Gene variants found to strongly improve bone density in girls

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Pediatric researchers have found that rare genetic changes strongly increase the likelihood that a child will have higher bone density, but only in girls. Because childhood and adolescence are critical periods for bone formation, these gene variants play an important role in increasing bone strength and reducing vulnerability to fractures later in a woman's life.

"We investigated whether the same gene variants that strongly affect bone density in adults also affected bone density in children," said co-first author Jonathan A. Mitchell, Ph.D., a pediatric growth researcher and Instructor of Pediatrics at The Children's Hospital of Philadelphia (CHOP). "We found the effect was even stronger in children, but only in girls. The effect may exert lifetime impacts on bone health."

The research appeared online March 11 in the *Journal of Bone and Mineral Research*. Alessandra Chesi, Ph.D., a genetics researcher at CHOP, was the other co-first author.

Scientists and clinicians have known for some time that osteoporosis, the long-term weakening of bone which is more common in women, often runs in families and has a genetic component. The current research sheds light on gene changes that may protect against osteoporosis, and carries implications for public health.

The study team, co-led by senior authors Babette S. Zemel, Ph.D., and Struan F.A. Grant, Ph.D., analyzed a cohort of 1,418 children and adolescents—733 girls and 685 males, all of European ancestry, who were part of a larger study group, the Bone Mineral Density in Childhood Study.

The researchers focused on rare variants near the gene *EN1*, because researchers led by a group at McGill University had discovered that this site showed strong effects on increasing bone density in a landmark 2015 whole-genome sequencing study in adults.

The CHOP authors noted that it can't be assumed that the same genes affect bone mineral density both in childhood, when bone is being built up, and in adulthood, when bone loss occurs. Therefore they performed the current study.

The researchers found that rare variants near the *EN1* gene were indeed the strongest variants to date found in children, but only in females. The study team noted that follow-up research needs to be done to replicate these findings. "In addition, functional studies should investigate how the same genetic variants have different effects in males and females," said Grant. "For instance," he added, "sex-specific differences in circulating sex hormones and other signaling molecules may play a role in altering bone."

"This study reinforces the well-established importance of promoting bone health during childhood and adolescence, when peak bone density occurs, so that young people can accrete strong bones for later life," said Zemel, the director of CHOP's Nutrition and Growth Laboratory, and a national expert on childhood growth and bone density.

As these gene variants act early on in life and have implications for future bone health in adulthood, the researchers say these findings open up new opportunities to potentially intervene in the mechanisms influencing the skeleton.

More information: Jonathan A. Mitchell et al. Rare EN1 variants and pediatric bone mass , *Journal of Bone and Mineral Research* (2016). DOI: 10.1002/jbmr.2833

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