

Germline variants in cancer patients with personal and family history of colorectal cancer: an update

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Multiple primary cancers in a single individual, as well as family history of the same cancer, are features of hereditary cancer. About 15% of colorectal cancer (CRC) patients have first-degree relatives affected by the same malignancy. However, for most families the cause of familial aggregation of CRC is unknown. To identify novel high-to-moderate-penetrance germline variants underlying CRC susceptibility, we performed whole exome sequencing (WES) in germline DNA of Polish CRC patients with personal and family history of colorectal cancer. After WES, we used *in silico* tools followed by protein-protein interaction and functional enrichment analysis to identify most likely rare pathogenic variants predisposing to CRC. In 9 patients sequenced we identified altogether 150 missense, 19 stop_gain, 22 frameshift and 13 canonical splice site variants fulfilling our filtering criteria. The protein-protein interaction analysis of the corresponding genes identified 5 clusters of proteins with enrichment of proteins related to DNA repair, cell cycle, focal adhesion, extracellular matrix interactions and TGF β signaling pathway. Our findings contribute to the identification of novel genes and pathways as genetic causes of familial CRC.