Role of Genetic Factors in Concussion Risk and Outcome

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Why is this Important?

• Most consistent clinical finding is:
  – Variability
    • Variability in concussion risk
      – Between individuals
      – Within individuals over time
      – Biomechanically
    • Variability in outcome
      – Return to play
      – Persistent symptoms
      – CTE?
Determinants of Outcome

Determinants of Chronic Effects of Neurotrauma

**Pre-Injury Factors**
- Genotype
- Psychiatric Dx
- Early Life Events
- Cognitive Capacity/Reserve
- Resilience

**Injury Factors**
- Blast vs. Other
- Severity
- Other injury

**Peri-Injury Factors**
- Treatment
- Complications

**Intervening Factors**
- Additional TBI or other injury
- Development of Psychiatric Disorders
- Ageing
- Compensation claims
- Other Life Events

**Outcomes**
- Cognition
- Vocational Function
- Somatic Symptoms/Pain
- Psychological Health
- Quality of Life
- Neurodegenerative Disorders

3-12 months  1-5 years  6-10 years
Genetics 101

**Figure 3:** Diagram of a chromosome

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**Figure 5:** Transcription Process. RNA Polymerase promotes formation of messenger RNA (mRNA) transcript of DNA
http://genome.gov/Glossary/index.cfm?id=197
Single Nucleotide Polymorphisms (SNPs)

Protein Folding and Function

Amino acid chain grows and folds into a 3-D structure.

SNPs in Coding Regions - Harmful Changes in Protein - Mutations

DNA SNP A to T

RNA Codon GUA to GUU

Aspartic acid to Valine

Protein

Change in shape
Epigenetics

Not just the genotype: Is it being expressed?
Genetic Factors in TBI: Where to Start?

**Representative Genes**
- **Catecholaminergic System Genes**
  - Dopaminergic Genes
    - Risk Taking Behavior
    - COMT, DAT
  - Cholinergic System Genes
    - Memory and Attention
  - Psychopathology Risk Genes
    - Serotonin Transporter gene
- **Modulation of Ca++ Influx Into Cell**
  - CACNA1A
  - Immediate Early Genes
  - Vascular response to trauma (ACE)
    - Inflammatory Response (IL-1, IL-6)
    - Initiation of Apoptosis (TP53)
- **Neurotrophins**
  - BDNF
  - Apolipoprotein E
    - APOE E4
    - APOE promoter SNP’s

**Point of Interaction**
- **Pre-Injury Function**
  - Personality
  - Sensorimotor Function
  - Cognition
  - Risk of Injury

- **Injury Event**

- **Extent of Injury**

- **Repair & Plasticity**

- **Functional Outcome**
  - Cognition
  - Sensorimotor Function
  - Neurobehavioral Status
  - Risk of future injury
  - Dementia?
<table>
<thead>
<tr>
<th>Domain Affected</th>
<th>Gene</th>
<th>Polymorphism</th>
<th>Functional Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to Neurotrauma</td>
<td>Tumor Suppressor Protein (TP53)</td>
<td>G/C (arg to pro) at codon 72</td>
<td>Arg allele more efficient initiator of apoptosis</td>
<td>Arg homoyzosity assoc. with lower GOS in one study (Martinez et al 2005)</td>
</tr>
<tr>
<td>Modulation of apoptosis</td>
<td>B Cell Lymphoma – 2 (BCL-2)</td>
<td>rs1759659</td>
<td>unknown</td>
<td>Variant allele associated with poor outcome following severe TBI in 205 patients. (Hoch et al 2011)</td>
</tr>
<tr>
<td>Modulation of apoptosis</td>
<td>PARP-1</td>
<td>rs3219119 rs2771347</td>
<td>Rs3219119 is tag SNP spanning catalytic domain; rs2771347 associated with activity and is tag SNP spanning promoter region</td>
<td>Rs3219119 AA associated with favorable 6 mos outcome Rs2771347 genotype assoc with PAR-modified protein levels in CSF</td>
</tr>
<tr>
<td>? Effect on vascular response to trauma</td>
<td>Angiotensin Converting Enzyme (ACE)</td>
<td>Insertion/deletion in intron 16</td>
<td>Alters circulating levels of ACE higher in D/D</td>
<td>D allele assoc. with poorer cognitive performance in moderate/severe TBI (Ariza et al 2006)</td>
</tr>
<tr>
<td>Vascular Response to trauma</td>
<td>Nitric Oxide Synthase (NOS3)</td>
<td>-786C variant</td>
<td>unknown</td>
<td>Altered cerebral hemodynamics following severe TBI in 51 patients (Robertson et al 2011)</td>
</tr>
<tr>
<td>Calcium influx into cell</td>
<td>Calcium channel subunit gene (CACNA1A)</td>
<td>C/T substitution at codon 218 (serine to leucine switch)</td>
<td>Alters configuration of Ca++ pore forming component</td>
<td>Small case series associated L allele with cerebral edema and seizures after mild TBI (Kors et al 2001; Stamm et al 2009)</td>
</tr>
<tr>
<td>Resilience to hypoxia/ischemia</td>
<td>Neuroglobin gene (NGF)</td>
<td>Tag SNP rs2783088</td>
<td>Unknown. Ngb may facilitate oxygen transfer across BBB</td>
<td>Wild-type homozygotes (TT) significantly more likely to have good outcome after severe TBI (Chuang et al 2010)</td>
</tr>
<tr>
<td>Inflammatory response</td>
<td>Interleukin-1 beta (pro-inflammatory cytokine) (IL-1)</td>
<td>Restriction site at position -1395 ( exon 5)</td>
<td>Not known – presumed effect on degree of inflammatory response</td>
<td>Poor six month outcome associated with allele*2 after moderate/severe TBI (Quan et al 2005)</td>
</tr>
<tr>
<td>Inflammatory response</td>
<td>Interleukin-6 (pro-inflammatory cytokine) (IL-6)</td>
<td>GC SNP in promoter region (position -174)</td>
<td>G allele associated with increased production of IL-6</td>
<td>Conflicting results on association of G allele with TBI outcome (Winter et al 2004; Minnabres et al 2003)</td>
</tr>
<tr>
<td>Repair and plasticity</td>
<td>Brain Derived Neurotrophic Protein Factor (BDNF)</td>
<td>G/A SNP in promoter region (codon 65) Results in val to met switch</td>
<td>Met allele assoc with ahn storage and secretion of BDNF</td>
<td>Preliminary study shows association with Met allele and lower memory and attention scores 1 month after mild TBI (McAllister et al 2012)</td>
</tr>
</tbody>
</table>
| Repair                                               | Apolipoprotein E (APOE)     | Three major alleles: c2, c3, e4 differ in amino acids at positions 112 and 158 Also several polymorphisms in the promoter region | Mechanism of allele effect for this gene is not known | e allele associated with poor outcome in several studies of TBI (e.g. see Alexander et al. 2007). T allele at the G-219T site in promoter region associated with poor outcome (Lendon et al. 2003).

Pre and Post Injury Cognitive Capacity and Reserve

| Catecholamine receptors                              | Dopamine D2 Receptor region (DRD2 and ANK1) | Numerous polymorphisms in this region. Unclear how many are functional | Rs 1800497 associated with reduced expression of D2 receptors in striatum | Rs 1800497 associated with measures of memory and attention one month after mild TBI (McAllister et al 2005, 2009) |
| Catecholamine transporters                           | Dopamine transporter (DAT) | 40 base pair variable number tandem repeat (VNTR) | Preliminary data suggests association of 10 allele with measures of memory and attention one month after mild TBI (McAllister et al. submitted) |
| Catecholamine metabolism                             | Catechol-o-methyltransferase (COMT) | G/A SNP (val158met) resulting in Met/Val switch at position 472. | Met allele less efficient in metabolizing DA | Met allele associated with reduced performance on some frontal-executive tasks after TBI (Lipsky et al 2005; McAllister et al 2006) |
| Catecholamine synthetics                             | Dopamine Beta-Hydroxylase (DBH) | Functional polymorphism effects gene transcription | Not known | 5 SNPs in DBH gene associated with memory and attention measures one month after mild TBI (McAllister et al 2009). |
| Monoamine Oxidase                                    | Monoamine Oxidase-A (MAO-A) | VNTR | 2, 3, and 5 repeats associated with lower transcriptional activity | Genotype associated with levels of aggression in controls and cohort with penetrating brain injury (Pardini et al 2011) |
Impact of DRD2 Alleles on Cognitive Function After TBI

Thomas Roland Terrell, MD, MPhil,* Roberd M. Bostick, MD, MPH,† Ruth Abramson, PhD,‡ Dawen Xie, MD, PhD,§ William Barfield, PhD,‖ Robert Cantu, MD,¶ Michele Stanek, MSH,%% and Trina Ewing, MS**

Brief Report

Effect of the Dopamine D2 Receptor T Allele on Response Latency After Mild Traumatic Brain Injury

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Objective: The authors tested the hypothesis that the dopamine D2 receptor T allele, formerly described as the A1 allele, would be associated with poorer performance on memory and attention tasks following mild traumatic brain injury.

Methods: Thirty-nine patients with mild traumatic brain injury and 27 comparison subjects were genotyped. All subjects completed memory and attention tasks, including the California Verbal Learning Test recognition task and the Continuous Performance Test.

Results: In both groups the T allele was associated with poorer performance on the California verbal learning test recognition task. There was also a significant genotype by allele interaction on measures of response latency (continuous performance test) for the subjects with mild traumatic brain injury and the T allele had the worst performance.

Conclusions: Genetic polymorphisms that modulate central dopaminergic tone can affect cognitive outcome following mild traumatic brain injury.

Apolipoprotein E Genotype and Concussion in College Athletes

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Objective: To evaluate the association between apolipoprotein E (APOE) polymorphisms (E2, E3, and E4) and traumatic brain injury (TBI) in college athletes. We hypothesized that carriers of 1 or more APOE rare (or minor) allele assessed in this study would be associated with having a history of 1 or more concussions.

Key Words: polymorphism, MTBI, APOE E2, APOE E4, APOE promoter g-219

Polymorphisms in the Brain-Derived Neurotrophic Factor Gene Influence Memory and Processing Speed One Month after Brain Injury

Thomas W. McAllister,‡ Anna L. Tyler,§ Laura A. Flashman, C. Harker Rhodes, Brenna C. McDonald, Andrew J. Saykin, Tor D. Tosteson, Gregory J. Tsongalis, and Jason H. Moore.


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Brain Injury, August 2008; 22(9): 703–714

Single nucleotide polymorphisms in ANKK1 and the dopamine D2 receptor gene affect cognitive outcome shortly after traumatic brain injury: A replication and extension study


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J Clin Imaging 2010;24:464-468

Clin J Sport Med 2010;20:464-468
Sports Concussion Studies

  – N= 30, interaction with exposure

  – Older e4+ players worse than e4- players on certain cognitive tests
Evidence for Genetic Variation in Sports Concussion

- Terrell et al. (2008):
  - risk of concussion (self-report) in collegiate athletes (n=195)
    - APOE
      - No assoc with e4 status
      - Increased risk with TT of promoter G-219T
    - Tau
      - No assoc with $^{\text{His47Tyr}}$ and $^{\text{Ser53Pro}}$
Evidence for Genetic Variation in Sports Concussion

• Tierney et al. (2010):
  – Risk of concussion (self-report) in collegiate athletes (n=196)
    • APOE polymorphisms (e2, e4, promoter G-219T)
      – No assoc with any for risk of concussion
      – 3 of 4 who had all three minor alleles had concussions
Summary

• Field is in its infancy
  – Genotype does matter in TBI
    • APOE e4 most common finding
    • Additive/Interaction effects have not been systematically tested
  – Less evidence for sports concussion
    • Some signal in APOE promoter?
    • Numbers very small
Future Directions

• Large-scale collaborative studies using common outcome metrics (CDE)
  – Candidate gene/allele/pathway
  – GWAS
  – Several underway (TRACK TBI; DoD Consortia; InTBIR; GAIN)
• Gene expression studies
• Epigenetic studies
• Role of genetic variation in CTE
References

