Crumbline Genome
Alexey Kondrashov

Is evolution spinning backwards? Are we becoming less fit?

Alexey Kondrashov, one of the world's leading evolutionary geneticists, writes about what he calls the Main Concern, a loss of fitness due to genetic deterioration.

The book is addressed to a general audience - those interested in genetics and evolution in general - and especially those interested in the threat that deleterious mutations potentially pose to humanity. The author intends it also for those who are touched by genetic disease.

The crux of the issue is this: Natural Selection ruthlessly purifies the genome by eliminating deleterious genes. It operated similarly among humans – until the Industrial Revolution, which started a few centuries ago in Europe continues to spread. In what is called the Demographic Transition, selection pressure was greatly relaxed.

Evolutionary geneticists use the term "fitness" to describe the quality of the genome. In wild populations it equates to the number of offspring that an individual will leave. This concept has been stood on its head: in the past two centuries people went from having as many children as they could to as many as they felt like. Perversely, the best and brightest among us don't feel like having many children. Populations are more and more dominated by gene lines that would have died out under harsher conditions of selection. The load of deleterious alleles for conditions such as diabetes, autism, schizophrenia and obesity appears to be growing.

It can be inferred that intelligence and personality, which are also largely genetically determined, are being impacted by the same mechanisms. Kondrashov's work with disorders that manifest themselves physiologically has wider implications. Among the authors whose works I have reviewed on this topic are Richard Lynn, Tatu Vanhanen, [[ASIN:0993000118 Helmuth Nyborg]], **[[ASIN:**B00DNL37X0 Satoshi Kanazawa]] and [[ASIN:B07M8NG2CN Edward Dutton and Michael Woodley of Menie]]

The Kindle format is ideal for this book. This field of study unavoidably involves a vast number of technical terms. Kondrashov has composed his work in such a way that it is generally possible to search through prior chapters to refresh your memory as to the meaning of a term.

Kondrashov opens his book re-explaining what the majority of readers will already have been exposed to: the basic mechanics of DNA.

DNA is a code, like the alphabet of a written language or like binary arithmetic and a computer. The English alphabet would be base-26 (A-Z), binary is base-2 (0-1). Each nucleotide in a DNA molecule, the element corresponding to a bit and binary, is made up of some combination of four small deoxyribose sugars the names of which began with the letters ACTG. They can appear in any sequence along a strand of DNA, hence it is a base-4 system of coding.

DNA is double-stranded, with a G on one strand connected to an C on the other, an A connected to T. The strand is directional: the ends of the phosphates that link the ACTG nucleotide sugars together are different, called 5' and 3', and

they are all aligned the same way. Operations such as duplication or creation of transfer RNA to create proteins know which end to start from.

The human genome consists of 46 such DNA molecules, called chromosomes. They are paired: 23 from the mother and 23 from the father. 22 of the pairs are congruent in organization. Only the 23rd, the sex chromosome, differs. Women have two X chromosomes, one from each parent. Men have an X and a Y, and they differ significantly in form, the X being rather small. Men, since they have only one copy of X-chromosome genes, are thus more susceptible than women to disorders on the X chromosome.

Thus there are two types of duality in the genome. The double helix of the chromosome, and the dual chromosomes, one from each parent. The chromosome received from each parent represents a rough 50:50 mix of that parent's two corresponding chromosomes, each of which, in turn, is a mixture of DNA from each grandparent.

In the process of cell duplication, a molecule of DNA – a chromosome – splits in two. Each half attaches new copies of corresponding deoxyribose sugars (A to T, C to G) and connects them appropriately using phosphate bonds. The process is vastly complex, and Kondrashov's genius lies in his ability to make it comprehensible without sacrificing too much detail. He has excellent diagrams.

Normal cell division, called mitosis, is involved as the body needs new cells to grow, or to retire depleted cells. All cells in the body with the exception of nerve cells are subject to duplication and replacement over the life of the phenotype.

Sexual cell division, called meiosis, involves a random reshuffling of genetic material from the genomes of mother and father to form a gamete, a sperm or egg cell with only 23 chromosomes. This haploid cell – haploid meaning half – combines with the haploid contributed by the other partner in sexual reproduction in the process of fertilization. After fertilization, with all 46 chromosomes present in the diploid embryo, further cell division is by mitosis until the new phenotype produces its own gametes.

Most of the variety among the phenotypes of any population depends on the variety of different genomes. Environment, nourishment, and accidents of course also contribute.

Culture contributes significantly to modern phenotypes. Dutton and Woodley of Menie take the notion further in [[ASIN:B07M8NG2CN At Our Wits End - Why We're Becoming Less Intelligent and What it Means for the Future]], contending that social epistasis can actually alter the of the expressed genome of humans. Woodley of Menie would contend that a man whom society molds into a soy boy may cause others to become soy boys. Though Kondrashov indicates that he entertains such concepts, this book confines itself rather rigorously to biology, remaining mostly silent on societal considerations.

The variety within a genome arises from mutations. Although mitosis is a very precise process, with an error rate on the order of one per 10^8copies – after four independent self-correction processes, which Kondrashov describes well – errors do occur. The most common is called a single nucleotide polymorphism or SNP. One of the deoxyribose sugars somewhere in the DNA molecule gets substituted. Other errors involve deleted segments of DNA, inserted segments of DNA, and misaligned segments of DNA.

Remaining in the realm of traditional genetics, Kondrashov notes that most of the human genome is invariant; only the ancestral allele being present. There are nonetheless many polymorphic nucleotides. One may have A:T, another T:A,

and a third C:G. Also, given the human population approaching 8 billion, the arithmetic would indicate that the population probably harbors at least one person with an SNP at any given location.

One variant must be the ancestral form, the others the result of more recent mutations. Recent mutations are usually deleterious to the organism. How long it takes to eliminate them as a function of how bad they are. On the other hand, some will be beneficial. This is the fount from which improvements to the species spring.

If an SNP corresponds 1:1 to a trait in the phenotype, it may be called a gene for that trait. Most SNP's take only two values, conventionally called A and a, the capital letter indicating the dominant gene. Since a child receives one gene from each parent, there are three combinations: AA, Aa and aa for all but genes on the X chromosome in a man. A deleterious trait is expressed when the offspring receive two recessive genes, or less frequently, a dominant and a recessive if the dominant gene is deleterious.

A trait that is governed by a single gene is called Mendelian, after Gregor Mendel who worked out the mathematical combinations. Human eye color is a widely observed example. Blue eyes are recessive. Blue eyes in a phenotype means that the genotype is aa. In general, two blue-eyed parents will have blue-eyed children. The only combination available to inherit is aa. An aa and an Aa parent will have half blue-eyed children. Two Aa parents will have three quarters brown eyed and one quarter blue-eyed. And in any pairing, the children of an AA parent will have brown eyes.

Most Mendelian diseases in the human genome are of a fairly recent origin. Not enough time has gone by for them to have been eliminated from the genome of the species. How long they will remain, and how many individuals will be affected by a deleterious gene, is a matter of some arithmetic that Kondrashov presents in elegant detail. Basically, the pervasiveness is the inverse of the allele's impact on fitness. An allele that reduces fitness by .01 can be expected show up 1/.01, or 100 times before it is eliminated. A lethal allele will remain for 1/1 = 1 generation. It will not reproduce – it will result in a spontaneous abortion, premature death or sterility.

Most genes are complex rather than Mendelian. They are controlled by polymorphisms at a number of nucleotides. Conversely the nucleotides involved are usually pleiotropic – they affect more than one trait. This is certainly true of the most interesting traits among normal people, such as hair color, intelligence, body mass index and blood pressure.

While researchers into genetic diseases are quite interested in Mendelian traits, researchers into the overall human condition are more interested in complex traits.

Mutations can be big or small. The majority of them affect only a single nucleotide, but they can affect large stretches of a DNA molecule, and even involve relocating stretches of DNA from one place to another.

Most mutations arise spontaneously, attributable to neither radiation nor chemical interference. It is simply a risk involved in the process of cell division and replication. Different organisms experience different rates of mutation. In human beings it is approximately 100 de novo mutations per generation, of which 10 are deleterious. These originate in the parents and are passed to children through gametes.

To keep the mutation load on a genome constant, that same number of mutations has to be eliminated in each generation – dropped from the genome, not passed along.

The germline cells in the mother do not duplicate themselves after her birth. The father's germline, on the other hand, continues to divide throughout his life. The number of mutations is a function of the number divisions.

As a rough approximation, a child will receive a number of de novo mutations equal to about twice his father's age. Since most are neutral, this means that the rate of deleterious de novo mutations will range between 10 and 30, depending primarily on paternal age.

This arithmetic would favor younger fathers. On the positive side, one could also expect that a disproportionate number of beneficial mutations would also come from older fathers. But this is hard to measure. Beneficial mutations are usually associated with complex traits, whereas the detrimental ones are frequently Mendelian.

Although de novo mutations tend to be more deleterious, their number is small alongside the thousand or so inherited mutations. Kondrashov presents a table showing that in the genome of a newborn, de novo mutations make up 10% of the most deleterious mutations (reducing fitness by 10% or more), 1% of the next tranche, those which reduce fitness by 1% or more, and 0.1% and .001% of the lesser orders of magnitude of deleterious mutations. However old a father may be, he can take comfort in the fact that a significantly greater percentage of his children's load of deleterious genes will be inherited rather than de novo. The increase in their risk of deleterious mutations would appear to be no more than about 25%. If his genome gives them a 25% edge in terms of charm, good looks and intelligence it would seem to be a fair trade.

Inbreeding depression is a result of the mating between closely related individuals. When mutations appear randomly the chances of the same mutation showing up in the same allele is small. However, it is quite likely that the common ancestor of a but closely related pair will have passed the same defective recessive allele down two gene lines. Disease manifests itself when they meet up. Looking at it from another perspective, our genome can sustain a higher load of deleterious alleles if they tend to pair up randomly rather than systematically through sexual reproduction.

In a broader population, there will be a continuous accumulation of slightly deleterious genes. The effect is not clear; Kondrashov mentions that there is a theory that phenotypic intelligence is as much a result of diminution of maximal possible intelligence by deleterious genes as it is of the additive action of beneficial genes.

In referring to the human population Kondrashov makes extensive use of a number of concepts from evolutionary genetics of wild populations that would appear not to apply.

The easiest to describe is fitness – the number of offspring that an individual leaves behind. It can be defined as actual fitness – the real number; inherited fitness, the number an individual is likely to produce, and transmitted fitness, the number that would theoretically be produced if an offspring were paired with a mate of similar fitness. Whatever the number, our observation is that the people who are having the most children are not what any of us would consider to be fit. Most of them appear to be living on the excess wealth of the society rather than contributing wealth themselves.

Another such concept is imperfection – deviation from ideal fitness. It appears to be a concept that is more useful in measuring wild populations than people. Evolvability, a third statistic, is a theoretical upper bound on the strength of selection.

Kondrashov introduces the idea of “wellness”, by which he means absence of disease. It is not quite the same as fitness, and would seem to be more applicable to human populations. From wellness follows the concept of weakly perfect human genotypes and phenotypes – individuals with no inheritance of deleterious genes. Such individuals could not exist -- the odds against it are astronomical. If they did, hypothetically, what would their fitness be? How many children would they have? Among modern human populations this seems like a pointless question. They would probably spend

their time admiring themselves in the mirror at the health club rather than procreating. And – Kondrashov says as much, after presenting a lot of theory that employs these concepts.

Most de novo mutations are deleterious. There is a hypothesis that fitness selection has diminished, as individuals with deleterious alleles affecting traits such as hemophilia, diabetes and the like are able to reproduce.

The total genomic fitness of developed countries has been diminishing over the last few centuries, accelerating in recent decades. Certainly some of the diminution is a result of failure to eliminate alleles that are inconsistent with reproduction, such as those for schizophrenia. Other diminution is due simply to a disinclination of those who used to be considered the fittest to have children. This correlates with the spread of traits that may have some genetic complement, such as atheism, homosexuality, obesity and the like.

Michael Woodley of Menie makes a case that social epistasis plays a strong role as well. As the elite, those who set the standards, engage in what would traditionally have been considered deviant behavior – homosexuality, pederasty, atheism, freeloading, the indulgence of uncontrolled anger – others are encouraged to emulate them. Social epistasis would imply that their genomes express themselves consistent with the antisocial belief systems espoused by the cultural elite. They may have lowered sperm counts, testosterone, muscle tone and agreeableness, and higher rates of depression and anxiety.

Kondrashov presents optimistic and pessimistic scenarios with regard to the future of the human genome. Things might sort themselves out, with selection against degraded genomes approximately equal to the rate at which they appear de novo. On the other hand, as his Crumbling Genome title implies, the individual load of detrimental alleles is likely to rise from present levels. Over the course of the coming tens of generations the genome could deteriorate significantly, our fitness going down several percentage per generation.

As Dutton and Woodley of Menie contend, it appears that the social causes for the degradation of the genome are markedly more significant than the biological ones. The fertility of the strata of society with above average intelligence is significantly below replacement level everywhere. The fitness of my tribe, white people, has fallen by almost half within my lifetime. Our intelligence is collapsing, and with it our civilization itself. This catastrophe is playing out in real time, not over generations.

Woodley attributes this to "spiteful" genes, those which express themselves in the form of psychopathic behavior on the part of elected leaders and encourage epistatic emulation throughout society. It is also in part purely cultural. Whichever it is, it is playing out in generations and even fractions of a generation, not the multiple generations that Kondrashov discusses.

Kondrashov discusses the emerging technologies that will allow us to manipulate genes. We are already able to identify genetic abnormalities in our phenotypes and in germ cells. With these tools we should be able to produce fairly healthy offspring even in the face of a deteriorating genome. We can simply avoid their effects. In a few decades we may be able to edit individual gametes to neutralize undesirable alleles.

Kondrashov devotes a long chapter to the ethical concerns involved in managing our genotype. He comes down strongly against the eugenicists of the early twentieth century, saying that decisions regarding reproduction belong to the individual, not the society. He discusses both sides of controversial issues such as in vitro fertilization, abortion, and "designer babies." He does not address the fact that the increasing number of children being born to increasingly less capable parents will simply have no place in the world. Society will have no use for their skills, and at some point must

run out of resources to support them. These are the arguments that were put forth by Thomas Malthus and Charles Darwin himself a century and a half ago. There will be no easy answer.

If Dutton and Woodley of Menie are right, our civilization will enter a long night well before the technologies to manage our genome are perfected. The issue is not the long-term fate of our genome, however interesting that may be. The issue is that society is collapsing quickly, right now. The existential question appears to be how to raise normal children in a very abnormal time, and prepare them to be the patriarchs of bloodlines that will survive a long Dark Age.