PATHOGENIC GERMLINE VARIANTS IN VERY EARLY ONSET COLORECTAL CANCER PATIENTS IN KAZAKHSTAN

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Background: The incidence of colorectal cancer (CRC) in young individuals has been increasing over the past 20 years. In Kazakhstan, CRC incidence in young patients has risen by approximately 2.3% annually. Among early-onset (EO) CRC cases, about 30% of patients carry germline mutations associated with hereditary cancer predisposition syndromes, while 20% have familial CRC. In Kazakhstan, only a few NGS-based studies have been published, focusing on the frequency and spectrum of pathogenic variants (PVs) in young patients.

Objective: To investigate the spectrum and prevalence of PVs in EO-CRC patients.

Materials and Methods: In this study, we performed gene-panel NGS analysis on germline DNA of 94 established/candidate cancer predisposing genes in 66 individuals with sporadic and familial EO-CRC (<45 years).

Results: PVs were identified in 25.7% of patients, affecting the following genes: *CHEK2, APC, BRCA1, MSH2, PMS1, TP53, EPCAM, NSD1, PMS2,* and *NBN*. The PVs were represented by missense (29.4%), frameshift (29.4%), nonsense (23.5%), and splice-site (17.6%) variants. Three novel PVs were detected in *PMS1, NBN*, and *EPCAM*. The median age at diagnosis was 36.8 years. A positive family history of CRC or other cancers was reported in 33.3% of cases. In our cohort, PVs were distributed among three gene groups: MMR genes (29.4%, 5/17), genes associated with polyposis syndromes (11.8%, 2/17), and genes not typically associated with CRC (58.8%, 10/17). Two *CHEK2* variants—missense c.470T>C and frameshift c.1100delC—were recurrent. Notably, PVs in young patients were predominantly identified in those without a family history of cancer.

Conclusions: Sporadic cancer cases at a young age are highly suggestive of an underlying genetic predisposition. Although novel cancer genes are associated with CRC in only a small percentage of cases, pathogenic variants in these genes should nevertheless be included in NGS- based CRC panels.

Key words: colorectal cancer, young patients, pathogenic variants, NGS.