



# Crumbling Genome

*Alexey S. Kondrashov*

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## **Crumbling Genome** Alexey S. Kondrashov

Our genome consists of DNA molecules of the combined length over 3 billion nucleotides, which contains over 20,000 protein-coding genes, each encoding either one protein or a set of similar proteins - and these genes and proteins interact with each other, forming mind-boggling networks of mutual influences. A human body, which develops on the basis of instructions provided by the genome, consists of billions of cells, also engaged in complex interactions. In particular, the human brain contains 100 billion of neurons, and a similar number of glial cells, and a typical neuron communicates directly with thousands other neurons.

A mutation which replaces just a single nucleotide may cause synthesis of a dysfunctional protein, and this can be fatal, or cause a severe disease, or have just a mild effect. Thus, deleterious mutations vastly outnumber beneficial mutations.

Far from being a moot point, our vulnerability is constantly exposed by a relentless pressure of spontaneous mutation. Despite all the efforts of our cells to handle their DNA carefully, a newborn human receives, from their parents, on average, 60 new mutations, and about 10% of them impair the fitness substantially. So far, no means of reducing the rate of human spontaneous mutation have been discovered. Over 1% of newborns suffer a clear cut disease, including a wide variety of so-called Mendelian diseases, as well as schizophrenia, mental retardation, or severe autism due to new mutations in their genotypes. Milder, but still substantial, effects of new mutations are harder to detect but likely are even more pervasive.

Under natural conditions, natural selection prevents accumulation of deleterious mutations with cruel efficiency. However, in societies where clean water, food, shelter, and advanced medicine are available, only the most severe mutations preclude reproduction of a human. In other words, in industrialized countries, natural selection against deleterious mutations is much weaker than it used to be at any point during the 3,500+ million years of the evolutionary history of our ancestral lineage. Charles Darwin, the discoverer of evolution by natural selection, immediately realized that this is bound to lead to undesirable consequences.

After the basic laws of heredity were discovered in early XX century, a number of geneticists, including Hermann Muller and James Crow, developed a framework for studying the effect of deleterious mutations on individual humans and on human populations. However, until very recently, estimates of the scale of the problem were rather fuzzy.

Recent flood of genomic data begun to change this situation. The role of deleterious mutation in human variation and disease, and the potential consequences of unchecked accumulation of deleterious alleles, can be now discussed with much more confidence than even 10 years ago. Still, substantial uncertainties remain, but postgenomic biology will likely remove many of them in the next 20-30 years.

This book will appeal to researchers interested in the ties between genetics and evolution, how these ties may influence social issues and human health.

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