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EDITORIAL

COMPARATIVE GENOMICS AND THE ROLE OF CHROMOSOMAL REARRANGEMENTS IN SPECIES DIVERGENCE: A PARADIGM REVISITED

I began my career in mammalian evolutionary biology in the, then, nascent field of comparative mammalian cytogenetics in 1963, and the first decade or more of my own research remained in this general area of scholarship. At the time, this was a vibrant, active field, in part because most species' karyotypes (including diploid number and morphological categories of autosomes and sex-chromosomes) had yet to be described, and the chromosomal complement had the potential both to delimit species boundaries and to establish phylogenetic relationships among taxa.

Among several of the "truths" that dominated the field of mammalian cytogenetics in those early days are two that deserve mention here, based on new data that have, or will, revolutionize and hopefully revitalize the discipline. First, genome duplication was widely believed to have been instrumental in the early diversification of vertebrates (e.g., Ohno, 1970) and polyploidy had been documented as a means of karyotypic evolution in several lower vertebrate groups. However, polyploidy was considered impossible as a means of lineage diversification in mammals because of the presumptive insurmountable problems imposed by the mammalian mechanism of sex determination. Indeed, genome size in mammals was considered rather constant, varying slightly around a mean of about 7 picograms of DNA per diploid nucleus despite a range in observable diploid number from 6-7 in muntjacs to nearly 100 in different species of rodents. With the recent elegant work of Milton Gallardo and his colleagues on the octodontid genus Tympanoctomys *(Gallardo et al., 1999) we now recognize this particular "truth" as false—the evidence for evolution by allotetraploidy in this family is strong, and mounting (e.g., Gallardo et al., 2004).*

A second, and more general, "truth" in mammalian cytogenetics, indeed of the field of comparative cytogenetics as a whole, was that structural rearrangements (fusions, fissions, translocations, inversions) were plausibly connected directly to species formation. One of the leading forces behind this idea was Michael J. D. White, an orthopteran cytogeneticist at the Australian National University in Canberra whose 1978 book "Modes of Speciation" solidly placed comparative karyology in the center of debates on mechanisms of speciation (see King, 1995; Coyne and Orr, 2004). The paradigm at the time was that recombination between rearranged chromosomes was assumed to generate gametes carrying duplications or deficiencies, which in turn imposed a severe fitness deficit on heterozygotes (negative heterosis, or underdominance) through imbalances in gamete formation. Chromosomal speciation by the reduction in the fitness of heterozygotes was highly appealing, and the empirical observations of both chromosomal differences among closely related species and the direct link between rates of chromosomal diversity and speciation in mammalian lineages (Bush et al., 1977) provided support.

*This paradigm of chromosomal underdominance as a force in speciation led to a paradox, however, because population genetic theory had demonstrated that structural rearrangements that cause large fitness deficits in heterozygotes can only be established in populations of small effective size (reviews by Patton and Sherwood, 1983; Coyne and Orr, 2004). While neutral or only weakly underdominant rearrangements are more easily fixed in populations, such will be ineffective in reproductive isolation. Complementing these theoretical constraints were empirical studies of natural populations of mammals wherein diverse structural rearrangements were maintained as balanced polymorphisms. European house mice (*Mus*; Nachman and Searle, 1995) and South American marsh rats (*Holochilus*; Nachman and Myers, 1989; Nachman, 1992) are two of the best case studies exemplifying such observations. The only model that circumvented the difficulties of strong underdominance is that of monobrachial homology, which applies specifically to reciprocal whole-arm translocations (centric fusions) where a single rearrangement might be only weakly underdominant, and thus easily fixed, but strongly underdominant in serial combination, as required for reproductive isolation (Baker and Bickham, 1986). As a result of both theoretical constraints and contradictory empirical observations, and despite attempts to resurrect the importance of "chromosomal speciation" (e.g., King, 1995), chromosomal diversification as a major force in the evolutionary history of species has largely faded from the recent literature.*

However, the comparative analysis of recently sequenced whole genomes, and the gene order mapping of the corresponding chromosomal complements of species, has brought chromosomal speciation to the forefront once again, but from a different direction (Navarro and Barton, 2003; see commentaries by Rieseberg and Livingstone, 2003, and Hey, 2003). Here, reproductive isolation is not the result of the fitness cost of chromosomal heterozygosity but rather from the strong suppressing effects that rearrangements can have on recombination within and near transposed chromosomal regions.

We humans and our closest living relative, the chimpanzee, differ in only approximately 1.24% of our respective genomic DNA sequences but with substantial rearrangements characterizing 10 of our 22 autosomes in comparison to the chimp karyotype. As is true with other mammals, however, the relation of both gene sequence and rearranged chromosomes to the diversification of our respective lineages has been unclear until now. To address this issue, Navarro and Barton (2003) compare the rates of protein evolution for genes on chromosomes that have the same gene order (i.e., are co-linear) in humans and chimps with those from chromosome regions that have undergone substantial structural rearrangements. They show that proteins from rearranged chromosomes have differentiated at a faster rate than those from chromosomes that are co-linear. They do this by comparing the rates of non-synonymous nucleotide substitutions per non-synonymous site relative to the underlying neutral mutation rate, or the rate of synonymous substitution per synonymous site. They calculated this ratio to be 0.84 for rearranged chromosomes, more than twice that (0.37) for co-linear chromosomes, a statistically and biologically significant difference. Positive selection is expected to increase this ratio, and thus can be argued to be at the base of these observed differences. Indeed, the likelihood of finding significantly different proteins are about five times greater in the rearranged than co-linear chromosomes of humans and chimps.

To explain these observations, Navarro and Barton propose a new model of chromosomal speciation, one where recombination is reduced in chromosomes heterozygous for rearrangements, thereby both minimizing their expected fitness consequences while allowing the genes contained within to evolve independent of gene flow. Since recombination is required for gene flow, the rearrangements themselves create a semi-permeable reproductive barrier where gene flow is reduced for the rearranged chromosomes but not for co-linear ones. Under such a model, selected differences will accumulate more rapidly in rearranged than in co-linear chromosomes, thus explaining the observed differences in substitution ratios between humans and chimps. Assuming that some of these genic differences will generate incompatibilities in hybrids, gene flow will eventually cease and speciation will be completed. Their model is thus one in which rearrangements act primarily as recombinational modifiers rather that the "classical" paradigm where rearrangements act to reduce fitness of heterozygotes. Equally interesting, moreover, is the fact that the human-chimp split may have represented speciation with gene flow, or parapatric divergence, since the Navarro and Barton model allows for continued recombination due to gene flow for co-linear chromosomes while, at the same time, permitting divergence leading to speciation for those genes located in rearranged chromosomes.

Navarro and Barton's recombination model of chromosomal "speciation" stems directly from our increasing ability to compare both the coding regions and cytological position of annotated genes, opportunities that in turn result from whole genome sequencing efforts. As complete genome sequences of many other taxa become available, the generality of their model can be assessed, and the ultimate role of chromosomal changes in speciation better understood. As always, the future holds much for those interested in the mechanisms by which sister species diverge from their immediate common ancestor.

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LITERATURE CITED

BAKER RJ and JW BICKHAM. 1986. Speciation by monobrachial centric fusions. Proceedings of the National Academy of Sciences, USA 83:8245-8248.

BUSH GL, SM CASE, AC WILSON, and JL PATTON. 1977. Rapid speciation and chromosomal evolution in mammals. Proceedings of the National Academy of Sciences, USA 74:3942-3946.

COYNE JA and HA ORR. 2004. *Speciation*. Sinauer Associates, Inc., Sunderland, MA, USA.

GALLARDO MH, JW BICKHAM, RL HONEYCUTT, RA OJEDA, and N KÖHLER. 1999. Discovery of tetraploidy in a mammal. Nature 401:341.

GALLARDO MH, G KAUSEL, A JIMÉNEZ, C BACQUET, C GONZÁLEZ, J FIGUEROA, N KÖHLER, and R OJEDA. 2004. Whole-genome duplications in South American desert rodents (Octodontidae). Biological Journal of the Linnean Society 82:443-451.

HEY J. 2003. Speciation and inversions: chimps and humans. BioEssays 25: 825-828.

KING M. 1995. Species Evolution: The role of chromosomal change. Cambridge University Press.

NACHMAN MW. 1992. Meiotic studies of Robertsonian polymorphisms in the South American marsh rat, *Holochilus brasiliensis*. Cytogenetics and Cell Genetics 61:17-24.

NACHMAN MW and P MYERS. 1989. Exceptional chromosomal mutations in a rodent population are not strongly underdominant. Proceedings of the National Academy of Sciences, USA 86:6666-6670.

NACHMAN MW and JB SEARLE. 1995. Why is the house mouse karyotype so variable? Trends in Ecology and Evolution 10:397-402.

NAVARRO A and NH BARTON. 2003. Chromosomal speciation and molecular divergence—accelerated evolution in rearranged chromosomes. Science 300:321-324.

OHNO S. 1970. Evolution by gene duplication. Springer-Verlag, Berlin.

PATTON JL and SW SHERWOOD. 1983. Chromosome evolution and speciation in rodents. Annual Review of Ecology and Systematics 14:139-158.

RIESEBERG LH, and K LIVINGSTONE. 2003. Chromosomal speciation in primates. Science 300:267-268.

WHITE MJD. 1978. Modes of speciation. W. H. Freeman & Co., San Francisco, CA.