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Opiate responses are controlled by interactions of *Oprm1* and *Fgf12* loci in rodents; correspondence to human GWAS findings

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We mapped high-precision time-series data (15 min bins for 3 hours) generated for ~700 adult BXD mice across 105 morphine- and naloxone-related traits using new sequence-derived marker maps and a linear-mixed model. We confirm a previously mapped sex-independent effect of initial locomotor responses to morphine (50 mg/kg ip) that maps precisely to *Oprm1* on chromosome (Chr)10, with the linkage score reaching -log-10-P of ~12.4 (with a high B allele) at 75 min and exhausted by 160 min. We detected a new modulator of opiate locomotor activation in both sexes on Chr 16, with a compelling candidate – *fibroblast growth factor 12* (*Fgf12I*). We also detected a strong, but transient epistatic interaction between these two loci. Single nuclei transcriptomic analyses in rates demonstrates that expression of *Oprm1* and *Fgf12* mRNA covary in one specific subtype of *Drd1* medium spiny neurons. Our Bayesian network analysis identified that a cascade of MAP kinases – *Mapk8ip2, Map3k11,* and *Map3k12* – are part of the *Oprm1 -Fgf12* network. This is the first demonstration of a time-dependent epistatic interaction modulating drug response in mammals with interesting mechanistic implications. Analysis of *OPRM1* and *FGF12* gene networks in human GWAS data highlights enrichment of signals associated with substance use disorder.