LETTERS TO THE EDITOR

Pancreatic cancer risk variant ABO rs505922 in patients with cholangiocarcinoma

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Abstract

The aim of this study was to investigate an association between the development of cholangiocarcinoma (CCA) and the ABO variant rs505922 (known to increase pancreatic cancer risk) in a large cohort of European individuals with CCA. In total, 180 individuals with CCA and 350 CCA-free controls were included. The ABO variant rs505922 was genotyped using a polymerase chain reaction-based assay. Association between this single nucleotide polymorphism (SNP) and CCA was tested in contingency tables. Neither allele distributions nor association tests and regression analysis provided evidence for an increased risk of CCA among carriers of the ABO variant (all $P > 0.05$). Nevertheless, we documented a deviation from Hardy-Weinberg equilibrium in the entire CCA cohort ($P = 0.028$) and for patients with intrahepatic ($P = 0.037$) but not extrahepatic tumor localization ($P > 0.05$). The association tests did not provide evidence for a prominent role of the investigated SNP in the genetic risk of CCA. However, Hardy-Weinberg disequilibrium in the entire cohort and the intrahepatic CCA subgroup warrants future studies investigating a potential CCA risk modulation by individual blood groups.

Key words: ABO; Biliary tract cancer; Blood groups; Genetic risk; Single nucleotide polymorphism

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TO THE EDITOR

We were very interested to read the recent report by Greer et al[1], which further substantiates the association between an individual’s blood group and the risk of pancreatic cancer. In line with previous data, Greer et al[2] demonstrate that individuals with blood group O have a lower risk of pancreatic cancer relative to blood groups A or B. These serological data are consistent with results from a large genome-wide association study comprising 2457 patients with pancreatic cancer, whereby the common variant rs505922 (C $>$ T) in the ABO locus was identified as a genetic risk factor for this malignancy. Interestingly, the [TT] genotype, which proved to be protective against pancreatic malignancy, is in complete linkage disequilibrium

References:

1. Greer et al. J Clin Oncol 2010; 28(35): 5355-5360
2. Greer et al. Gastroenterology 2010; 139(6): 1866-1873
(\(r^2 = 1.0\)) with blood group O. Conversely, the [C] allele is present in individuals with blood groups A, B or AB.

Cholangiocarcinoma (CCA) albeit uncommon, represents the second most prevalent primary liver cancer, and is globally increasing in incidence\(^1\). As with pancreatic cancer, CCA is usually diagnosed in the late stages with locally advanced or metastatic disease, and is therefore characterized by poor prognosis. Hence, the identification of genetic variants contributing to CCA development is warranted, to further elucidate the pathobiological mechanisms modulating disease risk, and to assist with the development of novel screening strategies for detecting patients at risk of biliary malignancy. Many low-risk variants have been postulated to confer an increased risk for cancers, including CCA\(^3\). Indeed, our previous study demonstrated the genetic risk of CCA to be modulated by heterozygosity for the \(\alpha_1\)-antitrypsin Z allele\(^9\).

In the current study, we therefore specifically assessed the potential role of blood groups in CCA risk using a single nucleotide polymorphism (SNP)-based approach in a large European CCA cohort consisting of 180 individuals with CCA and 350 CCA-free controls. The details of this cohort are described in our previous study\(^5\).

Table 1 summarises the genotyping results. The frequency of [TT] individuals (known to carry blood group O) is consistent with the distributions reported in European populations (http://www.bloodbook.com/world-abo.html). As shown in Table 1, allele distributions did not differ significantly between cases and controls (\(P > 0.05\)). The association tests (common odds ratio (OR) = 1.01, \(P = 0.83\)) and regression analysis (OR for the [TT] variant = 1.11, \(P = 0.56\)) did not provide evidence for the involvement of the \(ABO\) variant in CCA. Similarly, subsequent exploratory data analysis stratifying cases according to gender and intra- vs extrahepatic tumour localisation yielded no significant association between \(rs505922\) and CCA (all \(P > 0.05\)). Interestingly, we detected a departure from Hardy-Weinberg equilibrium (HWE) was verified by exact tests (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl). An association between the \(ABO\) variant and biliary cancer was tested in contingency tables (genotypes, Armitrage’s trend test; alleles, \(\chi^2\) test) and by regression analysis using SPSS software (version 18.0).

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In conclusion, the blood group polymorphism investigated in this study does not appear to alter the general risk of developing CCA. Furthermore, due to the relatively small number of patients with intrahepatic CCA, departure from HWE should be interpreted with caution. Nevertheless, further dedicated studies exploring the possible functional role of \(ABO\) blood types in cholangiocarcinogenesis in selected groups of patients (i.e., with
intrahepatic CCA) may provide further insight into the pathobiological mechanisms that enhance the risk of this malignancy.

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