COMMENTARY

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

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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 PNAS, 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 varies with the phenotype to produce a measure of the "magnitude" of natural selection. If the trait has some heritability and is associated with the number of children, 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 phenotypic approaches can differentiate between genetic and nongenetic—environmental—sources of variation (such as nutrition) in phenotypes. The crucial limitation is that they fail to differentiate between the genetic and environmental influences of the phenotype on the number of children. Consider the metaphor of a horse race where the outcome is the number of children. 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 conclude erroneously that natural selection favors genetically faster horses when the winners may have been highly adept jockeys riding mediocre horses (a case of negative gene–environment correlation). 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-based models can disentangle the genetic from the environmental association between the phenotype and the number of children. However, these methods require making 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) (8) can use the whole genome to assess how genes influence the relationship between a phenotype and the number of children, even using only individuals belonging to different families.

Beauchamp's (1) 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. The scores are derived from genome-wide association studies, where genetic variation is measured by 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 for the study of ongoing human evolution in finer detail. Beauchamp considered years of education and other complex physical and health-related traits, which have a polygenic basis. 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 (1) 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.

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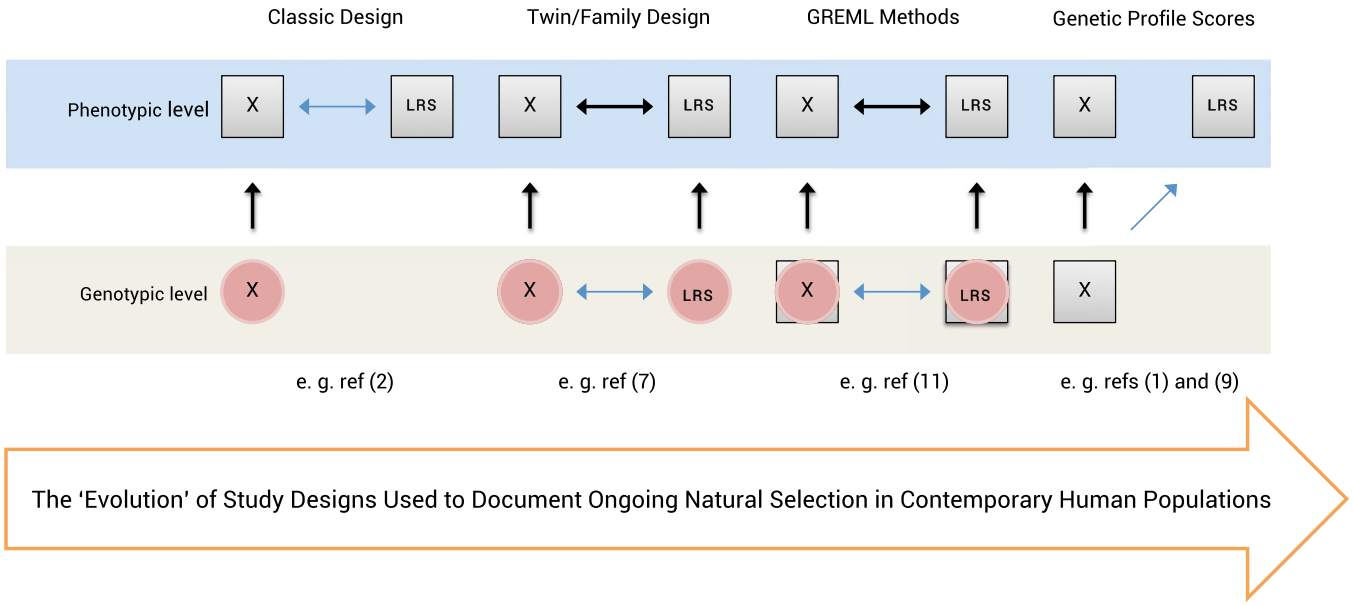

Fig. 1. The evolution of study designs used to document ongoing natural selection in contemporary human populations. The figure shows measurement and modeling approaches used to investigate ongoing natural selection. It differentiates between phenotypic and genotypic level and whether the level has been directly observed (gray box) or is inferred (red circles). The blue arrows mark the associations being used as evidence for natural selection. In classic study designs, the observed association between phenotype X (e.g., height, schizophrenia, or educational attainment) and the number of children (accounting for all children born during the lifespan of the individual and technically referred to as lifetime reproductive success or LRS) is interpreted as natural selection if X has a genetic basis. 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, whereas the association is itself inferred. Beauchamp (1) now uses a measured genetic score for phenotype X to investigate directly its association with LRS. Note that all approaches are still in use today and the "evolution of study designs" only represent the order in which these designs have been introduced.

The crux of Beauchamp's (1) 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 1 wk 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 (1) emphasizes, selection on education is weak and evolutionary changes associated with it are slow. SNPs do not capture all genetic effects so the genetic selection of 1 wk per generation is an underestimation. But even after rescaling results to account for this missing heritability, the genetic selection predicts changes in education of no more than around 1.5 mo per generation. Because 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 (1) is too short to shed light on this question.

Second, "genes for education" are also associated with many other cognitive and noncognitive 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 (1) 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 number of children, but we cannot exclude that other traits may be responsible for it.

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 (1) reports an increase of around 2 y 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 mo of education per generation is thus balanced by gains of 2 y of education per generation. 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 (1) and Conley et al. (9) both used data derived from the Health and Retirement Study, where Domingue et al. (13) have shown that mortality does not occur at random. Healthier and higher socioeconomic individuals were more likely to survive to be genetically sampled. Beauchamp (1) tailored his sampling procedure to minimize biases, but nonetheless recognizes that mortality bias may affect his results.

The studies by Beauchamp (1) and Conley et al. (9) mark a milestone in our understanding of human evolution and natural selection in contemporary populations. These authors 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 are others—capable of evolution by natural selection (e.g., refs. 14–16). For example, researchers provided strong evidence of why many adults can efficiently digest milk today (unlike most wild mammals) because of mutations selected since the advent of agriculture (17). Because natural selection occurs on phenotypes that have a genetic basis, phenotypic studies suggest that natural selection should still be acting at the genetic level in contemporary populations (3). Despite limitations, Beauchamp (1) and Conley et al. (9) 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 question 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. Future studies will undoubtedly provide direct proof of evolution in our species by documenting that the frequencies of gene variants change between generations. However, only selection sustained in one direction over many generations produces significant genetic change. These studies will therefore have to be based on long-term multigenerational surveys where measurements have been collected precisely and continuously.

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1 Beauchamp JP (2016) Genetic evidence for natural selection in humans in the contemporary United States. *Proc Natl Acad Sci USA* 113:7774–7779.
2 Byars SG, Ewbank D, Govindaraju DR, Stearns SC (2010) Natural selection in a contemporary human population. *Proc Natl Acad Sci USA* 107(Suppl 1): 1787–1792.
3 Stearns SC, Byars SG, Govindaraju DR, Ewbank D (2010) Measuring selection in contemporary human populations. *Nat Rev Genet* 11(9):611–622.
4 Visscher PM, et al. (2006) Assumption-free estimation of heritability from genome-wide identity-by-descent sharing between full siblings. *PLoS Genet* 2(3):e41.
5 Courtiol A, et al. (2013) The demographic transition influences variance in fitness and selection on height and BMI in rural Gambia. *Curr Biol* 23(10):884–889.
6 Stulp G, Barrett L, Tropf FC, Mills MC (2015) Does natural selection favour taller stature among the tallest people on earth? *Proc R Soc London B Biol Sci* 282(1806): 20150211.
7 Kirk KM, et al. (2001) Natural selection and quantitative genetics of life-history traits in Western women: A twin study. *Evolution* 55(2):423–435.
8 Yang J, Lee SH, Goddard ME, Visscher PM (2011) GCTA: A tool for genome-wide complex trait analysis. *Am J Hum Genet* 88(1):76–82.
9 Conley D, et al. (2016) Assortative mating and differential fertility by phenotype and genotype across the 20th century. *Proc Natl Acad Sci USA* 113(24): 6647–6652.
10 Okbay A, et al.; LifeLines Cohort Study (2016) Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* 533(7604): 539–542.
11 Tropf FC, et al. (2015) Human fertility, molecular genetics, and natural selection in modern societies. *PLoS One* 10(6):e0126821.
12 DiPrete T, Buchmann C (2013) *The Rise of Women: The Growing Gender Gap in Education and What it Means for American Schools* (Russell Sage Foundation, New York).
13 Domingue BW, et al. (2016) Mortality selection in a genetic sample and implications for association studies. *bioRxiv*, 10.1101/049635.
14 Yi X, et al. (2010) Sequencing of 50 human exomes reveals adaptation to high altitude. *Science* 329(5987):75–78.
15 Grossman SR, et al.; 1000 Genomes Project (2013) Identifying recent adaptations in large-scale genomic data. *Cell* 152(4):703–713.
16 Fumagalli M, et al. (2015) Greenlandic Inuit show genetic signatures of diet and climate adaptation. *Science* 349(6254):1343–1347.
17 Tishkoff SA, et al. (2007) Convergent adaptation of human lactase persistence in Africa and Europe. *Nat Genet* 39(1):31–40.