOSE 3/6 months | rs6311 | Complex topological analysis with multiple genes. No impact of rs6311 polymorphism on outcome |
| $\mu$ opioid receptor | Neilson and colleagues 2017[75] | 586 | GOSE 3/6 months | OPRM1: rs1799971 | Complex topological analysis with multiple genes. No impact of rs1799971 polymorphism on outcome |
| IL1A | Tanriverdi and colleagues 2006[36] | 71 | GOS at 6 months | IL-1A −889: rs18800587 | No significant effect of polymorphism on outcome |
| | Dardoitis and colleagues 2006[38] | 215 | GOS at 6 months | IL-1A −889: rs18800587 | No significant effect of polymorphism on outcome |
| | Waters and colleagues 2013[45] | 937 | GOS at 6 months | IL-1A −889: rs18800587 | No significant effect of polymorphism on outcome |
| IL1B | Uzan and colleagues 2005[40] | 69 | GOS at 6 months | IL1B +3953: rs1143634<br>IL1B −511: rs16944 | IL1B +3953 allele 2 showed worse outcomes.<br>No statistically significant impact of rs16944 on outcome |
| | Waters and colleagues 2013[45] | 937 | GOS at 6 months | IL1B −31: rs1143627<br>IL1B −511: rs16944<br>IL1B +3953: rs1143634 | No statistically significant impact of any of these polymorphisms on global outcome |
| IL1RN | Hadigeorgiou and colleagues 2005[41] | 151 | GOS at 6 months | VNTR in IL1RN gene | IL-1RN VNTR allele 2 has no impact on global outcome at predefined significance level ($p < 0.01$), but associated with more haemorrhage. |
| IL-6 | Minambres and colleagues 2003[43] | 40 | Mortality | IL-6 174: rs1800795 | No association between IL-6 174 GG/CC polymorphism |
| | Dallia Libera and colleagues 2011[42] | 77 | GOS at ICU discharge | IL-6 174: rs1800795 | GG homozygotes at IL-6 174 locus show reduced mortality in ICU survivors. |
| | Waters and colleagues 2013[45] | 937 | GOS at 6 months | IL6 −174: rs1800795<br>IL6 −572: rs1800796<br>IL6 −597: rs1800797 | No impact of any polymorphism on global outcome |
| | Sinha and colleagues 2015[44] | 456 | GOS and FIM | IL-6 174: rs1800795 | C allele possession at IL-1 74 locus associated with improved survival at 6 months |

TABLE 1. (CONTINUED)

| Gene | Study | Total n | Outcome assessed | SNPs explored | Findings |
|---|---|---|---|---|---|
| TNFA | Waters 2013[45] | 937 | GOS at 6 months | TNFA −238: rs361525, TNFA −308: rs1800629 | TNFA − 308: rs1800629 allele 2 carriers showed worse outcome. No effect of rs1800629 polymorphism |
| TGFB | Waters 2013[45] | 937 | GOS at 6 months | TGFB −509: rs1800469, TGFB −800: rs1800468 | No impact of either polymorphism on global outcome |
| Mitochondrial haplotype | Conley 2014[55] | 255 | GOS, NRS, and DRS at 6/12 months | mtDNA −10398 | mtDNA −10398 G haplotype carriers less disabled on DRS than mtDNA −10398 A haplotype at 6 and 12 months |
| Mitochondrial haplogroup | Bulstrode 2014[54] | 805 | GOS at 6 months | Haplogroups: H, J, T, U, K, other | Haplogroup K associated with better GOS at 6 months. Complex interactions of other haplogroups with age and APOE genotype on outcome |
| BCL2 | Hoh 2010[56] | 205 | GOS, NRS, and DRS at 3/6/12 months | BCL2: rs1026825, rs12454712, rs12968517, rs1381548, rs1481031, rs17756073, rs17759659, rs1801018, rs1944419, rs3810027, rs4456611, rs4941185, rs7230970, rs7236090, rs8083946, rs899968, rs949037 | Multi-variate analysis demonstrates that there were four SNPs of significant interest that had impact on outcome: rs17759659, rs1801018, rs7236090, and rs949037. |
| | Neilson and colleagues 2017[75] | 586 | GOSE 3/6 months | rs17759659 | No outcome impact reported for polymorphism at rs1775659 |
| BDNF | Fallia 2015[48] | 568 | Mortality at 7 days and 1 year | rs6265; rs7124442 | No impact of individual polymorphisms on mortality. However, Gene Risk Score (GRS) developed from multi-variate Cox regression shows association of combined possession of rs7124442 C allele and rs6265 M allele significantly associated with acute mortality, regardless of age. Post-acutely, BDNF-GRS interacted with age: In the no-risk group, younger participants had highest survival probability, whereas older participants had lowest survival probability. |
| | Fallia 2016[79] | 295 | GOS at 6/12 months; time to death | rs6265; rs7124442 | GRS score from Fallia and colleagues 2015 shown to interact with age and serum BDNF to predict mortality |
| | Munoz 2017[77] | 234 | GOS at 6 months; Time to death | rs6265; rs7124442 | GRS score from Fallia and colleagues 2015 used with CSF BDNF levels and cortisol trajectories to create a mediation model. GRS mediates outcome through BDNF differently in low- and high-cortisol trajectory groups. |
| ATP binding cassette | Cousar 2013[59] | 556 | GOS at 6 months | ABCB1: rs1045642, rs1128503; ABCC1: rs212093, rs35621, rs4148382 ABCC2: rs2273697 | When controlled for GCS, age, sex, and ISS, the ABCC1 G/G and the ABCB1 T/T genotypes were associated with better outcome. |
| | Wang 2015[61] | 182 | GOS at 6 months | ABCB1: rs1045642 ABCB1: rs2032582 | Patients carrying C/T or C/C genotype of ABCB1 C3435T were more likely to have a better neurological outcome when compared with the T/T genotype. |

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TABLE 1. (CONTINUED)

| Gene | Study | Total n | Outcome assessed | SNPs explored | Findings |
|---|---|---|---|---|---|
| Neuroglobin | Chuang 2010[63] | 196 | GOS, DRS, and NRS at 6/12 months | rs3783988, rs10133981 | Haplotype block represented by rs3783988 in NGB (which codes for oxygen binding region of neuroglobin) have better DRS and GOS at 3,6,12, 24 months. rs10133981 not significantly related to functional outcome |
| ACE | Dardoitis 2015[58] | 363 | GOS at 6 months | rs4343, rs4461142, rs7221780, rs8066276, rs8066114 | rs4461142, rs7221780, and rs8066276 showed significantly worse outcomes for heterozygous variants carrying the risk allele compared with the common alleles; outcomes were also significantly worse for rs7221780 C/C homozygotes and rs8066276 T/T homozygotes. |
| AQP4 | Dardoitis 2014[64] | 363 | GOS at 6 months | rs335929, rs3763043, rs11661256, rs335931, rs3763040, rs4800773, rs3875089 | rs3763043 T/T genotype carriers showed worse outcomes; and rs3875089 C allele carriers showed better outcomes. |
| Aromatase | Garringer 2013[65] | 110 | GOS at 6 months | rs700519, rs28757184, rs2236722, rs56658716, rs2470144, rs2470152, rs4646, rs6493496, rs7168331, rs8041933, rs2470151, rs3751592, rs12901187, rs1062033, rs7172156, rs11632036, rs12591359, rs10459592, rs12592697, rs2899472, rs6493487, rs2899470 | rs2470152 T/T and T/C genotype, rs4646 C/C genotype, and rs2470144 A/A genotype were associated with worse outcomes, and those with >1 risk SNP variant had a higher risk for poor outcome, compared with those with one risk variant. |
| p53 | Martinez-Lucas 2005[68] | 90 | GOS at ICU discharge | rs1042522 | Arg/Arg genotype of the Arg72Pro polymorphism at rs1042522 was associated with increased likelihood of a bad outcome at ICU discharge. |
| Calcineurin | Osier 2017[81] | 380 | GOS at 3/6/12 months | PPP3CC: rs2443504, rs2461491, rs2469749, rs10108011 | Calcineurin A-gamma gene (PPP3CC) rs2443504 AA genotype univariately associated with GCS ($p=0.022$), GOS at 3, 6, and 12 months, and mortality; significance for GOS retained in multi-variate analysis (including age and sex) at 3 and 6 months. |
| Lectin system | Osthoff 2017[80] | 44 | GOSE at 3 months | MBL2: rs1800451, rs1800450, rs5030737, rs7096206 FCN-2: rs3124953, rs17514136, rs17549193, rs7851696 | No impact of any polymorphism on outcome |
| PARP-1 | Sarnaik 2010[70] | 191 | GOS at 6 months | rs1109032, rs3219090, rs3219119, rs2271347 | rs3219119 A/A genotype independently predicted favorable outcome. rs2271347 A allele carriage resulted in higher CSF PAR-modified protein level, but did not affect outcome. |
| | Neilson and colleagues 2017[75] | 586 | GOSE 3/6 months | rs3219119 | Complex topological analysis. rs3219119 T/T and A/T genotypes had worse outcomes at 3–6 months |

GOS, Glasgow Outcome Score; GOSE, Glasgow Outcome Score-Extended; FIM, Functional Independence Measure; DRS, Disability Rating Scale; NRS, Numerical Rating Scale; ICU, intensive care unit; FDR, false discovery rate. Other abbreviations as in text.
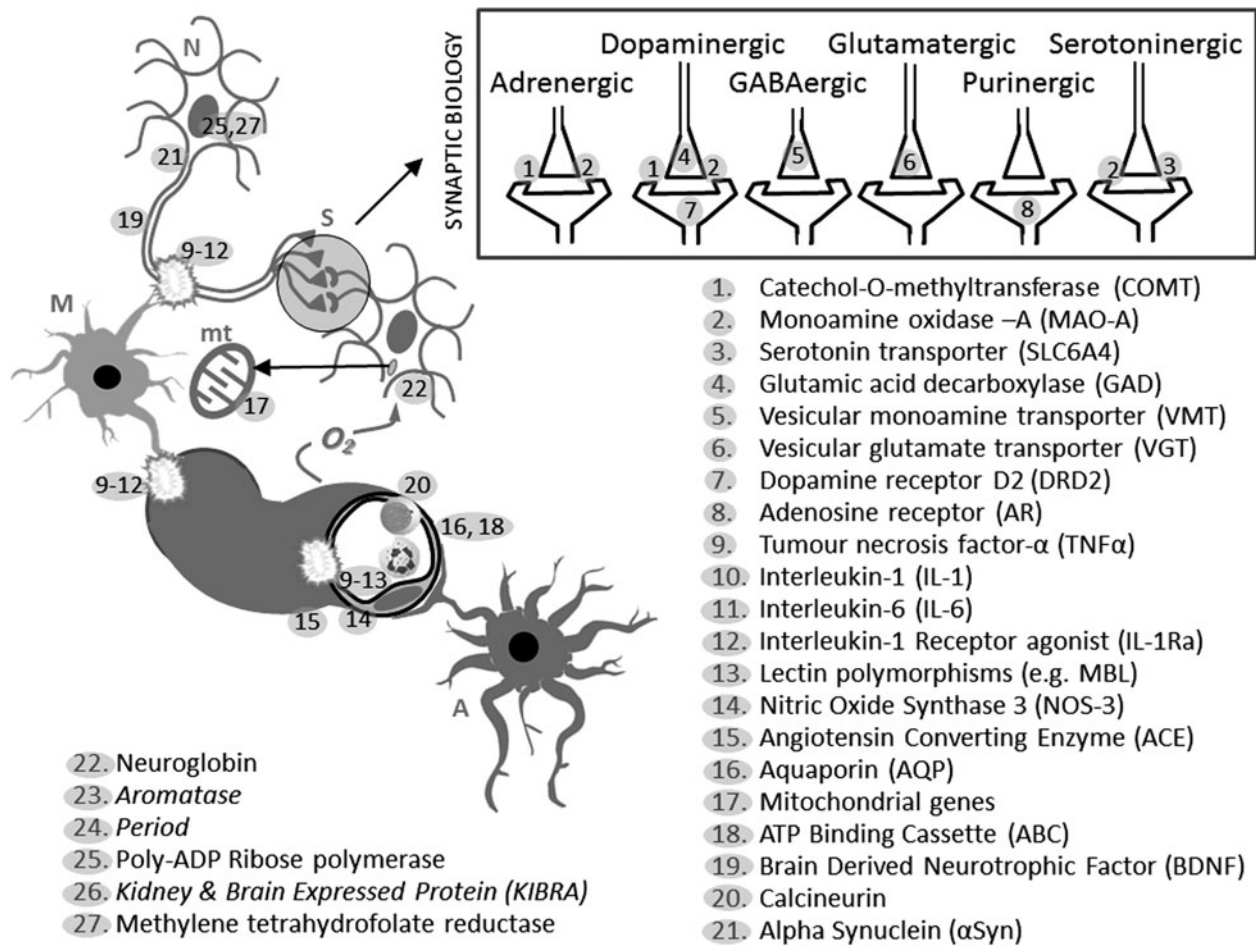
**FIG. 2.** Diagrammatic representation of tissue, cellular, and subcellular location of non-APOE target in candidate gene studies. The box at top right depicts a variety of neurochemical synapses and locates the target gene products in pre-synaptic sites, post-synaptic sites, or synaptic cleft. The vessel at bottom left shows interactions with astrocytes, microglia, and egressing neutrophils and lymphocytes. The star-bursts represent sites of inflammatory injury. A = astrocyte, ADP = adenosine diphosphate, ATP = adenosine triphosphate, GABA = gamma aminobutyric acid, M = microglia, MBL = mannose binding lectin, mt = mitochondria, N = neuron, $O_2$ = oxygen, S = synapse, and SNP = single-nucleotide polymorphism. Diagram depicts a theoretical framework for the interaction of various SNPs identified within the review. Diagram depicts neuronal, microglial, astrocytic, synaptic, endothelial, leukocyte, mitochondrial, nuclear, and cytosolic areas impacted by various SNPs. *Note: SNPs that are italicized could not be slotted into the diagram, but are listed secondary to their identification within the systematic review. APOE, apolipoprotein E.

uniformity in reporting populations and outcomes. The following discussion provides an overview of our findings, and subsequently explores the reliability and relevance of any inferences that emerge from our analysis.

First, many studies have explored the impact of SNPs in neurotransmitter-related genes. The majority of these focused on genetic variations associated with various aspects of monoamine NT metabolism and transport,[16–36,74,75] with COMT/DRD2/ANKK1 mutations being the most commonly reported, and the majority of outcomes focused on neuropsychiatric and behavioral assessments. Given that monoamine NT are believed to play significant roles in a variety of neuropsychiatric and neurodegenerative conditions, it is unsurprising that these NTs may be involved in psychiatric, behavioral, and cognitive sequelae of TBI.[84] The current literature is based on small patient numbers and provides conflicting evidence for these SNPs.

Second, cytokine-related SNPs represent a small proportion of the available literature, with only nine studies that have assessed an association with patient outcomes.[37–45] The poly-

morphisms addressed in these studies included the following cytokines: IL-1a, IL-1b, IL-1RN, IL-6, and TNFA, with most studies documenting the association between these SNPs and global patient outcome. Given the documented association between serum,[85] cerebrospinal fluid,[86] and cerebral microdialysis[87] cytokine profiles and patient outcome, the relationship between various cytokine SNPs and outcome is a logical extension. Changes in cytokine expression, and thus inflammatory response, in TBI represents a plausible mechanism by which such SNPs could affect outcomes in TBI.

Third, BDNF-related studies mainly focused on neuropsychiatric/ neurobehavioral outcomes associated with various SNPs.[46–53,76–79] Given that BDNF is involved in neuronal survival and axonal signaling/regeneration post-injury, the potential role of various BDNF SNPs is interesting.[88] Varying mutations in the genes that encode BDNF could modulate the pathophysiology of neuronal/ axonal injury and repair, and hence affect the incidence and severity of late cognitive, psychological, and psychiatric sequelae. This mechanistic framework explains the results of several studies,

which show that various neuropsychiatric/behavioral tests were related to BDNF SNP status.

Fourth, mitochondrial polymorphisms were assessed in only three studies.[54–56] All of these documented associations between various mitochondrial mutations and global patient outcome at 6–12 months post-injury. These findings are not unexpected, given that mitochondrial function is crucial in maintenance of metabolism and intracellular homeostasis.[89] However, with only three studies to date assessing mitochondrial SNPs or haplotypes, it is difficult to conclusively define the role of these SNPs on patient outcome.

Fifth, other individual SNPs were described in relation to a range of patient outcomes. Whereas these did not group into any of the SNP categories described above, it appears that these SNPs tend to populate some interesting potential "functional clusters" of genes. First, a cluster of SNPs related to neurovascular and blood–brain barrier (BBB) function were described. These included: ACE,[57,58] ATP binding cassette,[59–61] NOS, and AQP.[64] The ACE and NOS SNPs may play a role in vascular caliber and pre-capillary regulation of cerebral blood flow, whereas the ATP binding cassette protein and AQP are involved in solute transport[59] and water homeostasis[64] across the BBB. These functional links provides a framework through which genetic variation in the function of these proteins could impact survival and neuropsychiatric/behavioral function post-TBI.

A second class of SNPs involved neuroprotective/regulatory proteins: p53,[68] calcineurin,[62,83] neuroglobin,[63] aromatase,[65] and PARP.[70] All of these have recognized functions in central nervous system function, injury, and repair. p53 is involved in cell-cycle regulation,[90] whereas calcineurin is involved in immune regulation.[91] Aromatase regulates sex steroid hormone levels, and could modulate the tissue effects of estradiol, which is believed to possess neuroprotective properties.[92] Neuroglobin is believed to be protective in states of hypoxia,[93] whereas PARP is believed involved in the regulation of energy stores.[94] Altered function within these domains of regulation/neuroprotection could be expected to impact global and neuropsychiatric/behavioral outcome post-TBI.

Finally, the last cluster of miscellaneous SNPs were those specific to neuropsychiatric/degenerative states. These SNPs were related to: KIBRA[72] (involved in hippocampal functioning), PERIOD[67] (involved in circadian rhythm functionality), and SNCA[71] (known to play a function in synucleopathic degenerative processes). These proteins are believed to have effects in neuropsychiatric, sleep, and neurodegenerative conditions and could be expected to modulate psychiatric and behavioral outcome post-TBI.

Despite these interesting "clusters" of SNPs within the miscellaneous group of the review, the number of studies in these clusters were small with only preliminary results described.

It is worth noting that the vast majority of SNPs identified in association studies occur in noncoding regions of the genome, where their effect on phenotype cannot be explained by a direct effect on protein translation as is the case in common Mendelian diseases. The effects of these noncoding alleles is through more subtle mechanisms involving regulation of gene expression through multiple mechanisms involving RNA splicing, transcription factor binding, DNA methylation, and microRNA recruitment.[95] For a minority of the polymorphisms listed above, such allele differences have been associated with the expression of cognate proteins in humans. Failla and colleagues studied BDNF in patients with TBI and explored the effect of the rs6265 Met-allele and rs7124442 C-allele, both of which have been as-sociated with reduced BDNF signaling.[48,79] They found that genetic variance in BDNF demonstrated interactions with both age and serum BDNF levels in predicting outcome. Diamond and colleagues examined polymorphisms in the IL-1β gene in TBI, and displayed that the rs1143634 CT allele was associated with lower serum IL-1β, higher CSF/serum IL-1β ratios, and an increased risk of post-traumatic epilepsy,[39] whereas other studies have linked different SNPs to the development of post-traumatic epilepsy.[33,82,83,96] These narratives tie genetic polymorphisms into outcome effects through clear mechanistic effects. However, many polymorphisms that are associated with outcome in this context have not been studied for a mechanistic link in humans

## Limitations

The studies reviewed in this article address the impact of SNPs in genes other than APOE, and many provide evidence of association between cognate SNPs and outcome in TBI. The functional roles of these proteins, and their demonstrated role in non-TBI diseases, provides a plausible framework through which they might impact outcome in TBI. However, despite these interesting results, important limitations need to be highlighted.

First, given that our systematic review was conducted on all non-APOE SNPs in all degrees of TBI severity, the overall results are difficult to synthesize into a single unifying conceptual scheme. Further, the number of patients included in each individual study varied, with most studies reporting on fewer than 200 patients. The poor statistical power inherent in these small sample sizes not only reduces the confidence in the effect sizes reported, but is also likely to bias toward the finding of positive results.[97] This lack of statistical power is further compounded by (the often unrecognized) multiple testing in some patient populations, and may also account for some studies that showed no association between studied SNPs and outcome. Conversely, it is likely that many small negative studies simply did not reach publication, and the resulting publication bias means that our summary of the published literature may not accurately represent the research undertaken in this context.

Second, many of these studies originated from centers with a particular focus in this research area, with many articles studying different SNPs on the overlapping patient cohorts. Consequently, despite interesting results described in these articles, it may be difficult to generalize these findings to other regions within the world where certain genetic patterns may not be present or similarly represented within their populations.

Third, we purposefully avoided including studies looking at APOE genotype and outcomes in adult TBI. Thus, at the current time, we cannot make direct comments regarding the association, or added predictive power over existing models, of APOE genotyping on patient outcome in adult TBI. Given the comprehensive literature body on APOE in adult TBI, our group decided to exclude this from the above living systematic review on non-APOE SNPs to avoid a hasty overview of APOE in an already large overview of TBI genetics. We are currently in the process of completing a separate and distinct living systematic review on APOE in adult TBI, which will address the potential added benefit in outcome modeling.

Fourth, many studies failed to account for various confounding factors known to impact outcome in TBI. In particular, many failed to adequately account for injury severity at presentation, using one of the well-recognized risk adjustment schemes such as IM-PACT.[1,3] The absence of such risk adjustment makes it difficult to

parse out nongenetic drivers of outcome variation and more specifically study the effect of genetic variation on TBI outcome. Secondary brain injury events and disease course can also modify outcome significantly (especially in more severe TBI), and the absence of characterization of such events does not allow us to correct for such covariates, or indeed use them as intermediate outcomes in mediation analyses.[98] Similarly, the neuropsychiatric/neurocognitive assessment tools implemented varied significantly between studies. This limits our ability to treat similar outcomes, such as depression, as common phenotypic endpoints for meta-analysis across studies. Finally, given the significant heterogeneity between studies, including those addressing the same SNP, we were unable to conduct a meta-analysis.

Fifth, we chose to use the QuIPS tool to assess bias in the studies we reviewed, as a more specific tool for a study of the prognostic impact of genotype on outcome, rather than other risk of bias assessment tools, such as the RTI Item Bank[99] (designed to assess bias and precision in observational studies), the Cochrane Risk of Bias tool[100] for intervention studies, and the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool[101] for diagnostic studies. When assessed against QuIPS, all but one of the 68 associations reviewed had at least moderate risk of bias in one or more of the QuIPS categories, and 14 had a high risk of bias in one or more categories.

Sixth, whereas we did seek data on age and gender in our abstraction of studies, the results in these studies, with few exceptions, did not account for the impact of these variables on genetic associations. In any case, studies were rarely powered adequately to undertake such an analysis. We also considered exploring the impact of ethnic variance on associations, but discarded this option, because an initial assessment of the literature showed that these data were largely unavailable. This is an important omission, given that ethnic background is clearly a likely driver of differences in this context.[102]

It is worth emphasizing that our inclusion/exclusion criteria were strict in that studies with less than 5 patients were excluded. Although this sample size threshold would be very small for genetic association studies, we selected this because we wished to be as inclusive as possible in finding relevant data that might contribute to a potential meta-analysis. In the event, study heterogeneity made such a meta-analysis impossible. However, even with this low threshold, studies highlighting individual case reports or small case series on interesting SNPs as they relate to patient outcomes were not included or discussed in this review, even if they had suggested potential to impact outcome. An example of this would be mutations in the voltage gated calcium channel—CACNA1A—which have been shown to be related to epilepsy and disease-related edema in many studies,[103,104] and associated with cerebral edema after mild TBI.[105] This mutation, and potentially others, may prove important as future larger, prospective studies provide additional information.

Seventh, this living systematic review only focused on non-APOE polymorphisms and their association with clinically relevant outcomes in adult TBI. Thus, comments on the link between various SNPs and post-mortem histological changes cannot be made within this review. The scope of the systematic review was large in any case, and we needed to restrict the field to make it manageable, and this was one of the *a priori* restrictions set in the literature search. We elected not to include post-mortem findings because it would have required consideration of an entirely new set of outcomes (pathological and histological findings), which would have taken up a great deal of space in an already long article. Whereas all of the studies we encountered for this living systematic review were based on convenience samples, this is particularly the case in post-mortem studies, and though these provide clear insights into TBI biology, defining their quantitative relationship to the wider TBI population is not easy. Thus, a main limitation of this living systematic review is that this link with histological outcomes was not explored, though we acknowledge that this is something of importance and deserves attention during future renditions of this living systematic review.

Finally, the results of the studies in this review speak broadly to the role of host response in modifying disease course and outcome in TBI. It is highly unlikely that any individual gene functions in isolation in this context, and most of the networks that we discuss represent the interaction of several proteins. Consequently, in addition to examining the impact of individual genes on outcome, it may also be important to find ways of identifying the integrated impact of networks of genes that affect common pathways.[106] Table 1 provides an overview of the various SNPs and their impact on global outcomes measures in TBI.

Such a detailed exploration and synthesis of how polymorphisms in individual genes result in an integrated effect on outcome is beyond the scope of this review. However, it is possible to draw some broad conclusions about the mechanisms of outcome impact of the genetic variation discussed in this review (see Fig. 1). Genetic variation could affect TBI outcome by modulating critical components of injury response, vascular biology, or inflammation cascades, affecting molecules that govern repair and recovery (such as BDNF), or result in differences in pre-injury traits (such as resilience or cognition), with such ''adverse alleles'' only be expressed if cognitive reserve is challenged by injury. For example, polymorphisms in ANKK1 may modulate response latency after mild TBI and poorer performance on the CVLT-II and nonverbal processing speed.

The limitations that we discuss above may also, to some extent, account for some of the interstudy inconsistencies that we observed, given that variations in injury severity, timing of outcome assessment, and assessment tools used could result in legitimate, but varying inferences in analyses that address the impact of a given polymorphism.

### Considerations for future studies in adult traumatic brain injury

It is important to point out that any genetic study, regardless of whether it addresses candidate genes or uses a GWAS approach, needs to take account of the fundamentals of good genetic epidemiology. A detailed discussion is beyond the scope of this article (readers are referred to some excellent reviews[107–110]), but a few points are worth highlighting. For example, the results from GWAS studies are increasingly only perceived to be robust when the results in a Stage 1 (or *Discovery*) cohort are replicated in a Stage 2 (or *Replication*) cohort. Most current GWAS studies will address several hundred thousand (typically 500,000–1,000,000) SNPs. The risks from multiple comparison penalizes any statistical significance that is observed, meaning that in Discovery cohorts, for example, $p$ values $<5 \times 10^{-8}$ need to be achieved to demonstrate robust effects. This, in turn, mandates large sample sizes (see below). Several other confounders in such studies (e.g., such as racial differences in allelic frequency) are mentioned above, in the Limitations section.

Notwithstanding these limitations in the literature that we reviewed, we believe that the genetic variations explored in these studies have a plausible role in affecting outcome after TBI. If

confirmed, the insights obtained could be used to refine outcome prediction models, identify new therapeutic targets, and potentially stratify patients for precision medicine approaches with new agents. However, addressing these aspirations requires both additional studies and new approaches to analysis. There is a strong case to move from candidate gene studies to genome wide association studies (GWAS) in order to obtain a more complete, unbiased, and integrated understanding of the effect of genetic variation on disease course and outcome in TBI. GWAS studies exploring the impact of genotype on outcome are relatively uncommon, given that most such studies compare cases and controls to determine the impact of genetic variation on disease incidence, rather than outcome. However, the principles used in case control studies[111] can be extended to outcome studies, and application of these principles suggest that sample sizes required to reach the conventional $p < 5 \times 10^{-8}$ threshold will depend on various factors. The first of these is the frequency of the outcome of interest. Data from a 20,000-patient trial[112] suggest that we should expect unfavorable outcome rates of around 45% in moderate-to-severe TBI and around 30% across the entire TBI severity range. Other factors include the risk allele frequency (which ranges from 0.05 to 0.5) and the effect size of possessing this risk allele.

Data from the papers examined in this review suggest a wide range of effect sizes, but past experience from other diseases suggests that likely effect sizes for the impact of genetic variation on outcome in complex diseases are likely to show ORs in the range of 1.2–1.5. Given the heterogeneity in TBI at presentation, these effects are unlikely to be demonstrable in sample sizes less than 2000–4000 patients in a single severity category (assuming, e.g., 45% unfavorable outcomes in moderate-to-severe TBI), and robustly powered studies to detect small effect sizes may require sample sizes of about 10,000 (see Fig. 3). Simulations were done
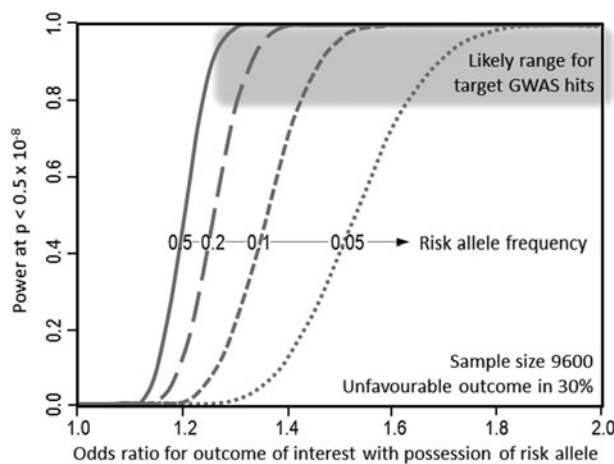
using simple logistic regression under additive genetic association assumption. The range of effect sizes reflect typical ORs observed in first rounds of genetic association studies for complex diseases, such as in the original Wellcome Trust Case-Control Consortium study (WTCCC).[113] With ∼50% more cases (unfavorable outcome) and ∼100% more controls (favorable outcome) than in the original WTCCC study, the figure illustrates that studies of this size should be well powered in this target OR range). The power of these samples to detect associations is not uniform, but will vary depending on the outcome being interrogated. Such studies are only possible through international collaborative efforts. Further, even with such large sample sizes, the parsing of genetic effects on outcome will require that we account for other covariates that modulate outcome, characterized (as a minimum) by recording the variables that contribute to common risk adjustment schemes such as IMPACT.[1,3] More detailed stratification of samples (e.g., by age and sex) or the need to account in a more detailed fashion for preinjury comorbidities (e.g., depression) will make greater demands on sample size, but could provide greater robustness and/or refinement of inferences regarding genotype-phenotype associations. With the hope of the widespread adoption of GWAS techniques, outlined above, future renditions of this living systematic review on non-APOE SNPs in adult TBI will be able to apply meta-analytic techniques, providing powered statistical support for the associations outlined in the current version of this review.

## Conclusion

Although the size and quality of past studies prevent rigorous inferences, the available data are consistent with the scientifically plausible conclusion that various NT-, cytokine-, and BDNF-based SNPs may be associated with patient global outcome at 6–12 months post-TBI. The association between NT, cytokine, and BDNF SNPs with neuropsychiatric and behavioral outcomes at 6–12 months post-TBI is less clear, with conflicting results for similar SNPs across various studies. These results suggest an important role for variations in host response in modulating disease course and outcome post-TBI. However, definitive conclusions in this regard will require adequately powered and better designed GWAS studies, which account for nongenetic covariates that drive outcome, and examine the role of network function in TBI. Such studies are underway and will yield new data over the next few years. This living systematic review will be revised and updated as new evidence becomes available from these and other studies.



**FIG. 3.** Analysis of sample size versus power in GWAS studies for different rates of risk allele frequency. These analyses have been conducted for a 9600 sample with a 30% unfavorable outcome. The shaded area shows the likely range of target genes in GWAS studies. Simulations were done using simple logistic regression under additive genetic association assumption. The range of effect sizes reflect typical odds ratios observed in first rounds of genetic association studies for complex diseases, such as in the original Wellcome Trust Case-Control Consortium study (WTCCC).[113] With ∼50% more cases (unfavorable outcome) and ∼100% more controls (favorable outcome) than in the original WTCCC study, the figure illustrates that studies of this size should be well powered in this target OR range. GWAS, genome-wide association studies; OR, odds ratio.

## Author Disclosure Statement

No competing financial interests exist.

## Supplementary Material

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