Introduction

- Precision medicine is a rapidly developing field that has produced many advances in cancer care, including prognostic information and genetic targets for therapy, but it has been largely neglected in symptom management for cancer survivors and supportive cancer care.
- Insomnia is a common symptom experienced by more than half of cancer patients; the current gold standard of treatment is modified cognitive behavioral therapy for insomnia (CBT-I), although emerging evidence supports the effectiveness of acupuncture for treating insomnia in cancer.

Objective

- The current study seeks to identify associations between selected genetic variants and the odds of treatment response in order to determine who is most likely to respond to acupuncture or psychotherapy for insomnia in cancer.

Methods

- Biological specimens were obtained from 132 cancer patients in a clinical trial, Choosing Options for Insomnia in Cancer Effectively (CHOICE), that randomized subjects to acupuncture or psychotherapy for insomnia in cancer survivors and supportive cancer care.
- The outcome of interest was change in Insomnia Severity Index score; patients were categorized as responders to therapy if their score was reduced at end of treatment by at least 8 points from baseline.
- I conducted a series of three PubMed searches:
  - (gene OR polymorphism) AND insomnia (gene OR polymorphism) AND acupuncture response
  - (gene OR polymorphism) AND treatment response AND cognitive behavioral therapy
- I then subjected promising genetic polymorphisms to two exclusion criteria:
  - Minor allele frequency <0.10
  - Uncertain effect on gene product function and lack of further support from the literature

Results

- A total of 1041 articles were screened and 90 full-text articles were retrieved
- 30 unique genetic variants were identified by the literature search before exclusion criteria were applied
- After applying exclusion criteria, 15 variants were included and 15 excluded (Figure 1)
- Polymorphisms were tiered on the basis of minor allele frequency and supportive level of support from the literature
- Included variants are associated with the nervous system, the immune system, and signal transduction (Table 1)

Table 1. Selected Genetic Variants

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein Product</th>
<th>Polymorphism</th>
<th>Major/minor allele</th>
<th>Global Minor Allele Frequency</th>
<th>Location/Context</th>
<th>Reported Effects &amp; Associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDNF</td>
<td>Brain-Derived Neurotrophic Factor</td>
<td>rs202495</td>
<td>G&gt;A</td>
<td>0.291</td>
<td>VarIII/Met</td>
<td>Several neuropsychiatric disorders (A allele)</td>
</tr>
<tr>
<td>AHRV</td>
<td>Arylhydrocarbon Receptor Repressor</td>
<td>rs2292595</td>
<td>C&gt;G</td>
<td>0.580</td>
<td>Exonic</td>
<td>Inhibition in women (C allele)</td>
</tr>
<tr>
<td>COMT</td>
<td>Catechol-O-Methyltransferase</td>
<td>rs4680</td>
<td>G&gt;A</td>
<td>0.472</td>
<td>Exonic</td>
<td>Reduced enzymatic activity (A allele)</td>
</tr>
<tr>
<td>AMRK1</td>
<td>Anthrax Repeat and Ankyrin Domain Containing 1 (associated with Dopamine D2 Receptor)</td>
<td>rs1800497</td>
<td>C&gt;T</td>
<td>0.296</td>
<td>Exonic</td>
<td>T allele associated with increased dopamine binding, addiction, poorer antidepressant response</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>Serotonin Transporter</td>
<td>rs13601</td>
<td>L&gt;S</td>
<td>-0.400</td>
<td>Promoter region</td>
<td>Short allele causes less transcription of gene and is associated with anxiety-related personality traits, phenotype is either microdeletion or presence of the G allele at rs205331</td>
</tr>
<tr>
<td>MAOA</td>
<td>Monoamine Oxidase A</td>
<td>rs6323</td>
<td>T&gt;G</td>
<td>0.347</td>
<td>Exonic</td>
<td>A allele confers more active form of enzyme, associated with lower plasma response</td>
</tr>
<tr>
<td>CLOCK</td>
<td>Circadian Locomotor Output Cycle Kaput Protein</td>
<td>rs181260</td>
<td>T&gt;C</td>
<td>0.230</td>
<td>3’ untranslation region</td>
<td>C allele is associated with higher prevalence of depression and sleep disturbance</td>
</tr>
<tr>
<td>FKBP5</td>
<td>FK506B Binding Protein 5</td>
<td>rs17190</td>
<td>A&gt;G</td>
<td>0.222</td>
<td>Promoter region</td>
<td>A allele is associated with stronger antidepressant response and better recovery from psychosocial stress without intervention</td>
</tr>
<tr>
<td>NFKB</td>
<td>NFKB1 Factor kappa B2</td>
<td>rs1056890</td>
<td>C&gt;T</td>
<td>0.290</td>
<td>3’ untranslation region</td>
<td>C allele is associated with long sleep phase delay, mapping and evening chronotype preference, also associated with less severe sleep disturbance</td>
</tr>
<tr>
<td>L1HR2</td>
<td>Interleukin 1 Receptor 2</td>
<td>rs1176498</td>
<td>T&gt;C</td>
<td>0.197</td>
<td>Intermic</td>
<td>Each dose of T and A allele, respectively, is associated with greater sleep disturbance, lower quality of life, and lower depression symptom progression over time</td>
</tr>
<tr>
<td>RBFOX3</td>
<td>RNA-Binding Protein, Fox-1 Homolog 3</td>
<td>rs900428</td>
<td>G&gt;A</td>
<td>0.215</td>
<td>Intermic</td>
<td>A and T (minor) alleles are associated with less sleep time latency</td>
</tr>
</tbody>
</table>

Conclusions

- I selected 15 genetic variants associated with signal transduction, the immune system, and the nervous system
- I designed PCR primers using the AgaenCASS Assay Design Suite and previously-reported assays for genotyping
- I hypothesize that the selected genes will associate with treatment response, warranting further investigation in a larger study

Future Direction

- For 132 patients, germline DNA will be extracted from blood and saliva samples and genotyped
- Associations between genotype at each locus and the proportion of individuals experiencing a significant reduction in insomnia will be analyzed for each treatment modality
- Identification of normal genetic variants associated with treatment response is a step in the direction of personalized medical care

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