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GUEST EDITORIAL

From species differences to individual differences

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In his seminal work, *The Origin of Species*, Darwin begins with a long discourse on variation in domesticated species.[1] He considers the differences in strains of pigeons, sheep, and dogs to address the fundamental questions of how and when new species form. Darwin suggests that new species are the result of extreme within-species variation. Individual changes become so extreme that a new species buds off from an existing one with either physical isolation or environmental pressure. Although Darwin could not know about modern genetics, in contemporary terms his hypothesis could be re-stated as within-species variation precedes between-species variation. Comparative genomics flips this hypothesis by proposing that regions that vary between species are likely to be hotspots that vary between individuals.

Over the past decade, a series of comparative papers by Larry Young and his co-workers have demonstrated the extraordinary species variation in the sequence of the vasopressin V1a receptor gene (*AVPR1a*).[2] This subtype of the vasopressin receptor is expressed in the brain, especially in the hypothalamus, lateral septum, amygdala, and, in some species, the ventral striatum. Activation of this receptor increases social interaction, but there are striking species differences in the behavioral response to activation and in the anatomic location of this receptor. As a general rule, the pattern of expression of this receptor correlates with social organization. Specifically, monogamous mammals, from rodents to primates, have abundant V1a receptors in the ventral striatum and non-monogamous species have few receptors in areas associated with reward.[3] Most important, the pattern of receptor expression appears to be determined by variation in the length of a microsatellite in the promoter region of the *AVPR1a*.[4] Readers of this journal are familiar with the variation in the serotonin transporter promoter and its role for altering the amount of protein. The *AVPR1a* promoter variation is similar, but its variation appears to influence not only the amount of protein, but where in the brain this protein is expressed. The model then is variation in promoter leads to variation in anatomical pattern resulting in species differences in social behavior following endogenous vasopressin release. Most recently, Hammock and Young have demonstrated the application of this model in a comparison of chimpanzees and bonobos, two closely related great apes with markedly different social behavior.[4]

Could this species difference in gene sequence, brain chemistry, and behavior be relevant to individual differences within the human species? In humans, *AVPR1a* is found on chromosome 12q14–15, with variation observed at three microsatellites (RS1 and RS3 in the promoter and an intronic allele identified as AVR). The paper by Yirmiya *et al.* in this issue of *Molecular Psychiatry* is the third report to test for an association between variations in one of these microsatellites and autism, which is fundamentally a deficit in social behavior.[5–7] Kim *et al.*[5] found 17 alleles of RS1, one of which showed increased transmission in a family-based study of 115 autism trios. Wassink *et al.*[6] found significant disequilibrium with both RS1 and RS3 but only in cases without language deficits. In this new paper, Yirmiya *et al.*[7] fail to find the association with either RS1 or RS3 but report significant transmission disequilibrium with the intronic microsatellite. They note moderate linkage disequilibrium between the intronic and the promoter microsatellites. The most significant association in this study is between the ADOS-G, a composite measure of autism deficits (especially social skills) and the microsatellite haplotypes. Taken together, these three papers suggest a link between variations in the *AVPR1a* and autism, possibly confirming the value of comparative genomics for identifying hot spots for variation in the human genome.

Now the challenge will be to move from genetics to biology, as has been done already in studies of the vole *AVPR1a*.[4] Are any of these variations in the human gene functional? Can a particular haplotype drive expression patterns in the human brain? Do patients with autism show altered patterns of V1a receptors in the social brain? Given the abundant evidence linking vasopressin and oxytocin to social behavior, we need comprehensive maps of the oxytocin and V1a receptors in the human brain and, with or without genotypes, we need measures of these receptors in brains from autistic patients. If, as suggested in this paper, the variations in *AVPR1a* genomic sequence are responsible for individual variations in social behavior, we will have a stunning confirmation of an idea that Darwin suggested 150 years ago: mechanisms of speciation can also be mechanisms of individual variation. Understanding the differences between species will lead inexorably to an understanding of differences within a species including those adverse individual differences we define as disease states.

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