

FOCUS ON RESEARCH

ASSOCIATION OF MUTATIONS IN THE HUMAN HOMOLOG OF THE *MUTY* GENE WITH EARLY ONSET COLORECTAL CANCER

Researchers

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Aim

To determine the contribution of identified *MUTYH* gene variants to colorectal cancer (CRC) burden using a population based approach and investigate the increase in risk of cancer imparted by inheriting these gene variants.

Project Outline/Methodology

The project involved analysing of ~3400 prospectively collected cases and 3500 age and sex matched controls for 2 gene variants, MYH Y176C and G393D which are part of the the base excision repair (BER) gene *MUTYH*, and is involved in ensuring accurate copying of DNA in the cell. Any samples in which these 2 variants were detected were then further screened for other variants in *MUTYH* and other players in BER pathway, *OGG1* and *MTH1*. Statistical analyses were performed to determine if Y176C and G393D were associated with CRC, what increase in risk inheriting these variants produces and how likely defects in *MUTYH* will result in CRC.

Key Results

Overall the results demonstrated that the *MUTYH* gene is significantly associated with the CRC disease. Indeed the variant G393D was in itself associated with disease, but due to the rarity of Y176C this was not associated, although there is strong *a priori* evidence that this amino acid change affects protein function and would lead to CRC. The increase in risk of developing CRC imparted by the gene is 117 fold for patients with 2 inherited mutations of the gene and there was a significant but modest increase (1.3 fold) for carriers of one mutant copy of the gene. Investigating tumour material identified two other genes that were sensitive markers to identify mutation carriers and examining the dataset for clinical/genotype relationships demonstrated a significant association between clinical characteristics and mutation carriers.

Conclusions

Inherited BER defects greatly increase the risk of developing colorectal cancer as a recessive syndrome (inheritance of gene mutations from both

parents). There is also evidence of a modest elevated risk for single copy carriers of mutations. Good predictors of a patient carrying 2 mutant *MUTYH* alleles include the presence of multiple colonic polyps and a mutation in another identified gene, although neither is 100% sensitive.

What does this study add to the field?

This was the first and largest population based study to demonstrate a significant association of defects of *MUTYH* gene with CRC and calculate the greatly elevated risk imparted by carrying two copies of the mutant gene. The study also demonstrated the first significant association of a modest increase in risk of developing CRC carrying one mutant copy of the gene. Functional work and clinical characteristic relationships further indicate the detrimental effect of being a single copy carrier.

Implications for Practice or Policy

The results of this study have provided strong evidence that defects in *MUTYH* vastly increase an individual's risk of developing CRC. Clinical Genetic centres across Scotland are now analysing patients with multiple polyps and families with an early onset history of disease to assess the *MUTYH* status of these patients. Clinical screening of carriers of 2 *MUTYH* mutations is currently being intensified due to the likelihood of further cancer development. Genetic counselling and testing is being offered to immediate relatives of patients.

Where to next?

DNA damage due to oxidation is highly prevalent in the body especially the gut and the BER pathway is fundamental in removing this damage. To further understand susceptibility to colorectal disease, other components of BER need to be investigated. Biomarkers for detecting samples deficient in BER may help to identify patients who are at an increased risk of developing further cancers.

Further details from:

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