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Genetic testing for hepatocellular carcinoma: An ambitious goal still to achieve

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COMMENTARY ON:

A functional polymorphism in the epidermal growth factor gene is associated with risk for hepatocellular carcinoma. Abu Dayyeh BK, Yang M, Fuchs BC, Karl DL, Yamada S, Sninsky JJ, O'Brien TR, Dienstag JL, Tanabe KK, Chung RT; HALT-C Trial Group. Gastroenterology. July 2011;141(1):141–9. Copyright (2011). Abstract reprinted with permission from the American Gastroenterological Association.

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Abstract: Background & Aims: *A single nucleotide polymorphism 61*G (rs4444903) in the epidermal growth factor (EGF) gene has been associated, in two case–control studies, with hepatocellular carcinoma (HCC). We tested associations between demographic, clinical, and genetic data and development of HCC, and developed a simple predictive model in a cohort of patients with chronic hepatitis C and advanced fibrosis.*

Methods: *Black and white subjects from the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial (n = 816) were followed up prospectively for development of a definite or presumed case of HCC for a median time period of 6.1 years. We used the Cox proportional hazards regression model to determine the hazard ratio for risk of HCC and to develop prediction models.*

Results: *Subjects with EGF genotype G/G had a higher adjusted risk for HCC than those with genotype A/A (hazard ratio, 2.10; 95% confidence interval, 1.05–4.23; P = .03). After adjusting for EGF genotype, blacks had no increased risk of HCC risk compared with whites. Higher serum levels of EGF were observed among subjects with at least one G allele (P = .08); the subset of subjects with EGF G/G genotype and above-median serum levels of EGF had the highest risk of HCC. We developed a simple prediction model that included the EGF genotype to identify patients at low, intermediate, and high risk for HCC; 6-year cumulative HCC incidences were 2.3%, 10.4%, and 26%, respectively.*

Conclusions: *We associated the EGF genotype G/G with increased risk for HCC; differences in its frequency among black and white subjects might account for differences in HCC incidence between these groups. We developed a model that incorporates EGF genotype and demographic and clinical variables to identify patients at low, intermediate, and high risk for HCC.*

In the current scenario of increasing costs for medical interventions, prevention and therapeutic algorithms need to be optimized by the selection of ideal target patients. Efforts for stratification of patients with chronic liver disease by hepatocellular carcinoma (HCC) risk using clinical and demographic variables have met with little success, not infrequently resulting in the identification of patients with excess risk of liver cancer, at the same time leading to deferral of an unacceptable high number of individuals who still have a significant residual risk of liver cancer [1]. In principle, a clinical model incorporating a single nucleotide polymorphism (SNP) for a potentially pathogenic gene, like the Epidermal Growth Factor (*EGF*) gene, might increase HCC prediction finalized to pretreatment stratification of patients with liver disease who are at risk of developing liver cancer. The SNP involving an A to G transition at position 61 in the 5′ untranslated region of the *EGF* gene (SNP rs4444903), which *in vitro* was associated with increased production of EGF protein [2], has been the focus of investigations in patients with chronic hepatitis. EGF is in fact recognized as an important driver of the malignant transformation of different epithelial cells [3], with some evidence that both EGF receptor and EGF signaling could have a pathogenic role in HCC development [4,5].

Tanabe *et al.* [6] in two independent case–control study populations in the USA (207 subjects with 59 HCC index cases) and in France (141 subjects with 44 HCC index cases) provided a preliminary evidence that genotyping for *EGF* polymorphism coupled with assessment of serum levels of EGF protein, may serve as novel markers of HCC risk in patients with cirrhosis of mixed etiology. The working hypothesis of this retrospective study was that *EGF* SNP modulates *EGF* mRNA half-life to the point of increasing the stability of *EGF* transcripts in human hepatoma cell lines carrying the G allele, thereby resulting in an increased *in vitro* expression of EGF protein in G/G compared to A/A cell lines that *in vivo* translated in greater accumulation of serum and liver EGF protein in the former patients (Fig. 1). These scientifically attractive findings provided a strong rationale to validate *EGF* SNP as a predictor of HCC in a set of prospectively recruited patients with advanced liver fibrosis who were framed into the

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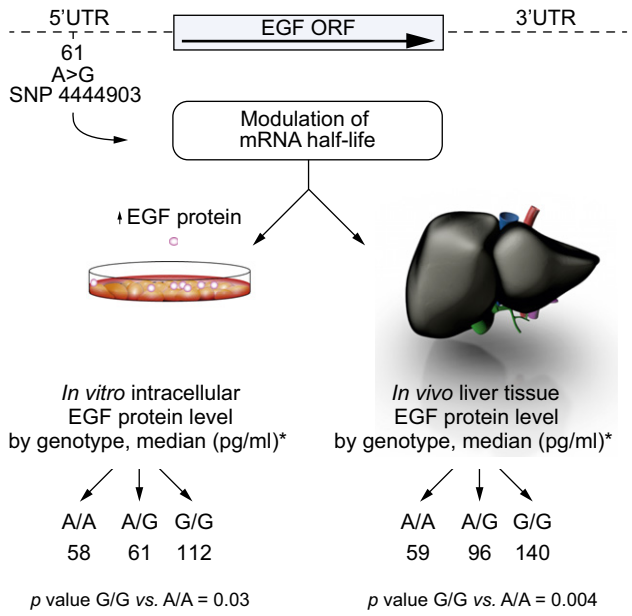

Fig. 1. Proposed mechanism for *EGF* polymorphism. *Data from Tanabe *et al.* [6].

HALT C protocol of prolonged treatment with low doses of pegylated interferon [7]. Patients carrying the genotype GG representing the 25% of the overall population of patients, showed a moderate (2-fold) cumulative risk of developing a HCC during a follow-up period of 6 years compared to patients with genotype AA, comprising 29% of the study cohort. When *EGF* polymorphism was associated with demographic and clinical predictors of HCC like age, gender, smoking, alkaline phosphatase and platelet count that were identified by univariate analysis, 14% of the patients were in the high score setting with a 26% cumulative rate of developing HCC in 6 years compared to 29% who were in the intermediate score setting with a HCC rate of 10.4% and 57% of the study population who were in the low score setting with a HCC rate of 2.3%, only. While at first glance these results are clinically attractive with respect to improving pretreatment stratification of patients with chronic hepatitis C, several aspects of the study question the interpretation and clinical applicability of the new score system. The HALT C cohort, in fact, is far from being a representative population to study HCC predictors, as it misses numerous HCC risk patients who were deferred from treatment because of intolerance or contraindications to interferon-based therapies or successfully responded to therapy. We should not forget that in the USA at the time of the conduct of HALT-C trial, 64% of the adult infected population did not meet the eligibility criteria for interferon therapy, and was therefore deferred, whereas 11.6% ultimately received pegylated interferon and ribavirin therapy, only [8]. Another potential source of bias in Dr. Abu Dayyeh report was the significant number (236 of 1050) of patients who did not consent or could not be recruited to genetic testing, not to mention the contradictory findings of the extended follow-up of the HALT C study. At year 6 of follow-up, less cirrhotics and patients with ⩽2 point decline of Knodell score following 3.5 years of weekly treatment with 90 μg pegylated interferon α2a developed a HCC compared to non-cirrhotics and those with unchanged or increased scores of liver inflammation [9]. On the other hand, mortality rates from liver unrelated causes were significantly increased among all interferon-treated patients [10]. All in all, these discrepancies highlight the need to externally validate the *EGF* SNP-based score in an appropriate setting of patients and to investigate patients with other than hepatitis C liver disease, as easily accessible genetic predictors of HCC look instrumental to optimize current algorithms of primary and secondary prevention of liver cancer.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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