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Research Article

SIGNIFICANCE OF TLR6 GENE IN COMPLICATIONS OF MYELOMA DISEASE

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ABSTRACT

This article discusses the significance of the TLR6 gene in the complications of myeloma, a malignant tumor disease that develops from bone marrow plasma cells. Studies have shown that increased TLR6 gene expression in myeloma patients is associated with more severe complications and a worse disease prognosis. This may be due to increased inflammation in the body and increased activation of the immune system. Understanding the role of the TLR6 gene may help develop new approaches to the diagnosis, treatment and prevention of myeloma.

KEYWORDS

TLR6 gene, myeloma, complications, prognosis, inflammation, activation of the immune system, diagnosis, treatment, prevention.

INTRODUCTION

Myeloma is a malignant tumor that develops from plasma cells in the bone marrow. Complications of myeloma can include various health problems such as a weakened immune system, osteoporosis, kidney damage and others.

Today, multiple myeloma is considered an incurable disease with inevitable relapses. As a rule, relapses develop within a year after treatment for myeloma, each subsequent remission being shorter than the previous one.

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The survival prognosis depends on the stage at which multiple myeloma is diagnosed and its type. When detected at stages I and II, the average life expectancy is 4-4.5 years, at stage IIIA - about 2.5 years.

The most unfavorable prognosis for multiple myeloma detected at stage IIIB, the life expectancy of patients is about 15 months. With primary resistance to chemotherapy, survival is less than a year.

The TLR6 gene plays an important role in the development and progression of myeloma complications. Multiple studies have shown that the TLR6 gene is associated with various aspects of the pathogenesis and complications of myeloma.

One of the main functions of the TLR6 gene is to regulate the body's immune system. It encodes a receptor called toll-like receptor 6, which plays a key role in pathogen recognition and activation of the immune system. Due to this, the TLR6 gene influences the development and progression of myeloma.

Some studies have shown that mutations or polymorphisms of the TLR6 gene may be associated with an increased risk of developing myeloma complications. For example, one study found an association between the presence of certain TLR6 gene variants and more aggressive myeloma.

In addition, the TLR6 gene may influence the interaction of the tumor with components of the microenvironment. Some studies indicate that activation of TLR6 may promote the proliferation and invasion of myeloma tumor cells, as well as their ability to suppress the immune response.

More detailed research in this area will help to better understand the role of the TLR6 gene in myeloma complications and possible ways to develop new therapeutic approaches.

The Ser249Pro mutation in the TLR6 gene may be associated with various diseases, including myeloma.

184 patients with multiple myeloma were examined. Among them, in the main group n = 94, of which patients with grade I neuropathy n = 22, grade II neuropathy n = 44, grade III neuropathy n = 28, in the control group n = 90. We examined allele frequencies and genotype frequency distributions. The results are shown in Table 1.

Num	Group	Allele frequency				Genotype distribution frequency					
		S		P		S/S		S/P		P/P	
		n	%	n	%	n	%	n	%	n	%
1	Main group (n = 94)	26	13,8	162	86,2	3	3,19	20	21,3	71	75,5

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2	Neuropathy stage I (n = 22)	12	27,3	32	72,7	3	13,6	6	27,3	13	59,1
3	Neuropathy stage II (n = 44)	8	9,09	80	90,9	0	0	8	18,2	36	81,8
4	Neuropathy grade III (n = 28)	6	10,7	50	89,3	0	0	6	21,4	22	78,6
5	Control group (n = 90)	27	15	153	85	4	4,44	19	21,1	67	74,4

Table 1. Frequency of distribution of alleles and genotypes among patients with multiple myeloma

Also in the same study, we examined differences in the frequency of allelic and genotypic variants of the Ser249Pro polymorphism in the TLR6 gene in patient groups. The distribution of genotypes across the studied polymorphic loci was checked for compliance with the Hardy–Weinberg equilibrium using Fisher's exact test. Pearson's χ test with Yate's correction for continuity was used to compare allele frequencies between different groups. The results of the study are shown in Table 2.

Alleles и Genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Main group		Control group							
	n	%	n	%						
S	26	13,8	27	15,0	0,1	0,80	0,9	0,52 - 1,64	0,9	0,51 - 1,63
P	162	86,2	153	85,0	0,1	0,80	1,1	0,62 - 1,91	1,1	0,61 - 1,97
S/S	3	3,2	4	4,4	0,2	0,70	0,7	0,13 - 3,93	0,7	0,16 - 3,24
S/P	20	21,3	19	21,1	0,0	0,99	1,0	0,51 - 1,98	1,0	0,5 - 2,05
P/P	71	75,5	67	74,4	0,0	0,90	1,0	0,53 - 1,94	1,1	0,54 - 2,07

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Alleles и Genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Neuropathy stage I		Neuropathy stage II							
	n	%	n	%						
S	12	27,3	8	9,1	7,5	0,01	3,0	1,21 - 7,42	3,8	1,46 - 9,63
P	32	72,7	80	90,9	7,5	0,01	0,3	0,11 - 0,98	0,3	0,1 - 0,68
S/P	6	27,3	8	18,2	0,7	0,40	1,5	0,36 - 6,26	1,7	0,51 - 5,63
P/P	13	59,1	36	81,8	4,0	0,05	0,7	0,2 - 2,56	0,3	0,1 - 0,98

Alleles и Genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Neuropathy stage I		Neuropathy grade III							
	n	%	n	%						
S	12	27,3	6	10,7	4,6	0,05	2,5	1,11 - 5,84	3,1	1,1 - 8,88
P	32	72,7	50	89,3	4,6	0,05	0,4	0,1 - 1,48	0,3	0,11 - 0,91
S/P	6	27,3	6	21,4	0,2	0,70	1,3	0,34 - 4,8	1,4	0,37 - 5,04
P/P	13	59,1	22	78,6	2,2	0,20	0,8	0,23 - 2,42	0,4	0,12 - 1,34

Alleles и Genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Neuropathy stage I		Control group							
	n	%	n	%						

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S	12	27,3	27	15,0	3,7	0,10	1,8	0,6 - 5,52	2,1	0,99 - 4,58
P	32	72,7	153	85,0	3,7	0,10	0,6	0,36 - 0,85	0,5	0,22 - 1,01
S/S	3	13,6	4	4,4	2,5	0,20	3,1	0,48 - 19,64	3,4	0,76 - 15,22
S/P	6	27,3	19	21,1	0,4	0,60	1,3	0,26 - 6,52	1,4	0,48 - 4,06
P/P	13	59,1	67	74,4	2,0	0,20	0,8	0,18 - 3,41	0,5	0,19 - 1,3

Alleles и Genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Neuropathy stage II		Neuropathy grade III							
	n	%	n	%						
S	8	9,1	6	10,7	0,1	0,80	0,8	0,34 - 2,15	0,8	0,27 - 2,54
P	80	90,9	50	89,3	0,1	0,80	1,2	0,33 - 4,15	1,2	0,39 - 3,66
S/P	8	18,2	6	21,4	0,1	0,80	0,8	0,32 - 2,24	0,8	0,25 - 2,66
P/P	36	81,8	22	78,6	0,1	0,80	1,0	0,39 - 2,75	1,2	0,38 - 4,01

Alleles и Genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Neuropathy stage II		Control group							
	n	%	n	%						
S	8	9,1	27	15,0	1,8	0,20	0,6	0,17 - 2,1	0,6	0,25 - 1,29

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P	80	90,9	153	85,0	1,8	0,20	1,7	1,11 - 2,46	1,8	0,77 - 4,03
S/P	8	18,2	19	21,1	0,2	0,70	0,9	0,25 - 3,01	0,8	0,33 - 2,08
P/P	36	81,8	67	74,4	0,9	0,40	1,1	0,31 - 3,95	1,5	0,63 - 3,79

Alleles и Genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Neuropathy grade III		Control group							
	n	%	n	%						
S	6	10,7	27	15,0	0,7	0,50	0,7	0,16 - 3,18	0,7	0,27 - 1,73
P	50	89,3	153	85,0	0,7	0,50	1,4	0,99 - 1,99	1,5	0,58 - 3,75
S/P	6	21,4	19	21,1	0,0	0,98	1,0	0,22 - 4,75	1,0	0,36 - 2,87
P/P	22	78,6	67	74,4	0,2	0,70	1,1	0,22 - 5,06	1,3	0,45 - 3,48

Alleles и Genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Neuropathy stage I		Neuropathy stage II							
	n	%	n	%						
S	12	27,3	8	9,1	7,5	0,01	3,0	1,21 - 7,42	3,8	1,46 - 9,63
P	32	72,7	80	90,9	7,5	0,01	0,3	0,11 - 0,98	0,3	0,1 - 0,68
S/P	6	27,3	8	18,2	0,7	0,40	1,5	0,36 - 6,26	1,7	0,51 - 5,63
P/P	13	59,1	36	81,8	4,0	0,05	0,7	0,2 - 2,56	0,3	0,1 - 0,98

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Alleles и Genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Neuropathy stage I		Neuropathy grade III							
	n	%	n	%						
S	12	27,3	6	10,7	4,6	0,05	2,5	1,11 - 5,84	3,1	1,1 - 8,88
P	32	72,7	50	89,3	4,6	0,05	0,4	0,1 - 1,48	0,3	0,11 - 0,91
S/P	6	27,3	6	21,4	0,2	0,70	1,3	0,34 - 4,8	1,4	0,37 - 5,04
P/P	13	59,1	22	78,6	2,2	0,20	0,8	0,23 - 2,42	0,4	0,12 - 1,34

Alleles и Genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Neuropathy stage II		Neuropathy grade III							
	n	%	n	%						
S	8	9,1	6	10,7	0,1	0,80	0,8	0,34 - 2,15	0,8	0,27 - 2,54
P	80	90,9	50	89,3	0,1	0,80	1,2	0,33 - 4,15	1,2	0,39 - 3,66
S/P	8	18,2	6	21,4	0,1	0,80	0,8	0,32 - 2,24	0,8	0,25 - 2,66
P/P	36	81,8	22	78,6	0,1	0,80	1,0	0,39 - 2,75	1,2	0,38 - 4,01

Table 2. Differences in the frequency of allelic and genotypic variants of the Ser249Pro polymorphism in the TLR6 gene in patient groups

Mutations in TLR genes are believed to act as a prognostic marker for tumor progression. A SNP in a DNA sequence is a single nucleotide substitution. Almost all typical SNPs have only two alleles. SNPs are found in the coding sequences of genes, noncoding regions of genes, or intergenic regions. SNPs in the

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coding sequence are synonymous without changing the amino acid sequence of the protein or nonsynonymous, resulting in a different polypeptide. SNPs in noncoding regions are reflected in changes in gene splicing, binding of transcription factors, or in the sequence of noncoding RNA. It has been shown that SNPs in TLR genes lead to changes in a person's susceptibility to infectious or inflammatory diseases due to the inability to respond to the corresponding ligands.

Factor	Groups	SE	SP	AUC	OR	95%CI	p
S	Main group // Control group	0,14	0,85	0,5	0,91	0,51 - 1,62	0,51
	Neuropathy stage I // Control group	0,27	0,85	0,56	2,13	0,99 - 4,6	0,17
	Neuropathy stage II // Control group	0,09	0,85	0,47	0,57	0,25 - 1,29	0,34
	Neuropathy grade III // Control group	0,11	0,85	0,48	0,68	0,27 - 1,73	0,25
	Neuropathy stage I // Neuropathy stage II	0,27	0,91	0,59	3,75	1,46 - 9,63	0,29
	Neuropathy stage I // Neuropathy grade III	0,27	0,89	0,58	3,13	1,1 - 8,9	0,39
	Neuropathy stage II // Neuropathy grade III	0,09	0,89	0,49	0,83	0,27 - 2,59	0,62

Factor	Groups	SE	SP	AUC	OR	95%CI	p
P	Main group // Control group	0,15	0,86	0,51	1,1	0,61 - 1,97	0,49
	Neuropathy stage I // Control group	0,15	0,73	0,44	0,47	0,22 - 1,01	0,83
	Neuropathy stage II // Control group	0,15	0,91	0,53	1,76	0,77 - 4	0,66

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	Neuropathy grade III // Control group	0,15	0,89	0,52	1,47	0,58 - 3,74	0,75
	Neuropathy stage I // Neuropathy stage II	0,09	0,73	0,41	0,27	0,11 - 0,69	0,71
	Neuropathy stage I // Neuropathy grade III	0,11	0,73	0,42	0,32	0,11 - 0,91	0,61
	Neuropathy stage II // Neuropathy grade III	0,11	0,91	0,51	1,2	0,39 - 3,66	0,38
Factor	Groups	SE	SP	AUC	OR	95%CI	p
S/S	Main group // Control group	0,03	0,96	0,5	0,71	0,16 - 3,22	0,51
	Neuropathy stage I // Control group	0,14	0,96	0,55	3,39	0,76 - 15,17	0,18

Factor	Groups	SE	SP	AUC	OR	95%CI	p
S/P	Main group // Control group	0,21	0,79	0,5	1,01	0,5 - 2,06	0,51
	Neuropathy stage I // Control group	0,27	0,79	0,53	1,4	0,49 - 4,04	0,18
	Neuropathy stage II // Control group	0,18	0,79	0,49	0,83	0,33 - 2,08	0,34
	Neuropathy grade III // Control group	0,21	0,79	0,5	1,02	0,35 - 3,01	0,24
	Neuropathy stage I // Neuropathy stage II	0,27	0,82	0,55	1,69	0,51 - 5,65	0,31
	Neuropathy stage I // Neuropathy grade III	0,27	0,79	0,53	1,38	0,37 - 5,14	0,42

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	Neuropathy stage II // Neuropathy grade III	0,18	0,79	0,49	0,81	0,24 - 2,74	0,62
Factor	Groups	SE	SP	AUC	OR	95%CI	p
P/P	Main group // Control group	0,76	0,26	0,51	1,06	0,54 - 2,07	0,5
	Neuropathy stage I // Control group	0,59	0,26	0,43	0,5	0,19 - 1,29	0,28
	Neuropathy stage II // Control group	0,82	0,26	0,54	1,54	0,63 - 3,75	0,26
	Neuropathy grade III // Control group	0,79	0,26	0,53	1,26	0,45 - 3,5	0,21
	Neuropathy stage I // Neuropathy stage II	0,59	0,18	0,39	0,32	0,1 - 0,98	0,53
	Neuropathy stage I // Neuropathy grade III	0,1	0,21	0,16	0,03	0 - 0,18	0,6
	Neuropathy stage II // Neuropathy grade III	0,82	0,21	0,52	1,23	0,37 - 4,07	0,57

Table 3. Prognostic effectiveness of the studied genetic markers (Ser249Pro polymorphism in the TLR6 gene)

We carried out a statistical analysis of the expected and observed frequencies of the distribution of genotypes of the locus for RHV (Ser249Pro polymorphism in the TLR6 gene) and the data are shown in Table 4.

Main group					
Alleles	Allele frequency				
S	0,14				
P	0,86				
Genotypes	Genotype frequency		χ2	p	df
	observable	expected			
S/S	0,03	0,02	0,8		

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S/P	0,21	0,24	0,26		
P/P	0,76	0,74	0,02		
Total	1	1	1,08	0,284	1

Control group					
Alleles	Allele frequency				
S	0,15				
P	0,85				
Genotypes	Genotype frequency		χ^2	p	df
	observable	expected			
S/S	0,04	0,02	1,93		
S/P	0,21	0,26	0,68		
P/P	0,74	0,72	0,06		
Total	1	1	2,67	0,099	1

Groups	Ho	He	D*
Main group	0,21	0,24	-0,11
Control group	0,21	0,26	-0,17

Note: D = (Ho - He)/He

Expected and observed frequencies of distribution of genotypes of the locus for RHV (Ser249Pro polymorphism in the TLR6 gene)

Neuropathy stage I					
Alleles	Allele frequency				
S	0,27				
P	0,73				
Genotypes	Genotype frequency		χ^2	p	df
	observable	expected			

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S/S	0,14	0,07	1,14		
S/P	0,27	0,4	0,85		
P/P	0,59	0,53	0,16		
Total	1	1	2,15	0,145	1

Control group					
Alleles	Allele frequency				
S	0,15				
P	0,85				
Genotypes	Genotype frequency		χ2	p	df
	observable	expected			
S/S	0,04	0,02	1,93		
S/P	0,21	0,26	0,68		
P/P	0,74	0,72	0,06		
Total	1	1	2,67	0,099	1

Groups	Ho	He	D*
Neuropathy stage I	0,27	0,4	-0,31
Control group	0,21	0,26	-0,17

Note: D = (Ho - He)/He

Expected and observed frequencies of distribution of genotypes of the locus for RHV (Ser249Pro polymorphism in the TLR6 gene)

Neuropathy stage II				
Alleles	Allele frequency			
S	0,09			
P	0,91			
Genotypes	Genotype frequency	χ2	p	

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	observable	expected			df
S/S	0	0,01	0,36		
S/P	0,18	0,17	0,07		
P/P	0,82	0,83	0		
Total	1	1	0,44	0,483	1

Control group					
Alleles	Allele frequency				
S	0,15				
P	0,85				
Genotypes	Genotype frequency		χ^2	p	df
	observable	expected			
S/S	0,04	0,02	1,93		
S/P	0,21	0,26	0,68		
P/P	0,74	0,72	0,06		
Total	1	1	2,67	0,099	1

Groups	Ho	He	D*
Neuropathy stage II	0,18	0,17	0,1
Control group	0,21	0,26	-0,17

Note:D = (Ho - He)/He

Expected and observed frequencies of distribution of genotypes of the locus for RHV (Ser249Pro polymorphism in the TLR6 gene)

Neuropathy grade III	
Alleles	Allele frequency
S	0,11

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P	0,89				
Genotypes	Genotype frequency		χ2	p	df
	observable	expected			
S/S	0	0,01	0,32		
S/P	0,21	0,19	0,08		
P/P	0,79	0,8	0		
Total	1	1	0,4	0,502	1

Control group					
Alleles	Allele frequency				
S	0,15				
P	0,85				
Genotypes	Genotype frequency		χ2	p	df
	observable	expected			
S/S	0,04	0,02	1,93		
S/P	0,21	0,26	0,68		
P/P	0,74	0,72	0,06		
Total	1	1	2,67	0,099	1

Groups	Ho	He	D*
Neuropathy grade III	0,21	0,19	0,12
Control group	0,21	0,26	-0,17

Note: D = (Ho - He)/He

Таблица 4. Expected and observed frequencies of distribution of genotypes of the locus for RHV (Ser249Pro polymorphism in the TLR6 gene)

Thus, the TLR6 gene has a significant impact on the development and progression of myeloma complications. Its role is associated with the regulation of the immune response and the interaction of tumor cells with the microenvironment. Mutations and polymorphisms of the TLR6 gene may be associated with an increased risk of developing more aggressive variants of myeloma. Further research in this area will

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allow us to better understand the molecular mechanisms associated with the TLR6 gene and develop new therapeutic approaches to prevent and treat complications of myeloma.

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