References

1 Stevenson, R.E. and Schwartz, C.E. (2009) X-linked intellectual disability: unique vulnerability of the male genome. *Dev. Disabil. Res. Rev.* 15, 361–368
2 Gecz, J. *et al.* (2009) The genetic landscape of intellectual disability arising from chromosome X. *Trends Genet.* 25, 308–316
3 Inlow, J.K. and Restifo, L.L. (2004) Molecular and comparative genetics of mental retardation. *Genetics* 166, 835–881
4 Kuss, A.W. *et al.* (2011) Autosomal recessive mental retardation: homozygosity mapping identifies 27 single linkage intervals, at least 14 novel loci and several mutation hotspots. *Hum. Genet.* 129, 141–148
5 Tsurusaki, Y. *et al.* (2012) Mutations affecting components of the SWI/SNF complex cause Coffin–Siris syndrome. *Nat. Genet.* 44, 376–378
6 Marin, O. and Gleeson, J.G. (2011) Function follows form: understanding brain function from a genetic perspective. *Curr. Opin. Genet. Dev.* 21, 237–239
7 MacArthur, D.G. *et al.* (2012) A systematic survey of loss-of-function variants in human protein-coding genes. *Science* 335, 823–828
8 Coufal, N.G. *et al.* (2009) L1 retrotransposition in human neural progenitor cells. *Nature* 460, 1127–1131
9 Baillie, J.K. *et al.* (2011) Somatic retrotransposition alters the genetic landscape of the human brain. *Nature* 479, 534–537
10 Han, J.S. *et al.* (2004) Transcriptional disruption by the L1 retrotransposon and implications for mammalian transcriptomes. *Nature* 429, 268–274
11 Westra, J.W. *et al.* (2010) Neuronal DNA content variation (DCV) with regional and individual differences in the human brain. *J. Comp. Neurol.* 518, 3981–4000
12 Kingsbury, M.A. *et al.* (2005) Aneuploid neurons are functionally active and integrated into brain circuitry. *Proc. Natl. Acad. Sci. U.S.A.* 102, 6143–6147
13 Cook, E.H., Jr and Scherer, S.W. (2008) Copy-number variations associated with neuropsychiatric conditions. *Nature* 455, 919–923
14 1000 Genomes Project Consortium (2010) A map of human genome variation from population-scale sequencing. *Nature* 467, 1061–1073
15 Crabtree, G.R. (2012) Our fragile intellect. Part II. *Trends Genet.* http://dx.doi.org/10.1016/j.tig.2012.10.003
16 Kong, A. *et al.* (2012) Rate of *de novo* mutations and the importance of father's age to disease risk. *Nature* 488, 471–475

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Our fragile intellect. Part II

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Analysis of human mutation rates and the number of genes required for human intellectual and emotional fitness indicates that we are almost certainly losing these abilities. If so, how did we get them in the first place, and when did things begin to change?

In the previous piece I argued that we are slowly losing emotional and intellectual traits [1]; but how did we get them in the first place? This is one of the most important questions of modern anthropology and the subject of much investigation and debate. Although not my area of expertise, I offer the following thoughts on the topic. Expansion of the human frontal cortex and endocranial volume (Figure 1), to which we likely owe our capacity for abstract thought, predominately occurred between 50 000 and 500 000 years ago [2,3] in our prehistoric African ancestors, well before written language and before we had the modern voice-box to produce sophisticated verbal language [2,4], but after the first tools. Thus, the selective pressures that gave us our mental characteristics operated among non-verbal hunter–gatherers living in dispersed bands or villages, nothing like our present-day high-density, supportive societies. Furthermore, it seems that our intellectual capacity has not evolved at different rates since our African ancestors began their migrations, based on the fact that geographically disparate societies have near-identical intellectual capacities. For example, written language was independently invented by the group with the longest migration path, the Indians of Middle and South America, and by the people with the one of the shortest migration paths, the Sumerians. In addition, whether a migration group lived a high-density urban life or as dispersed hunter–gatherers did not greatly influence their intellectual development. Thus, to understand how 2000–5000 genes [1] were optimized for abstract thought, we almost certainly have to look to this period 50 000–500 000 years ago and to ancestors common to all humans today. Somehow the selective pressures on these ancestors led to the evolution of a brain capable of writing symphonies and performing higher mathematics, indicating that life as a hunter–gatherer was more intellectually demanding than we might think.

To understand the extremes of selection that must have occurred as our ancestors went from using speed, strength, and agility, to employing intellect to survive (a process that occurred over about 1 million years), consider the difficulty of optimizing 2000–5000 genes. Because retrotransposon insertion and aneuploidy of neurons reduce the heritability of neuronal traits [1], the selective pressure required is increased. Present studies indicate that the heritability of intelligence, judged largely by IQ scores, is between 0.5 and 0.7, and have called attention to important variables affecting these estimates [5–7]. This level of heritability indicates that greater natural selection is necessary to maintain this trait compared to eye color, for example, where the heritability is much higher. In addition, one would need to sum the selective pressure for each of the genes operating independently to produce the trait. Thus, extraordinary natural selection was necessary to optimize and maintain such a large set of intelligence genes. This optimization probably occurred in a world where every individual was exposed to nature's raw selective

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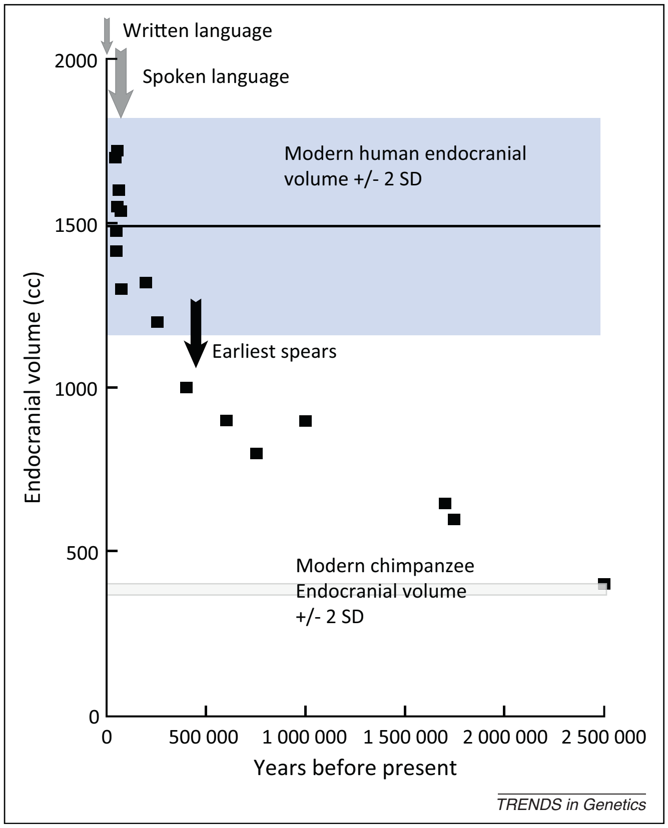

Figure 1. Expansion of endocranial volume during the past 2.5 million years among *Homo sapiens* ancestors. Modified from R.G. Klein [2]. Note that language follows the increase in endocranial volume and therefore the use of language cannot cause the expansion. Also, note that the appearance of first tools such as spears correlates well with increased cranial volume.

mechanisms on a daily basis. In the transition to surviving by thinking, most people (our non-ancestors) probably died simply due to errors of judgment or a lack of an intuitive, non-verbal comprehension of things such as the aerodynamics and gyroscopic stabilization of a spear while hunting a large, dangerous animal.

How did we get from accurately throwing a spear to the theory of relativity? The field of artificial intelligence (AI) may shed light on this question. AI promised household robots that would wash dishes, mow the lawn, and bring us freshly cooked croissants and coffee in the morning. Needless to say we do not have these robots now and none of the readers of this piece will probably ever see them, despite the immense financial impetus to build them. This is because common tasks are actually conceptually complex. However, AI is very good at things we superficially consider intellectual, such as playing chess, winning Jeopardy, flying a jet plane, or driving a car. To understand this paradox, consider the game Foldit, in which players predict protein structures [8]. Humans beat supercomputers at this game in much the same way that we can wash the dishes and put them away better than a robot. We win because Foldit uses spatial reasoning skills that were perfected and selected for in our hunter–gatherer ancestors. Many kinds of modern refined intellectual activity (by which our children are judged) may not necessarily require more innovation, synthesis, or creativity than more ancient forms: inventing the bow-and-arrow, which seems to have occurred only once about 40 000 years ago, was probably as complex an intellectual task as inventing language. Selection could easily have operated on common (but computationally complex) tasks such as building a shelter, and then computationally simple tasks, such as playing chess, became possible as a collateral effect. Loss of any one of 2000–5000 genes prevents us from effectively doing everyday tasks, and selection for the ability to perform them would optimize the function of the entire group of genes.

When might we have begun to lose these abilities? Most likely we started our slide with high-density living, which was enabled by the transformative invention of agriculture. Selection may have begun operating on resistance to the diseases that naturally grow out of high-density living, switching the pressure from intelligence to immunity. It is also likely that the need for intelligence was reduced as we began to live in supportive societies that made up for lapses of judgment or failures of comprehension. Community life would, I believe, tend to reduce the selective pressure placed on every individual, every day of their life. Indeed that is why I prefer to live in such a society.

Several considerations could mitigate the validity of the argument that intellectual and emotional fitness are slowly decaying. For example, genes required for intellectual and emotional function could be needed for early development or even fertility, and would thus be maintained through selection. Indeed, some genes associated with X-linked intellectual deficiency (XLID) are also involved in the development or function of other tissues or organs. However, these other syndromic features are not lethal, and many do not impair reproduction. Although the multiple usage of genes could slow the rate of accumulation of mutations in intellectual fitness genes, if the estimates for the number of genes required and mutation rate are correct, and selection is only slightly relaxed, one would still conclude that nearly all of us are compromised compared to our ancient ancestors of 3000–6000 years ago.

Another common counter-argument is that we are under constant selection for our intellectual traits (Box 1).

Box 1. The Flynn effect

The famous Flynn effect, in which absolute IQ scores increased during the first 50 years after the institution of these tests, seems at first glance to contradict the hypothesis that we are losing our intellectual abilities. However, these changes in IQ scores are probably linked to environmental influences including reduction in lead and other heavy metals used in gasoline and paint and the virtual elimination of hypothyroidism in children due to the widespread use of iodinated salt. These and many other advances in prenatal care and prevention of anoxia during childbirth have clear effects on our average intellectual abilities. In addition, scores on these tests have been shown to correlate well with preschooling and other societal influences instituted during the period over which test scores were compared. Consistent with these hypotheses, the gains recorded are predominantly in the raising of lower scores. However, since about 1985 or 1990 these absolute IQ scores have been dropping in some studies, despite considerable 'teaching to the test' as well as the general awareness among children that it is important to score well on the test. Most likely these short-term effects are not genetic because the genetic effects at issue are only likely to operate over hundreds of years, not decades. In addition, Flynn points out that we are not getting more intelligent, but instead we are getting 'smarter' at taking the tests because our everyday experiences are becoming more like the tests. This is similar to the way that practicing tennis makes one a better badminton player.

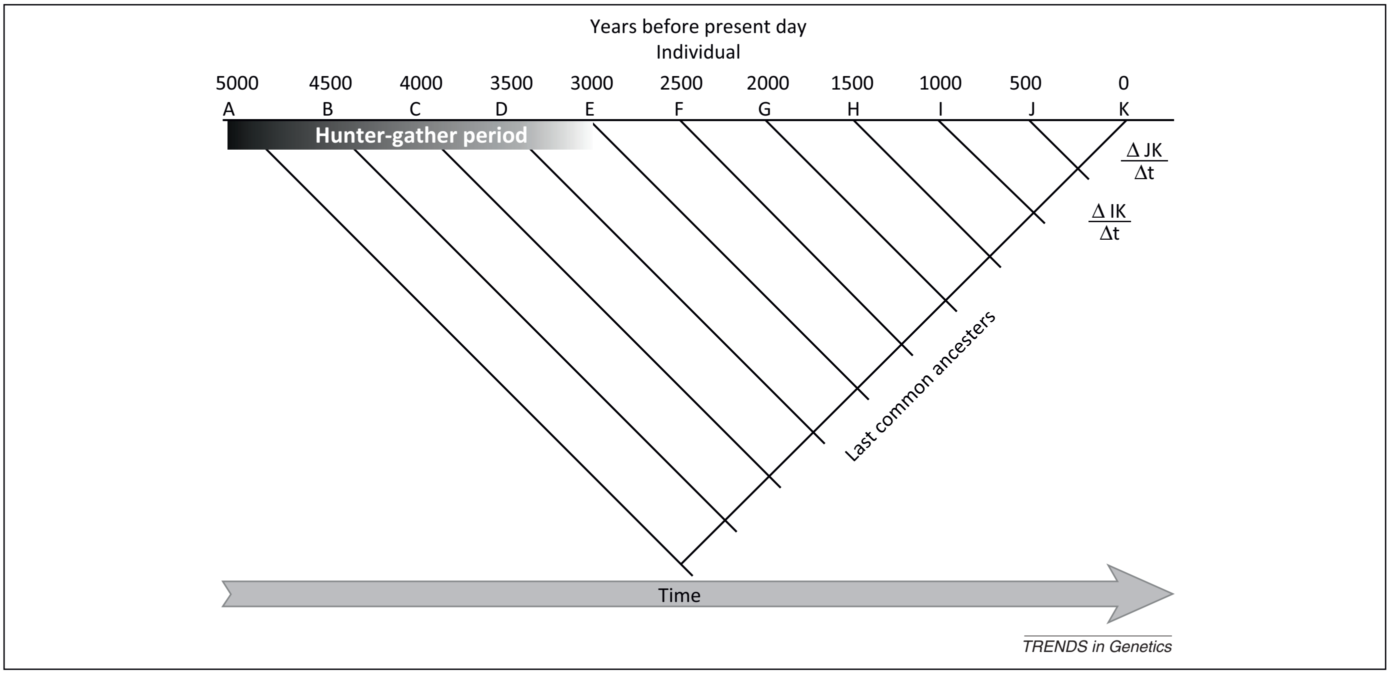

Figure 2. Genetic triangulation to measure rate of change of ID genes over the past 5000 years based on genome sequences of present-day individuals with last common ancestors separated by specific times, Δt (500 years in this case for illustration). The bar at the top indicates the transition from hunter–gatherer to a more high-density lifestyle when selection based on resistance to infection might have begun to dominate over selection for intellectually or emotional fitness.

Intellectual capacity and emotional stability have mating advantages that would reduce the rate at which mutations affecting these traits become fixed in our genome. This is true, but I fear does not take into account the extreme selection required to maintain traits dependent upon thousands of genes with reduced heritability. A hunter–gatherer who did not correctly conceive a solution to providing food or shelter probably died, along with his/her progeny, whereas a modern Wall Street executive that made a similar conceptual mistake would receive a substantial bonus and be a more attractive mate. Clearly, extreme selection is a thing of the past.

The hypothesis that genes critical to intellectual function are decaying could be tested by a form of genetic triangulation (Figure 2). Sequencing many individuals whose last common ancestors ranged from present day to 5000 years ago should produce an estimate of the rapidity of change and the level of selection operating on these genomes at various time-intervals during this 5000 year period (an interval that would span the emergence of cities for several population groups). These genomes would have sequence variations in intellectual deficiency (ID) genes but, because each generation produces only about 40 new signature mutations, these would not be enough to guide the temporal ordering. However, using the 400 million retroviral insertion sites as signatures of a specific ancient generation to estimate the age of nearby new mutations, sufficient fineness might be produced to permit dating of mutations in ID genes. Because mutations that control the evolution of specific characteristics have often been found in regulatory rather than coding regions, full genome sequences would need to be assayed. I would be very happy to learn from this test that there is no substance to my argument.

However, if such a study found accelerating rates of accumulation of deleterious alleles over the past several thousand years then we would have to think about these issues more seriously. But we would not have to think too fast. One does not need to imagine a day when we could no longer comprehend the problem, or counteract the slow decay in the genes underlying our intellectual fitness, or have visions of the world population docilely watching reruns on televisions they can no longer build. It is exceedingly unlikely that a few hundred years will make any difference for the rate of change that might be occurring. Remarkably, it seems that although our genomes are fragile, our society is robust almost entirely by virtue of education, which allows strengths to be rapidly distributed to all members. The sciences have come so far in the past 100 years that we can safely predict that the accelerating rate of knowledge accumulation within our intellectually robust society will lead to the solution of this potentially very difficult problem by socially and morally acceptable means. But in the meantime I'm going to have another beer and watch my favorite rerun of 'Miami CSI' (if I can figure out how to work the remote control).

References

1 Crabtree, G.R. (2012) Our fragile intellect. Part I. *Trends Genet.* http://dx.doi.org/10.1016/j.tig.2012.10.002
2 Klein, R.G. (1999) *The Human Career*, University of Chicago Press
3 Aiello, L.C. and Dunbar, R.J.M. (1993) Neocortical size, group size and the evolution of language. *Curr. Anthropol.* 34, 184–192
4 Holden, C. (1998) No last word on language origins. *Science* 282, 1455
5 Turkheimer, E. *et al.* (2003) Socioeconomic status modifies heritability of IQ in young children. *Psychol. Sci.* 14, 623–628
6 Devlin, B. *et al.* (1997) The heritability of IQ. *Nature* 388, 468–471
7 Bouchard, T.J., Jr *et al.* (1990) Sources of human psychological differences: the Minnesota Study of Twins Reared Apart. *Science* 250, 223–228
8 Cooper, S. *et al.* (2010) Predicting protein structures with a multiplayer online game. *Nature* 466, 756–760

http://dx.doi.org/10.1016/j.tig.2012.10.003 Trends in Genetics, January 2013, Vol. 29, No. 1