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A genome end-game: understanding gene function in the nervous system

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The mouse has offered great promise as a model organism to study brain function and behavior; however, neurological phenotypes in mice are often detected by individual investigators in a low-throughput fashion, studying natural variants of mice or mice with spontaneous mutations or gene knockdowns. In 2000, because of the success of large-scale mutagenesis programs in other model organisms (the fruit fly *Drosophila melanogaster*, the nematode *Caenorhabditis elegans* and zebrafish) and the success of large-scale mouse mutagenesis efforts in Europe (www.mgu.har.mrc.ac.uk/mutbase/; www.gsf.de/ieg/groups/

enumouse.html), the National Institutes of Health (NIH) began to support three mutagenesis centers in the US. Their collective purpose was to detect, characterize and distribute new mouse mutants with primarily neurological phenotypes. These centers are located at Northwestern University (<http://genome.northwestern.edu>), The Jackson Laboratory (JAX; <http://nmf.jax.org>) and the Tennessee Mouse Genome Consortium (TMGC; www.tnmouse.org).

These centers use *N*-ethyl-*N*-nitrosourea (ENU) to create mutations in the mouse genome and then screen the resulting mutants for neurological phenotypes. ENU is an ethylating agent that is both mutagenic and cytotoxic in mouse spermatogonial stem cells¹. ENU is particularly valuable for inducing allelic series of mutations because it causes primarily base-pair substitutions², resulting in a wide range of mutation outcomes. Importantly, of the 38,000 mutations in about 1,500 genes that cause aberrant phenotypes in humans, about 70% of these are of the single-base pair variety (<http://archive.uwcm.ac.uk/uwcm/mg/docs/ahaha.html>), and so it would appear that the ENU-based approach in mice mimics human genetic disease.

Producing mutant mice at the ‘industrial’ level brings considerable challenges in laboratory information management systems. It requires a database architecture that is flexible and scalable with reliable and secure data storage, and that allows acquisition of data from multiple locations. It should permit tracking of mice individually or collectively as families, and should allow the user to create automated reports and use statistical analysis tools. Effective sharing of data and information about mice and their phenotypes requires the use of standardized data exchange formats, the use of existing community databases and resources, and the development of common vocabularies for new types of data. To address these issues, the three NIH-funded neuroscience mutagenesis centers have formed a virtual distribution center (www.neuromice.org), which allows researchers to learn about and acquire mutant mice of interest. The website uses a standardized XML data exchange format; each mouse file includes a description of the mutant mouse, heritability and mapping status information, distribution notes and links to the web page of the center from which the mutant was derived.

To help searches, a common vocabulary of phenotypic classification terms is used to group mice into meaningful bins. On the neuromice.org site, mouse models are classified by both phenotypic domain and by assay. The phenotypic domain terms include Aging, Epilepsy, Metabolism, Neuroendocrine, Social Behavior, Eye, Drug Abuse, Alcohol, Circadian Rhythm and Pain/Nociception. Within each of these domains, the mice are further subdivided according to the type of assay that was used to measure the phenotype. For example, in the phenotype domain of Alcohol there are mutants that have been identified using the following assays: activity after an injection of ethanol, and the two-bottle ethanol choice test. The use of controlled vocabularies to classify mice allows the individual centers to name mouse lines according to their own conventions while providing the research community with a consistent mechanism for searching for mice with specific characteristics.

Each group also regularly submits data and information on the mutant phenotypes they have discovered to well-established community databases. For example, all of the mutants are being registered with the Mouse Genome Informatics (MGI) database at JAX (www.informatics.jax.org), which is the primary community database for the laboratory mouse³. Integrating the data allows researchers to get a comprehensive overview of the connections between genes, alleles and phenotypes in the mouse. In the longer term, the extensive strain-specific and mutant phenotypic data produced by each center will provide great synergy with other databases of mouse phenotypic data such as the Mouse Phenome Database at JAX (<http://aretha.jax.org/pub-cgi/phenome/mpdcgi?rtn=docs/home>) and the

gene expression profiling of BXD recombinant inbred strains at the University of Tennessee (<http://nervenet.org>).

The mission of the three centers is to provide the scientific community with new mouse models for understanding gene function in the nervous system. To date, over 100 new mouse mutants relevant to neurological disorders in humans have been generated by these centers. The mutants include mice with defects in balance, blindness, susceptibility to seizures and abnormalities in circadian rhythm, open field behavior, pain responses and hearing. These mutant lines can be used as models to study disorders of neural function. For example, the Center for Functional Genomics at Northwestern University discovered a new mutant named '*overtime*' that defines a clock locus that maps to a region of mouse chromosome 14 where there are no known circadian genes. The Neuroscience Mutagenesis Facility at JAX, using an electroconvulsive threshold screen, has identified two new mutant alleles in the *Kcnq2* gene, whose human homolog is mutated in a form of human epilepsy. Finally, the Neuromutagenesis Program of the TMGC, using tail suspension and open-field behavioral screens, has identified several distinct anxiety/depression or emotional behavior mutants, four of which are localized to mouse chromosome 7 and one to mouse chromosome 15. The discovery of the mutant genes that give rise to these and other mutant phenotypes is another powerful strategy for the functional annotation of the genome.

References

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Figure 1.