

Multicenter Study of OPRM1 A118G and Promoter-region DNA Methylation Associations with Opioid Outcomes and Chronic Postsurgical Pain after Pediatric Musculoskeletal Surgery

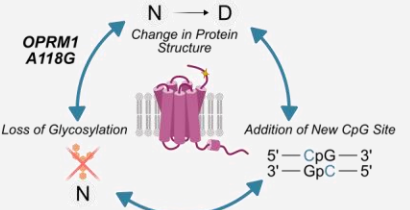
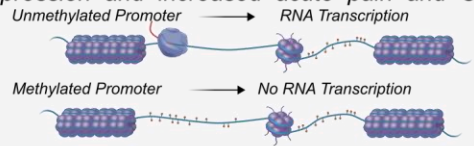


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Background

- Chronic postsurgical pain (CPSP) is pain lasting beyond 2-3 months after surgery with an incidence as high as 11-60%, depending on surgery type.
- Genetic and epigenetic variants have been associated with variability in the pain response and management.
- OPRM1 encodes the mu opioid receptor (MOR), the primary target of endogenous and exogenous opioids. DNA methylation (DNAm) in the promoter region of OPRM1 has demonstrated reduced MOR expression and increased acute pain and CPSP.
- The single nucleotide polymorphism (SNP) rs1799971 or OPRM1 A118G is a missense variant known to reduce expression of MOR and response to various receptor ligands. Multiple hypotheses have been proposed to mediate these effects.

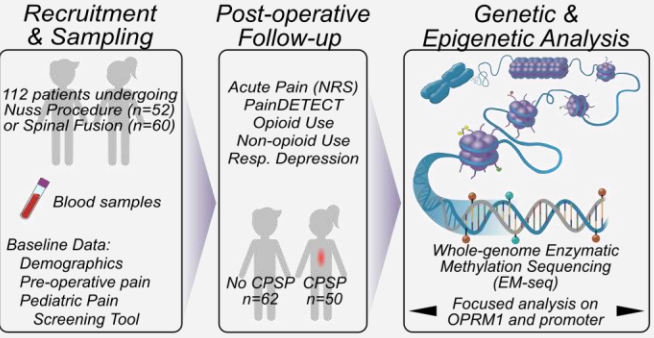


Objectives

- Evaluate the effect of OPRM1 A118G on promoter methylation and opioid/pain outcomes.
- Identify CPSP-associated methylation quantitative trait loci (meQTLs) in the OPRM1 promoter.

Methods

- Inclusion Criteria:**
8 to 21 years old with a diagnosis of adolescent idiopathic scoliosis or pectus excavatum scheduled to undergo posterior spinal fusion or endoscopic pectus excavatum repair respectively were included.
- Exclusion Criteria:**
- Opioid-use in the last 2 years
 - Severe respiratory problems or cardiac conditions
 - Renal or liver disease
 - Severe developmental delays
 - Pregnant or breastfeeding
 - Non-English speaking



Conclusions

- OPRM1 A118G is not associated with increased DNAm, at the location of the SNP or promoter.
- Additional CpG sites within the OPRM1 promoter, including at position 118, are associated with CPSP (-329), acute pain (+118), and respiratory depression (-25, +27).



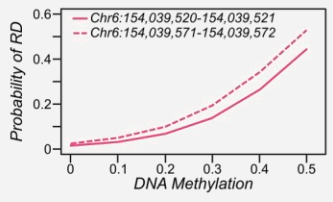
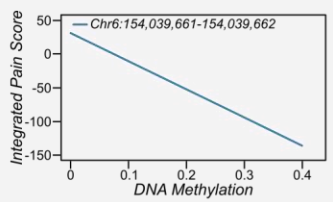
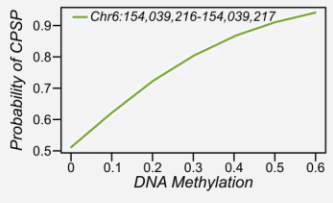
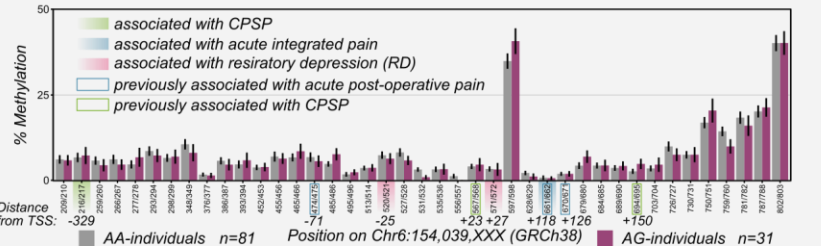
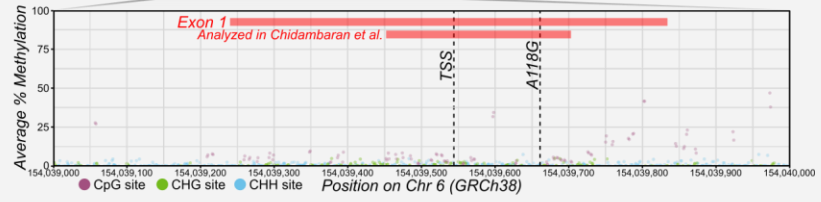
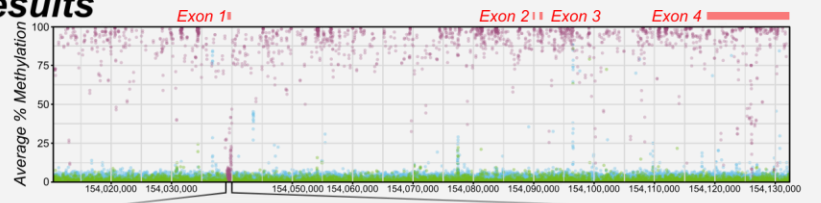
Limitations

- No individuals homozygous for rs1799971 (i.e. GG-individuals) were present in this study.
- Low sequence coverage when compared to targeted analysis.
- Analysis is limited to immune cells from blood samples.

Future Directions

- Epigenetic analysis across the entire genome using EM-seq and ATAC-seq to identify additional regions associated with the risk for and development of CPSP.
- Combining the above results with RNA-seq data to identify possible mechanisms of CPSP development and identification of therapeutic targets.

Results



References

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