100 gene deletions in mice identifies 9 new genes that determine bone strength

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A genetic screening approach to studying bone disease has found nine new genes associated with bone health and suggests a new way to discover genes that may be implicated in human skeletal diseases. A collaborative study of the mineral content, strength and flexibility of bones has found clues to the cause of bone disorders such as osteoporosis, osteogenesis imperfecta, and high bone density syndromes. The study, which brings together specialist skills in mouse gene deletion and bone measurement to assess the strength of bones in 100 mutant mouse lines, is the largest reported screen of its type for genes that regulate bone health.

All nine of the new genes discovered had not previously been implicated in skeletal disorders and were discovered by randomly screening different strains of mice engineered such that a single gene had been inactivated in their genome.

Chronic diseases such as osteoporosis represent a global healthcare burden but little is known about their genetic basis. Osteoporosis is the most common of skeletal disorders, affecting hundreds of millions of people worldwide at a cost of billions of pounds each year. Although it is known there is a strong genetic component to this disease, few of the genes that control bone structure and density are known.

"We are developing new ways of finding genes that are essential for normal development of the skeleton, and which maintain the structure and integrity of bone during adulthood. These genes will provide new

understanding of the mechanisms responsible for bone diseases and may ultimately lead to the development of new treatments," explains Professor Graham Williams, senior author from Imperial College London. "We collaborated with outstanding colleagues at the Sanger Institute and several Universities. Our studies span many areas of expertise and we have developed a detailed and specific rapid-throughput system to screen bones from mice that lack a single gene. This strategy makes use of existing shared resources at Sanger and greatly reduces the number of mice required."

The team used an approach that looked at many different physical traits and identified a new classification system for bone mutants based on mineral content, strength, and the density and flexibility of bone. The bones from some mutants were found to be brittle, while others were flexible but weak.

The Sanger Institute Mouse Genetics Projects, the largest centre for genetically engineered mice, generated the mice strains used in the study. These strains of mice were first screened at the Sanger Institute before being sent on to the other collaborating Institutes for further analysis.

"The Mouse Genetics Project's broad primary trait screen independently identified five genes that when deleted cause bone abnormalities. The other groups used X-ray microradiography, micro-CT and biomechanical testing to further characterise these 5 genes and identified an additional 5 genes that affect bone composition" says Dr Jacqueline White, one of the authors from the Wellcome Sanger Institute. "Our study is an example of where approaching biology without any prior assumptions and looking broadly at the effects of inactivating a gene allows you to find new biological insights that wouldn't be possible in other, more focused studies."

Serendipitously, one of the random genes selected, Sparc, is a well-studied gene whose deletion results in weak, brittle bones. The screen positively identified this gene as affecting bone health and this acted as a well-characterised positive control for the identification of the nine new genes that the study uncovered.

This study demonstrates that the loss of function of the each of these 10 genes can disrupt the structure and composition of bone. This disruption can be classified into three distinct, different categories: weak and flexible bone with low mineral content similar to postmenopausal osteoporosis, weak and brittle with low mineral content similar to osteogenesis imperfecta and high bone mass which is rare in humans.

"This genome-wide approach is extremely exciting and holds great promise for discovery of genetic susceptibilities and influences in bone disease in addition to providing potential targets for drug development" says Jim Lupski MD, PhD, DSc, a medical genomicist and the Cullen Professor and Vice Chair of Genetics at the Baylor College of medicine in Houston, Texas, USA. "As we learn more about common diseases that affect millions of individuals it is apparent that many such conditions can have genetically heterogeneous etiologies. The approach outlined by these investigators, although labour intensive, is a terrific example of the power of functional genomics."

"Human genetics studies require these model organisms to get a better understanding of disease and find plausible targets for treatments. This approach has allowed the teams to gain biological insights into the pathways in the body that may be potential therapeutic targets and, perhaps more importantly, help us to start to understand the biology behind bone structure."

The team are currently applying this same technique to study different disease traits in the eye and the brain. As these models are freely

available to researchers worldwide from the Mouse Genetics Project, the hope is that other organisations will use these resources to continue the study of these gene deletions.

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