Our Fragile Intellect

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I would be willing to wager that if an average citizen from Athens of 1000 BC were to appear suddenly among us, he or she would be among the brightest and most intellectually alive of our colleagues and companions. We would be surprised by our time-visitor's memory, broad range of ideas and clear-sighted view of important issues. I would also guess that he or she would be among the most emotionally stable of our friends and colleagues. I do not mean to imply something special about this time in history or the location, but would also make this wager for the ancient inhabitants of Africa, Asia, India or the Americas of perhaps 2,000 to 6,000 years ago. I mean to say simply that we *Homo sapiens* may have changed as a species in the past several thousand years and will use 3000 years to emphasize the potential rapidity of change and to provide a basis for calculations, although dates between 2,000 and 6,000 years ago might suffice equally well. The argument that I will make is that new developments in genetics, anthropology and neurobiology make a clear prediction about our historical past as a species and our possible intellectual fate. The message is simple: our intellectual and emotional abilities are genetically surprising fragile.

How many genes are required to carry out our everyday tasks, read a book, care for a loved one, conceive of a just law or compose a song? An accurate answer to these questions is critical to understanding our genetic fragility. The larger the number of genes required, the more susceptible we are as a species to random genetic events that reduce our intellectual and emotional fitness. Recently the means to answering this question have emerged from genetic studies and insights into the human genome. Several lines of evidence and classic as well as modern genetic studies have converged to indicate that the number of genes required for normal human intelligence and abilities might be surprisingly large.

As biologists we commonly think in terms of traits controlled by single genes. Indeed, the one-gene one-protein paradigm was a critical part of our education and the thought that one protein did one thing governed much of the thinking during the past 50 years. Hence, when I recently mentioned to a group of my colleagues that the average Greek of 1000 BC might be intellectually and emotionally superior to our average present day colleagues they raised the objection that this was impossible because the most recent estimates of the frequency of random mutations in yeast is about 3.80×10^{-10} to 8.4×10^{-9} per-base-pair per generation[1]. Furthermore, the vast majority of these random mutations do not influence the function of a gene. Hence, if you imagine a small number of intelligence genes that control this trait, our abilities would not be affected during the course of 3000 years (100 to 150 generations). However, modern genetic studies in mammals are suggesting something very different than this simple analysis.

Perhaps the most effective way to estimate the number of genes in humans needed for full intellectual function comes from studies of X-linked intellectual deficiency (XLID). Because there is but one X chromosome in males, the affects of X chromosome mutations cannot be rescued or compensated by the second copy as for other chromosomes. Present studies indicate that mutation of about 215 intellectual deficiency genes (ID genes) on the X chromosome gives rise to XLID and/or emotional disability [2,3]. Present estimates indicate that there are 818 human X chromosome protein-coding genes of a total of 19, 586 genes; taken from: (Vertebrate Gene Annotation version 35 [Vega v35; March 2009]; http://vega.sanger.ac.uk/index.html). Thus, this line of evidence indicates that about ¼ of genes on the human X chromosome are needed for full intellectual and emotional function. Of the 215 genes on the X chromosome that give rise to XLID when mutated 86 have been characterized and do not seem to be neomorphs (a gain of inappropriate function). If we derive our estimate from this group of characterized genes a more conservative estimate of about 10% of the genes on the X chromosome are necessary for normal intellectual and emotional function. Because mutation of any one of the genes gives rise to compromise, we can state that these genes do not operate as a robust network, but rather

as links on a chain in which failure of any one of the links gives rise to deficiency. If the X chromosomal is not enriched for those required for intellectual development, there should be between 2,000 and 5,000 genes needed for intellectual and emotional function. The X chromosome does not appear to be enriched for ID genes as shown by the distribution of unmapped autosomal loci[4]. In addition, autosomal recessive mental retardation seems to be very heterogenous even within a genetically similar background indicating that it is due to mutations in many genes[4,5]. Many of these genes appear to function quite indirectly, such as Brm, one of two ATPase subunits of BAF chromatin regulatory complexes[6]. Although Brm would not normally be considered an intelligence gene or to contribute to the origins of abstract thought in humans, even minor point mutations give rise to mild to severe mental retardation in humans[6]. Brm and its homologue SWI2/Snf2 play critical roles in chromatin regulation in many species. A critical point is that a gene need not be human or brain specific in its function to be essential for our specific human intellectual abilities. A third estimate of the number of genes that function like links on a chain to support normal intellectual and emotional function can be made by assaying how frequently human genetic diseases in general have an intellectual deficiency component. This analysis is more difficult than it might seem but, a recent study of the OMIM database indicates that about ½ of all human genetic diseases have a neurologic component[7] frequently including some aspect of intellectual deficiency. These figures are consistent with the rough estimate of 2,000 to 5,000 genes required for intellectual and emotional function. With this estimate in hand we can revisit the calculations of how quickly our intellects might change with a reduction in selection.

If the proper function of 2,000 to 5,000 genes are necessary for our intellectual ability, then in the simplest case the complex traits of emotional and intellectual fitness will drift with reduced selection at 2,000- to 5,000-times that of a trait specified by a single gene. Independent studies in humans using phenotypic methods have estimated that the germline suffers about one deleterious mutation per average protein-coding gene per 100,000 generations[8-11]. These are mostly point mutations that lead to compromise of gene function without totally inactivating it. Recently, direct sequencing of parents and their children have found about 35 to 50 new mutations per genome per generation[8], or about 5,000 new mutations in the past 3000 years (120 generations). Of these germ-line mutations only a small fraction (less than 1%) will be harmful and some vanishingly small fraction will increase fitness. Thus direct sequencing as well as phenotypic analysis indicates that the germline suffers at least one deleterious mutation per average protein-coding gene per 100,000 generations[8-11]. If indeed 2,000 to 5,000 genes are necessary for our intellectual and emotional stability then about one child in 20 to 50 should suffer a new mutation effecting intellectual function. Another way to state the same information is that every twenty to fifty generations we should sustain a deleterious mutation. Within 3000 years or about 120 generations we have all very likely sustained two or more mutations harmful to our intellectual or emotional stability.

A test of this estimated frequency of deleterious heterozygous mutations was recently published[12]. A survey of 185 human genomes contained on average about 100 heterozygous mutations predicted to produce a loss of function. Remarkably, about 20 of these were found to be homozygous. Often these mutations were in genes such as olfactory receptors that seem less important in humans and may be deteriorating due to lack of selection. This estimate was made on the basis of exon sequences and hence would miss regulatory mutations that are much more difficult to predict. Hence, it represents an underestimate of the number of deleterious mutations in current human genomes derived from different human populations with different migration routes in the past 50,000 years. The number of mutations that lead to intellectual deficiency can be derived from examination of the frequency of mental retardation in the children of consanguineous marriages. If our genomes were free of such heterozygous mutations, there would be no tendency for mental retardation to occur in children of consanguineous marriages. Needless to say this is not the case. For reasons mentioned below the best estimates are derived from 1st degree consanguinity, for which there is relatively little information. However, incidental reports indicate that 1st degree consanguinity (in which ¼ of the genome is reduced to homozygosity) leads to mental retardation in about ¼ to ½ of off spring[13] and lesser degrees of consanguinity to

lower frequencies[5]. These figures are roughly consistent with the estimate of 2 or 3 deleterious heterozygous ID mutations per genome. However, heterozygous mutations (effecting only one copy) are generally not considered likely to produce a problem without reduction to homozygosity by consanguinity or random chance. But new discoveries indicate that the human nervous system is uniquely susceptible to heterozygousity.

Recently Gage and colleagues have reported[14] that Line 1 repetitive elements in humans transpose and appear to lead to gene inactivation in neurons. The somatic origin of these transpositions was demonstrated by direct sequencing of different brain regions by Faulkner and colleagues[15], who found that other repetitive elements could also transpose and insert into or control critical neurodevelopmental genes. Indeed they have a strong tendency to insert into coding regions and these insertions lead to transcriptional interruption[16]. Thus, even if they insert into a long intron they can be damaging. Over 7000 L1 insertions were detected in three individuals. The Line 1 insertions occur in neural stem cells and lead to clones of neurons with specific insertion sites. Gage and colleagues estimate that each neuron sustains about 80 Line 1 insertions, indicating that most neurons would have a number of genes whose activity could potentially be affected. These could be beneficial and lead to greater diversity, but this seems less likely based on the prior work of Boeke and colleagues[16]. Transposon inactivation would not be a problem if we were dealing with a single or small number of intelligence genes, rather than several thousand that could lose function in a specific brain region. By random L1 insertion heterozygosity is transformed to homozygous loss of function in a clone of neural stem cells and a focal defect in the brain. L1 insertions do not occur randomly, but rather target transcribed genes indicating that they have a high probability of inactivating a gene, and indeed insertion sites in ID genes have already been documented[15]. Thus, if one were heterozygous for a gene involved in formulating speech, and this gene were lost in some of the neural progenitors for the speech regions, one would expect a specific loss of speech function, even if this gene were used for other essential embryonic processes (see below). Many neurons with deleterious insertions might be eliminated by their failure to form effective neural circuits, which could lower their impact on neural functions. One could argue that anything that occurs in Nature must be good for us, but this line of reasoning is quite incorrect. More species have become extinct by natural means than are presently present on our planet and internal parasites could be quite harmful. A practical implication of these studies is that identical twins will be non-identical genetically in neuronal subpopulations and hence the contribution of genetic factors will be underestimated in classic identical twin studies. It is also worth noting that the number of genes that could comprise intellectual function by this means would be much larger than that estimated by the analysis of the X-chromosome, because even embryonic lethal mutations could be inactivated by insertion of mobile elements such as Line 1 transposons. Another less obvious consequence is that that this route to homozygosity will make intellectual ability less heritable. The consequence is that selective pressure must be higher to maintain neurologic traits in general. This makes the job of maintaining the 2,000 to 5,000 genes in good working order even more difficult. The simple lesson is that as a species we are almost certainly more susceptible to heterozygous inactivation of ID genes than we had previously understood.

Another route to homozygous inactivation (removing or altering both gene copies) in individuals already bearing a germline mutation in one allele of the estimated 2,000 to 5,000 genes required for intellectual fitness is a feature of the nervous system that has recently come to light. For reasons that are unclear apparently between 10 and 50% of human neurons are aneuploid, i.e. have chromosomal abnormalities that lead to breaks, losses and duplications of genetic material[17]. Again, it appears that aneuploidly might originate in neural stem cells[18] and hence be clonal, thereby resulting in a focal loss of function in a specific region of the brain. Furthermore, neurons with aneuploid genomes form genetically mosaic neural circuitries as part of the normal organization of the mammalian brain[19]. Aneuploidy of chromosome 21 is of course the basis of Down Syndrome, which is accompanied by a reduction in intellectual function and illustrates the effect of alterations in gene copy number. Copy number variation appears to have a role in several neurologic diseases[20] including autism[21], which for uncertain reasons has become more common in recent years[22]. However, the apparent recent increase in incidence of autism may simply be due to greater awareness of the condition and in any event

would probably not be impacted by the rate of mutation accumulation within a 50-year period. The above two arguments suggest that focal loss of heterozygousity might be an underlying feature of neurologic diseases that would be difficult to detect by present day genome sequencing approaches designed to find the genes at fault in human disease. In order to detect focal loss of heterozygousity, neurons from many regions of the brain would need to be sampled and their DNA sequenced. Aneuoploidly and transposon insertion are non-germline routes to homozygous inactivation of a gene and are the reason that 1st degree consanguinity gives the best estimate of the frequency of heterozygous mutations in the human genome. As is the case with transposon inactivation of genes, clonal aneuoploidly would lead to misinterpretation of studies with identical twins causing one to underestimate the genetic contribution to intellectual or emotional traits. As with retrotransposon insertion, focal aneuploidly would also reduce heritability of neurologic traits, making them more difficult to maintain by selection.

A third and perhaps even more likely way that inactivation of one of the two copies of an ID gene could be damaging is through compound heterozygosity. The calculations mentioned above and recent population genome sequencing studies[8] suggest that most of us are heterozygous for two or more of the 2,000-5,000 genes that appear to be required for intellectual function. This brings up the complex issue of cooperativity between the ID genes. Presently, there are not easy ways of defining gene pairs that lead to reduced function when one allele of both genes is defective. Heterozygous inactivation of two or more genes encoding proteins within the same biochemical pathway, genetic circuit or protein complex is known to produce reduced function. One recent example is that human intellectual deficiency is produce by mutation of at least six subunits of nBAF complexes[6,23,24], which are large ATP-dependent chromatin remodeling complexes found in a specialized assembly in the nervous system[25]. It seems quite likely that compound heterozygousity of genes encoding subunits within these complexes would reduce intellectual fitness, and indeed this is the case for nBAF subunits[24]. In general, it is quite difficult to know if loss of one allele in, for example an enzyme removing a neurotoxic intermediate would exaggerate or lead to defects in an individual heterozygous for a gene required for dendritic morphogenesis. These considerations make human genetic studies designed to find the genes at fault in human cognitive disorders quite difficult, yet double- or compound-heterozygosity would almost certainly contribute to reduced function among the estimated 2,000 to 5,000 genes required for full intellectual and emotional function. One could argue that this group of genes operates as a robust network, however this can not be the case since the criteria used for selecting these genes is that inactivation of any one of the 2,000 to 5,000 leads to reduced function, demonstrating that they function like links on a chain rather than a robust, fail-safe network. Reduced function due to double- or compound-heterozygousity may be expected to operate exponentially over time as deleterious heterozygous mutations accumulate in our genome at a linear rate.

If we are losing emotional and intellectual traits, how did we get them in the first place? Needless to say this is one of the most important questions of modern anthropology and the subject of much investigation and debate. I can only speculate, but it seems necessary and also just plain fun to step outside my comfort zone and comment. One clear fact is that the expansion of the human frontal cortex and endocranial volume (Fig 1), which is thought to have given humanity our capacity for abstract thought occurred about 50,000 and 500,000 years ago[26 27] in our pre historic African ancestors. These ancestors did not have a written language and for most of their history probably did not have much of a verbal language[26],[28]. They also did not have organized agriculture that permitted life at high density in cities and societies. Thus, the selective pressures that gave us our capacity for abstract thought and human mental characteristics operated among hunter-gathers living in dispersed bands, nothing like our present day high-density, supportive societies. It is also seems clear that both written and verbal language first appeared well after endocranial expansion (Fig 1) and hence could not have been a driving force to acheive our present brain size (blue area in Fig 1) about 50,000 years ago. Furthermore, it seems that our intellectual capacity has not changed very much in the last 50,000 years since our African ancestors began their migrations. How do we know this? Because the societies with different migration routes that experienced quite different environments seem to have near identical intellectual capacities. For example,

written language was independently invented by the group with the longest migration path as hunter gathers: the Indians of Middle and South American and also independently by the people with the one of the shortest migration paths and the earliest cities: Sumerians, in what would now be Iraq. In addition, whether a migration group lived a high density city-life made possible by agriculture or as dispersed hunter gathers did not greatly influence their intellectual development. If we are to understand how 2,000 to 5,000 genes were optimized for abstract thought to produce our present abilities we almost certainly have to look to this period 50,000 to 500,000 years ago and to ancestors common to all humans on earth today. Yet somehow the selective pressures that allowed survival as dispersed hunter gatherers led to the evolution of a brain capable of writing symphonies and performing higher mathematics. Almost certainly our present day abilities are a collateral effect of being selected for more fundamental tasks. Because it seems clear that we developed the ability for abstract thought by being selected for abstract thought, it must be that life as a dispersed hunter-gather was more intellectually demanding than we would commonly think. The fact that the expansion of the frontal cortex and with it the capability for abstract thought was driven by evolution forces that appear to have operated before the development of verbal or written language (Fig 1) might seem an affront to people like myself that make our living by writing and speaking. We seem to be forced to the conclusion that life as a hunter gather required at least as much abstract thought as operating successfully in our present society. We know that most of our ancestors lived the dispersed hunter gather life until about 5- to 10-thousand years ago, when the invention of agriculture lead to our high density societies, written language and to a life style something like what we have today. Regardless of how we have lived since we began our migrations: hunter-gather or cosmopolitan, we are intellectually about the same. Surprisingly, it seems that if one is a good architect, mathematician or banker, these skills were an offshoot of the evolutionary perfection of skills leading to our ancestor's survival as nonverbal, dispersed hunter-gathers.

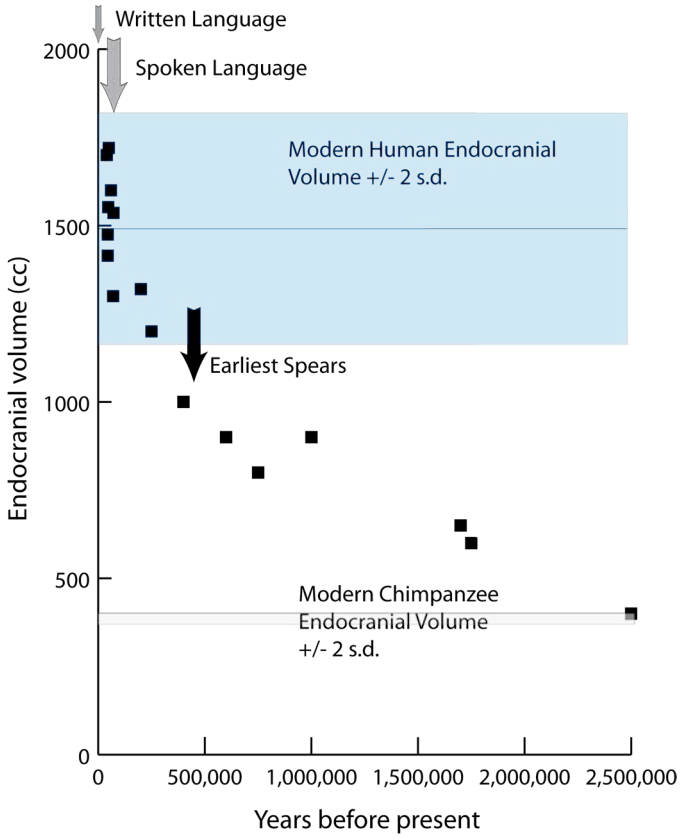

Figure 1. Expansion of endocranial volume during the past 2.5 million years among *Homo Sapiens* ancestors. Modified from R.G. Klein (ref 24). Note that language follows the expansion.

To understand the extremes of selection that must have occurred when our ancestors went from using speed, strength and agility to survive and began to survive by using thought, we have to consider the difficulty of optimizing 2,000 to 5,000 genes. For the reasons mentioned above it seems that retrotransposon insertion and aneuploidy of neurons substantially reduce heritability of neuronal traits. Without going into the mathematics, when heritability of a trait is reduced, the selective pressure required to maintain the trait is increased. In addition, one would need to sum the selective pressure for each of the genes operating independently to produce the trait. Thus, extraordinary selective pressure was necessary to optimize and maintain such a large group of intelligence genes. This optimization probably occurred in a world where every individual was exposed to nature's raw selective 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.

One might think that our modern abilities could not have originated from a time 50,000 to 500,000 years ago and selection based on hunter-gather abilities. We think of the common hunter-gather abilities as crude and unrefined and not intellectually challenging, how could our modern abilities be an offshoot of being selected in this way? It seems that the field of artificial intelligence may be making a significant contribution to this question. When this field was first born several decades ago, it promised household robots that would do all our daily tasks: cook meals; take the dishes off the table, wash them and put them away; mow the lawn; fix that leaky rain gutter, repair a child's toy 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 benefit from such a household robot. (Although one AI expert I consulted said computers might have this kind of computational power in 10 years). This is true even though such a robot would have the commercial value of the world's automotive industry and hence there is immense impetus to design them. Paradoxically, things that we consider intellectual, such as playing chess, winning at Jeopardy, flying a jet plane or driving a car are fairly straightforward for a computer and do not require even a small fraction of the computational power required for common human actions. The point is that selection could easily have operated on common (but computationally complex) tasks, like building shelter, with the result of allowing us to do more computationally simple tasks, like playing chess. Indeed, mutation of any one of 2,000 to 5,000 genes prevents us from effectively doing these common everyday tasks and selection for the ability to perform them would tend to optimize the function of the entire group of genes. But, as mentioned above the selective pressure would have to be remarkable.

When might we have begun to loss these abilities? Most likely we started our slide with the invention of agriculture, which enabled high density living in cites. Selective pressure was then turned to resistance to diseases that naturally grow out of high density, urban living. A principal of genetics is that when one selects highly for one trait (such as resistance to infectious disease) other traits are inadvertently selected against. It is also quite likely that the need for intelligence was reduced as we began to live in supportive, high-density cities that made up for lapses of judgment or failure of comprehension. Community life would, I believe tend to reduce the selective pressure placed on every individual, every day of their life; indeed that's 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. The most significant is the assumption that modern society has reduced selective pressure for intellectual fitness. Even if one agrees with the assumption that selection for intellectual fitness has decreased, selective pressure for the genes required for intellectual and emotional function could originate from other sources. Probably the most significant is that genes used for intellectual development could be needed for early development or even fertility. Indeed, this is true of some of the genes required for diverse cellular functions where retardation or emotional compromise is found only with alleles that partially impair the function of the gene. An estimate of the frequency with which XLID genes are also required for other functions can be derived from the observation that about ½ of XLID patients have syndromes that suggest these genes are used in the development or function of other tissues or organs. However, these other syndromic features appear not to be lethal and many do not impair reproduction, hence, there would be little limit on the ability of these genes to be prevalent in the human population without selection. The estimate that 215 of 818 genes on the X chromosome are required for intellectual function accounts for the possible use of these genes in early development, because these estimates are derived from viable individuals. While multiple usage of genes could slow the rate of accumulation of mutations in intellectual fitness genes, if the estimate of the number of genes required is correct, and the rate of accumulation of deleterious mutations is correct and selection only slightly relaxed, then one would still conclude that nearly all of us are compromised compared to our ancient ancestors of Asia, Africa, Europe and the Americas of say 3,000 to 6,000 years ago.

Another common counter argument to the possibility that we are losing our intellectual fitness raised by my colleagues is that we are under constant selection for our intellectual traits. Presumably, musical ability, employment and emotional stability may all have mating advantages that would reduce the rate at which mutations that affect these traits become fixed in our genome. This argument is clearly correct, but I fear does not take into account the extreme selection that must operate to maintain traits dependent upon thousands of genes in the face of relatively low heritability of the traits due to non-germline inactivation operating within the group of genes. Needless to say a hunter gather that did not correctly conceive a solution to providing food or shelter probably died along with their progeny, while a modern Wall Street executive that made a similar conceptual mistake would receive a substantial bonus.

Yet another, less compelling counter argument goes like this: Our generation has an intricate written language, uses computers, drives cars, designs space crafts, and plays chess; which the ancients of several thousand years ago did not. Hence, we must be smarter than they were. This argument presumes that operating a computer or playing chess is more complex that building a house, farming, surviving in the jungle or washing the dishes and putting them away. However, as mentioned above our nervous system evolved until recently to do common, but computation complex task very well, hence none of our modern abilities are different than just a retrofit of modes of thought that we have been selected to do as hunter gathers until the very recent invention of farming. Furthermore, the faults in this argument are easily revealed by the fact that an inexpensive hand-held computer can beat all but the best chess players in the world. In addition, relatively little computational power is needed for flying a plane or driving a car. In contrast, the computational complexity of many common practical tasks is revealed by the immense difficultly of building a computer that could direct a household robot to do what humans do very well. Although obvious, the frequently drawn analogy between a computer and a brain is not a very good one. Among other differences, our nervous system has far more computational units than any existing computer, operates in analogue mode(s) and is electrochemical in nature. Humans play chess and accomplish other tasks using different strategies than computers. Nevertheless, the difficulty of reproducing human tasks is one measure of how computationally complex a given task might be and what its intrinsic value might be. This is not to negate in anyway rare intellectual skills that are very valuable to society.

In addition to common house hold tasks another example of a very difficult computational problem that humans do very well is the game Foldit, in which players use their spatial intuition to predict protein structures[29]. Foldit has been described as resembling a Rubix cube with a thousand faces. Yet humans beat supercomputers at this game much in the same way that we can take the dishes off the table, wash them and put them away better than a supercomputer. Almost certainly we are very good at Foldit, because the game uses spatial reasoning and skills that were perfected and selected for in our non-verbal, hunter-gather ancestors 50,000 to 500,000 years ago. In contrast humans are bad chess players, probably because our brains were not selected for this kind of game designed to perfect skills for organized warfare. Organized warfare, being a communal activity was not invented till after our brains had undergone nearly all evolutionary selection, at a time when it was too late to perfect chess-playing (or warfare) abilities. As a result we are rather poor warriors, but we are excellent at spatial reasoning critical to Foldit, building shelter and other common tasks. If we had survived for the past million years based on our chess-playing skills we would almost certainly play a master game in far less than one second. Indeed, the only way the game could be made challenging would be to have a 1000 pieces, that could each make a dozen or more different moves. In other words a chess board would look like a table full of dirty dishes that needed to be washed and put away: a truly massive intellectual exercise, which should not be diminished by the fact that many of us can do it. It seems too obvious to state, but the tautology applies: our brains are good at the things they have been selected to be good at. Many kinds of modern refined intellectual activity (that our children are judged by) may not necessarily require more innovation, synthesis and creativity than more ancient forms. Inventing a bow-and-arrow, which seems to have occurred once about 40,000 years ago was probably as complex an intellectual task as inventing language or coming up with the theory of

relativity. Our intellectual abilities were highly selected at immense human expense to accomplish seemingly common tasks that require the perfected actions of 2,000 to 5,000 genes.

If the above argument is correct one would predict that individuals in undisturbed hunter gather societies would be more intellectually capable than those of us in more modern, urban, distributive societies. Certainly, Jered Diamond, who has spent his career of 50 years among one of the few remaining such societies feels that this is the case, but also acknowledges the difficulty with testing the idea. Because, all remaining hunter gather societies are restricted geographically, they have higher frequencies of reduction of heterozygous mutations to homozygousity, which as mentioned above is a particular concern when large numbers of genes are at issue.

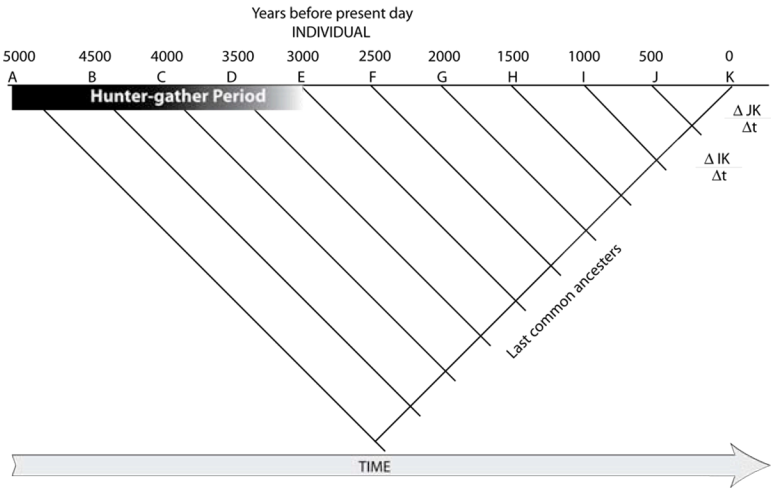

Fig 2. Genetic triangulation to measure rate of change of ID genes over the past 5000 years based on genome sequences of present day individuals with last common ancestors separated by specific times, Δt. (500 years in this case for illustration). The bar at the top indicates the transition from hunter-gather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

The hypothesis that genes critical to intellectual function are decaying could be tested by a form of genetic triangulation (Fig 2). The sequences of genomes of many individuals whose last common ancestors spanned the period from present day to 5,000 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 5,000-year period. Five thousand years would probably be an adequate interval since it would span the invention of agriculture for several population groups, which enabled high density living in cities and the shift to selection for resistance to infection. To obtain the required fineness and discrimination, many genomes would need to be sequenced. If we focus on the interval between 5,000 years ago and present day, we would need 100 genome sequences for a 50-year fineness map. Since each generation produces 2,000-4,000 signature new mutations these could guide the temporal ordering. If the genes that control our intellectual development act like links on a chain, only one conservative mutation in any of 2,000 to 5,000 genes would diminish our intellectual abilities and also be difficult to detect with certainty. 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 determined. In addition, many of the mutations would almost certainly produce weak alleles that might erode our abilities in subtle ways. However, as a first pass an examination of the coding regions of XLID genes and those from the OMIM data base having ID phenotypes as well as memory and learning genes from other organisms would be a good place to begin and give estimates of the rate of emergence of alleles that might be deleterious in this large set of genes. I would very happy to learn from this test that there is no substance to my argument.

If on the other hand such a study found accelerating rates of accumulation of deleterious alleles in 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 might no longer be able to comprehend the problem or the means to do anything about the slow decay in the genes underlying our intellectual fitness. Nor do we need to have visions of the world's population docilely watching reruns on televisions that they can no longer understand or build. It is exceedingly unlikely that one hundred or two hundred years will make any difference at the rate of change that might be occurring. Remarkably, it seems that while our genomes are

fragile and built like a chain with many links, 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 hundred 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).

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