Precision Medicine in Supportive Oncology: Identifying Candidate Genetic Variants

Timothy Genovese, B.S., Irene Orlow, Ph.D., and Jun Mao, M.D., M.S.C.E.

Memorial Sloan Kettering Cancer Center, Department of Integrative Medicine

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 receive acupuncture (n=68) or CBT-I (n=64) for insomnia
- 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)

Figure 1. Flow Diagram of Genetic Variant Selection

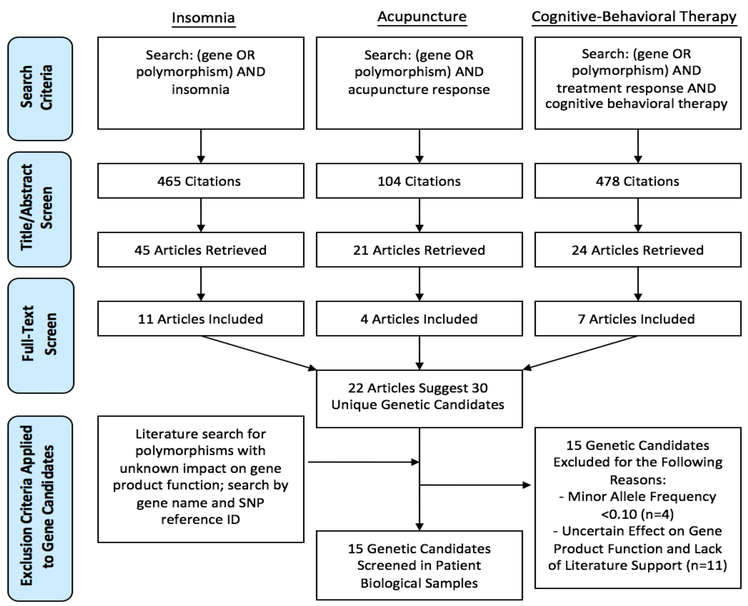

Table 1. Selected Genetic Variants

	Gene	Product	Polymorphism	Allele Distribution	Global Minor Allele Frequency	Location/Context	Note
Priority 1	BDNF	Brain-Derived Neurotrophic Factor	rs6265	G>A	0.201	Exonic Val66Met	A allele is associated with several neuropsychiatric disorders
	AHRR	Aryl Hydrocarbon Receptor Repressor	rs2292596	C>G	0.380	Exonic Pro189Ala	Homozygosity for C allele is associated with insomnia in women
	COMT	Catechol-O-Methyltransferase	rs4680	G>A	0.472	Exonic Val158Met	A allele reduces enzyme activity by 75%; associated with neurological and psychiatric disorders and medication response
	ANKK1	Ankyrin Repeat and Kinase Domain Containing 1 (associated with Dopamine D2 Receptor)	rs1800497	C>T	0.296	Exonic Glu713Lys	T allele associated with decreased dopamine binding, addiction, poorer antidepressant response
	SLC6A4	Serotonin Transporter	Repeats in promoter region: long (16) vs. short (14)	L>S	~0.400	Promoter region	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 rs25531
			rs25531	A>G	0.138	Promoter region	
	MAOA	Monoamine Oxidase A	rs6323	T>G	0.347	Exonic	G allele codes for more active form of enzyme, associated with lower placebo response
	CLOCK	Circadian Locomotor Output Cycles Kaput Protein	rs1801260	T>C	0.230	3' untranslated region	C allele is associated with higher prevalence of depression and sleep disturbance
	FKBP5	FK506 Binding Protein 5	rs4713916	A>G	0.222	Promoter region	A allele is associated with stronger antidepressant response and better recovery from psychosocial stress without intervention
Priority 2	NFKB2	Necrosis Factor Kappa B2	rs1056890	C>T	0.290	3' untranslated region	T allele is associated with long daytime napping and evening chronotype preference; also associated with less severe sleep disturbance
	IL1R2	Interleukin 1 Receptor 2	rs11674595	T>C	0.187	Intronic	Each dose of T and A allele, respectively, is associated with greater sleep disturbance, lower quality of life, and lower depressive symptom progression over time
			rs7570441	G>A	0.467	Intronic	
	RBFOX3	RNA-Binding Protein, Fox-1 Homolog 3	rs9900428	G>A	0.215	Intronic	A and T (minor) alleles are associated with less sleep time latency
			rs9907432	G>A	0.163	Intronic	
			rs7211029	C>T	0.230	Intronic	

Conclusions

- I selected 15 genetic variants associated with signal transduction, the immune system, and the nervous system
- I designed PCR primers using the AgenaCx 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

- 132 patient blood and saliva samples will have DNA extracted and genotyped
- Reduction in insomnia severity scale score will be analyzed by genotype and treatment modality
- 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

Acknowledgements

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number R25CA020449. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Research reported in this publication was also funded through a Patient-Centered Outcomes Research Institute (PCORI) Award (CER-1403-14292)

Thank you to Jun Mao for active and engaged mentorship – I would not have been able to complete this project without your support, advice, and interest in my personal development.

Thank you as well to Lydia Singerman, Sally Romero, and the rest of the Integrative Medicine Department at Sloan Kettering for your support and contributions to this project.