In Reply:

The authors appreciate the letter regarding the significance of the previous work on the subject. The purpose of the article was to evaluate the significance of ulnar variance on outcomes of arthroscopic repair. The authors previously reported that ulnar positive variance might be a factor that contributed to a worse outcome following arthroscopic repair. The purpose of the study was to evaluate this single factor in a cohort of patients who are otherwise comparable. The results indicate that positive ulnar variance of 2 mm or less does not preclude arthroscopic repair. Indeed, as the previous letter points out, this might be preferable because ulnar shortening osteotomy does carry with it the risk of delayed union or nonunion of the ulna following osteotomy.

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Genome-Wide Association Scan of Dupuytren's Disease

To the Editor:

We read with interest the article "Genome-Wide Association Scan of Dupuytren's Disease," by Ojwang et al.[1] We agree with the authors that Dupuytren's disease represents an archetypal complex disease, with a clear polygenic genetic predisposition and multiple environmental influences, leading to the final expression of the disease phenotype. As such, the logical way to dissect the genetic predisposition is a genome-wide association study (GWAS).

In a GWAS using modern genotyping platforms, hundreds of thousands of genetic markers are compared in cases and controls to detect an association between the disease and a particular marker. Because hundreds of thousands of independent hypotheses are being tested in each experiment, the possibility of a false-positive result is high, and false associations can be easily discovered.[2]

There are 2 ways to guard against the reporting of such false associations. The first is to perform a Bonferroni correction[3,4] to reduce the p value that is taken as the threshold for accepting an association as statistically significant and therefore likely to be truly positive. In most published GWAS, the calculated p value accepted as demonstrating genome-wide significance is $p < 5 \times 10^{-7}$.[5] Even $p < 5 \times 10^{-8}$ has been suggested as a predefined significance level in GWAS. More advanced methods incorporate a more specific prior significance threshold based on Bayesian analysis. We have calculated the Bonferroni correction for the Illumina CytSNP platform used by Ojwang et al, and $p = 2 \times 10^{-7}$ would result in a type 1 error rate of 5%, a level that is the minimal standard accepted in the literature. This equates to $p = .05$ in the studies that will be most familiar to readers of the *Journal of Hand Surgery*. Thus, none of the associations in this study reach genome-wide significance, and it is highly likely that most represent false-positive results. This interpretation is further corroborated by the fact that none of the markers described showed clustering of single nucleotide polymorphisms associated with disease. Most reported GWAS have case and control numbers in the thousands to combat this problem.[5]

To provide evidence that these associations are false positives, we ran a permutation analysis on our own Dupuytren's disease GWAS, of 2,325 patients and 11,562 controls from the Dutch Dupuytren's Study Group, the British Society for Surgery of the Hand Genetics of Dupuytrens Disease Consortium, and the German Dupuytren's Study Group. We randomly assigned 80 people to be either cases ($n = 40$) or controls ($n = 40$) irrespective of whether they were actual cases or controls. We then analyzed their genotype data for association with case status. We repeated this experiment 5 times. For the 5 runs, we discovered between 17 and 53 variants associated with being a case at $p < 10^{-4}$, results comparable to those reported by Ojwang et al.

The second method of guarding against the reporting of false-positive results is to replicate the results in a second independent cohort. The authors of the current study have made no attempt to replicate their results. Owing to these fundamental problems, we feel that the conclusions reached in this study are not supported by the data.

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In Reply:

We thank the authors of the Letter to the Editor for their interest in our study as well as their concern for false positives in association studies. We acknowledge that we did not employ the Genome-Wide Association (GWA) significance level set forth by the Wellcome Trust Consortium[1] in their study of over 500,000 single nucleotide polymorphisms (5×10^{-7}, a p value 5-fold less stringent than Bonferroni). In our study we used a genotyping panel designed for much smaller-scale investigation and analyzed only 251,837 (thus reducing the number of tests conducted by half). We also chose not to impose Bonferroni correction on the analysis of this rare disease so as not to be exclusionary of possible effects. Dubois et al[2] proposed the threshold we use as suggestive for association. Certainly, the debate on balancing type I error and power and the stringency (or in many cases, the overstringency) of the Bonferroni correction is one that continues, and if readers are interested, they can reference the articles in the literature.[3–6] However, rather than debating the merits of Bonferroni correction, we would like to call attention to the novel and compelling aspects of our study. First, mapping by admixture linkage disequilibrium (MALD) analysis presented (and not referenced by the authors of the letter) shows convincing evidence of effects on chromosomes 6, 8, 11, and 16, even when imposing the most strict Bonferroni correction ($p = .05/3{,}133 = 1.6 \times 10^{-5}$). Second, the effects on both chromosomes 6 and 11 were seen in both the MALD and association analyses, strengthening the evidence that they are indeed real effects. In conclusion, we appreciate the authors' warning that caution must be taken when interpreting GWA analyses, particularly in cohorts of modest size. Indeed, that is exactly why we approached this unique phenotype using both the standard GWA analysis and the more novel MALD approach. Finally, whereas we remain confident that the regions found in our article are worth further investigation, we look forward to the findings of the authors of the letter so that we can all work together to help patients with this debilitating disease.

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