

P008 Influence of defective DNA mismatch repair on mutation frequency of *APC* gene.

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APC is mutated in most colorectal cancers, thought to be due to selection pressure. However, frequent mutations in cancer initiation genes may also be due to inherent sequence instability, compounded by lack of DNA repair capacity. We determined mutation frequency of *APC* in a Mismatch repair (MMR) proficient and deficient context by cloning and sequencing individual alleles from *APC* exon15. *APC* mutation frequency was compared in (MMR) deficient lymphoblastoid line (Ibl-1261), control lymphoblastoid line (Ibl-c5) and MMR defective HCT116 colon cancer line.

APC mutation frequencies of Ibl-1261 and HCT116 were 0.19 and 0.23 mutations/Kb respectively, compared to Ibl-c5 (0.58 mutations/Kb) ($\chi^2=30.78$, $p<0.0001$). Mutation frequency in a control genomic region (*TGF β 2*) was 0.17 mutations/Kb for Ibl-1261, significantly less than Ibl-c5 (0.24 mutations/Kb). This suggests that *APC* mutation frequency is reduced in MMR defective cells over control cells.

To address the situation *in vivo*, *APC* mutation frequency is being compared to *TGF β 2* in normal mucosa/tumour tissue from patients with apparently proficient MMR. Analysis of further MMR deficient tissue is also underway.

Overall the results indicate that this region of *APC* is hypermutable when MMR is intact, but that defective MMR appears associated with a lower mutation frequency. The mechanism of this novel observation is under investigation.