

When genes and environment disagree: Making sense of trends in recent human evolution

Alternative title: Natural selection using genetic data from contemporary populations:
(mis)interpretations of recent studies

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See companion article [ADD REFERENCE TO BEAUCHAMP]

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In humans, for the first time, we are now able to observe ongoing natural selection at the molecular level. Natural selection operates when particular genetic variants render the individuals who bear them more likely to reproduce. As a consequence, those genetic variants increase in frequency in the next generation. In this issue, Beauchamp (1) presents evidence of negative natural selection on genes implicated in higher educational attainment in a contemporary population in the United States. To understand his conclusion and avoid misinterpretation, we unpack the central concepts.

The empirical study of natural selection in humans started with the examination of phenotypes—that is, individual traits, such as height or schizophrenia, measured without reference to genetics (Fig. 1). The simplest design establishes heritability of a phenotype by showing how much variation is attributed to genetic differences between relatives (using twins or other family members) (2). To claim evidence of natural selection, studies measure how much the number of children (lifetime reproductive success, LRS) varies with the phenotype to produce a measure of the ‘magnitude’ of natural selection. If the trait has some heritability and is associated with LRS, researchers conclude that the traits are evolving as a result of natural selection (3). Height is highly heritable (4), so if taller individuals have more children, genes important for tall stature may become more frequent in future generations (5, 6).

These approaches can differentiate between genetic and non-genetic – environmental – sources of variation (such as nutrition) in phenotypes. The crucial limitation is that they fail to differentiate between the genetic and environmental influence of the phenotype on the LRS. Consider the metaphor of a horse race where the outcome is LRS. Each competitor (the phenotype) consists of both a horse (genetics) and its jockey (environment). If some horses are naturally faster (speed is heritable) and some competitors prevail and win (selection on the combined horse-jockey phenotype), analysis of phenotypes may lead us to erroneously conclude that natural selection favors genetically faster horses when the winners may have been highly adept jockeys riding mediocre horses. Only methods looking directly at the characteristics of horses (genetics) at the end of the race can provide direct evidence of natural selection for genetic variants.

More advanced twin and other family models can disentangle the genetic from the environmental association between the phenotype and LRS. However, this requires to make assumptions about the genetic relationship between family members and their shared environment (see ref 7 and Fig. 1). The recent decreased cost of DNA sequencing has led to an explosion of genetic data that can be used to solve this limitation. For example, genetic-relatedness matrix methods (GREML, see ref 8) can use the whole genome to assess how genes influence the relationship between a phenotype and LRS, even using only individuals belonging to different families.

Beauchamp’s study as well as a recent one from Conley et al. (9) also make use of the new abundance of genetic data, but they do so in a different way. These studies use ‘polygenic scores’ for phenotypes, such as height or education, where many different genes are involved. The scores are derived from genome-wide-association studies (GWAS), where genetic variation is measured by single-nucleotide polymorphisms (SNPs) that are then tested for

their association with a trait. The scores measure the individual genetic disposition for a trait. The main advantage of relying on these scores is that their simplicity increases the range of possible analyses one can perform, which allows to study ongoing human evolution in finer details. Beauchamp considered years of education and other complex physical and health related traits, which have a polygenic basis (10). We focus on the strong result for education, where misinterpretations are most likely to arise. Using information on more than a half a million SNPs, Beauchamp computed a polygenic score summarizing how an individual's genetic composition contributes to educational attainment. He then assesses whether those who have genetic variation related to lower or higher education, as measured by the score, are predisposed to having more or fewer children.

The crux of Beauchamp's finding is that individuals endowed with 'genes' predisposing them to more years of education are having fewer children; natural selection for those born from the 1930s to 1953 thus favors variants associated with less education. His estimates imply a decrease in years of education caused by genetic selection of around one week per generation. Does Beauchamp's study mean that Americans are getting dumber by the generation? No. There are several reasons why this is not the case.

First, as Beauchamp emphasizes, selection on education is weak and evolutionary changes associated with it are slow. SNPs do not capture all genetic effects, but even after rescaling results to account for this limitation, the genetic selection predicts changes in education of only 1.5 month per generation. Since the direction and magnitude of natural selection varies as humans modify their environment (5), natural selection on education may well not remain negative over enough generations to lead to noticeable changes. The time span covered by Beauchamp is too short to shed light on this question.

Second, 'genes for education' are also associated with many other cognitive and non-cognitive outcomes (10). The genetic score for education therefore reflects genetic associations that might not be causal for education, but influence education via other traits. Whether the phenotype 'education' is under selection can thus also depend on how those other traits influence education over time. Beauchamp's analysis shows that none of the other traits he investigated (body mass index, fasting glucose concentration, height, schizophrenia, plasma concentrations of total cholesterol, and age at menarche in females) could be responsible for the association observed between the polygenic score for education and the LRS, but we cannot exclude that other traits may be.

Third, in shaping education, the environment largely prevails over genetics: there is an 'evolutionary override' (11), caused by cultural, economic and social factors. The United States experienced educational expansion over the past century (12); Beauchamp finds an increase of 2 years of schooling per generation. The educational bar has been raised, with American women now outperforming men in higher educational enrollment and completion (12). The selected decrease in up to 1.5 months of education per generation is thus balanced by gains of 2 years of education per generation, particularly for women. Returning to our metaphor – the jockey has become more skilled as the power of the horse dwindles. Similar

studies have found that although there was both a genetic disposition to an earlier age at first birth and natural selection over the 20th Century, environmental forces (contraception, educational expansion, social norms) resulted in a massive postponement of age at first birth (11).

Fourth, the findings are also influenced by the precision of phenotypic measurements. Although ‘years of education’ is readily available, it is not perfectly correlated with cognitive abilities and is not the way specialists measure IQ. Readers cannot therefore conclude anything certain about changes in the IQ of the next generation of Americans. Even if natural selection on gene variants underlying IQ *per se* were negative (as for education), once again an evolutionary override could still prevent Americans from being dumb or getting progressively dumber.

Finally, Beauchamp and Conley et al. both used data derived from the Health and Retirement Study (HRS), where Domingue et al. (13) has shown that mortality does not occur at random. Healthier and higher socioeconomic individuals were more likely to ‘survive’ to be genetically sampled. Beauchamp tailored his sampling procedure to minimize biases, but nonetheless recognizes that mortality bias may affect his results.

The studies by Beauchamp and Conley et al. mark a milestone in our understanding of human evolution and natural selection in contemporary populations. They fill the gap between SNP-based studies reporting natural selection acting in the past and phenotypic studies suggesting it is acting now. Researchers working on past evolutionary change confirmed that our species is – as others – capable of evolution by natural selection (e. g. 14, 15, 16). They provided strong evidence of why many adults can efficiently digest milk today (unlike most wild mammals) due to mutations selected since the advent of agriculture (17). Because natural selection occurs on phenotypes that have a genetic basis, phenotypic studies suggested that natural selection should still be acting at the genetic level in contemporary populations (3). Despite limitations, Beauchamp and Conley et al. provide unambiguous evidence in support of this hypothesis.

The question now shifts from whether or not natural selection is present to an examination of its effects. This is difficult for at least two reasons. First, relationships between genotypes and phenotypes remain poorly understood. Like others before us (3) we emphasize that there is little point in engaging in deep genetic analyses if phenotypic data remain weak indirect proxies. The next innovation must unite rich genetic data with equally rich phenotypic data, collected over several generations. Second, much of natural selection on contemporary human populations is driven by cultural and environmental factors that themselves change very rapidly. Only selection sustained in one direction over many generations produces significant genetic change. Future studies will undoubtedly provide direct proof of evolution in our species by documenting that the frequencies of gene variants change between generations. But these studies will have to be based on long-term multi-generational surveys where measurements have been collected precisely and continuously.

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Fig. 1. *The ‘evolution’ of evidence for ongoing natural selection in contemporary human populations.*

The figure shows measurement and modeling approaches used to investigate ongoing natural selection. It differentiates between phenotypic and genotypic level and whether the level has been directly observed (grey box) or is inferred (red circles). The blue arrows marks the associations being used as an evidence for natural selection. In classic designs, the observed association between phenotype X (e.g. height, schizophrenia and educational attainment) and lifetime reproductive success (LRS) is interpreted as natural selection if X has a genetic influence. Given that it remains unknown whether this association is driven by genetic or environmental factors, twin and other family designs infer the association between X and LRS at the genetic level. GREML approaches use observed genetic information to model the genetic association between X and LRS, so the genetic information is directly observed, while the association is itself inferred. Beauchamp now uses a measured genetic score for phenotype X to directly investigate its association with LRS. Note that all approaches are still in use today and the 'evolution of study designs' only represents the order in which these designs have been introduced.

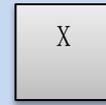
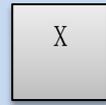
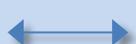
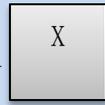
Classic Design

Twin/Family Design

Genetic Profile Scores



Phenotypic level



Genotypic level



e. g. ref (2)

e. g. ref. (1)ref (7)

e. g. refs (1) and (9)

The 'Evolution' of Study Designs Used to Document Ongoing Natural Selection in