

Genetic predisposition to colorectal cancer: Identification of novel cancer susceptibility genes

Asta Försti

Hopp Children's Cancer Center (KiTZ), Heidelberg, Germany; Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Heidelberg, Germany

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 (WES) and whole genome sequencing (WGS) in Polish CRC families showing a Mendelian inheritance pattern. After WES or GWS, we used our in-house developed Familial Cancer Variant Prioritization Pipeline to identify novel cancer predisposition variants. We identified both nonsense, missense and 5'UTR variants involved in the regulation of innate immune response (*SLC15A4*), apoptosis and AKT pathway (*PTK7*), reactive oxygen species and mucus biology (*CYBA*, *TRPM4*), Wnt signaling (*APCDD1*) and histone modification (*HDAC5*) and in a protooncogene (*SRC*). Some of the identified variants may show their effect according to a synergistic or polygenic model. Our findings contribute to the identification of unrecognized genetic causes of familial CRC.