Uncovering the spectrum of inherited risk in colorectal cancer: A scoping review of low- and moderate-penetrant germline variants

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It is well known that inherited colorectal cancer (CRC) risk is linked to high-penetrant germline variants in cancer-predisposing genes. However, recent studies highlight the significance of low- and moderate-penetrant genetic variants as well. This scoping review summarizes the current evidence on such variants, with a focus on their distribution, clinical correlation, and prevalence in different populations. A comprehensive search was conducted across PubMed, Scopus, Web of Science, and Google Scholar to identify studies published in English from January 2010 to April 2025. Eligible studies documented low- to moderate-penetrant germline variants linked to CRC, supported by either statistical associations or functional evidence. Out of 697 studies screened, 171 met the inclusion criteria, reporting 422 unique variants across 282 genes. The most frequently reported genes included MUTYH (5.7%, OR 1.1–2.8), CHEK2 (5.7%, OR 1.5–2.0), SMAD7 (5.7%, OR 1.2), ATM (3.9%, OR 1.6), BMP4 (3.9%, OR 1.1–1.2), BMP2 (3.6%, OR 1.1–1.2), TP53 (3.6%, OR 1.2–1.7), GALNT12 (3.2%, OR 1.8), and EIF3H (3.2%, OR 1.2-1.7), all with $p<0.05$. Key variants included CHEK2: c.1100delC (2.4%); SMAD7: rs4939827 (2.1%), BMP4: rs4444235 (2.1%), GREM1: rs4779584 (2.1%), and an enhancer variant rs6983267 near the MYC gene (2.8%). Biallelic MUTYH variants were linked to early-onset, proximal colorectal cancer and polyposis, while the ATM:rs189037 variant was associated with rectal tumors and poorly differentiated neoplasms. Other variants did not show consistent clinical patterns. The study populations were predominantly Caucasian (56.5%), with limited data from other regions. Notably, MDM2:rs2279744 (0.5%, OR 1.2-2.1) was mainly reported in Asian populations. Low- and moderate-penetrant germline genetic variants significantly contribute to inherited CRC risk. However, clinicopathological correlations remain underexplored, and population diversity is lacking. Future research should focus on increasing population representation and conducting functional validation of variants to improve risk assessment and translate findings into personalized screening and prevention strategies.

Keywords: *Colorectal cancer*, *Germline variants*, *Low-penetrant*, *Moderate-penetrant*, *Genetic susceptibility*