Human *INHBB* Gene Variant (C.1079T>C:P.Met360Thr) Is Disruptive for Pregnancy and Labouring in Female Mice

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Ovarian-derived inhibin A and inhibin B (α/β dimers) suppress follicle-stimulating hormone (FSH) production at the pituitary by blunting receptor activation by the activins (β/β dimers). This hypothalamic-pituitary-gonadal (HPG) loop is integral to reproductive function, and consequently, imbalances in inhibin/activin can negatively impact fertility. In a recent study, human *INHBB* gene variant (c.1079T>C:p.Met360Thr), identified in an infertile man, was shown to significantly reduce serum activin B levels and alter testis germ cell content in corresponding $Inhbb^{M364T/M364T}$ male mice. Here, we aimed to determine if the identified *INHBB* gene variation also altered female reproductive function. To address this, we examined ovarian and uterine function in $Inhbb^{M364T/M364T}$ adult female mice and $Inhbb^{WT/WT}$ littermate controls. As observed in the $Inhbb^{M364T/M364T}$ male mice, female $Inhbb^{M364T/M364T}$ mice tended to have reduced (p=0.62) circulating levels of activin B as well as significantly reduced (p<0.01) activin A levels relative to $Inhbb^{WT/WT}$ littermates. Despite the reduction in serum activins, serum FSH levels

and ovulation rates were comparable between *Inhbb*$^{M364T/M364T}$ and *Inhbb*$^{WT/WT}$. However, pregnant *Inhbb*$^{M364T/M364T}$ dams were found to carry significantly more (p<0.01) and significantly smaller (p<0.01) foetuses to late gestation (17.5 days post coitus) relative to *Inhbb*$^{WT/WT}$ pregnant controls. Furthermore, *Inhbb*$^{M364T/M364T}$ females were found to experience dystocia, with significantly extended gestation periods (p<0.05) and labour (p<0.01) relative to *Inhbb*$^{WT/WT}$ pregnant controls. In these female mice, dystocia is attributed to weakened uterine contractility. Our findings support that the inhibin βB-subunit is essential for maintenance of pregnancy and normal labouring in females.