A break for bone disease research

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Credit: AI-generated image (disclaimer)

Osteoporosis is the reduction in bone strength that occurs during aging, which increases the chance of elderly people experiencing breaks. A genome-wide association study in the Japanese population has revealed that a genomic variant within a newly identified gene, which the discoverers have named FONG, enhances susceptibility to osteoporosis.

Led by Shiro Ikegawa of the RIKEN Center for Genomic Medicine, the

researchers began by examining the entire genomes of 190 Japanese individuals with osteoporosis and 1,557 controls. Based on the results of this initial study, they focused on 3,000 single nucleotide changes in the genomes of an additional 526 individuals with osteoporosis and 1,537 controls. Additional analyses in two further population samples led to the identification of the genomic variant, found on chromosome 2; however, there was no known gene around the variant. Instead, the researchers found only representations of portions of expressed genes in the form of several expressed sequence tags.

By analyzing messenger RNAs (mRNAs) expressed from the genomic region around the variant, Ikegawa and colleagues discovered that the genomic variant is within FONG, which stands 'formiminotransferase N-terminal sub-domain containing gene'. This previously unknown gene is expressed in various human tissues, including bone. Because the genomic variant resides outside of the FONG protein-coding region, Ikegawa and colleagues hypothesized that the variant may somehow affect the expression levels of the FONG gene.

One domain of the FONG gene, the formiminotransferase N-terminal sub-domain, is common in many different species, which indicates that it could have a very important function for maintaining life. "This domain appears to be an enzyme that is responsible for converting the amino acid histidine to the amino acid glutamic acid," says Ikuyo Inaba (nee Kou), a researcher in Ikegawa's laboratory and the first author of the study.

Glutamic acid and its breakdown products are known to play an important role in maintaining the bones, so any problems with the creation of these compounds may lead to osteoporosis. "The glutamic acid signaling pathway may also affect osteoporosis risk in non-Japanese individuals," she explains. "So, the association of this variant of the FONG gene with disease in other populations is worth investigating in

the future."

According to Inaba, further work is needed to determine how the osteoporosis-linked variant of the FONG gene can affect its expression. The identification of this variant in FONG—and its link to osteoporosis—can aid in the development of new therapies for this disease.

More information: Kou, I., et al. Common variants in a novel gene, FONG on chromosome 2q33.1 confer risk of osteoporosis in Japanese. *PLoS ONE* e19641 (2011). doi:10.1371/journal.pone.0019641

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