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PREVENTION, RISK REDUCTION, AND HEREDITARY CANCER

Variants of unknown significance (VUS) in patients with hereditary CRC without a known pathogenic variant.

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Background: Nearly 5-10% of all newly diagnosed colorectal cancer (CRC) cases develop due to the presence of a highly penetrant pathogenic variant in one of the hereditary colorectal cancer (hCRC) associated genes. NGS technology raised the opportunity for fast and efficient detection of these variants, but still in~20-30% of patients with hCRC the genetic defect remains unknown. Recent data shows that 6-8% of these cases harbor pathogenic/VUS variant in low/moderate penetrance genes not directly associated with hCRC. **Methods:** A total of 109 patients with hCRC (43 with polyposis and 66 with non-polyposis syndromes) were analyzed by NGS covering coding and exon/intron sequences of 109 genes, of which 25 associated with known hCRC syndromes and 83 other cancer predisposition genes. **Results:** Pathogenic variants were detected in 63/109 (57.7%) of analyzed patients; 54/63 (85.7%) of these had a pathogenic variant in one of the genes associated with hCRC (APC, MMR genes, MUTYH, NTHL1, BMPR1A) and 9/63 (14.3%) had a pathogenic variant detected in genes not directly related to hCRC (CHEK2, FANCL, FANCM, ERCC2, BRIP1, FLCN, BLM). In 26/109 (23.8%) patients a rare VUS variant was detected, of which 14/26 (53.8%) in double strand repair (DRG) genes (BLM, CHEK2, PALB2, ATM, MRE11A, BRIP1, FANCM, FANCL and ERCC2), 8/26 (30.8%) in one of the known hCRC genes (APC, MSH6, PMS2 and POLE) and 4/26 (15.4%) in other cancer predisposition genes (KIT, NSD1, CDH1, EZH1 and FH). VUS variants in DRG genes were more common in patients with MSI- HNPCC (9/15, 60%), compared to

patients with polyposis syndromes (6/15, 40%). The VUS variants in other cancer predisposition genes were dominantly present in patients with oligopolyposis. Most (21/26, 80.8%) VUS variants were detected as single variants, while only five patients (5/26, 19.2%) had two different variants in two different genes. In 20/109 (18.3%) patients who presented primarily with MSI- HNPCC or oligopolyposis phenotypes, no pathogenic and/or VUS variants were detected in the 109 analyzed genes. **Conclusions:** Genetic basis of hereditary CRC was not clearly defined in a large proportion (42.3%) of patients in our cohort. Although a VUS variant was detected in a significant portion (23.8%), a major fraction (18.3%) of patients had no known genetic variant detected. The presence of a high frequency of VUS variants in DRG genes indicates that this pathway plays an important role in CRC carcinogenesis. Although we cannot exclude the presence of deep intronic and/or regulatory region pathogenic variants in the analyzed genes, it appears that the current list of identified cancer predisposition genes responsible for the hereditary CRC is far from being complete. The influence of environmental factors in conjunction with polygenic inheritance might also play a key role in a fraction of hCRC in our population.

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