Re: IGF-1 Gene Polymorphism and Risk for Hereditary Nonpolyposis Colorectal Cancer

Recently, Zecevic et al. (1) reported an association between the size of the CA-repeat sequence residing in the 5′ untranslated promoter region upstream of the start site of the IGF-1 gene and age of disease onset in 121 hereditary nonpolyposis colorectal cancer patients who harbored germline mutations in the mismatch repair (MMR) genes hMLH1 or hMSH2 (1). In their study, an association between the length of the polymorphism and age of disease onset in patients harboring hMSH2 germline mutations was observed.

To determine if this relationship was applicable to other populations, to only hMSH2 mutation carriers, or to only men or women, we investigated the IGF-1 CA-repeat polymorphism in a total of 220 MLH1 and MSH2 mutation–positive patients from 36 families, including 123 probands/single family members with confirmed hMLH1 or hMSH2 germline mutations. Polymerase chain reaction conditions and CA-repeat analyses were as previously described (1,2). Allele sizes were categorized as reported by Zecevic et al. (1) such that patients were grouped as having one allele with 17 or fewer CA repeats (≤17 CA) or both alleles with 18 or more CA repeats (≥18 CA).

A clear relationship was observed for early-onset disease in the patient group with 17 or fewer CA repeats. Overall, patients with 17 or fewer CA repeats were more likely than patients with 18 or more repeats to have early onset of colorectal cancer using the log-rank (LR) test (LR \( df = 1 \) = 4.71, \( P = .03 \)). Kaplan–Meier analysis also revealed a 15-year difference in the age of colorectal cancer onset between patients in the two groups (≤17 CA, median age = 48 years, 95% confidence interval [CI] = 44.5 to 51.3 years, range 21–84 years versus ≥18 CA, median age = 63 years, 95% CI = 51.8 to 74.2 years, range 21–95 years). When patients with hMSH2 and hMLH1 mutations were analyzed separately, a statistically significant difference in the age of disease onset was observed only among the hMLH1 mutation carriers (≤17 CA versus ≥18 CA, LR \( df = 1 \) = 5.05, \( P = .025 \)).

For proportional hazard Cox regression modeling, two models were tested including hMLH1–hMSH2 mutation group, IGF-1 CA-repeat group alone, and IGF-1 CA-repeat group plus sex with or without family clustering. No association between colorectal cancer risk and hMLH1–hMSH2 mutation or interaction between hMLH1–hMSH2 mutation group and the two CA-repeat IGF-1 groups was observed, which contradicted the Kaplan–Meier results based on MMR mutation type. The Cox model interpretation is preferred over the individual Kaplan–Meier survival curves, and it appears from the interaction test that it is the IGF-1 CA-repeat group alone, which is associated with risk of colorectal cancer and not the MMR mutation type. The final model from Cox regression analysis included the IGF-1 group plus sex and family as a cluster variable. The smaller number of IGF-1 CA repeats had the strongest association with colorectal cancer risk compared with the 18 or more CA group, (≤17 CA group, hazard ratio = 1.5, 95% CI = 1.02 to 2.16; \( P = .044 \)). The association between sex and risk of colorectal cancer approached borderline statistical significance (compared with females, for males, hazard ratio = 1.40, 95% CI = 0.97 to 2.03; \( P = .071 \)).

Our results indicate that the increased risk for colorectal cancer is equal in both hMLH1 and hMSH2 carriers. Although the association was not statistically significant in this study, the risk of colorectal cancer may be slightly more profound in males.

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Fig. 1. Kaplan–Meier analysis of time to onset of colorectal cancer for patients with 17 or fewer IGF-1 gene CA repeats (red) and patients with 18 or more CA repeats (green). The hatched curves represent 95% confidence intervals. Kaplan–Meier analysis was used to conduct univariate analysis with mutation type and sex along with time to onset of colorectal cancer in regards to CA-repeat length. The age of diagnosis was used as the age of onset in all patients with colorectal cancer. For the unaffected mismatch repair gene mutation carriers, the age at last follow-up was used as the age of onset, and these subjects were censored in the analysis. All proportional hazard assumptions were verified using Schoenfeld residuals, and statistical tests were two-sided and performed using Intercooled Stata 8.2 (Stata Corp, College Station, TX).
RESPONSE

Hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant disorder caused by DNA mismatch repair (MMR) gene mutations with hMLH1 and hMSH2 being the most frequently mutated (1). Reeves et al. have genotyped a series of MMR gene mutation carriers for a CA-repeat polymorphism in the 5′ untranslated region of the insulin-like growth factor 1 (IGF-1) gene to determine whether findings from our recent study on this polymorphism were applicable to other populations. In our study, a group of 121 MMR gene mutation carriers for either MSH2 or MLH1 were genotyped for the IGF-1 gene polymorphism. We found a statistically significant association between shorter IGF-1 CA-repeat lengths and increased age-associated risk for HNPCC among the mutation carriers. When we stratified by MMR gene mutation, the association between HNPCC risk and IGF-1 CA-repeat length was statistically significant for MSH2 gene mutation carriers but not for MLH1 mutation carriers.

It is exciting that the work by Reeves et al. confirms the association between shorter IGF-1 gene CA-repeat lengths (≤17) and earlier disease onset in their study of 220 MMR gene mutation carriers. It will be interesting to find out whether shorter IGF-1 gene CA-repeat lengths influence risk for other cancer types as well.

When Reeves et al. stratified by MMR gene mutation, they observed the opposite from what we reported—a statistically significant association between HNPCC risk and IGF-1 CA-repeat length for MLH1 gene mutation carriers but not for MSH2 mutation carriers. Although it is possible that differences between the findings of the studies may have been due to differences in environmental and genetic backgrounds between the two study populations, it is also likely that they are due to the small sample sizes of the study groups created after stratification for the underlying MMR gene mutations. However, because the Cox regression modeling of Reeves et al. suggested that it is the IGF-1 CA-repeat group that was associated with the risk for HNPCC development and not the MMR mutation type per se, we tend to favor the latter hypothesis. Larger studies are needed to determine whether the type of MMR gene that is mutated influences the effect of the IGF-1 CA-repeat polymorphism.

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