LETTERS TO THE EDITOR
DOI: 10.4274/tjh.galenos.2025.2024.0386

IRF4 rs12203592 Risk Variant shows Effect in European but not in Non-European and Admixed Myelodysplastic Neoplasm Patients

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October 8, 2024
January 28, 2025

To the Editor,
Myelodysplastic Neoplasm (MDS) are a diverse and complex group of blood cancers, marked by abnormal hematopoiesis, resulting in cytopenias, decreased survival, and an elevated risk of progression to acute myeloid leukemia (AML)[1]. Some studies have focused on exploring the risk associated with different polymorphisms in MDS and how these risks vary across the clinical variables of these 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 applicable.
For example, Wang et al.[6], through Genome-Wide Association Studies (GWAS), 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 (OR=1.38)[6]. However, the relevance of this finding to non-European populations, like Brazil, remains underexplored. Here, to address this gap, we evaluated the rs12203592 variant in a genetically diverse Brazilian cohort by quantitative real-time PCR 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.
In our cohort, the distributions of allele and genotype frequencies of *IRF4* rs12203592 in bone marrow from 80 MDS patients and whole blood from 108 healthy elderly volunteers have been shown in Table 1. The genotype distributions for *IRF4* rs12203592 in the MDS and controls groups were in Hardy–Weinberg's equilibrium with $p>0.05$ (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.
About this topic, Ribeiro Jr.[7] emphasized the critical need to address ethnic diversity in MDS prognostication, as tools like the IPSS-M[1], although valuable, mainly reflect European cohorts. This raises concerns about their applicability to non-European populations[8]. Therefore, robust genomic ancestry studies are urgently needed to create more inclusive prognostic models that ensure equitable, personalized treatments. Finally, 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 highlights the necessity for new GWAS that includes non-European and admixture 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 admixture populations.

Keywords: IRF4, Myelodysplastic Neoplasm; Polymorphism; Risk.
Funding: Howard Lopes Ribeiro Junior is recipient of a CNPq Research Productivity Scholarship - Level 2 (Project: Chamada CNPq Nº 09/2023 - Bolsas de Produtividade em Pesquisa - PQ # 305659/2023-5). This research was funded by the Fundação Cearense de Apoio ao Desenvolvimento Científico e Tecnológico (FUNCAP) (UNI-0210-00007.01.00/23) entitled: “Estabelecimento de um Escore de Risco Poligênico (PRS) para a Neoplasia Mielodisplásica no idoso: uma coorte Brasileira”.
Conflict of Interest: The author declares that they have no competing interests.
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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Table 1: Allele and Genotype Frequencies of *IRF4* rs12203592 and their Association with healthy elderly volunteers (control group) and clinical features in MDS Patients.

	Allele Frequency			**Genotype Frequency**				**Hardy-Weinberg Equilibrium**
Groups	**T**	**C**	**p-value**	**T/T**	**C/T**	**C/C**	**p-value**	**x^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								
Gender (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; %)								
Absence	-	-	-	0; (0.0)	4; (66.7)	38; (77.6)	0.619	-
Presence	-	-	-	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-<10 g/dL	-	-	-	0; (0.0)	2; (22.2)	19; (26.8)		-
≥10 g/dL	-	-	-	0; (0.0)	4; (44.4)	16; (22.5)		-
Neutrophil (n; %)								
<8 x $10L^{-1}$	-	-	-	0; (0.0)	1; (11.1)	18; (25.4)	0.446	-
≥8 x $10L^{-1}$	-	-	-	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-<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)		-
Complex Karyotype (n; %)								
Absence	-	-	-	0; (0.0)	8; (100.0)	57; (95.0)	1.000	-
Presence	-	-	-	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)		-

Legend. 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.