Genetic entropy and the human intellect

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Two recent articles in *TiGS* by Gerald Crabtree float the notion that we, as a species, are gradually declining in average intellect because we are accumulating mutations that deleteriously affect brain development or function [1,2]. The observations that prompted this view seem to be: (i) intellectual disability can be caused by mutations in any one of a very large number of genes; and (ii) *de novo* mutations arise at a low but steady rate in every new egg or sperm. He further proposes that (iii) genes involved in brain development or function are especially vulnerable to the effects of such mutations. Considered in isolation, these could reasonably lead to the conclusion that mutations reducing intelligence must be constantly accumulating in the human gene pool. Thankfully, these factors do not act in isolation.

If we, as a species, were simply constantly accumulating new mutations, then one would predict the gradual degradation of every aspect of fitness over time, not just intelligence. Indeed, life could simply not be sustained over evolutionary time in the face of such genetic entropy. Fortunately (for the species, although not for all individual members), natural selection is an attentive minder.

Analyses of whole-genome sequences from large numbers of individuals demonstrate an 'excess' of rare or very rare mutations [3,4]. That is, mutations that might otherwise be expected to be at higher frequency are observed only at low frequency. The strong inference is that selection is acting, extremely efficiently, on many mutations in the population to keep them at a very low frequency.

One of the key misconceptions in the Crabtree articles [1,2] is that mutations happen to 'us', as a species. His back-of-the-envelope calculations lead him to the following conclusions: 'Every 20–50 generations we should sustain a mutation in one copy of one of our many ID [intellectual deficiency] genes. In the past 3000 years then (~120 generations), each of us should have accumulated at the very least 2.5–6 mutations in ID genes' [1].

The loose phrasing of these sentences reveals a fundamental underlying fallacy. 'We' have not sustained mutations in 'our' intellectual deficiency (ID) genes, and 'each of us' has not accumulated anything over the past 3000 years, having only existed for a fraction of that time. Mutations arise in individuals, not populations. Neither does it matter that there are many thousands of genes involved in the developmental systems that generate a well-functioning human brain; selection can very effectively act, in individuals, on new mutations that impair these systems.

Mutations causing intellectual disability dramatically impair fitness, and many are only observed *de novo* because the effects are often too severe for them to be inherited [5]. Furthermore, this selective pressure extends into the normal range of intelligence, as described in a recent paper: 'One standard deviation advantage in intelligence was associated with 24% lower risk of death over a follow-up range of 17 to 69 years. . .The range of causes of death with which intelligence is significantly associated. . .include deaths from cardiovascular disease, suicide, homicide, and accidents' [6].

Crabtree suggests, however, that brains and intelligence are special cases when it comes to the effects of genetic variation and natural selection. First, he argues that ID genes are members of a chain, where every link is fragile, rather than of a robust network. This view is mistaken, however, because it ignores all the genes in which mutations do not cause ID; this is the robust network in which ID genes are embedded. He also cites several studies reporting high rates of retrotransposition and aneuploidy in neurons in human brains. He argues that these processes of somatic mutation would make brain cells especially susceptible to loss of heterozygosity, because an inherited mutation in one copy of a gene might be followed by loss of the remaining functional copy in many cells in the brain.

If these reports are accurate, such processes would indeed exacerbate the phenotypic consequences of germline mutations, but this would only make them even more visible to selection. However, it seems unlikely, *a priori*, that these mechanisms play an important role. First, it would seem bizarre that evolution would go to such lengths to craft a finely honed human genome over millions of years only to let all hell break loose in what Woody Allen calls his second favorite organ. If such mechanisms really prevailed, we would all be riddled with brain cancer. Furthermore, if these processes had a large effect on intelligence in individuals, this would dramatically reduce the heritability of the trait. However, the heritability of IQ is extremely high (estimated to be approximately 0.7– 0.8), suggesting these are not important mechanisms [6]. This view is directly reinforced by a recent study that used the more direct method of sequencing entire genomes of hundreds of individual human neurons and found vanishingly low rates of retrotransposition and aneuploidy [7].

Crabtree additionally suggests that modern societies shelter humans from the full scrutiny of natural selection, permitting dullards to thrive and deleterious mutations to accumulate. He speculates that high intelligence would have been more important in hunter–gatherer societies than in more modern societies that arose with high-density living. No evidence is offered for this idea, which contradicts models suggesting just the opposite: that the complexities of social interactions in human societies were a main driver of increasing intelligence [8]. Indeed, over the

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past millennium at least, there is evidence of a strong association between economic success (itself correlated with intelligence) and number of surviving children, suggesting selection on intelligence at least up until very recent times. By contrast, the number of offspring in contemporary hunter–gatherer societies has been linked more to aggression and physical prowess [9].

Arguments that reduced intelligence does not impair fitness in modern societies can thus be directly refuted. However, there is another way to think about this association, which considers intelligence from a very different angle (http://www.wiringthebrain.com/2012/07/genetics-of-stupidity.html). Rather than a dedicated cognitive faculty affected by variation in genes specifically for intelligence or, conversely, degraded by mutations in ID genes, intelligence may be a nonspecific indicator of general fitness. In this scenario, the general load of deleterious mutations in an individual cumulatively impairs phenotypic robustness or developmental stability, including development of the brain. The inability of the genome to direct robust developmental stability will affect multiple physiological parameters, intelligence being just one of them [10].

This model is supported by observed correlations between intelligence and measures of developmental stability, such as minor physical anomalies and fluctuating asymmetry (as more robust developmental program generates a more symmetric organism) [11]. Intelligence is also correlated with diverse physical and mental health outcomes, from cardiovascular to psychiatric disease [6]. Under this model, intelligence gets a free ride. It is maintained not by selection on the trait itself, but also on the coat-tails of selection against mutational load generally.

Whether causally or as a correlated indicator, intelligence is strongly associated with evolutionary fitness, even in current societies. The threat posed by new mutations to the intellect of the species is therefore kept in check by the constant vigilance of selection. Thus, despite ready counter-examples from nightly newscasts, there is no scientific reason to think that we humans are on an inevitable genetic trajectory towards idiocy.

References

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