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3 **Gene Expression Biomarkers for Identifying Vigilance Impairment from Total Sleep**
4 **Deprivation**

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24 **Problem:** Fatigue is included as a contributing factor or finding in a large percentage of
25 transportation accidents, and poses a risk to all individuals in safety-critical roles. Although
26 fatigue is associated with psychological and performance decrements, it is difficult to objectively
27 quantify fatigue for accident investigation and prevention. We seek to provide objective metrics
28 in the form of gene expression biomarkers. Fatigue can be caused by many factors such as heavy
29 workload levels and stress. Here we begin to address this complex issue by focusing on
30 biomarkers for impairment from sleep deprivation.

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32 **Method:** We conducted a controlled laboratory assessment of human adults exposed to a sleep
33 deprivation treatment, with Institutional Review Board approval from both the Civil Aerospace
34 Medical Institute and Washington State University. Healthy adults aged 22-40 y were recruited
35 to a sleep laboratory at Washington State University, and remained there for 7 days, 6 nights
36 consecutively. Subjects were randomly subdivided into a Control (N= 6) and Sleep Deprivation
37 group (N= 11). Individuals in the Control group were allowed a 10 h sleep opportunity every
38 night. After two baseline nights of 10 h in bed, the Sleep Deprived group underwent sustained
39 wakefulness from 8:00 on Day 3 through 22:00 on Day 5, a total of 62 h. Afterward, they
40 received two recovery nights with 10 h sleep opportunity. Throughout the study, cognitive
41 performance was assessed by measuring failed attention in terms of lapses on the Psychomotor
42 Vigilance Test (PVT). Blood samples were collected through an intravenous catheter every other
43 day at 4 h intervals. This led to four measurements each during one baseline, one experimental,
44 and one recovery day for the Sleep Deprivation group, and likewise for the Controls. Total
45 ribonucleic acid was extracted from the blood samples, and whole transcriptome microarrays

46 were used to measure gene expression changes over time in both the Sleep Deprived and Control
47 groups.

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49 **Results:** Psychomotor Vigilance Lapses increased significantly in Sleep Deprived relative to
50 Control individuals. Gene expression differences related to the Treatment effect (difference in
51 Control vs. Sleep Deprived groups) showed a substantial impact of sleep loss on the immune
52 system. This included differential expression of *interleukin-1 beta* and other genes previously
53 identified as responsive to sleep deprivation. In total, we report 212 Treatment effect genes, the
54 vast majority of which decreased expression in response to sleep deprivation. Of greatest
55 relevance to transportation safety, we further identified a panel of 28 genes with expression
56 levels associated with PVT lapses. These genes represent strong candidates for objective
57 biomarkers of vigilance impairment from sleep deprivation. Besides genes related to the immune
58 system, the PVT effect genes include members involved in cell cycle regulation.

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60 **Discussion:** Many studies have sought to identify genes that change in response to impaired
61 sleep, including chronic sleep restriction, total sleep deprivation, and mistimed sleep that disrupts
62 circadian rhythms. Here we present one of the first studies to extend the question from how gene
63 expression changes in response to sleep loss, to how gene expression reflects vigilance
64 impairment from sleep deprivation. Future work will be needed to verify our results with
65 additional subjects, and better address contributions of both homeostatic (time awake) and
66 circadian (daily rhythm) processes to cognitive impairment from sleep deprivation.

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68 **Summary:** Managing fatigue is critical to transportation safety, and indeed to a wide range of
69 professionals in other safety-critical roles such as medical professionals. However, accurate
70 management requires a means for objectively measuring not only the presence of fatigue, but
71 more specifically, the presence of cognitive *impairment* that hinders job performance. Here we
72 advance the field by describing gene expression biomarkers associated with vigilance
73 impairment from total sleep deprivation.