Genetic Influences on Patient Oriented Outcomes in TBI: A Living Systematic Review of Non-APOE Single Nucleotide Polymorphisms
SUPPLEMENTARY MATERIAL (ONLINE APPENDIX)

Appendix 1: Search Strategies

MEDLINE 1946 to present, via NICE Healthcare Database:

(exp BRAIN INJURIES/ OR exp CRANIOCEREBRAL TRAUMA/ OR ((head* OR brain*) ADJ2 (injur* OR trauma*)).ti,ab) AND (exp GENETIC VARIATION/ OR exp GENOTYPE/ OR genetic*.ti,ab OR mitochond*.ti,ab OR exp INTRACELLULAR SIGNALING PEPTIDES AND PROTEINS/ OR genomic* OR genome OR allele) AND (EXP NEUROPSYCHOLOGICAL TESTS/ OR "Glasgow outcome" OR GOS OR functional OR outcome OR discharge OR rehab* OR recover* OR GCS OR "Glasgow coma" OR Glasgow OR disability OR mortality OR ICU OR "intensive care" OR "critical care" OR rankin)

EMBASE 1980 to present, via NICE Healthcare Database:

(exp BRAIN INJURIES/ OR exp CRANIOCEREBRAL TRAUMA/ OR ((head* OR brain*) ADJ2 (injur* OR trauma*)).ti,ab) AND (EXP GENOTYPE/ OR exp GENOTYPE ENVIRONMENT INTERACTION/ OR exp GENETIC POLYMORPHISM/ OR exp DNA POLYMORPHISM/ OR exp SINGLE NUCLEOTIDE POLYMORPHISM/ OR exp INTRACELLULAR SIGNALING/ OR mitochond*.ti,ab OR genetic*.ti,ab OR genomic* OR GENOME OR allele) AND (EXP NEUROPSYCHOLOGICAL BATTERY,LURIA NEBRASKA/ OR exp NEUROPSYCHOLOGICAL TEST/ OR exp NEUROPSYCHOLOGICAL TESTS/ OR exp NEUROPSYCHOLOGY/ OR rankin OR "Glasgow outcome" OR GOS OR functional OR outcome OR discharge OR rehab* OR recover* OR GCS OR "Glasgow coma" OR Glasgow OR disability OR mortality OR ICU OR "intensive care" OR "critical care")

CINAHL 1981 to present, via NICE Healthcare Database:

(exp HEAD INJURIES/ OR exp BRAIN INJURIES/ OR "traumatic brain injury".ti,ab OR ((head* OR brain*) ADJ2 (injur* OR trauma*)).ti,ab) AND (exp GENETICS/ OR exp POLYMORPHISM,GENETIC/ OR genetic*.ti,ab OR mitochond*.ti,ab OR genomic* OR genome OR allele)

Google Scholar:

("brain injury" OR "head injury") AND (genetics OR allele OR polymorphism) AND (outcome OR "glasgow outcome")

Appendix 2: Background to genes covered

Interleukin-1
The interleukin-1 family includes multiple proinflammatory cytokines, chief amongst them IL-1α and IL-1β (encoded by the IL1A and IL1B genes, respectively). Within the *IL1A* gene, a C->T polymorphism at position -889 has been observed, with associations between Allele 2 (IL1A*2) of this SNP and juvenile arthritis.[3] Also within this group are the IL-1 receptor gene (IL1R), and the endogenous IL-1 antagonist peptide (IL-1Ra), encoded by the IL1RN gene. Within IL1RN there is a variable number tandem repeat (VNTR) within intron 2 - allele 2 (IL-1RN*2) carriers have higher serum levels of IL-1RN but lower production at sites of inflammation, and higher serum IL-1β (a generally pro-inflammatory phenotype).[4]

Interleukin-6
Interleukin-6 (IL-6), encoded by the *IL6* gene, is one of the most prominent pro-inflammatory cytokines, playing a crucial role in generating and driving the acute phase response to injury or infection[5]. It is a major messenger molecule in auto-immune disease, with an IL-6 receptor antagonist (Tocilizumab, Chugai/Hoffman-La Roche) recently licensed for the treatment of rheumatoid arthritis. Neuroinflammation following TBI is hypothesized to result in secondary injury due to blood-brain barrier breakdown and microglial activation, and IL-6 is suggested as one of the cytokines which may drive this response. The C allele of the -174 G->C SNP in the IL6 gene is associated with lower circulating levels of IL-6,[6] and it is this mutation which has been studied in the context of TBI.

Tumor Necrosis Factor (TNF)
Previously known as TNF-alpha, this pro-inflammatory cytokine can induce apoptotic cell death, as well as interacting with IL-1 and IL-6 in the acute inflammatory response following TBI.[7]

Catechol-O-methyltransferase (COMT)
COMT is one of three enzymes responsible for the breakdown of dopamine and other catecholamines in the central nervous system, the others being the Monoamine Oxidases (A and B). Within the COMT gene exists a Val158Met polymorphism (rs4680) which is functional:[8] the Met isoform is 4x less active than the Val isoform. As the pre-frontal cortex does not express dopamine reuptake transporters and depends disproportionately on COMT for clearance of synaptic dopamine, it is the tissue most affected by this decrease in activity, with Met/Met homozygotes thought to have more synaptic dopamine. FMRI imaging studies have previously demonstrated that Val/Val individuals, who clear dopamine more avidly in the PFC, have a higher degree of neuronal activation at a given level of performance on a task relative to Met/Val or Met/Met subjects, i.e. demonstrate less efficient processing.[9]

Monoamine Oxidase A (MAO-A)
MAO-A is another enzyme crucial for the metabolism of catecholamine neurotransmitters in the CNS. It has a relatively higher affinity for serotonin in comparison to COMT and MAO-B; excess levels of serotonin have been causally implicated in pathological aggression. Within the gene encoding MAO-A, a Variable Number Tandem Repeat (VNTR) region modulates transcriptional activity; 3.5 or 4 tandem repeats give a high activity allele, whereas 2, 3 or 5 repeats give a low activity allele.[10] The latter genotypes result in reduced production of functional MAO-A, and therefore higher neuronal 5-HT, and are possibly associated with aggression in those exposed to other pre-disposing psychosocial events.

ANKK1
The ANKK1 TAQ1A polymorphism (rs1800497), a T->C SNP, affects expression of the DRD2 gene (encoding a dopamine receptor) – the A1 allele (T) results in 40% lower expression[11] of the D2 receptor – given equal amounts of dopamine release, this could theoretically lead to greater receptor saturation.

Serotonin Transporter (SLC6A4)
The Serotonin transporter gene, encoded by SLC6A4, contains a polymorphic region referred to as 5-HTTLPR (5-HTT long polymorphic region) which varies by a 44bp insertion/deletion mutation. This variation produces a "long" (5-HTTLPR L) or "short" (5-HTTLPR S) allele of SLC6A4; the S-allele has lower functional activity in vitro. There is a second SNP within the 5-HTTLPR region, an A->G substitution, giving 4 variants - L(A), L(G), S(A), S(G). In vitro, the L(G) polymorphism results in lower activity of the 5-HTT protein, akin to the S variant.[12]

Glutamic Acid Decarboxylase (GAD)

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the CNS.[13] GABA signaling is crucial following TBI to maintain normal neuronal processing and prevent the occurrence of seizures, which are well documented to have a negative impact on overall recovery from TBI. GABA is synthesized from glutamate by GAD, and disruption of enzyme activity by genetic mutations affects the seizure threshold in animal models.[14]

GRIN2A

Excitatory neurotoxicity leading to the activation of apoptosis pathways, mediated in part by excessive calcium influxes, plays a significant role in the initial damage caused by TBI. The major receptor responsible for inward calcium currents in the CNS is the N-methyl-D-aspartate (NMDA) glutamate receptor, which is also thought to play a major role in the encoding of memories through the calcium mediated process of synaptic potentiation. One of the subunits of this receptor, encoded by the GRIN2A gene, has been shown to be a marker of neuronal death.[15]

Brain Derived Neurotrophic Factor (BDNF)

Following TBI, in addition to inflammatory and apoptotic pathways, there is simultaneous activation of neurotrophic protective pathways. A major messenger molecule promoting synaptic plasticity and neuronal survival is BDNF, which is also crucial for the development of new synaptic connections, a potential mechanism of recovering function following structural damage to the brain.[16] Within the BDNF gene exists an SNP, rs6265, which results in the substitution of valine for methionine at position 66 of the BDNF pro-peptide. The Val66Met polymorphism has been extensively studied in the setting of neuropsychiatric disease, with the methionine containing variant thought to result in impaired transportation and processing of BDNF in the endoplasmic reticulum;[17] carriage of the Met allele has been shown to associate with higher incidences of Alzheimer's disease and Bipolar Depression.

Mitochondrial Genetics

As the organelles responsible for cellular energy homeostasis, Mitochondria have a central role to play in neuronal survival following injury. In addition to generating the energy necessary for cellular functions to proceed, mitochondria play an active role in triggering cell death pathways, in part via the formation of the mitochondrial outer membrane permeability transition pore. The formation of this ion channel can result from mechanical or chemical cellular injury, and has been observed in cardiac myocytes at autopsy, as well as in neural tissue following ischemic injury. In particular, it is one of the key mechanisms of cell death due to excitotoxic calcium influxes, such as occur following TBI. As well as overall analysis of the mitochondrial genome, the gene BCL2 has been studied in isolation – a proto-oncogene, its normal function is to regulate the formation of the transition pore.[18]

P53

This tumor suppressor gene holds a crucial role as the gatekeeper to cell cycle progression or apoptotic cell death, and contains an SNP with results in an arginine to proline substitution (Arg72Pro); the Arg isoform has been shown to induce apoptosis more efficiently.[19]

Angiotensin Converting Enzyme (ACE)

functions as a central regulator of blood pressure, via the conversion of Angiotensin I into Angiotensin II (a potent vasopressor). Following TBI the maintenance of cerebral perfusion (whilst avoiding vasospasm) is crucial to preventing cerebral oligemia and subsequent secondary injury. The ACE gene contains a 287bp insertion/deletion polymorphism, with Del/Del subjects having higher levels of circulating and tissue ACE;[20] carriage of the Del allele has been previously associated with greater risk of cerebrovascular disease, and ACE inhibition has been shown to reverse experimentally induced vasospasm.[21] It could therefore be hypothesized that Del/Del homozygotes would be at a greater risk of secondary ischemic injury following TBI, and may therefore have a worse functional recovery.

Calcineurin

A pro-inflammatory protein phosphatase which plays a role in T-cell activation,[22] and is blocked by immunosuppressants such as ciclosporin. The enzyme has a catalytic subunit, of which 3 isozymes exist (alpha, beta, gamma). These are encoded by the genes PPP3CA, PPP3CB, and PPP3CC respectively.

Neuroglobin
A neuron specific hemoprotein with a higher affinity for oxygen than hemoglobin, acts to prevent neuronal hypoxia,[23] and so could be hypothesized to have a neuroprotective role following TBI. The NGB gene displays two haploblocks, each tagged by a single SNP (rs3783988 and rs10133981).

ATP-binding cassette transporters
Three isoforms (B1, C1 and C2) regulate solute transport across the blood-brain barrier and so influence bioavailability of medications and endogenous substances.[24]

Aromatase
The steroid hormone Estradiol is formed from testosterone in a process catalyzed by the aromatase enzyme (Cytochrome p450 19A1), the gene for which contains numerous SNP's. Estradiol has been hypothesised to have a neuroprotective effect in animal models.[25]

Nitric Oxide Synthetase 3
Nitric oxide is now widely acknowledged as a universal regulator of vascular tone in all tissues. One of the enzymes responsible for the generation of nitric oxide, NOS3 contains multiple SNP's. The C allele of the promoter region –T786C polymorphism has been previously associated with reduced maximal forearm blood flow in response to acetylcholine[26] (i.e. a reduced capacity to produce nitric oxide) and vasospasm in coronary and cerebral territories.

Poly(ADP-ribose) polymerase-1 (PARP-1)
An enzyme which uses NAD+ as a substrate to add long-branching ADP-ribose chains to DNA repair proteins and transcription factors, as well as nuclear proteins, in order to flag single strand DNA breaks for repair following cellular injury. Overactivation can result in exhaustion of NAD+ stores (and therefore apoptosis due to energy failure); PARP-1 deletion or inhibition seem protective in experimental trauma.[27]

Kidney and Brain Expressed Protein (KIBRA)
Acts as a substrate for protein kinase zeta, which has been shown in rat models to play an essential role in both the induction and maintenance of hippocampal synaptic long term potentiation, and the storage and maintenance of spatial memory. CC homozygote status at rs17070145 of KIBRA has been implicated in worse performance in tests of long term storage of semantically unrelated words in otherwise healthy adults.[28]

Vesicular Monoamine Transporter (VMAT)

A vesicular membrane protein that is responsible for the transport of monoamine neurotransmitters into synaptic vesicles from the cytosol[29]. Believed to be of importance in dopamine transport and potentially in cognitive function in a variety of neurological illness, including TBI.[30]

Vesicular Glutamate Transporter (VGLUT)

Mediate synaptic uptake of glutamate. Various transporters within this family (VGLUT 1 – 3)[31]. Mutations within the genes encoding these transporters could impact glutamate transmission and impact cognitive outcomes during various neuropathology[32].

Aquaporin (AQP)

Various AQP channels are expressed within neural tissues. AQP-4 is commonly expressed within astrocytes and their foot processes. It is believed that AQP-4 is heavily involved in water homeostasis during normal and pathological conditions[33]. Thus, genetic alteration leading to impaired function could impact patient outcome after TBI[34].

PERIOD

PERIOD genes had recently been linked to circadian function and sleep quality. Genetic variations in this gene may lead to impaired sleep function/recovery post TBI[35].

Alpha-synuclein (SNCA)

Alpha-synuclein has been known to accumulate in various neurodegenerative processes. It is unclear as to how this protein leads to cognitive dysfunction in dementia. Mutations in the SNCA gene may lead to increased risk of synucleinopathies and subsequent cognitive impairment[36].

Adenosine

Adenosine receptors (AR) are involved in various aspects of neuronal signaling, and are implemented in susceptibility to seizures. They are known to be located in similar regions as N-methyl D-aspartate receptors, and may play a role in glutamate mediated ecotoxicity.[37,38]

Methyenetetrahydrofolate Reductase (MTHFR)

An enzyme involved in the metabolism of methionine. Variations in enzymatic function lead to alterations in levels of homocysteine, which has been linked to reduced seizure thresholds and pro-epileptic activity in animal models.[39,40]

Lectin

One of the complement mediated pathways, dictating inflammatory response, is regulated via lectin proteins, such as mannose-binding lectin (MBL) and ficolin 2 (FCN2). These inflammatory mediators could potentially dictate the cerebral inflammatory response to TBI.[41]

Reference List for Online Appendix 2: Gene Background Information

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Appendix 3: Excluded Studies from 2nd Filter Process (Minus APOE Studies)

Reason for exclusion	Study Identifier
Conference abstract with insufficient data or data subsequently published in full	Carter 2011,[1] Carter 2012,[2] Garnett 2003,[3] Jacobs 2009,[4] Ponsford 2010,[5] Rubio Lopez 2010,[6] Cousar 2009,[7] Adams 2014,[8] McDevitt 2014,[9] Nogueras 2014,[10] Sinha 2014,[11] Yue 2015[12], Nielson 2016[13]
Outcome data not reported for each genotype individually	Ashman 2008[14]
No genotyping performed	Lankford 1994[15], Terrel 2017[45], Wilcox 2017[46]
No genetic variation identified within cohort	Romeiro 2007[16]
Comment letter in response to included study	Collie 2004,[17] Harden 2004[18]
Ineligible outcome measure	Hiekkanen 2007,[19] Horsburgh 2000,[20] Isoniemi 2006,[21] Jiang 2011,[22] Kerr 2003,[23] Koponen 2004,[24] Leclercq 2005,[25] Smith 2006,[26] Terrell 2008,[27] Tanriverdi 2008,[28] Tierney 2010,[29] Neselius 2013,[30] Xiao-Chuan 2011[31], Diamond 2015[32], Failla 2016[33], Kassam 2016[34], Xaio 2015[35], Narayanan[36], Gill 2016[47], Hayes 2017[48], Kurowski 2017[50]
Foreign language paper with original manuscript or English translation unavailable	Krupa 2003,[37] Martinez 2009[38]
Non-TBI study	Kutner 2000,[39] Lyons 2013[40]
Pediatric Only	Kurowski 2016[41], Kurowski 2017[49], Treble-Barna 2017[51]
Full text not available	Jordan 1997,[42] Poovindran 2013,[3] Willmott 2013[44]

Reference List for Online Appendix 3: Excluded Articles from 2nd Filter

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Appendix 4: Study characteristics and Patient Demographics of included studies

Please note that for this and all subsequent tables, the references are arranged alphabetically at the end for ease of reference

4.1 Neurotransmitter SNPs

Study Characteristics				**Patient Characteristics**								
Study ID	**Gene**	**Setting (country)**	**Design**	**Number of Patients (n =)**		**Age (years) (m, SD)**	**Gender (Ma, %)**	**GCS (m, SD)**	**GCS 3-8 (n, %)**	**GCS 9-12 (n, %)**	**GCS 13-15 (n, %)**	**Outcome Measure**
Chan 2008	5-HTT (S allele vs L'/L' homozygote)	Clinic (Can.)	Pros. Case-control	Depressed: 75		39.0 ± 17.4	41 (54.7)	5-HTTLPR S+: n=61 (81.3)	4 (5.3)	6 (8)	54 (72)	HAM-D
				Controls: 99		37.3 ± 18	66 (66.7)	5-HTTLPR S+: n=81 (81.8)	2 (2)	10 (10.1)	82 (82.8)	
Darrah 2013	GAD1	Hosp. (USA)	Retr. Cohort	Whole cohort:257		35.4 ± 0.9	201 (78.2)	6 (med)	NR	NR	NR	Seizures (1w, 6, 6+)
Failla 2013	5-HTT (5-HTTLPR S vs L(A) vs L (G) alleles)	Hosp., USA	Retr. Cohort	Depressed: 27		37.8 ± 14.6	21 (77.7)	7.9 ± 2.6	5-HTTLPR S: 11 (40.7)	5-HTTLPR L(A): 23 (85.2)	5-HTTLPR L(G): 6 (22.2)	PHQ-9 at 6 and 12 Months
				Not depressed: 53		33.3 ± 14.4	46 (86.8%)	7.9±2.8	5-HTTLPR S n=35 (66.0%)	5-HTTLPR L(A) n=43 (81.1%)	5-HTTLPR L(G) n=7 (13.2%)	
Failla 2015	DRD2/ANKK1 TAQ1A	Hosp./Clinic (USA)	Pros. Cohort	ANKK1 rs1800497	CC: 55	35.4 ± 13.8	47 (85.5)	7	NR	NR	NR	CVLT-II, DKEFS, TMT-A, PHQ-9, GOS at 6 and 12 months
					CT: 40	34.0 ± 14.8	30 (75.0)	7	NR	NR	NR	
					TT: 4	25.5 ± 7.3	3 (75.0)	8	NR	NR	NR	
				DRD2 rs6279	CC: 61	34.4 ± 14.5	51 (83.6)	7	NR	NR	NR	
					CG: 30	33.5 ± 14.0	23 (76.7)	7	NR	NR	NR	

					GG: 6	37.8 ± 12.1	5 (83.3)	6	NR	NR	NR	
				DRD2 rs2734838	AA: 9	31.4 ± 14.0	6 (66.7)	7	NR	NR	NR	
					AG: 45	34.3 ± 13.1	33 (73.3)	7	NR	NR	NR	
					GG: 43	34.6 ± 14.5	39 (90.7)	7	NR	NR	NR	
				DRD2 rs17529477	AA: 10	32.6 ± 15.2	8 (80.0)	7.5	NR	NR	NR	
					AG: 47	34.6 ± 15.1	38 (80.9)	7	NR	NR	NR	
					GG: 40	34.5 ± 13.1	32 (80.0)	7	NR	NR	NR	
				DRD2 rs4245147	CC: 21	34.9 ± 15.2	18 (85.7)	8	NR	NR	NR	
					CT: 49	32.9 ± 13.4	38 (77.6)	7	NR	NR	NR	
					TT: 25	37.4 ± 15.2	20 (80.0)	7	NR	NR	NR	
				DRD2 rs7131056	AA: 14	38.5 ± 13.2	13 (92.9)	7	NR	NR	NR	
					AC: 55	32.2 ± 13.8	44 (80.0)	7	NR	NR	NR	
					CC: 29	36.4 ± 14.8	22 (75.9)	8	NR	NR	NR	
				DRD2 rs4630328	AA: 11	34.2 ± 15.9	9 (81.8)	9	NR	NR	NR	
					AG: 53	34.0 ± 14.3	41 (78.9)	7	NR	NR	NR	
					GG: 34	35.2 ± 13.6	29 (85.3)	7	NR	NR	NR	

Juengst 2017	ANKK1 TAQ1A	Hosp (USA)	Pros. Cohort	Moderate/Severe TBI: 68	NR	NR	NR	NR	NR	NR	FrSBe, PHQ-9 at 6 and 12 months post injury
Lipsky 2005	COMT	Hosp. (USA)	Pros. Cohort	COMT M/M: 25	24.6 ± 5.6	24 (96)	PTA <7d n=13 (52)	LOC <1h n=12 (48)	COMT M/M: 25	24.6 ± 5.6	WCST
				COMT V/M: 46	26.5 ± 7.0	43 (93.5)	PTA <7d: 28 (60.9)	LOC <1h: 24 (52.2)	COMT V/M: 46	26.5 ± 7.0	
				COMT V/V: 42	24.6 ± 5.5	39 (92.9)	PTA <7d: 27 (64.3)	LOC <1h: 24 (57.1)	COMT V/V: 42	24.6 ± 5.5	
Madura 2016	VGLUT1 (SLC17A7)	Clinic (USA)	Pros. Cohort	SLC17A7 CC: NR	NR	NR	NR	NR	NR	NR	BESS, ImPACT
				SLC17A7 CG: NR	NR	NR	NR	NR	NR	NR	
				SLC17A7 GG: NR	NR	NR	NR	NR	NR	NR	

Markos 2016	VMAT2	Hosp. (USA)	Pros. Cohort	VMAT rs363223	AA:39	29.9 ± 12.0	31 (79.5)	7	NR	NR	NR	Comp-Cog, ROCFT, DKEFS-fluency subset, TMT-A and B, COWAT, CVLT-LD, DST, WAIS-R
					AG:68	37.3 ± 14.6	58 (85.3)	7	NR	NR	NR	
					GG:27	32.0 ± 12.5	21 (77.8)	7	NR	NR	NR	
				VMAT rs363226	GG:14	35.3 ± 13.9	11 (78.6)	7	NR	NR	NR	
					CG:51	35.7 ± 14.8	43 (84.3)	7	NR	NR	NR	
					CC:68	32.5 ± 13.0	55 (80.9)	7	NR	NR	NR	
				VMAT rs363251	GG:20	35.2 ± 15.6	15 (75.0)	7	NR	NR	NR	
					AG:64	36.2 ± 14.6	53 (82.8)	8	NR	NR	NR	
					AA:47	30.3 ± 10.7	40 (85.1)	7	NR	NR	NR	
				VMAT rs363341	TT:8	31.4 ± 10.6	7 (87.5)	9.5	NR	NR	NR	
					TC:56	35.2 ± 14.7	49 (87.5)	7	NR	NR	NR	
					CC:71	33.5 ± 13.4	55 (77.5)	7	NR	NR	NR	
McAllister 2005	ANKK1 TAQ1A	Hosp. (USA)	Pros. Cohort	mTBI: 39		31.8 ± 13.2	21 (53.8)	NR	NR	NR	39 (100)	CVLT
McAllister 2008	ANKK1 TAQ1A	Hosp. (USA)	Pros. Cohort	TBI: n=54		35.2 ± 13.6	39 (72.2)	14.1 ± 1.5	NR	NR	NR	CVLT
McDevitt 2015	GRIN2A	Clinic (USA)	Pros. Cohort	GRIN2A LL: 18		NR	All were mTBI (concussion patients).					BESS, ImPACT
				GRIN2A LS: 48		NR						
				GRIN2A SS: 21		NR						

Myrga 2016	DRD2/ANKK1/COMT/ VMAT2/DAT1	Hosp. (USA)	Pros. Cohort	ANKK1 TAQ1A	CT:66	33.30 ± 13.45	53 (80.3)	7	NR	NR	NR	DKEFS-Fluency section, COWAT, TMT-A, WAIS-R, CVTL-LD, ROCFT, TMT-B
					TT:115	32.61 ± 13.26	94 (81.7)	7	NR	NR	NR	
				DRD2 rs6279	CC:96	33.95 ± 13.51	82 (85.4)	7	NR	NR	NR	
					G-car:77	31.64 ± 13.06	60 (77.9)	7	NR	NR	NR	
				COMT rs4680	Val-car:121	32.47 ± 13.41	96 (79.3)	7	NR	NR	NR	
					M/M:50	33.30 ± 13.14	44 (88.0)	7	NR	NR	NR	
				VMAT2 rs363226	G-car:86	33.43 ± 14.01	68 (79.0)	7	NR	NR	NR	
					C/C:96	32.23 ± 12.65	80 (83.3(	7	NR	NR	NR	
				DAT1	10/10	32.65 ± 12.69	62 (82.7)	7	NR	NR	NR	
					9-car:99	33.10 ± 13.97	79 (79.8)	7	NR	NR	NR	
Myrga 2016	COMT/ANKK1	Hosp. (USA)	Pros. Cohort	COMT M/M: 24		37.38 ± 15.44	21 (87.5)	7	NR	NR	NR	FrSBe, PHQ-9 at 6 and 12 months
				COMT V/M or V/V: 63		34.16 ± 13.99	49 (57.8)	8	NR	NR	NR	
				ANKK1 A1/A2 or A1/A1: 37		34.19 ± 15.10	27 (73.0)	8	NR	NR	NR	
				ANKK1 A2/A2: 50		35.00 ± 13.70	43 (86.0)	8	NR	NR	NR	
Nielson 2017	COMT/ANKK1/DRD2	Hosp. (USA)	Pros. Cohort			43.3 ± 18.5	419 (71.5)	NR	42 (7.6)	28 (5.1)	480 (87.3)	GOS-E, PTSD diagnosis, PTSD Checklist-Civilian, WAIS Processing Speed, CVLT Short Delay Recall, CVLT Long Delay Recall; all at 6 months post-injury

Pardini 2011	MAO-A (HA vs LA allele)	Hosp. (USA)	Pros. cohort	PFC L, MAO-A HA: 65	58.1 ± 0.4	NR	NR	NR	NR	NR	NPI-a
				PFC L, MAO-A LA: 41	58.5 ± 0.6	NR	NR	NR	NR	NR	
				nPFC L,MAO-A HA:29	59.4 ± 0.7	NR	NR	NR	NR	NR	
				nPFC L,MAO-A LA:20	58.2 ± 1.0	NR	NR	NR	NR	NR	
Pardini 2014	DRD1/DRD2/COMT	Outpatient (USA)	Pros. Cohort	TBI: 141 Control: 29	NR	NR	NR	NR	NR	NR	NPI-a

Pronger 2013	ANKK1 TAQ1A	Hosp. (USA)	Retr. Cohort	ANKK1 A1/A1: NR	Prior TBI (50)			Unemployed (37.5)			CVLT, SWL
				ANKK1 A1/A2: NR	Prior TBI (19.4)			Unemployed (15.8)			
				ANKK1 A2/A2: NR	Prior TBI (20.1)			Unemployed (16.4)			
Raymont 2008	GRIN2A	Hosp. (USA)	Retr. Cohort	Whole cohort: 182	58.1 ± 2.9	(100)	NR	NR	NR	NR	IQ (AFQT)
Willmott 2014	COMT	Rehab. (Aust)	Retr. Cohort	COMT M/M: 40	38.9 ± 16.8	NR	NR	21 (52.5)	4 (10)	15 (37.5)	GOS-E, TMT , RALVT
				COMT V/M: 110	35.4 ± 15.5	NR	NR	52 (47.3)	25 (22.7)	33 (30)	
				COMT V/V: 61	35.7 ± 17.7	NR	NR	33 (52.4)	8 (12.7)	22 (34.9)	
Winkler 2016	COMT	Hosp. (USA) mTBI	Pros. Cohort	COMT M/M or M/V: 70	40 ± 17	42 (60)	NR	N/A	N/A	70 (100)	GOSE, PCL-C at 6 months
				COMT V/V: 23	42 ± 14	14 (61)	NR	N/A	N/A	23 (100)	
Winkler 2016	COMT	Hosp. (USA) mTBI	Pros. Cohort	COMT M/M or M/V: 76	40.5±15.7	49 (65)	NR	N/A	N/A	76 (100)	WAIS-PSI, TMT B-A, CVTL-II at 6 months
				COMT V/V: 24	42.2±14.1	27 (35)	NR	N/A	N/A	24 (100)	
Yue 2016	DRD2	Hosp. (USA)	Pros. Cohort	DRD2 C957 T/T or T/C: 86	45.1 ± 16.7	57 (66)	13.6 (3.2)	10 (12)	1 (1)	75 (87)	WAIS-PSI, RAVLT, TMT B-A at 6 months
				DRD2 C957 C/C: 42	43.1 ± 15.9	25 (60)	13.4 (3.3)	3 (7)	5 (12)	34 (81)	
Yue 2015	ANKK1 TAQ1A	Hosp. (USA)	Pros. Cohort	ANKK1 T/T: 40	39.0 ± 13.0	39±13	NR	34 (10)	2 (5)	4 (4)	CVLT, WAIS-PSI, GOSE, SWLS, TMT, BSI18 GSI
				ANKK1 C/T: 175	40.0 ± 16.0	40±16	NR	125 (36)	18 (47)	32 (31)	
				ANKK1 C/C: 277	41.0 ± 16.0	41±16	NR	189 (54)	18 (47)	67 (65)	

4.2 Cytokine SNPs

Study Characteristics				**Patient Characteristics**							
Study ID	**Gene**	**Setting (country)**	**Design**	**Number of Patients (n =)**	**Age (years) (m, SD)**	**Gender (Ma, %)**	**GCS (m, SD)**	**GCS 3-8 (n, %)**	**GCS 9-12 (n, %)**	**GCS 13-15 (n, %)**	**Outcome Measure**
Dalla-Libera 2011	IL6	Hosp., Brazil	Pros. Cohort	IL6 -174GG: 43	35.2 ± 12	(100)	5.8 ± 1.9	(100)	NR	NR	GOS (at D/C from ICU)
				IL6 -174CC/CG: 34	39.2 ± 14	(100)	5.3 ± 1.6	(100)	NR	NR	
Dardiotis 2006	IL1A	Greece	Pros. Cohort	IL1A*2-: 125	NR	NR	NR	38 (30.4)	14 (11.2)	73 (58.4)	GOS (6 months)
				IL1A*2+: 90	NR	NR	NR	26 (28.9)	13 (14.4)	51 (56.7)	
Diamond 2014	IL1B	Hosp. (USA)	Retr. Cohort	Whole cohort: 256	35±14.88	209 (81.6)	NR	212 (82.8)	31 (12.1)	9 (3.5)	PTE
				IL1B-3953*2-: 44	24	35 (79.5)	NR	14 (31.8)	26 (59.1)	4 (9.1)	
				IL1B-3953*2+: 25	22	20 (80)	NR	8 (32)	13 (52)	4 (16)	
Hadjigeorgiou 2005	IL1RN (VNTR)	Hosp. (Gre)	Pros. Cohort	IL1RN*2 C: 64	NR	55 (85.9)	9.9 ± 3.8	34 (53.1)	7 (10.9)	23 (36)	GOS (6 months), ICH
				IL1RN*2 NC: 87	NR	73 (83.9)	11.1 ± 3.9	25 (28.8)	17 (19.5)	45 (51.7)	
Minambres 2003	IL6	Hosp. (Spain)	Pros. Cohort	Whole cohort: 40	32.2 ± 18.2	NR	5.9 ± 2.1	NR	NR	NR	Mort. (6), serum IL-6
Sinha 2015	IL6	Unclear	Pros Cohort	IL6-174 GC: 13	32.7 ± 10.5	NR	NR	NR	NR	NR	GOS and FIM at 6 months
				IL6-174 CC: 1		NR	NR	NR	NR	NR	
				IL6-174 GG: 31		NR	NR	NR	NR	NR	

Tanriverdi 2006	IL1A	Hosp. (Turk)	Pros. Cohort	IL1A*2-: 31	26	23 (74.2)	NR	12 (38.7)	16 (51.6)	3 (9.6)	GOS (6 months)
				IL1A*2+: 40	24	33 (82.5)	NR	11 (27.5)	24 (60)	5 (12.5)	
Uzan 2005	IL1B	Hosp. (Turk)	Pros. Cohort	IL1B-511*2-: 41	25	33 (80.5)	NR	14 (34.1)	23 (56.1)	4 (9.8)	GOS (6 months)
				IL1B-511*2+: 28	21	22 (78.6)	NR	8 (28.6)	16 (57.1)	4 (14.3)	
Waters 2013	TNFA	Hosp. (UK)	Retr. Cohort	TNFA-308*2-: 595	34.9 ± 21.6	483 (81)	GCS M1-2: 70 (12)	GCS M3-4: 71 (12)	GCS M5: 111 (19)	GCS M6: 343 (58)	GOS (6 months)
				TNFA-308*2+: 342	35.7 ± 21.6	281 (82)	GCS M1-2: 40 (12)	GCS M3-4: 27 (8)	GCS M5: 60 (18)	GCS M6: 215 (63)	

4.3 BDNF SNPs

Study Characteristics				**Patient Characteristics**								
Study ID	**Gene**	**Setting (country)**	**Design**	**Number of Patients (n =)**		**Age (years) (m, SD)**	**Gender (Ma, %)**	**GCS (m, SD)**	**GCS 3-8 (n, %)**	**GCS 9-12 (n, %)**	**GCS 13-15 (n, %)**	**Outcome Measure**
Bagnato 2012	BDNF Val66Met	Rehab. (Ital)	Pros. Cohort	BDNF Val/Val: n=33		31.5 ± 11.2	29 (87.9)	NR	NR	NR	NR	VS emergence (12 months)
				BDNF Met+: 20		30.8 ± 11.4	15 (75)	NR	NR	NR	NR	
Barbey 2014	BDNF Val66Met	Hosp. (USA)	Pros. Cohort	BDNF Val/Val: 97		58.7	(100)	NR	NR	NR	NR	WAIS
				BDNF Met+: 59		59.5	(100)	NR	NR	NR	NR	
Failla 2015	BDNF Val66Met (rs6265 and rs7124442)	Hosp. (USA)	Pros. Cohort	rs6265	V/V: 170	35.55 ± 15.48	134 (78.8)	6	NR	NR	NR	Mortality (1wk, at 1 yr)
					V/M or M/M: 114	36.57 ± 15.46	96 (84.2)	6	NR	NR	NR	
				rs7124442	C/C or C/T: 126	33.38 ± 14.02	102 (80.9)	6	NR	NR	NR	
					T/T: 158	38.01 ± 16.25	128 (81.0)	6	NR	NR	NR	
Failla 2016	BDNF Val66Met (rs6265 and rs7124442)	Hosp. (USA)	Pros. Cohort	rs6265	V/V: 96	37.7 ± 16.3	163 (80.7)	7	NR	NR	NR	Time Until Death; GOS at 6 and 12 months
					V/M or M/M: 61							
				rs7124442	C/C or C/T: 54							
					T/T: 84							
Krueger 2011	BDNF Val66Met	Hosp. (USA)	Pros. Cohort	BDNF val/val: 73		58.2 ± 2.8	(100)	NR	NR	NR	NR	DKEFS, AFQT
				BDNF met+: 48		58.1 ± 2.9	(100)	NR	NR	NR	NR	
Lanctot 2010	BDNF Val66Met	Hosp. (Can.)	Pros. Cohort	Whole cohort:90		39.9 ± 18.0	50 (55.6)	NR	1 (1.1)	45 (50)	44 (48.9)	HAMD post-citalopram Rx

McAllister 2012	BDNF Val66Met	Hosp. (USA)	Pros. Cohort	Whole cohort: 75		33.1 ± 13.1	46 (61)	14.1 ± 1.7	NR	NR	NR	Continuous Performance Test, SRT
Munoz 2017	BDNF Val66Met (rs6279 and rs7124442)	Hosp. (USA)	Pros. Cohort	rs6265	V/V: 68	36.0 ± 1.5	99 (85.3)	7 (IQR: 6-7)	NR	NR	NR	Mortality, GOS at 6 Months
					V/M or M/M: 49							
				rs7124442	C/T or C/C: 56							
					T/T: 61							
Narayanan 2017	BDNF Val66Met (rs6275)	Hosp. (Malaysia)	Pros. Cohort	rs6265	Whole Cohort: 61 Unspecified carrier status	27.1 ± 8.6	NR	NR	NR	NR	NR	Unspecified neurocognitive battery – assessed attention, language, memory, visuospatial and executive function at 6 months
					Healthy Controls: 12	29.0 ± 5.8						

Narayanan 2016	BDNF (rs6265, rs1048218, rs1048220, rs1048221, rs8192466, rs139352447)	ER (Malaysia)	Pros. Cohort	Whole population: 48		27.4 ± 8.9	NR	NR	NR	NR	48 (100)	GOSE, S-NAB Form 1 + 2
				rs6265	V/V:16	NR	NR	NR	NR	NR	16 (100)	
					V/M or M/M: 32	NR	NR	NR	NR	NR	32 (100)	
				rs1048218	Wild G: 45	NR	NR	NR	NR	NR	45 (100)	
					Minor T: 3	NR	NR	NR	NR	NR	3 (100)	
Rostami 2011	BDNF rs7124442	Hosp. (USA)	Pros. Cohort	BDNF CT: 50		57.4 ± 2.2	(100)	NR	NR	NR	NR	AFQT (IQ)
				BDNF CC: 8		58.4 ± 3.6	(100)	NR	NR	NR	NR	
Veeramuthu 2016	BDNF Val66Met	Hosp. (Malaysia)	Pros. Cohort	Unclear rs number (suspect rs6265)		NR	NR	NR	NR	NR	NR	Unspecified neurocognitive assessment at 6 months

4.4 Mitochondrial SNPs Coding for Mitochondrial Proteins

Study ID	Gene	Setting (country)	Design	Number of Patients (n =)	Age (years) (m, SD)	Gender (Ma, %)	GCS (m, SD)	GCS 3-8 (n, %)	GCS 9-12 (n, %)	GCS 13-15 (n, %)	Outcome Measure
Bulstrode 2014	mtDNA Haplotypes	Hosp. (UK)	Retr. Cohort	Haplogp J: 122	38 ± 24.5	96 (78.7)	GCS M1-2: 13 (10.7)	GCS M3-4 n=12 (9.8%)	GCS M5: 23 (18.9)	GCS M6: 70 (57.4)	GOS (6 months)
				Haplogp T: 78	34 ± 22.5	62 (79.5)	GCS M1-2: 8 (10.3)	GCS M3-4: 9 (11.5)	GCS M5: 20 (25.6)	GCS M6: 40 (51.3)	
				Haplogp U: 146	34 ± 20.6	115 (78.8%)	GCS M1-2: 26 (17.8)	GCS M3-4: 13 (12)	GCS M5: 26 (17.8)	GCS M6: 77 (52.7)	
				Haplogp K: 74	33 ± 21.6	65 (87.8)	GCS M1-2: 8 (12)	GCS M3-4: 3 (8.9)	GCS M5: 18 (24.3)	GCS M6: 43 (58.1)	
				Other Haplogps: 103	25 ± 21.7	83 (80.6)	GCS M1-2: 9 (8.7)	GCS M3-4: 10 (9.7)	GCS M5: 14 (13.6)	GCS M6: 67 (65)	
Conley 2014	mtDNA SNP's	Hosp., USA	Pros. Cohort	mtDNA-10398A: 210	36.1 ± 15.7	168 (80)	NR	208 (99)	(0)	(0)	DRS, GOS, NRS(3, 6, 12 months)
				mtDNA-10398G: 45	36.6 ± 14.0	32 (71)	NR	45 (100)	(0)	(0)	
Hoh 2010	BCL2	Hosp. (USA)	Retr. Cohort	Whole cohort: 205	34.5 ± 14.7	79.5%	NR	(100)	(0)	(0)	GOS (6 months)
				Haplogp H: 357	35 ± 20.7	297 (83.2)	GCS M1-2: 39 (10.9)	GCS M3-4: 43 (12)	GCS M5: 74 (20.7)	GCS M6: 196 (54.9)	

4.5 Miscellaneous SNPs

Study ID	Gene	Setting (country)	Design	Number of Patients (n =)	Age (years) (m, SD)	Gender (Ma, %)	GCS (m, SD)	GCS 3-8 (n, %)	GCS 9-12 (n, %)	GCS 13-15 (n, %)	Outcome Measure
Ariza 2006	ACE	Hosp. (Spain)	Pros. Cohort	ACE I/I: 16	28 ± 10.2	NR	NR	9 (56)	7 (44)	(0)	AVLT, TMT, GPT
				ACE I/D: 32	28.4 ± 12.3	NR	NR	18 (56)	14 (44)	(0)	
				ACE D/D: 25	31.9 ± 14.8	NR	NR	15 (60)	10 (40)	(0)	
Bales 2011	PPP3CC	Hosp. (USA)	Pros. Cohort	PPP3CC rs2443504 AA	NR	NR	NR	NR	NR	NR	GOS (12 months)
				PPP3CC rs2443504 GG	NR	NR	NR	NR	NR	NR	
Chuang 2010	Neuroglobin	Hosp. (USA)	Pros. Cohort	rs3783988 C+: 71	34.4 ± 15.5	57 (80.3)	NR	(100)	(0)	(0)	GOS (3, 6, 12, 24 months)
				rs3783988 TT: 122	33.3 ± 14	94 (78.3)	NR	(100)	(0)	(0)	
Cousar 2013	ATP Binding Cassette (C1 and B1)	Hosp., USA	Retr. cohort	ABCC1 GG: 228	36.4 ± 15.9	(80)	6 Med (IQR 5-7)	NR	NR	NR	GOS (6 months)
				ABCC1 GA/AA: 46	34.8 ± 14.4	(76)	6 Med (IQR 5-7)	NR	NR	NR	
				ABCB1 TT: 61	38 ± 15.6	(71)	6 Med (IQR 4-7)	NR	NR	NR	
				ABCB1 CT/CC: 221	35.2 ± 15.6	(80)	6 Med (IQR 4-7)	NR	NR	NR	

Dardiotis 2014	AQP4	Clinic (Greece)	Pros. Cohort	rs335929	A/A: 205	42.7 ± 21.8	292 (80.4)	NR	130 (35.8)	54 (14.9)	179 (49.3)	GOS (6 months)
					A/C: 125							
					C/C: 24							
				rs3763043	C/C: 196							
					C/T: 131							
					T/T: 28							
				rs11661256	T/T: 297							
					T/A: 51							
					A/A: 4							
				rs335931	A/A: 207							
					A/G: 123							
					G/G: 20							
				rs3763040	G/G: 219							
					G/A: 110							
					A/A: 32							
				rs4800773	G/G: 137							
					G/A: 161							
					A/A: 49							
				rs3875089	T/T: 289							
					T/C: 61							
					C/C: 7							
Dardiotis 2015	ACE	Hosp. (Greece)	Pros. Cohort	rs4343	A/A: 78	42.7 ± 21.8	292 (80.4)	NR	130 (35.8)	54 (14.9)	179 (49.3)	GOS (6 months)
					A/G: 140			NR				
					G/G: 142			NR				
				rs4461142	C/C: 62			NR				
					C/T: 173			NR				
					T/T: 113			NR				
				rs7221780	T/T: 131			NR				
					T/C: 184			NR				
					C/C: 47			NR				
				rs8066276	C/C: 156			NR				
					C/T: 173			NR				
					T/T: 31			NR				
				rs8066114	C/C: 108			NR				
					C/G: 186			NR				
					G/G: 62			NR				

Garringer 2013	Aromatase	Hosp. (USA)	Retr. Cohort	rs2470144 AA: 36		37.7 ± 3.1	28 (77.8)	6.5 Med	NR	NR	NR	GOS (6 months)
				rs2470144 GG/GA: 69		34 ± 1.6	57 (82.6)	6 Med	NR	NR	NR	
Grafman 2015	Oxytocin – various SNPs (rs7632287, rs53576, rs2254298)	Clinic (USA)	Pros. Cohort	Whole cohort: 131		NR	NR	NR	NR	NR	NR	KAS
Hong 2015	PERIOD3	ER (Taiwan)	Pros. Cohort	PER3 4-/4-: 74		41.2 ± 13.8	33 (46.0)	14.9 ± 0.5	NR	NR	NR	PSQI, BAI at 6 weeks
				PER3 4-/5-: 24		42.0 ± 14.6	9 (37.5)	15 ± 0	NR	NR	NR	
Jha 2016	ATP Binding Cassette (C8) – Various SNPs	Hosp. (USA)	Pros. Cohort	rs2283261	A/A: 137	37.9 ± 16.8	304 (79.0)	5.8 ± 1.5	NR	NR	NR	Mean/Peak ICP over 1st 5 days, Edema on CT, need for DC
					A/C: 194							
					C/C: 54							
				rs3819521	C/C: 164							
					C/T: 181							
					T/T: 40							
				rs2283258	G/G: 184							
					G/A: 171							
					A/A: 20							
				rs1799857	G/G: 124							
					G/A: 189							
					A/A: 72							
Martinez-Lucas 2005	p53	Hosp. (Spain)	Pros. cohort	p53 Arg/Arg: 55		33.6 ± 18.9	47 (85.5)	5.5 ± 1.8	NR	NR	NR	GOS (at ICU D/C)
				p53 Pro+: 35		34.2 ± 19.2	27 (77.1)	5.6 ± 2	NR	NR	NR	
Osier 2017	Calcineurin (PPP3CC)	Hosp. (USA)	Retr. Cohort	rs10108011	A/A: 133	39.2 ± 16.9	106 (80.0)	6	NR	NR	NR	GOS at 3, 6, 12 Months
					A/G or G/G: 244	40.1 ± 16.7	193 (79.0)	6				
				rs2469749	C/C: 156	38.9 ± 16.3	123 (79.0)	6				

					C/T or T/T: 205	40.4 ± 17.0	166 (81.0)	6				
				rs2443504	G/G: 152	40.2 ± 17.5	116 (76.0)	6				
					A/G or A/A: 216	39.4 ± 16.0	177 (82.0)	6				
				rs2461491	A/A: 102	40.8 ± 17.4	80 (78.0)	6				
					A/G or G/G: 267	39.4 ± 16.7	214 (80.0)	6				
Osthoff 2017	MBL2 and FCN2	Hosp. (Switzerland)	Pros. Cohort	MBL2 (rs1800451, rs1800450, rs5030737, rs7096206 FCN2 (rs3124953, rs17514136, rs17549193, rs7851696)		39.5 (IQR: 25.8-55.0)	33 (75.0)	7 (IQR: 3-10.5)	NR	NR	NR	GOS-E at 3 Months
Robertson 2011[69]	Nitric Oxide Synthetase	Hosp., USA	Pros. Cohort	NOS3 -786 T/T : 25		38.2 ± 2.9	NR	GCS Motor score mean±SD = 3.2±0.4				Mortality (6 months), cortical blood flow
				NOS3 -786 C/T: 24		31.1 ± 2.3	NR	GCS Motor score mean±SD = 3.3±0.4				
				NOS3 -786 C/C: 2		44.0 ± 23.0	NR	GCS Motor score mean±SD = 3.5±2.5				

Sarnaik 2010	PARP-1	Hosp., USA	Retr. Cohort	PARP-1 rs3219119 AA: 83		34.1 ± 15.5	(75)	5.5 ± 1.7	NR	NR	NR	GOS (6 months)
				PARP-1 rs3219119 AT: 77		33.9 ± 14.7	(82)	5.4 ± 2.0	NR	NR	NR	
				PARP-1 rs3219119 TT: 26		36.8 ± 13.3	(73)	5.4 ± 2.0	NR	NR	NR	
				PARP-1 rs3219090 TT: 84		34.6 ± 15.7	(77)	5.4 ± 1.8	NR	NR	NR	
				PARP-1 rs3219090 AT (n=79)		33.1 ± 14.0	(84)	5.4 ± 1.9	NR	NR	NR	
				PARP-1 rs3219090 AA (n=24)		37.5 ± 13.6	(71)	5.5 ± 2.0	NR	NR	NR	
Scher 2011	MTHFR C677T	Hosp. (USA)	Retr. Cohort	Controls: 668	C/C: 366	32.0 ± 8.5	80.4%	NR	NR	NR	NR	Development of post-traumatic epilepsy at any time during follow-up (military study). Duration of study not specified.
					C/T or T/T; 302							
				Epilepsy: 689	C/C: 350	32.0 ± 8.5	80.4%					
					C/T or T/T: 339							
				Epilepsy Cohort #2: 261	C/C: 127	32.8 ± 8.3	78.1%					
					C/T or T/T: 134							
Shee 2016	SNCA – Various SNPs (rs2736994, rs1372525, rs1023777, rs2583988, rs2619364, rs2301134, rs2301135, rs10005233,	ER (USA)	Pros. Cohort	Whole Cohort: 91		33.7 ± 13.7	56 (61.5)	All mTBI				CVLT-SD, CVLT-LD

	rs1812923, rs2737029, rs356188, rs7684318, rs356219)			Control: 86	47.9 ± 10.2	27 (31.8)	Controls, no head injury.	

Wagner 2012	KIBRA	Hosp., USA	Retr. cohort	KIBRA CC: 63		31.06 ± 1.58	50 (79.4)	6.3 ± 1.4	NR	NR	NR	CVLT, ROCFT, Buschke Selective Reminding Test
				KIBRA CT/TT: 66		33.24 ± 1.74	53 (80.3)	6.3 ± 1.5	NR	NR	NR	
Wagner 2011	Adenosine A1 Receptor (A1AR)	Hosp. (USA)	Pros. Cohort	rs3766553, rs903361, rs10920573, rs6701725, rs1751192	Numbers for each SNP and genotype not provided within manuscript Total Cohort: 187	34.4 ± 1.1	150 (80.2)	6	NR	NR	NR	Development of post-traumatic seizures; GOS at 6 Months
Wang 2014	BMX	Hosp. (China)	Pros. Cohort	mTBI: 51		42.33 ± 15.8	17 (33.3)	NR	NR	NR	NR	BAI, BDI, DHI (1 wk and 6 wk)
				Control: 54		30.85 ± 7.9	22 (40.7)	NR	NR	NR	NR	
Wang 2015	ATP Binding Cassette (B1) – C3435T + G2677T/A	Hosp. (China)	Pros. Cohort	ABCB1 C3435T	T/T: 31	34.8 ± 11.6	123 (67.6)	5.8 ± 1.6	NR	NR	NR	GOS (6 months)
					T/C: 96							
					C/C: 55							
				ACB1 G2677T/A	G/G: 26							
					G/T: 87							
					T/T: 69							

Appendix 5: Abstracted results from included studies: Non-APOE SNPs and Global Outcomes

Table 5.1 Neurotransmitter SNPs

Study ID	Gene	Group		Outcome	6 Mo	12 Mo	Outcome summary	Comment
Failla 2015	DRD2/ANKK1	ANKK1 rs1800497 DRD2 rs6279	CC: 55 CT: 40 TT: 4 CC: 61	GOS at 6 and 12 Months	Not possible to abstract details of outcome for individual SNPs at individual timepoints.		1. ANKK1 rs1800497 heterozygote status was associated with 6 month GOS. 2. No DRD2 SNPs were associated with outcome at 6 or 12 months.	
Nielson 2017	COMT/ANKK1/DRD2	ANKK1 rs4938016 ANKK1 rs11604671 DRD2 rs6277 COMT rs4680 PARP-1 rs3219119	Raw number of patients with each genotype for the listed SNPs not available.	GOSE at 3 to 6 Months	NR	NR	1. This study utilized topological data analysis (TDA) to reveal patterns of genetic biomarkers associated with patient GOSE at 3 and 6 months 2. PARP-1 rs3219119 T/T and A/T genotypes had worse GOSE at 3 to 6 months post-injury. 3. ANKK1 Taq1A rs11604671 A/A genotype was associated with better GOSE in patients with negative computed tomography, where the A/G genotype was associated with better GOSE in those with positive computed tomography. 4. Similar findings for the ANKK1 Taq1A rs4938016 C/G genotype in computed tomography negative patients, and the C/C genotype in the computed tomography positive patients. 5. COMT rs4680 M/V genotype was associated with improved GOSE in computed tomography negative patients, while the M/M genotype was associated with improved GOSE in those with positive computed tomography. 6. DRD2 rs6277 T/T genotype was associated with improved GOSE in computed tomography negative patients, while the C/C genotype was associated with improved GOSE in computed tomography positive patients.	

						*NOTE: computed tomography positive or negative status refers to the presence or absence of lesions on computed tomography of the brain.	
Willmott 2014	COMT rs4680	COMT M/M: 40	GOSE 7/8	17.9%	34.6%	Not statistically significant between genotype differences for GOSE at 1 or 2 year follow-up.	This remained the case after 3x2 ANCOVA (3 genotypes x frontal lobe pathology yes/no) controlling for age at injury, years of education and length of PTA.
		COMT V/M: 110	GOSE 7/8	33.3%	40.9%		
		COMT V/C: 61	GOSE 7/8	33.3%	40%		
Winkler 2016	COMT rs4680	COMT M/M or M/V: 70	GOSE 5/6/7/8	6%/17%/37%/40%	NR	Through both univariate and multivariate logistic regression Met carriers maintain a higher chance of higher GOSE scores at 6 months, OR 2.87 (95% CI [1.20-6.86]) and OR 2.68 (95% CI[1.03-6.94]).	
		COMT V/V: 23	GOSE 5/6/7/8	35%/9%/30%/26%	NR		

5.2 Cytokine SNPs

Study ID	Gene	Group	Outcome	6 Mo	12 Mo	Outcome Summary	Comment
Dalla-Libera 2011	IL6 rs1800795	IL6 -174GG: 43	GOS (Mean±SD)	*3.8±4.2**		***Note that outcomes are at ICU discharge** OR for death with GG vs other genotypes: 0.34 (0.13 to 0.86); p=0.023. In assessment of prevalence per se, G allele over-represented in survivors (81% G allele vs 65% C allele), p=0.031. GOS figures exclude deaths on ICU, demonstrating that although CC/CG less likely to survive initial phase of injury, overall level of recovery amongst those who do is statistically similar to GG homozygotes.	
			Survived	*67.40%**			
			Death on ICU	*32.60%**			
		IL6 -174CC/CG: 34	GOS (Mean±SD)	*3.6±4.5**			
			Survived	*41.20%**			
			Death on ICU	*58.80%**			
Dardiotis 2006	IL1A rs1800587	IL1A*2-: 125	GOS 4/5	84.4%	No data	No statistically significant effect of genotype on outcome. OR for bad outcome in carriers of IL1A-889 allele 2: 1.25 (0.58 to 2.72); p=0.57.	
		IL1A*2+: 90	GOS 4/5	87.2%			
Hadjigeorgiou 2005	IL1RN (VNTR)	IL1RN*2 C: 64	GOS 4/5	87.5%	No data	Raw OR for poor outcome (carriers vs non-carriers) 0.3750 (0.1559 to 0.9017) p=0.0284. Note that this indicates that IL-1RN*2 carriage is protective against poor TBI outcome, despite greater number of carriers having severe TBI at baseline in this cohort. Authors selected alpha level of p<0.01 (no reason given) so this trend is not significant, even after adjustment for baseline GCS, age, gender, hemorrhage/hematoma volume, diffuse brain edema, neurosurgery (p=0.02). Despite trend for better outcome, IL-1RN*2 carriers significantly more likely to have experienced hemorrhagic event (SAH, contusion, DAI, EDH, SDH, hematoma, IVH): Adjusted OR 4.57 (1.67-12.96) p=0.004 (note n=60 for total IL-1RN*2 carriers on hemorrhagic events measure) (i.e. this persists despite adjustment for greater numbers of carriers having severe TBI - adjustment for baseline GCS, age, gender, diffuse brain edema, neurosurgery)	
		IL1RN*2 NC: 87	GOS 4/5	72.4%			
Minambres 2003	IL6 rs1800795	IL-- 174 SNP in cohort of 40 patients	Mortality at 6 Months	No GOS/GOSE		No association between the IL-6 SNP and mortality at 6 months.	
Sinha 2015	IL6 rs1800795	IL6-174 GC: 13 IL6-174 CC: 1 IL6-174 GG: 31	GOS and FIM	Meeting abstract. No other details available		At 1 month, C allele carriers displayed a trend towards better outcome (not statistically significant). At 6 months, C allele carriers displayed a 6.4x likelihood of a better outcome (p = 0.024). C allele carriers displayed better FIM at 6 months (p=0.030).	
Tanriverdi 2006	IL1A rs1800587	IL1A*2-: 31	GOS 4/5	74.2%	No data	Number for favorable vs unfavorable outcome in paper differ from overall totals so recalculated from raw data.	No significant difference in outcome between groups, either on raw data or after authors' regression analysis controlling for age, gender, GCS and CT findings.
		IL1A*2+: 40	GOS 4/5	62.5%	No data		

Uzan 2005	IL1B rs1143634, rs16944	IL1B +3953*2-: 44	GOS 4/5	81.8%	No data	3953 allele 2 carriers OR for poor outcome 5.73 (1.91 to 17.2), p=0.0019 511 allele 2 carriers OR for poor outcome 1.76 (0.63 to 4.92), p=0.2779	Authors also note that all 10 subjects carrying allele 2 at both loci had an unfavorable outcome (GOS 1-3), and that this is significantly different to remaining 59 patients with allele 2 at one/neither loci (p=0.00001). Characteristics and outcome table for those 10 patients does list poor outcome for all of them. Percentages given in text and table for numbers with poor outcome to do not tally with numbers allocated to each GOS category Authors quote p=0.005 for worse outcome in -511*2+ - cannot be substantiated from the raw data they provide.
		IL1B +3953*2+: 25	GOS 4/5	44%	No data		
		IL1B-511*2-: 41	GOS 4/5	73.2%	No data		
		IL1B-511*2+: 28	GOS 4/5	60.7%	No data		
Waters 2013	TNFA rs1800629	TNFA-308*2-: 595	GOS 4/5	69%	No data	OR for poor outcome following adjustment for age, GCS motor response, pupil reactivity, CT classification, traumatic SAH, hypoxia, hypotension, APOE e4 allele and interaction between APOE e4 allele and age: GOS 1-3 at 6 months, allele 2 carriers (vs non carriers) - OR 1.63 (1.14-2.34), p=0.007 *Note: SNPs for TGFB, IL1A, IL1B, IL6 were also evaluated within this study with no statistically significant impact noted.	
		TNFA-308*2+: 342	GOS 4/5	61%			

5.3 Mitochondrial SNPs Coding for Mitochondrial Proteins

Study ID	Gene	Group	Outcome	6 Mo	12 Mo	Outcome Summary	Comment
Bulstrode 2014	mtDNA Haplotypes	Haplogp H: 357	GOS 4/5	65.8%	No data	OR (95% CI) of poor outcome (i.e. <1 favors good outcome) for each Haplogroup (in comparison to non-carriers of that haplogroup): H: 1.57 (0.84-2.96) J: 1.2 (0.55-2.63) T: 1.23 (0.52-2.88) U: 1.14 (0.55-2.39) K: 0.21 (0.07-0.56) Other: 0.83 (0.38-1.82) i.e. Only haplogroup K has a statistically significant protective effect in isolation. Age significantly associated with worse outcome, and both haplogroup K (p=0.017) and T (p=0.015) significantly reduce effect of age on outcome. APOE4 not associated with outcome in this cohort (as reported previously), but APOE x Haplogroup interaction p=0.001. This is due to better outcome in APOE4 carriers carrying mtDNA K - OR for good outcome 5.86 (2.14-17.44), p=0.002. Not clear from article whether this is simply because any defined subgroup of haplotype K carriers in this cohort will on average have better outcomes, giving a falsely significant Group x K interaction.	
		Haplogp J: 122	GOS 4/5	71.3%	No data		
		Haplogp T: 78	GOS 4/5	71.3%	No data		
		Haplogp U: 146	GOS 4/5	63.7%	No data		
		Haplogp K: 74	GOS 4/5	74.3%	No data		
		Other Haplogps: 103	GOS 4/5	63.1%	No data		
Conley 2014	mtDNA SNPs	mtDNA -10398A: 210	GOS 4/5	66.5%	62%	Also recorded DRS and NRS scores. Lower DRS scores = less disabled; 0=healthy, 1-11 = mild disability, 12-29 = moderate-severe disability, 30 = death. Note GOS, NRS differences not significant at any time point. N-numbers not given for DRS so those for GOS assessments at same time points used to calculate SD from published SE. p<0.02 for 10398G less disabled than A at 6 and 12 months on DRS.	
		mtDNA-10398G: 45		75%	72.7%		
Hoh 2010	BCL2	Whole cohort: 205	GOS at 3,6 and 12 months, but outcomes by group could not be abstracted	No Data	No Data	3 month GOS: p<0.0001 for Var/Var or Wt/Var having worse outcomes - raw data for global outcomes not supplied in publication mortality: OR 4.23 (1.31-13.61) for death (Var+ vs Wt/Wt), p=0.02, Of all tSNP's analyzed, only 3 month GOS for rs17759659 meets Bonferroni correction significance. rs17759659 is located in intron II region of BCL2 - additional tSNPs representing this region that were significant (using a traditional alpha of p=0.05) in the global function outcomes analyses: rs12968517, rs7236090, and rs949037.	

5.4 BDNF SNPs

Study ID	Gene	Group		Outcome	6 Mo	12 Mo	Outcome Summary	Comment
Failla 2015	BDNF	rs6265	V/V: 170	Mortality with 1st 7 days and at 1 year, but not abstractable by SNP	Not available		No association between any allele and mortality within the 1st 7 days. Multivariate Cox regression displayed an association between C and M carriers and mortality at 7 days (p=0.0286). Similarly, at 1 year those with V/V and T/T for both SNPs had the highest survival (p=0.006). A genetic risk score was developed (GRS), in which the presence of "at risk" alleles were attributed a score, for inclusion in a Cox multivariate regression analysis with outcome. The GRS score included: 0 – "no risk" (Val/Val, T/T), 1 – "1 risk allele" (Val/Val, C-carriers or Met-carriers, T/T), and 2 – "double carriers" (both Met- and C-carriers). Logistic regression (adjusting for: age, GCS, pulmonary complications, cardiac complications and neurological burden) displayed complex results. Patients under the age of 45 displayed worse outcomes with GRS >0, while those over age 45 displayed the opposite outcome in the first week post injury. Similar trends were displayed for post-acute survival (ie. from day 8-365 post-injury).	
			V/M or M/M: 114					
		rs7124442	C/C or C/T: 126					
			T/T: 158					
Failla 2016	BDNF	rs6265	V/V: 96	Time Until Death; GOS at 6 and 12 Months	Not available		Evaluated the outcome prediction benefit of serum/CSF based BDNF levels with the addition of GRS (described in cell above). Found CSF BDNF levels were associated with time until death (p=0.042; HR=10.973). Multivariate analysis including serum BDNF and BDNF GRS displayed added outcome prediction (p=0.047; HR=0.987).	
			V/M or M/M: 61					
		rs7124442	C/T or C/C: 54					
			T/T: 84					
Munoz 2017	BDNF	rs6265	V/V: 68	Time Until Death; GOS at 6 Months	Not available		Evaluated outcome prediction benefit of CSF based cortisol and BDNF, with addition of BDNF GRS (see above Failla 2015). Found that mean CSF BDNF and cortisol were both statistically higher in those patients which died (p=0.045 and p<0.0001 respectively). Addition GRS added predictive ability for patient mortality in those patients <48 years old (p=0.028). Patients with GRS or 2 had lowest CSF BDNF levels. CSF cortisol levels appear to mediate some of the BDNF association with mortality. GOS data not reported in detail within manuscript.	
			V/M or M/M: 49					
		rs7124442	C/T or C/C: 56					
			T/T: 61					

5.5 Miscellaneous SNPs

Study ID	Gene	Group	Outcome	6 Mo	12 Mo	Outcome Summary	Comment
Cousar 2013	ATP Binding Cassette	ABCC1 GG: 228	GOS 4/5	35.5%	Data incomplete	Raw data for favorable vs unfavorable outcomes show a trend towards better outcomes in ABCC1 GG but not significant. Once controlled for initial GCS, age, sex, ISS the OR for poor outcome was 0.73 (5-95% CI 0.55-0.98) for GG vs GA/AA (p=0.04). Raw data for favorable vs unfavorable outcomes show a trend towards better outcomes in ABCB1 TT but not significant. Once controlled for initial GCS, age, sex, ISS the OR for poor outcome was 0.71 (5-95% CI 0.55-0.92) for TT vs CT/CC (p=0.01).	
		ABCC1 GA/AA: 46	GOS 4/5	25%			
		ABCB1 TT: 61	GOS 4/5	39.3%			
		ABCB1 CT/CC: 221	GOS 4/5	31.2%			
Chuang 2010	Neuroglobin (NGB) rs3783988	C+: 71	GOS 4/5	24.1%	25%	P-values (Chi-Square) for Neuroglobin SNP rs3783988 TT homozygotes having significantly higher chance of good outcome: 3 months: p<0.02 6 months: p<0.01 12 months: p<0.01 24 months: p<0.04	
		TT: 122	GOS 4/5	45.4%	51.9%		
Dardiotis 2015	ACE	rs4343 A/A: 78 A/G: 140 G/G: 142 rs4461142 C/C: 62 C/T: 173 T/T: 113 rs7221780 T/T: 131 T/C: 184 C/C: 47 rs8066276 C/C: 156 C/T: 173 T/T: 31 rs8066114 C/C: 108 C/G: 186 G/G: 62	GOS 4/5	71.8% 89.3% 70.4% 64.5% 87.9% 70.8% 84.7% 78.3% 59.6% 84.6% 73.4% 71.0% 67.3% 83.9% 77.4%	No data	rs4461142 (OR 0.26, (5% CI [0.12-0/57]), rs7221780 (OR2.67, 95% CI 1.25-5.72]), rs8066276 (OR 3.82, 95% CI [1.80-8.13]) heterozygotes were associated with GOS at 6 months. Minor allele presence was associated with worse outcome.	

Dardiotis 2014	AQP4	rs335929 A/A: 205 A/C: 125 C/C: 24 rs3763043 C/C: 196 C/T: 131 T/T: 28 rs11661256 T/T: 297 T/A: 51 A/A: 4 rs335931 A/A: 207 A/G: 123 G/G: 20 rs3763040 G/G: 219 G/A: 110 A/A: 32 rs4800773 G/G: 137 G/A: 161 A/A: 49 rs3875089 T/T: 289 T/C: 61 C/C: 7	GOS 4/5	74.1% 83.2% 79.2% 84.7% 71.8% 57.1% 78.8% 74.5% 100% 73.4% 82.9% 85.0% 77.6% 83.6% 62.5% 75.9% 80.7% 69.4% 78.2% 78.7% 100%	No data	rs3763043 TT genotype (OR 5.15, 95% CI [1.60-16.5], p=0.006) was associate with poor outcome. rs3875089 C allele carriers (OR 0.18, 95% CI [0.07-0.50], p=0.0009) were found to be associated with better outcomes. This was after controlling for age, sex, admission GCS and presence of a hemorrhagic event.
Garringer 2013	Aromatase rs2470144	AA: 36 GG/GA: 69	GOS 4/5 GOS 4/5	19.4% 43.5%	No data	"Aromatase SNP rs2470144 raw data OR for poor outcome (AA vs GG/GA) 3.19 (1.23 to 8.26) p=0.017. rs2470152, rs2470144 and rs4646 identified as making up "risk genotype". Of these rs2470152 was shown to be related to enzyme activity, with C/C-genotype carriers displaying significantly higher Estradiol:Testosterone ratios than T-allele carriers (0.07±0.01 vs. 0.10± 0.02; p=0.026). OR for a poor outcome amongst rs2470152 TT/TC subjects (relative to CC homozygotes) was 2.945 (95%CI 1.082-8.014 p=0.034), once age and GCS were accounted for. Overall, in multivariate model taking into account age and GCS, the OR for a poor outcome (GOS 1-3)at 6 months in carriers of 2 or 3 risk alleles at these three SNP's (vs 1 or none) was 4.575 (95% CI 1.999-10.473, p<0.0001).

Martinez-Lucas 2005	p53 rs1042522	p53 Arg/Arg: 55		GOS 4/5 at discharge from ICU	41.8%	No data	Odds ratio calculated by authors using multivariate logistic regression model (including initial GCS and APACE II score at admission to ICU): Arg/Arg genotype predisposes to poor outcome - OR 2.96 (1.05-8.31), p=0.039
		p53 Pro+: 35		GOS 4/5 at discharge from ICU	48.6%	No data	
Osier 2017	Calcineurin (PPP3CC)	rs10108011	A/A: 133 A/G or G/G: 244	GOS at 3, 6 and 12 Months	NR	NR	No significant association between any minor allele presence and odds of unfavorable outcome at any time frame. (p>0.05 for all) The rs2443504 AA genotype was associated with unfavorable GOS (ie. 1 or 2) at 3, 6, and 12 months (p=0.002, p=0.034, p=0.004; respectively). This held true during multivariate testing controlling for age, sex and admission GCS.
		rs2469749	C/C: 156 C/T or T/T: 205				
		rs2443504	G/G: 152 A/G or A/A: 216				
		rs2461491	A/A: 102 A/G or G/G: 267				
Osthoff 2017	MBL2 and FCN2	MBL2 (rs1800451, rs1800450, rs5030737, rs7096206 FCN2 (rs3124953, rs17514136, rs17549193, rs7851696)		GOS-E at 3 Months	NR	NR	No association between any of the SNPs for MBL2 or FCN2 and GOS at 3 months.
Sarnaik 2010	PARP-1 rs3219119	AA: 83		GOS 4/5	Data not abstract-able	Data not abstract-able	Raw data for outcomes not given. After controlling for age, gender and initial GCS: OR for poor outcome rs3219090 TT vs AT/AA: 0.49 (0.26-0.93), p=0.03 OR for poor outcome rs3219119 AA vs AT/TT: 0.46 (0.24-0.89), p=0.02 Both SNP's tag a haploblock from intron7 to exon 20, which includes auto-modification and catalytic domain of PARP-1. Note neither SNP's polymorphisms were associated with variation in CSF levels of PAR-modified proteins so functional significance of mutations studied unclear.
		AT: 77		GOS 4/5			
		TT: 26		GOS 4/5			
	PARP-1 rs3219090	TT: 84		GOS 4/5			
		AT: 79		GOS 4/5			
		AA: 24		GOS 4/5			

Wang 2015	ATP Binding Cassette (rs1045642, rs2032582)	ABCB1 C3435T ACB1 G2677T/A	T/T: 31 T/C: 96 C/C: 55 G/G: 26 G/T: 87 T/T: 69	GOS dichotomized at 3/2 – favorable outcomes	Data not reported by individual SNP	No data	Multivariate logistical regression displayed ABCB1 C3435T was independently associated with 6 month GOS, after adjusting for gender, age, GCS, ISS and those carrying the CT and CC genotypes. TT genotypes were associated with better outcome (OR 2.71, 85% CI [1.12-6.86]). No association between outcome and the ABCB1 G2677T/A SNP.

***Nielson 2017 – included PARP-1 within the complex statistical modelling. This study is listed under NT section given description of COMT, DRD2 and ANKK1 SNPs.**

Note on Appendices 6-9:

The subsequent tables (Appendices 6-9) include studies which examine the effect of genetic variations on outcomes other than global outcome, with each appendix addressing a class of SNP (e.g. neurotransmitter, cytokine, etc.). Studies within each section are in alphabetical order (based on first author). Tables are formatted individually due to variations in type and detail of information provided in each paper

Appendix 6. Results of studies on NT SNPs measuring outcomes other than global outcomes

Tables are formatted individually due to variations in type and detail of information provided in each paper

	SNP	Outcome	Clinic Assessment		Comment
			mean	SD	Mean days from injury at assessment: Depressed - 118.2 (SD 101.7), Control - 99.7 (SD 75.8); p=0.176 for difference. p=1.00 for difference in incidence of depression by genotype. p=0.092 for HAMD measured difference in severity of depression by genotype.
Chan 2008	5-HTTLPR S'+ (n=61)	HAMD	24.23	6.69	
	5-HTTLPR L'/L' (n=14)	HAMD	20.77	6.06	

	SNP	OC	Seizures <7d	Seizures 7d to 6 months	Comment
			%	%	OR of remaining seizure free in 1st week post TBI for rs3828275 CC (vs CT/TT): 5.601 (1.211-25.908, p=0.028) - once adjusted for age, gender, GCS, incidence of aSDH, neurosurgery; i.e. CC suggested as "protection genotype" against early PTS. OR of having a seizure between 1 week and 6 months for rs3791878 GG (vs GT/TT): 4.892 (1.244-19.246, p=0.0231) - once adjusted for age, gender, GCS, incidence of aSDH, neurosurgery; i.e. GG suggested as "risk genotype" for late PTS.
Darrah 2013	GAD1 rs3828725 CC (n=67)	Seizure occurrence	2.99	No data	
	GAD1 rs3828725 CT/TT (n=109)	Seizure occurrence	14.7	No data	
	GAD1 rs3791878 GG (n=75)	Seizure occurrence	No data	16	
	GAD1 rs3791878 GT/TT (n=78)	Seizure occurrence	No data	3.85	

	SNP	OC	6 months		12 months		Comment
			%	Cohort size	%	N	
Failla 2013	5-HTTLPR S	Depressed	23.9	46	26	50	At 6 months post-injury, authors' multivariate model including age, pre-morbid history, anti-depressant use, gender, GCS, education gives odds ratio for risk of depression: OR (LL vs LS/SS) 3.343 (1.135-9.849), p=0.029p=1.00 However, the multivariate model does not include the L(A) vs L(G) allele difference, and as can be seen from the table, rates of depression amongst L(A)
		Not depressed	76.1	46	74	50	
	5-HTTLPR L(A)	Depressed	34.8	66	28.8	66	
		Not depressed	65.2	66	71.2	66	
	5-HTTLPR L(G)	Depressed	46.2	13	0	12	
		Not depressed	53.8	13	100	12	

							allele carriers are similar to S allele carriers.

	SNP	Outcome	Comment
Failla 2015	DRD2/ANKK1 TAQ1A	CVLT-II, DKEFS, TMT-A, PHQ-9	1. DRD2 rs2734838 was association with PTD at 12 months (p=0.023). 2. ANKK1 rs1800497 heterozygotes and DRD2 rs6279 C-homozygotes had higher FIM-cog scores at 6 months (p=0.028 and p=0.021) 3. ANKK1 rs1800497 heterozygotes displayed better cognitive scores, attention (p=0.007), executive functioning at 6 months (p=0.048), language fluency at 12 months (p=0.041). 4. DRD2 rs6279 C-homozygotes displayed improved cognition at 6 months, executive function (p=0.013), attention (p=0.006) and language fluency at 6 months (p=0.003).

	SNP	Outcome	Comment
Jeungst 2017	ANKK1 TAQ1A	FrSBe, PHQ-9	Unclear from abstract as to timeline for outcomes. A2 homozygote carriers displayed 86% poor cognition vs.45% without poor cognition (p=0.016) in those with post-traumatic depression.

	SNP	Outcome	40-60 days post-injury		Comment
			mean	SD	
Lipsky 2005	COMT Val/Val (n=42)	WCST perseverative responses	20.9	20.9	p<0.03 for both Val/Val performing worse (more perseveration) than Met carriers, and for Met/Met performing better (less perseveration) than Val carriers. Note this is what could be expected - Met/Met thought to have more central dopamine - could this be protective after TBI, preserving function? Previous study showing that Bromocriptine boosts function (reducing perseveration) following TBI and that healthy Val/Val have more neuronal activation but same performance (i.e. less efficiency) than Met/Met (Val/Met in between - dose effect of Met allele).
	COMT Val/Met (n=46)	WCST perseverative responses	14	10.9	
	COMT Met/Met (n=25)	WCST perseverative responses	12.1	5.1	

	SNP	Outcome	Comment
Madura 2016	VGLUT1 (SLC17A7)	BESS, ImPACT	1. The presence of G allele (either of GC or GG genotypes) was associated with prolonged recovery (p=0.0179). 2. C allele carriers (GC or CC) were found to have worse motor ImPACT scores (p=0.01) after the initial injury.

	SNP	Outcome	Comment
Markos 2016	VMAT2	Comp-Cog, ROCFT, DKEFS-fluency subset, TMT-A and B, COWAT, CVLT-LD, DST, WAIS-R	1. rs363226 genotype was association with 6 month Comp-Cog (p=0.006). 2. rs363226 GG genotype was associated with worse FIM-cog scores and Comp-Cog.

	Comment
McAllister 2005	Preliminary paper elaborated on in McAllister 2008 - initial finding that ANKK1 TAQ1A polymorphism T-allele was associated with worse performance on CVLT after mild TBI: T allele carriers: mean score 13.6±3.7 T-: mean score 14.9±1.6 p<0.05

	Comment
McAllister 2008	Subjects analyzed 1 month after TBI on CVLT - TAQ1A (rs1800497) polymorphism in ANKK1 possibly associated with performance. Specifically, there was a trend towards T-allele carriers performing worse on CVLT (T+ mean score 12.6±3.72 vs T- 12.9±3.0, p=0.1) By combining TBI patients from this study with those from previous McAllister study: T+ mean CVLT 11.52±4.02, T-allele absent mean 13.86±2.30, p=0.007. Also able to show that variation in a haploblock of ANKK1 (defined by rs11604671-rs4938016-TAQ1A) showed strongest association with outcome. Five haplotypes identified, frequencies 0.51, 0.31, 0.18, 0.004, 0.004 respectively. Note 1, 3 & 5 all contain T-allele at TAQ1A. Specifically, haplotype 2 (G-G-C) outperforms others - mean CVLT 14.21±2.21 vs grouped mean for others 12.65±3.66; p=0.006. (haplotype 2 is only common one which doesn't contain TAQ1A T-allele).

	SNP	Outcome	Comment
McDevitt 2016	GRIN2A	BESS, ImPACT	1. LL carriers were 6x more likely to have a recovery period longer than 60 days (p=0.0433) compared to the SS group. 2. L allele carriers were more frequently in the prolonged recovery group (p=0.048).

	SNP	Outcome	Comment
Myrga 2016	DRD2/ANKK1/COMT/VMAT2/DAT1	DKEFS-Fluency section, COWA, TMT-A, WAIS-R, CVTL-LD, ROCFT, TMT-B	Significant sex × gene interaction was observed at 6 and 12 months for ANKK1 rs1800497 (6M: P = 0.002, 12M: P =0.001) and COMT rs4680 (6M: P = 0.048; 12M: P = 0.004); DRD2 rs6279 (P = 0.001) and VMAT rs363226 (P = 0.043) genotypes were independently associated with cognition at 6 months, with trends for a sex × gene interaction at 12 months.

	SNP	Outcome	Comment
Myrga 2016	COMT/ANKK1	FrSBe, PHQ-9 at 6 and 12 months	1. COMT Val158Met status was associated with PTD at 12 months (p=0.028), with the Met allele associated with worse behaviour. 2. COMT Met homozygotes had worse FrSBe scores and more behaviour issues. 3. ANKK1 A2 allele carriers had a trend towards worse PHQ-9 scores and FrSBe scores, compared to A1 allele carriers.

	SNP	Outcome	Aggression		Comment
			Mean	SD	
Pardini 2011	PFC lesion, MAO-A high (n=65)	NPI-a	1.1	0.3	Neuropsychiatric Inventory agitation/aggression subscale (NPI-a) used to assess behavioral disturbance. Each dimension rated 1-4 for frequency and 1-3 for severity, the product of the two values is used to give a score. Here, NPI-a least square means (rather than raw mean values) used for ANCOVA comparison, controlling for MAO-A activity, lesion location, current PTSD symptomatology and previous psychological trauma (Early Trauma Inventory scores) - raw scores recorded below. 2x3 ANCOVA reveals no effect of MAO-A genotype on aggression in subjects with PFC lesions, but significantly higher aggression in MAO-A high activity subjects with non-PFC lesions (MAO-A high vs MAO-A low least squares means: 2.1 (SD 0.2) vs 0.6 (SD 0.2), p= 0.007). Note that opposite relationship seen in control group of Vietnam veterans who were otherwise healthy and did not sustain TBI during their service: MAO-A high subjects had significantly lower aggression scores.
	PFC lesion, MAO-A low (n=41)	NPI-a	1.2	0.3	
	non-PFC lesion, MAO-A high (n=29)	NPI-a	1.7	0.2	
	non-PFC lesion, MAO-A low (n=20)	NPI-a	0.6	0.5	

	SNP	Outcome	Clinic Assessment		Comment
			mean	SD	
Pardini 2014	mPFC DRD1 rs686G/G	NPI-a	0.52	0.2	Significant lesion location x Genotype interaction in aggression scores - A allele carriers (more transcriptionally active) significantly associated with lower aggression in LPFC lesion subjects (p=0.004), but higher aggression in mPFC lesion subjects (p=0.002)
	mPFC DRD1 rs686 A+	NPI-a	2.7	0.2	
	LPFC DRD1 rs686 G/G	NPI-a	2.4	0.3	
	LPFC DRD1 rs686 A+	NPI-a	0.46	0.2	

	Comment
Pronger 2013	Mental health: TAQ1A T-homozygotes report more symptoms by the BSI18 Global Symptoms Inventory Score - mean 60.1, SD 13.2 vs non-TT mean 55.7, SD 12.2; p = 0.03. Cognition: TT performed worse on the CVLT (mean 45.1, SD 11.8) than non-TT (mean 51.7, SD 13.4), p = 0.003. Quality of Life: Satisfaction with Life Scale (SWLS) was dichotomized (satisfied >20, unsatisfied <20): 55% of TT were unsatisfied versus 39.2% of non-TT (p=0.05).

	Comment
Raymont 2008	GRIN2A rs968301 allele (dominant vs recessive) significantly predicted increased decline in intelligence from pre-injury to Phase 3 of VHIS (on AFQT score), p=0.025. Trend towards dominant homozygotes having greatest decrease in IQ but individual genotype comparisons (dominant homozygote -9.429 SD 22.849, heterozygote -8.021 SD18.432, recessive homozygote -5.548 SD18.205) did not reach significance. GRIN2A rs968301 also significantly predicted overall P3 AFQT score, and change in score from P2 to P3. GRIN2B, GRIN2C, GAD2 polymorphisms all predicted pre-injury AFQT.

	SNP		Outcome	Comment
Winkler 2016	COMT	M/M or M/V: 70	PCL-C at 6 months	1. Presence of Met allele was independently association with a *lower* incidence of PTSD (OR 0.25, 95% CI[0.09 – 0.69]) via univariate analysis. 2. Presence of Met allele was independently associated with lower incidence of PTSD (OR 0.32, 95% CI [0.11-0.97]) on multivariate analysis.
		V/V: 23		

	SNP		Outcome	Comment
Winkler 2016	COMT	M/M or M/V: 76	WAIS-PSI, TMT B-A	1. COMT Met158 carriers showed significantly higher nonverbal processing speed on WAIS-PSI when compared to COMT Val158/Val158 homozygotes (Met158 103.8 ± 13.3; Val158/Val158 94.1 ± 15.7; p=0.004) 2. COMT Met158 subjects did not associate with a task requiring mental flexibility on TMT B-A (Met158 46.6 ± 51.5; Val158/Val158 63.8 ± 42.0, p=0.139) 3. COMT Val158Met polymorphism did not associate with verbal learning and fluency as measured by the CVLT-II
		V/V: 24		

	SNP	Outcome	6 months		Comment
			Mean	SE	
Yue 2015	ANKK1 T/T (n=40)	CVLT	45.1	1.9	Full results of Pronger 2013 conference abstract. Authors report dose-dependent effect of T-allele causing worse performance on CVLT. Actual between group comparisons only for T homozygotes vs other groups - TT vs CT p=0.027, TT vs CC p=0.006.
	ANKK1 C/T (n=175)	CVLT	51.1	1.0	
	ANKK1 C/C (n=277)	CVLT	52.1	0.8	

	SNP		Outcome	Comment
Yue 2016	DRD2 C95T	T/T or T/C: 86	WAIS-PSI, RAVLT, TMT B-A at 6 months	1. T allele carriers had better cognitive performance at 6 months on CVLT-II (p=0.033). 2. No differences in short delay, long delay, TMT-B-A, or WAIS-PSI on univariate analysis. 3. T allele was association with improved performance on CVTL-II Trials 1-5 on multivariate analysis (p=0.018). 4. T allele was found to be associated with better CVLT-SD (p=0.046) and CVLT-LD (p=0.041) via multivariate analysis.
		C/C: 42		

Appendix 7. Results of studies on Cytokine SNPs measuring outcomes other than global outcomes

Tables are formatted individually due to variations in type and detail of information provided in each paper

	SNP	OC	Time to first seizure (days from injury)		Comment
			mean	95% CI	Total cohort n=199 but not given by genotype; p=0.005 for CT having significantly higher incidence of seizures. Hazard Ratio for seizures (CT vs CC/TT) 2.845 (1.372-5.900), p=0.005.
Diamond 2014	IL1B rs1143634 CT	Time (days)	854.37	759.28-949.46	
	IL1B rs1143634 CC/TT	Time (days)	1,010.51	959.4-1061.62	

	SNP	OC	6 months	Comment
			%	Raw OR for poor outcome (carriers vs non-carriers) 0.3750 (0.1559 to 0.9017) p=0.0284. Note that this indicates that IL-1RN*2 carriage is protective against poor TBI outcome, despite greater number of carriers having severe TBI at baseline in this cohort. Authors selected alpha level of p<0.01 (no reason given) so this trend is not significant, even after adjustment for baseline GCS, age, gender, hemorrhage/hematoma volume, diffuse brain edema, neurosurgery (p=0.02). Despite trend for better outcome, IL-1RN*2 carriers significantly more likely to have experienced hemorrhagic event (SAH, contusion, DAI, EDH, SDH, hematoma, IVH): Adjusted OR 4.57 (1.67-12.96) p=0.004 (note n=60 for total IL-1RN*2 carriers on hemorrhagic events measure) (i.e. this persists despite adjustment for greater numbers of carriers having severe TBI - adjustment for baseline GCS, age, gender, diffuse brain edema, neurosurgery)
Hadjigeorgiou 2005	IL-1RN*2 carrier (n=64)	Hemorrhage (any kind)	90.6	
	IL-1RN*2 noncarrier (n=87)	Hemorrhage (any kind)	67.8	

Appendix 8. Results of studies on BDNF SNPs measuring outcomes other than global outcomes

Tables are formatted individually due to variations in type and detail of information provided in each paper

	SNP	OC	3 months		6 months		12 months		Comment
			%	Cohort size	%	Cohort size	%	Cohort size	
Bagnato 2012	BDNF Met+	Out of VS	30	20	70	20	87.5	16	p≥0.3 for all time points and comparisons, no statistical difference in rates of emergence from vegetative state (VS) or on LCF score between genotypes at any of the 3 timepoints.
		Still in VS	70	20	30	20	12.5	16	
	BDNF Val/Val	Out of VS	36.3	33	63.4	33	70	20	
		Still in VS	63.4	33	36.3	33	30	20	

	Comment
Barbey 2014	Statistically significant differences in general intelligence, verbal comprehension, perceptual organization, working memory, processing speed domains of Wechsler Adult Intelligence Scale - p<0.01 for all differences except VC (p<0.05). In all cases met allele carriers outperform Val/Val homozygotes by between 6-8 IQ points. Met allele protective in this study but previously associated with impaired cognitive function in healthy, stroke and psychiatric populations.

	SNP	OC	Pre-injury		Post-injury		Comment
			mean	SD	mean	SD	
Krueger 2011	BDNF Val/Val (n=73)	IQ (percentile)	63	22.3	51.8	23.2	p=0.49 for between genotype difference on pre-injury IQ p=0.48 for between genotype difference on post-injury IQ On executive functioning (D-KEFS) total score, Met+ performed significantly better post-TBI than Val/Val (p<0.005) - raw scores not given in article.
	BDNF Met+ (n=48)	IQ (percentile)	65.9	20.8	54.9	24.4	

	Comment
Lanctot 2010	In regression analysis (dependent variable % HAMD change following citalopram treatment): BDNF val66met p=0.015 for effect (val/val greater treatment response) MTHFR C-(677)T p=0.023 for effect (C/C greater treatment response).

	Comment
McAllister 2012	Reaction speeds tested using Gordon Continuous Performance Test Simple Reaction Time Test Reaction Time (SRTRT). Authors report that Met/Met had significantly slower reaction times than either Met/Val or Val/Val, p=0.0003. Raw data for group means not given but effect appears from graphs to be in the order of a 200ms difference in mean reaction time.

	Comment
Narayanan 2017	Focused on the BDNF Val66Met (rs6265) SNP, assessing neurocognitive function at 6 months post-injury. Specific score break-downs for the neurocognitive tests were not provided. Overall, Met carriers were noted to have worse global cognitive functioning and worse sub-category function (attention, language, memory, executive function), compared to Val/Val genotype. Only visuospatial testing was worse in the Val/Val group.

	SNP		OC	Difference Pre and Post Injury		Comment
				Mean	SD	
Narayanan 2016	rs6265	V/V:16	SNAB Attention	-5.89	9.5	Met carriers performed worse on SNAB Form 1 and 2 both pre and post injury (6 months). Memory function was statistically significant between the two alleles (p=0.05).
			SNAB Language	2.89	16	
			SNAB Memory	-11.44	10	
			SNAB Spatial	2.89	11	
			SNAB Executive	-11.56	11.7	
			SNAB Overall	-6.89	5.3	
		V/M or M/M:32	SNAB Attention	-11	13.1	
			SNAB Language	-6.95	25.1	
			SNAB Memory	3.2	15.8	
			SNAB Spatial	-2	13.2	
			SNAB Executive	-6	16.6	
			SNAB Overall	-5.25	8.1	

	Comment
Rostami 2011	BDNF SNP rs7124442 (C > T polymorphism) most strongly associated with change in AFQT score following TBI, with CC genotype suffering greatest decline in IQ. Excess decline in IQ in CC subjects occurred from injury to phase 2 of VHIS, whereas IQ remained largely stable from phase 2 to phase 3. For phase 2, variance explained by: 1. Pre-injury intelligence - 47.0% of variance, p=0.001 2. SNP rs7124442 genotype CC - 4.9% of variance p=0.001 3. Percentage of total brain volume loss - 2.1% of variance p=0.041 4. Premorbid level of education - 1.5% of variance p=0.018

	Comment
Verramuthu 2017	Focused on association between BDNF Val66Met SNP and neurocognitive outcome at 6-months. Exact tests and scores not specified. Overall, worse cognitive recovery was seen in the Met alleles carriers, compared to the Val/Val genotype at 6-months post injury.

Appendix 9. Studies on "Other" Miscellaneous SNPs measuring outcomes other than global outcomes

Tables are formatted individually due to variations in type and detail of information provided in each paper

	SNP	OC	average time post-TBI = 36 days		Comment
			mean	SD	
Ariza 2006	ACE I/I (n=16)	Trail Making A	53.56	23.75	ACE D-allele carriers perform worse than I/I homozygotes on all three measures post-TBI (all comparisons significant at p=0.001).
		Trail Making B	129.31	37.13	
		Grooved Pegboard (Right)	82.57	15.8	
	ACE D+ (n=57)	Trail Making A	83.86	51.03	
		Trail Making B	229.63	199.88	
		Grooved Pegboard (Right)	122.75	68.28	

	SNP	OC	Comment
Grafman 2015	Oxytocin – various SNPs (rs7632287, rs53576, rs2254298)	KAS	There was a significant difference between rs7632287 AG (mean 34) and G (mean 38, p =0.011) for R2 (social participation), G homozygotes more likely to participate. There was a significant difference between rs2254298 AB (mean 38) and G (mean 43, p=0.024) for R4 (leisure activity participation), with G homozygotes participating more.

	SNP	OC	Comment
Hong 2015	PERIOD3 two types: 4-/4- or 4-/5-	PSQI, BAI at 6 weeks	PERIOD3 5- non-carriers exhibited marginal improvement in sleep quality at 6 weeks post injury (p=0.07). All aspects of the PSQI were better for the 5- non-carriers.

	SNP		OC	Comment
Jha 2016	rs2283261	A/A: 137	Mean/Peak ICP over 1st 5 days, Edema on CT, need for DC	rs2283261 CC homozygotes (minor allele) had higher mean/peak ICP (p<0.001) and more CT based edema (OR 2.46, p=0.006). Heterozygotes were protected against CT edema and had lower ICPs. rs3819521 TT homozygotes (minor allele) had high mean/peak ICP (p=0.002 and p=0.004) and increased CT based edema (OR 2.43, p=0.005). Heterozygotes were protective. rs2283258 AA homozygotes (minor allele) had higher mean/peak ICP (p=0.002 and p=0.017) and increased CT based edema (OR 3.13, p=0.01). Heterozygotes were protected. rs799857 AA homozygotes (minor allele) (OR 2.13, p=0.002).
		A/C: 194		
		C/C: 54		
	rs3819521	C/C: 164		
		C/T: 181		
		T/T: 40		
	rs2283258	G/G: 184		
		G/A: 171		
		A/A: 20		
	rs799857	G/G: 124		
		G/A: 189		
		A/A: 72		

	SNP	OC	6 months	Comment
			n (%)	
Robertson 2011	NOS3 -786 T/T (n=25)	Mortality	5 (20%)	Mortality 20% (T/T), 17% (T/C), 100% (C/C) - although only 2 subjects had C/C genotype. p=0.022 for difference. Also found significantly lower average cortical cerebral blood flow in C/C genotype (p=0.0146), with highest flow in T/T subjects.
	NOS3 -786 C/T (n=24)	Mortality	4 (16.7%)	
	NOS3 -786 C/C (n=2)	Mortality	2 (100%)	

	SNP	OC	Comment
Scher 2011	MTHFR C677T	Development of post-traumatic epilepsy (unclear follow-up period)	This was a military based study with unclear duration of follow-up and end-point to the study. The goal was to evaluate the link between the MTHFR C677T SNP with the development of post-traumatic epilepsy. Overall, TT genotypes had an increased risk of epilepsy (OR=1.52, p=0.031) versus the CC genotype. *NOTE: Another MTHFR SNP (A1298C) was tested – it failed to display any significant results.

	SNP	OC	Comment
Shee 2016	SNCA – Various SNPs (rs2736994, rs1372525, rs1023777, rs2583988, rs2619364, rs2301134,	CVLT-SD, CVLT-LD	rs1372525 (G to A) had improved CVLT-SD (p=0.029) and LD (p=0.006). rs2301134 (A to G) had improved CVLT-SD (p=0.023). rs356219 (G to A) had improved CVLT-SD (p=0.02) and LD (p=0.016).

	rs2301135, rs10005233, rs1812923, rs2737029, rs356188, rs7684318, rs356219)		

	SNP		Comment
Wang 2014	BMX rs16979956 T+	n=3	Authors report higher levels of anxiety at 1 week post-mTBI in T-allele carriers. This is based on dividing Beck Anxiety Inventory scores into 4 grades; 1 T-allele carrier in each of grades 1, 3 and 4. Overall OR 12.08 (1.06-138.01) p=0.0117. Comparison does not survive Fischer Exact Test comparison, note very wide 95% CI. Three other SNPs in BMX also analyzed - no significant associations.
	BMX rs16979956 C/C	n=183	

	Treatment / Comparator	OC	12 months			Comment
			mean	SE	N	
Wagner 2012	KIBRA CC	SRLL LTR	31.24	2.69	49	Multiple significant associations - domain with most significant p-value from each test (SRLL immediate, Rey Osterrieth, CVLT) extracted - TMT, Global outcomes (GOS, DRS, NRS) had no significant results. SRLL Long term retrieval p=0.013 RO immediate recall p=0.007 CVLT List B p=0.012 Note CVLT remains significantly worse amongst CT/TT (compared to CC) patients after adjustment for age and GCS (p<0.05), despite the CC genotype's association with worse performance on verbal memory tests in uninjured patients.
		Rey-Osterrieth IR	15.36	1.1	62	
		CVLT List B	4.7	0.32	33	
	KIBRA CT/TT	SRLL LTR	21.58	2.63	53	
		Rey-Osterrieth IR	10.96	1.13	57	
		CVLT List B	3.11	0.44	35	

	SNP	OC	Comment
Wagner 2017	rs3766553, rs903361, rs10920573, rs6701725, rs1751192	Post-traumatic seizures	1. rs3766553 AA genotype had a 17.4% risk of early post-traumatic seizures, versus <4% for G allele carriers. (p=0.032) This held true during multi-variate analysis controlling for age, sex, admission GCS and neurosurgical intervention (OR=5.482, p=0.028) 2. rs3766553 GG genotype had a 32.4% risk, versus 15.2%, of late post-traumatic seizures (p=0.044). This held true during multi-variate analysis controlling for age, sex, admission GCS and neurosurgical intervention (OR=2.993, p=0.078). 3. rs3766553 GG genotype had a 28.1% risk, versus 7.1%, of delayed post-traumatic seizures (p=0.005). This held true during multi-variate analysis controlling for age, sex, admission GCS and neurosurgical intervention (OR=5.049, p=0.006). 4. rs109220573 CT genotype had a 28.8% risk, versus, <15%, of early post-traumatic seizures (p=0.039), this held true during multi-variate analysis (OR=3.547, p=0.024). 5. No statistically significant associations between rs109220573 and late or delay post-traumatic seizures were found. 6. Multiple risk genotype (rs3766553 GG and rs109220573 CT genotypes): a. carriers of either genotype had increased risk of late (OR=3.812,

			p=0.052) and delayed (OR=7.612, p=0.065) post-traumatic seizures; b. carriers of both genotypes had both increase risk of late (OR=13.124, p=0.001) and delayed (OR=28.869, p=0.005) post-traumatic seizures.
	rs3766553, rs903361, rs10920573, rs6701725, rs1751192	GOS at 6 Months	Neither rs3766553 or rs10920573 were associated with GOS at 6 months.

Appendix 10: Abbreviations Used in Appendix Tables

5-HTT = Serotonin transporter gene
5-HTTLPR = 5-HTT polymorphic region
5-HTTLPR L = long allele
5-HTTLPR S = short allele (lower transcription levels)
ABC = ATP binding cassette protein
ABCB1/ABCC1 = ABC subtype B1/C1
ACE = angiotensin converting enzyme
AFQT = Armed Forces Qualification Test
ANKK1 = Ankyrin repeat and kinase domain containing 1 Gene
ANKK1 A1 = A1 (T) allele at TAQ1A
ANKK1 A2 = A2 (C) allele at TAQ1A
AQP4 = aquaporin 4
AQP-4 = aquaporin 4
Aust. = Australia
BCL2 = B-cell lymphoma 2 gene
BDNF = Brain Derived Neurotrophic Factor
BDNF Val66Met = BDNF valine -> methionine substitution SNP
BESS = balance error scoring system
BMX = bone marrow tyrosine kinase gene on chromosome X
BSI18 GSI = Brief Symptom Inventory 18 Global Severity Index
C = cytosine
Can. = Canada
Comp-Cog = cognitive composite score
COMT = Catechol-O-methyltransferase
COWAT = controlled oral word association test
CSF = cerebrospinal fluid
CT = computed tomography
CVLT = California Verbal Learning Test
CVLT-LD = CVLT long delay
CVLT-SD = CVLT short delay
d = day(s)
DAI = diffuse axonal injury
D/C = discharge
DC = decompressive craniectomy
DHI = dizziness handicap inventory
D-KEFS = Delis-Kaplan Executive Function System
DNA = deoxyribonucleic acid
DRS = Disability Rating Score
DST = digit span test
EDH = epidural hematoma
FCN2 = ficolin-2
FIM = Functional Independence Measure
FIM-Cog = functional independence measure-cognitive
FrSBe = Frontal Systems Behavior Scale
G = guanine
GAD1 = Glutamate decarboxylase 1
GCS = Glasgow Coma Scale
GOS = Glasgow Outcome Scale
GOSE = Glasgow Outcome Scale – Extended
GPT = Grooved Pegboard Test
Gre. = Greece
h = hour(s)
HA = High activity
HAMD = Hamilton Depression Rating Scale
HAM-D = Hamilton Rating Scale for Depression

hosp. = hospital
ICHE = intracranial hemorrhagic events
ICP = intra-cranial pressure
ICU = Intensive care unit
IL1A = Interleukin-1 alpha, IL1A*: IL1A C889T SNP, IL1A*1: -889 C allele, IL1A*2: -889 T allele
IL1B = Interleukin 1 beta
IL6 -174G = Interleukin 6 T174G SNP
ImPACT = immediate post-concussion assessment and cognitive test
Ital. = Italy
IVH = intraventricular hemorrhage
KIBRA = Kidney and brain expressed protein
LA = low activity
LOC = Loss of consciousness
Ma = male
m = mean
M = methionine
MAO-A = Monoamine oxidase-A
MBL2 = mannose binding lectin -2
med = median
Mo = month
Mort. = mortality
mTBI = mild traumatic brain injury
mtDNA = mitochondrial DNA
MTHFR = methylentetrahydrofolate reductase
n = number
NA = Not applicable
NAB = neuropsychological assessment battery
NC = non-carrier
nPFC L = non-prefrontal cortex lesions
NPI-a = Neuropsychiatric Inventory agitation/aggression subscale
NR = Not reported
NRS = Neurobehavioral Rating Scale
OC = outcome
OR = odds ratio
PARP-1 = Poly[ADP-ribose] Polymerase 1
PCL-C = PTSD checklist – civilian version
PFC L = prefrontal cortex lesions
PPP3C = Serine/threonine-protein phosphatase 2B catalytic subunit gamma isoform
Pros. = prospective
PSQI = Pittsburgh Sleep Quality Index
PTA = Post-traumatic amnesia
PTE = post-traumatic epilepsy
RAVLT = Rey Auditory Verbal Learning Test
Rehab. = rehabilitation
retr. = retrospective
ROCFT = Rey-Osterrieth Complex Figure Test
Rx = treatment
SAH = subarachnoid hemorrhage
SD = standard deviation
SDH = subdural hematoma
SNCA = alpha-synuclein gene.
SNPs = single nucleotide polymorphisms
SRT = Simple Reaction Time
SWL = Satisfaction with Life Scale
T = thymine
TAQ1A polymorphism = C->T SNP within ANKK1 gene causing Glu713Lys substitution
TBI = traumatic brain injury
TMT = Trail Making Test

TNFA = Tumor Necrosis Factor Alpha
Turk. = Turkey
U = uracil
V = valine
VGLUT = vesicular glutamate transporter
VMAT = vesicular monoamine transporter
VNTR = variable number tandem repeat
VS = vegetative state
w = week(s)
WAIS = Weschler Adult Intelligence Scale
WAIS-PSI = WCST = Weschler Adult Intelligence Scale – processing speech index
WCST = Wisconsin Card Sorting Test

Appendix 11: QuIPS Tool Risk of Bias Assessment Table

Neurotransmitter SNPs

Study ID	Study Participation	Study Attrition	Prognostic Factor Mx	Outcome Mx	Confounding	Statistical Ax & Reporting
Chan 2008	Moderate	Low	Low	Low	Low	Low
Darrah 2013	Moderate	Low	Low	Low	Moderate	Low
Failla 2015	Moderate	Low	Low	Low	High	Low
Failla 2013	Moderate	Moderate	Low	Low	Low	Low
Juengst 2017	High	High	Moderate	Low	High	Moderate
Lipsky 2005	Moderate	Low	Low	Low	Moderate	Moderate
Madura 2016	High	High	Low	Low	Low	Low
Markos 2016	Moderate	Low	Low	Low	Moderate	Low
McAllister 2005	Moderate	Moderate	Low	Low	Moderate	Low
McAllister 2008	Moderate	Moderate	Low	Low	Moderate	Low
McDevitt 2015	Moderate	Moderate	Low	Low	Low	Low
Myrga 2016	Moderate	Moderate	Low	Low	Moderate	Low
Myrga 2016	Moderate	Moderate	Low	Low	High	Low
Nielson 2017	Low	Low	Low	Low	Moderate	Low
Pardini 2011	Moderate	Low	Low	Low	Moderate	Low
Pardini 2014	Low	Low	Low	Low	Moderate	Low
Pronger 2013	High	High	Low	Low	High	Moderate
Raymont 2008	Moderate	Low	Low	Low	Moderate	Low
Willmott 2014	Low	Moderate	Low	Low	Low	Low
Winkler 2016	Low	Moderate	Low	Low	Low	Low
Winkler 2016	Low	Moderate	Low	Low	Low	Low
Yue 2016	Low	Moderate	Low	Low	Low	Low
Yue 2015	Low	Moderate	Low	Low	Moderate	Low

Cytokine SNPs

Study ID	Study Participation	Study Attrition	Prognostic Factor Mx	Outcome Mx	Confounding	Statistical Ax & Reporting
DallaLibera 2011	Moderate	Low	Low	Low	Moderate	Moderate
Dardiotis 2006	High	High	Low	Low	High	Low
Diamond 2014	Moderate	Low	Low	Low	Moderate	Low
Hadjigeorgiou 2005	Moderate	Low	Low	Low	Low	Low
Minambres 2003	Moderate	Moderate	Low	Low	High	Moderate
Sinha 2015	High	Moderate	Low	Low	Moderate	Moderate
Tanriverdi 2006	Moderate	Low	High	Low	Moderate	Moderate
Uzan 2005	Moderate	Moderate	Low	Low	Moderate	Moderate
Waters 2013	Low	Low	Moderate	Low	Low	Low

BDNF SNPs

Study ID	Study Participation	Study Attrition	Prognostic Factor Mx	Outcome Mx	Confounding	Statistical Ax & Reporting
Barbey 2014	Moderate	Low	Moderate	Low	Moderate	Moderate
Bagnato 2012	Low	High	Moderate	Low	Moderate	Low
Failla 2015	Low	Low	Low	Low	Low	Low
Failla 2016	Low	Low	Low	Low	Moderate	Low
Krueger 2011	Moderate	Low	Moderate	Low	Moderate	Moderate
Lanctot 2010	Moderate	Low	Moderate	Low	Moderate	Low
McAllister 2012	Moderate	Low	Low	Low	Moderate	Low
Munoz 2017	Low	Moderate	Low	Low	Moderate	Low
Narayanan 2016	Moderate	Moderate	Low	Low	Moderate	Low
Narayanan 2017	Moderate	Moderate	High	High	High	High
Rostami 2011	Moderate	Low	Moderate	Low	Moderate	Moderate
Veeramuthu 2016	Moderate	Moderate	High	High	High	High

Mitochondrial SNPs Coding for Mitochondrial Proteins

Study ID	Study Participation	Study Attrition	Prognostic Factor Mx	Outcome Mx	Confounding	Statistical Ax & Reporting
Bulstrode 2014	Moderate	Moderate	Low	Low	Moderate	Low
Conley 2014	Low	Low	Low	Low	Moderate	Low
Hoh 2010	Low	Moderate	Low	Low	Low	Moderate

Miscellaneous SNPs

Study ID	Study Participation	Study Attrition	Prognostic Factor Mx	Outcome Mx	Confounding	Statistical Ax & Reporting
Ariza 2006	Moderate	Moderate	Low	Low	Moderate	Low
Bales 2011	High	High	Low	Low	High	Moderate
Chuang 2010	Low	High	Low	Low	Moderate	Low
Cousar 2013	Low	Moderate	Low	Low	Moderate	Low
Dardiotis 2015	Moderate	Low	Low	Low	High	Moderate
Dardiotis 2014	Moderate	Low	Low	Low	High	Moderate
Garringer 2013	Low	Moderate	Moderate	Low	Low	Low
Grafman 2015	Moderate	Moderate	Low	Low	High	High
Hong 2015	Low	High	Low	Low	Low	Low
Jha 2016	Low	Moderate	Low	Low	Moderate	Low
Martinez-Lucas 2005	Moderate	Low	Low	Low	Low	Low
Osier 2017	Low	Low	Low	Low	Moderate	Low
Osthoff 2017	Moderate	Moderate	Low	Low	Moderate	Moderate
Robertson 2011	Low	Low	Low	Low	Low	Moderate
Sarnaik 2010	Low	Moderate	Low	Low	Moderate	Low
Scher 2011	Moderate	Moderate	Low	Low	Moderate	Low
Shee 2016	Low	Moderate	Low	Low	Moderate	Low
Wagner 2012	Moderate	Moderate	Moderate	Low	Low	Low
Wagner 2011	Low	Moderate	Low	Low	Moderate	Low
Wang 2015	Moderate	Moderate	Low	Low	Moderate	Low
Wang 2014	High	Moderate	Moderate	Low	Moderate	Moderate

Ax = analysis, Mx = measurement

Appendix 12: References for Included Articles in Systematic Review (Alphabetical Arrangement):

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