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Research Article

Impact of Vascular Endothelial Growth Factor (VEGF) rs2010963 Polymorphism on Painful Crisis Frequency in Sickle Cell Anemia

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Abstract

Objectives: Sickle cell anemia is a hemoglobinopathy characterized by painful crises. Vascular endothelial growth factor (VEGF) has been implicated in vaso-occlusive pathogenesis. This study aimed to investigate the relationship between the VEGF-A rs2010963 gene polymorphism and the frequency of vaso-occlusive painful crises in patients with sickle cell anemia (SCA).

Methods: In this case-control study, biochemical blood analysis and VEGF-A rs2010963 genotyping were performed using real-time polymerase chain reaction (PCR) in 89 patients with SCA and 100 healthy volunteers. The relationship between the frequency of painful crises and genotype distribution was investigated in the patient group.

Results: In the patient group, the mean values of white blood cell count, platelet count, ferritin, C-reactive protein (CRP), and lactate dehydrogenase were significantly higher than those in the control group ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, and $p<0.001$, respectively). The genotype distribution of VEGF-A rs2010963 did not differ significantly between the patient and control groups ($p=0.164$). No relationship was found between genotype distribution and the frequency of painful crises in the patient group ($p=0.536$).

Conclusion: The VEGF-A rs2010963 polymorphism alone does not appear to predict vaso-occlusive crisis frequency in SCA, highlighting the polygenic nature of pain susceptibility in this disease. Broader genetic and functional analyses are warranted.

Keywords: Gene, painful crisis, polymorphism, sickle cell anemia

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Sickle cell disease (SCD) affects approximately 7.7 million individuals worldwide, with more than 500,000 affected births occurring annually; the majority of cases, approximately 80%, are concentrated in Africa.[1] Sickle cell anemia (SCA) is a clinically severe phenotype of SCD, characterized by significant morbidity and mortality, with erythrocyte sickling representing the fundamental underlying pathophysiological mechanism.

Acute and chronic pain are among the most common complications of SCA. While acute painful episodes are generally more frequent, the prevalence of chronic pain increases progressively with advancing age.[2-4] Painful vaso-occlusive crises

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(VOCs) typically arise from tissue infarction caused by sickled erythrocytes, most often affect a single anatomical site, and are usually characterized by severe intensity. VOCs are the most common acute complications of SCA and can contribute to the development of chronic pain, tissue-organ damage, and early mortality.[5-9] Acute VOCs frequently necessitate hospitalization and substantially impair quality of life.[10-14]

Vascular endothelial growth factor (VEGF), a glycoprotein closely linked to hypoxic signaling, plays a pivotal role in the generation of painful episodes by increasing vascular permeability, driving angiogenic remodeling, and enhancing endothelial cell adhesion through the upregulation of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1, acting as a potent mitogen for the vascular endothelium.[15-17] Beyond its proliferative effects, VEGF modulates endothelial integrin expression and promotes chemotaxis, thereby amplifying local inflammatory responses at the vessel wall.[18-20] This cycle of endothelial activation and injury is integral to the emergence of SCA-related complications.

The VEGF gene is highly polymorphic, and specific variants within its regulatory regions have been proposed as potential modulators of vaso-occlusive susceptibility in SCA. Despite the biological plausibility of a VEGF-VOC axis, empirical data directly linking VEGF gene polymorphisms to vaso-occlusive painful crisis frequency in SCA remain sparse. Against this background, the present study was undertaken to evaluate the potential relationship between the VEGF-A rs2010963 polymorphism and the frequency of vaso-occlusive painful crises in a cohort of adult patients with SCA.

Materials and Methods

This study was designed as a prospective investigation conducted by the Hematology Department of Hatay Mustafa Kemal University Research Hospital. A total of 189 subjects were enrolled, including 89 patients diagnosed with sickle cell anemia (SCA) carrying the HbSS genotype and aged 18 years or older who presented to the Hematology Clinic, and 100 healthy individuals serving as the control cohort. Ethical approval was obtained from the Ethical approval was obtained from the Ethics Committee of Hatay Mustafa Kemal University (Approval No: 01, dated 03/09/2020). Exclusion criteria included individuals younger than 18 years, persons with disabilities, pregnant women, and individuals lacking the legal capacity to provide informed consent. All participants underwent detailed medical history taking and physical examination, and the annual frequency of painful crises was recorded for patients with SCA. Biochemical analyses, including complete blood count, CRP, LDH, ferritin, vitamin B12, and folate, and genotyping were performed on peripheral blood samples. Comparative analyses were conducted to elucidate differences between the SCA cohort and healthy controls.

DNA Extraction and Genotyping

Genomic DNA isolation was performed from peripheral blood samples using a commercially available purification kit (GeneJET Genomic DNA Purification Kit; Thermo Fisher Scientific, Catalog No: K0721) in strict accordance with the manufacturer's instructions (Table 1). All samples were processed in 2 mL microcentrifuge tubes.

The extraction procedure involved sequential lysis, Proteinase K digestion at 55°C, ethanol precipitation, and spin-column purification with two wash steps, followed by elution in 50 µL of buffer. DNA concentration and purity were assessed spectrophotometrically (Multiskan GO; Thermo Fisher Scientific) using 260/280 nm absorbance ratios, and working stocks were prepared at 4 ng/µL in nuclease-free water. Genotyping of the VEGF-A rs2010963 variant was subsequently performed using allele-specific TaqMan SNP Genotyping Assays (Thermo Fisher Scientific, Catalog No: 4351379.rs2010963), as detailed in Table 2.

Statistical Analysis

All continuous variables were first evaluated for normality of distribution using the Kolmogorov-Smirnov test, and variance homogeneity was assessed using Levene's test. Demographic characteristics and laboratory parameters were summarized using descriptive statistics and frequency distributions. Given the non-normal distribution of continuous data, between-group comparisons were performed using the Mann-Whitney U test. Genotype frequencies were compared between groups and across clinical subgroups using Pearson's chi-square test. A two-tailed p-value of less than 0.05 was considered statistically signifi-

Table 1. Components of the DNA extraction kit

GeneJET Genomic DNA Purification Kit	#K0721 50 preps
Proteinase K Solution	1.2 ml
RNase A Solution	1 ml
Digestion Solution	11 ml
Lysis Solution	24 ml
Wash Buffer I	10 ml
Wash Buffer II	10 ml
Elution Buffer (10 mM Tris-Cl, PHT 9.0, 0.5 mM EDTA)	30 ml
Collection Tubes (2 ml)	50
Collection Tubes (1.5 ml)	50

Table 2. Contents of the Real- time PCR kit used

Component	20µL/reaction
5X HOT FIREPol Probe Universal qPCR Mix	4 µL
Prob	0.4 µL
Template DNA	5 µL
dH_2O	11 µL
Total	20 µL

cant. All analyses were conducted using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA).

Results

The SCA patient cohort consisted of 48 male and 41 female individuals, whereas the control group comprised 55 males and 45 females. The mean age was 34.83±10.71 years among patients and 38.35±16.69 years among controls (Table 3). A summary of laboratory parameters is provided in Table 3. Leukocyte counts were elevated in the patient group (13.11±8.87×10^3/µL) relative to controls (7.55±3.43×10^3/µL; p=0.001). Platelet counts were higher in patients (388.16±213.72×10^3/µL) than in healthy subjects (246.96±92.89×10^3/µL; p=0.001). Serum ferritin concentrations were greater in the SCA cohort (1215.28±1679.20 ng/mL) compared with controls (120.91±206.63 ng/mL; p=0.001). Inflammatory markers were also elevated in patients: CRP levels averaged 14.28±30.81 mg/L versus 3.17±3.93 mg/L in controls (p=0.001), and LDH values were 612.65±442.52 IU/L compared with 207.77±73.05 IU/L (p=0.001). Serum vitamin B12 concentrations did not differ between the two groups (442.18±283.32 pg/mL in patients vs. 491.16±282.22 pg/mL in controls; p=0.316). Folate levels, however, were higher in patients with SCA (15.75±14.47 ng/mL) than in controls (10.47±8.73 ng/mL; p=0.007).

Table 4. Distribution of VEGF-A (rs2010963) genotypes in patients and controls

		Patient n (%)	Control n (%)	p
VEGF-A (rs2010963)	Wild type (GG)	22 (24.7)	14 (14.0)	0.164
	Mutant (CC)	29 (32.6)	35 (35.0)	
	Heterozigous (GC)	38 (42.7)	51 (51.0)	

Table 5. VEGF rs2010963 polymorphism and painful crisis frequency

		Wild Type n (%)	Mutant n (%)	Heterozigous n (%)	p
Annual number of painful crises	No	8 (27.6)	10 (34.5)	11 (37.9)	0.536
	1-2	5 (15.6)	10 (31.3)	17 (53.1)	
	>2	9 (32.1)	9 (32.1)	10 (35.7)	

Genotypic analysis of the VEGF rs2010963 polymorphism revealed that the heterozygous GC genotype was the most prevalent variant in both the SCA and control groups, followed by the homozygous mutant CC genotype and the wild-type GG genotype. The distribution of genotypes did not differ between patients and healthy controls (p=0.164) (Table 4). Furthermore, when patients with SCA were stratified according to their annual painful crisis frequency, no

Table 3. Characteristics of the patient and control groups

	Patient	Control	
	n (%)	n (%)	
Sex			
Male	48 (53.9)	55 (55)	p
Female	41 (46.1)	45 (45)	
Age (Mean±SD)	34.83±10.71	38.35±16.69	
	Mean±SD (min-max)	Mean±SD (min-max)	
WBC (10^3/µl)	13.11±8.87 (1.54 – 73.31)	7.55±3.43 (0.44 – 25.29)	**<0.001**
Platelet (10^3/µl)	388.16±213.72 (33.00 – 1192.00)	246.96±92.89 (60.00 – 547.00)	**<0.001**
Ferritin(ng/ml)	1215.28±1679.2 (36.00 – 7947.00)	120.91±206.63 (3.50 – 1164.00)	**<0.001**
CRP (mg/L)	14.28±30.81(2.00 – 171.00)	3.17±3.93(0.00 – 24.00)	**<0.001**
LDH (IU/L)	612.65±442.52 (218.00 – 2724.00)	207.77±73.05 (118.00 – 548.00)	**<0.001**
Vitamin B12 (pg/ml)	442.18±283.32 (114.00 – 2010.00)	491.16±282.22 (158.00 – 1613.00)	0.316
Folat (ng/ml)	15.75±14.47 (22.50 – 95.00)	10.47±8.73 (2.00 – 64.00)	**0.007**

statistically significant association was identified between rs2010963 genotype and VOC frequency (p=0.536) (Table 5).

Discussion

The present study examined whether the VEGF rs2010963 polymorphism exerts a measurable influence on the frequency of vaso-occlusive crises (VOCs) in adult patients with sickle cell anemia (SCA). Our analyses did not reveal a relationship between rs2010963 genotype distribution and VOC occurrence, a finding that both diverges from and aligns with various lines of evidence in the existing literature, collectively underscoring the complex nature of genotype-phenotype correlations in SCA.

Although a mechanistic basis for linking aberrant VEGF expression to VOC development in SCA is biologically plausible, direct empirical evidence connecting VEGF polymorphisms or circulating VEGF concentrations to VOC pathogenesis remains relatively limited. Antwi-Boasiako et al. reported elevated serum VEGF levels in Ghanaian patients with SCA compared with healthy volunteers, with further increases noted during active VOC episodes.[21] Amle et al.[22] described an 18-base pair insertion-deletion polymorphism within the VEGF promoter, in which the deletion allele was associated with higher VEGF expression, greater microalbuminuria risk, and accelerated nephropathy progression in SCA. Farhan et al. reported an association between the AA genotype of the VEGF 2578 C/A (rs699947) polymorphism and elevated VOC risk in patients with SCA.[23] In a study by Al-Habboubi et al.[24], higher frequencies of the rs2010963 C allele, rs833068 A allele, and rs3025020 C allele were documented in patients with SCA experiencing VOC relative to those in steady state. Moreover, they reported differences in genotype distributions of rs2010963, rs833068, and rs3025020 between these groups. The risk of VOC was increased among heterozygous and, more prominently, homozygous carriers of the rs2010963 polymorphism, whereas the association with VOC was observed only in homozygous carriers for rs833068 and rs3025020.[24] Although no differences in serum VEGF levels were found between VOC and steady-state controls, a decline in serum VEGF levels was observed in heterozygous and homozygous genotypes of rs2010963 and rs833068, while the opposite trend was seen in patients with VOC. Additionally, rs2010963, rs833068, and rs3025020 polymorphisms were associated with VOC type, and rs3025020 was further linked to hospitalization, VOC treatment, and crisis duration.[24] Elevated VEGF levels have been demonstrated during vaso-occlusive painful crisis episodes.[25] In pediatric patients, the VEGFA −583C>T (rs3025020) polymorphism has been linked to the development of acute chest syndrome, with the minor −583T allele and the −583T/T genotype increasing the risk of acute chest syndrome.[26] Several considerations may account for these discrepant findings. The multifactorial etiology of VOC suggests that no single genetic variant is likely to function as a robust independent predictor of crisis susceptibility. Painful episodes in SCA emerge from a complex interplay among genetic determinants, particularly variants modulating fetal hemoglobin levels, environmental exposures such as infection and dehydration, dysregulated inflammatory pathways, oxidative stress, and hydration status.[27] Within this intricate pathophysiological matrix, the phenotypic contribution of rs2010963 may be attenuated or masked by other, more dominant genetic or environmental influences, rendering its effect size too modest to detect without adequately powered studies. Sample size represents another pertinent limitation; genetic association studies typically require large cohorts to reliably identify variants with small-to-moderate effect sizes, and the present study may have lacked sufficient statistical power to detect such associations. Genetic heterogeneity further complicates interpretation, as the functional impact of specific polymorphisms often varies across ethnic and geographic populations, implying that rs2010963 may behave differently depending on the ancestral background of the cohort under investigation.

The genetic architecture of acute pain in SCA appears to be considerably more complex than previously appreciated. A meta-analysis identified polymorphisms across multiple pain-related and inflammatory genes as contributors to acute pain susceptibility in SCA, while variants in several globin-regulatory loci were associated with attenuated pain responses.[28] Complementing these observations, Rampersaud et al. constructed a polygenic risk score for acute pain crises in a pediatric SCA population, integrating 21 variants distributed across 9 independent genomic loci.[29] Taken together, these findings reinforce the notion that pain susceptibility in SCA is governed by a polygenic framework, within which the contribution of any individual variant, including rs2010963, is likely to be modest and context-dependent.

Several limitations inherent to this study warrant acknowledgment. The scope of genetic analysis was confined to the rs2010963 variant, precluding a broader evaluation of other potentially relevant VEGF or inflammatory gene polymorphisms. The absence of serum VEGF measurements limits our ability to draw inferences regarding the functional consequences of rs2010963 on protein expression in this cohort. The ethnic homogeneity of the study population may restrict the generalizability of our findings to other demographic groups. Finally, important clinical covariates

known to modulate VOC frequency, including hydroxyurea use, infection status, and lifestyle-related factors, were not comprehensively controlled, introducing potential confounding that may have influenced the observed results.

Future investigations should consider haplotype-based analyses incorporating rs2010963 alongside other functionally relevant VEGF SNPs, as well as multigene panels targeting inflammatory and pain-related pathways. Functional studies designed to assess VEGF transcription, circulating protein levels, and vascular responsiveness in relation to genotype would substantially advance mechanistic understanding. Expanding recruitment to ethnically diverse, multicenter cohorts will be essential for disentangling the effects of genetic background. Integrating pharmacogenetic dimensions, particularly with respect to hydroxyurea efficacy and opioid responsiveness, may ultimately inform the development of genotype-guided, individualized therapeutic strategies in SCA.

Conclusion

The present study provides evidence that the VEGF-A rs2010963 polymorphism, considered in isolation, does not serve as a reliable predictor of vaso-occlusive crisis frequency in adult patients with sickle cell anemia. Rather than diminishing the relevance of the VEGF pathway in SCA pathophysiology, this null finding redirects attention toward the broader genomic and environmental context within which individual variants operate. Vaso-occlusive crises are not driven by a single molecular switch; they emerge from the convergence of multiple interacting risk factors spanning inflammatory signaling, hemoglobin polymerization dynamics, endothelial dysfunction, and patient-specific environmental exposures. Single-variant association studies, while informative, are inherently limited in their capacity to capture this complexity. Progress in this field will therefore depend on shifting toward multilocus haplotype analyses, polygenic risk modeling, and integrative studies that incorporate serum biomarker data alongside genotypic information. Equally important is the inclusion of ethnically and geographically diverse cohorts to ensure that findings are broadly applicable rather than population-specific. Ultimately, a deeper and more nuanced understanding of the genetic contributors to VOC susceptibility holds real clinical promise, offering a pathway toward risk stratification tools and personalized therapeutic interventions that could meaningfully reduce the burden of this devastating complication in patients with sickle cell anemia.

Disclosures

Ethics Committee Approval: This study was approved by The Research Ethics Committee of Hatay Mustafa Kemal University (Approval No: 01, dated 03/09/2020) and conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The author declare that there is no conflict of interest.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

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