

REFERENCES

- Altschul, S.F., T.L. Madden, A.A. Schaffer, J. Zhang, Z. Zhang, W. Miller, and D.J. Lipman. 1997. Gapped BLAST and PSI-BLAST: a new generation of protein database search programs. *Nucleic Acids Res.* 25: 3389-3402.
- Alvarez J., M. Balbin, M. Fernandez, and J.M. Lopez. 2001. Collagen metabolism is markedly altered in the hypertrophic cartilage of growth plates from rats with growth impairment secondary to chronic renal failure. *J Bone Miner Res.* 16:511-24.
- Andersson-Eklund, L., H. Uhlhorn, N. Lundeheim, G. Dalin, and L. Andersson. 2000. Mapping quantitative trait loci for principal components of bone measurements and osteochondrosis scores in a wild boar x large white intercross. *Genet Res.* 75(2):223-30.
- Angelo, M., P.C. Billings, M. Pacifici, P.S. Leboy, and T. Kirsch. 2001. Authentic matrix vesicles contain active metalloproteases (*MMP*); A role for matrix vesicle associated *MMP13* in activation of transforming growth factor-beta. *J Biol Chem.* 276:11347-53.
- Ballock, R.T., A. Heydemann, L.M. Wakefield, K.C. Flanders, A.B. Roberts, and M.B. Sporn. 1993. TGF-beta 1 prevents hypertrophy of epiphyseal chondrocytes: regulation of gene expression for cartilage matrix proteins and metalloproteases. *Dev Biol.* 158:414-29.
- Barone, L.M., T.A. Owea, M.S. Tassinari, R. Bortell, G.S. Stein, and J.B. Lain. 1991. Developmental expression and hormonal regulation of the rat matrix gla protein (*MGP*) gene in chondrogenesis and osteogenesis. *J Cell Biochem.* 46: 351-365.
- Barlet, J.P., V. Coxam , and M.J. Davicco. 1995. Physical exercise and the skeleton. *Arch Physiol Biochem.* 103(6): 681-98.
- Böneker, C.D. 2006. Molecular genetic analysis of quantitative trait loci (QTL) for osteochondrosis in Hanoverian warmblood horses. Hannover, Germany.

- Boström, K., A. F. Zebboudj, Y. Yao, T. S. Lin, A. Torres. 2004. Matrix gla protein stimulates VEGF expression through increased *TGFβ1* activity in endothelial cells. *J Biol Chem.* 279:52904–52913.
- Brown, M.F., M.V. Hukkanen, I.D. McCarthy, D.R. Redfern, J.J. Batten, H.V. Crock, S.P. Hughes, and J.M. Polak. 1997. Sensory and sympathetic innervation of the vertebral endplate in patients with degenerative disc disease. *J Bone Joint Surg Br.* 79:147-153.
- Buckwalter, J.A., V.C. Mow, and A. Ratcliffe. 1994. Restoration of injured or degenerated articular cartilage. *J Am Acad Orthop Surg.* 2(4):192-201.
- Carlson, C.S., D.J. Meuten, and D.C. Richardson. 1991. Ischemic necrosis of cartilage in spontaneous and experimental lesions of osteochondrosis. *J Orthop Res.* 9(3):317-329.
- Carter, T.R. 2006. Cartilage restoration - knee anatomy [Online]. Available <http://www.azcartilagerestoration.com/cartilage.htm> (24 May 2008).
- Cancela, M.L., M.C. Ohresser, J.P. Reia, C.S. Viegas, M.K. Williamson and P.A. Price. 2001. Matrix gla protein in *Xenopus laevis*: molecular cloning, tissue distribution, and evolutionary consideration. *J. Bone. Miner. Res.* 16:1611-1621.
- Chen, F.H., K.T. Rousche, and R.S. Tuan. 2006. Technology insight: adult stem cells in cartilage regeneration and tissue engineering. *Nat Clinic Pract Rheum.* 2:373-382.
- Crenshaw, T.D. 2006. Arthritis or OCD - identification and prevention. *Adva in Pork Prod.* 17:199-208.
- Deng, H.W., W.M. Chen, T. Conway, Y. Zhou, K.M. Davies, M.R. Stegman, H. Deng, and R.R. Recker. 2000. Determination of bone mineral density of the hip and spine in human pedigrees by genetic and life-style factors. *Genet Epidemiol.* 19:169-177.
- Dijkgraaf, L.C., L.G. De Bont, G. Boering, and R.S. Liem. 1995. The structure, biochemistry, and metabolism of osteoarthritic cartilage: a review of the literature. *J Oral Maxillofac Surg.* 53:1182-1192.
- Farquharson, C., and D. Jefferies. 2000. Chondrocytes and longitudinal bone growth: the development of tibial dyschondroplasia. *Poul Sci Assoc.* 78:994-1004.

- Farquharson, C., C. Whitehead, S. Rennie, B. H. Thorp, and N. Loveridge. 1992c. Cell proliferation and enzyme activities associated with the development of avian tibial dyschondroplasia: an *in situ* biochemical study. *Bone*. 13:59-62.
- Ferrari, S.L., and R. Rizzoli. 2005. Gene variants for osteoporosis and their pleiotropic effects in aging. *Mol Aspects Med.* 26:145-167.
- Frantz, N.Z. 2006. The effect of dietary nutrients on osteochondrosis in swine and evaluation of serum biomarkers to predict its occurrence. Animal Sciences and Industry College of Agriculture, Kansas State University, Manhattan.
- Frenkel, S.R., P.E. Di Cesare. 1999. Degradation and repair of articular cartilage. *Front Biosci.* 4:671-685.
- Firth, E.C., P.R. Weeren, D.U. Pfeiffer, J. Delahunt, and A. Barneveld. 1999. Effect of age, exercise and growth rate on bone mineral density (BMD) in third carpal bone and distal radius of Dutch Warmblood foals with osteochondrosis. *Equine Vet J Suppl.* 31:74-8.
- Fürst, A., D. Meier, S. Michel, A. Schmidlin, L. Held, and A. Laib. 2008. Effect of age on bone mineral density and micro architecture in the radius and tibia of horses: An Xtreme computed tomographic study. *BMC Vet Res.* 4(3).
- Glimcher, M.J. 1992. The nature of the mineral component of bone and the mechanism of calcification. In: *Disorders of bone and mineral metabolism*, pp. 265-286. Raven Press, New York.
- Grundberg, E., H. Brandstrom, E.L. Ribom, O. Ljunggren, A. Kindmark, and H. Mallmin. 2003. A poly adenosine repeat in the human vitamin D receptor gene is associated with bone mineral density in young Swedish women. *Calcif Tissue Int.* 73:455-462.
- Hackeng, T.M., J. Rosing, H.M.H. Spronk, and C. Vermeer. 2001. Total chemical synthesis of human matrix Gla protein. *Protein Sci.* 10(4):864-870.
- Hardingham, T.E., and M.T. Bayliss. 1990. Proteoglycans of articular cartilage change in aging and joint disease. *Semin Arth Rheum Suppl.* 1:12-33.
- Hartikka, H. 2005. Genetic factors in bone disorders; Osteogenesis imperfecta, juvenile osteoporosis and stress fractures. University of Oulu, Finland.
- Hashimoto, S., R. L. Ochs, F. Rosen, J. Quach, G. McCabe, J. S. J., E. Seegmiller, R. Terkeltaub, and M. Lotz. 1998. Chondrocyte-derived apoptotic bodies and

- calcification of articular cartilage. *Proceedings of the National Academy of Sciences* 95:3094-3099.
- Hill, M.A. 1990. Causes of degenerative joint disease (osteoarthritis) and dyschondroplasia (osteochondrosis) in pigs. *J Am Vet Med Assoc.* 197:107-13.
- Hill, M.A. 1990. Economic relevance, diagnosis, and countermeasures for degenerative joint disease (osteoarthritis) and dyschondroplasia (osteochondrosis) in pigs. *J Am Vet Med Assoc.* 197(2):254-9.
- Holderbaum, D., T.M. Haqqi, and R.W. Moskowitz. 1999. Genetics and osteoarthritis: Exposing the iceberg. *Arthritis & Rheumatism.* 42(3):397-405.
- Horvath S., X. Xu, and N.M. Laird. 2001. The family based association test method: strategies for studying general genotype – phenotype associations. *Euro J Hum Gen.* 9: 301-306.
- Hunter, D.J., M.D. Lange, T. Andrew, H. Snieder, A.J. MacGregor, and T.D. Spector. 2001. Genetic variation in bone mineral density and calcaneal ultrasound: a study of the influence of menopause using female twins. *Osteoporos Int.* 12:406-411.
- Irrechukwu, O. N. 2007. The role of matrix composition and age in solute diffusion within articular cartilage. School of Chemical & Biomolecular Engineering, Georgia Institute of Technology.
- Jefferies, D., C. Farquharson, J. Thomson, W. Smith, E. Seawright, H. McCormack, and C. Whitehead. 2002. Differences in metabolic parameters and gene expression related to osteochondrosis/osteoarthritis in pigs fed 25-hydroxyvitamin D3. *Vet Res.* 33(4):383-96.
- Jorgensen, B. 2000. Osteochondrosis/osteoarthritis and claw disorders in sows, associated with leg weakness. *Acta Vet Scand.* 41(2):123-38.
- Junqueira, L., J. Carneiro, and R. Kelley. 1998. Basic Histology. Stamford, Connecticut, Appleton & Lange.
- Kadarmideen, H.N. 2008. Biochemical, *ECF18R*, and *RYRI* gene polymorphisms and their associations with osteochondral diseases and production traits in pigs. *Biochem Genet.* 46:41-53.

- Kadarmideen, H.N., and L.L.G. Janss. 2005. Evidence of a major gene from bayesian segregation analyses of liability to osteochondral diseases in pigs. *Genetics*. 171(3):1195-1206.
- Kadarmideen, H.N., D. Schworer, H. Ilahi, M. Malek, and A. Hofer. 2004. Genetics of osteochondral disease and its relationship with meat quality and quantity, growth, and feed conversion traits in pigs. *J. Anim Sci.* 82(11):3118-3127.
- Kamphorst, J. J., R.V. Heijden, J. DeGroot, F. P. Lafeber, T. H. Reijmers, B. VanEl, U. R. Tjaden, J. Greef, and T. Hankemeier. 2007. Profiling of endogenous peptides in human synovial fluid by nano LC-MS: method validation and peptide identification. *J. Proteome Res.* 6:4388-4396.
- Kim, D.Y. 2002. Role of chondrocyte apoptosis in the pathogenesis of equine osteoarthritis, Pathobiological Sciences, Louisiana State University.
- Kirk, R.K., B. Jørgensen, and H.E. Jensen. 2008. The impact of elbow and knee joint lesions on abnormal gait and posture of sows. *Acta Vet Scand.* 50(5):1-8.
- Koo, W., M. Hammami, and E.M. Hockman. 2004. Validation of bone mass and body composition measurements in small subjects with pencil beam dual energy x-ray absorptiometry. *J Am Coll Nutr.* 23(1):79-84.
- Krane, S.M. 2006. Connective tissue structure and function. Available from www.geocities.com/SoHo/gallery/6412/ConnTiss.htm.
- Kuettner, K.E., M.B. Aydelotte, and E.J. Thonar. 1991. Articular cartilage matrix and structure: a minireview. *J Rheum Suppl.* 27:46-48.
- Kuroki, K., J. L. Cook, A. M. Stoker, S. E. Turnquist, J. M. Kreeger, and J. L. Tomlinson. 2005. Characterizing osteochondrosis in the dog: potential roles for matrix metalloproteinases and mechanical load in pathogenesis and disease progression. *Osteo and Cart.* 13(3):225-234.
- Kwok, P.Y. 2000. High-throughput genotyping assay approaches. *Pharma.* 1: 95-100.
- Kwok, P.Y. 2001. Methods for genotyping single nucleotide polymorphisms. *Annu. Rev. Genomics Hum. Genet.* 2: 235-258.
- Lepine, A.J. 2000. A morphologic and physiologic review of articular cartilage. Paper in: Articular cartilage and joint health, March 7.
- Lundeheim, N. 1987. Genetic analysis of osteochondrosis and leg weakness in the Swedish pig progeny testing scheme.

- Lou, G., P. Ducy, M. D. McKee, G. J. Pinero, E. Loyer, R. R. Behringer, and G. Karsenty. 1997. Spontaneous calcification of arteries and cartilage in matrix GLA protein. *Nature*. 386:78–81.
- Malemud, C.J., and V.M. Goldberg. 1999. Future directions for research and treatment of osteoarthritis. *Front Biosci*. 4:762-771.
- McInnes, I.B., and G. Schett. 2007. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Rev Immun*. 7:429-442.
- Mow, V.C. 1997. Structure and function of articular cartilage and meniscus. Paper in: Basic orthopedic biomechanics, at Philadelphia.
- Muir, H. 1978. Cartilage structure and metabolism and basic changes in degenerative joint disease. *Aust/NZ J Med*. 8:1-5.
- Munroe, P.B., R.O. Plgunturk, J.P. Fryns, L.V. Maldergem, F. Ziereisen, B. Yuksel, R.M. Gardiner, and E. Chung. 1999. Mutations in the gene encoding the human matrix Gla protein cause Keutel syndrome. *Nat. Genet*. 21:142–144.
- Mwale F., E. Tchetina, C.W. Wu, and A.R. Poole. 2002. The assembly and remodeling of the extracellular matrix in the growth plate in relationship to mineral deposition and cellular hypertrophy: an *in situ* study of collagens II and IX and proteoglycan. *J Bone Miner Res*. 17:275-83.
- Nakano, T., and F.X. Aherne. 1988. Involvement of trauma in the pathogenesis of osteochondritis dissecans in swine. *Can J Vet Res*. 52(1):154-5.
- Nakano, T. 1994. The pathogenesis of osteochondrosis - A hypothesis. *Medical Hypotheses*. 43(1):1-5.
- Nakano, T., F.X. Aherne, and J.R. Thompson. 1984. Relative amounts of chondroitin sulfate and hyaluronic acid in synovial fluid from normal and osteochondrotic swine joints. *Can J Comp Med*. 48(4):434-6.
- Newman, B., L.I. Gigout, L. Sudre, M.E. Grant, and G.A. Wallis. 2001. Coordinated expression of matrix Gla protein is required during endochondral ossification for chondrocyte survival. *J. Cell Biol*. 154(3):659-666.
- Ohata, H., K. Zushida, T. Sugiyama, and S. Kusuhara. 2002. Immunohistochemical study of matrix metalloproteinase-3 (MMP3) at the articular cartilage in osteochondrotic pigs. *Ani. Sci. J*. 73:517-522.
- Olsson, S.E. 1978. Osteochondrosis in domestic animals. *Acta Radiol Suppl*. 358:9-14.

- Olsson, S.E. 1987. General and local [corrected] aetiological factors in canine osteochondrosis. *Vet Q.* 9(3):268-78.
- Orita, M., H. Iwahana, H. Kanazawa, K. Hayashi, and T. Sekiya. 1989. Detection of polymorphisms of human DNA by gel electrophoresis as single-strand conformation polymorphisms. *PNAS.* 86: 2766-2770.
- Pedrozo, H.A., Z. Schwartz, R. Gomez, A. Ornoy, W. Xin-Sheng, S.L. Dallas, L.F. Bonewald, D.D. Dean, and B.D. Boyan. 1998. Growth plate chondrocytes store latent transforming growth factor (TGF)-beta 1 in their matrix through latent TGF-beta 1 binding protein-1. *J Cell Physiol.* 177:343-54.
- Persson, Y. 2007. Breeding soundness evaluation of young beef bulls, Department of Clinical Sciences, Swedish University of Agricultural Sciences.
- Poole, A.R., S. Laverty, and F. Mwale. 2000. Endochondral bone formation and development in the axial and appendicular skeleton. In Henderson, J.E. and D. Goltzman (Ed.), *The osteoporosis primer*, pp. 3-17, Cambridge University Press.
- Price, P. A., J. S. Riceand, and M. K. Williamson. 1994. Conserved phosphorylation of serines in the Ser-X-Glu/Ser(P) sequences of the vitamin K-dependent matrix gla protein from shark, lamb, rat, cow, and human. *Protein Sci.* 3:822-830.
- Ralston, S.H. 2002. Genetic control of susceptibility to osteoporosis. *J Clin Endocrinol Metab.* 87(6):2460-2466.
- Rand, T., G. Seidl, F. Kainberger, A. Resch, K. Hittmair, B. Schneider, C. C. Glüer, and H. Imhof. 1997. Impact of spinal degenerative changes on the evaluation of bone mineral density with dual energy x-ray absorptiometry (DXA). *Calcified Tissue International.* 60(5):430-433.
- Reiland, S. 1978. Pathology of so-called leg weakness in the pig. *Acta Radiol Suppl.* 358:23-44.
- Risch, N. and K. Merikangas. 1996. The future of genetic studies of complex human diseases. *Science.* 273:1516–1517.
- Robey, P.G. 1988. The cellular biology and biochemistry of bone formation. Paper in: *Disorders of bone and mineral metabolism*, pp. 241-263, New York, Raven Press.
- Sahlman, J. 2007. Chondrodysplasias caused by defects in the *Col2a1* gene. Biomedicine, Anatomy, University of Kuopio, Finland.

- Sanchez, J.J., C. Børsting, C. Hallenberg, A. Buchard, A. Hernandez, and N. Morling. 2003. Multiplex PCR and minisequencing of SNPs—a model with 35 Y chromosome SNPs. *Forensic Sci. Int.* 137:74–84.
- Schipani E., B. Lanske, J. Hunzeman, A. Luz, C.S. Kovacs, K. Lee, A. Pirro, H.M . Kronenberg, and H. Juppner. 1997. Targeted expression of constitutively active receptors for parathyroid hormone and parathyroid hormone-related peptide delays endochondral bone formation and rescues mice that lack parathyroid hormone-related peptide. *Proceedings of the National Academy of Sciences U S A.* 94:13689-94.
- Scott, J.C., M.S. Koylass, M.R. Stubberfield, and A.M. Whatmore. 2007. Multiplex assay based on single-nucleotide polymorphisms for rapid identification of *Brucella* isolates at the species level. *Appl Environ Microbiol.* 73:7331-7337.
- Semevolos, S. A., A. J. Nixon, and B. D. Brower-Toland. 2001. Changes in molecular expression of aggrecan and collagen types I, II, and X, insulin-like growth factor-I, and transforming growth factor-beta1 in articular cartilage obtained from horses with naturally acquired osteochondrosis. *Am J Vet Res.* 62(7): 1088-94.
- Serenius, T., M. L. Sevon-Aimonen, A. Kause, E. A. Mantysaari, and A. Maki-Tanila. 2004. Genetic associations of prolificacy with performance, carcass, meat quality, and leg conformation traits in the Finnish Landrace and Large White pig populations. *J Anim Sci.* 82(8):2301-6.
- Spotila, L.D., A. Colige, L. Sereda, C.D. Constantinou-Deltas, M.P. Whyte, B.L. Riggs, J.L. Shaker, T.D. Spector, E. Hume, and N. Olsen. 1994. Mutation analysis of coding sequences for type I procollagen in individuals with low bone density. *J Bone Miner Res.* 9(6):923-32.
- Stern, S., N. Lundeheim, K. Johansson, and K. Andersson. 1995. Osteochondrosis and leg weakness in pigs selected for lean tissue growth rate. *Lives Prod Sci.* 44(1):45-52.
- Tsukamoto, K., H. Orimo, T. Hosoi, M. Miyao, H. Yoshida, S. Watanabe, T. Suzuki, and M. Emi. 2000. Association of bone mineral density with polymorphism of the human matrix gla protein locus in elderly women. *J Bone Minerl Metab.* 18(1):27-30.

- Uitterlinden, A.G., Y. Fang, J.B. Meurs, H.A. Pols, and J.P. Leeuwen. 2004. Genetics and biology of vitamin D receptor polymorphisms. *Gene*. 338(2):143-156.
- Vu T.H., J.M. Shipley, G. Bergers, J.E. Berger, J.A. Helms, D. Hanahan, S.D. Shapiro, R.M. Senior, and Z. Werb. 1998. MMP9/gelatinase B is a key regulator of growth plate angiogenesis and apoptosis of hypertrophic chondrocytes. *Cell*. 93:411-22.
- Wang, D.G., J.B. Fan, C. J. Siao, A. Berno, P. Young, R. Sapolksy, G. Ghandour, N. Perkins, E. Winchester, J. Spencer, L. Kruglyak, L. Stein, L. Hsie, T. Topaloglou, E. Hubbell, E. Robinson, M. Mittmann, M. S. Morris, N. Shen, D. Kilburn, J. Rioux, C. Nusbaum, S. Rozen, T. J. Hudson, R. Lipshutz, M. Chee, and E. S. Lander. 1998. Large-scale identification, mapping, and genotyping of single-nucleotide polymorphisms in the human genome. *Science*. 280:1077-1082.
- Warburton, D., Schwarz, M., Tefft, D., Flores-Delgado, G., Anderson, K. D., and Cardoso, W. V. 2000. The molecular basis of lung morphogenesis. *Mech. Dev.* 92:55-81.
- Wardale, R.J., and V.C. Duance. 1994. Characterisation of articular and growth plate cartilage collagens in porcine osteochondrosis. *J Cell Sci.* 107(1):47-59.
- Yagami, K., J.Y. Suh, M. Enomoto-Iwamoto, E. Koyama, W.R. Abrams, I.M. Shapiro, M. Pacifici, and M. Iwamoto. 1999. Matrix gla protein is a developmental regulator of chondrocyte mineralization and, when constitutively expressed, blocks endochondral and intramembranous ossification in the limb. *J. Cell Biol.* 147(5):1097-1108.
- Ytrehus, B., C.S. Carlson, and S. Ekman. 2007. Etiology and pathogenesis of osteochondrosis. *Vet Pathol.* 44(4):429-48.
- Ytrehus, B., S. Ekman, C.S. Carlson, J. Teige, and F.P. Reinholt. 2004. Focal changes in blood supply during normal epiphyseal growth are central in the pathogenesis of osteochondrosis in pig. *Bone*. 35(6):1294-306.
- Zebboudj, A.F., M. Imura, and K. Bostrom. 2002. Matrix gla Protein, a regulatory protein for bone morphogenetic protein-2. *J Biol Chem.* 277(6):4388-4394.