Unique and Shared Genetic Pathways for postoperative pain, Chronic Postoperative Pain and anxiety – a systems biology approach

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Introduction

Anxiety is a predisposing factor for poor pain coping and transition to chronic postsurgical pain (CPSP). While there is high interindividual variability in CPSP and anxiety predisposition, a genetic basis has been elusive due to lack of replicability of genetic association studies¹ and inconsistent results². A systems biology approach integrates genetic-level data with biologic processes, pathways and networks thereby overcoming the pitfalls of hypothesis-driven candidate marker association studies. We have used this approach to identify unique and shared genetic pathways involved in chronic postsurgical pain (CPSP) and anxiety.

Methods

A systematic review of literature (01/01/1997 - 10/31/2017) was performed to identify genes associated with postoperative pain, CPSP and anxiety in humans. The identified genes were then used to perform a systems biology-based integrative computational analysis using ToppGene Suite (<https://toppgene.cchmc.org>), a comprehensive platform for functional enrichment analyses and machine learning based candidate gene identification and ranking. We also curated gene sets associated with similar mouse phenotype – knockout studies, and did a pathway enrichment analysis. We then compared the top 100 processes and pathways associated with postoperative pain, CPSP and anxiety to identify gene sets involved in the three phenotypes.

Results

Systematic review identified a training set of 38 genes associated with postoperative pain, 31 genes with CPSP and 61 genes with anxiety. The training and candidate sets (Fig) were used together for enrichment. Significant enrichment (p-value 0.05; Benjamini-Hochberg correction) was found for known and novel biologic processes (network shared by all phenotypes are presented in Fig). New shared genes identified included ligand-gated glutamate receptor gene family, which includes AMPA, kainate, and NMDA receptors encoded by GRIA, GRIK, and GRIN genes; Opioid, GABA, Dopamine, serotonin, adrenergic, cholinergic, Ca channel genes. While inflammatory and drug metabolism pathways were generally more associated with postoperative pain, immune pathways were more relevant in CPSP and dopamine-serotonin pathways in anxiety.

Conclusion

Using a systems biology-based approach, we identified unique and shared biological processes involved in acute postoperative pain, CPSP and anxiety. This information provides a framework for future research in mechanistic processes and treatment of CPSP.

References:

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2. Mogil JS. *Proc Natl Acad Sci USA* 1999;96(14):7744-51