（課程博士・様式７）（Doctoral qualification by coursework, Form 7）

学 位 論 文 要 旨

Abstract of Doctoral Thesis

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論文題目：
Title of Thesis：

The *MC4R* gene is responsible for the development of ovarian teratomas

論文要旨：
Abstract：

Teratomas in mice, composed of different tissue types, are derived from primordial germ cells (PGCs) in the fetal gonads. The strongest candidate gene in the teratoma locus (*Ter*) responsible for testicular teratoma formation was identified as *Dnd1*. However, the phenotype of mice with a mutated *Dnd1* gene was germ cell loss. Thus, it was suggested that other genes are involved in teratoma formation. Testicular teratomas can also be induced experimentally (experimentally testicular teratomas: ETTs) in 129/Sv mice by transplanting E12.5 fetal testes into adult testes. Previously, we mapped the *ett1* locus, which is the locus responsible for ETT formation on chromosome 18. We established the LT-*ett1* congenic strain, which introduced the locus responsible for ETT formation genetically into the genomes of a testicular teratoma non-susceptible strain. In this study, we crossed LT-*ett1* and a previously established LT-*Ter* strain to establish the double congenic strain LT-*Ter*/*ett1*. Separately, we conducted exome sequence analysis of the 129 and LT strains to identify the genes responsible for ETT formation, and we identified a missense mutation in the *MC4R* gene among 8 genes in the *ett1* region. Thus, this gene is most likely a candidate for ETT formation. In this study, we tried to establish a strain with a point mutation in the *MC4R* gene of the LT strain by genome editing. After establishing the knock-in strain LT-$MC4R^{G25S}$, we

also attempted to establish the double genetically modified strain LT-*Ter/MC4R*^{G25S} to address the relation between *Ter* and *MC4R*. Surprisingly, highly developed ovarian teratomas (OTs), instead of testicular teratomas, appeared not only in the LT-*Ter/MC4R*^{G25S} and LT-*MC4R*^{G25S} strains but also in the LT-*ett1* and LT-*Ter*/*ett1* strains. The incidence of OT formation was high in double genetically modified strains. The results demonstrated that *MC4R* is one of the genes responsible for OT formation. It was suggested that the effect of the missense mutation in *MC4R* on teratoma formation was promoted by abnormal germ cell formation by the mutation in *DND1*.

During the study alongside the OTs we also observed other organs as we found some abnormalities in kidney and spleen in LT-*Ter*/*MC4R*^{G25S} double mutant mice. This study is under investigation to find whether there is any relation with the *MC4R* or not.