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Characterization of the effects of a SOCS2 point mutation on mammary gland development and function

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Introduction

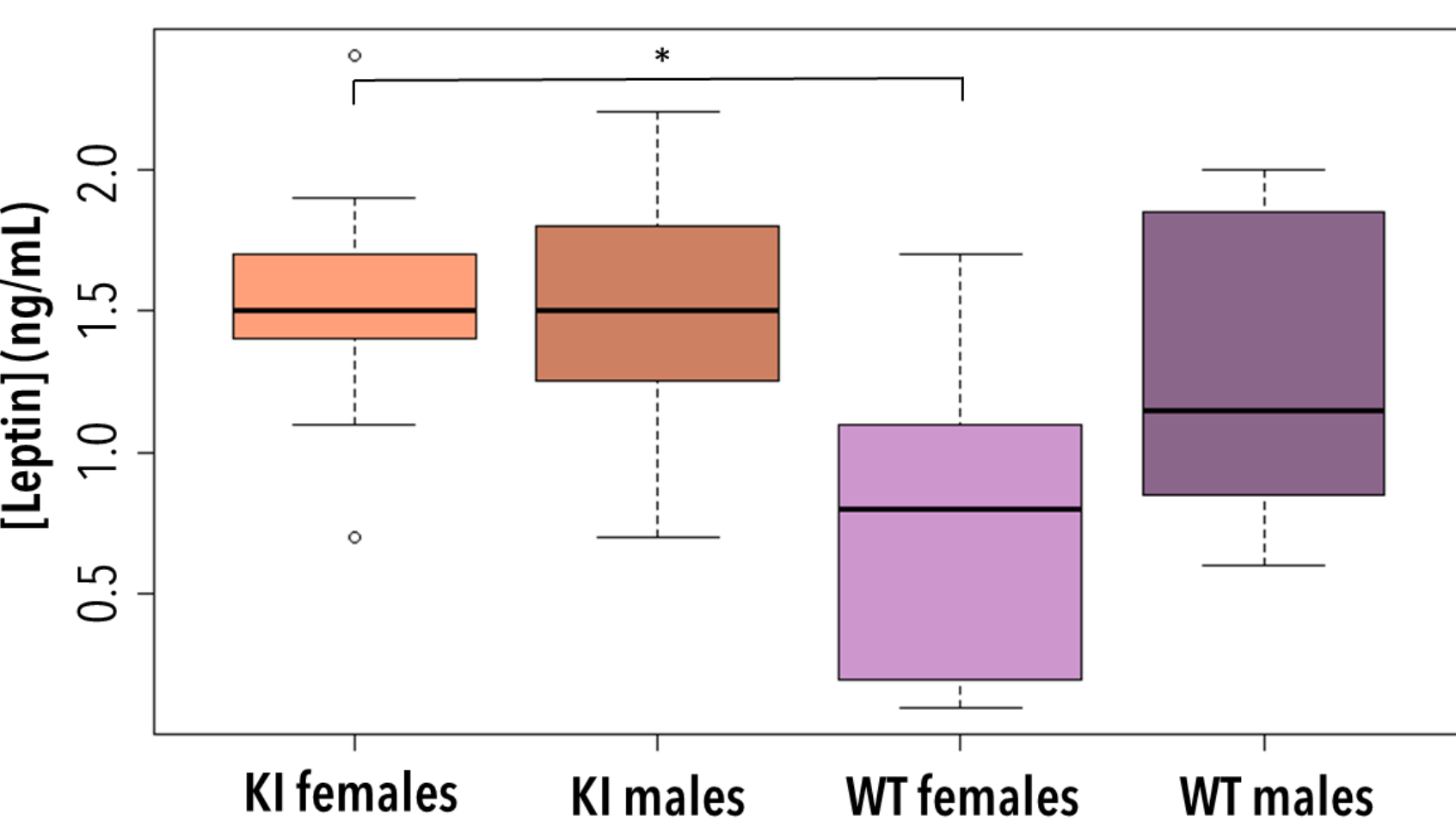
Mastitis is among the main reasons women cease breastfeeding, which leads to them supplementing breast milk with artificial formula. In farm animals, mastitis results in significant economic losses and the premature culling of some animals. Any factor that could regulate sensitivity to mastitis warrants further study. In 2015, Rupp et al reported a point mutation (R96C) in the SH2 domain of SOCS2 (suppressor of cytokine signaling 2) that leads to a loss of ligand recognition. Twenty-one percent of the Lacaune sheep studied were carriers of the mutation. Their size, weight, and milk production were significantly increased compared to controls; however, so was their sensitivity to mastitis. These findings suggest that SOCS2 is a potential regulator of mammary gland function and, thus, of milk production.

Methods

Proof of concept: **mouse knock-in** model, carrier of the R96C SOCS2 mutation

- Blood serum samples** from adult (12-15 weeks) male and female mice
- Mammary gland samples** from virgin (8-week old) mice, 18th day of pregnancy, and 7th day of lactation
- **Metabolic assay** (leptin)
- **Structural characterization** (WM, H&E, and TEM imaging)
- **Gene expression** via microarray (Agilent)

Leptin resistance in female KI mice

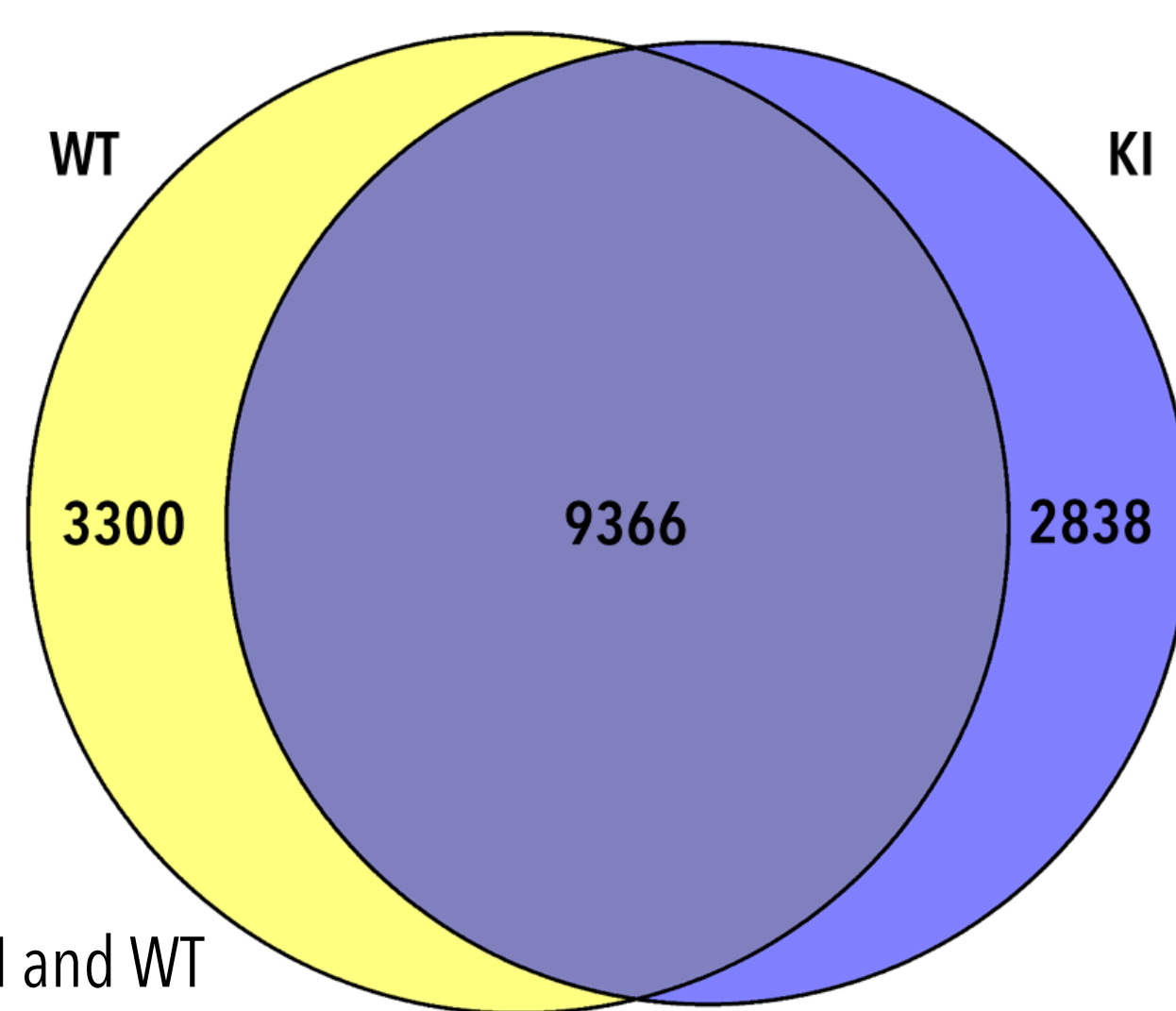


Female KI mice have twice as much leptin as WT females.

Leptin (ng/mL) assay of blood serum from adult mice (n=10 per condition)

Differences in virgin to pregnancy gene expression dynamic (KI versus WT)

15 504 differentially expressed genes in the mammary gland between **virgin** and **pregnant** mice → **only 9 366 shared** between **KI** and **WT**. Enrichment analysis shows **KI specific genes** indicating **mitochondrial dysfunction**.

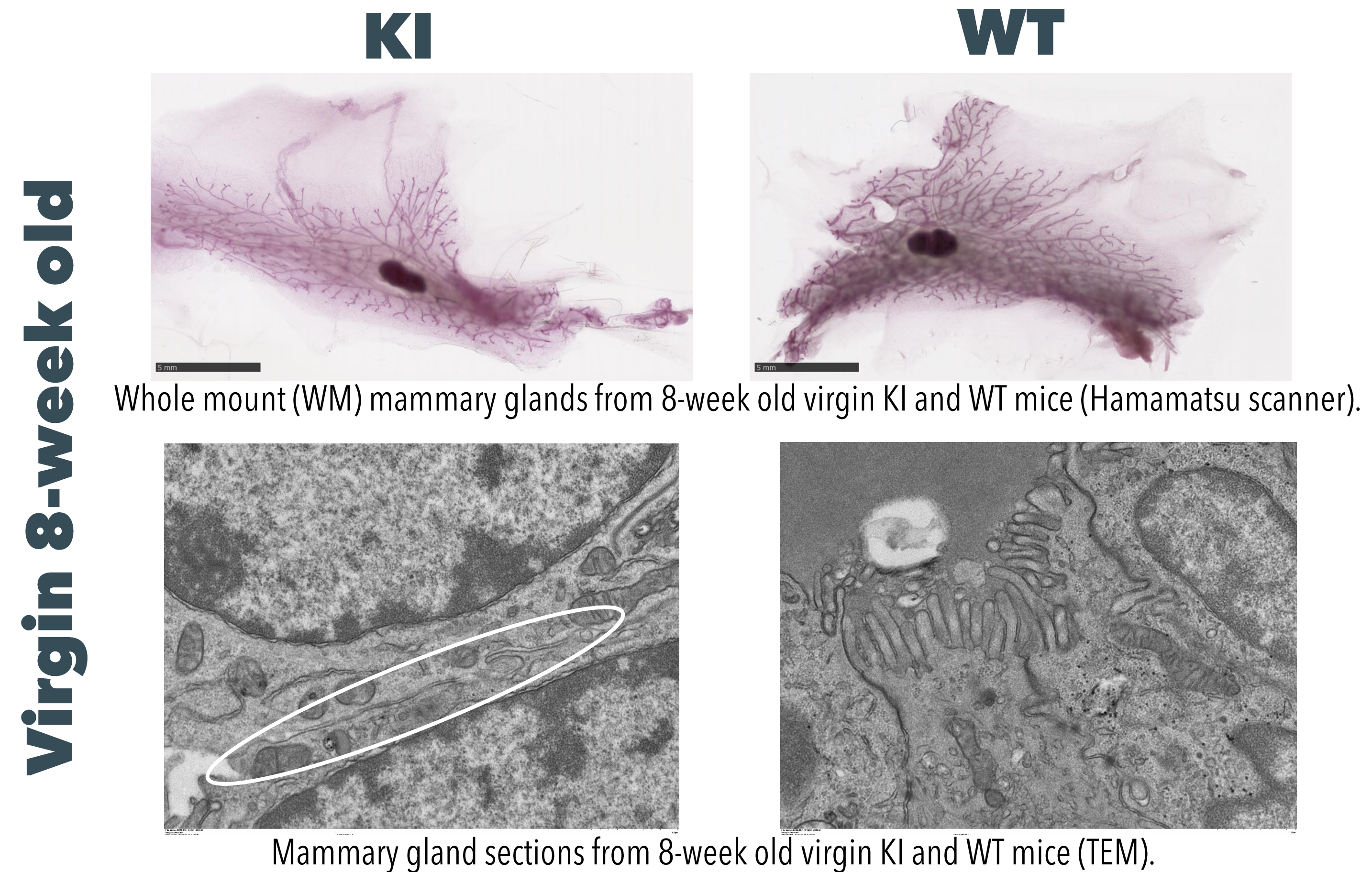


Shared and specific differentially expressed genes in KI and WT mammary glands (n=7 virgin mice, n=5 pregnant mice per condition)

Conclusion

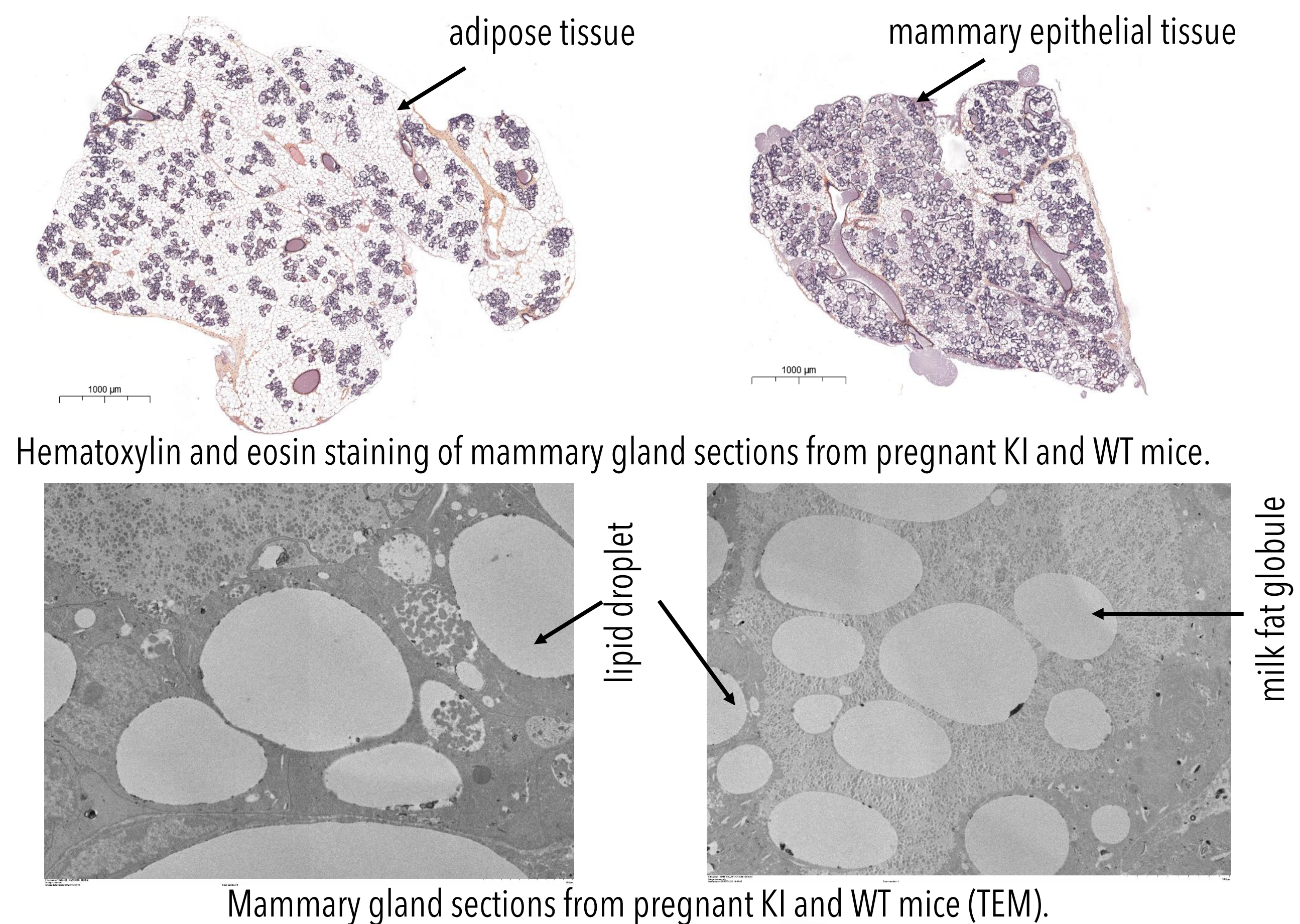
We found that the R96C mutation of SOCS2 causes **leptin resistance** in female mice. It affects mammary gland development as it **reduces ductal branching** in virgin glands and leads to **less mammary epithelial tissue development** in pregnancy and lactation. It influences **lipid droplet production** and **lowers milk fat globule secretion**. Furthermore, KI mice have a **different gene expression dynamic** (virgin to pregnant mice) compared to WT. Thus, SOCS2 is a **pleiotropic factor** essential in **mammary gland development and function**.

Structural characterization of the KI phenotype



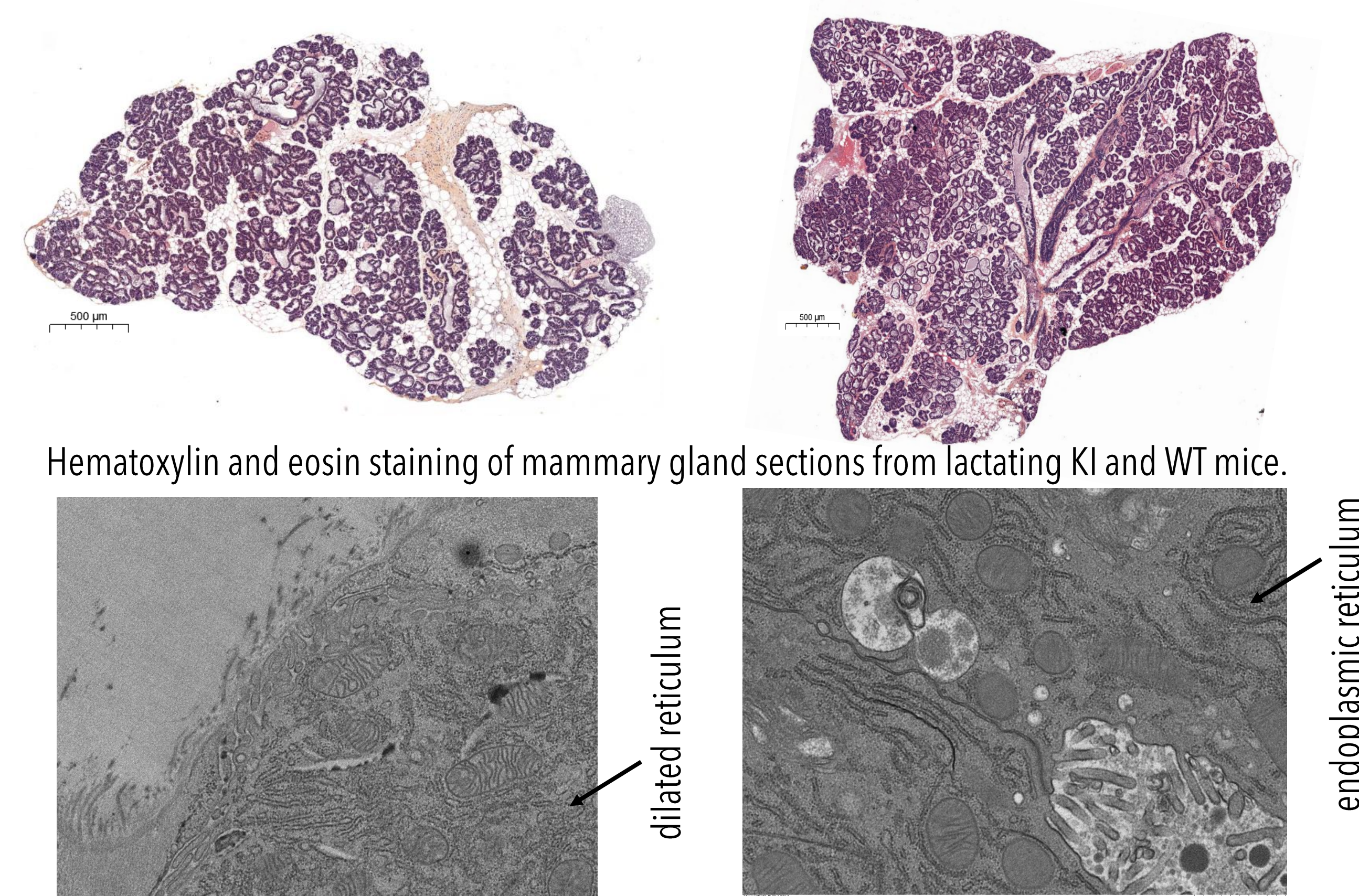
Mammary glands from **virgin KI mice** have **deficient branching of the ductal network** compared to WT. TEM shows **aberrant plasma membranes** in KI mice.

Pregnancy Day 18



Mammary gland sections from pregnant KI and WT mice (TEM).

Lactation Day 7



Mammary gland sections from lactating KI and WT mice (TEM).

Mammary glands from **pregnant and lactating KI mice** have a **higher ratio of adipose to mammary tissue** compared to WT. TEM shows **lipid droplet retention** in **pregnant KI mice** and **dilated endoplasmic reticulum** in **lactating KI mice**.