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Investigation of influence of the gut microbial composition associated with colitis on mice behavior

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Motivation and Aim: Inflammatory bowel diseases (IBD) are chronic and relapsing inflammatory disorders of the gastrointestinal tract with complex etiology and no strategies for complete cure. IBD are often complicated by mental disorders like anxiety and depression, indicating substantial shifts in the gut-brain axis. However, the mechanisms connecting IBD to mental diseases are still under debate.

Methods and Algorithms: Here we use *Muc2* mutant mouse model of chronic colitis to uncouple the effects of the intestinal microbiota on host behavior from chronic inflammation in the gut.

Results: *Muc2* mutant male mice exhibit high exploratory activity, reduced anxiety-related behaviors, impaired sensorimotor gating, and altered social preference towards males and females. Microbial transfer to wild-type mice via littermate co-housing shows that colitis-associated microbiota rather than inflammation *per se* defines behavioral features in *Muc2* colitis model (Fig. 1). Metagenomic profiling and combination of antibiotic treatments revealed that bacterial species *Akkermansia muciniphila* is associated with the behavioral phenotype in mutants, and that its intestinal abundance correlates with social preference towards males. Metabolomic analysis together with pharmacological inhibition of Gly and NMDA receptors helped us to determine that brain glycine is responsible for the behavioral phenotype in *Muc2* mice. Blood and brain metabolic profiles suggest that microbiota-dependent changes in choline metabolism might be involved in regulation of central glycine neurotransmission.

Conclusion: Taken together, our data demonstrates that colitis-associated microbiota controls anxiety, sensorimotor gating and social behavior via metabolic regulation of the brain glycinergic system, providing new venues to combat neurological complications of IBD.

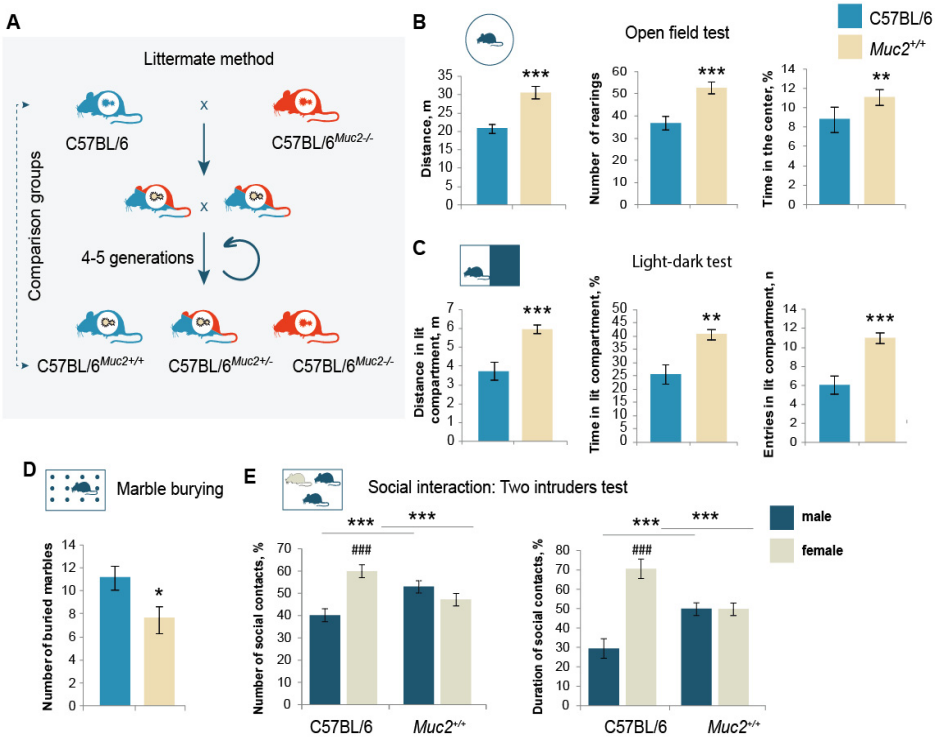

Fig. 1. Behavioral traits are associated with microbiota of Muc2$^{-/-}$ mice. (A) The scheme of the littermate co-housing method. (B) Open field test (n = 18–20). Distance: t = –3.895, p < 0.001; rearings: t = –4.97, p < 0.001, Student's t-test; time in the center: Z = –2.997, p < 0.001, Mann-Whitney u test. (C) Light-dark test (n = 17-20). Distance: t = 4.019, p < 0.001; time: t = –3.584, p < 0.001; entries: t = –4.26, p < 0.001, Student's t-test. (D) Marble burying test (n = 18–20). Number of buried marbles: Z = 2.22, p = 0.026; Mann-Whitney u test. (E) Z = 2.22, p = 0.026; Mann-Whitney u test. (F) Two intruders test (n = 10–11). Two-way ANOVA revealed a statistically significant interaction between the resident group and the intruder gender (number of contacts: F(1, 38) = 15.490, p < 0.001; duration: F(1, 38) = 28.306, p < 0.001 Number of contacts (C57BL/6, male *vs*. female): p < 0.001, Fisher's LSD test; duration (C57BL/6, male vs. female): p < 0.001, Fisher's LSD test. Number of contacts with a male/female intruder *vs*. C57BL/6: p = 0.008, Fisher's LSD test; duration of contact with a male/female intruder *vs.* C57BL/6: p < 0.001, Fisher's LSD test. * = p < 0.05, ** = p < 0.01, *** = p < 0.001, *vs*. C57BL/6. ### = p < 0.001, male *vs*. female

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