BoneKEy-Osteovision. 2005 November;2(11):1-6
http://www.bonekey-ibms.org/cgi/content/full/ibmske;2/11/1
DOI: 10.1138/20050180

# *NOT TO BE MISSED*

# Clinical and Basic Research Papers – October 2005 Selections

## Serge L. Ferrari, Associate Editor
## Ego Seeman, Clinical Editor
## Gordon J. Strewler, Editor

### Epidemiology

Onland-Moret NC, Peeters PH, van Gils CH, Clavel-Chapelon F, Key T, Tjonneland A, Trichopoulou A, Kaaks R, Manjer J, Panico S, Palli D, Tehard B, Stoikidou M, Bueno-De-Mesquita HB, Boeing H, Overvad K, Lenner P, Quiros JR, Chirlaque MD, Miller AB, Khaw KT, Riboli E. Age at menarche in relation to adult height: the EPIC study. *Am J Epidemiol.* 2005 Oct 1;162(7):623-32. [Abstract]

> *Age at menarche has decreased; final height has increased. In 286,205 women, age at menarche decreased by 44 days per 5-year birth cohort. Women grew 0.29 cm taller per 5-year birth cohort. Women grew 0.31 cm taller when menarche occurred 1 year later. More recent birth cohorts have menarche earlier and grow taller. Women with earlier menarche reach a shorter adult height. —ES*

### Genetics

Mehrabian M, Allayee H, Stockton J, Lum PY, Drake TA, Castellani LW, Suh M, Armour C, Edwards S, Lamb J, Lusis AJ, Schadt EE. Integrating genotypic and expression data in a segregating mouse population to identify 5-lipoxygenase as a susceptibility gene for obesity and bone traits. *Nat Genet.* 2005 Nov;37(11):1224-33. [Abstract]

> *Moving on from QTL mapping to identification of trait-related gene(s) in mouse crosses, or moving back from extreme phenotypes in transgenic mice to the influence of a particular gene in complex disorders, remains difficult. This paper describes an approach in which gene expression analyses are integrated with forward genetics in a* DBAxB6 *mouse cross and reverse genetics in* Alox5 *KO mice to demonstrate pleiotropic effects of the gene encoding 5-lipoxygenase on fat mass, BMD and circulating lipid levels.* DBAxB6 *liver gene expression levels (by micro-arrays) were treated as quantitative traits. 1991 expressed genes were linked to a chromosome 6 QTL (far more than the 331 genes located on this QTL); most regulated genes belonged to 11 pathways associated with obesity-related traits. The authors reasoned that the region within QTL6 that contains regulatory gene(s) for these metabolic pathways should be non-identical by descent (non-IBD) between* DBA *and* B6*, thereby excluding* Ppar gamma*, for instance. Among the 32 genes located in non-IBD regions, a single missense SNP was identified that is known to affect the enzymatic activity of* Alox5*. By profiling livers from* Alox5 *KO mice, the authors then showed overlap with expression traits linked to QTL6, phenotypic similarity with* DBAxB6 *QTL6 homozygotes (F2), and common genetic networks for the metabolic traits of interest in these two mouse models. —SLF*

Michaelsson K, Melhus H, Ferm H, Ahlbom A, Pedersen NL. Genetic liability to fractures in the elderly. *Arch Intern Med.* 2005 Sep 12;165(16):1825-30. [Abstract]

*In a cohort of 33,432 twins, 6021 had any fracture, 3599 had an osteoporotic fracture, and 1055 had hip fractures. Less than 20% of the fracture variance was explained by genetic variation. Heritabilities were low except in young individuals with hip fractures. —ES*

Parsons CA, Mroczkowski HJ, McGuigan FE, Albagha OM, Manolagas S, Reid DM, Ralston SH, Shmookler Reis RJ. Interspecies synteny mapping identifies a quantitative trait locus for bone mineral density on human chromosome Xp22. *Hum Mol Genet.* 2005 Nov 1;14(21):3141-8. [Abstract]

*This is the first study exploiting mouse-human synteny to successfully identify a new gene for lumbar spine BMD. First, the authors identified a QTL at the Xp22 locus for post-maturity spine BMD changes in a cross of* SAMP6 *and* AKR/J *mice. Then, they used public databases (dbSNP) to identify SNPs in the syntenic human Xp22 region and established allelic frequencies in pooled DNA samples from post-menopausal women with high and low BMD. They identified two closely linked polymorphic markers within intron 6 of the* PIR *gene (that codes for a protein of a transcription factor complex) to be differentially distributed in women with high and low BMD. They confirmed their findings by individual genotyping in both the two groups of women with extreme bone densities and in a population-based cohort of women unselected for BMD. Functional analyses remain to be performed, but this study demonstrates that integrating mouse and human genomics will be an efficient and powerful approach to identify new genes for bone density and structure. —SLF*

The International HapMap Consortium. A haplotype map of the human genome. *Nature*. 2005 Oct 27;437(7063):1299-1320.

*In a January 2004 BoneKEy perspective (Ferrari SL. Genomics and osteoporosis: what are the implications? BoneKEy-Osteovision. 2004 January), we announced that the HapMap project would characterize the patterns of linkage disequilibrium and haplotypes across the human genome and identify subsets of SNPs that capture most of the information about these patterns. Less than two years later, an incredibly rich and clear article from the HapMap Consortium reports a comprehensive linkage disequilibrium map of the human genome. It was built with 1 million "common" SNPs (out of nearly 10 million SNPs currently in dbSNP) typed in 269 DNA samples from Africans, Asians and Caucasians. Hence a limited set of common SNPs (frequency >5%) now contained (or captured through LD) in existing databases (dbSNP) appears sufficient to explain about 90% of heterozygous sites in each person. By identifying haplotype tags, i.e., variants that serve as markers for a particular combination of alleles with little or no recombination along a chromosome, the HapMap allows us to capture genetic variation more efficiently than randomly chosen SNPs. The authors also report that SNPs discovered by resequencing ten previously characterized 500 kb regions (from ENCODE) mostly had very low frequency (<0.5%). An accompanying editorial argues to establish a functional-variant database using medical resequencing (MRS), which would capture "low frequency variation" in addition to the more common SNPs (>5% frequency). —SLF*

## Pathophysiology

Bellido T, Ali AA, Gubrij I, Plotkin LI, Fu Q, O'Brien CA, Manolagas SC, Jilka RL. Chronic elevation of parathyroid hormone in mice reduces expression of sclerostin by osteocytes: a novel mechanism for hormonal control of osteoblastogenesis. *Endocrinology*. 2005 Nov;146(11):4577-83. [Abstract] [Full Text]

*Sclerostin, the product of the* SOST *gene, is an osteocyte-specific inhibitor of bone formation. A single injection or chronic infusion of PTH suppresses the expression of* SOST *mRNA and sclerostin protein in osteocytes. PTH could produce anabolic effects on bone by relieving the inhibitory effect of sclerostin on osteoblasts. Daily injections of PTH have no effect on* SOST *after day one, however, making it unlikely that sclerostin is the primary mediator of anabolic regimens of PTH administration. —GJS*

Martin A, de Vittoris R, David V, Moraes R, Begeot M, Lafage-Proust MH, Alexandre C, Vico L, Thomas T. Leptin modulates both resorption and formation while preventing disuse-induced bone loss in tail-suspended female rats. *Endocrinology*. 2005 Aug;146(8):3652-9. [Abstract] [Full Text]

*Evidence is provided to suggest that leptin may prevent disuse-induced bone loss through an inhibitory effect on resorption and a delayed effect that prevents a decrease in bone formation. —ES*

Yokoyama A, Somervaille TC, Smith KS, Rozenblatt-Rosen O, Meyerson M, Cleary ML. The menin tumor suppressor protein is an essential oncogenic cofactor for MLL-associated leukemogenesis. *Cell*. 2005 Oct 21;123(2):207-18. [Abstract]

*Menin is a good guy, a suppressor of tumors in neuroendocrine cells. This work shows that menin can be a bad guy as well. The Mixed Lineage Leukemia (MLL) protein is a histone methyltransferase that is mutated in various leukemias. Menin associates with mutant as well as normal versions of MLL, is part of the transcriptional complex with MLL, and is required for oncogenesis by MLL. The protective role of menin in endocrine tissues may involve different complexes on different promoters, but it is too soon to tell how leukemogenesis and endocrine tumor suppression are related. —GJS*

## Physiology and Metabolism

Miura Y, Miura M, Gronthos S, Allen MR, Cao C, Uveges TE, Bi Y, Ehirchiou D, Kortesidis A, Shi S, Zhang L. Defective osteogenesis of the stromal stem cells predisposes CD18-null mice to osteoporosis. *Proc Natl Acad Sci USA*. 2005 Sep 27;102(39):14022-7. [Abstract] [Full Text]

*This paper shows that CD18 (beta-2 integrin), a constituent of leukocyte integrins, is also expressed on bone marrow stromal stem cells.* CD18*(-/-) mice have trabecular osteoporosis with no increase in resorption markers. Stromal cells from* CD18*(-/-) mice do not form bone normally in vitro, but their bone-forming capacity is restored by expression of CD18. —GJS*

Syed FA, Modder UI, Fraser DG, Spelsberg TC, Rosen CJ, Krust A, Chambon P, Jameson JL, Khosla S. Skeletal effects of estrogen are mediated by opposing actions of classical and nonclassical estrogen receptor pathways. *J Bone Miner Res.* 2005;20(11):1992-2001. [Abstract]

*In mice expressing mutant estrogen receptors that cannot signal via DNA binding instead of the wild type receptor, estrogen can signal only by nonclassical pathways, including genomic signaling by protein-protein interactions as well as nongenomic signaling. Such mice have reduced cortical bone and respond to ovariectomy with a paradoxical increase in cortical bone volume, which is suppressed by estrogen replacement. The balance of estrogen signaling in classical and nonclassical pathways determines the net response to estrogen. —GJS*

## Reviews, Perspectives and Editorials

Allen DB. Inhaled steroids for children: effects on growth, bone and adrenal function. *Endocrinol Metab Clin North Am*. 2005 Sep;34;555-64, viii. [Abstract]

Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. *Am J Med.* 2005 Oct;118(10):1094-101. [Abstract]

Gubitosi-Klug RA, Cuttler L. Idiopathic short stature. *Endocrinol Metab Clin North Am*. 2005 Sep;34;565-80, viii. [Abstract]

Janssens K, ten Dijke P, Janssens S, Van Hul W. Transforming growth factor-beta1 to the bone. *Endocr Rev*. 2005 Oct;26(6):743-74. [Abstract] [Full Text]

Mishra L, Derynck R, Mishra B. Transforming growth factor-beta signaling in stem cells and cancer. *Science*. 2005 Oct 7;310 (5745):68-71. [Abstract] [Full Text]

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Neumann E, Gay S, Muller-Ladner U. The RANK/RANKL/osteoprotegerin system in rheumatoid arthritis: new insights from animal models. *Arthritis Rheum*. 2005 Oct;52(10):2960-7. [Info]

Niu T, Rosen CJ. The insulin-like growth factor-I gene and osteoporosis: A critical appraisal. *Gene*. 2005 Nov 21;361:38-56. [Abstract]

Poole KE, Reeve J. Parathyroid hormone - a bone anabolic and catabolic agent. *Curr Opin Pharmacol.* 2005. Dec;5(6):612-7. [Abstract]

## Other Studies of Potential Interest

Akiyama H, Kim JE, Nakashima K, Balmes G, Iwai N, Deng JM, Zhang Z, Martin JF, Behringer RR, Nakamura T, de Crombrugghe B. Osteo-chondroprogenitor cells are derived from Sox9 expressing precursors. *Proc Natl Acad Sci USA.* 2005 Oct 11;102(41):14665-70. [Abstract] [Full Text]

Alos N, Ecarot B. Downregulation of osteoblast Phex expression by PTH. *Bone*. 2005 Oct;37(4):589-98. [Abstract]

Baumert U, Golan I, Redlich M, Aknin JJ, Muessig D. Cleidocranial dysplasia: molecular genetic analysis and phenotypic-based description of a Middle European patient group. *Am J Med Genet A*. 2005 Dec 1;139(2)78-85. [Abstract]

Bilic-Curcic I, Kalajzic Z, Wang L, Rowe DW. Origins of endothelial and osteogenic cells in the subcutaneous collagen gel implant. *Bone*. 2005 Nov;37(5):678-87. [Abstract]

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Chesnut CH 3rd, Majumdar S, Newitt DC, Shields A, Van Pelt J, Laschansky E, Azria M, Kriegman A, Olson M, Eriksen EF, Mindeholm L. Effects of salmon calcitonin on trabecular microarchitecture as determined by magnetic resonance imaging: results from the QUEST study. *J Bone Miner Res*. 2005 Sep;20(9):1548-61. [Abstract]

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Fang Y, van Meurs JB, d'Alesio A, Jhamai M, Zhao H, Rivadeneira F, Hofman A, van Leeuwen JP, Jehan F, Pols HA, Uitterlinden AG. Promoter and 3'-untranslated-region haplotypes in the vitamin D receptor gene predispose to osteoporotic fracture: the Rotterdam study. *Am J Hum Genet*. 2005 Nov;77(5):807-23. [Abstract]

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Germain-Lee EL, Schwindinger W, Crane JL, Zewdu R, Zweifel LS, Wand G, Huso DL, Saji M, Ringel MD, Levine MA. A mouse model of albright hereditary osteodystrophy generated by targeted disruption of exon 1 of the Gnas gene. *Endocrinology.* 2005 Nov;146(11):4697-709. [Abstract] [Full Text]

Gunther T, Poli C, Muller JM, Catala-Lehnen P, Schinke T, Yin N, Vomstein S, Amling M, Schule R. Fhl2 deficiency results in osteopenia due to decreased activity of osteoblasts. *EMBO J.* 2005 Sep 7;24(17):3049-56. [Abstract]

Karsak M, Cohen-Solal M, Freudenberg J, Ostertag A, Morieux C, Kornak U, Essig J, Erxlebe E, Bab I, Kubisch C, de Vernejoul MC, Zimmer A. Cannabinoid receptor type 2 gene is associated with human osteoporosis. *Hum Mol Genet*. 2005 Nov 15;14(22):3389-96. [Abstract]

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Lisignoli G, Toneguzzi S, Piacentini A, Cristino S, Grassi F, Cavallo C, Facchini A. CXCL12 (SDF-1) and CXCL13 (BCA-1) chemokines significantly induce proliferation and collagen type I expression in osteoblasts from osteoarthritis patients. *J Cell Physiol*. 2006 Jan;206(1):78-85. [Abstract]

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**Conflict of Interest:** Dr. Ferrari and Dr. Strewler report that no conflicts of interest exist. Dr. Seeman reports that he is an advisory committee member for Sanofi-Aventis, Eli Lilly, Merck Sharp & Dohme, Novartis and Servier, and that he lectures occasionally at conference symposia for those companies.