

Novel animal model for understanding hypothalamic neuromodulatory systems and social behavior disruption in frontotemporal dementia

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We have generated a novel genetic model of progranulin (Grn) deficiency in the prairie vole, a socially monogamous rodent that forms long term pair bonds. We find that this model mimics the haploinsufficiency sensitivity seen in frontotemporal dementia (FTD) patients and allows us to model the social attachment deficits in FTD patients.

INTRODUCTION	METHODS	BEHAVIOR RESULTS	PVN RESULTS	CONCLUSIONS
Changes in social behavior affecting social attachments are significant behavioral symptoms in patients with Alzheimer's Disease and Alzheimer's Disease Related Dementias (AD/ADRD). Patients with frontotemporal dementia (FTD), in particular, exhibit striking deficits in social cognition. However, the mechanisms by which disease pathology results in social deficits is unclear, and standard genetic animal models, like mice, do not replicate the social attachment phenotypes of FTD. Here, we use the socially monogamous prairie vole to examine how progranulin (Grn) deficiency, one of the most common genetic forms of FTD leads to social deficits. Prairie voles are small rodents that display long-term, adult social attachments and have emerged as an ideal model to examine social bonds. The paraventricular nucleus of the hypothalamus (PVN) produces key neuromodulators, including oxytocin (OT) and vasopressin (AVP), that regulate both physiology and social behavior. We ask whether Grn deficiency preferentially disrupts neuromodulatory systems in the PVN, suggesting a role in mediating the social attachment deficits in FTD.	Our laboratory used CRISPR/Cas9 to generate prairie voles bearing mutations in <i>Grn</i>. We delivered guide RNAs targeting exon 2 of the vole <i>Grn</i> gene as in the figure below. Pups born following embryo transfer were screened for indels leading to protein truncating mutations (Fig 1A,B). Targeted molecular genetics in prairie voles CRISPR injection into single cell zygotes Gene expression following zygote injection Embryo transfer to recipient female Pups born following embryo injection and transfer A Peptide sequence from wildtype and mutant GRN allele GRN_WT 1 MPPRELGPRSRQTHWILGKALVAGLVSGTRCPDQFCPVACCLDLGVSYSCNPLLD 68...696 GRN_mut1 1 MPPRELGPRSRQTHWILGKALVAGLVSGTRCPDQFCPVACGRSQQLL*STOP 53 truncation B GRN DAPI	We find that heterozygous, 12 month-old male <i>Grn</i>^{+/-} voles show no deficits in overall sociability (Fig 2A)but males show increased preference for social novelty relative to wild type animals (Fig 2B). We also see deficits in bonding behavior, as indicated by increased aggression towards novel animals and reduced time in contact with their partner (Fig 3A,B). A Female TCT Chamber Time Male TCT Chamber Time B Female Social Novelty Interaction Time Male Social Novelty Interaction Time Figure 2: Social novelty in WT and <i>Grn</i>^{+/-} voles A Novel animal B Partner preference	In pilot data, we used immunofluorescence to examine expression of GRN in the PVN and the relative expression in specific cell types. We find that the numbers of AVP+ and OXT+ cells change with age in Grn deficiency. GRN expression may also selectively decrease in oxytocin producing cells (Fig 4A,B). A WT 2mo HT 2mo WT 12mo HT 12mo B %Avp*Grn⁺ %Oxt*Grn⁺	Importantly, a model of genetic progranulin deficiency in the prairie vole mimics the haploinsufficiency sensitivity seen in FTD patients, allowing us to model the deficits in social attachment that accompany changes to social cognition. Our results suggest a potential role for disruptions to hypothalamic cellular morphology and function in mediating the social behavioral deficits in FTD. Future work validating these findings in vole and human postmortem tissue will be important to confirm these findings in disease. References Miller, et al. <i>Neurology</i>. 2001. Chitramuthu et al. <i>Brain</i>. 2017. Carter and Getz. <i>Sci. Am.</i> 1996. Lim & Young, <i>Horm. Behav.</i> 2006. Insel et al. <i>Adv. Exp. Med. Biol.</i> 1998. CONTACT Kristen Berendzen kristen.berendzen@ucsf.edu University of California, San Francisco ALZHEIMER'S ASSOCIATION AAIC 26