The Period 3 Gene as a Marker of Susceptibility to Sleep Disruption in Patients with Obstructive Sleep Apnea

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Background

• Period 3
  – Expressed as a clock gene in the SCN
  – Has a variable number tandem repeat (VNTR) sequence coding for phosphorylation sites on protein
  – Phosphorylation of protein $\rightarrow$ degradation
  – Polymorphism in number of repeat sequences ($\text{PER3}^{4/4}$, $\text{PER3}^{4/5}$, $\text{PER3}^{5/5}$)

• Hypothesis: shorter VNTR variant = more stable protein
Clock Gene Mechanism

~24h

Takahashi, JS. Research Abstract, Howard Hughes Medical Institute Website
Modulation of Clock Gene Mechanism

± 24 hr?

Takahashi, JS. Research Abstract, Howard Hughes Medical Institute Website
## Background

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Condition</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viola et al. (2007)</td>
<td>24</td>
<td>TSD</td>
<td>PER3^{5/5}</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>-↓ cognitive performance (composite)</td>
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<tr>
<td></td>
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<td></td>
<td>-↑ sleep propensity (↓ sleep latency, ↑ SWS)</td>
</tr>
<tr>
<td>Groeger et al. (2008)</td>
<td>24</td>
<td>TSD</td>
<td>PER3^{5/5}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-↓ executive function only</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-↑ sleep propensity</td>
</tr>
<tr>
<td>Goel et al. (2009)</td>
<td>129</td>
<td>PSD</td>
<td>-no difference between PER3^{4/4} &amp; PER3^{5/5}</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(cognitive &amp; propensity)</td>
</tr>
</tbody>
</table>
Hypothesis

• Patients with OSA carrying the PER3^{5/5} haplotype will be more “sleepy” (per PVT, ESS, and MSLT outcomes) after a night of sleeping with untreated OSA compared to their PER3^{4/4} counterparts.
Methods

“Sleepiness” measures:
- PVT (mean # of lapses)
- MSLT (mean sleep latency test)
- ESS (Epworth Sleepiness Scale)
Genotyping

5/5 4/5 4/4
## Preliminary Data

- As of 8/12/09
- N=47
  (46 genotyped)

<table>
<thead>
<tr>
<th>PER3</th>
<th>4/4</th>
<th>4/5</th>
<th>5/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>22</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>48.2 (15.1)</td>
<td>46.6 (11.9)</td>
<td>47.0 (10.1)</td>
</tr>
<tr>
<td>M:F</td>
<td>8:3</td>
<td>5:2</td>
<td>0:3</td>
</tr>
</tbody>
</table>
RDI vs. ESS_{Dx}

PER3^{4/4}
N=22
r=0.129
p=0.567

PER3^{4/5}
N=21
r=0.447
p=0.042

PER3^{5/5}
N=3
r=0.875
p=0.321
RDI vs. PVT Lapses

PER3^4/4
N=13
r=0.688
p=0.009

PER3^4/5
N=18
r=0.247
p=0.322
RDI vs. MSLT/MWT

PER3\textsuperscript{4/4}
N=19
r=−0.674
p=0.002

PER3\textsuperscript{4/5}
N=18
r=−0.356
p=0.147
Summary (All subjects, n=46)

<table>
<thead>
<tr>
<th></th>
<th>PER3⁴/⁴</th>
<th>PER3⁴/⁵</th>
<th>PER3⁵/⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDI</td>
<td>44.5±31.5</td>
<td>43.7±36.0</td>
<td>29.9±30.9</td>
</tr>
<tr>
<td>ESS</td>
<td>12.5±5.7</td>
<td>12.2±5.8</td>
<td>11.2±6.8</td>
</tr>
<tr>
<td>PVT lapses</td>
<td>5.6±4.9</td>
<td>6.1±4.1</td>
<td>3.1±2.0</td>
</tr>
<tr>
<td>MSLT</td>
<td>6.9±6.8</td>
<td>7.2±3.5</td>
<td>15</td>
</tr>
<tr>
<td>MWT</td>
<td>17.8±3.6</td>
<td>18.7±2.2</td>
<td>14.8</td>
</tr>
</tbody>
</table>
Summary (RDI < 50, n=30)

<table>
<thead>
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<th></th>
<th>PER3⁴/⁴</th>
<th>PER3⁴/⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDI</td>
<td>24.9±13.4</td>
<td>24.0±10.6</td>
</tr>
<tr>
<td>ESS</td>
<td>12.3±5.2</td>
<td>10.3±5.0</td>
</tr>
<tr>
<td>PVT lapses</td>
<td>2.3±1.2</td>
<td>5.2±3.9*</td>
</tr>
<tr>
<td>MSLT</td>
<td>11.4±7.8</td>
<td>7.5±3.8</td>
</tr>
<tr>
<td>MWT</td>
<td>17.8±3.6</td>
<td>18.8±2.2</td>
</tr>
</tbody>
</table>
Conclusions

• Patients with OSA showed a distribution of the PER3 haplotype similar to that reported in the general population (10% PER3\(^{5/5}\))

• Overall, PER3\(^{4/4}\) were not different from PER3\(^{4/5}\) in subjective and objective outcomes of sleepiness

• For those with mild/mod OSA, there was a trend suggesting resistance to sleepiness (as measured by PVT) in those carrying the PER3\(^{4/4}\) haplotype
Many Thanks

• NYU Sleep Lab
  – Indu Ayappa, David Rapoport, Joe Keating, Bien Lee
• Washington Sq. NYU Genetics Lab
  – Justin Blau, Ben Collins, Harris Kaplan
• Sleep West Lab
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• Bellevue 6N
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• Penn CNST Program
  – Drs. Siegel & Hamilton