carrying one or two copies of the G allele was associated with 13% higher grade – corresponding to lower disc signal intensity – than that of AA homozygotes (adjustment as before, \( p < 0.02 \)). The SNP detected maps to chromosome 15q22 and a gene of as yet unknown function. Of interest, this gene has been shown in human tissue microarray experiments to be up-regulated in bone from non-healing versus normal healing fracture, pointing to a role in bone formation and/or remodeling. Furthermore, we went on to test this SNP for association with spine bone mineral density (BMD). In the TwinsUK cohort the genotype was significantly associated with spine BMD (after adjustment, \( p < 0.002 \)). A similar trend was observed among women from the Chingford cohort (\( p < 0.06 \)) but only among women who did not report back pain.

**Conclusions:** These results from two independent population based cohorts of women point to a novel genetic variant involved in the susceptibility to LDD. It is possible that this variant acts to promote LDD through altering local bone metabolism.

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**A50a** **VARIATION AT THE ANP32A AND WNT5A GENES – BOTH INVOLVED IN WNT SIGNALING – IS ASSOCIATED WITH RISK OF HIP OSTEOARTHRITIS IN WOMEN

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**Purpose:** The Wnt-beta-catenin signaling pathway is a powerful stimulator of chondrocyte matrix catabolic action and may have a role in excessive remodeling and degradation of cartilage matrix in osteoarthritis (OA). The ANP32A gene encodes a tumor suppressor molecule – pp32 – involved in ERK signaling and shown to inhibit canonical Wnt signaling via its interaction with Axin1. Wnt5a is a mediator of non-canonical Wnt signaling, involved in inflammation, angiogenesis and down-regulation of the canonical Wnt pathway. We tested whether variation at genes encoding these two Wnt signaling molecules was associated with OA of the hip or the knee in women in 2479 women from the UK and 1987 women from the Netherlands.

**Methods:** Two SNPs in the WNT5A gene and 8 SNPs in the ANP32A gene were genotyped in 435 controls, 643 knee OA cases and 571 hip OA female cases from Nottingham (UK). Results were replicated in a population based cohort, the Chingford study of 830 women. The top SNP from the ANP32A gene was also replicated in women from the Rotterdam study (131 total hip replacement cases and 1856 controls).

**Results:** Five SNPs in the ANP32A gene and both of the WNT5A SNPs were significantly associated with hip OA in the Nottingham cases (\( p < 0.009 \) and \( p < 0.002 \) best \( p \)-values respectively) but not knee OA. The Wnt5A SNPs were not associated with knee OA or the Chingford cohort but had \( p \)-values of \( p < 0.02 \) and \( p < 0.08 \) for hip OA. Combining Chingford and Nottingham data resulted in a Mantel-Haenszel odds ratio of 1.49 (95% CI 1.18–1.88; \( p < 8 \times 10^{-6} \)) for the minor allele of rs648872 and an OR\(_{MH}\) = 0.79 (95% CI 0.66–0.94; \( p < 0.009 \)) for the minor allele of rs1047898. Of the five ANP32A SNPs significant in the Nottingham hip OA cases, two were also associated with hip OA (rs7164503 \( p < 0.016 \) and rs1551343 \( p < 0.049 \)) and rs7164503 also with knee OA (\( p < 0.048 \)) in the Chingford study. A meta-analysis of hip OA incorporating data of the Rotterdam cohort yielded an OR\(_{MH}\) = 0.69 (95% CI 0.54–0.90; \( p < 0.0033 \)) for the minor allele of rs7164503. The ANP32A transcript was found to be abundantly expressed in articular cartilage from OA patients and the minor allele at rs7164503 was associated with significantly lower cis-acting allelic expression levels of the ANP32A transcript in lymphoblast cell lines.

**Conclusions:** Our results demonstrate two novel gene loci are associated with OA and provide further evidence that Wnt-beta-catenin signaling molecules are involved in the pathogenesis of cartilage related diseases. This work was supported by the Arthritis and Research Campaign project grant 17716 and by the European Union FP7 large collaborative project grant 200800 TREAT-OA