

# From Eden to a hell of uniformity? Directed evolution in humans

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## Summary

For the first time during evolution of life on this planet, a species has acquired the ability to direct its own genetic destiny. Following 200,000 years of evolution, modern man now has the technologies not only to eradicate genetic disease but also to prolong life and enhance desired physical and mental traits. These technologies include preimplantation diagnosis, cloning, and gene therapy in the germline on native chromosomes or by adding artificial ones. At first glance, we should all be in favor of eliminating genetic diseases and enhancing genetic traits. Evolutionary considerations, however, uncover hidden dangers and suggest caution against the total embracement of such actions. The first major concern is that the genome will never be a completely reliable crystal ball for predicting human phenotypes. This is especially true for predictions concerning the performance of alleles in future generations whose populations might be subjected to different environmental and social challenges. The second, and perhaps more important, concern is that the end result of germline intervention and genetic enhancement will likely lead to the impoverishment of gene variants in the human population and deprive us of one of our most valued assets for survival in the future, our genetic diversity.

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## Phenotype is more than just genotype

“Nothing in biology makes sense except in the light of evolution.” This citation by the 20<sup>th</sup> century geneticist, Theodosius Dobzhansky, (1900–1975) is valid even in today’s world full of manipulated genomes and cloned sheep. Even *ethical* human behavior is deeply rooted in our biology. This means that our species, *Homo sapiens*, by being able to influence its own genes stands at the brink of a significant transition. We will soon have the ability to use gene therapy to correct genetic disease, clone individuals from somatic cells, introduce desired traits or remove undesirable ones, design genes from scratch and introduce additional chromosomes. Lamarckism is raising its head, after all, albeit without violating the Darwinian principles.<sup>(1)</sup>

Do the new technologies of prenatal selection, germline manipulations, or human cloning promise the “remaking of Eden” as Lee Silver called it<sup>(2)</sup> (if there ever was one) or will they rather result in a “brave new world”, in which we are controlled by controlling our genomes? Mutation is one of the necessary forces driving the process of evolution, however slow it may be. The problem is that the eternal variation of genes alone only rarely provides new winners. More often mutations are neutral, without effect, or have negative consequences—that is, individuals carrying the corresponding alleles (gene variants) suffer various minor to major disadvantages including genetic disease. What Silver and other proponents of germline intervention propose is to apply germline manipulating technology in perhaps two stages. First, genetic disease should either be eliminated by prenatal diagnosis and selection against unwanted traits that lead to genetic disease or should be “cured” by introducing the correct allele on one of the human chromosomes or by delivering artificial chromosomes into the germline. The second stage involves the introduction of desired cosmetic or performance-related traits into the human germline. As desirable as it might be to alleviate human suffering by eradicating alleles that lead to genetic disease, upon more careful analysis, made in the light of evolutionary considerations, such practice would have the serious drawback of potentially jeopardizing the future of our species.<sup>(3)</sup> The following takes a closer look at some of these considerations and starts with examples illustrating what a complex, perhaps insoluble, problem it would be to choose which genes to manipulate.

Usually, organisms that procreate sexually have two sets of virtually but not quite identical chromosomes, as one is derived maternally and the other paternally. Consequently, an individual has two similar “copies” of a given gene. If the nucleotide sequences of the two “copies” of a given gene are identical, an individual has only one variant of the gene and is homozygous for this particular variant or allele. Another individual may have inherited two alleles with different sequences, and hence is heterozygous with respect to a given gene. Of course, any given individual can be homozygous for some genes and, at the same time, heterozygous for others, depending on the respective allelic variants of the parents. In a population, many different alleles (“copies” with different sequences) exist for some genes. Most of the time, the differences, or mutations, lie in regions that do not affect the quantity or quality of the gene product (i.e., the amino acid

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sequence of the corresponding protein). However, if the mutations improve the protein, the frequency of that specific allele may increase in the population. Conversely, a disadvantageous allele would decrease in a population. Often, a negative allele has an impact only when it is homozygous. In the heterozygous state, it may even convey a selective advantage, which may explain its spread in a population. For example, one specific allele of the beta-globin gene, which encodes an oxygen-transporting protein in the blood, protects its carrier from malaria when it occurs in the heterozygous state, while an individual homozygous for this allele is seriously incapacitated by sickle cell anemia.

Therefore the futility of “eugenic” selection against recessive alleles (especially rare ones causing major diseases) is further substantiated by the fact that most of the “mutated” alleles also occur in heterozygotes. To completely remove a particular genetic disease from the population, one would have to “correct” also these single alleles. That would mean counterselecting also those individuals with only one diseased allele and one healthy one, even though the individual would have been healthy and would only have carried the danger of having (homozygous) sick offspring. As early as four decades ago, Ernst Mayr argued that counterselection will not work to improve our species<sup>(4)</sup> and John Maynard Smith foresaw our ability to alter the human genome and, with remarkable precision, the fallacies of such applications.<sup>(5)</sup>

Humans have 30,000–40,000 genes and many of them occur as allelic variants. In addition, often the combined genetic background of all the different alleles of an individual determines whether a given allele will have a positive, neutral, or negative effect. Similar considerations are particularly relevant for genetic diseases in which multiple genes are involved and can determine the penetrance of the disease. To complicate things further, often epigenetic factors, for example, the maternal or paternal origin of the allele, determine whether a given disease state develops or not.<sup>(6–9)</sup> Monogenic diseases are relatively rare and even *their* outcome can depend on the genetic background within which they occur.<sup>(10)</sup> In the process of generating animal models for genetic disease, scientists are currently learning the hard way how much the mixed genetic background of hybrids resulting from two inbred mouse strains can distort the phenotype of mice. Often it is difficult, sometimes impossible, to assess the impact of a particular gene deletion on the phenotype of animals due to this mixed genetic background.<sup>(11–17)</sup>

For most of the genetic “diseases”, it is doubtful that genetic profiles will have the necessary predictive power to properly select and, in contrast, often will discriminate unjustifiably. The importance of the overall genetic background of an individual for a genetic disorder to penetrate the phenotype cannot be stressed enough. If this did not complicate matters enough, even the environment determines penetrance of a genetic disease. Monozygotic twin studies in schizophrenia

reveal the importance of environmental factors in addition to genetic background. If one of the twins is diagnosed with this multifactorial mental disease, the second twin has significantly less than a 100% chance of becoming schizophrenic.<sup>(18–21)</sup>

The difficulty of predicting a given phenotype based on gene variants is demonstrated by the genomic analysis of our closest relative, the chimpanzee. Many of the phenotypic differences, including behavioral ones, are quite obvious to us and probably also to the chimpanzees, yet our genomes are almost 99% identical in alignable regions, not interrupted by insertions or deletions in one of the lineages since speciation.<sup>(22–24)</sup> It will be hard to pinpoint which of the ~40 million nucleotide differences are meaningful and which ones are simply noise. Furthermore, the correlation of a meaningful change with a particular phenotypic change will be even more challenging. Likewise, the problems involved in explaining the ~0.1 % intraspecies differences between two humans will be at least equally taxing. In other words, which of the potential 3 million nucleotide changes between two humans lead to particular phenotypes and which do not? Even if we restrict ourselves to perhaps the 30,000 changes that might be meaningful, as they are located within the coding regions of genes, a tremendous amount of work lies ahead of us. Furthermore, in these considerations, the potential interplay of two or more allelic variations in establishing a phenotype has not yet been considered.

A more concrete example is given by the discovery that the highly conserved human FOX2P gene product differs from that of the chimpanzee, gorilla and rhesus monkeys by only two out of 715 amino acid building blocks. Moreover, various statistical analyses make the point that the FOX2P gene, which encodes a transcription factor, was probably the target of selection in recent human evolution.<sup>(25)</sup> However, while disruptions in this gene do appear to lead to severe problems in language acquisition and use in humans, the evolution of speech had to have been a hugely complex evolutionary process and thus it is nearly impossible to conclude that mutations in this gene alone may have triggered the evolution of speech in our species. This does, however, demonstrate both the exciting prospects of such research and, at the same time, we are disquieted by the realization that we have a long road ahead of us to fully understand the effect of subtle changes in genotype on phenotype.

The laws of physics are far less fuzzy than the principles of biology. However, even when using physical laws, often the sheer number of different parameters makes predictions, such as the weather forecast, little more than a gamble over the long term. In biology, it is both the number and fuzziness of the parameters that preclude, with a few exceptions of simple traits, precise correlations between phenotype and genotype.

Hence, eradication of today's undesired traits by preimplantation genetic diagnosis, propagation of desired traits by germline gene therapy, and amplification of desired traits

by cloning at the cost of reducing or eliminating currently less-desired alleles would be a vain, if not ill-fated, attempt to “improve” the human race. Prenatal diagnosis would eliminate allele combinations before their phenotype could be assessed. As described above, some alleles are beneficial in one context and detrimental in another and we do not yet, and may never fully, understand the many complex factors that allows one aspect or the other of a particular allele to be integrated into the phenotype. Every new sexual pairing creates an entirely new mix of genes and so it would be impossible to test for every possible combination of alleles that might constitute the genetic background of a particular gene.

Although we have learned so much in the last three-quarter century about genetics, the last part of J.B.S. Haldane’s 1927 assessments appears more valid than ever. “We know very little about human heredity as yet, though about hardly any subject are more confident assertions made by the half-educated; and many of the deeds done in America in the name of eugenics are about as much justified by science as were the proceedings of the Inquisition by the gospels”.<sup>(26)</sup>

### Gene variability is essential for the preservation of a species

The diversity of existent gene variants (alleles) is an essential asset for the future of the human species and for all other species. An artificial reduction of this genetic diversity would lead to an evolutionary standstill or, at last, slow down. Frequently, when a species is at the brink of extinction, it receives the final blow from infections due to its reduced allelic repertoire.<sup>(27)</sup> A list of species that have become extinct or endangered by allelic impoverishment would probably exceed the allotted space of this contribution. At any level, monocultures are highly susceptible to environmental change. In agriculture, varieties that were selected for desirable traits are vulnerable to pests and other adverse environmental conditions. They can only be maintained with artificial intervention and would lose out in competition with less uniform varieties;<sup>(28)</sup> see also <http://www.wri.org/sustag/lba-03b.html>). To some extent a similar analogy can even be drawn from the field of technology. Take computers. Today, electronic commerce, education, communication and leisure depend almost entirely on PCs, all of which run on basically one operating system, and thus as close as one can get to a monoculture. Consequently, a computer virus could potentially cripple, at least temporarily, almost the entire world.

### Sexual reproduction ensures a variable genome

One of Nature’s best solutions to the problem of monocultures was the evolution of sexual reproduction. At first glance, the evolution of sexual reproduction appears to be a great disadvantage. (see <http://www.pbs.org/wgbh/evolution/sex/advantage/>). Why would an individual give up 50% of its gene

variants (alleles) for the next generation (remember each of us inherits only one half of our alleles from each parent) while a clonally reproducing organism transmits 100% of its alleles to the next generation. There must be a tremendous selective advantage for an individual to recombine its own alleles with those of another individual during sexual reproduction. The key is probably that sexual reproduction provides individual variations from which selection has a choice of the favored combinations at any given time. Such a strategy is an effective countermeasure in, for example, the constant arms race against parasites.<sup>(29,30)</sup> Strategies to promote such genetic variability are frequent in nature. Mice select their mating partners using olfactory cues to promote heterozygosity in the major histocompatibility complex (MHC). This prevents close inbreeding and produces offspring with increased immune responsiveness.<sup>(31)</sup> For similar reasons, inbreeding-avoidance has evolved independently in many species of plants and animals. Tellingly, most of these documented strategies are geared towards increasing and not impoverishing genetic variability. If environmental conditions remained stable, asexual reproduction might be an advantage for some. However, since this can never be guaranteed, the cloning or engineering of successful individuals would remove genetic variability from the human gene pool and thus limit the choices that selection could act upon in a future changed environment.

### Today’s “bad” gene may be tomorrow’s “good” gene

Today’s successful individuals would most likely have been quite maladapted for the requirements of a hunter gatherer lifestyle in the Stone Age and vice versa. Even without catastrophic events, environmental and social conditions can change drastically, even in the course of one or a few generations. For instance, in less than seven decades, the desired human “product” of the criminal ruling class in the Third Reich might have been hopelessly outdated. Likewise, we cannot foresee what genetic makeup will be most beneficial in a rapidly changing world during the lifetimes of future generations.

Environmental changes, such as the appearance of novel pathogens (AIDS), are impossible to predict. Well-intended genetic “improvements” might backfire within a few generations. A few examples should illustrate how the evolutionary value of alleles can change over time. The allele responsible for the lethal iron overload disorder, *hereditary hemochromatosis*, one of the most common genetic diseases of Northern Europeans, may have arisen as a selectively favored allele to combat low iron in diets.<sup>(32)</sup> This is a reminder of how environmental factors, including diets, can determine the value of a given allele.<sup>(21)</sup> As another example, chemokines and their receptors are thought to be essential to inflammation, thus a deletion of a gene encoding a member of the chemokine receptor family would be expected to be deleterious or, at best, neutral. In light of the AIDS epidemic, however, the role of an

inactive *CCK5* allele takes on a totally new significance. Since the *CCK5* receptor is a co-receptor necessary for infection by macrophage-tropic HIV-1 strains, a deletion in this allele renders homozygous individuals relatively resistant to infection.<sup>(33)</sup> While heterozygous individuals become infected, they seem to have a slower progression to AIDS<sup>(34)</sup> and lower levels of viremia than individuals without the deletion.<sup>(35)</sup> Thus, mutations in the human population range from the devastatingly deleterious (Mendelian lethals) to benign common phenotypic variants to the clearly advantageous. We would be deceiving ourselves to think that we can draw the line sensibly regarding which mutations to eliminate and which to retain—especially in the light of our inability to predict future environmental challenges, as convincingly demonstrated by the *CCK5* story.

Other traits that might be “undesirable” in today’s societies can also be considered in a different way. For example, alleles that predispose one to alcoholism or other addictions may only be problematic as long as the respective substances can be easily obtained. They were probably less problematic in the past, when individuals generally did not have unlimited access to some of these toxins. Again, they are not negative, *per se*. Carriers of such alleles have been associated with “novelty seeking” behavior.<sup>(36–38)</sup> Thus these individuals may have been the driving forces in the building of our knowledge and culture—our civilization.

It might be detrimental for our species to eliminate, for example, the alleles leading to autism. Autism is a multigenic neurodevelopmental disorder. Depending on which of the genes are affected and the modulating influence of numerous other gene products, the effects can range from severe to subclinical.<sup>(39–43)</sup> There is speculation that many outstanding personalities in the arts and sciences, including A. Einstein,<sup>(44)</sup> could be placed within the broader phenotype of the autism spectrum. Recently, more anecdotal reports have acquired broader substantiation.<sup>(45–49)</sup> Further scientific support comes from family studies indicating that the broader autistic phenotype may include a cognitive style that can confer information-processing advantages.<sup>(50)</sup>

Thus, with the well-intended efforts to eliminate human suffering that goes hand in hand with severe forms of autism, we would risk eradicating alleles that, in a different genetic background and or under different developmental circumstances, might enable their carriers to have remarkable careers in science, technology or the arts (see for example <http://www.autism.org/asperger.html>).

The prevalence of many “undesired”, disease-causing alleles in today’s populations may be an indication that these same genes were once instrumental in the survival of entire populations, perhaps during past epidemics. It cannot be ruled out that such “defective” alleles or other “undesired” alleles now marked for eradication will be instrumental for the survival of our species in the future.

Is another possible explanation for the prevalence of these “undesired” traits in our population perhaps tied to one of the very reasons for the past success of our species? Did the establishment of family and social structures provide, as a fortuitous by-product, a suitable environment for individuals with suboptimal allele combinations? The offspring of such individuals could then have been highly successful during different environmental or socioeconomic conditions. Moreover, the striving of individuals to overcome personal handicaps or deficiencies has sometimes been a driving force towards extraordinary achievement.

In conclusion, it is extremely difficult, if not impossible, to ascertain whether a given allele is a good or bad allele. Moreover, any determination made today may only be valid during a narrow window of time. Hence, it is doubtful that future generations would appreciate our well-intended manipulations.

### Hope for the future

All this said and done, it is not my intention to categorically deny individual parents the right to have a child free of a genetic “defect”. However, in supporting the freedom of choice that may result in discarding otherwise viable embryos or aborting fetuses—measures that counter the ethical values of a large segment of the population, one must, at the same time, vigorously defend and support the decision of parents who decide in *favor* of a genetically compromised child. My hope is that the evolutionary considerations presented here will help to clarify the difficulties in individual decision making and reduce the anticipated stigma of non-desired combinations of alleles, which will surely follow when extensive genotyping becomes feasible.<sup>(51,52)</sup> In their groundbreaking book entitled “Why we get sick”, Nesse and Williams answer the question “Is there even such a thing as a normal genome?” as follows. “Certainly no one string of DNA code is ideal, with all deviations to be stigmatized as abnormal. While we humans have so much in common, our genes are diverse. There is no ideal type but only the many varied phenotypes that express the diversity of human genes, all competing in varying environments to get copies of themselves into the next generation”.<sup>(21)</sup> Consequently, if there is no ideal genome, there is no ideal human being. Exclusion of any one genetic disease may appear to be a simple decision for prospective parents. However, as technology advances and we correlate more alleles with numerous health risks or other traits, the choice will become more and more excruciating.<sup>1</sup>

The hope that I place in the Human Genome Project and the continued efforts in Biotechnology and Molecular Medicine is

<sup>1</sup>“Science promised man power. But, as so often happens when people are seduced by promises of power, the price exacted in advance and all along the path, and the price actually paid, is servitude and impotence. Power is nothing if it is not the power to choose”.<sup>(53)</sup>



not so much on the ability to “weed out” undesired traits but on the development of preventive and/or symptomatic therapies, including somatic gene therapy, that will not invade the germline. This will enable many affected persons to live more or less normal lives. Nevertheless, genetic manipulations of humans are being promoted and will be backed by a powerful lobby of reproductive medicine anticipating that it will become a billion dollar enterprise. For those who claim that genetic manipulation of humans will be isolated cases, the following should be a reminder. Amidst the turmoil surrounding the birth of the first test-tube baby, Louise Brown (25 July 1978), there were many that foresaw only a few additional, isolated cases. However, within two decades these “isolated cases” now total one million test-tube babies generated by a new field of clinical medicine, called assisted reproduction.<sup>(54)</sup>

The real volume of genetic enhancement will come not from Silver’s stage I therapy (correction of genetic diseases) which would be difficult to withhold from affected individuals and/or their kin but from his stage II treatments (cosmetic and enhancement of performance). Once the technology is established and routine, who could draw a line between what should be done and what not? Rightfully, Silver, Stock and other proponents for genetic enhancement<sup>(2,55)</sup> argue that affluent parents send their children to elite Universities to optimize their professional success. On what basis should one prevent affluent parents from attempts to increase genetically the IQ of their offspring? Moreover, the question is then, who, with the financial means, would really have a choice to abstain from the IQ arms race? Apart from the fact that there is no single gene responsible for IQ in individuals and probably the entire genetic background and the individual’s environment might affect it, IQ is a highly incomplete and often inaccurate indication of academic and especially professional performance. For the fallacies of IQ, the reader is referred to the Refs. 56–61.

Body height has been shown to be an asset in achieving professional and reproductive success.<sup>(62–69)</sup> In a matter of a few engineered generations, this realization would soon drive human body height to excessive levels and, thus, lead to yet another evolutionary compromise.<sup>(21)</sup> There is no limit to imagining the grotesque results of a favorite US-American past-time, “one-upmanship”: If not the whole individual, would certain parts of the body grow from generation to generation by the inch? With broadly attainable technologies would all African Americans desire to become Michael Jackson look-alikes with sculpted noses and a whiter shade of pale? The country would lose one of its main attractions, the beauty of ethnic diversity. Worse, just like the fashion industry depends on setting and changing trends, the question will arise, as to what cheekbone design or breast-form will be in vogue for the next generation.

If an embryo were to have an 80% chance of becoming homosexual, how would even the most liberal parents decide?

Would they stick to their convictions that sexual orientation is a totally insignificant indicator of the value of a human being or chose an easier life for a heterosexual.

Here we do have a serious problem of gradualism. It will become virtually impossible for the legislator (or anyone else) to draw the line between necessary and useful genetic intervention and plain human stupidity. I am anything but a notorious adversary of scientific progress and technology. However, due to the fact that the technologies for genetic selection and enhancement are already available or will be shortly and the presence of proponents of a perfect world without human suffering, I feel that the genie is already out of the bottle. What is left for concerned scientists and citizens alike is to determine whether there will be a two-lane road or a six-lane highway towards this “Brave New World”.

Most genetic enhancement technologies constitute directed evolution, a new form of Lamarckism, as few could have imagined a mere three decades ago. It would seem that organisms that can alter their genomes in response to environmental requirements and challenges would have a selective advantage—or would they? In a series of mathematical simulations, Hayes<sup>(70)</sup> pitted Darwinian and Lamarckian “organisms” against each other. While there were short-term advantages of the Lamarckian organisms, in the long run the Darwinian organisms always won. Is this the first time in ~3.5 billion years that Lamarckism is about to arise, or has it been tried before and proven to be inferior (e.g., too costly) compared to Darwinian selection?

Perhaps, evolution will regulate the problem of genetic “enhancements” in a less dramatic way. While many opponents of genetic intervention fear that a large rift will form between the genetically enhanced who can afford it and the wild types who cannot, I consider this two-tier society an insurance policy for the survival of our species. Should there be drastic changes in environmental conditions, including such disasters as the outbreak of epidemics, not the genetically enhanced but the wild types, due to their allelic diversity, might have better chances for survival.<sup>(71)</sup>

Although our highly developed central nervous system often deceives us into believing that we know it all, neither evolution nor one of its products, *Homo sapiens*, have foresight. History is a painful reminder of our failures, and human-induced ecological catastrophes have led to the mass extinction of many species. Now, human-directed evolution may possibly lead to our own.

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