00483 Assessment of PARP4 as a Candidate Breast Cancer Susceptibility Gene

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Aims: The PARP4 gene has been proposed in numerous studies as a candidate cancer susceptibility gene, including in breast cancer. However, the function of PARP4 and its involvement in cancer is largely not understood. The aims of this study were to determine the mutation frequency of PARP4 in BRCA-negative breast and/or ovarian cancer patients from Singapore and to perform functional analyses to decipher the role of PARP4 in cellular transformation.

Methodology: Next-generation sequencing was used to screen for mutations in the exonic regions of the PARP4 gene from 199 patients. Fisher's exact tests were used for association studies of PARP4 rare variants in cancer cases from our Singaporean cohort (n = 199) analysed against healthy controls from the Exome Aggregation Consortium (ExAC). PARP4 CRISPR-Cas9 knockout of MDA-MB-231 (breast cancer) and MCF10A (normal breast) cells were generated and in vitro assays were performed to elucidate the effect of loss of PARP4 in these cells.

Result: Eight deleterious missense mutations were identified in 11 of 199 (5.5%) Singapore patients. Case-control association studies for cases from our Singapore patient cohort showed no significant association. PARP4 knockout did not affect the clonogenicity, proliferation, and migration of normal breast cells, however, it appeared to slow down the growth rate of breast cancer cells.

Conclusion: Our results do not provide strong support for PARP4 as a cancer susceptibility gene. The loss of PARP4 by itself may be insufficient to drive carcinogenesis, but it might be involved in fully transformed cells. This study highlights the importance of performing functional analyses for candidate cancer predisposition genes.