Abstract:

Chd8 haploinsufficiency interacts with genetic background and sex to regulate the developmental trajectory of social dominance.

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Loss of function mutations in the chromodomain helicase DNA binding protein 8 (*CHD8*) gene are penetrant for autism spectrum disorder (ASD), macrocephaly, intellectual disability, and anxiety, with variable penetrance and severity. We have previously leveraged Collaborative Cross (CC) and BXD mouse genetic reference panel strains with a model of *Chd8* haploinsufficiency and shown that genetic background regulates the severity of trait disruptions due to *Chd8* haploinsufficiency in adults, including increased social dominance. Here, we characterized the developmental trajectory of social dominance alterations due to *Chd8* haploinsufficiency across mouse strains that displayed differential susceptibility to *Chd8*-driven social dominance in adulthood. To determine the developmental trajectory of *Chd8*$^{+/-}$ on social dominance across strains, we used the same breeding and testing strategy as we reported prior. *Chd8*$^{+/-}$-C57B/6J (B6) dams were paired with CC and B6 sires to produce genetically diverse F1 B6-CC and B6-B6 WT and *Chd8*$^{+/-}$ males and females. *Chd8*$^{+/-}$ mice were tested in the social dominance tube test against WT same sex and strain counterparts over multiple matches at different ages including preweaning (P14-16), juvenile (P27-P32; peripubertal), young adult (mean P92), and adult (mean P160) ages. While *Chd8*$^{+/-}$ mice from some strains and sexes were susceptible or resilient to social dominance over WT mice as both juveniles and adults (e.g., B6-B6 males and females), other groups remarkably showed *Chd8*$^{+/-}$ susceptibility to social dominance as juveniles and then resiliency or reduced susceptibly as adults (e.g., B6-CC18 females, B6-CC17 males). Moreover, while the time it took to complete each match decreased with age in the combined strain population, there were dramatic strain and sex dependent age effects on match times. These data indicate that the maturation of the social dominance circuit is regulated by interactions between *Chd8*, genetic background, and sex and indicate developmental compensatory mechanisms that are strain and sex specific.