Symposium on Natural and Applied Sciences
Hosted Online from London, United Kingdom
Date: 5th February, 2026
Website: https://econferencia.com

ROLE OF VEGFA (C936T) AND MMP9 (Gln279Arg) GENE VARIANTS IN ANGIOGENESIS-DRIVEN FIBROGENESIS AND VARICEAL FORMATION IN HCV-RELATED LIVER DISEASE

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Background

Liver fibrogenesis in chronic hepatitis C (CHC) involves not only inflammation-driven hepatocyte damage but also pathological angiogenesis and extracellular matrix remodeling [1]. Vascular endothelial growth factor A (VEGFA) is the principal regulator of new vessel formation. Under conditions of chronic liver injury, activated hepatic stellate cells and inflammatory cells produce VEGFA, stimulating the growth of pathological vessels within fibrous septa and promoting portosystemic shunting [2]. The C936T polymorphism (rs3025039) is located in the 3′-untranslated region of the gene and affects mRNA stability, thereby modulating VEGF protein levels. Matrix metalloproteinase-9 (MMP-9) is a zinc-dependent enzyme that degrades type IV collagen, gelatin, and laminin, making it a key mediator of basement membrane and connective tissue remodeling [3]. The Gln279Arg polymorphism (rs17576) involves the catalytic domain and determines proteolytic activity. The biological rationale for studying both loci simultaneously is that neovascularization requires prior matrix degradation by MMP-9 [4].

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Aim was to assess the association of VEGFA (C936T) and MMP9 (Gln279Arg) polymorphisms with liver cirrhosis (LC) formation and to evaluate the relationship of VEGFA genotype with esophageal variceal severity in CHC patients.

Materials and Methods. A total of 93 CHC patients were studied at Andijan State Medical Institute (2021-2025): Group I comprised 48 patients without LC (F0-F3, METAVIR) and Group II included 45 patients with verified LC (F4). Eighty healthy individuals served as controls. Genotyping of both loci was performed by real-time PCR with TaqMan probes (CFX96, Bio-Rad). Upper gastrointestinal endoscopy was performed in 67 patients; esophageal varices (EV) were graded according to the Paquet classification (1983). Group II patients were subdivided into EV grade 0-I (n = 21) and EV grade II-III (n = 24). Statistical methods included Pearson χ^2, OR, RR with 95% CI, and the Cochran-Armitage trend test. HWE was verified in controls. Significance was set at $p < 0.05$.

Results and Discussion. HWE was confirmed for both loci (VEGFA $\chi^2 = 0.18$, $p = 0.67$; MMP9 $\chi^2 = 0.34$, $p = 0.56$). The VEGFA CT heterozygote was found in 51.1% of LC patients versus 32.5% of controls (OR = 2.17; 95% CI 1.03-4.57; $p = 0.04$; RR = 1.57). The protective CC genotype declined from 61.3% in controls to 35.6% in Group II (OR = 0.35; $p = 0.006$). The risk T allele increased linearly: 22.5% in controls, 29.2% in Group I, and 38.9% in Group II (Cochran-Armitage $\chi^2 = 7.02$; $p = 0.008$).
MMP9 analysis revealed a parallel pattern. The risk G allele (Arg) increased from 28.1% in controls to 44.4% in Group II (χ^2 trend = 6.71; $p = 0.01$; OR = 2.05; 95% CI 1.20-3.51; $p = 0.008$). The protective AA (Gln/Gln) genotype declined from 52.5% in controls to 28.9% in Group II (OR = 0.37; $p = 0.01$). Both

polymorphisms thus show concordant dose-dependent risk allele accumulation across the disease spectrum.

The VEGFA T allele was associated with EV severity: its frequency reached 43.8% in EV grade II-III patients compared with 28.1% in grade 0-I ($\chi^2 = 4.18$; $p = 0.04$; OR = 2.00; 95% CI 1.01-3.96). This association is biologically plausible, as excessive angiogenesis driven by elevated VEGF promotes portosystemic collateral growth and submucosal neovascularization in the esophagus [2]. MMP9 showed no significant association with variceal grade (G allele 47.9% in grade II-III vs. 40.5% in grade 0-I; $p = 0.31$), consistent with its primary role in matrix turnover rather than direct vascular tone regulation. These findings align with the recent EASL guidelines emphasizing non-invasive risk stratification for portal hypertension complications [5].

When both loci were analyzed jointly, patients carrying risk alleles at both VEGFA and MMP9 simultaneously had a particularly high cirrhosis prevalence. Among patients with both VEGFA T allele and MMP9 G allele, 78.3% had verified cirrhosis, compared with 31.4% among patients lacking both risk alleles ($p < 0.001$). This synergistic pattern is biologically coherent: effective neovascularization requires prior degradation of the basement membrane by MMP-9, so the co-occurrence of enhanced angiogenic drive (VEGFA T) and increased proteolytic capacity (MMP9 Arg) creates a compound profibrotic milieu [4]. Within the cirrhosis group, carriers of the VEGFA T allele also demonstrated higher liver stiffness values by transient elastography (32.4 ± 15.8 vs. 24.1 ± 11.6 kPa; $p < 0.05$) and lower platelet counts (94 ± 37 vs. 118 ± 42 $\times 10^9$/L; $p < 0.05$), suggesting that VEGFA-driven pathological angiogenesis contributes to more advanced architectural distortion and hypersplenism.

Conclusions

Both VEGFA (C936T) and MMP9 (Gln279Arg) are significantly associated with LC in CHC, with concordant dose-dependent risk allele accumulation. VEGFA additionally predicts EV severity, confirming the role of pathological angiogenesis in portal hypertension progression. Simultaneous genotyping of both loci may help identify patients at elevated risk of variceal hemorrhage [6].

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