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NEWS

Why mouse genetics matters in the age of human GWAS

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Recent *IBMS BoneKEy* webinar described tools of the trade and their uses for osteoporosis research

For investigators seeking to understand the inherited basis of musculoskeletal diseases such as osteoporosis, is there still a role for mouse genetics in a biomedical research landscape dominated by human genome-wide association studies (GWASs)? In *Genetics of Osteoporosis: Using Mouse Models for Gene Discovery*, a recent *IBMS BoneKEy* webinar, presenter Cheryl Ackert-Bicknell (The Jackson Laboratory, Bar Harbor, ME, USA) made a convincing case that the humble mouse still has much to teach those researching the genetic foundations of bone disease. Although mouse genetics may have been overshadowed by human GWASs, Dr Ackert-Bicknell provided evidence showing that the former can inform the latter in important and interesting ways—the two approaches are complementary, rather than antagonistic. In this regard, one of the greatest strengths of mouse genetics, she said, is its ability to illuminate gene by environment interactions, an area attracting growing interest in the field of bone research.

After Dr Ackert-Bicknell's talk, a distinguished panel including Charles Farber (University of Virginia, Charlottesville, VA, USA), Karl Jepsen (University of Michigan, Ann Arbor, MI, USA) and Fernando Rivadeneira (Erasmus MC, Rotterdam, The Netherlands) participated in a discussion moderated by David Karasik (Hebrew Senior Life, Boston, MA, USA), *IBMS BoneKEy* Associate Editor.

The webinar is available for viewing at: http://www.nature.com/bonekey/webinars/index.html?key=webinar30.

Tools of the Trade

There is no shortage of tools available to the mouse geneticist, as the first part of Dr Ackert-Bicknell's presentation made clear (see Ackert-Bicknell and Hibbs[1] for recent review). One tool is the inbred mouse strain, a line of mice resulting from at least 20 generations of inbreeding; inbred strains are the result of crosses between brothers and sisters, or parents and offspring. 'The goal,' Dr Ackert-Bicknell said, 'is to achieve a population of mice that are essentially identical to all other mice of that strain.' 'The result,' she emphasized, 'is that generation after generation, all mice within an inbred strain should reproduce heritable phenotypes.' For instance, an inbred strain of mice with low bone mineral density (BMD) will continue to exhibit that phenotype generation after generation. Familiar examples of inbred strains include the C57 black 6 (C57BL/6) mouse, also known commonly as B6, and the 129 mouse.

In contrast to inbred mice, outbred mice are a closed (housed in one facility) population of mice within which genetic diversity is present, and the mice are bred to maintain that diversity. Consequently, among outbred mice, of which the CD1 mouse is a familiar example, 'each mouse is a 'genetic one-in-a-million,' Dr Ackert-Bicknell explained. 'Phenotypically, each mouse might look different for genetically regulated phenotypes,' she said. She emphasized that outbred mice are 'ideal for genetic studies,' including the mouse equivalent of GWASs.

Dr Ackert-Bicknell next turned to a number of genetic reference mouse populations. These refer to a collection of lines of mice, all descended from a common set of founder individuals (typically inbred strains), with fixed genomes that can be replicated generation after generation. Examples of genetic reference populations include consomic strains (inbred strains in which one chromosome has been substituted by a chromosome from another inbred strain); congenic strains (similar to consomic strains except that pieces of chromosomes, rather than entire chromosomes, have been substituted); recombinant inbred (RI) lines (sets of inbred lines made by intercrossing two or more inbred strains); the Hybrid Mouse Diversity Panel (consisting of both inbred and RI strains); and the Collaborative Cross (a series of RI lines including classic inbred strains such as the B6 mouse as well as wild-derived strains).

Putting the Tools to Work

In the next part of her presentation, Dr Ackert-Bicknell turned to work from her group and that of others showing the uses to which mouse genetics tools have been put, in the service of furthering understanding of the genetic basis of musculoskeletal diseases. The goal is to use reference populations to identify the genes responsible for phenotypes such as low BMD. In this regard, genetic mapping studies in mice have long relied on identifying quantitative trait loci (QTLs), which are regions of the genome associated with a phenotype of interest. QTL studies have been limited, however, by poor mapping resolution; the studies identify very large regions of the genome,

containing many genes, making it difficult to pinpoint the location of a specific gene of interest.

Nonetheless, results from QTL studies have been intriguing. For instance, in 2010, using a new mouse genetic map that corrected errors in the map that had been used previously, Dr Ackert-Bicknell and colleagues[2] compared mouse QTLs for BMD phenotypes with BMD loci that had been identified in human GWASs. They found that most loci identified in human GWASs were located within the confidence interval of a mouse QTL, and that many of them mapped very closely (to within 3 centimorgans) of a mouse QTL peak. 'This means that when we map something in humans, there is a good chance that we are also going to map it in mice,' Dr Ackert-Bicknell said. In addition, in her study, Dr Ackert-Bicknell was able to identify loci for which there are no concordant human GWAS loci. 'These loci become potentially very exciting because they could be the undiscovered genetic contributors to bone phenotypes,' she said.

Dr Ackert-Bicknell and colleagues would go on to use block haplotyping, which exploits the fact that the common inbred strains of mice contain regions of DNA that are identical by descent, to confirm a candidate gene, *Trps1*, for a QTL they had identified on chromosome 15.[3] But the real value of mouse genetics, she said, was taking the information on *Trps1* gleaned from mice and applying that knowledge to human GWAS data, particularly to genetic associations from GWASs that do not quite reach levels of statistical significance but could nonetheless be real associations. Specifically, she and her co-investigators examined associations of single-nucleotide polymorphisms (SNPs) in the region of the human *TRPS1* gene with BMD and hip geometry, using GWAS data from the GEnetic Factors for OSteoporosis (GEFOS) consortium. They were able to identify SNPs associated with femoral neck BMD, as well as with femoral neck width. One major advantage to this approach of using a 'prior' (that is, a locus or gene identified in mice) to look at a small piece of the human genome data (in this case, SNPs in and around the human *TRPS1* gene) is that it helps to overcome the multiple testing problem that is an inherent limitation of hypothesis-free GWASs. 'Because we already had a prior, we could focus on a small bit of human genome data, which meant there were less multiple testing correction penalties that we had to apply,' Dr Ackert-Bicknell said.

Dr Ackert-Bicknell then turned to the role that mouse genetics can have in understanding how genes and environment interact. Her focus was on work she has conducted using a congenic mouse—a mouse with a B6 background but also with a small piece of chromosome 6 from the inbred C3H mouse—to examine how genes and diet work together to affect bone.[4] To begin, the investigators fed both a control B6 strain and the congenic strain either a low-fat, medium-fat or high-fat diet. They found that only the congenic mice were sensitive to dietary fat intake, and, further, that congenics fed a high-fat diet exhibited decreased areal BMD and decreased volume fraction of trabecular bone (BV/TV%) at the distal femur compared with control mice. The researchers were also able to identify the peroxisome proliferator-activated receptor γ (*Pparg*) gene as a candidate gene responsible for the environment by gene interaction they had observed in the congenic mice.

Next, just as she had done for her work on *Trps1*, Dr Ackert-Bicknell looked to human data, in this case genetic association data from the Framingham Offspring Cohort. The goal here was to identify interactions between SNPs in the human *PPARG* gene and dietary fat for the BMD phenotype. She found that, indeed, there was such an interaction for areal BMD in both men and women from the Framingham Offspring Cohort, and she was able to identify it because she had started with a mouse. 'We could determine what this gene by environment interaction was using the mouse as a prior to direct our studies in humans,' she emphasized. Dr Ackert-Bicknell also noted that others are now following similar approaches to understand how gene and environment interact to affect bone. 'This is becoming a rapid and emerging area in the bone biology field,' she said.

The webinar ended on the optimistic note that in addition to complementing human GWASs, mouse genetics can provide information that human studies will never be able to deliver. In particular, mouse studies allow researchers to study phenotypes that are difficult to study in humans, such as fracture healing or bone turnover rates. 'We can use mice to look at things that we could never possibly look at in humans…this is such a wide open field,' Dr Ackert-Bicknell said.

Conflict of Interest

The author declares no conflict of interest.

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