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Our fragile intellect. Part I

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New developments in genetics, anthropology, and neurobiology predict that a very large number of genes underlie our intellectual and emotional abilities, making these abilities genetically surprisingly fragile.

I would 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, with a good memory, a broad range of ideas, and a clear-sighted view of important issues. Furthermore, I would guess that he or she would be among the most emotionally stable of our friends and colleagues. I would also make this wager for the ancient inhabitants of Africa, Asia, India, or the Americas, of perhaps 2000–6000 years ago. The basis for my wager comes from new developments in genetics, anthropology, and neurobiology that make a clear prediction that our intellectual and emotional abilities are genetically surprisingly fragile.

To assess this fragility we must first know how many genes are required for our intellectual abilities. 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 answer this question have emerged from genetic studies and insights into the human genome. Several lines of evidence indicate that the number of genes required for normal human intelligence might be quite large.

Perhaps the most effective way to estimate the number of genes in humans that are needed for full intellectual function is to rely on studies of X-linked intellectual deficiency (XLID). Because males have only one X chromosome, the effects of X-chromosome mutations cannot be rescued or compensated for by the second copy, in contrast to mutations on other chromosomes. Present studies indicate that mutation of about 215 intellectual deficiency (ID) genes on the X chromosome give rise to XLID and/or emotional disability [1,2]; this represents about 25% of the genes on the X chromosome. Of these, 86 have been characterized and do not seem to be neomorphs (a gain of inappropriate function). This gives a conservative estimate that about 10% of all human genes are implicated in intellectual function. Because mutation of any one of these genes can give rise to intellectual disability, it can be concluded that they do not operate as a robust network, but rather as links in a chain, failure of any one of which leads to intellectual disability. The X chromosome does not appear to be enriched for genes required for intellectual development [3], and therefore we can extrapolate that between 2000 and 5000 genes are needed for intellectual and emotional function. This is supported by the finding that autosomal recessive mental retardation seems to be very heterogeneous, even within a genetically similar background, indicating that it is due to mutations in many genes [3,4]. Many of these genes appear to function indirectly, such as the subunits of nBAF chromatin regulatory complexes, which are global transcriptional regulators [5]. This highlights that a gene need not be functionally brain- or even human-specific to be essential for our specific human intellectual abilities. Finally, the number of genes that function as links in a chain to support normal intellect is reflected in the frequency with which human genetic diseases in general have an ID component. A recent study of the Online Mendelian Inheritance in Man (OMIM) database, although incomplete, indicates that about half of all human genetic diseases have a neurologic component [6], frequently including some aspect of ID, consistent with the notion that many genes are required for intellectual and emotional function. The reported mutations have been severe alleles, often *de novo* mutations that reduce fecundity. However, each of these genes will also be subject to dozens if not hundreds of weaker mutations that lead to reduced function, but would not significantly impair fecundity, and hence could accumulate with time.

Based on estimates of the frequency with which deleterious mutations appear in the human genome (Box 1), and the assumption that 2000–5000 genes are required for intellectual ability, it is very likely that within 3000 years (~120 generations) we have all sustained two or more mutations harmful to our intellectual or emotional stability. Recent human genome studies revealed that there are, per generation, about 60 new mutations per genome and about 100 heterozygous mutations per genome that are predicted to produce a loss of function [7], some of which are likely to affect genes involved in human intellect. However, heterozygous mutations (affecting only one copy) are generally not considered problematic until they are reduced to homozygosity. But new discoveries indicate that the human nervous system is uniquely susceptible to loss of heterozygosity (LOH).

LINE-1 (L1) repetitive elements were recently reported to transpose in human neurons, leading to neuronal gene inactivation [8]. The somatic origin of these transpositions was demonstrated by direct sequencing of different brain regions [9], which revealed that other repetitive elements could also transpose and insert into or regulate critical neurodevelopmental genes. Indeed, they have a tendency to insert into transcribed genes, modifying transcription [10]. The L1 insertions occur in neural stem cells and lead to clones of neurons with specific insertion sites. Each

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Box 1. Estimation of the rate of accumulation of harmful mutations in ID genes

If the proper function of 2000–5000 genes is necessary for our intellectual ability, then in the simplest case emotional and intellectual fitness will drift with reduced or absent selection 2000–5000-fold more rapidly that a trait specified by a single gene. Studies in humans using phenotypic methods have estimated that the germline suffers about one new deleterious mutation per average protein-coding gene per 100 000 generations [9]. These are probably mostly point mutations that compromise gene function without totally inactivating it. Recently, an independent estimate of the rate of germline mutations was made from direct genomic sequencing of parents and their children, which found about 25 new mutations (if the father was under 20 years old) and about 65 new mutations (if the father was over 40) over the non-repetitive regions of the genome per generation [14,16]. This analysis predicts about 5000 new mutations in the past 3000 years (~120 generations). Of these new germline mutations in non-repetitive regions only a small fraction (variously estimated to be about 1–10%) will produce a change within a gene or its regulatory regions that will be harmful, and a vanishingly small fraction will increase fitness. This approach gives estimates of the rate of appearance of new mutations consistent with the older phenotypic estimates. However, the most recent estimate is that each child suffers six new harmful heterozygous mutations [16]. Thus the probability of any random gene suffering a harmful mutation in a given generation is at the very least 1/100 000. If indeed 2000–5000 genes are necessary for our intellectual and emotional stability, then we need to multiply this rate by 2000 or 5000 for the full collection of ID genes. Recall that mutation in any one of these genes produces intellectual or emotional deficiency. Thus the probability that any child will have a new mutation affecting intellectual ability is between 2000 and 5000 over 100 000. This figure predicts that about one newborn child in 20–50 should harbor such a mutation. Put another way, every 20–50 generations we should sustain a mutation in one copy of one of our many ID 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. Of course, these will be haploid mutations and will usually be rescued by the other normal allele, highlighting the importance of examining the effect of being haploid for any one of these genes.

neuron is estimated to sustain about 80 L1 insertions, indicating that gene expression is dysregulated in most neurons. These insertions can lead to inactivation of the remaining normal allele of a heterozygous essential gene in a clone of neural stem cells, thereby creating a focal defect in the brain. Many neurons with deleterious insertions might be eliminated by their failure to form effective neural circuits, but this is clearly not always the case because L1 insertions into ID genes have been documented [9]. A practical implication of these studies is that identical twins will have different neuronal subpopulations, and hence the contribution of genetic factors will be underestimated in classic twin studies. It is also worth noting that the number of genes estimated to underlie intellectual function by this means would be much larger than that estimated by the X chromosome analysis because even genes whose mutation causes embryonic lethality could be inactivated by the insertion of mobile elements such as L1 transposons. Another less obvious consequence is that that this route to homozygosity will make intellectual ability less heritable, which necessitates stronger selective pressure to maintain neurologic traits (more on this later).

Another route to homozygous inactivation, in individuals already bearing a germline mutation in one allele of a gene required for intellectual fitness, is a feature of the nervous system that has recently come to light: apparently between 10% and 50% of human neurons are aneuploid (i.e., they have chromosomal abnormalities that lead to breaks, losses, and duplications of genetic material) [11]. Again, it appears that aneuploidy might originate in neural stem cells 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 [12]. 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 including autism [13]. The above two arguments suggest that focal LOH might be an underlying feature of neurologic diseases, which would be difficult to detect by present-day genome sequencing approaches. To identify focal LOH, neurons from many regions of the brain would need to be sampled and their DNA sequenced. Because aneuploidy and transposon insertion are non-germline routes to homozygous gene inactivation, both would lead to misinterpretation of studies with identical twins and make neurologic traits more difficult to maintain by selection.

A third, and possibly even more harmful, effect of heterozygosity occurs when alleles of two or more genes involved in intellectual or emotional function are mutated. The calculations in Box 1, and recent population genome sequencing studies [14], suggest that most of us are heterozygous for mutations affecting two or more of the 2000–5000 genes estimated to be required for intellectual function. Heterozygous inactivation of two or more genes encoding proteins within the same biochemical pathway, genetic circuit, or protein complex can reduce function, similarly to a single homozygous mutation. One recent example is the finding that ID can be produced by mutation of at least six subunits of the nBAF complex. In a given individual, different heterozygous mutations appear to lead to reduced function and ID [5]. In general, it is difficult to know if loss of one allele in, for example, an enzyme removing a neurotoxic intermediate would cause 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 difficult, but double or compound heterozygosity would almost certainly contribute to reduced function among the estimated 2000–5000 genes required for full intellectual and emotional function, and compound heterozygosity will operate exponentially over time as deleterious heterozygous mutations accumulate in our genome at a linear rate.

Taken together, the large number of genes required for intellectual and emotional function, and the unique susceptibility of these genes to loss of heterozygosity, lead me to conclude that we, as a species, are surprisingly intellectually fragile and perhaps reached a peak 2000–6000 years ago. But if we are losing our intellectual abilities, how did we acquire them in the first place? This will be the topic of the next section [15].

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