Matt Ridley

The DNA behind human nature: gene expression and the role of experience

The idiosyncrasies of one person cannot be human nature, nor can a feature of human behavior that is merely typical of many animals, such as hunger. Human nature must be the product of a uniquely human, but near species-universal, combination of DNA sequences suitably refracted through typically human environmental experiences.

Those sequences do not have to be only genes. Indeed, recent evidence suggests that regulatory sequences, rather than coding sequences, may be the best place to search for 'human nature DNA.' As Steven Pinker has pointed out, it is a historical accident, and the source of much confusion, that genes are equated with the genome by lay people but strictly defined as protein-coding regions by molecular biologists.

Right up until the sequencing of the human genome, a piece of conventional wisdom was confidently repeated as truth by scientists, journalists, and commentators: there were a hundred thousand genes in the human genome, about half of which were unique to the brain. So widely was this 'fact' disseminated that it is hard now to discern its original source.[1] But it was about as wrong as a scientific assertion can be. We now know that human beings have approximately twenty-five thousand genes (humiliatingly, that is fifteen thousand less than a rice plant has); that most are expressed in both the brain and the body; and that very few indeed, perhaps none, are unique to the human species. Not only do mice also have twenty-five thousand genes, but they have essentially the same twenty-five thousand.

Yet mice are not men. Something must be different. The sequencing of genomes has suggested a new hypothesis: that animal evolution usually works not by inventing new protein-coding genes (this appears to be commoner in plants), but by altering the timing, intensity, and location of the expression of preexisting

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1 See, for example, J. Madeleine Nash, "Fertile Minds," *Time* 149 (5) (3 February 1997): "There are only 100,000 genes in human DNA. Even though half these genes – some 50,000 – appear to be dedicated to constructing and maintaining the nervous system."

genes.[2] For instance, the Hoxc8 gene essentially tells a developing fetus where to grow a thorax with ribs. Hoxc8 is turned on farther back in a chicken than in a mouse, giving a chicken a longer neck. It is turned on throughout the body of a python, which is almost all thorax. Yet it is essentially the same gene: equivalent Hox genes can be swapped between animal species and still work. Somewhere in each species' DNA are sequences that cause slightly different tissue-specific expression of Hoxc8.[3]

A literary analogy is helpful. Any two novels, say, *David Copperfield* and *The Catcher in the Rye*, are written using roughly the same set of words. Some words appear in one but not the other – 'caul' and 'pettish' appear in Dickens; 'crap' and 'elevator' appear in Salinger – but they are very few. The difference between the books' plots lies in the order and pattern of the words, not in the words themselves. The difference between a man and a mouse lies in the order and pattern of gene expression. And that difference is achieved by variations in the regulatory sequences of the genome (hereafter referred to as promoters), of which more shortly.

In this context, the genes that lie behind human nature are universal to mammals, possibly to all animals, but the pattern and timing of their expression during normal development results in typical human behavior. This has an unexpected bonus for scientists interested in human nature. It means that the discovery of a gene's function in an animal will almost certainly lead directly to the discovery of the same gene's function in a human being. As our knowledge of the genes that affect behavior is deepened by experiments in mice, as well as in dogs and other species with behaviorally distinct breeds, that knowledge will quickly and inevitably improve our understanding of human behavior, too. Of course, there will be differences, but discovering these differences will itself be both easy and instructive.

Likewise, the source of genetic variability in human nature among individual people will be found mainly in sequence differences that affect gene expression. It has been known since the work of Jacques Monod and François Jacob in the late 1950s that a gene is expressed, or transcribed into messenger RNA, by the binding of a protein called a transcription factor to a promoter, a special sequence of bases usually found immediately upstream of the gene itself. Furthermore, a gene may be switched off by the binding of another protein to another sequence nearby. In some cases, more than one protein must bind to the DNA before a gene is expressed, and the regulatory sequences may be spread out over long stretches of DNA – even longer than the gene itself. For example, the 'eve' gene in fruit flies, whose job is to control other genes during development, is switched on at least ten separate times during development, and it has eight separate regulatory sequences attached to it, three upstream of the gene and five downstream. Each of these sequences requires ten to fifteen proteins to attach to it to switch on expression of the eve gene, and together they cover thousands of letters of DNA text. In different tis-

2 Sean B. Carroll, "Endless Forms: The Evolution of Gene Regulation and Morphological Diversity," *Cell* 101 (6) (2000): 577 – 580.

3 Heinz-Georg Belting, Cooduvalli S. Shashikant, and Frank H. Ruddle, "Modification of Expression and Cis-Regulation of Hoxc8 in the Evolution of Diverged Axial Morphology," *Proceedings of the National Academy of Sciences* 95 (5) (1998): 2355 – 2360; Martin J. Cohn and Cheryll Tickle, "Developmental Basis of Limblessness and Axial Patterning in Snakes," *Nature* 399 (1999): 474 – 479.

sues, different promoters and enhancers (distant or downstream switches) are often used to express the gene.[4]

This implies that many, perhaps most, of the interesting differences between a human being and a mouse, or between one human being and another, will be found in the sequence of bases in promoters, rather than in protein-coding genes. Intriguingly, this hypothesis opens the door for cultural and environmental influence, because the efficient binding of transcription factors, and therefore the expression of genes, can in some cases be altered by factors extrinsic to the organism – by, in a word, experience. Steroid hormones, for example, once they have formed a complex with their receptors, act as transcription factors, activating or suppressing the expression of genes. So elevation of cortisol – following the sensory detection of a stressful experience – can alter gene expression, particularly in the immune system. It indirectly reduces expression of Interleukin-2 and turns down the activity, number, and life span of lymphocytes.[5]

Even more strikingly, it is now clear that a genetic mechanism underlies the very un-hereditary process of forming new memories by associative learning. Such learning in flies, mice, and people consists mainly of changes in the expression of CREB genes in response to experience. These changes result in shifts in the strength of particular synaptic connections between neurons – and these shifts are the manifestation of new memories. It is clearly misleading to call the CREB gene a determinant of human nature, because what it determines depends on what the organism experiences, and yet it is human nature to have a responsive CREB gene that enables us to learn.[6]

4 Mark Ptashne and Alexander Gann, *Genes and Signals* (Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press, 2002).

5 Paul R. Martin, *The Sickening Mind: Brain, Behaviour, Immunity and Disease* (London: HarperCollins, 1997).

The twenty-five thousand genes in a mammalian genome, played like a great piano by their many thousand promoters, and probably able to express at least three times as many proteins through alternative splicing, are amply capable of encoding a subtle and complex human nature throughout the tissues of a hundred-trillion-cell body, even without supposing a role for experience. There is no reason to assume that the 'higher' and more peculiarly human faculties such as intelligence, language, and social empathy are less influenced by genes than are features we normally think of as more primitive, such as aggression or hunger.

Here follow three genes that distinguish human beings from other animals, not by their existence, but by their sequence – in either the coding or the regulatory region – and by their pattern of expression. The first bears on intelligence, the second on language learning, the third on pair-bond formation – all 'higher' human faculties.

The first gene concerns the place where human anatomy meets human nature: brain structure. Having an unusually large brain for its body size is characteristic of the human being. If the gene expression theory is correct, this feature should result from the differential expression or activity of a gene or genes in human beings. One candidate gene is already known, thanks to the study by Geoffrey Woods and colleagues

6 Josh Dubnau and Tim Tully, "Gene Discovery in Drosophila: New Insights for Learning and Memory," *Annual Review of Neuroscience* 21 (1998): 407 – 444.

of inherited microcephaly in a group of inbreeding Kashmiri immigrants in Bradford, England. Microcephaly is the development of a small but otherwise normal brain.

Four separate mutations in the same gene were found to be one cause of the condition. The gene, first isolated in drosophila, is called ASPM, for abnormal spindle protein. Found on chromosome 1, it is a gene that varies considerably in length between species, producing a protein that is 1,186 amino acids long in nematode worms; 1,861 in fruit flies; 3,123 in mice; and 3,477 in human beings. This elongation is caused mainly by extra repetitions of a 75-base-pair calmodulin-binding motif, which is repeated seventy-four times in human beings, sixty-one in mice, twenty-four in flies, and twice in nematodes. (The motif, by a happy accident, is called the IQ motif, after the first two letters of its amino acid sequence, isoleucine and glutamine.) It appears that the longer the protein, the more effective it is at assisting mitosis in neuronal stem cells in the developing brain. Since stem cells multiply only for a set period during development, faster mitosis will yield more neurons and a bigger brain.[7]

ASPM is not in itself sufficient to explain the expansion in human brain size over the past five million years, because all higher primates have approximately the same number of IQ repeats in the gene.[8] The gene may have altered to make primates brainier than other mammals, but not to make human beings brainier than other primates. The search for the source of that difference has now turned to other genes affecting brain size. Yet the ASPM story serves as a strong reminder of just how simple it might be for a species to acquire an increased brain size merely by lengthening one gene with extra copies of a motif. In this case, the change is not in a promoter but in the gene itself, resulting in a more active protein from a longer gene.

The second gene affecting higher human function concerns language. Human beings are not just chimpanzees with bigger brains; they also have qualitatively different natures. Some differences of degree between human beings and all other mammals are so wide that they qualify as differences in kind. One such is language. The human capacity for learning languages shows all the hallmarks of an instinct underpinned by genes: it emerges unbidden and shows universal similarities in all people.

Once again, the study of people with linguistic defects has led to insights into which genes are especially important in differentiating human language skills from other primates' communication talents. By examining an extended family in which speech and language deficits are plainly inherited as a dominant allele, Simon Fisher and Cecilia Lai found a candidate gene, called FOXP2, on chromosome 7.[9] Other cases now confirm that lack of a functional form of FOXP2 seems to impair learning that uses sensory feedback to alter the circuitry in the brain to lay down new sequences of

7 Jacquelyn Bond, Emma Roberts, Ganesh H. Mochida, Daniel J. Hampshire, Sheila Scott, Jonathan M. Askham, Kelly Springell, Meera Mahadevan, Yanick J. Crow, Alexander F. Markham, Christopher A. Walsh, and C. Geoffrey Woods, "ASPM Is a Major Determinant of Cerebral Cortical Size," *Nature Genetics* 32 (2) (2002): 316–320.

8 C. Geoffrey Woods, personal communication, March 2004.

9 Cecilia S. L. Lai, Simon E. Fisher, et al., "A Forkhead-Domain Gene is Mutated in a Severe Speech and Language Disorder," *Nature* 413 (2001): 519–523.

orofacial gestures and new memories thereof.

How might FOXP2 do this? Fox, or forkhead box, genes are transcription factors whose job seems to be to activate or repress transcription of other genes. They are universal to animals and fungi. In mammals, which have at least forty Fox genes, FOXP2 shows remarkably little variation between species. Of 136 nucleotide substitutions in the gene between chimpanzee and mouse, only one alters the amino acid sequence of the protein; the rest are synonymous. Since the common human-chimp ancestor, however, there have been two amino-acid-altering changes, making the human FOXP2 protein stand out from all other mammal versions so far studied. And all but a very few human beings have identical versions of FOXP2.[10]

Moreover, a study by Svante Pääbo and colleagues of the number and pattern of silent substitutions in noncoding DNA nearby seems to show that the two mutations were involved in a selective sweep about two hundred thousand years ago, during which they elbowed aside all other versions of the gene, presumably as a result of natural selection. This date is intriguing because it does not predate by much the Upper Paleolithic Revolution in Africa and, therefore, possibly the beginning of symbolic communication and modern language, according to physical anthropologists. After a million years of technological stasis, there was sudden and cumulative cultural change – new tools, artifacts, pigments, trade – some time before one hundred thirty thousand years ago, the time when long-distance trade was definitely established.[11] Some small band of African human beings apparently took over the world starting at this time, and we are all their descendants.

Of course, there is no direct evidence that FOXP2 was anything other than a fortunate bystander at this revolution, and even if it did play a role, it has plenty of other functions in the body besides facilitating language – it is expressed in the lung, for example. But it is also expressed during early development in those parts of the brain crucial to speech. People with mutated FOXP2 genes show under-activation of Broca's speech area when engaged in linguistic tasks, implying that some deficiency in the structure of that part of the brain resulted from that mutation.[12]

Birds have a FoxP2 gene that is surprisingly similar to that of mammals, given the evolutionary distance between the two classes, which suggests extreme conservation or convergent evolution.[13] This gene (and another, FoxP1) is expressed especially strongly in male songbirds in the striatal nucleus known as Area X – part of the 'song circuit.' For instance, expression here rises during the period when young zebra finches learn their songs and during the season when adult canary songs become unsta-

10 Wolfgang Enard, Molly Przeworski, Simon E. Fisher, Cecilia S. L. Lai, Victor Wiebe, Takashi Kitano, Anthony P. Monaco, and Svante Pääbo, "Molecular Evolution of FOXP2, a Gene Involved in Speech and Language," *Nature* 418 (2002): 869 – 872.

11 Sally McBrearty and Alison S. Brooks, "The Revolution That Wasn't: A New Interpretation of the Origin of Modern Human Behaviour," *Journal of Human Evolution* 39 (2000): 453 – 563.

12 Gary F. Marcus and Simon E. Fisher, "FOXP2 in Focus: What Can Genes Tell Us About Speech and Language?" *Trends in Cognitive Sciences* 7 (2003): 257 – 262.

13 Note that the current convention is to express the names of human genes in uppercase letters, mouse genes in lowercase letters, and bird genes in a mixture of the two. This absurd system cannot last.

ble. Both these results hint that FoxP2 expression is somehow vital to the laying down of new vocal procedures in birds' brains.[14]

Assuming human FOXP2 does alter the development of Broca's area in such a way as to facilitate the learning of language, there is an obvious problem. The first human being with a modern FOXP2, somewhere in Africa two hundred thousand years ago, would have been in the same fix as Victor of Aveyron, Kaspar Hauser of Nuremberg, or Genie of Los Angeles – children reared largely in isolation from spoken language until their teens and who thus missed the critical period when the brain is most open to language learning. He or she would have developed little of his or her full linguistic potential. However, once there were several children with the new gene, a sort of bootstrapping might have been possible as they practiced their language skills among themselves; something similar happened in Nicaragua in 1979 when deaf children were suddenly brought together in one school and spontaneously developed their own Creole sign language. Then each generation would have added to the complexity, and within a few generations this chattering group of people would have been capable of feats of planning and organization foreign to their fellow human beings.

I repeat: it is highly implausible that changes in FOXP2 alone made language possible. Rather, it was probably one of many genetic changes that helped improve the emerging communication skills of proto-people. But the principle, that species-wide changes in single genes can affect 'higher' behavioral traits in predictable ways, is well supported.

The third gene that affects a human trait concerns love. One way in which human beings differ markedly from their closest evolutionary relatives, the chimp and the bonobo, is in habitually forming long-term pair bonds. These are so intrinsic to human nature that they form even in libertarian communes that expressly try to outlaw them. Of course not all human beings form long-term or exclusive pair bonds, but human beings show all the hallmarks of a long-bonding species: sexual jealousy, paternal care, sexual division of labor, etc. Chimpanzees and bonobos, on the other hand, maintain only brief pair bonds that do not last longer than the estrus period of the female, if that.[15]

In this respect, human beings resemble prairie voles and chimpanzees resemble montane voles, two equally closely related species that also differ in mating systems. The control of pair-bonding in voles is now well understood. In both sexes in both species of vole, sexual intercourse stimulates the release of the small peptide hormones oxytocin and vasopressin in the brain. Injecting the hormones into the brain brings on pairing behavior in prairie voles but not in montane voles. Increasing the expression of the receptor genes also makes prairie voles quicker to form pair bonds.[16]

14 Sebastian Haesler, Kazuhiro Wada, A. Nshdejan, Edward E. Morrisey, Thierry Lints, Eric D. Jarvis, and Constance Scharff, "FoxP2 Expression in Avian Vocal Learners and Non-Learners," *Journal of Neuroscience* 24 (2004): 3164 – 3175.

15 Matt Ridley, *The Red Queen: Sex and the Evolution of Human Nature* (New York: Penguin, 1995).

16 Expressing the prairie-vole version of the gene in a mouse markedly increases its social-affiliation behavior. See Thomas R. Insel and Larry J. Young, "The Neurobiology of Attachment," *Nature Reviews in Neuroscience* 2 (2001): 129 – 136.

Receptors for these hormones are distributed differently in the brains of the two species. In prairie voles, the receptors are found in the nucleus acumbens (oxytocin) and the ventral pallidum (vasopressin). These brain areas contain a dopamine system that is responsible for addictive behavior. A prairie vole therefore becomes 'socially addicted' to its mate following sex. A montane vole does not. Likewise, when human beings who are in love are asked to contemplate a picture of their beloved, the area of the brain that is active is a dopamine region implicated in cocaine addiction.[17]

The different distribution of the receptors is in turn caused by the presence (in prairie voles) or absence (in montane voles) of a long segment of highly repetitive DNA text in the promoter upstream of the gene. Inserting this text into the promoter of a promiscuous vole species essentially monogamizes the rodent.[18] Human beings also have a repetitive segment in this region, though it is shorter than that in prairie voles. As of this writing, the equivalent region of the chimpanzee genome has not yet been looked at. I predict it will be shorter than the human one.

These three cases illustrate very graphically that it is possible to isolate genes that have disproportionate influence on behavior, and to do so in features relevant to 'higher' human nature, such as intelligence, language, and love. In the 1960s, the idea of finding 'behavior genes' at all would have been astonishing, not to say heretical, but people such as Benson Ginsburg working with mice and Seymour Benzer with flies soon established that behavioral mutants could be produced just as easily as anatomical mutants. The unexpected similarity of human and animal genomes has now made it possible to study in other species the evolution of genes relevant to human intelligence, language, and love. The development of behavior, in other words, proves to be just as amenable to genetic reductionism as anatomy and physiology.

Human nature, however, is not identical in all people, and much of that diversity in behavior is a consequence of the fact that we are not clones. Studies of identical and fraternal twins raised apart, but in similar social settings, have unambiguously revealed that different people have different personalities largely because they have different genes, rather than because they have different upbringings. However, these studies, which prove so powerful in showing the influence of genes, have been largely incapable of shedding light on precisely which genes influence personality. From the other end of the telescope, however, genetic differences among individuals are emerging that correlate with differences in how people behave. The haystack is revealing its first few needles.

One example is the gene on chromosome 11 for a protein called brain-derived neurotrophic factor (BDNF). The gene spells out the recipe for a protein that acts as a sort of fertilizer in the brain, encouraging the growth of neurons, and that probably does much else besides. In most people, the 192nd letter in the gene is G, but in about one-quarter of people it is A. This causes a slightly different protein to be built – with methionine instead of valine at the 66th

17 Andreas Bartels and Semir Zeki, "The Neural Basis of Romantic Love," *NeuroReport* 11 (2000): 3829 – 3834.

18 Miranda M. Lim, Zuoxin Wang, Daniel E. Olazabal, Xianghui Ren, Ernest F. Terwilliger, and Larry J. Young, "Enhanced Partner Preference in a Promiscuous Species by Manipulating the Expression of a Single Gene," *Nature* 429 (6993) (2004): 754 – 757.

(out of 247) codon. Since everybody has two copies of each gene, there are three kinds of people in the world: those with two methionines in their BDNFs, those with two valines, and those with one of each. Personality questionnaires reveal that, at least in one population, the met-mets are noticeably less neurotic than the val-mets, who are in turn noticeably less neurotic than the val-vals.[19]

However, this kind of single-nucleotide polymorphism (SNP), while frequently found to cause rare hereditary diseases, is proving to be the exception rather than the rule in the study of normal human variation. It is much commoner to find a polymorphism that consists of different lengths of sequences of promoters upstream of genes. To return to the vasopressin receptor gene, for instance, it appears that the repetitive box in the promoter is highly variable in length in wild prairie voles. Its length ranges from 350 to 550 base pairs in a typical sample of the rodents. Likewise, in a sample of 150 human beings, there were seventeen different lengths of the equivalent box next to the same gene. It is perhaps too simplistic, and possibly unethical, to ask if those people with longer boxes generally form more lasting pair bonds. But note that divorce rates show surprisingly high heritability in studies of twins raised apart.[20]

Meanwhile, the study of twins shows that the same upbringing does not necessarily produce similar personalities in two different people, whereas the same genome often does. A possible explanation of this surprising result is that genes do not decide personality directly, but they do decide how an individual will respond to a particular upbringing. Hard evidence for this hypothesis is now beginning to accumulate. Perhaps the best example is the study of childhood maltreatment and genotype in a New Zealand cohort.

In a study of 442 young men from Dunedin born in the year 1972 – 1973, Terrie Moffitt and her colleagues found evidence that an abusive upbringing does predispose a boy to later antisocial behavior (including getting into trouble with the law), but much more strongly if the boy has a particular genotype: a low-activity version of the monoamine oxidase A gene on the X chromosome. In the promoter upstream of the gene there is a 30-base pair phrase repeated three, three and a half, four, or five times. Those genes with three or five repeats are much less active than those with three and a half or four repeats. About one-third of men have low-activity versions of the gene (women, having two X chromosomes, present a more complicated picture). The low-activity allele itself does not appear to cause antisocial behavior, nor does childhood maltreatment alone, but together they have a marked effect.[21]

The correlation between parental abuse and antisocial behavior in the Dunedin study cannot be assumed to be causal. It may be that another undiscovered gene causes both the abuse and the antisocial behavior in combination with

19 Srijan Sen, Randolph M. Nesse, Scott F. Stoltenberg, Sheng Li, Lillian Gleiberman, Aravinda Chakravarti, Alan B. Weder, and Margit Burmeister, "A BDNF Coding Variant Is Associated with the NEO Personality Inventory Domain Neuroticism, a Risk Factor for Depression," *Neuropsychopharmacology* 28 (2003): 397 – 401.

20 Judith Rich Harris, *The Nurture Assumption: Why Children Turn Out the Way They Do* (London: Bloomsbury, 1998).

21 Avshalom Caspi, Joseph McClay, Terrie E. Moffitt, Jonathan Mill, Judy Martin, Ian W. Craig, Alan Taylor, and Richie Poulton, "Role of Genotype in the Cycle of Violence in Maltreated Children," *Science* 297 (2002): 851 – 854.

the low-activity MAO-A gene. A long history of fallacious assumption teaches us to be cautious before presuming that parents cause effects in children by their actions rather than by passing on genes.[22]

This precaution, however, does not apply to a similar result in another gene. Again using the Dunedin cohort, Moffitt found that a functional polymorphism in the promoter region of the serotonin transporter (5-HTT) gene affects the way people react to stressful life events. Stressful life events are less likely than abusive treatment to be even indirectly caused by genes. People with one or two copies of the short allele of the 5-HTT promoter showed more symptoms of depression following at least three stressful life events than people with two copies of the long allele.[23]

Considering that genes influence depression by altering people's ability to cope with life events, can anybody doubt that the genes that influence personality and intelligence work this way – that they are genes for responding differentially to experience? A person with high intelligence is a person whose genes enable him to react efficiently to the experience of learning. A person with an athletic talent is one whose genes enable her to respond easily to practice and training.

Notice, in passing, how important the length of, rather than the sequence of, a promoter often proves to be. This is a general principle that is emerging from many studies of gene function. The diversity in the human population is starting to be explained at least as much by variations in the number of repeats of a genetic phrase in the regulatory region of the gene as by single-nucleotide polymorphisms. The phrase may be two or three letters long (as in the case of the vasopressin receptor), twenty-two letters long (5-HTT serotonin transporter gene), thirty letters long (monoamine oxidase gene), or seventy-five letters long (ASPM gene). Varying the number of repeats of a phrase has a much subtler effect on gene function than does changing a single nucleotide in a codon, which tends to shut the gene down. It seems to be the principal way in which natural selection alters the intensity, and perhaps the pattern, of gene expression. Nor is this phenomenon confined to the regulatory regions of the genome. At least six neurological diseases are now known to be caused by excessively long polyglutamine runs – most notably Huntington's disease, whose severity depends on the number of repeats of a three-letter phrase (CAG) in the gene for the huntingtin protein.

Precisely how does a gene open the organism to experience? A nice example of how, paradoxically, the capacity for nurture can be genetically programmed comes from features that show critical, or sensitive, periods in development. There are many features of animal and human behavior that are sensitive to environmental influences only during a limited period in youth. Language learning is one. Filial imprinting in birds is another. The best-studied case, however, is that of ocular dominance, or the sorting of cells in layer 4c of the visual cortex into those that take their signal from the right eye and those that take it from the left. Ocular dominance emerges in response to experience soon after a mam-

22 Harris, *The Nurture Assumption*.

23 Avshalom Caspi, Karen Sugden, Terrie E. Moffitt, Alan Taylor, Ian W. Craig, HonaLee Harrington, Joseph McClay, Jonathan Mill, Judy Martin, Antony Braithwaite, and Richie Poulton, "Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene," *Science* 301 (2003): 291 – 293.

mal's eyes first open and is thereafter irreversible. Experiments have revealed that the gene for a protein called GAD65 must be switched on for the sorting to occur, and that another protein, BDNF, brings the sorting to an end. Genetically modified mice with no GAD65 gene never enter the critical period; those with overactive BDNF genes close down the critical period prematurely.[24]

Both genes regulate the activity of GABA, a neurotransmitter that has also been shown to be vital to filial imprinting in chicks. This finding hints at a general genetic mechanism, based in GABAergic neurons, for opening the organism's brain to calibration by experience during a narrow window in infancy. If individuals' critical periods differ in length or openness, this may be because they differ in sequences of promoters attached to GABA-related genes. These variations, in turn, would produce a different pattern of learning in different individuals. Thus, even the acquired differences between people in skills and interests might be partly caused by sequence differences at promoter sites. A good tennis player is the product of much practice, but the ability to benefit from practice could prove to be innate. Nurture, in that sense, is a form of nature.

There was an old joke, first told by Jane Gitschier, that we would one day be able to find out where on the Y chromosome lie the male tendencies to flip between channels on the television, to sit on the john reading, and to be incapable of expressing affection over the telephone (the ME-2 gene). It was a joke that exposed not only the absurdity of men, but also the absurdity of specific genes for specific behaviors – the old Daltonian, particulate, 'blueprint' model of a genome, in which one gene corresponds to one attribute of behavior. Genes are not, of course, like that. As Pat Bateson has argued, they act more like recipes than blueprints. Attributes of an organism no more map directly to single genes than pieces of a cake map directly to lines in a recipe: they are the product of a transaction between many genes and the environment in which they find themselves.

Nonetheless, it was widely assumed in the heyday of the blank slate in the 1950s – 1970s that specifically behavioral mutations would not be found, and that therefore behavior would remain a P2C2E (a process too complicated to explain), at least in genetic terms. The studies of twins raised apart, and the discoveries of DNA sequence changes that cause predictable changes in behavior, even in 'higher' behavior, demolish this assumption. The magnitude of that paradigm shift has yet to dawn on many social and even biological scientists.

A different hypothesis is needed if we are to reconcile the evident fact that there is an innate human nature with the equally evident feeling that experience molds individual lives. That hypothesis, I suggest, must hold that human nature is specified in species-typical DNA sequences, that many of those sequences determine the expression rather than the protein product of genes, and that the expression of many of these sequences is actually 'designed' (by natural selection) to be affected or calibrated by expected kinds of environmental experience.

24 Z. Josh Huang, Alfredo Kirkwood, Tommaso Pizzorusso, Vittorio Porciatti, Bernardo Morales, Mark F. Bear, Lamberto Maffei, and Susumu Tonegawa, "BDNF Regulates the Maturation of Inhibition and the Critical Period of Plasticity in Mouse Visual Cortex," *Cell* 98 (1999): 739 – 755; Michela Fagiolini and Takao K. Hensch, "Inhibitory Threshold for Critical-Period Activation in Primary Visual Cortex," *Nature* 404 (2000): 183 – 186.