Letter

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Our robust intellect

Alex T. Kalinka, Iva Kelava, and Eric Lewitus

Max Planck Institute for Molecular Cell Biology and Genetics, Pfotenhauerstrasse 108, Dresden 01307, Germany

In two recent *TiG* articles, Gerald Crabtree argues that there is an ongoing, and inevitable, decline in the average intellect of the human species [1,2]. Crabtree attributes this purported decline to various different phenomena, although chief among them is the suggestion that the genes underpinning human intellect are uniquely susceptible to accumulating deleterious germline and somatic mutations. Germline mutations, it is argued, will gradually accumulate in intellectual deficiency (ID) genes in human populations because the genes underlying human intellect are numerous and recent estimates of the germline deleterious mutation rate suggest that *de novo* mutations occur in every individual. Somatic mutations, by contrast, are expected to affect ID genes disproportionately, because recent studies have shown that retrotransposition of repetitive elements into actively transcribed genes occurs in neural progenitors during development and can lead to dysregulated expression of genes in the adult brain. Crabtree goes on to conclude from these facts that ID genes will suffer a greater rate of loss of heterozygosity (LOH) in which heterozygous individuals, who carry both a 'wild type' and a mutated copy of an ID gene, lose the wild type allele due to a retrotransposition event in a progenitor cell, thereby becoming homozygous at the level of the deleterious phenotype. He further suggests that, in current society, this effect will lead to a reduction in the heritability of human intellect.

Although Kevin Mitchell has successfully put many of Crabtree's arguments to the sword [3], we believe that the subject is of sufficient interest to warrant a more thorough analysis of Crabtree's claims on population genetics and human brain evolution. Here, we discuss the notion that human intellect is declining in the context of population genetic theories regarding the evolutionary dynamics of deleterious mutations and, by analysing a simple one-locus model, we show that LOH can, *contra* Crabtree, lead to an increase in the heritability of human intellect (Box 1). We further highlight the ill-founded assumptions that Crabtree makes regarding early selection pressures on human brain expansion and explain how the human brain is well adapted for its current environment.

Hermann Muller was the first geneticist to contemplate the potential for a population to decline gradually in fitness over time due to the accumulation of deleterious mutations [4]. Muller's ratchet is a phrase intended to capture the one-way decline in fitness that a finite, asexual population will experience due to the inevitable appearance, and subsequent inheritance, of deleterious mutations in the fittest genomes in the population. Each time the genomes carrying the fewest mutations in the population sustain

deleterious mutations, the ratchet clicks forward one more place, making the population irreversibly less fit. Key to this scenario, however, is the asexual and, therefore, non-recombining nature of the population. In a sexual population, recombination can recreate the fittest genotype by combining different alleles into individual genomes, thereby reversing the movement of the ratchet. Hence, there does not appear to be any *a priori* reason why humans, a sexual species, and their nervous system, which is controlled by many genes that are scattered across the chromosomes of the genome, ought to be preferentially affected by a process such as Muller's ratchet.

Nonetheless, Crabtree's thesis is provocative and deserves careful consideration. Although the existence of a large number of brain-related genes together with the *de novo* appearance of germline mutations does not imply that there will be a continual accumulation of deleterious mutations affecting intellect [3], we can ask whether there are known features of the human brain that predispose it to an elevated risk of mutational decay. The efficacy with which recombination can purge a population of deleterious mutations is highly dependent upon the type of interaction, or epistasis, that exists between different mutations. If the presence of two deleterious mutations leads to much lower fitness than the effect of either mutation in isolation (synergistic epistasis), then recombination will be able to drive down effectively the mutation load of the population [5]. If, however, the effect of two mutations is not as severe as we would predict from the effect of each mutation in isolation (antagonistic epistasis), then the population will suffer a large mutation load, even in the presence of recombination [5]. Thus, if mutations affecting human intellect tend to interact antagonistically (which is far from certain), then we would predict a large mutation load for genes impacting the brain. However, this does not imply that there will be a continuous decline in intellect over time. Instead, a tendency for a high mutation load might place an upper limit on the complexity that the brain can sustain, although this prediction itself might be partially refuted by the large number of genes claimed to be responsible for the human brain.

One perhaps peculiar aspect of the human brain is how rapidly it has increased in size over relatively short periods of evolutionary time. It is well known that so-called 'selective sweeps', in which a beneficial variant rapidly fixes in a population, can often be associated with genetic hitchhiking events, whereby an allele that is closely linked to the beneficial variant also increases in frequency solely by virtue of its linkage to the beneficial variant. If, for example, a strongly beneficial variant of a brain-related gene arises on the genetic background of a weakly deleterious

Box 1. LOH and the heritability of fitness

Crabtree argues that retrotransposition events in neural progenitors can lead to LOH if the beneficial variant of a gene is inactivated in heterozygous individuals [1]. He further suggests that this LOH will in turn make human intellect less heritable and, therefore, more difficult to maintain evolutionarily. Here, we test this prediction using a one-locus model of LOH in which we compare the heritability of fitness with and without transposition events.

In this deterministic model, we assume that transposition events occur within a locus with probability t and that transposition into the deleterious allele, a, has no impact upon its fitness. In addition, we assume that, at most, a single transposition event occurs at the locus (i.e., there is no double loss of homozygosity). The fitnesses of the three diploid genotypes are shown in Table I, where h is the dominance coefficient of the deleterious allele (when $h = 0$, a is recessive, when $h = 1$ a is dominant), and s is the strength of selection against a.

Heritability is a feature of a population, instead of an individual, and hence depends on genetic variation. It is defined, in the narrow sense, as the fraction of phenotypic variation that can be attributed to

additive genetic variation. Figure Ia shows the heritability of fitness in this one-locus scenario when the deleterious allele is partially recessive. The results demonstrate that, when the deleterious allele is at least partially recessive, LOH will lead to an increase in the heritability of fitness. This is the case because the effect of LOH is proportional to the genotype of an individual, and when the deleterious allele is recessive the effect of LOH is to expose this allele to natural selection (Figure Ib). Therefore, the effect of LOH on heritability depends strongly on the nature of intralocus effects.

Finally, we note that it is possible that transposition events in neural progenitors could contribute to neuronal and behavioural plasticity [12] and, hence, may be an integral part of human brain development.

Table I. Diploid fitnesses under LOH

AA	Aa	aa
$W_{AA}(1 - t) + W_{Aa}t$	$W_{Aa}(1 - t) + (W_{Aa} + W_{aa})\frac{t}{2}$	W_{aa}
$1 - ths$	$1 - hs - \frac{t}{2}s(1 - h)$	$1 - s$

(a)

(b)

$\hat{p}_t = 0$ $\hat{p}_t = 0.2$

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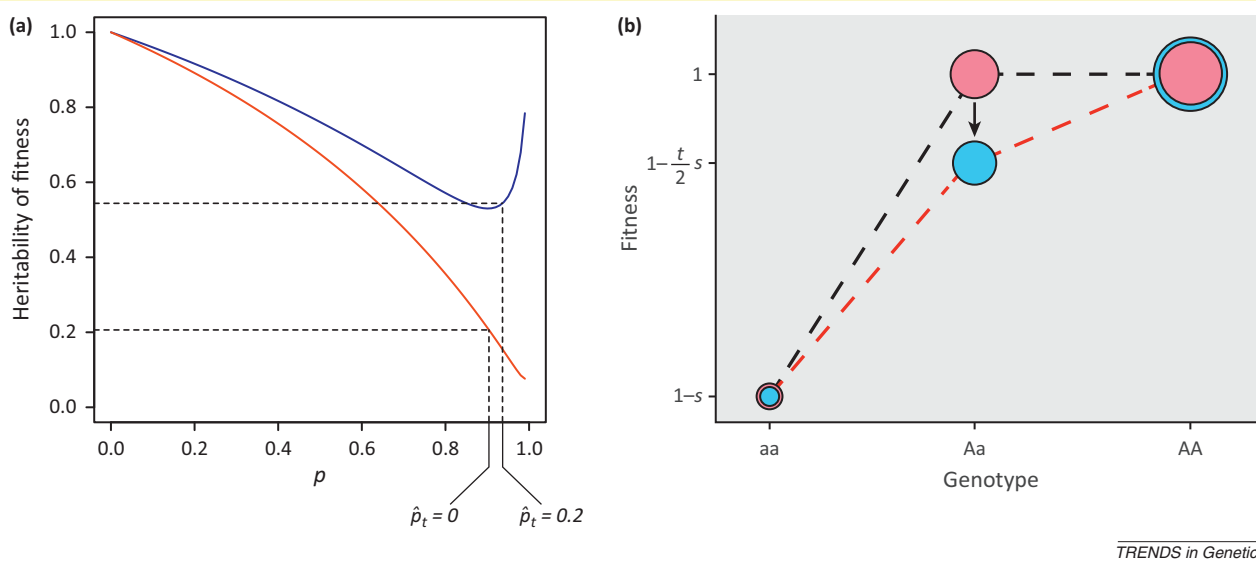
Figure I. Loss of heterozygosity (LOH) enhances the heritability of fitness when the deleterious allele is recessive. In **(a)**, the heritability of fitness is shown as a function of the allele frequency (p) of the 'wild type' allele (A). Heritability is greater (more than twofold) under LOH when the deleterious allele is at least partially recessive ($h = 0.01$). Dashed lines indicate the equilibrium frequency of A under mutation–selection balance of the deleterious allele ($\mu = 0.001$, $s = 0.1$). Note that the equilibrium frequency of A is higher under LOH; this is because higher heritability enables more effective selection against the deleterious allele. Key: blue line, $t = 0.2$; red line, $t = 0$. **(b)** The relation between fitness and genotype when there are transposition events (LOH; blue circles, broken red line) compared with when there are none (no LOH; pink circles, broken black line), when the deleterious allele is fully recessive ($h = 0$). The relative proportion of each genotype is depicted using circles of differing sizes. Under LOH, the heterozygote suffers a loss of fitness, which has the effect of making fitness more additive and, therefore, more heritable.

mutation in the same gene, this weakly deleterious mutation will end up at a high frequency in the population after the selective sweep of the beneficial allele. For this reason, there might be an unusually large number of weakly deleterious mutations involved in brain function that are segregating in the human population. In this case, however, these mutations would be driven down to mutation–selection balance after completion of the selective sweeps, and so, rather than expect a gradual increase in their abundance, we would expect their frequencies to be gradually declining over time.

In arguing for both the meteoric rise and snowballing decline of the human brain, Crabtree makes two cardinal assumptions: the human brain uses 2000–5000 brain-specific genes that operate independently and evolved in response to selection pressures absent in current society; and that these genes are especially susceptible to the accumulation of weakly deleterious mutations. Both

assumptions are necessary for arriving at Crabtree's conclusion, but both are wrong. Crabtree arrives at his estimate of 2000–5000 ID genes by extrapolating from the X chromosome, stating that the 'X chromosome does not appear to be enriched for genes required for intellectual development....' However, there is not only an excess of genes highly expressed in the brain on the X chromosome [6], but also a superabundance of neurological disorders linked to this chromosome [7], presenting it as atypically brain-specific and, therefore, likely to give an overestimate of the number of ID and mental retardation-linked genes in the brain. In reality, it is unknown how many ID genes exist or how many of these genes may have been adapted primarily for brain function.

More crucially, even the concept of ID genes is problematic when considered with respect to human evolution. Crabtree argues that ID genes evolved among 'non-verbal hunter-gatherers' in the context of expanding 'our capacity

for abstract thought'. Although he admits this is not his area of expertise, Crabtree fails to assess seriously the literature available to him. The physiology for verbal language, if not direct evidence of its use, is believed to have evolved no more recently than 500 000 years ago, at the time of modern human divergence from Neanderthals [8]. This damages the claim, which Crabtree makes, that language could not have been a major factor in human brain expansion. More importantly, language signifies, although is not a prerequisite for, a complex social system, an aspect of human behaviour that is positively linked to human and indeed primate evolution [9]. Because IQ is nearly nonheritable in low socioeconomic groups [10], the transmission of information in Palaeolithic societies would have been paramount and selection pressures strongest on those genes associated with complex social tasks. Forkhead box protein P2 (*FOXP2*), a well-studied gene associated with language evolution, nicely illustrates the pleiotropic nature of ID genes. A single arginine-to-histidine substitution in *FOXP2* results in verbal apraxia, as well as significant reductions in cerebellar and cortical grey matter volume [11]. That is, the large network of gene targets of this decidedly ID gene means that any accumulation of deleterious mutations would lead to a severe loss of fitness in a population. Many of the ID genes that, according to Crabtree, constitute our fragile intellect will consist not only of genes such as *FOXP2*, but also genes adapted for non-ID functions (e.g., cell division or glucose transport), noncoding regions integral to brain development and evolution, and genes that have evolved under mostly social selection pressures similar to those present in current society. Therefore, the evolutionary maintenance of genes such as these is not vulnerable to shifting social landscapes.

In summary, we can think of no obvious reasons why the genes underpinning intellect ought to be accumulating deleterious mutations faster than they can be purged. Although brain-related genes might suffer an unusually high mutation load, this does not *de facto* predict a continuous decline in intellect. While there might be scenarios under which weakly deleterious mutations are expected to accumulate in human populations, there is no reason to suppose, or any evidence to show, that such processes would be limited to, or especially exaggerated in, the human brain. In fact, neither brain-specific LOH nor our changing intellectual environment is likely to lead to a loss of heritability in our impressive intellect.

References

1 Crabtree, G.R. (2012) Our fragile intellect. Part I. *Trends Genet.* 29, 1–3
2 Crabtree, G.R. (2012) Our fragile intellect. Part II. *Trends Genet.* 29, 3–5
3 Mitchell, K.J. (2012) Genetic entropy and the human intellect. *Trends Genet.* http://dx.doi.org/10.1016/j.tig.2012.11.010
4 Muller, H.J. (1932) Some genetic aspects of sex. *Am. Nat.* 66, 118–138
5 Kimura, M. and Maruyama, T. (1965) The mutational load with epistatic gene interactions in fitness. *Genetics* 54, 1337–1351
6 Nguyen, D.K. and Disteche, C.M. (2006) Dosage compensation of the active X chromosome in mammals. *Nat. Genet.* 38, 47–53
7 Ropers, H-H. and Hamel, B.C.J. (2005) X-linked mental retardation. *Nat. Rev. Genet.* 6, 46–57
8 Arensburg, B. *et al.* (1990) A reappraisal of the anatomical basis for speech in Middle Palaeolithic hominids. *Am. J. Phys. Anthropol.* 83, 137–146
9 Dunbar, R.I.M. (2009) The social brain hypothesis and its implications for social evolution. *Ann. Hum. Biol.* 36, 562–572
10 Turkheimer, E. *et al.* (2003) Socioeconomic status modifies heritability of IQ in young children. *Psychol. Sci.* 14, 623–628
11 Preuss, T.M. (2012) Human brain evolution: from gene discovery to phenotype discovery. *Proc. Natl. Acad. Sci. U.S.A.* 109 (Suppl. 1), 10709–10716
12 Singer, T. *et al.* (2010) LINE-1 retrotransposons: mediator of somatic variation in neuronal genomes? *Trends Neurosci.* 33, 345–354