00102 Pathogenic Germline Variants in an Asian Cohort With Young Onset Colorectal Cancer

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Aims: Majority of young onset colorectal cancers develop sporadically. Thirty percent arise from germline mutations, of which one-third involves known colorectal cancer predisposition genes. The rest remain unclear. Growing evidence suggests a role for cancer susceptibility genes such as BRCA2 and PALB2 in young-onset colorectal cancers. We sought to identify the associated pathogenic variants and explore the functional consequences of BRCA2, PALB2 variants.

Methodology: We recruited 88 patients with young-onset colorectal cancers seen at a general oncology centre. Variants in 43 DNA repair and 21 colorectal cancer predisposition genes were curated using American College of Medical Genetics and Genomicsguidelines. Pathogenic variants of BRCA2 and PALB2 were analyzed using immunoblot and immunofluorescence on patient-derived lymphoblastoid cells.

Result: In general, our cohort displayed the characteristic features of young-onset colorectal cancers. Average age of diagnosis was 41 years, with both genders represented equally. The majority of patients had left-sided tumors and were diagnosed at late stages.Most patients (54.2%) did not have any first-degree relative with cancer. Four patients had familial adenomatous polyposis and all had pathogenic APC variants. Targeted exome sequencing identified 12 pathogenic variants evenly distributed between the traditional colorectal cancer and DNA repair genes. Six patients had pathogenic variants in colorectal cancer predisposition genes: APC (n=4) and monoallelic MUTYH (n=2). Another 6 had pathogenic variants in DNA repair genes:ATM (n=1), BRCA2 (n=1), PALB2 (n=1), NTHL1 (n=1) and WRN (n=2). Pathogenic variants BRCA2 c.9154C>T and PALB2 c.1059delA showed deficient homologous recombination repair, evident from the impaired RAD51 nuclear localization and foci formation.

Conclusion: Complementing previous Caucasian studies, we found half of all pathogenic variants in homologous recombination genes. Impaired homologous recombination predisposes patients to highly damaging DNA breaks, potentially contributing to tumorigenesis. Large population-based studies are needed to ascertain the enrichment of BRCA2, PALB2 pathogenic variants in colorectal cancers.