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論 文 内 容 の 要 旨
Synopsis of Thesis

氏　名 Name	増田　達郎
論文題名 Title	GWAS of five gynecologic diseases and cross-trait analysis in Japanese （日本人集団における婦人科５疾患の横断的ゲノム研究）

論文内容の要旨

〔目　的(Purpose)〕

Uterine fibroma (UF), endometriosis, ovarian cancer (OC), uterine endometrial cancer (UEC), and uterine cervical cancer (UCC) are all common proliferative diseases arising from gynecologic organs. They are heterogeneous diseases with diverse range of proliferative and infiltrative properties. Clinical and epidemiological studies suggest that these diseases are mutually associated or often occur as comorbidity. Studies of shared background risk, namely genetics, would offer understanding of the causes of these diseases, along with identifying targets to be treated.

To increase our understanding of shared genetic determinants influencing gynecologic diseases, we report genetic correlations among the five gynecologic diseases in Japanese population using the linear mixed model approach.

〔方法ならびに成績(Methods/Results)〕

We performed genome-wide association studies of five gynecologic diseases using data of 46,837 subjects (5,236 uterine fibroid, 645 endometriosis, 647 ovarian cancer (OC), 909 uterine endometrial cancer (UEC), and 538 uterine cervical cancer (UCC) cases allowing overlaps, and 39,556 shared female controls) from Biobank Japan Project. We used the population-specific imputation reference panel (n = 3,541), yielding 7,645,193 imputed variants. Analyses performed under logistic model, linear mixed model, and model incorporating correlations identified nine significant associations with three gynecologic diseases including four novel findings (rs79219469:C > T, *LINC02183*, $P = 3.3 \times 10^{-8}$ and rs567534295:C > T, *BRCA1*, $P = 3.1 \times 10^{-8}$ with OC, rs150806792:C > T, *INS-IGF2*, $P = 4.9 \times 10^{-8}$ and rs140991990:A > G, *SOX9*, $P = 3.3 \times 10^{-8}$ with UCC). Random-effect meta-analysis of the five GWASs correcting for the overlapping subjects suggested one novel shared risk locus (rs937380553:A > G, *LOC730100*, $P = 2.0 \times 10^{-8}$). Reverse regression analysis identified three additional novel associations (rs73494486:C > T, *GABBR2*, $P = 4.8 \times 10^{-8}$, rs145152209:A > G, *SH3GL3/BNC1*, $P = 3.3 \times 10^{-8}$, and rs147427629:G > A, *LOC107985484*, $P = 3.8 \times 10^{-8}$). Estimated heritability ranged from 0.026 for OC to 0.220 for endometriosis. Genetic correlations were relatively strong between OC and UEC, endometriosis and OC, and uterine fibroid and OC ($r_g > 0.79$) compared with relatively weak correlations between UCC and the other four ($r_g = -0.08$ ~ 0.25).

〔総　括(Conclusion)〕

We successfully identified genetic associations with gynecologic diseases in the Japanese population. Shared genetic effects among multiple related diseases may help understanding the pathophysiology.

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論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

婦人科５疾患（子宮筋腫、子宮内膜症、卵巣癌、子宮体癌、子宮頸癌）について、遺伝学的な研究はほとんどが欧米次人集団での結果であり、日本人集団における遺伝的要因を検討した研究は限られている。本論文では大規模日本人集団を対象に、複数の手法を用いてゲノムワイドに関連解析を行い、新規の関連領域や、日本人特異的な関連 SNP を同定した。また、複数婦人科疾患で共有される遺伝的要因を示した。さらに、複数婦人科疾患間のゲノムワイドな遺伝的相関について線形混合モデルで検討し、臨床的・疫学的に観測される、子宮内膜症と卵巣癌とは合併が多い、子宮頸癌と他の4疾患とでは病態・病因が異なる、といった現象をゲノム情報のみを用いて再現した。臨床的・疫学的に観測される関連性は遺伝学的な要因が大まかに規定していることが示され、病態学的理解を深める一助となった。今後の日本人特異的なゲノム医療に必要な背景データを構築した研究論文で、学位に値するものと認める。