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Research Article

GENETIC MECHANISMS OF DEVELOPMENT OF NEUROPATHIES IN MYELOMA

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ABSTRACT

The article discusses the genetic mechanisms underlying the development of neuropathies in myeloma - a tumor of bone marrow plasma cells. Although these mechanisms are not yet fully understood, research points to several potential factors, including mutations in myeloma cell lineage-associated genes such as the MMSET/NSD2 gene and transcription factors such as IRF4. Another important factor is the immune system disorder that accompanies myeloma and can lead to damage to nerve fibers. More detailed studies are required to fully understand the genetic mechanisms of the development of neuropathies in myeloma.

KEYWORDS

Genetic mechanisms, neuropathies, myeloma, mutations, MMSET/NSD2, IRF4, immune system, nerve fibers.

INTRODUCTION

Myeloma is a tumor of bone marrow plasma cells that can lead to various complications, including neuropathies. Although the genetic mechanisms underlying the development of neuropathies in myeloma are still being studied, some studies point to several potential factors.

One such factor is the presence of mutations in genes associated with the myeloma cell line. For

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example, mutations in the MMSET/NSD2 gene and genes encoding transcription factors such as IRF4 are thought to be associated with neuropathies in myeloma.

In addition, immune system disorders may also play a role in the development of neuropathies in myeloma. Myeloma causes immune system dysfunction and inflammation, which can damage nerve fibers.

More detailed studies and analyzes of the genetic mechanisms of the development of neuropathies in myeloma are necessary to fully understand this process. But existing evidence points to the importance of genetic factors and immune system dysfunction in this context.

Gene polymorphism, polymorphism is a structural difference between alternative variants of a gene (usually normal and mutant). The occurrence of gene variants is caused by mutations. Genotyping of polymorphic loci of selected immune response genes revealed differences in the frequency of detection of haplotypes of the TLR6(Ser249Pro), IL1β (G-1473C), IL2(T-330G), IL4(C-589T) and IL10(G-1082A) genes.

Interleukin-4 (IL-4) is a cytokine that plays a significant role in immune responses and is involved in the growth and survival of certain immune cells, including B cells and plasma cells. Changes in IL-4 levels due to genetic polymorphisms can potentially influence the immune response and consequently the risk or progression of diseases such as myeloma.

The C-589T polymorphism, also known as rs2243250, is a genetic variation located in the promoter region of the IL4 (interleukin-4) gene. This polymorphism has been investigated in various diseases, including myeloma, due to its potential role in modulating interleukin-4 production.

In myeloma, it has been found that IL-4 levels may be elevated in both the blood and myeloma cells of patients. This cytokine may stimulate the growth and survival of myeloma cells and may also help protect them from the cellular immune response. Moreover, IL-4 may participate in the formation of the tumor microenvironment, creating favorable conditions for the progression of myeloma.

Studies confirm that IL-4 plays an important role in the pathogenesis and progression of myeloma, and may be a potential target for new therapeutic approaches. Further studies are needed to more fully understand the role of IL-4 and its impact on the development and progression of myeloma.

To study allele frequency and genotype frequency distribution in myeloma, a study was conducted in which participants were divided into two groups: main and control. The total number of participants in the main group was n=94, of which grade I neuropathy: n = 22, grade II neuropathy: n = 44, grade III neuropathy: n = 28. The study results are shown in Table 1:

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Num	Group	Allele frequency				Genotype distribution frequency					
		C		T		C/C		C/T		T/T	
		n	%	n	%	n	%	n	%	n	%
1	Main group (n = 94)	117	62,2	71	37,8	42	44,7	33	35,1	19	20,2
2	grade I neuropathy (n = 22)	25	56,8	19	43,2	8	36,4	9	40,9	5	22,7
3	grade II neuropathy (n = 44)	63	71,6	25	28,4	26	59,1	11	25	7	15,9
4	grade III neuropathy (n = 28)	29	51,8	27	48,2	8	28,6	13	46,4	7	25
5	Control group (n = 90)	130	72,2	50	27,8	51	56,7	28	31,1	11	12,2

Table 1. Percentage of mutation frequencies in the main and experimental groups

The study also examined the prognostic effectiveness of the studied genetic markers (C-589T polymorphism in the IL4 gene). The results are shown in Table 2.

Factor	Groups	SE	SP	AUC	OR	95%CI	p
C	Main group// Control group	0,62	0,28	0,45	0,63	0,4 - 0,98	0,59
	grade I neuropathy // Control group	0,57	0,28	0,43	0,51	0,26 - 0,99	0,28
	grade II neuropathy // Control group	0,72	0,28	0,5	0,97	0,56 - 1,68	0,33
	grade III neuropathy // Control group	0,52	0,28	0,4	0,41	0,22 - 0,76	0,35
	grade I neuropathy // grade II neuropathy	0,57	0,28	0,43	0,52	0,24 - 1,11	0,43
	grade I neuropathy // grade III neuropathy	0,06	0,48	0,27	0,05	0,01 - 0,25	0,41
	grade II neuropathy // grade III neuropathy	0,72	0,48	0,6	2,35	1,17 - 4,71	0,48

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Factor	Groups	SE	SP	AUC	OR	95%CI	p
T	Main group // Control group	0,72	0,38	0,55	1,58	1,02 - 2,45	0,41
	grade I neuropathy // Control group	0,72	0,43	0,58	1,98	1,01 - 3,89	0,72
	grade II neuropathy // Control group	0,72	0,28	0,5	1,03	0,6 - 1,76	0,67
	grade III neuropathy // Control group	0,72	0,48	0,6	2,42	1,32 - 4,45	0,65
	grade I neuropathy // grade II neuropathy	0,72	0,43	0,58	1,92	0,9 - 4,08	0,57
	grade I neuropathy // grade III neuropathy	0,52	0,43	0,48	0,82	0,38 - 1,78	0,59
	grade II neuropathy // grade III neuropathy	0,52	0,28	0,4	0,43	0,22 - 0,85	0,52

Factor	Groups	SE	SP	AUC	OR	95%CI	p
C/C	Main group // Control group	0,45	0,43	0,44	0,62	0,35 - 1,1	0,57
	grade I neuropathy // Control group	0,36	0,43	0,4	0,44	0,17 - 1,13	0,26
	grade II neuropathy // Control group	0,59	0,43	0,51	1,1	0,55 - 2,22	0,32
	grade III neuropathy // Control group	0,29	0,43	0,36	0,31	0,13 - 0,75	0,34
	grade I neuropathy // grade II neuropathy	0,36	0,41	0,39	0,4	0,14 - 1,12	0,44
	grade I neuropathy // grade III neuropathy	0,07	0,71	0,39	0,2	0,03 - 1,4	0,41
	grade II neuropathy // grade III neuropathy	0,59	0,71	0,65	3,61	1,33 - 9,76	0,47

Factor	Groups	SE	SP	AUC	OR	95%CI	p
C/T	Main group // Control group	0,35	0,69	0,52	1,2	0,64 - 2,23	0,5

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	grade I neuropathy // Control group	0,41	0,69	0,55	1,53	0,59 - 3,96	0,17
	grade II neuropathy // Control group	0,25	0,69	0,47	0,74	0,33 - 1,66	0,35
	grade III neuropathy // Control group	0,46	0,69	0,58	1,92	0,81 - 4,54	0,19
	grade I neuropathy // grade II neuropathy	0,41	0,75	0,58	2,08	0,7 - 6,14	0,28
	grade I neuropathy // grade III neuropathy	0,41	0,54	0,48	0,8	0,26 - 2,45	0,46
	grade II neuropathy // grade III neuropathy	0,25	0,54	0,4	0,38	0,14 - 1,04	0,69

Factor	Groups	SE	SP	AUC	OR	95%CI	p
T/T	Main group // Control group	0,2	0,88	0,54	1,82	0,82 - 4,05	0,49
	grade I neuropathy // Control group	0,23	0,88	0,56	2,11	0,66 - 6,73	0,18
	grade II neuropathy // Control group	0,16	0,88	0,52	1,36	0,49 - 3,79	0,32
	grade III neuropathy // Control group	0,25	0,88	0,57	2,39	0,84 - 6,76	0,21
	grade I neuropathy // grade II neuropathy	0,23	0,84	0,54	1,55	0,44 - 5,51	0,31
	grade I neuropathy // grade III neuropathy	0,23	0,75	0,49	0,88	0,23 - 3,37	0,45
	grade II neuropathy // grade III neuropathy	0,16	0,75	0,46	0,57	0,18 - 1,82	0,64

Studies indicate that the frequency of allelic and genotypic variants of the C-589T polymorphism in the IL4 gene may vary among different groups of myeloma patients.

For example, patients with multiple myeloma (MM) were found to have a significantly higher frequency of the T allele of the C-589T polymorphism compared to controls. We also note that the presence of a homozygous TT genotype was associated with an earlier age of onset and progression of MM.

In general, we can see the differences in the frequency of alleles and genotypes of the C-589T polymorphism in the IL4 gene between groups of myeloma patients in Table 3.

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Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Main group		Control group							
	n	%	n	%						
C	117	62,2	130	72,2	4,2	0,05	0,9	0,58 - 1,27	0,6	0,41 - 0,98
T	71	37,8	50	27,8	4,2	0,05	1,2	0,72 - 1,87	1,6	1,02 - 2,45
C/C	42	44,7	51	56,7	2,6	0,20	0,8	0,45 - 1,38	0,6	0,35 - 1,1
C/T	33	35,1	28	31,1	0,3	0,60	1,1	0,64 - 2	1,2	0,65 - 2,22
T/T	19	20,2	11	12,2	2,2	0,20	1,7	0,89 - 3,08	1,8	0,82 - 4,05

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	grade I neuropathy		grade II neuropathy							
	n	%	n	%						
C	25	56,8	63	71,6	2,9	0,10	0,8	0,31 - 2,01	0,5	0,25 - 1,11
T	19	43,2	25	28,4	2,9	0,10	1,3	0,71 - 2,22	1,9	0,9 - 4,06
C/C	8	36,4	26	59,1	3,0	0,10	0,6	0,15 - 2,53	0,4	0,14 - 1,12
C/T	9	40,9	11	25,0	1,8	0,20	1,6	0,44 - 6,06	2,1	0,7 - 6,12
T/T	5	22,7	7	15,9	0,5	0,50	1,4	0,31 - 6,54	1,6	0,43 - 5,58

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	grade I neuropathy		grade III neuropathy							
	n	%	n	%						
C	25	56,8	29	51,8	0,3	0,70	1,1	0,46 - 2,64	1,2	0,55 - 2,71
T	19	43,2	27	48,2	0,3	0,70	0,9	0,46 - 1,8	0,8	0,37 - 1,81
C/C	8	36,4	8	28,6	0,3	0,60	1,3	0,37 - 4,41	1,4	0,43 - 4,71
C/T	9	40,9	13	46,4	0,2	0,70	0,9	0,25 - 3,09	0,8	0,26 - 2,47
T/T	5	22,7	7	25,0	0,0	0,90	0,9	0,21 - 4,01	0,9	0,24 - 3,28

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	grade I neuropathy		Control group							
	n	%	n	%						
C	25	56,8	130	72,2	3,9	0,05	0,8	0,28 - 2,2	0,5	0,26 - 0,99

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T	19	43,2	50	27,8	3,9	0,05	1,3	0,93 - 1,74	2,0	1,01 - 3,87
C/C	8	36,4	51	56,7	2,9	0,10	0,6	0,14 - 2,99	0,4	0,17 - 1,13
C/T	9	40,9	28	31,1	0,8	0,40	1,3	0,3 - 5,75	1,5	0,59 - 3,99
T/T	5	22,7	11	12,2	1,6	0,30	1,9	0,35 - 9,74	2,1	0,66 - 6,75

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	grade II neuropathy		grade III neuropathy							
	n	%	n	%						
C	63	71,6	29	51,8	5,8	0,03	1,4	0,75 - 2,56	2,3	1,17 - 4,69
T	25	28,4	27	48,2	5,8	0,03	0,7	0,33 - 1,58	0,4	0,21 - 0,85
C/C	26	59,1	8	28,6	6,4	0,03	2,1	0,98 - 4,39	3,6	1,33 - 9,77
C/T	11	25,0	13	46,4	3,5	0,10	0,5	0,21 - 1,37	0,4	0,14 - 1,04
T/T	7	15,9	7	25,0	0,9	0,40	0,6	0,21 - 1,9	0,6	0,18 - 1,83

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	grade II neuropathy		Control group							
	n	%	n	%						
C	63	71,6	130	72,2	0,0	0,95	1,0	0,47 - 2,08	1,0	0,55 - 1,71
T	25	28,4	50	27,8	0,0	0,95	1,0	0,7 - 1,46	1,0	0,59 - 1,82
C/C	26	59,1	51	56,7	0,1	0,80	1,0	0,4 - 2,74	1,1	0,53 - 2,3
C/T	11	25,0	28	31,1	0,5	0,50	0,8	0,26 - 2,46	0,7	0,33 - 1,67
T/T	7	15,9	11	12,2	0,3	0,60	1,3	0,37 - 4,54	1,4	0,49 - 3,78

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	grade III neuropathy		Control group							
	n	%	n	%						
C	29	51,8	130	72,2	8,1	0,01	0,7	0,3 - 1,73	0,4	0,22 - 0,76
T	27	48,2	50	27,8	8,1	0,01	1,4	0,98 - 1,98	2,4	1,32 - 4,45
C/C	8	28,6	51	56,7	6,7	0,01	0,5	0,12 - 2,13	0,3	0,13 - 0,75
C/T	13	46,4	28	31,1	2,2	0,20	1,5	0,43 - 5,22	1,9	0,81 - 4,53
T/T	7	25,0	11	12,2	2,7	0,20	2,0	0,53 - 7,95	2,4	0,84 - 6,79

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Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	grade I neuropathy		grade II neuropathy							
	n	%	n	%						
C	25	56,8	63	71,6	2,9	0,10	0,8	0,31 - 2,01	0,5	0,25 - 1,11
T	19	43,2	25	28,4	2,9	0,10	1,3	0,71 - 2,22	1,9	0,9 - 4,06
C/C	8	36,4	26	59,1	3,0	0,10	0,6	0,15 - 2,53	0,4	0,14 - 1,12
C/T	9	40,9	11	25,0	1,8	0,20	1,6	0,44 - 6,06	2,1	0,7 - 6,12
T/T	5	22,7	7	15,9	0,5	0,50	1,4	0,31 - 6,54	1,6	0,43 - 5,58

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	grade I neuropathy		grade III neuropathy							
	n	%	n	%						
C	25	56,8	29	51,8	0,3	0,70	1,1	0,46 - 2,64	1,2	0,55 - 2,71
T	19	43,2	27	48,2	0,3	0,70	0,9	0,46 - 1,8	0,8	0,37 - 1,81
C/C	8	36,4	8	28,6	0,3	0,60	1,3	0,37 - 4,41	1,4	0,43 - 4,71
C/T	9	40,9	13	46,4	0,2	0,70	0,9	0,25 - 3,09	0,8	0,26 - 2,47
T/T	5	22,7	7	25,0	0,0	0,90	0,9	0,21 - 4,01	0,9	0,24 - 3,28

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	grade II neuropathy		grade III neuropathy							
	n	%	n	%						
C	63	71,6	29	51,8	5,8	0,03	1,4	0,75 - 2,56	2,3	1,17 - 4,69
T	25	28,4	27	48,2	5,8	0,03	0,7	0,33 - 1,58	0,4	0,21 - 0,85
C/C	26	59,1	8	28,6	6,4	0,03	2,1	0,98 - 4,39	3,6	1,33 - 9,77
C/T	11	25,0	13	46,4	3,5	0,10	0,5	0,21 - 1,37	0,4	0,14 - 1,04
T/T	7	15,9	7	25,0	0,9	0,40	0,6	0,21 - 1,9	0,6	0,18 - 1,83

In conclusion of the article on the genetic mechanisms of the development of neuropathies in myeloma, the following can be noted:

1. The development of neuropathies in myeloma may be associated with genetic factors. Research suggests that certain genetic variants may

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increase the risk of developing neuropathies in myeloma patients.

2. Some genetic polymorphisms, such as polymorphisms in genes associated with drug metabolism or inflammation, may influence an individual's susceptibility to developing neuropathies.

3. Genetic variants may influence various pathways and mechanisms associated with neuropathy in myeloma, such as nerve fiber damage, vasculitis, and inflammation.

4. Further research is needed to better understand the genetic mechanisms of the development of neuropathies in myeloma and to develop personalized approaches to their prevention and treatment.

Overall, genetic factors are important in the development of neuropathies in myeloma, and understanding these mechanisms may help improve the diagnosis, prognosis, and treatment of this complication.

REFERENCES

1. Palumbo, A., & Anderson, K. (2011). Multiple myeloma. New England Journal of Medicine, 364(11), 1046-1060.
2. Rajkumar, S. V., & Kumar, S. (2016). Multiple myeloma: diagnosis and treatment. Mayo Clinic Proceedings, 91(1), 101-119.
3. Dimopoulos, M. A., Terpos, E., & Niesvizky, R. (2019). How to treat patients with relapsed/refractory multiple myeloma. Leukemia, 33(4), 1099-1112.
4. Cavo, M., Terpos, E., & Nanni, C. (2020). Role of imaging techniques in the management of multiple myeloma: a consensus statement from the International Myeloma Working Group. The Lancet Oncology, 21(8), e360-e376.
5. Usmani, S. Z., Heuck, C., & Mitchell, A. (2019). Extramedullary disease portends poor prognosis in multiple myeloma and is over-represented in high-risk disease even in the era of novel agents. Haematologica, 104(5), e211-e214.
6. Sonneveld, P., Avet-Loiseau, H., & Lonial, S. (2016). Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. Blood, 127(24), 2955-2962.