The role of genetic polymorphisms as biomarkers for HCC risk in Caucasian population

Hepatocellular carcinoma (HCC) is a frequent malignancy in many regions of the world, and the second leading cause of cancer-related deaths. Incidence and mortality are dramatically increasing in USA and Europe.

The major risk factors for HCC development are well defined and include chronic HCV/HBV infection, liver cirrhosis, heavy alcohol intake, tobacco smoking, exposure to environmental and dietary carcinogens (e.g. aflatoxin B1), genetic/metabolic liver disease, and other conditions capable of inducing liver damage. Moreover, the HCC prevalence increases with age and male sex.

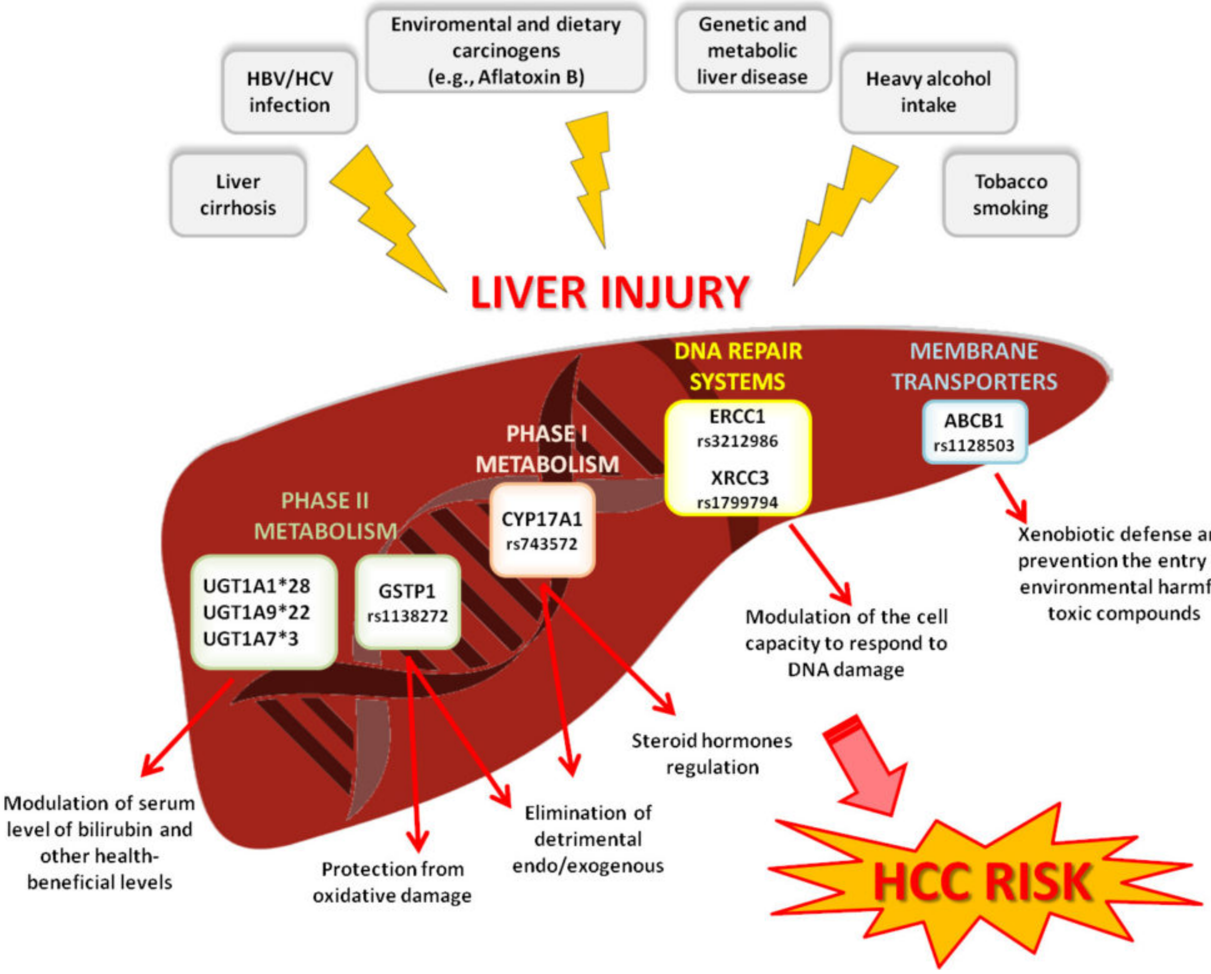


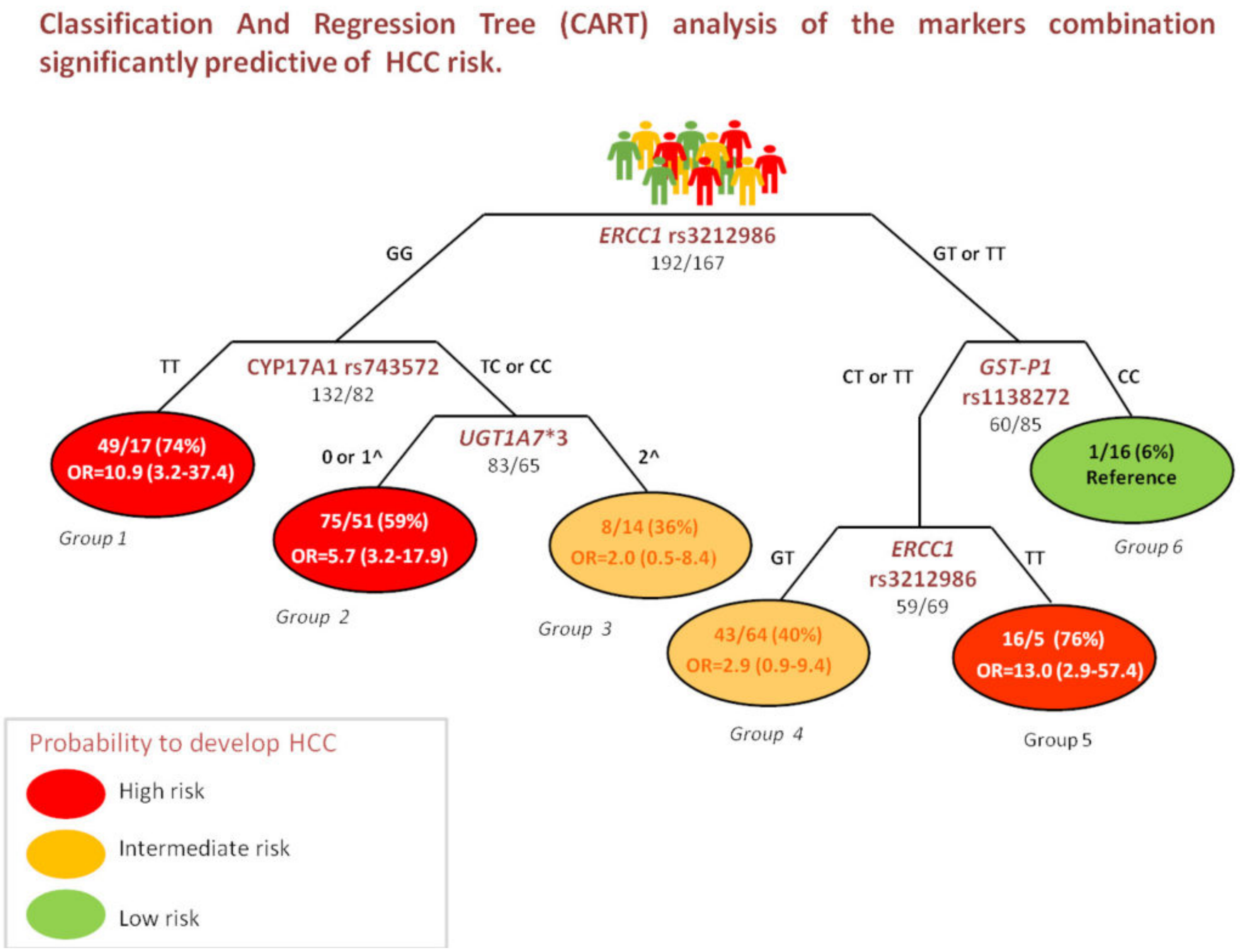
Fig. 1. Genetic markers and related biological pathwahy potentially involved in the definition of the individual suceptibility to hepatocellular carcinoma (HCC) development.

While the etiology of HCC is well-defined, the majority of patients are still diagnosed at an advanced-stage disease excluding them from potentially curative therapy. Hence, the definition of novel biomarkers of HCC susceptibility is of potential clinical interest for improving cancer surveillance, allowing early diagnosis and curative therapy. On this context, host genetic factors (i.e. genetic polymorphisms) could be important predictors of the individual predisposition to develop HCC.

We reported for the first time that some variants, in specific genes, could increase the risk of developing HCC in Caucasians. Particularly, patients that carry the low-activity alleles of *UGT1A1**28, *UGT1A7**3, *UGT1A9**22 polymorphisms and related haplotypes (*UGT1A* haplotype I and II) were shown to be protected against the HCC development, regardless the presence or absence of risk factors as HBV/HCV infection. The observed effects could probably be linked to the positive modulation of serum levels of bilirubin and other health-beneficial molecules that could contribute to protecting the liver cell from toxic injury induced by HCC risk factors.

A subsequent study was performed to widen the panel of genes analyzed. This second work identified other five polymorphisms, that could highlight individuals at higher HCC susceptibility. Specifically, the identified genetic risk markers affect: 1) DNA repair mechanisms, that modulate the cell capacity to respond to DNA damage induced by toxic agents and affect the accumulation of DNA mutagenic lesions (*ERCC1*-rs3212986, *XRCC3*- rs1799794); 2) Phase I (*CYP17A1*-rs743572) and Phase II (*GSTP1*-rs1138272) detoxification systems that facilitate the elimination from the body of detrimental endo/exogenous and protect cells from oxidative damage; 3) Membrane transporters that play an essential role in xenobiotic defense and prevent the entry of some harmful environmental toxic compounds that could damage the liver tissue *(ABCB1*-rs112850).

An exploratory Classification And Regression Tree (CART) analysis was further applied to investigate the potential interaction among the genetic risk factors identified. One polymorphism in DNA repair system (*ERCC1* rs3212986) was demonstrated to interact with polymorphisms in genes encoding for phase I (*CYP17A1*-rs74357), and phase II (*GSTP1*-rs1138272, *UGT1A7**3) metabolic enzymes. These findings highlight the importance to combine the genetic markers to better define the individual HCC risk and to better represent the biological cooperation of multiple pathways in the hepatocarcinogenesis process.



Classification And Regression Tree (CART) analysis of the markers combination significantly predictive of HCC risk.

Fig. 2. CART representation of the markers combination significantly predictive of hepatocellular carcinoma (HCC) risk. Fractions indicate the number of HCC cases versus the number of HBV/HCV infected patients (percentage of cases in parenthesis). Odds ratios (OR) and 95% confidence intervals were calculated for each group in respect to the reference group (lower HCC risk) through logistic regression model, adjusted for sex, age and viral status.
^number of alleles carried by the patient

In conclusion, the definition of genetic traits susceptible to modify the individual predisposition to develop HCC is of potential clinical interest to improve preventive, diagnostic, and therapeutic strategies of HCC management. Once prospectively validated, the markers herein identified could be used, in combination with other well-known serum biomarkers (e.g. alphafetoprotein) and diagnostic imaging (e.g. ultrasonography), to figure out more personalized surveillance programs, both in patients already at high risk of HCC (HBV/HCV-positive) and in the general population. Furthermore, an improved understanding of the genetic risk factors associated to the evolution of HCV infection to cancer could be helpful to optimize the use of the recently developed and highly expensive direct acting antivirals. This would be an important step to help the health care system in containing cost and ensuring the most clinically appropriate treatment. Globally, these findings may fulfil a great challenge in HCC management and help in advancing HCC patient care.

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Publications

Genetic biomarkers for hepatocellular cancer risk in a caucasian population.
De Mattia E, Cecchin E, Polesel J, Bignucolo A, Roncato R, Lupo F, Crovatto M, Buonadonna A, Tiribelli C, Toffoli G
World J Gastroenterol. 2017 Sep 28

UGT1A polymorphisms as genetic biomarkers for hepatocellular carcinoma risk in Caucasian population.
De Mattia E, Cecchin E, Polesel J, Lupo F, Tiribelli C, Crovatto M, Buonadonna A, Toffoli G
Liver Int. 2017 Sep