# 公益財団法人 セコム科学技術振興財団
# 研究成果報告書

研究課題名

ゲノム変動に対する経世代交代による生存適応の機構解析

Analyses on adaptive response of animals to genomic fluctuation through generational transition

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## Abstract

Generally, inheritable diseases are derived from genetic fluctuations, so called mutations. However, their penetrations for symptoms are variable and not following Mendelian rules, thus, usually not 100%. This could be matter for variation of penetrance of phenotype or for inheritance distortion of chromosomal transmission to next generations.

Among many mouse lines we created, there are a few lines showing 1) complementation against phenotype from genetic disorder, 2) unequal inheritance of autosome among sex. We decided to study these mice to learn novel mechanisms for manifestations of diseases to find the way to prevent. In addition, we expect to study mechanisms for evolutional adaptation by analyzing these mice.

1) Fluctuation in phenotypic manifestation

In mammalian genome, there are plenty of stretch of sequence called CGI, especially within promoters of developmental genes. They are bound and regulated by Polycomb chromatin factors. These CGI's, including promoters, assemble via polymerization of Polycomb complexes. It is yet known whether these assembly are required for gene regulation by Polycomb, we, therefore decided to delete one of CGI's at the terminal region of Meis2 gene to clarify its function on gene regulation. Although the sequence called RBS is required for repression of Meis2 promoter, there are some survivors existed. This result indicated that there is (or are) mechanism(s) to escape lethality from RBS deletion and the way to adapt the genetic fluctuation. We discovered the Meis2 promoter of adapted derivatives found the novel association sites which may contribute to compensation for transcriptional regulation. We are under detailed analyses for this novel chromosomal architecture and its function for adaptive response.

2) Distortion of chromosomal transmission across generation

In principle, all the chromosomes transmit with equal chance to descendants under Mendelian rules. However, we found one of mutant allele we created at the Meis2 transcriptional regulatory sequence exhibited unequal transmission of mutated chromosome with sex. When the mutated chromosome derived from male parents, it transmits almost only to male descendants. We already found that the distortion of chromosomal transmission is not derived from lethality of animals with specific combination of chromosomes. We also found that the distortion was resulted from the process of spermatogenesis. Detailed analyses on the spermatogenetic organs and cells revealed that the 2$^{nd}$ chromosomal region containing Meis2 associates with some region of X chromosome at specific step of meiotic division even in wild type testes. We are currently analyzing whether this association is the cause of unequal transmission of chromosome.