Reply to Webb et al.

To the Editor: Biallelic inheritance of *MYH* (MIM 604933) defects has been consistently shown to increase risk of colorectal disease (MIM 608456) in a number of different populations.[1–3] However, the increase in risk due to monoallelic inheritance is still under debate. Croitoru et al.[2] alluded to a monoallelic effect, presenting indirect evidence of nonrandom loss of heterozygosity of the wild-type alleles in tumors of heterozygous patients, and they also demonstrated an excess of familial clustering of disease in these patients. Our previously published data[3] suggested a monoallelic effect, which was statistically significant only for later-onset disease. Rather than a "data-dredging" exercise, the rationale for the analysis of age subgroups was our a priori hypothesis of an age effect. We conducted significance testing by permutation tests, because empirical significance levels are generally considered to be more robust to violations of the underlying statistical assumptions than are the asymptotic significance levels. However, we recognized that this effect was of borderline statistical significance at the 5% level, and we emphasized that this evidence should be interpreted with caution. We concluded that this preliminary observation merited further study.

Since publication of that work in the *Journal,*[3] we have performed a replication study, using Scottish population-based samples and a meta-analysis of all published case-control *MUTYH* association studies, and this work was recently published.[4] The pooled results confirmed the reported biallelic effect and gave more-precise estimates of the associated risk. However, we again observed a monoallelic effect of borderline statistical significance (OR 1.27; 95% CI 1.01–1.61). These findings are comparable to those of the meta-analysis presented by Webb et al.,[5] with additional primary data from English samples, although their analysis fails to achieve statistical significance at the 5% level (OR 1.26; 95% CI 0.99–1.60). The overall lack of association with the *MUTYH* gene in the Webb study is in contrast to the other two large association studies with >1,000 cases and controls.[2,3] Similarly, the results of the kin-cohort study performed by Webb et al.[5] is in contrast to the published work of Jenkins et al.,[6] who demonstrated a threefold increase in risk for monoallelic carriers by use of a similar analysis. These differences may be due to study bias and confounding due to imperfect case-control matching, rather than to true population differences.

Overall, we think that the available data support a small monoallelic effect of *MYH* variants. However, it is clear that meta-analysis is needed to achieve the very large sample sizes required to confirm the small effects that are typical of such variants. A road map for this effort was recently proposed.[7] To this end, we have already invited all other seven groups with published case-control data on *MYH* variants to pool all available data, to address this issue and to investigate evidence of age, sex, or other effects associated with tumor pathology.

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Web Resource

The URL for data presented herein is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for *MYH* and colorectal disease)

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