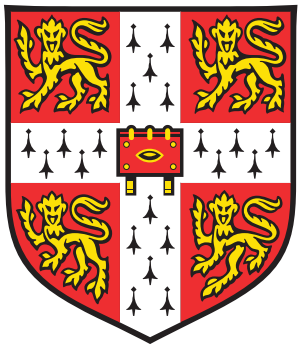
# DNA polymerase mutations as drivers of genome instability and cancer



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“Think, think, think.”
- Winnie-the-Pooh

# Declaration

I hereby declare that except where specific reference is made to the work of others, the contents of this dissertation are original and have not been submitted in whole or in part for consideration for any other degree or qualification in this, or any other University. This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration, except where specifically indicated in the text. This dissertation contains less than 60,000 words excluding appendices, bibliography, footnotes, tables and equations and has less than 150 figures.

Mareike Herzog
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# Abstract

Genomic stability is essential to preserve the genetic information encoded in DNA, and many biochemical pathways are devoted to repair DNA damaged by external factors, or during the course of essential cellular processes such as transcription and DNA replication. Malfunctioning of these processes may alter the DNA, leading to abnormal cellular behaviour or cell death, which in multicellular organisms may be associated with disease. For this reason, the machineries that safeguard the integrity of eukaryotic genomes are of prime interest to research in the areas of ageing, rare disease and cancer. Every time a cell divides, duplication of the genome is principally carried out by two DNA polymerases — Pol $\delta$ and Pol $\varepsilon$ — which are highly processive and accurate. Together with polymerase gamma, which is active in mitochondria, these are the only human polymerases known to possess "proofreading" activity, making them extremely accurate. In parallel, cells have also evolved a repair system for base mismatches, to identify and correct mispaired bases occasionally produced by DNA polymerases. While it has been known that defects in mismatch repair promote carcinogenesis, mutations in replicative DNA polymerases driving tumorigenesis in mismatch repair proficient cells have only been recently identified. Here, I report the interrogation of twelve such DNA polymerase mutations for their potential to alter genetic information and contribute to genomic instability using the budding yeast *Saccharomyces cerevisiae* as model system. Of all the polymerase mutations tested, a subset caused significant increases in mutation accrual, and a shift in the observed mutation patterns/signatures. Most intriguingly, I observed that these increases are more severe than those caused by mutations disrupting the proofreading activity of the corresponding DNA polymerase, with my results further indicating that in some cases the high mutagenic potential depends on the proofreading activity. These strong increases in mutation rates do not likely result from inhibition of mismatch repair, as combination of these mutations with loss of mismatch repair factors results in synthetic sickness or lethality. My results point to these DNA polymerase mutations as driving extensive alterations of the genetic information, and are consistent with them being drivers of colorectal and endometrial cancer. Future work will be required to determine the exact mechanisms by which these mutations impair the fidelity of DNA replication.

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