

P007 Elevated colorectal cancer risk associated with base excision repair defects.

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Repair processes are vital to the integrity of the genome and germline defects in repair genes can predispose to cancer. Recent evidence has suggested that germline defects in the base excision repair (BER) gene *MUTYH* are responsible for a proportion of multiple adenoma families. However it is important to show that these defects are responsible for colorectal cancer development and to evaluate what risk they may impart. Here we demonstrate in a large case-control association study that variants of *MUTYH* are associated with colorectal cancer. A total of 2239 prospectively collected population-wide colorectal cancer cases and 1845 healthy, age and sex matched population-based controls were screened for variants Y165C and G382D. Bi-allelic inactivation of *MUTYH* imparted a 93-fold excess risk (CI 42-213) with complete penetrance by age 60yrs. Screening of the coding region of *MUTYH* in heterozygous patients and in the BER genes, *OGG1* and *MTH1*, have implicated all three BER genes as susceptibility genes for colorectal cancer, acting in a complex and recessive manner. These data provide direct evidence of causative role for BER defects in colorectal cancer aetiology and have relevance for genetic testing of early-onset colorectal cancer cases and genetic counselling of relatives.