Genetic Pathways of Postoperative Pain Identified by a Systems Biology Approach: Novel Gene Associations with Chronic Post-Surgical Pain (CPSP) in a Prospective Surgical Cohort

Vanessa A. Olbrecht, MD, MBA[1], Anil G. Jegga, DVM[2], Lisa J. Martin, PhD[3], Valentina Pilipenko, PhD[3], Vidya Chidambaran, MD[1]

[1]Department of Anesthesiology, Cincinnati Children's Hospital Medical Center; [2]Division of Biomedical Informatics, Cincinnati Children's Hospital; [3]Division of Human Genetics, Cincinnati Children's Hospital;

Cincinnati Children's
changing the outcome together

Introduction

Although pain has a heritable risk of ~ 45% and genetic risk factors explain some individual differences in pain perception[1], the genetic basis for postoperative pain remains elusive due to a lack of replicability[2] and inconsistent findings of genetic association studies[3]. A systems biology approach integrates genetic-level data with biologic pathways and networks thereby overcoming the pitfalls of hypothesis-driven candidate marker association studies. While such pathway analyses have been conducted to study chronic pain conditions and traumatic brain injury, no study has used this methodology to study postoperative pain. The goal of this study was to use a systems biology approach to identify genetic pathways involved in postoperative pain to enable novel SNP evaluations in a prospective study of chronic postsurgical pain (CPSP).

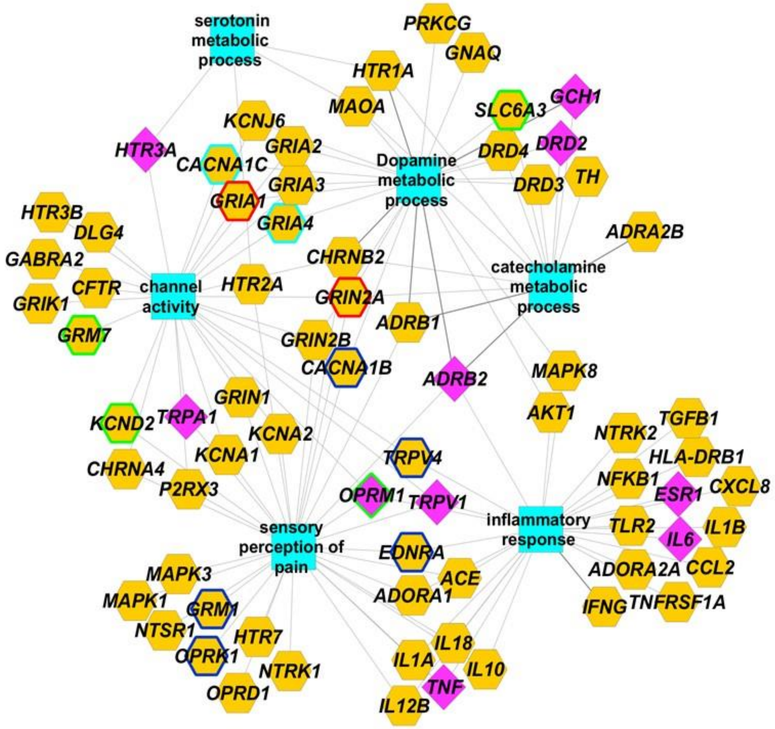

Figure: Representation of candidate and training set genes and biological processes associated with pain, as identified by systems biology. Also indicated in the key below are the genes that were found to be associated with CPSP by prospective study in spine surgical patients.

Key
Pink diamonds: Training
Orange hexagon: Top 10% ranked candidates
Colored border identifies the top genes associated with CPSP in our prospective data analysis

Methods

A systematic review of the literature of articles published between 01/01/1997 and 10/31/2017 was undertaken to identify genes associated with postoperative pain. This training set was then used to perform a systems biology-based integrative computational analysis using ToppGene Suite (www.toppgene.cchmc.org), a comprehensive platform for gene set enrichment analyses and machine learning based candidate gene ranking to identify candidate gene sets and processes. In addition, we analyzed Omni5M array data from 184 prospectively recruited children undergoing posterior spinal fusion for idiopathic scoliosis, along with demographic, perioperative and psychological data for genotype associations with CPSP, using additive models.

Results

Our systematic review identified a training set of 16 genes. For candidate gene ranking using the training set, we compiled a set of ~680 pain genes based on functional similarity using a variety of gene annotations. The top 10% of the ranked list (68 genes) and training set together were used for enrichment analysis. The results showed significant enrichment (p-value 0.05; Bonferroni correction) for biologic processes such as inflammatory response, cytokine activity, sensory perception of pain, channel activity, dopamine, catecholamine and serotonin metabolic processes (Fig). For our prospectively collected data, association analysis was conducted for the 84 genes identified (5,085 SNPs). We found 284 SNPs from 36 of the genes to be associated with CPSP at p-values<0.05. Genes with the top decile (28 SNPs) are also indicated in the Fig.

Conclusions

Using a systems-based approach, we identified key biological processes and important novel genes involved in the development of postoperative pain and CPSP that would not have been possible with the initial training set. This information can guide future research in individualization of pain management focused on these processes.

References

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