# 学 位 論 文 の 要 旨

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学 位 論 文 名　Exploring the Genetic and Clinical Landscape of Dedifferentiated Endometrioid Carcinoma

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## 論 文 内 容 の 要 旨

### INTRODUCTION

Dedifferentiated endometrioid carcinoma (DDEC) is a rare and highly aggressive subtype of endometrial carcinoma characterized by the coexistence of a well-differentiated endometrioid component and an undifferentiated carcinoma component. Although DDEC has been increasingly recognized as a distinct pathological entity, its clinicopathological characteristics remain insufficiently understood, particularly in Asian populations. Moreover, the genetic mechanisms underlying the dedifferentiation process have not been fully elucidated, and effective treatment strategies are yet to be established. Previous studies have suggested frequent mismatch repair deficiency and occasional SWI/SNF complex abnormalities; however, the prevalence of TP53 mutations and the significance of molecular differences between the two components have not been clarified.

This study aimed to characterize the clinicopathological and molecular features of DDEC in Japanese patients and explore potential therapeutic approaches by performing detailed immunohistochemical and genomic analyses.

### MATERIALS AND METHODS

We retrospectively identified 18 cases of DDEC diagnosed at our institution and reviewed their clinical information, pathological findings, and treatment outcomes. The incidence of DDEC among all endometrial carcinomas was calculated. For each case, tumor samples were

manually dissected into well-differentiated and undifferentiated components. Immunohistochemical analyses included mismatch repair proteins (MLH1, PMS2, MSH2, MSH6), p53, and markers useful for confirming loss of differentiation. Whole-exome sequencing (WES) was performed on paired components from three representative cases to investigate differences in mutational profiles, mutational signatures, and potential driver events involved in dedifferentiation. Ethical approval was obtained from the Research Ethics Committee of Shimane University.

## RESULTS AND DISCUSSION

DDEC accounted for 2.0% of endometrial carcinomas in our cohort. Patients showed poor outcomes, with 5-year progression-free survival and overall survival rates of approximately 40% and 30%, respectively. Immunohistochemistry demonstrated mismatch repair deficiency (dMMR) in 66.7% of cases, supporting the notion that DDEC frequently arises within the context of the MMR-deficient molecular subtype. Notably, TP53 mutations were more common than previously reported, and the presence of TP53 mutations specifically in the undifferentiated component correlated with markedly worse prognosis, suggesting a possible role for TP53 alterations in tumor aggressiveness and dedifferentiation.

WES revealed distinct genomic landscapes between the well-differentiated and undifferentiated components in all three analyzed cases. While no novel or recurrent gene mutation shared across all undifferentiated components was identified, differences in mutation signatures suggested that dedifferentiation involves complex, heterogeneous molecular events rather than a single driver alteration. Of the three cases, one showed homologous recombination deficiency (HRD), whereas the remaining two exhibited MSI-High and hypermutator phenotypes, consistent with their dMMR status.

Our findings confirm that DDEC is associated with poor clinical outcomes and frequently exhibits dMMR, TP53 abnormalities, or HRD/MSI-High molecular phenotypes. The higher-than-expected prevalence of TP53 mutations in undifferentiated components highlights a potential prognostic biomarker. The absence of common new mutations in undifferentiated areas across cases suggests that dedifferentiation may not result from a uniform genetic event but rather from tumor-specific evolutionary trajectories. These molecular characteristics have direct therapeutic implications. dMMR or MSI-High cases may benefit from immune checkpoint inhibitors, whereas tumors with HRD may be responsive to PARP inhibitors. Furthermore, TP53-mutated tumors may be candidates for emerging therapies targeting aberrant p53 pathways.

This study is limited by its retrospective design, small sample size, and the inclusion of only three WES-analyzed cases. Multicenter studies with larger cohorts are needed to further

clarify the mechanisms of dedifferentiation and optimize treatment approaches.

## CONCLUSION

Comprehensive clinicopathological and genomic analyses of Japanese DDEC cases revealed frequent dMMR, TP53 mutations, and heterogeneous mutational processes underlying dedifferentiation. These findings suggest that personalized treatment strategies incorporating immune checkpoint inhibitors, PARP inhibitors, and p53-targeted therapies may improve outcomes for patients with DDEC. Further studies involving larger cohorts are warranted to validate these results and deepen understanding of dedifferentiation mechanisms.