Published in final edited form as:

Pain. 2017 August ; 158(8): 1622–1623. doi:10.1097/j.pain.0000000000000946.

Pain versus Analgesia: *TAOK3* as a Pharmacogene

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We read with interest the recent work of Matic *et al.* investigating single nucleotide polymorphisms (SNPs) in select candidate genes for experimental pain,[8] and were grateful for their inclusion and study of rs795484 within *TAOK3*. Using genome-wide association study (GWAS) methodology, we had previously shown this and other supporting SNPs at the *TAOK3* locus to be associated with perioperative morphine requirement and postoperative pain in a healthy pediatric day surgery population.[4] However, the rs795484 variant did not associate with cold and heat pain thresholds studied by Matic and colleagues. Why might this be?

Were *TAOK3* a “pain gene,” we might have anticipated congruent results. This expectation may be oversimplified for such a multi-faceted, complex trait as pain, however. *TAOK3* could yet be a relevant pain gene but phenotypic, racial, and/or prior pain and opioid exposure differences between studies may have precluded association replication. Even though several experimental pain modalities, especially heat pain sensitivity, may correlate with acute postoperative pain, none entirely equates with the post-incisional, post-electrocautery pain and inflammatory conditions following tonsillectomy and adenoidectomy. Because the genetic contribution to pain response variability critically depends on the pain modality tested,[1] lack of association here could well be the consequence of mismatched phenotype. In our study, the *TAOK3* rs795484 minor allele was primarily associated with increased morphine dose requirement in children of European Caucasian (EC) ancestry, although it was disproportionately represented in children of either EC or African American (AA) ancestry who had high maximum postoperative pain scores. While the Dutch study cohort was likely of EC-predominant ancestry, subject race was not recorded, such that underlying population stratification may have prevented association signals from appearing. Potential further evidence of the influence of race in the findings of Matic and colleagues was the strong association with rs1799971 minor allele variant (G) at

OPRM1 and decreased thermal pain sensitivity, demonstrating opposite effect direction when compared to results in a recent meta-analysis heavily weighted with subjects of Asian descent.[5] Finally, compared to our opioid-naïve cohort, 59% of subjects in the Dutch study had had extensive opioid exposure prior to testing and although their subpopulation analyses did not reveal response heterogeneity, the possibility of confounding experiential pain history and persistent alteration of pain pathways remains.

We believe the most likely explanation for the differences between the study findings is that *TAOK3* functions not as a “pain gene,” but rather as an “analgesic gene,” more generally a pharmacogene. While we were unable to prove this in our original study, there are several lines of evidence consistent with this theory. In that first study, the strongest GWAS signal had been for morphine dose as a quantitative trait (analgesia required to bring pain to a level suitable for hospital discharge) as opposed to an association signal for high pain phenotype. Importantly, there was no interaction between SNP genotype and maximum pain. For oral methadone, our collaborative group recently demonstrated that maintenance dose requirement was increased in opioid dependent adults with a genetic scoring panel that included the rs795484 minor variant.[9]

From a mechanistic standpoint, TAO3, the serine/threonine kinase *TAOK3* gene product, may phosphorylate and modify function of several key proteins in drug-induced analgesia pathways. We previously posited that TAO3 variants conferring analgesic resistance could alter mu opioid receptor (MOR) and/or beta arrestin phosphorylation patterns, changing signal transduction following morphine-MOR binding. In a related paradigm, homologous murine *Taok3Gt* heterozygotes are more resistant to the acute sedative effects of ethanol,[6] raising the possibility that TAO3 variants could also alter ethanol-induced analgesia. Of note, Weaver mutant mice which have a missense mutation in the GIRK2 channel show loss of ethanol-induced analgesia[7] and because the phosphorylation status of a serine residue alters this channel’s recycling,[3] the tantalizing possibility of interaction between TAO3 and GIRK2, and their variants, emerges. Indeed, GIRK2 is central to the mechanism of analgesic action of a diverse set of drugs including ethanol and opioids.[2]

The work of Matic *et al.* furthers our understanding of the interrelated entities of pain and analgesia, and demonstrates the complexity of their genetic influences. Opioid dose response data added to graded experimental pain phenotype, as Angst et al studied in twins treated with alfentanil,[1] would be required to demonstrate variation in opioid analgesia associated with rs795484. We believe that ligand-specific effects are likely to occur. Validation and mechanistic infill studies are especially important for those phenotype/genotype associations generated by GWAS and other mathematical techniques. Further research that includes studying the molecular biology of opioid and ethanol-induced signal transduction with *TAOK3* variants as compared to wild type will be required to determine whether *TAOK3* prevails as a pharmacogene.

Acknowledgments

Dr. Hakonarson is the recipient of funding from the National Institutes for Health, NHGRI eMERGE-grant U01HG006830. The authors report no conflict of interest.

References

1. Angst MS, Phillips NG, Drover DR, Tingle M, Ray A, Swan GE, Lazzeroni LC, Clark JD. Pain sensitivity and opioid analgesia: a pharmacogenomics twin study. *Pain*. 2012; 153:1397–409. [PubMed: 22444188]
2. Blednov YA, Stoffel M, Alva H, Harris RA. A pervasive mechanism, for analgesia: activation of GIRK2 channels. *Proc Natl Acad Sci USA*. 2003; 100:277–82. [PubMed: 12493843]
3. Chung HJ, Qian X, Ehlers M, Jan YN, Jan LY. Neuronal activity regulates phosphorylation-dependent surface delivery of G protein-activated inwardly rectifying potassium channels. *Proc Natl Acad Sci USA*. 2009; 106:629–34. [PubMed: 19118198]
4. Cook-Sather SD, Li J, Goebel TK, Sussman EM, Rehman MA, Hakonarson H. *TAOK3* a novel genome-wide association study locus associated with morphine requirement and postoperative pain in a retrospective pediatric day surgery population. *Pain*. 2014; 155:1773–83. [PubMed: 24909733]
5. Hwang IC, Park JY, Myung SK, Ahn HY, Fukuda KI, Liao Q. *OPRM1* A118G gene variant and postoperative opioid requirement: A systematic review and meta-analysis. *Anesthesiology*. 2014; 121:825–34. [PubMed: 25102313]
6. Kapfhammer D, King I, Zou M, Lim J, Heberlein U, Wolf F. JNK pathway activation is controlled by Tao/TAOK3 to modulate ethanol sensitivity. *PLoS One*. 2012; 7:e50594. [PubMed: 23227189]
7. Kobayashi T, Ikeda K, Kojima H, Niki H, Yano R, Yoshioka T, Kumanishi T. Ethanol opens G-protein-activated inwardly rectifying K⁺ channels. *Nat Neurosci*. 1999; 12:1091–7.
8. Matic M, van den Bosch GE, de Wilt SN, Tibboel D, van Schaik RNH. Genetic variant associated with thermal pain sensitivity in a paediatric population. *Pain*. 2016; 157:2476–82. [PubMed: 27541715]
9. Smith AH, Jensen KP, Li J, Nunez Y, Farrer LA, Hakonarson H, Cook-Sather SD, Kranzler HR, Gelernter J. Genome-wide association study of therapeutic opioid dosing identifies a novel locus upstream of *OPRM1*. *Mol Psych*. 2017; online publication, 24 January 2017. doi: 10.1038/mp.2016.257