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CANCERS OF THE COLON, RECTUM, AND ANUS

DNA damage response pathway mutations contribute to a high proportion of hereditary colorectal cancer in patients from the Republic of Macedonia.

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Abstract Disclosures

Abstract

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Background: Hereditary factors are assumed to play a role in 35-45% of all colorectal cancers with 5%-10% associated with high penetrant disease-causing mutations in genes correlating to hereditary polyposis (HP) or hereditary nonpolyposis syndromes (HNPCC). Although inherited germline mismatch repair and *APC* gene mutations contribute significantly to CRC, still a genetic diagnosis cannot be obtained in > 50% of familial cases. **Methods:** We performed a targeted NGS sequencing of 103 probands with clinically diagnosed HP (39) or HNPCC (64) using a multigene panel on two different platforms (Illumina Cancer Panel and Ion Torrent custom

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panel) covering coding and exon/intron sequences of 100 genes implicated in hereditary cancers. **Results:** Overall, the molecular defect was identified in 60 (58%) index patients. As expected, a large percentage (82%) of these patients exhibited the presence of clearly pathogenic mutations in well-known genes associated with hCRC (APC, MUTYH, BMPR1A, NTHL1 in HP, MLH1, MSH2, PMS6, MSH6 in HNPCC). Surprisingly, all except one (FLCN c.1285dupC, detected in a family with classical FAP), of the remaining mutations were located in genes involved in the DNA damage response pathway, of which 3 in CHEK2 (c.1031delT; c.1229delC; c.599T>G), 2 in BRIP1 (c.2392C>T) and 1 in each of BLM (c.1642C>T), BRCA2 (c.4446_4451dupAACAGA), FANCM (c.2953delG), FH (c.1431_1433dupAAA) and ERCC2 (c.1403C>T). Clinically, six of these cases exhibited the HNPCC type X phenotype (mutations in BRCA2, BRIP1, FANCM and CHEK2) while the other four were classified as oligopolyposis (mutations in BLM, FH and CHEK2). **Conclusions:** Our data indicate a significant association of DNA damage response pathway deficiencies and carcinogenesis in patients with hCRC syndromes exhibiting either the HNPCC type X or oligopolyposis phenotype. No genetic defect was detected within the analyzed gene panel in 44 (42%) families, indicating the need of extended exome/whole genome analyses in a substantial portion of patients with this disease.

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