

Functional analysis of human GWAS finding for opioid overdose

Marked inter-individual variability in opioid responses leads to wide differences in lethal dose, making opioid use particularly dangerous. Although genome-wide association studies (GWAS) have identified numerous genetic signals linked to opioid-related phenotypes, the functional mechanisms underlying most of these associations remain unclear. A GWAS of opioid overdose sensitivity in individuals who had used opioids at least once identified a locus containing three SNPs near the MCOLN1 gene.

MCOLN1 encodes mucolipin-1, a transmembrane TRP cation channel localized to intracellular vesicular membranes that regulates late endocytic trafficking and lysosomal exocytosis. In mice, loss of Mcoln1 causes mucopolipidosis type IV, characterized by progressive neurodevelopmental and visual deficits, with otherwise normal growth and survival through early adulthood.

We found that mice homozygous for Mcoln1 deletion exhibit significantly higher mortality and earlier death following administration of a 282 mg/kg dose of morphine compared to wild-type or heterozygous littermates. Mice retaining at least one functional Mcoln1 allele display reduced respiratory depression and are able to recover, whereas knockouts are not. Arterial blood gas analysis reveals that within 15–30 minutes of morphine exposure, null mice experience a pronounced reduction in arterial pO₂, while wild-type mice show minimal change at the sublethal dose.

Together, these findings implicate Mcoln1 as a key modulator of opioid-induced respiratory depression and suggest that pharmacological activation of MCOLN1—using agonists such as ML-SA5, alone or in combination with naloxone may offer a novel, centrally acting strategy to mitigate opioid overdose.

Authors:

Submitter: Jason Bubier, Senior Research Scientist, The Jackson Laboratory, Bar Harbor
Manisha Barse, M.S., Lieber Institute for Brain Development
Emma Chaloux-Pinette, Ph.D., Johns Hopkins University
Robin Magnard, Ph.D., Johns Hopkins University
Sarah Maguire, Ph.D., Lieber Institute for Brain Development
Ryan Miller, Ph.D., Lieber Institute for Brain Development
Beau Oster, B.S., Lieber Institute for Brain Development
Jason Regh, B.S., Lieber Institute for Brain Development
Felix Siewe, B.S., Lieber Institute for Brain Development
Ege Yalcinbas, Ph.D., Lieber Institute for Brain Development