Commentary

In our genes

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The D4 dopamine receptor (DRD4) locus may be a model system for understanding the relationship between genetic variation and human cultural diversity. It has been the subject of intense interest in psychiatry, because bearers of one variant are at increased risk for attention deficit hyperactivity disorder (ADHD) (1). A survey of world frequencies of DRD4 alleles has shown striking differences among populations (2), with population differences greater than those of most neutral markers. In this issue of PNAS Ding *et al.* (3) provide a detailed molecular portrait of world diversity at the DRD4 locus. They show that the allele associated with ADHD has increased a lot in frequency within the last few thousands to tens of thousands of years, although it has probably been present in our ancestors for hundreds of thousands or even millions of years.

There is a repeat polymorphism in exon III of the gene at which a variable number of 48-bp motifs can occur. The common and probable ancestral allele has four repeats (4R), whereas the allele associated with novelty seeking and ADHD has seven (7R). Ding *et al.* (3) show that there are essentially two allele classes at the locus: most variants are easily derived from 4R by simple recombinations or mutations, whereas 7R differs from 4R by a minimum of seven events. This means either that the coalescence of the 4R and 7R allele classes is ancient or that 7R was generated by an extremely improbable mutation and recombination event more recently. At any rate the allelic diversity within the 4R class and the lack of linkage disequilibrium with markers around it show that it has been the common variant in our species for a long time. 7R alleles, with little diversity within the class and high linkage disequilibrium with neighboring markers, must have a recent common ancestor. If the 7R class has been rare for a long time, coalescence within the class could be recent, whereas coalescence between the 7R and 4R classes could be ancient. This curious pattern, an allele that has been in the population for a very long time at a very low frequency, suggests that some kind of balancing selection has been maintaining 7R, but preventing it from becoming common until recently. An alternative is that 7R was incorporated from another hominid species during the expansion of modern humans.

It is clear from association studies with childhood ADHD that the allele affects behavior, but it is not so clear what it does. The recent positive selection for 7R denies that it causes pathology in any evolutionary sense. Adaptive genetic variants cannot be the cause of fitness-reducing mental illness unless that illness in some way is a product of recent environmental change or is compensated by other increases in fitness as in classical balanced polymorphisms. Natural selection would have purged common alleles that induce crippling disorders such as schizophrenia in premodern conditions. On the other hand, it is entirely possible that some psychological traits are adaptive yet, because they are irritating or undesirable, are called mental illness. There is an important distinction to be made between fitness-reducing mental illnesses, behaviors that can never have been adaptive, and psychological syndromes that we happen not to like (4). Another hint that 7R does not cause pathology in an evolutionary sense is the finding that children diagnosed with ADHD often show specific neurological deficits, whereas children bearing 7R and diagnosed with ADHD do not show such deficits (5).

A survey of world frequencies of DRD4 alleles has shown striking differences among populations.

Neurotransmitter receptors are especially good candidates for genetic variation that modulates behavior. The polymorphisms we see in dopamine metabolism all seem to be in receptor and transporter molecules rather than in the dopamine molecule itself. Dopamine is involved in a wide spectrum of functions, acting through five different receptors. Any change that affected all of those systems at once would almost certainly be maladaptive. A mutation that affects a smaller range of systems, by changing a single dopamine receptor or transporter, has a better chance. The same principle may apply to other neurotransmitters, which typically have a number of different receptors. We know that serotonin, for example, has 14 (6).

Evidence of adaptive genetic variation affecting human psychology should be of interest to evolutionary psychologists, particularly because they have argued that it cannot exist. For example Tooby and Cosmides (7) claim that there are only two kinds of human nature, male and female, and that apparent variation in personality is either facultative response to environmental cues or nonadaptive. They argue that complex adaptations require the coordinated action of many genes, and that if individuals of a sexually reproducing species differed in the genes required to build these adaptations, sexual reproduction would disrupt the necessary gene complexes. They also argue that there has been insufficient time since the advent of modern humanity for the development of significant novel mental adaptations.

As has been pointed out by D. Wilson (8), their arguments are unconvincing. They imply that no sexual species should have heritable adaptive morphs, whereas in fact many examples are known, such as the male morphs of the side-blotched lizard *Uta stansburiana* that act out a scissors–paper–rock game, in which morph A beats morph B, morph B beats morph C, and morph C beats morph A (9). The "insufficient time" argument is probably just incorrect; considering the measured heritability of psychological traits and the expected response to mild selection over hundreds of generations, it is instead surprising that we seem to have changed little over historical time.

Even if 40 or 50 thousand years were too short a time for the evolutionary development of a truly new and highly complex mental adaptation, which is by no means certain, it is certainly long enough for some groups to lose such an adaptation, for some groups to develop a highly exaggerated version of an adaptation, or for

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changes in the triggers or timing of that adaptation to evolve. That is what we see in domesticated dogs, for example, who have entirely lost certain key behavioral adaptations of wolves such as paternal investment. Other wolf behaviors have been exaggerated or distorted. A border collie's herding is recognizably derived from wolf behaviors, as is a terrier's aggressiveness, but this hardly means that collies, wolves, and terriers are all the same. Paternal investment may be particularly fragile and easily lost in mammals, because parental investment via internal gestation and lactation is engineered into females but not males.

If, as seems likely, the basis for selection at DRD4 has been the effect of the 7R allele on behavior, the selective advantage of 7R is probably frequency-dependent rather than absolute. Even a small absolute advantage would eventually make this allele go to fixation or nearly so. In the case of simple directional selection the new advantageous allele takes a long time to reach an appreciable frequency, then approaches fixation in a much smaller number of generations. There would be only a relatively small time interval in which one would see both new and old alleles at intermediate frequency, and the new allele would be most common near its place of origin. What we see today looks much more likely to be the consequence of some kind of frequency-dependent selection, in which the frequency of the new allele increases up to a certain point and then stabilizes. These selective forces must not be the same in all populations, because the 7R allele is quite common in some populations (South American Indians), exists at intermediate frequencies in others (Europeans and Africans), and is rare to nonexistent in yet others (East Asia, !Kung Bushmen) (2).

When the advantage of an allele is frequency-dependent, two or more different alleles can persist indefinitely at polymorphic frequencies. In evolutionary game theory, such a stable mix is known as an evolutionary stable strategy or ESS (10). The most famous example is the hawk–dove game, in which doves always yield to hawks, whereas aggressive hawks incur fitness costs from fighting other hawks, costs that increase as hawks become more common. If the cost of fighting is greater than the gains from intimidation, hawks and doves coexist. Consider, for example, the game of chicken. A player who throws his steering wheel out the window always wins in a world of cautious opponents, but as the wheel-discard players become common their fitness declines and a stable proportion of the two types can result. Many examples of species with such alternate morphs are known. Some vary in aggression, others in sexual behavior, diet, or dispersal tendencies. A continuous distribution of some trait, not just discrete morphs, can also be an ESS. Such forces seem particularly likely to exist in humans, because the evolutionary payoff of an individual's behavior in a complex society will depend strongly on the reaction of others to that behavior.

Because the prominent phenotypic effects of 7R are in males, we need to ask what is the niche in human societies for males who are energetic, impulsive (i.e., unpredictable), and noncompliant? Whereas tests of hypotheses ought to be careful and conservative, generation of hypotheses ought to be speculative and free-ranging. There is a tradition of caution approaching self-censorship in discussions of human biological diversity, but we will break that tradition in what follows.

There are at least two hypotheses to explain the world distribution of 7R. The first, due to Chen *et al.* (2), is that it is a dispersal morph. They argue that the allele increases the likelihood that its bearers migrate. As modern humans colonized the earth, bearers of 7R were more likely to be movers so that populations far away from their ancient places of origin have, in effect, concentrated 7R. The world high frequencies in South America reflect the great distance of South America from the original human homeland: similarly migrations from China led to the presence of the allele in southeast Asian and Pacific populations, whereas none remained in China. This hypothesis does not account for the apparent long persistence at low frequency of 7R in human ancestors before the population movements occurred that were responsible for population frequency differences.

The second hypothesis is that 7R bearers enjoy a reproductive advantage in male-competitive societies, either in competition for food as children or in face-to-face and local group male competition. Societies in which this advantage would be present were rare before the spread of agriculture, but common after it. This hypothesis requires a brief review of human ecological history. We acknowledge our abuse of detail and of ethnographic diversity in the summary that follows.

The evolutionary payoff of an individual's behavior in a complex society will depend strongly on the reaction of others to that behavior.

Modern humans were successful colonizers of much of the Old World by 40,000 years ago. They lived by hunting and gathering and, later, by agriculture. The archaeological evidence suggests that agriculture appears soon after the end of the Pleistocene, but the antiquity of occasional tropical gardening is not known. Where human densities were low, agriculture was most often extensive, involving shifting cultivation of gardens that were then left fallow for years. Increasing human densities led to agricultural intensification with ever higher inputs of labor to ever scarcer land, resulting in plow agriculture and organized irrigation.

Among most hunting and gathering people both sexes work to provision offspring; in particular males allocate much of their reproductive effort to parental effort. These "dad" societies contrast with "cad" societies in which males allocate reproductive effort to mating effort, that is to competition with other males for access to females.

The general theory of the "war between the sexes" is described by Dawkins (11), whereas the human version of it is described in a landmark paper by Whiting and Whiting (12) and elaborated by others (13, 14). In general, in societies where males are dads, men and women live together with their offspring; they eat and sleep together; the males are not particularly gaudy; and they do not make fancy weapons and art. Pair bonds are durable, divorce rates are low; and nuclear families are the primary context for care of children.

In cad societies, the public relations between men and women are aloof; men and women often do not eat and sleep together; and males are involved in personal adornment, fancy and decorative weapons and art, and local raiding and warfare. In many such groups, for example, men eat and sleep in a men's house rather than with families. Marriages are not durable, and children from an early age are likely to be left to the care of siblings and other children. The latter societies are called "peer-rearing" societies in the literature, whereas dad societies are more often "parent-rearing" societies.

Most foraging people are dad societies, the exceptions being cases where there are periodic rich resource streams like salmon runs on the North American northwest coast. There is some controversy in the literature about whether apparently parental males in dad societies are really parental or whether they are instead engaged in many subtle forms of male competition and mate guarding (15). At any rate the end result is that men work and provide food to children.

Among low density gardeners, on the other hand, the typical pattern is that most of the gardening work is done by women, freeing men from subsistence responsibilities. Boserup (16) calls these "female

farming systems," a euphemism for societies where men live off women. Freed from domestic responsibility, men can occupy their time decorating themselves and planning the next raid. Widespread systems of such societies, as in highland New Guinea or lowland South America, seem to be stable as the chronic raiding and warfare suppress population growth. But powerful polities can break the stability, suppressing local male coalitional violence, leading to population growth, agricultural intensification, and ultimately to males again working at farming to provision their families. Thus there are drab males working at subsistence among foragers and, at the other end of the density continuum, among intensive agriculturalists and peasants. In between we see decorative competitive males engaged in local male coalitional violence. There is an unsettling parallel with the dad males of the working class in contemporary industrial societies and the cad males of the underclass (17).

There are several ways in which female farming systems might have opened up new behavioral niches or greatly expanded existing ones. Females in these societies often have children by more than one male, because pair bonds are fragile. Hence siblings are more likely to be half rather than full siblings. This increases the extent to which individuals in the same family have genetic conflicts of interest; it exacerbates such conflicts between parents, between parent and offspring, and between siblings. Children that are in some sense "difficult" may have a survival advantage in these conditions. One study found that a sample of difficult infants survived a drought at a higher rate than easy infants (18). Further, whenever paternal investment decreases, paternal genetic quality becomes relatively more important. The 7R allele may facilitate risky "show-off" behaviors that exhibit good genes: cad societies are characterized by male posturing and machismo, "protest masculinity" in an older terminology. Most obviously, energetic unpredictable adult males may enjoy a competitive advantage in the face-to-face male competition and violence that characterize these groups. Chagnon (19) has shown that there is a fitness payoff to warriors and those with such a reputation among the Yanomamo of Amazonia.

In a preagricultural world of hunters and gatherers, males with an advantage in face-to-face competition would have enjoyed a limited advantage, perhaps being favored only in those niches where periodic resource abundance allowed male competition to flourish elsewhere new ecological circumstances led to transient plenty as on the Great Plains after the introduction of the horse. Otherwise they would have been disadvantaged, especially because there were more of them. But the advent of gardening technology freed males from subsistence work and, in the new social environment of display, aggression, and male coalitional violence bearers of 7R may have flourished, accounting for the evidence given by Ding *et al.* (3) of the recent increase in frequency of the allele. Finally, as polities emerged that suppressed the system of local anarchy, population growth occurred, land became scarce; agriculture became more labor intensive; and men were again forced into work to provision their families. The archetypes in the literature of anthropology of dad hunter-gatherers are !Kung Bushmen of southern Africa; the archetypes of labor intensive farmers are east Asians; and the archetypes of local anarchy are Indians of lowland South America like the Yanomamo. It is probably no accident that two of the best known ethnographies of the twentieth century are titled "The Harmless People," about the !Kung who have few or no 7R alleles, and "The Fierce People," about the Yanomamo with a high frequency of 7R.

There are several ways in which female farming systems might have opened up new behavioral niches.

Our hypothesis suggests that the absence of 7R in East Asia is recent, consequent to the establishment of powerful polities that allowed population growth and forced agricultural intensification. It is of interest in this context that 2R alleles in China are probably derived from 7R alleles by recombination, suggesting that the loss of 7R is indeed recent.

Besides lowland South America, another well known region with local anarchy and female farming is highland New Guinea. Our model of the dynamics of 7R predict that the frequency is very high in those populations. Because they have been there for tens of thousands of years and they have not moved, the Chen *et al.* (2) model predicts a low frequency of 7R there. This is a natural test to distinguish the two hypotheses. A 7R frequency of 0.25 was reported (2) for a sample from New Guinea, but it is not reported even in the original source of the data whether it was from a highland or coastal population.

In some societies 7R allele may lower fitness even when rare, as is probably the case in East Asia and among the !Kung Bushmen. In such populations it would stay rare even in the presence of gene flow from neighboring populations, even from neighbors with a social system that favors 7R alleles. Neutral genes would show no sharp boundary between the two populations, whereas alleles affecting behavior should show a sharp spatial gradient. This is likely to be the case with the 7R allele because some adjacent populations have very different 7R frequencies.

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