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INVITED PRESENTATION

Functional Annotation of Mammalian DNA Sequence by Large-Scale, Phenotype-Driven Recovery of Mouse Mutations. E. M. Rinchik,^{1,2} D. A. Carpenter,¹ Y. You,¹ P. R. Hunsicker,¹ D. R. Miller,¹ and D. K. Johnson.¹ ¹Life Sciences Division, Oak Ridge National Laboratory, PO Box 2009, Oak Ridge, Tennessee 37831-8077, and ²Department of Biochemistry, Cellular, and Molecular Biology, University of Tennessee, Knoxville, TN 37996.

A major goal of the mouse-genetics program at the Oak Ridge National Laboratory is to apply our experience in chemical germ-cell mutagenesis, mutation recovery and propagation, and broad-based phenotype screening, for creating a large, user-friendly mouse-mutation resource that can be used by the wider biological community for functional annotation of human DNA sequence. Our current overall program expands previous work that molecularly characterized regions of mouse Chromosome (Chr) 7 while also recovering *N*-ethyl-*N*-nitrosourea (ENU)-induced, recessive single-gene mutations. For example, in one screen of a ~5-cM Chr-7 region (human 11p and 15q homologies), simple phenotype-screening criteria was able to ascertain 19 new mutations in 1218 gametes, and, recently, more broadly based phenotype-screening has yielded additional variants currently undergoing heritability testing. Mutations within four additional chromosomal regions covering ~8% of the mouse genome (on Chrs 7, 15, 10, and X) are being recovered using strategies employing dominant and recessive visible markers and chromosomal rearrangements. These strategies allow easy detection and low-cost maintenance of chromosomally “pre-mapped” deleterious recessive mutations without any molecular genotyping. In parallel, chromosomal deletions are being developed in embryonic stem cells for use as finer-mapping and gene-identification reagents. Our experimental design also provides for the generation of many parallel pedigrees containing multiple mutant test-class mice of a singular genotype for comprehensive multi-site phenotype screening (e.g., across the Tennessee Mouse Genome Consortium) and for establishment of aging colonies to be screened for later-onset recessive phenotypes.