LETTER TO THE EDITOR

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IRF4 rs12203592 Risk Variant Shows Effect in European But Not Non-European and Admixed Myelodysplastic Syndrome Patients

IRF4 rs12203592 Risk Varyantı, Avrupalı Miyelodisplastik Sendrom Hastalarında Etkili Ancak Avrupalı Olmayan ve Karışık Kökenli Hastalarda Etkili Değil

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To the Editor,

Myelodysplastic syndrome (MDS) constitutes a diverse and complex group of blood cancers, marked by abnormal hematopoiesis resulting in cytopenia, decreased survival, and an elevated risk of progression to acute myeloid leukemia [1]. Some studies have focused on exploring the risk associated with different polymorphisms in cases of MDS and how these risks vary across the clinical variables of the patients [2,3,4]. It is well established that the risk conferred by polymorphic variants can differ significantly depending on a patient's genetic ancestry [5]. However, this critical factor is often overlooked, leading to the application of risk models that may not be universally relevant.

For example, Wang et al. [6], based on genome-wide association studies, identified the *IRF4* rs12203592 variant as a risk factor for MDS in a European population, where the T allele was associated with an increased risk of de novo MDS (odds ratio: 1.38). However, the relevance of this finding for non-European populations, like Brazil, remains underexplored. In this study, to address this gap, we evaluated the rs12203592 variant in a genetically diverse Brazilian cohort by quantitative real-time polymerase chain reactions based on the TaqMan® methodology (#C__31918199_10, Applied Biosystems, Carlsbad, CA, USA). To the best of our knowledge, this is the first report suggesting that rs12203592 polymorphisms may contribute to MDS susceptibility in this population.

The distributions of allele and genotype frequencies of *IRF4* rs12203592 in bone marrow from 80 MDS patients in our cohort and whole-blood samples from 108 healthy elderly volunteers are shown in Table 1. The genotype distributions for *IRF4* rs12203592 in the MDS and controls groups were in Hardy-Weinberg equilibrium at $p>0.05$ (Table 1). Contrary to the findings in the European population [6], we did not identify any significant associations between this variant and MDS risk in our cohort ($p=0.689$; Table 1). Moreover, our analysis of clinical variables did not reveal any notable correlations with the rs12203592 variant ($p>0.05$; Table 1). These results confirm that the rs12203592 polymorphism does not show a significant association with MDS risk in our cohort, contrary to what was observed in the European population.

Ribeiro Júnior [7] emphasized the critical need to address ethnic diversity in MDS prognostication, as tools such as the International Prognostic Scoring System-Molecular [1], though valuable, have largely been established based on European cohorts. This raises concerns about their applicability in non-European populations [8]. Therefore, robust genomic ancestry studies are urgently needed to create more inclusive prognostic models that will ensure equitable, personalized treatments. Our findings suggest that risk variants identified in European populations, such as *IRF4* rs12203592, may not be directly translatable to other populations, particularly those with a high degree of admixture. These results underscore the importance of considering genetic ancestry when studying risk variants for MDS. This also highlights the need for new genome-wide association studies that include non-European and admixed populations to ensure that risk models are accurate and applicable across different ancestral backgrounds. This approach is essential for developing more inclusive and effective risk models, which will ultimately contribute to the advancement of precision medicine and improve the management of MDS patients in admixed populations.

Table 1. Allele and genotype frequencies of *IRF4* rs12203592 and their associations with clinical features in patients with myelodysplastic syndrome and healthy elderly volunteers (control group).

	Allele frequency			Genotype frequency				Hardy-Weinberg equilibrium
Groups	**T**	**C**	**p**	**T/T**	**C/T**	**C/C**	**p value**	**χ^2/p value**
Control	13 (59.9)	202 (57.22)	0.863	1 (0.9)	12 (11.1)	95 (88.0)	0.689	0.752/0.385
MDS	9 (40.91)	151 (42.78)		0 (0.0)	9 (11.2)	71 (88.8)		0.284/0.594
MDS clinical variables								
Sex, n (%)								
Male	-	-	-	0 (0.0)	3 (33.3)	37 (52.1)	0.481	-
Female	-	-	-	0 (0.0)	6 (66.7)	34 (47.9)		-
Age, years, n (%)								
<60	-	-	-	0 (0.0)	2 (22.2)	19 (26.8)	0.564	-
≥60	-	-	-	0 (0.0)	7 (77.8)	52 (73.2)		-
Cellularity, n (%)								
Hypocellular	-	-	-	0 (0.0)	1 (16.7)	13 (26.5)	0.561	-
Normocellular	-	-	-	0 (0.0)	0 (0.0)	6 (12.2)		-
Hypercellular	-	-	-	0 (0.0)	5 (83.3)	30 (61.2)		-
Fibrosis, n (%)								
Absent	-	-	-	0 (0.0)	4 (66.7)	38 (77.6)	0.619	-
Present	-	-	-	0 (0.0)	2 (33.3)	11 (22.4)		-
Number of dysplasias, n (%)								
0	-	-	-	0 (0.0)	0 (0.0)	2 (2.8)	0.081	-
1	-	-	-	0 (0.0)	6 (66.7)	22 (31)		-
2	-	-	-	0 (0.0)	3 (33.3)	22 (31)		-
3	-	-	-	0 (0.0)	0 (0.0)	25 (35.2)		-
Cytopenias, n (%)								
1	-	-	-	0 (0.0)	6 (66.7)	24 (33.8)	0.085	-
2	-	-	-	0 (0.0)	3 (33.3)	26 (36.6)		-
3				0 (0.0)	0 (0.0)	21 (29.6)		-
Hemoglobin, n (%)								
<8 g/dL	-	-	-	0 (0.0)	3 (33.3)	36 (50.7)	0.381	-
≥8 to <10 g/dL	-	-	-	0 (0.0)	2 (22.2)	19 (26.8)		-
≥10 g/dL	-	-	-	0 (0.0)	4 (44.4)	16 (22.5)		-
Neutrophils, n (%)								
<8x10/L	-	-	-	0 (0.0)	1 (11.1)	18 (25.4)	0.446	-
≥8x10/L	-	-	-	0 (0.0)	8 (88.9)	53 (74.6)		-
Platelets, n (%)								
<50,000 mm^3	-	-	-	0 (0.0)	2 (22.2)	17 (23.9)	0.355	-
≥50 to <100,000 mm^3	-	-	-	0 (0.0)	1 (11.1)	24 (33.8)		-
≥100,000 mm^3	-	-	-	0 (0.0)	6 (66.7)	30 (42.3)		-
Karyotype, n (%)								
Normal	-	-	-	0 (0.0)	7 (77.8)	42 (59.2)	0.554	-
Altered	-	-	-	0 (0.0)	1 (11.1)	18 (25.4)		-
Absence of metaphases	-	-	-	0 (0.0)	1 (11.1)	11 (15.5)		-

Table 1. Continued.

	Allele frequency			Genotype frequency				Hardy–Weinberg equilibrium
Groups	**T**	**C**	**p**	**T/T**	**C/T**	**C/C**	**p value**	**χ^2/p value**
Complex karyotype, n (%)								
Absent	-	-	-	0 (0.0)	8 (100.0)	57 (95.0)	1.000	-
Present	-	-	-	0 (0.0)	0 (0.0)	3 (5.0)		-
IPSS-R risk group, n (%)								
Very low	-	-	-	0 (0.0)	1 (12.5)	6 (10.0)	0.554	-
Low	-	-	-	0 (0.0)	6 (75.0)	28 (46.7)		-
Intermediate	-	-	-	0 (0.0)	1 (12.5)	10 (16.7)		-
High	-	-	-	0 (0.0)	0 (0.0)	10 (16.7)		-
Very high	-	-	-	0 (0.0)	0 (0.0)	6 (10.0)		
WHO classification, n (%)								
MDS-BB	-	-	-	0 (0.0)	4 (44.4)	33 (46.5)	0.814	-
MDS-EB1	-	-	-	0 (0.0)	1 (11.1)	8 (11.3)		-
MDS-EB2	-	-	-	0 (0.0)	1 (11.1)	7 (9.9)		-
MDS-Del(5q)	-	-	-	0 (0.0)	2 (22.2)	5 (7.0)		-
MDS-f	-	-	-	0 (0.0)	0 (0.0)	1 (1.4)		-
MDS-h	-	-	-	0 (0.0)	0 (0.0)	4 (5.6)		-
MDS-SA-BB	-	-	-	0 (0.0)	1 (11.1)	13 (18.3)		-
Transfusion dependence, n (%)								
Yes	-	-	-	0 (0.0)	4 (44.4)	36 (50.7)	1.000	-
No	-	-	-	0 (0.0)	5 (55.6)	35 (49.3)		-
AML progression, n (%)								
Yes	-	-	-	0 (0.0)	0 (0.0)	2 (3.4)	1.000	-
No	-	-	-	0 (0.0)	8 (100.0)	57 (96.6)		-
Death, n (%)								
Yes	-	-	-	0 (0.0)	1 (33.3)	6 (21.4)	1.000	-
No	-	-	-	0 (0.0)	2 (66.7)	22 (78.6)		-

MDS: Myelodysplastic syndrome; MDS-BB: myelodysplastic syndrome with bone marrow blasts; MDS-EB1: myelodysplastic syndrome with excess blasts type 1; MDS-EB2: myelodysplastic syndrome with excess blasts type 2; MDS-Del(5q): myelodysplastic syndrome with deletion of chromosome 5q; MDS-f: myelodysplastic syndrome unclassified (formerly known); MDS-h: hypoplastic myelodysplastic syndrome; MDS-SA-BB: myelodysplastic syndrome with single lineage dysplasia and bone marrow blasts; WHO: World Health Organization; IPSS-R: Revised International Prognostic Scoring System; AML: acute myeloid leukemia.

Keywords: *IRF4*, Myelodysplastic neoplasm, Polymorphism, Risk

Anahtar Sözcükler: *IRF4*, Myelodisplastik neoplasmlar, Polimorfizm, Risk

Ethics

Informed Consent: The study was approved by the Research Ethics Committee of the Federal University of Ceará (PROPESQ - UFC) under CAAE number 79772124.1.0000.5054. Informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: J.N.F.M.G., J.V.C.G., R.F.P., H.L.R.J.; Concept: J.N.F.M.G., A.C.C., H.L.R.J.; Design: J.N.F.M.G., H.L.R.J.; Data Collection or Processing: J.N.F.M.G., A.C.C., J.V.C.G., R.F.P., H.L.R.J.; Analysis or Interpretation: J.N.F.M.G., A.C.C., J.V.C.G., R.F.P., H.L.R.J.; Literature Search: J.N.F.M.G., A.C.C., J.V.C.G., H.L.R.J.; Writing: J.N.F.M.G., A.C.C., J.V.C.G., R.F.P., H.L.R.J.

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