Human germ line and somatic mutation rates: evolution, biology and statistical genetics

Sunyaev S.R.

Division of Genetics, Brigham & Women's Hospital and Harvard Medical School, 77 Avenue Louis Pasteur, Boston MA 02115, ssunyaev@rics.bwh.harvard.edu

Sequencing technology enabled systematic identification of *de novo* germ line mutations and somatic mutations in cancer. Mutation rate appears to be variable along the human genome. Replication timing, chromatin accessibility and negative selection maintaining hypermutable sequence contexts all contribute to the mutation rate heterogeneity. Mutation density in cancer genomes is highly variable at the 1Mb scale. Local mutation density can be predicted from epigenetic marks in tissue of origin. At a smaller scale, mutation density depends on chromatin accessibility. The data implicate Global Genome Repair (GGR) system as responsible for this dependence. Sequencing of a large cohort of parent-child trios by the Genome of Netherlands (GoNL) consortium reveals that germ-line mutation rate is less heterogeneous along the genome. However, context-specificity and epigenetic variables influence local germ-line mutation rate. Two evolutionary models may potentially explain the origin of mutation rate heterogeneity. The heterogeneity of mutation rate along the human genome has important consequences for evolutionary genomics and for statistical genetics approaches based on recurrent mutations. Analysis of de novo mutations also helps finding genes underlying Mendelian diseases.