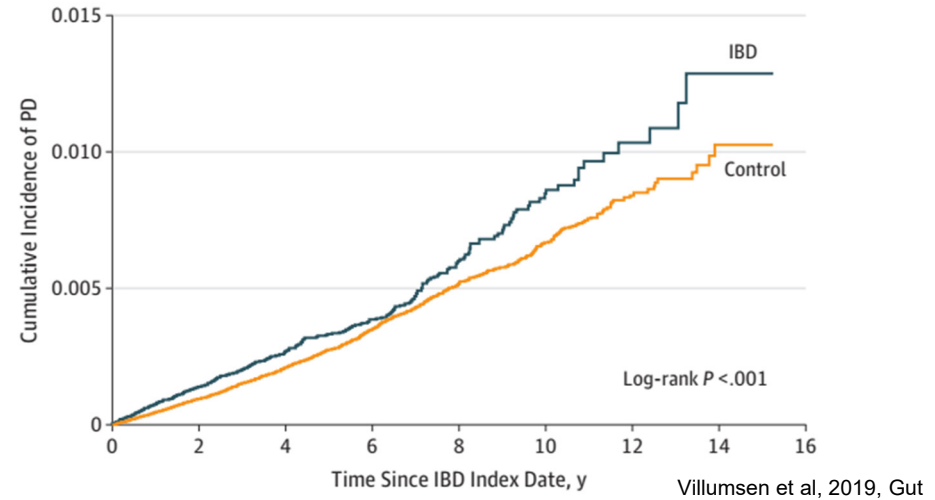
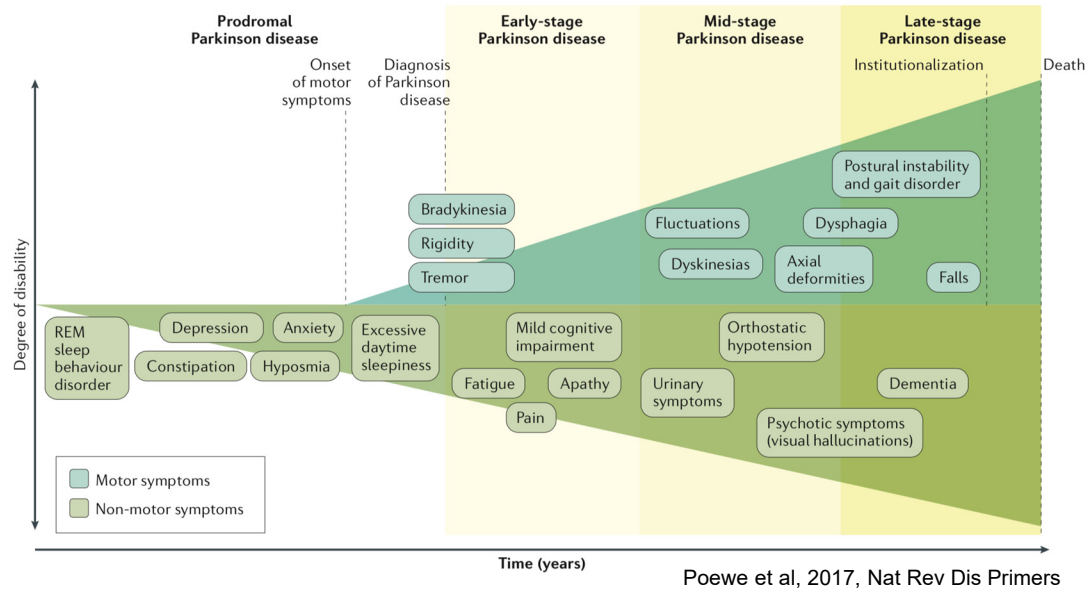




## Dissecting contributions of prodromal intestinal inflammation to the manifestation of Parkinson's disease

**Ping Fang, Lewis Yu, Hannah Espey, Yongning Deng, Hayley Hrcir,  
Arthur P. Arnold, Elaine Y. Hsiao**

# Introduction



- Inflammatory bowel disease (IBD) and gastrointestinal disruptions are seen during prodromal Parkinson's disease (PD), up to 20 years before classical motor deficits of PD are evident.

- Sex differences have been reported in prevalence of IBD and PD, where males exhibit higher risk for both ulcerative colitis and PD.

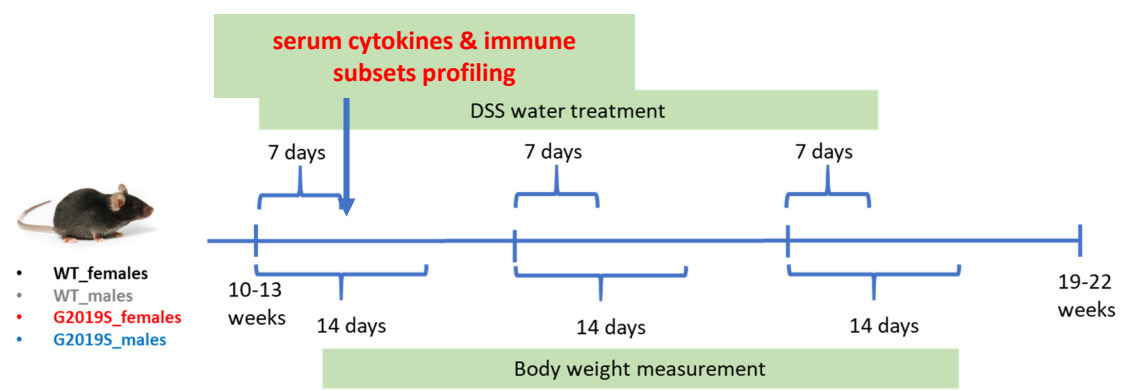
- Patients with IBD exhibit increased risk for PD compared to unaffected controls. This risk is abrogated in IBD patients that receive anti-tumor necrosis factor (TNF) therapy compared to those who do not.

- Mutations in leucine-rich repeat kinase 2 (LRRK2) have been associated with PD and with IBD.

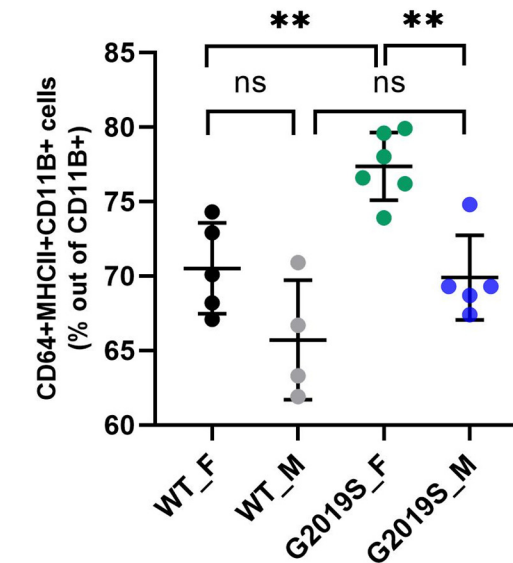
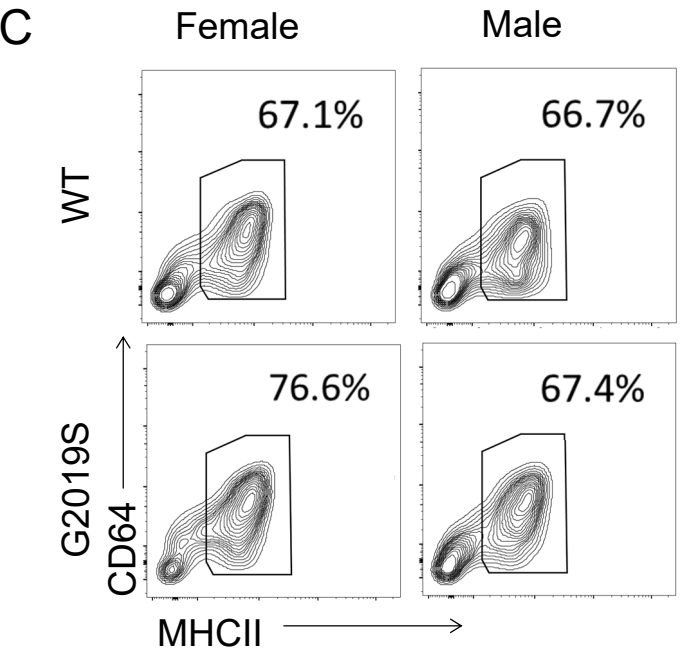
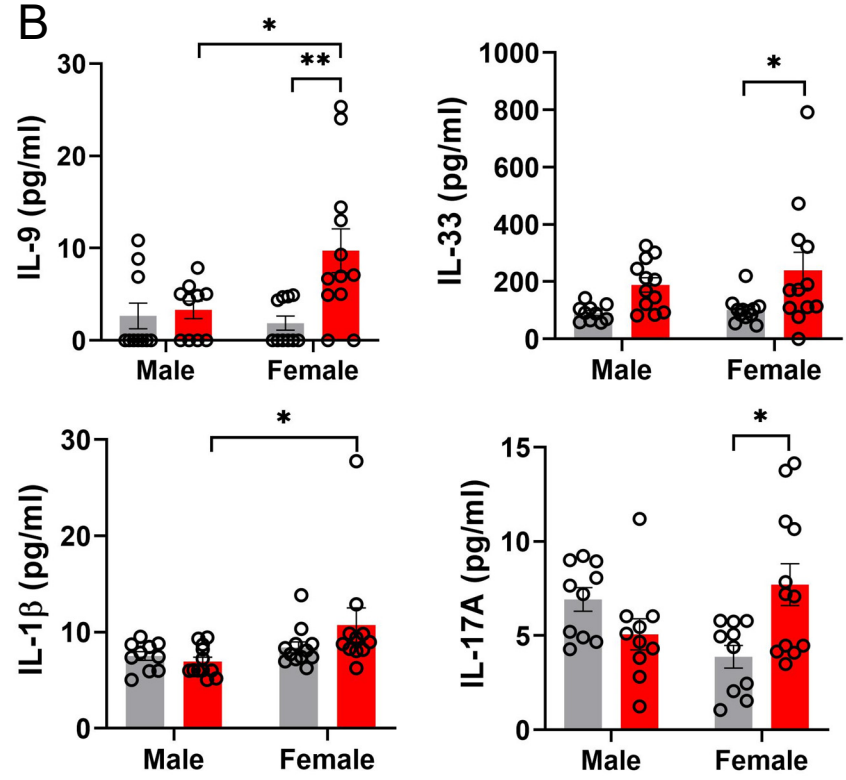
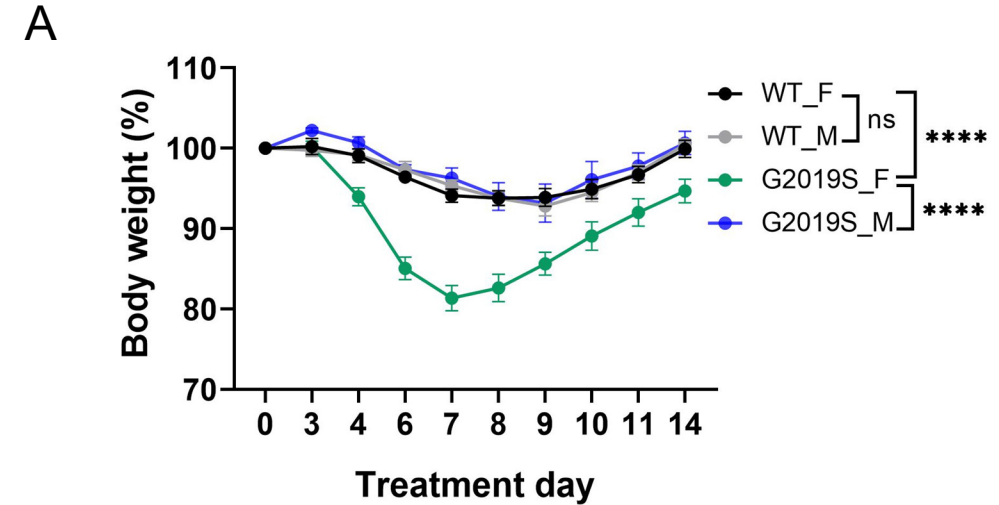
- The G2019S mutation in LRRK2 is the most common monogenetic cause of PD, which yields elevated kinase activity and alterations in cell autophagy and lysosomal function.

- **While accumulating studies highlight potential interactions between intestinal disorders, PD and sex, little is known regarding the molecular and cellular mechanisms underlying these phenomena**

# Modeling chronic prodromal intestinal inflammation in LRRK2<sup>G2019S</sup> Tg mice with DSS treatment

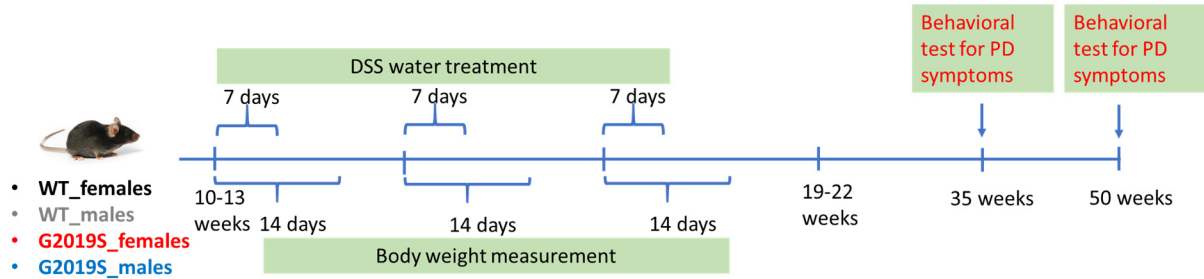


- WT\_females
- WT\_males
- G2019S\_females
- G2019S\_males

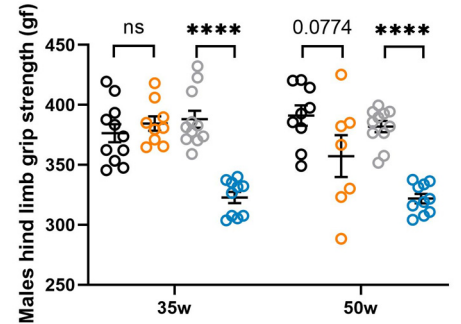
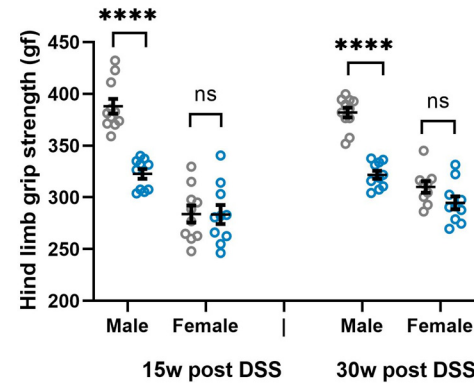
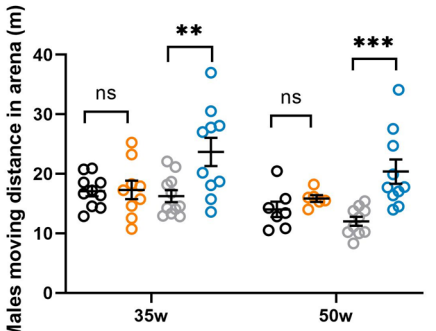
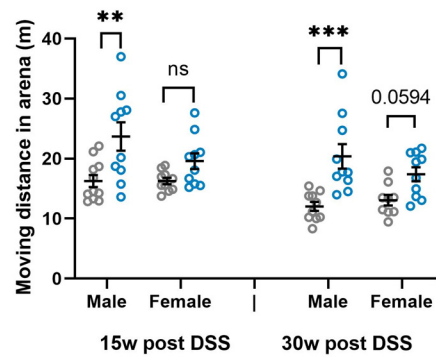
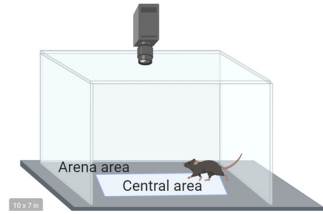


- WT
- G2019S

# PD symptoms developed in DSS treated LRRK2<sup>G2019S</sup> Tg mice

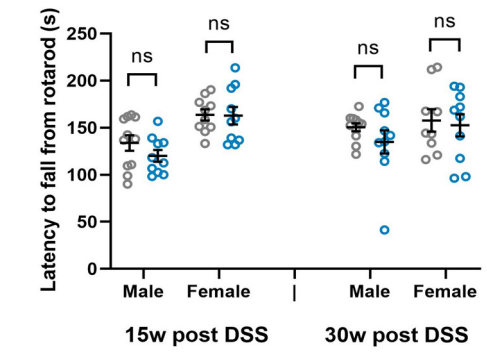
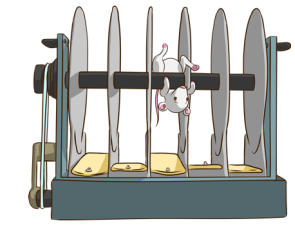
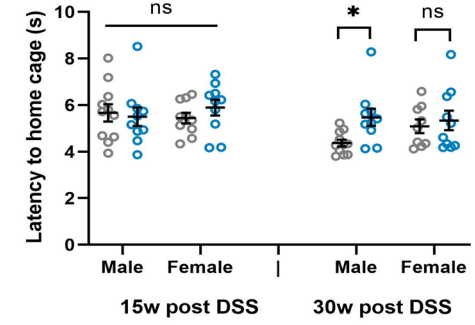
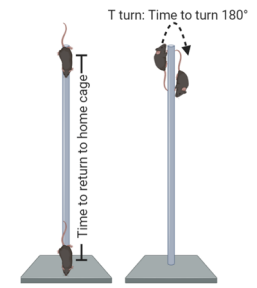


- WT\_females
- WT\_males
- G2019S\_females
- G2019S\_males

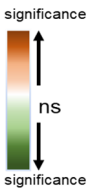


- WT
- G2019S

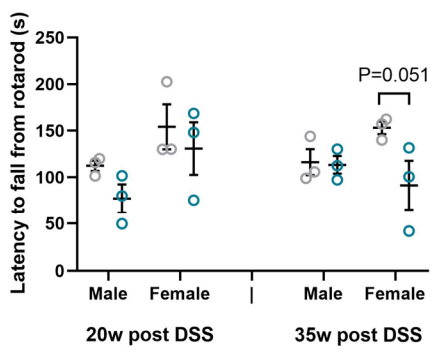
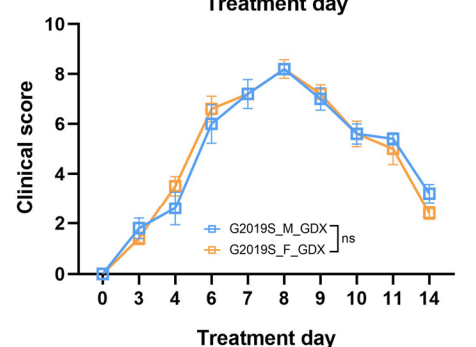
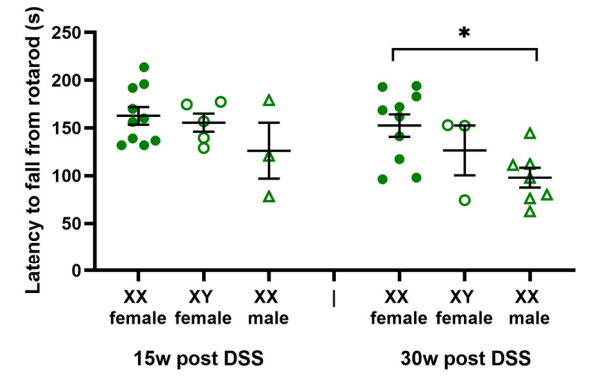
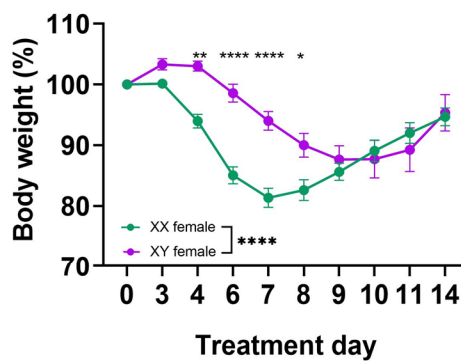
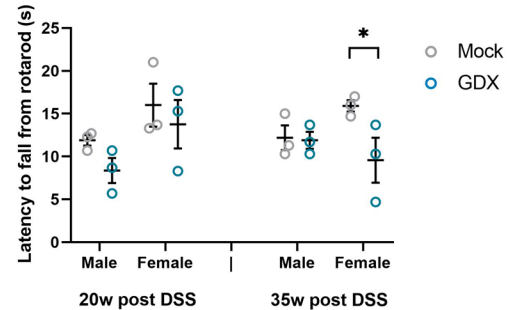
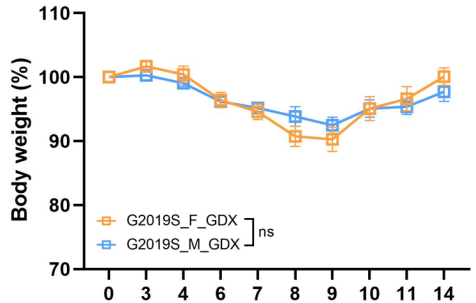
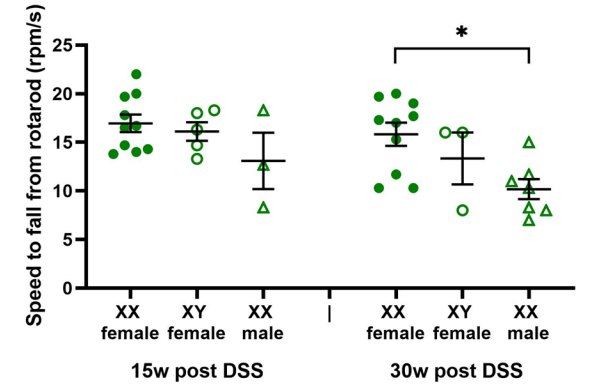
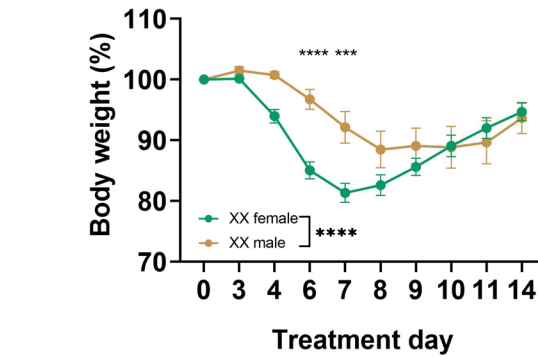
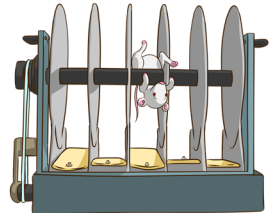
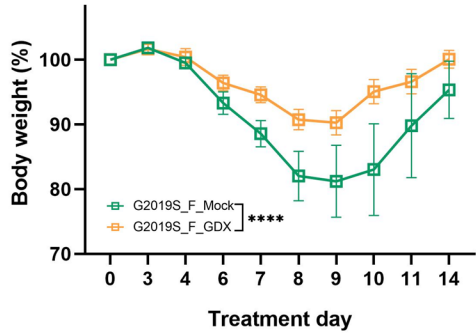
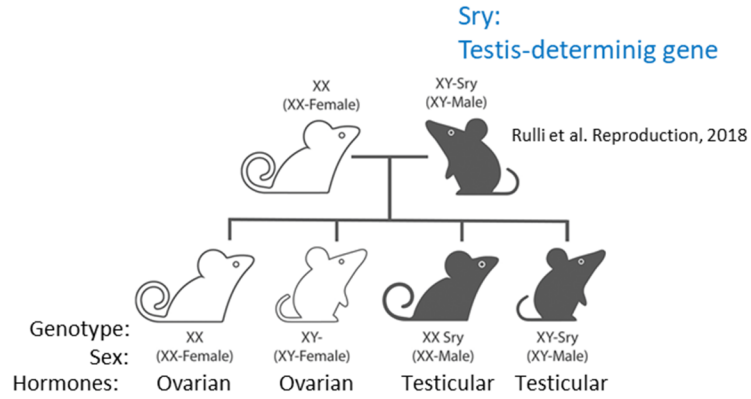
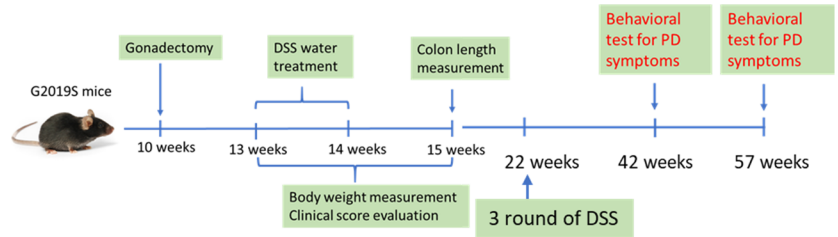
- WT\_water
- G2019S\_water
- WT-DSS
- G2019S\_DSS



Compared to DSS treated wildtype mice	G2019S male		G2019S female	
	15w	30w	15w	30w
Time post DSS	15w	30w	15w	30w
Open field(Moving distance Arena)	**	***	ns	ns
Open field (Moving distance Centre)	**	**	*	ns
Open field (Entries to centre)	**	***	ns	ns
Rotarod	ns	ns	ns	ns
Pole test (Latency to home)	ns	ns	*	ns
Pole test (T turn time)	0.0727	ns	ns	*
Grip strength (Fore limbs)	***	**	ns	ns
Grip strength (Hind limbs)	****	****	ns	ns



# Sex hormones and sex chromosome affect sex dimorphism of LRRK2<sup>G2019S</sup> Tg mice in intestinal inflammation and PD symptoms



## Gut inflammation

- **Genotype-dependent severity:**  
LRRK2<sup>G2019S</sup> Tg mice show reduced resistance
- **Sex-dependent severity:**  
Female, but not male LRRK2<sup>G2019S</sup> Tg mice show exacerbated body weight loss and inflammation
  - Negative effects by ovarian hormones
  - Protective effects by sexual chromosome