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The impact of variable recombination on human mutation load

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A major prediction in population genetics is that linked functional mutations interfere with each other's rate of loss or accumulation, thus reducing the overall efficacy of natural selection in non-recombining systems. To date, it remains unclear whether variation in crossover rate across recombining chromosomes translates in variation in the rate of adaptation along the human genome. To investigate the efficacy of selection across different recombining environments, we report genomic analyses of mutational load in 521 French-Canadian transcriptomes from the CARTaGENE project and 911 high-coverage exomes from the 1000 Genomes Project from European, Asian and African populations. In each population, we estimated the differential mutational load between high and low-recombining regions for variants with different impact on fitness. Both at the population and individual levels, variants in low-recombining regions are significantly enriched for highly constrained, low frequency missense mutations relative to variants in regions of high recombination. Using paired-end sequencing reads to unambiguously determine phased haplotypes, we observed that rare and weakly deleterious variants are preferentially linked with each other in low recombining regions, the signature of a Muller's ratchet process. We further observed that the mutational burden in regions of low recombination varies among human populations, with recently founded populations showing a larger differential mutational load at the individual level. These results together indicate that weakly deleterious variants, accumulating on degenerating haplotypes, are less efficiently removed by natural selection in regions of low recombination rate. As low-recombining regions are enriched for genes with essential cellular functions, primordial for response to DNA damage or cell cycle progression, this phenomenon likely impacts disease susceptibility at the individual level.

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