Timing, rates and spectra of human germline mutation

Germline mutations are a driving force behind genome evolution and genetic disease. We investigated genome-wide mutation rates and spectra in multi-sibling families. The mutation rate increased with paternal age in all families, but the number of additional mutations per year differed by more than twofold between families. Meta-analysis of 6,570 mutations showed that germline methylation influences mutation rates. In contrast to somatic mutations, we found remarkable consistency in germline mutation spectra between the sexes and at different paternal ages. In parental germ line, 3.8% of mutations were mosaic, resulting in 1.3% of mutations being shared by siblings. The number of these shared mutations varied significantly between families. Our data suggest that the mutation rate per cell division is higher during both early embryogenesis and differentiation of primordial germ cells but is reduced substantially during post-pubertal spermatogenesis. These findings have important consequences for the recurrence risks of disorders caused by de novo mutations.

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