Review of: "Zhx2 is a candidate gene underlying oxymorphone metabolite brain concentration associated with state-dependent oxycodone reward"

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This manuscript from Beierle et al provides novel findings that link the transcriptional regulator Zhx2 with oxycodone addiction behavior. The authors use the highly related BALB/cByJ and BALB/cJ mouse substrains to provide compelling behavioral, genetic, genomic, and proteomic evidence that link Zhx2 to this behavior. This comprehensive study in mice is an important addition to sex-biased traits and the genetics of addiction. Although the mechanism by which Zhx2 control of gene expression leads to this behavior is not fully understood, a reasonable model (Fig. 7) is proposed and this data provides the framework for future studies. The paper is well-written, the experimental design is appropriate and the conclusions are justified and consistent with the data. As the authors note, it is not clear whether the mechanism is due to the Zhx2-mediated changes in gene expression in the liver or brain; it is possible that both organs, and possibly other organs since Zhx2 is ubiquitously expressed, are involved. Also, while the authors state that Zhx2 has been shown to be a transcriptional repressor (Kawata et al and others), it can also act as a transcriptional activator (Jiang, et al, PMCID: PMC5399123). Furthermore, while a number of genes with altered expression in the presence of absence of Zhx2 are shown in this paper (Fig. 5), it is not known which are direct or indirect targets of Zhx2.