IMMUNE GENETIC VARIABILITY IS ASSOCIATED WITH GULF WAR ILLNESS: A PRELIMINARY STUDY REPORT

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Introduction

Gulf War Illness (GWI)

- 32% of US soldiers who served in 1990-1991 Gulf War (GW)[1]
- GWI symptoms: fatigue, musculoskeletal dysfunction, changes in neurological / CNS function
- Key roles: CNS inflammatory markers and immune system activation in development of chronic illness in GW veterans
- No validated biomarker for GWI risk susceptibility

CNS inflammation

- CNS glial cells: activated by myelin & neuronal breakdown products via toll-like receptor, TLR4, activation
- TLR4 activation: release of proinflammatory cytokines, e.g. interleukin (IL)-1, IL-6, Tumor Necrosis Factor (TNF) = inflammatory response[2]
- Inflammatory response = sickness response behaviors, e.g. fatigue, muscle / joint pain, cognitive changes
- Genetic variability in immune response = Possible biomarker for GWI

Study Objective

To investigate the impact of immune genetic variability on both risk and severity of GWI in Caucasian veterans of the Gulf War.

Materials and Methods

Study Participants

87 GW veterans

- 71 with GWI - Cases: 79% male, mean age 51.5 years
- 16 without GWI - Controls: 100% male, mean age 52.6 years
- GWI defined by the Kansas GWI criteria[3]
- Questionnaires & MRI data: McGill pain scores, CPT3: hit reaction time raw scores, MFI-20: multi-dimensional fatigue inventory scores, MRI: brain region volume
- Study approved by study-site institutional boards

Genotyping

- DNA extracted from saliva samples: Oragene collection kit (DNA Genotek Pty Ltd)
- Analysis for 21 single nucleotide polymorphisms (SNPs) with a customized Sequenom MassArray (iPLEX GOLD)[4]:

IL-1B - rs16944, rs1143627, rs1143634
IL-2 - rs2069762
IL-6 - rs10499563
IL-6R - rs8192284/rs2228145
IL-10 - rs1800871, rs1800896
TNFA - rs1800629
TGFB - rs11466314, rs1800469
TLR2 - rs3804100
TLR4 - rs4986790, rs4986791
MD2 / LY96 - rs11466004
MYD88 - rs6853
BDNF - rs6265
CRP - rs2794521
ICE / CASP1 - rs554344, rs580253
OPRM1 - rs1799971

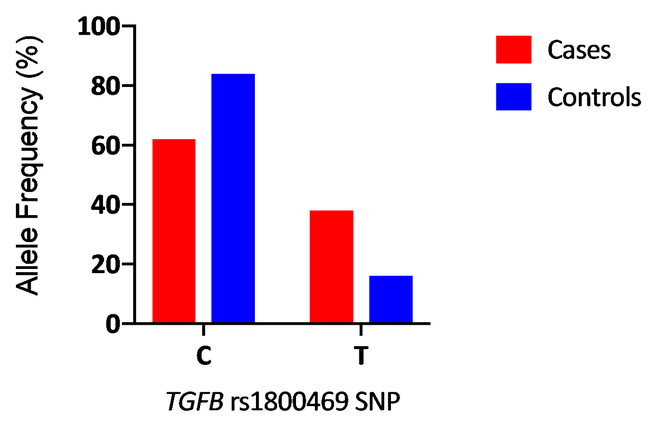
Statistical analysis

Odds ratios (OR, 95% confidence intervals [CI]), Fishers exact test: associations between genetic variability and risk of GWI

Mann-Whitney or Kruskal-Wallis test: impact of genetic variability on symptom scores and brain region volumes (subset of 43 veterans with GWI)

Results

***TGFB* (transforming growth factor beta, rs1800469) variant (T) allele significantly associated with GWI:** OR [95% CI] = 3.3 [1.2 – 9.1], P = 0.02



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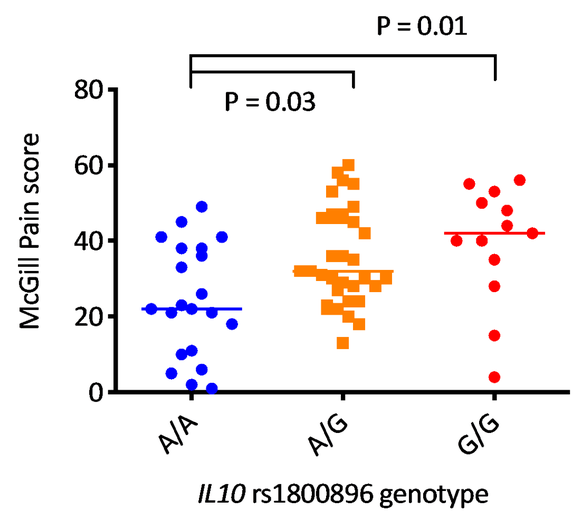
No other SNPs were significantly associated with GWI

***IL10* (interleukin-10, rs1800896) genotype was significantly associated with McGill pain scores in veterans with GWI (overall P = 0.007):** Line indicates medians; A/A = homozygous wild-type, A/G = heterozygote, G/G = homozygous variant genotypes



No other SNPs were significantly associated with pain, CPT3 or MFI-20 scores

Conclusions

Preliminary results from this ongoing study indicate:

TGFB genotype potential predictor of GWI risk

- rs1800469: promoter SNP
- variant associated with increased TGF-β, a multifactorial cytokine, serum concentrations[5]
- possible heightened immune response to deployment exposures

IL10 genotype potential predictor of pain severity in veterans with GWI

- rs1800896: promoter SNP
- variant associated with decreased IL-10, an anti-inflammatory cytokine, mRNA and serum concentrations[6]
- less immune response dampening = more CNS inflammation = increased pain signalling from activated glia / neuronal axis and hence pain severity

References: 1. RAC-GWVI (2008). *Gulf War Illness and the Health of Gulf War Veterans: Scientific Findings and Recommendations*. Washington DC: U.S. Government Printing Office; 2. Takada et al. (2015). Current Protoc Immunol 109:1-14; 3. Steele (2000). Am J Epidemiol 152:992-1002; 4. Coller et al (2015). Support Care Cancer 23:1233-36; 5. Grainger et al (1999). Hum Mol Genet 8:93-7; 6. Suarez et al (2003). Transplantation 75:711-7.

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