Abstract
A genetic association of the ENPP1 gene with primary hand osteoarthritis was recently reported in this journal. ENPP1 encodes an enzyme that regulates soft tissue calcification. The study as it stands is far from complete because the actual causal variant(s) within ENPP1 has not been identified and no functional study on the activity of the enzyme in hand osteoarthritis was presented. Nevertheless, the study stimulates interest and will encourage others in the field to test ENPP1 as a possible osteoarthritis susceptibility gene in their cohorts. The genetic basis of osteoarthritis is slowly being uncovered, and this report constitutes another interesting find.

Crystal deposition is often observed in osteoarthritic joints but its role as a causative agent in the disease is unclear. Suk and coworkers [1] have taken a genetic approach to answering this question by determining whether common DNA variants in the gene encoding the enzyme ecto-nucleotide pyrophosphatase phosphodiesterase (ENPP)1 are associated with osteoarthritis of the hand. ENPP1 generates inorganic pyrophosphate (PP) from nucleoside triphosphates, which acts as an inhibitor of hydroxyapatite and therefore prevents soft tissue calcification. Suk and colleagues were stimulated to investigate common polymorphisms in the ENPP1 gene following their previous genetic investigation of the rare Mendelian condition generalized arterial calcification of infancy. This disease is characterized by calcification of the arteries, but many patients also exhibit periarticular calcifications and inflammation [2]. Suk and coworkers therefore hypothesized that common variants in ENPP1 may be risk factors for common osteoarthritis.

To answer this question the investigators initially carried out a radiographic examination of the hands of 574 adults from 126 pedigrees derived from a relatively isolated population of Chuvashians from southern Russia. Hand osteoarthritis status was then determined using the Kellgren-Lawrence scale. DNA from each patient was subsequently genotyped for three short tandem repeat polymorphisms (also known as microsatellites) and for four common single nucleotide polymorphisms, two of which encode amino acid substitutions (nonsynonymous single nucleotide polymorphisms). The seven variants provided physical coverage of the whole gene. The genotype data were then tested for association with osteoarthritis using the transmission disequilibrium test. This is a neat statistical method for testing associations that uses internal controls and therefore avoids the potential pitfall of inadequately matched controls that can lead to false-positive results in case-control association studies.

The transmission disequilibrium test analysis revealed a number of associations when the individual variants were tested and when the genotype data from several variants were examined in combination in a haplotype analysis. The most compelling results were obtained for a short tandem repeat located immediately upstream of ENPP1. This is an intriguing find because it implies that susceptibility to hand osteoarthritis may be encoded by polymorphism in cis elements that regulate the expression of ENPP1, rather than in DNA changes that lead to amino acid substitution in the protein. It is becoming increasingly apparent that polymorphism in the regulation of gene expression is common and that this can have a significant influence on the development of complex diseases [3,4]. To determine whether polymorphism in cis regulatory elements of ENPP1 occurs, Suk and colleagues should be encouraged to test the gene for differences in expression at the allelic level.

Suk and coworkers [1] conducted their study on an isolated population of Chuvashians. To assess the global relevance of their find it will be necessary to test the association in cohorts derived from different ethnic groups. Two centres have recently reported genome-wide linkage scans for hand osteoarthritis; the Framingham study in the USA and DeCode in Iceland [5]. Neither scan reported a linkage to
chromosome 6q23.2, which is the position of ENPP1. However, linkage scans can miss loci of weak to moderate effect, and it would be desirable if these two centres examined ENPP1 in their cohorts. To assess the relevance of ENPP1 to osteoarthritis development at sites other than the hand, the ENPP1 variants should be genotyped in patients with severe disease at the hip, knee, or spine. The osteoarthritis research community is relatively fortunate in that many groups have collected OA cohorts suitable for genetic analyses [6], making confirmatory studies feasible.

The genetic investigation of osteoarthritis has had a fillip in recent years, with compelling associations reported to several genes, including FRZB, ASPN, CALM1 and the interleukin-1 gene cluster [5,7]. This latest result reported by Suk and coworkers [1] is another interesting find. However, before we get carried away it is essential that the actual causal variant(s) at ENPP1 be identified and substantiated with compelling functional tests. These are difficult but essential goals.

Conclusion
Finally, it is interesting to dwell a little on recent genetic finds. The genes so far identified encode proteins that have a diverse range of normal physiological roles, from regulating the expression of extracellular matrix structural protein genes through to regulating a number of cartilage anabolic and catabolic factors. As many have expected, it appears that there are several paths that can lead toward the development of osteoarthritis. ENPP1 and its regulation of PPi and calcification may be highlighting another.

Competing interests
The author(s) declare that they have no competing interests.

Acknowledgements
The Arthritis Research Campaign and Research into Ageing fund my group’s research.

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