Table 3. The Minimum Detectable ORs for Our Analysis under the Log-Additive Model with Power ⩾80% and a Significance Level of 5%

Comparison	Minimum Detectable OR	
	RHOB SNP *rs585017*	*TXNDC3* SNP *rs4720262*
All case patients vs. all control subjects	1.23	1.30
Female case patients vs. female control subjects	1.34	1.42
Male case patients vs. male control subjects	1.36	1.45
All knees vs. all control subjects	1.35	1.43
Female knees vs. female control subjects	1.49	1.62
Male knees vs. male control subjects	1.54	1.68
All hips vs. all control subjects	1.25	1.31
Female hips vs. female control subjects	1.36	1.47
Male hips vs. male control subjects	1.38	1.49

dbSNP, http://www.ncbi.nlm.nih.gov/projects/SNP/ (for *rs585017* and *rs4720262*)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for osteoarthritis, *RHOB,* and *TXNDC3*)
Quanto, http://hydra.usc.edu/gxe (for power calculations)

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Reply to Loughlin et al.

To the Editor:

We very much appreciate the effort Loughlin and colleagues[1] took in trying to replicate our finding of an association between osteoarthritis (MIM 165720) and the *RHOB* (MIM 165370) SNP *rs585017* and the *TXNDC3* (MIM 607421) SNP *rs4720262*.

In our study,[2] odds ratios (ORs) of 2.1 and 2.3 describe the association between osteoarthritis and the *RHOB* and *TXNDC3* SNPs, respectively, and we had 80% power to detect ORs as small as 1.6 and 1.8, respectively. Both SNPs were in Hardy-Weinberg equilibrium in the control group, so we can confidently rule out obvious methodological flaws.

Loughlin et al.[1] used the same disease ascertainment that we did (joint replacement of the hip and/or knee), and they too analyzed Europeans of white ethnicity. Why then did the study fail? And, by extension, why did all the previous genomewide scans—no matter how comparable the strategies to elucidate the genetics of osteoarthritis[3,4]—not culminate in a coherent set of results?

Obviously, one can always call for an even higher statistical power or claim that reported associations are spurious. But let us refocus on the disease at hand; osteoarthritis is a complex disease, and if there was a simple genetic pattern involved, surely we would have identified it by now.[5] Assuming that the osteoarthritis pathogenesis requires a delicate interplay between individual genetic polymorphisms and regional environmental changes, we need to question the comparability of a British study and an eastern German study for disease-associated genes. Additionally, we need to identify the strata that reflect the different etiologies. In fact, table 3 in the letter by Loughlin et al.[1] might also suggest that increased ORs cannot be excluded for the strata "osteoarthritis of the knee." Our own data support a recessive model for *RHOB* and a dominant model for *TXNDC3*. The combination of both risk factors yields an OR >9; however, our sample numbers are small. To facilitate testing our hypothesis in the U.K. cohort, we emphasize the suggestion that all tested data be reported as online supplements in their original forms.[5]

Loughlin et al.[1] also raise the issue of the different frequencies for the *TXNDC3* SNP *rs4720262* in the control subjects—13.4% in our cohort and 28.8% in the U.K. cohort. Indeed, the Ensembl Genome Browser reports a high variability for this particular SNP, with 2.2% in African Americans as the lowest. Among Americans of European descent, the frequencies vary from 21.7% (in HapMap, among 60 individuals) to 31.2% (in PERLEGEN, among 25 individuals). This points to an elevated variability in

whites, since these particular PERLEGEN and HapMap cohorts are not independent of each other (Coriell Institute for Medical Research, Ensembl Genome Browser, and HapMap).

Indeed, the frequency of 13.4% in our white control subjects is striking. However, there is a precedent of different SNP frequencies in British and German populations,[6] which calls for detailed investigations of individual European populations—down to the haplotype level. We will certainly perform further analyses to increase the understanding of our control population. It is also important, in this context, to specify the origin of all individuals genotyped; in the study of Loughlin et al.,[1] 268 of the patients are not mentioned in the reference cited. The situation for *RHOB* SNP *rs585017* is different; the recessive effect of the GG genotype is reflected by a frequency of 4.9% in our control subjects and 20.5% in our case patients. Loughlin et al. found a comparable frequency in control subjects (6.8%; $P = .4$), but the frequency in case patients was much different (8.3%; $P = 3 \times 10^{-6}$), which illustrates the points we discussed above.

We are confident that the future of osteoarthritis genetics will encompass both (i) the analysis of even larger cohorts, with sample cohorts crossing regional boundaries—either genetic or environmental—and thus the possible dilution of effects, and (ii) strategies for zooming in on regional effects and for designing smart experiments to test individual traits.

SANDRA MAHR, HOLGER KIRSTEN, AND BRIGITTE MÜLLER

Web Resources

The URLs for data presented herein are as follows:

Coriell Institute for Medical Research, http://www.coriell.org/
Ensembl Genome Browser, http://www.ensembl.org/
HapMap, http://www.hapmap.org/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for OH, *RHOB,* and *TXNDC3*)

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