

Research implicates causative genes in osteoporosis, suggesting new targets for future therapy

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Struan F.A. Grant, PhD, is a genomics scientist at Children's Hospital of Philadelphia. Credit: Children's Hospital of Philadelphia

Scientists have harnessed powerful data analysis tools and three-dimensional studies of genomic geography to implicate new risk genes

for osteoporosis, the chronic bone-weakening condition that affects millions of people. Knowing the causative genes may later open the door to more effective treatments.

"Identifying a disease's actual underlying cause often helps to steer us toward correct, targeted treatments," said study leader Struan F.A. Grant, Ph.D., a director of the Center for Spatial and Functional Genomics (CSFG) at Children's Hospital of Philadelphia (CHOP). "We have identified two novel [genes](#) that affect bone-forming cells relevant to fractures and osteoporosis. Furthermore, the [research methods](#) we used could be applied more broadly to other diseases with a [genetic component](#)."

Grant and colleagues published their research March 19, 2018 in *Nature Communications*. He co-led the study with Andrew D. Wells, Ph.D., an immunology researcher at CHOP and the other director of the CSFG; and Kurt D. Hankenson, DVM, Ph.D., an expert in bone formation and remodeling at the University of Michigan. Genetics researcher Alessandra Chesi, Ph.D., also from CHOP, was the first author, along with three additional joint first authors. Grant and Wells also are faculty members in the Perelman School of Medicine at the University of Pennsylvania.

The study team investigated genetic loci, or DNA regions, previously established to be associated with bone mineral density in [genome-wide association studies](#) (GWAS), both in adults and children. "Scientists have known for some time now that the nearest gene to a variant associated with a disease is not necessarily the cause of the disease," said Wells. Because GWAS research detects single-base changes in DNA that are usually not located in obvious parts of the genome, much research has turned to the broader context of interactions within the genome—the entire complement of DNA within cells.

Sometimes the changes, called single-nucleotide polymorphisms, or SNPs, found in GWAS are located close to a culprit gene. More often the signal comes from a non-coding region of the DNA that regulates another gene that may be thousands of bases away on the DNA sequence. "The geography of the genome is not linear," said Grant. "Because DNA is folded into chromosomes, parts of the genome may come into physical contact, enabling key biological interactions that affect how a gene is expressed. That's why we study the three-dimensional structure of the genome."

In analyzing how chromatin, the fibers that make up chromosomes, is arranged into specific shapes, spatial genomics offers insight into how genes physically interact with the regulatory regions in DNA that initiate transcription. Transcription is the process in which DNA is copied into RNA, the first event in gene expression.

Grant and colleagues used state-of-the-art massively parallel, high-resolution tools to analyze genome-wide interactions in human osteoblasts—bone-forming cells derived from mesenchymal stem cells. Their analytical tools use a "multi-omic" approach, integrating data from the genome sequence and details of chromatin structure to map interactions between potential BMD-related gene promoters and regions harboring genetic variants related to BMD biology.

The study pinpointed two novel genes, *ING3* and *EPDR1*, which in turn revealed strong effects on human osteoblasts. "While we're not ruling out other possible [causative genes](#) in these regions, the *ING3* gene particularly stood out because we found that the genetic signal at this region was the [strongest one associated with bone density at the wrist—the major site of fracture in children](#)," said Chesi.

Hankenson noted, "This suggests to us that follow-up studies investigating biological pathways affected by this gene may present

targets for therapies to strengthen bone mineral density and ultimately prevent fractures." Researchers have long known that bone accrual during childhood may bolster bone health in adulthood. This new line of research may present strategies to build on that knowledge.

Grant added that the analytical approach used in this study could have a broader use in studying other genetic diseases—including pediatric conditions. His team is collaborating with researchers at CHOP and other centers to generate atlases of promoter-variant interactions across multiple cell types. "Our hope is that this approach and these atlases could offer up great resources in crafting targeted treatments for many different diseases, including certain pediatric cancers, diabetes and lupus."

More information: Alessandra Chesi et al, "Genome-scale Capture C promoter interactions implicate effector genes at GWAS loci for bone mineral density," *Nature Communications*, March 19, 2019.

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