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Of Rats and Men

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http://dx.doi.org/10.1016/j.cell.2013.07.022

The selective breeding of rats as physiological, behavioral, and disease models generated a wealth of variation relevant to the genetics of complex traits. In this issue, Atanur and colleagues sequence the genomes of 25 inbred rat strains to understand how artificial selection shaped their genomes.

Humans and rats have shared habitats for millennia, an intimacy that has seldom engendered respect. We use rats as metaphors for human frailties and the most unseemly aspects of our nature, including disloyalty, opportunism, and unwholesome smell. Scientists, however, have come to appreciate many more analogies between rats and humans: some 1.5 million biomedical research papers—the most for any model organism—testify to the rat's value as a model for human physiology and disease. In this issue, Atanur et al. (2013) probe the genomic consequences of humans' selective breeding of rats to model human diseases.

Rats' strengths as a model for human biology are compelling. Not only do rats share much of our genomes, they also share our dwellings and our food. Rats have served as laboratory animals since the early 1800s, when they were used to study the effects of fasting and nutrition. Large-scale selective breeding began in 1909, the same year as comparable efforts for the mouse (Jacob, 1999). But thenceforth, rats and mice took different paths through the maze of human scientific aspiration.

The rat's greater size and cognitive capacity made it the preferred choice for physiological experiments and studies of learning and other behaviors: experimental manipulations are easier in a larger animal, and behavioral studies are richer in a smarter one. The rat's calm demeanor and generous proportions are more forgiving of human experimenters, facilitating reproducibility. As laboratory animals, rats contributed to most of the pharmaceuticals of the 20th century—an extraordinary contribution to human health.

Mice, by contrast, excelled as a genetic model. Small and exuberantly reproductive, mice are suited to large, multigenerational breeding experiments. Mice also got a genetic head start from humans' tendency to find mice cute. Early mouse breeders enjoyed a lively market for mice selected for unusual coat colors and odd behaviors, such as "waltzing," a neurological disorder in which mice lurch in circles instead of walking in a straight line. (One wonders whether the same behavior in rats would have been granted as charming a name.) Propagation by mouse "fanciers" produced many strains and genetic markers (Wade et al., 2002). Above all, though, the more facile culturing of mouse embryonic stem cells for knockout and transgenic experiments would accelerate the scientific utilization of mice in the genome era (Figure 1).

The breeding of rats to scientific ends was hardly neglected; scientists bred more than 500 inbred strains of rat (Aitman et al., 2008), including models for hypertension, obesity, diabetes, multiple sclerosis, and scores of other human diseases. However, such breeding often took a different form than in the mouse. Laboratory rat strains were bred to enhance specific phenotypes or traits but only rarely backcrossed to determine whether the traits of interest were mono- or polygenic. These practices preserved complex patterns of genetic causation, creating a valuable asset for the study of polygenic phenotypes. The rat was the first vertebrate (indeed, the first non-plant) in which quantitative trait locus (QTL) mapping was successfully performed (James and Lindpaintner, 1997). Today, rats' utility for mapping complex traits is increasing with modern genetic tools: the Rat Genome Database reports 995 mapped QTLs, and a new study maps another 355 QTLs for 122 phenotypes in the outbred descendants of eight classic inbred rat strains (Baud et al., 2013).

Many genetic insights are hidden in the variation preserved in artificially selected strains, but reaching these insights requires this variation to be ascertained

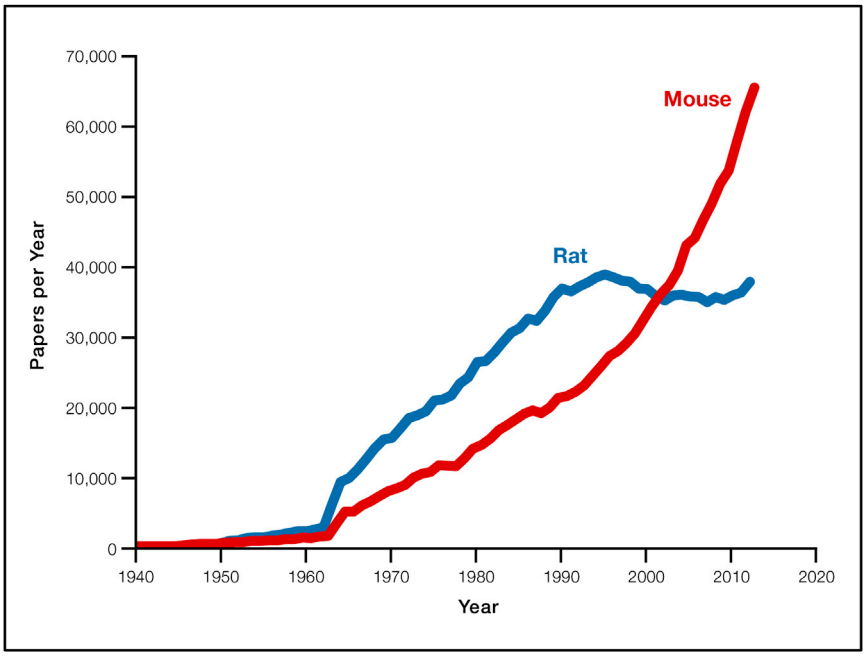

Figure 1. The Changing Fortunes of the Laboratory Rat

The rat was for decades the most widely used model organism, but rat studies plateaued with the advent of the genome era. Meanwhile, studies in mice accelerated with the emergence of genome manipulation technologies. The data plotted are PubMed search results for papers in which the term "rat(s)" or "mouse (mice)" appears in any field.

and analyzed. Atanur et al. begin by sequencing the genomes of 25 rat strains in common laboratory use, including many strains selected for cardiovascular and metabolic phenotypes. They then analyze the observed variation to ascertain the effects of artificial selection.

Breeding animals to homozygosity produces many effects. Genetic variants that contribute to the selected trait rise quickly to fixation. Many other variants become fixed accidentally during inbreeding; still others become fixed due to their ability to ameliorate the deleterious effects of variants fixed elsewhere in the genome. In the inbred strain ultimately produced, the reasons for fixation at each locus are opaque.

To begin to elucidate these selective pressures, Atanur et al. look for patterns across the genomes of many strains. In one analysis, they seek sets of genes that exhibit similar genetic phylogenies across multiple strains, with the idea that these "coevolved" gene clusters might reflect gene-gene interactions. In another analysis, they look for genetic signatures of the primary selective events. A variant that is selected to fixation will carry nearby genetic variation with it, causing many otherwise rare variants to become fixed in its genomic neighborhood. The presence of many fixed rare variants along a genomic segment can therefore flag a segment as containing one or more variants that contributed to selection. Several observations suggest that these "putative artificial selective sweep (PASS)" regions are biologically meaningful. For example, many of them colocalize with QTLs, indicating that genetic variation in these regions also influences traits. The PASS regions are also enriched in genes that are known to be relevant to the disease-like phenotypes for which the strains were artificially selected. In several cases, they contain genes in which variation associates with disease phenotypes in humans.

The data in this study should facilitate use of the rat genome in several ways. QTLs can now be more readily connected to specific variants in each strain, helping scientists to work from genetic loci toward causal alleles and mechanisms. Information about each strain's genetic composition at each locus can be used to inform crosses and refine the mapping of QTLs. Large-scale association studies can make use of a larger set of strains, increasing opportunities to find QTLs and specific genes that contribute to phenotypes.

A contemporaneous study (Baud et al., 2013) reveals the enormous amount of functional variation hidden in the sequence differences among inbred rat strains. Analyzing the descendants of a cross among eight classic inbred rat strains, the researchers map 355 QTLs for 122 phenotypes and identify 35 causal genes. Intriguingly, they find that, at 40% of QTLs, the effect on phenotype cannot be explained by a single variant and is more likely explained by the combined effects of multiple variants at the locus.

Together with new molecular tools for manipulating the rat genome, rat genome studies may contribute to a renaissance in rat research. After decades as the most widely utilized model organism, rats' popularity in research plateaued during the past two decades, contemporaneous with the advent of genome manipulation technology that favored the mouse (Figure 1). New genomic technology and data resources, however, may turn a sinking ship into a nimble vessel. Targeted knockout technology and technology for genome editing (Brown et al., 2013) will allow an advanced genomic toolkit to complement rats' inherent strengths as a laboratory model.

The selective breeding of hundreds of rat strains over many decades generated an archive of information about genetic influences on complex phenotypes. The encounter of this long 20th century genetics experiment with 21st century genome analysis methods, as in Atanur et al. (2013) and Baud et al. (2013), is uncovering insights in this archive.

What then might be our own century's decades-long genetic experiment that will meet a new genome analysis technology in 30, 50, or 100 years? Perhaps such an experiment is already underway. We already routinely collect information about ourselves and store it in vast databases; these efforts will only expand. We carry devices that log our movements and are readily adapted to log information on diet, health, and exercise. It may become common for people's genomes to be sequenced at birth. Thus,

researchers of the future might possess data that allow them to reap substantial insight from the human model for the human. The research subjects of the future may no longer need to be metaphorical repositories of human frailties, as their frailties will be our own.

If this is what the future holds, then humans would do well to honor the laboratory rat. Our appreciation of our biological kinship and our shared experience is likely to increase as the years go on.

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