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Clinical relevance of multi-drug resistance gene C3435T polymorphism in diffuse large B-cell lymphoma in Xinjiang

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Abstract

To explore the relationship between C3435T polymorphism of multi-drug resistance gene (MDR1) gene and susceptibility, clinicopathological characteristics, curative effect and hematological toxicity of diffuse large B-cell lymphoma (DLBCL) in XinJiang.

The peripheral venous blood samples of 54 patients with DLBCL and 60 healthy controls were collected. The alleles and genotypes of MDR1 gene C3435T were detected by DNA direct extraction with PCR technique, and the frequency of C3435T allele and genotypes were detected by the chi-square test. The relationship between the allele and genotype distribution of C3435T locus and the susceptibility, clinicopathological characteristics, curative effect and hematological toxicity of DLBCL were analyzed.

1 the frequency of CT heterozygote and CC homozygote mutation was significantly higher in the case group (46.3% in CT genotype and 42.6% in CC genotype) compared to the control group ($P < 0.05$). The frequency of CC genotype mutation in the case group was 42.6%, which was significantly higher than that in the control group ($P < 0.05$, OR 3.209, 95% CI: 1.288-7.997). 2 the genotypes of C3435T locus of MDR1 gene were distributed in age, sex, nationality, pathological characteristics, clinical-stage, IPI index, B symptoms, infection with EB virus, clinicopathological characteristics and clinical efficacy of hepatitis B in patients with DLBCL. There was no significant difference in myelosuppression ($P > 0.05$).

The homozygous mutation genotype of CC is the risk genotype of DLBCL. The alleles and genotypes are not associated with the clinicopathological characteristics, efficacy and myelosuppression toxicity of DLBCL.

Abbreviations: DLBCL = diffuse large B-cell lymphoma, MDR1 = multi-drug resistance gene, SNP = single nucleotide polymorphism.

Keywords: C3435T, diffuse large B-cell lymphoma, multi-drug resistance gene, single nucleotide polymorphism

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid tissue tumor in adults, accounting for approximately 32% of newly diagnosed non-Hodgkin lymphoma cases per year.[1] And it accounts for approximately 35% to 50% in China.[2] DLBCL is 1 of the common malignancies in Xinjiang. Among them, 40% to 50% of patients may achieve good outcomes, but a significant number of patients would relapse or die after treatment. In addition to the high heterogeneity of DLBCL, genetic polymorphisms play an important role in the development and progression of DLBCL. Multi-drug resistance gene (MDR1), which is located on chromosome 7q21.1 encodes P-glycoprotein (P-gp),[3] the line of defense in body cells against drugs and poisons, and also reduces the concentration of chemotherapeutics in tumor cells by efflux of drugs, leading to drug resistance. C3435T (Exon 26, rs1045642) is 1 of the most extensively studied MDR1 gene loci.[4,5] More and more studies have shown that the polymorphism of MDC35T is closely associated with susceptibility, efficacy and prognosis of malignancies,[6–8] indicating that MDR1 single nucleotide polymorphism may be another predisposing factor and prognostic marker for cancer. The research on C3435T polymorphism in DLBCL may provide a prognostic, predictive, and therapeutic reference for the individualized treatment of DLBCL. MDR1 MDC35T was therefore tested for DLBCL patients admitted.

2. Methods and materials

2.1. Subjects

From January 2017 to March 2019, 54 patients with DLBCL were admitted to the Affiliated Tumor Hospital of Xinjiang Medical

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The study has passed the institutional ethical review of our hospital (Ethics No. K-201711), and informed consent was obtained from all the subjects.

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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University, including 35 Han patients and 19 Uygur patients. The median age was 67.5 years (26 - 83 years). All patients were newly diagnosed and confirmed by pathology and immunohistochemistry, except for the central nervous system and bone marrow infiltration. It was staged according to the Ann Arbor staging system. R-CHOP regimen was given for chemotherapy. Patients ≥80 years were given the dose-adjusted R-miniCHOP regimen to complete at least 4 cycles of chemotherapy. The efficacy was assessed by PET/CT every 2 cycles. By RECIL criteria, the treatment outcome was divided into complete response, partial response, stable disease and progressed disease. complete response and partial response were judged as effective treatment, stable disease and progressed disease were judged as ineffective treatment. The bone marrow suppression was classified into grade I, II, III, and IV according to 1979 WHO classification standard for toxic side effects of chemotherapy. The age and gender of 60 subjects performing physical examination in our hospital were comparable to the case group. The study has passed the institutional ethical review of our hospital (Ethics No. K-201711), and informed consent was obtained from all the subjects.

2.2. Materials and Reagents

Collect 3 ml of peripheral venous blood from all newly diagnosed patients before chemotherapy and from healthy subjects into EDTA anticoagulant tubes. Centrifuge, discard the supernatant and store in a refrigerator at −80°C. Agarose was purchased from Sangon Biotech (Shanghai), Trans2K DNA Marker and 2× EasyTaq PCR SuperMix (+dye) were purchased from TransGene Biotech; DNA extraction kit was purchased from Genenode.

2.3. Experimental Methods and Procedures

DNA extraction: DNA of whole blood was extracted with DNA extraction kit, the concentration of extracted DNA was detected by nucleic acid protein quantifier, and the integrity of DNA was detected by agarose electrophoresis; amplification of target gene: upstream primer rs1045642-F, with the sequence of 5'-TTGTGCTACATTCAAAGTGTGCTGG-3'. Downstream primer rs1045642-R with the sequence of 5'-GGGAGACCAGCCCCTTATAAATCAA-3'. Initial denaturation in 94°C for 2 minute, denaturation in 94°C for 30 second, annealing in 57°C for 30 second, extension in 72°C for 30 second, and major extension in 72°C for 10 minute, for 35 cycles, amplify a DNA fragment of 351 bp in size; sequencing result: rs 1045642: blue background was the primer match position

ATTAGCAACCTTACATCTACTACTTTAGTTTCTTTTTGCCATGTAACATAACACATTCACAGGATCCAGGGATTAGGACACAGATGTCTTGTGGGAGAGGGAACATTATTCTGCCTACCACATGCATACATCAGAAACCATGGTTGAAACACAGGAAACATGACAGTTCCTCAAGGCATACAATTATGACCTTGTTGGGTTAACCTTCACTATCCAAATTTTAATCACACAAACTTTTCCTTAATCTCACAGTAACTTGGCAGTTTCAGTGTAAGAAATAATGATGTTAATTGTGCTACATTCAAAGTGTGCTGGTCCTGAAGTTGATCTGTGAACTCTTGTTTTCAGCTGCTTGATGGCAAAGAAATAAAGCGACTGAATGTTCAGTGGCTCCGAGCACACCTGGGCATCGTGTCCCAGGAGCCCATCCTGTTTGACTGCAGCATTGCTGAGAACATTGCCTATGGAGACAACAGCCGGGTGGTGTCACAGGAAGAGATC/TGTGAGGGCAGCAAAGGAGGCCAACATACATGCCTTCATCGAGTCACTGCCTAATGTAAGTCTCTCTTCAAATAAACAGCCTGGGAGCATGTGGCAGCCTCTCTGGCCTATAGTTTGATTTATAAGGGGCTGGTCTCCCAGAAGTGAAGAGAAATTAGCAACCAAATCACACCCTTACCTGTATACAAGCATCTGGCCACACTTCCTGTTTGGGTTAGTTGTTACCTTTACCTGATCACCTGACCCTCCTTGTGAGGAAGGGATGAAAGTGTTCGACCACTTCAGGTTTAGGAGAGAGGAACATTTCTGGGATAGGAGAACTGGAACAATTGTCTTGATCCAAAGCTATAGGCTTGAGGCTCCACCTTTGTCAGCCTTAGGGGTAAGTACAATATCTGGAAAGCCTTTCACTTTAAGTCCAAGTACAGAGTCTGGGTCCCCACCTGCACATGCTGCTTCTGGCCTGCTGAGGAAGTAGGCATGACTGTCTCTCCCCATGTC

Mutation types [C/T]

2.4. Experimental results

2.4.1. PCR Quality inspection result. Interpretation of result (Fig. 1): The strip was single and bright, indicating that the quality is qualified.

2.4.2. PCR Amplification Results, see Figure 2 and Figure 3. In Figure 1, Figure 2, and Figure 3, the size and content of DNA ladder from top to bottom are: 2000 (50ng/ 5 μL) bp, 1000 (50ng/ 5 μL) bp, 750 (100ng/ 5 μL) bp, 500 (50ng/ 5 μL) bp, 250 (50ng/ 5 μL) bp, 100 (50ng/ 5 μL) bp.

2.4.3. MDR1 C3435T (rs1045642) genotyping, see Figure 4, Figure 5, Figure 6.

2.5. Statistical Methods

χ^2 test was used to examine the genotype distribution differences between case patients and control subjects. Association between polymorphisms and the risk of DLBCL was estimated by binary logistic regression with adjustment for sex, age and ethnicity. Comparisons of genotype between case and control groups, clinical characteristics, response rate, and myelosuppression of different genotypes in the case group were performed using χ^2

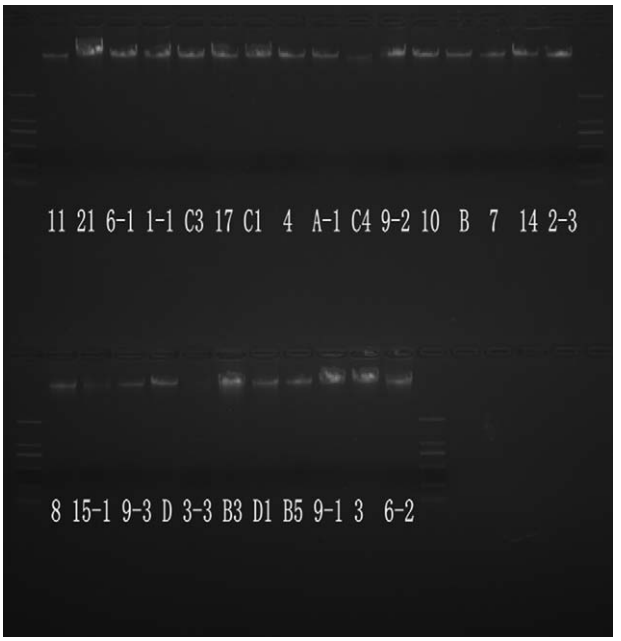

Figure 1. DNA electropherogram.

Figure 2. Electropherogram of PCR amplification of whole blood cells from No. 1 to 46 study individuals. PCR = polymerase chain reaction.

test. SPSS 22.0 software was used for data analysis, test level was $\alpha = 0.05$, difference with $P < .05$ was statistically significant.

3. Results

3.1. Genetic susceptibility of DLBCL with MDR1 C3435T genotypes

3.1.1. Hardy-Weinberg equilibrium test. Hardy-Weinberg equilibrium test showed that MDR1 C3435T was consistent with the genetics in the study population, as shown in Table 1.

3.1.2. Difference in the distribution of MDR1 C3435T polymorphism between case and control groups. The results showed that the frequencies of mutant genotypes CT heterozygote and CC homozygote were higher in the case group (CT 46.3% and CC 42.6%), and the difference was significant compared with the control group ($P < .05$), as shown in Table 2; the frequency of CC genotype mutation, in the case group was 42.6%, which was significantly higher than that in the control group ($P < 0.05$, OR = 3.209, 95%CI: 1.288–7.997), as shown in Table 3. It indicated that CC homozygous mutant genotype was the risk genotype of DLBCL.

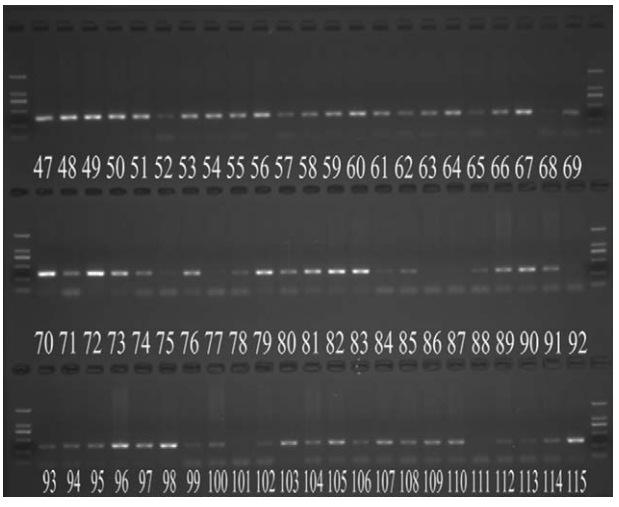

Figure 3. Electropherogram of PCR amplification of whole blood cells from No. 47 to 115 study individuals. PCR = polymerase chain reaction.

3.2. Difference of MDR1 C3435T polymorphism in clinical pathology of DLBCL patients

There were no significant differences in the distribution of MDR1 C3435T genotypes in terms of age, gender, ethnicity, pathological characteristics, clinical-stage, International Prognostic Index (IPI), B symptom, whether infected with EB virus, and whether combined with hepatitis B in DLBCL patients, as shown in Table 4.

3.3. Difference in the distribution of MDR1 C3435T polymorphism in DLBCL patients

There was no significant difference in the distribution of MDR1 C3435T genotypes in terms of clinical efficacy ($P > .05$), as shown in Table 5.

3.4. Difference in the distribution of MDR1 C3435T polymorphism in myelosuppression of DLBCL patients after chemotherapy

There was no significant difference in the distribution of MDR1 C3435T genotypes in terms of myelosuppression ($P > .05$), as shown in Table 6.

4. Discussion

MDR-1 plays a fundamental role in transporting endogenous and exogenous noxious compounds from cells to protect them from external influences.[4] Therefore, it plays an important role in removing the effect of carcinogens on cells,[8] and is involved in the development of cancer and intervenes in the therapeutic effect of cancer. C3435T is an important site on the MDR1 gene and is located in exon 26, which is directly involved in MDR1 expression and functioning. However, with the in-depth study of C3435T, the results are diverse and inconclusive. Therefore, we would like to further explore the role and mechanism of MDR1 C3435T polymorphism in the susceptibility, clinical pathology, efficacy and hematologic toxicity of DLBCL in various ethnic groups in Xinjiang, so as to better provide a feasible basis for level 1 prevention of lymphoma, accurate judgment of prognosis and efficacy prediction, as well as prescribing individualized dose in patients of all ethnic groups in Xinjiang subject to economic conditions.

Our study showed that the frequencies of CT heterozygote and CC homozygous mutant genotype of MDR1 C3435T were higher in the case group, CC homozygous mutant genotype was the risk genotype of DLBCL. A meta-analysis also showed that patients with CC genotype were more predisposed to hematologic malignancies. However, contrary to our findings, a study of Chinese scholars[9] showed that the TT genotype at C3435T was significantly associated with susceptibility to DLBCL. A study

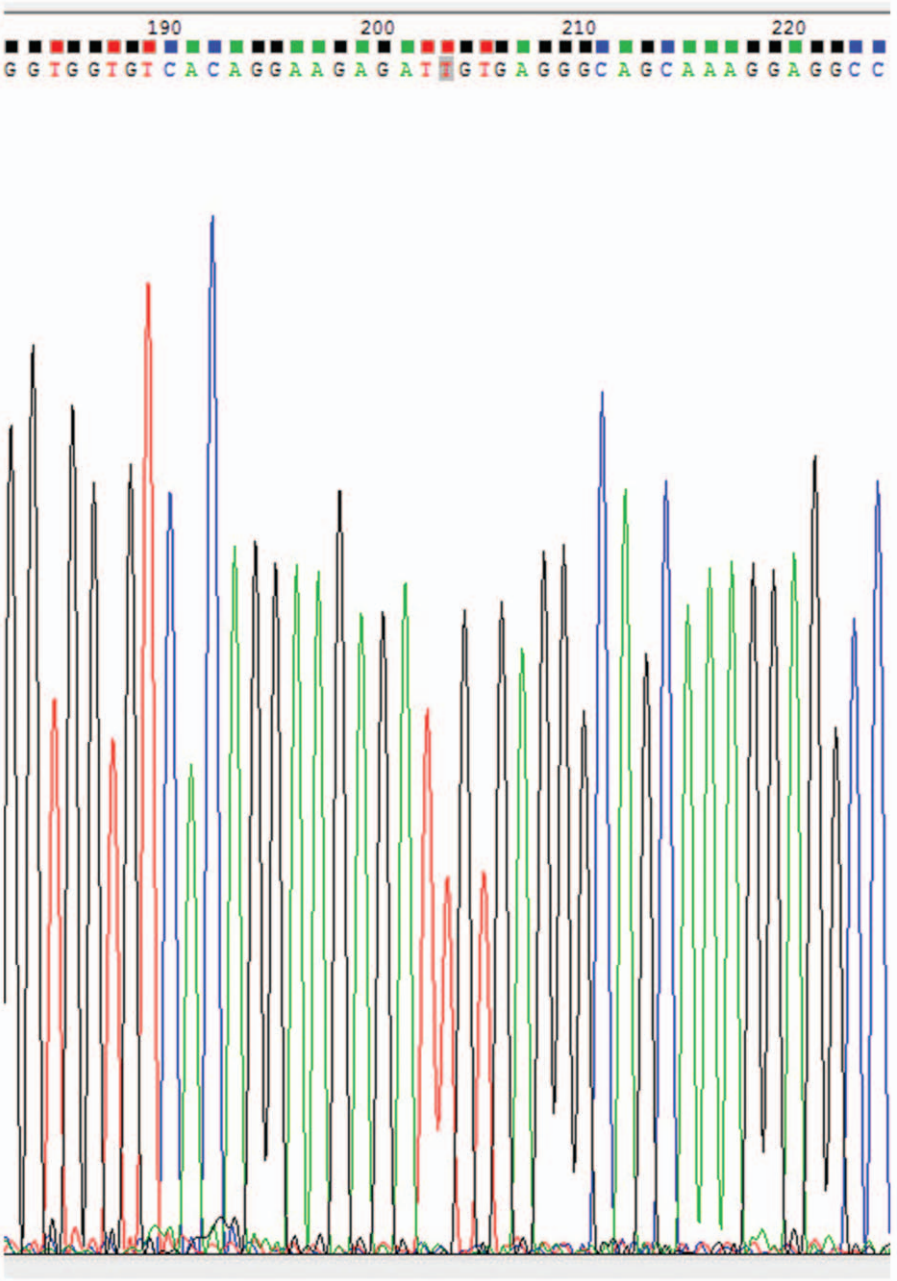

Figure 4. C3435T (rs1045642) (11) TT genotype.

from Korea[10] also showed that CT and TT genotypes at C3435T were associated with NHL development (OR 3435CT = 1.50, $P < .0001$, OR3435TT = 0.02, $P = .02$). The study of Mhaidat et al[11] concluded that T allele was associated with an increased risk of Hodgkin lymphoma. The Egyptian study[3] showed that children with homozygous T allele were significantly associated with a lower incidence of acute lymphoblastic leukemia, indicating that the homozygous T gene is a protective factor for childhood acute lymphoblastic leukemia. However, another meta-analysis[12] showed that the MDR1 C3435T gene did not increase the risk of childhood acute lymphoblastic leukemia. These inconsistencies in findings may be caused by differences in the activity of enzymes involved in the transport and metabolism of self-mutagens determined by tumor genetic polymorphisms in different organisms.[13] Or it may be caused by the linkage relationship between the C3435T gene and other pathogenic genes.

Our study showed that the MDR1 C3435T allele was not associated with age, gender, ethnicity, pathological stage, pathological features (originate in germinal center or not), IPI score, presence of B symptom, concurrent EB virus infection and chronic hepatitis B of patients with DLBCL. This is consistent with 2 China's studies.[14,15] One study of central nervous system lymphoma in 91 cases in China[7] showed that patients carrying

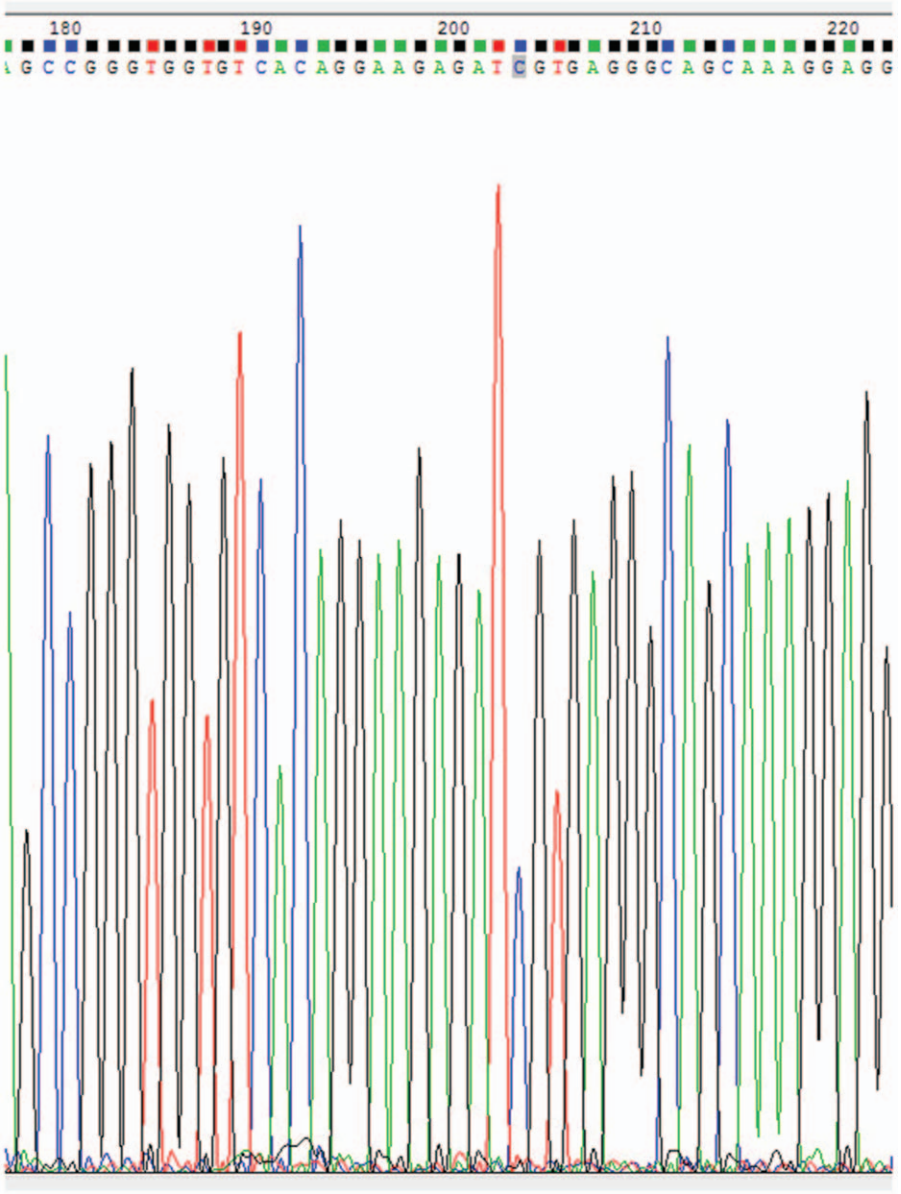

Figure 5. C3435T (rs1045642) (1) CC genotype.

CC genotype were significantly associated with shorter PFS ($P = .020$), indicating that CC genotype is an independent prognostic risk factor for CNS lymphoma. Another study[3] showed that CT genotype was associated with poor prognosis of childhood acute lymphoblastic leukemia. The mechanism may be that molecules on the surface of tumor cells induce expression of G-protein-coupled receptors, which up-regulate the level of MDR1 and lead to the development of tumor drug resistance.[16] In contrast, the study of Ni Y et al[15] showed that C allele and CC genotype of C3435T were associated with a better prognosis in DLBCL. Our study did not get any statistically significant results. It is possibly related to the different laboratory methods and tumor cell microenvironment,[17] as well as a small sample size of the study. The study[18] showed that EB virus-infected lymphomas had up-regulated MDR1 expression, which is responsible for drug resistance and poor prognosis of EBV-associated lymphomas. However, this study showed that none of the genotypes at MDR1 C3435T was associated with complicated EBV infection ($P > .05$), which may be due to the fact that the mechanism of up-regulation of MDR1 gene expression caused by EBV-infected lymphoma did not result from C3435T gene mutation or action on C3435T gene signaling pathway, but related to Akt signaling pathway.[18]

This study suggested that none of the alleles and genotypes at MDR1 C3435T was associated with the response of DLBCL to R-CHOP regimen, which was consistent with the study of Nizar M Mhaidat et al[11] While the study of Ying Ni et al[15] showed that DLBCL patients carrying C allele achieved better efficacy ($P = .009$), whose mechanism may be siRNA-mediated down-regulation of ABCB1 (MDR1), thereby leading to the accumula-

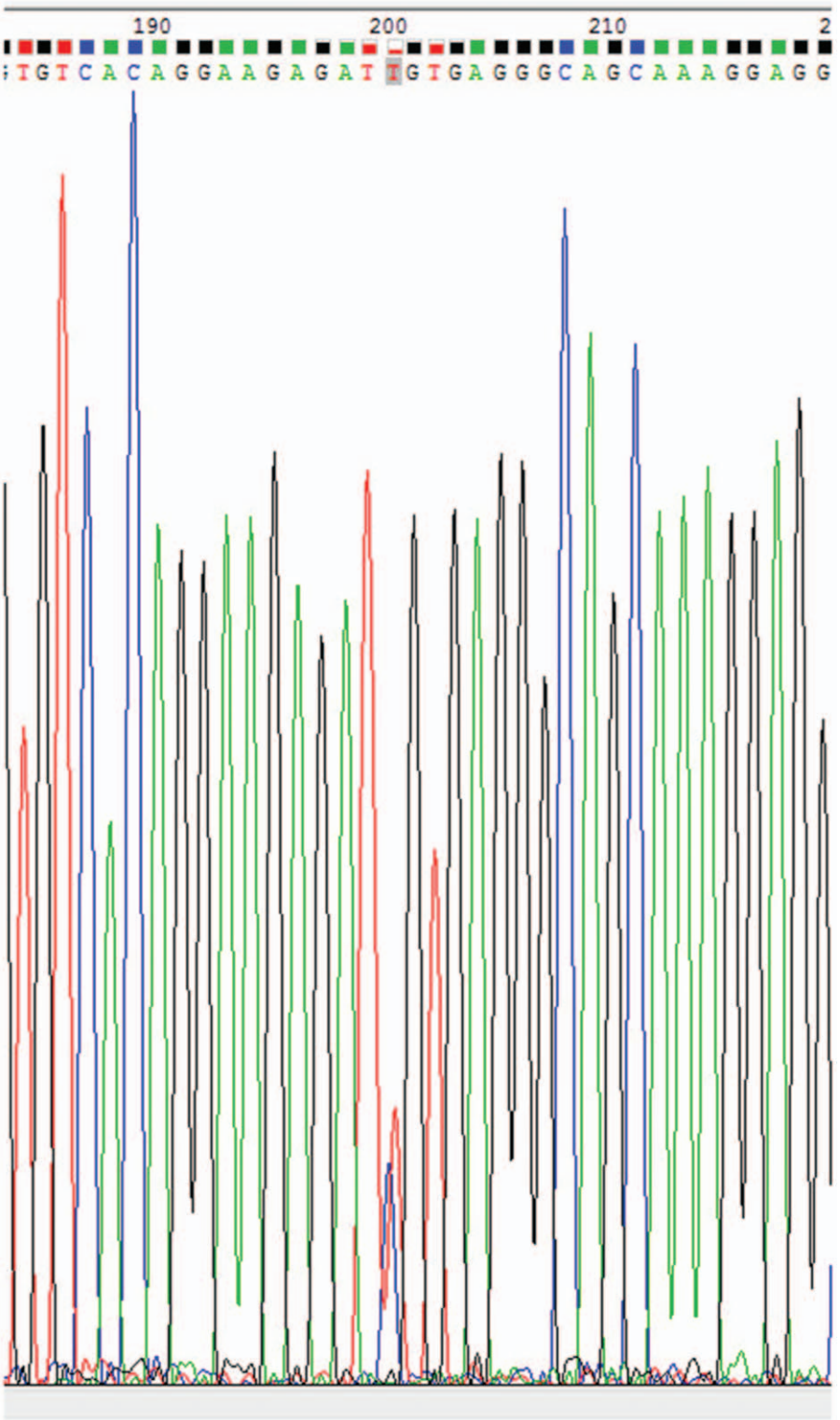

Figure 6. C3435T (rs1045642) (9) TC genotype.

Table 1

Hardy-Weinberg equilibrium test for genotype distribution of 1 C3435T.

C3435T	Allele	Group	Observed Genotype Frequency (Expected Value) TT	CT	CC	*P* value
rs1045642	T/C	Case Group (n=54)	6 (6.34)	25 (24.32)	23 (23.34)	.838
		Healthy Group (n=60)	16 (18.15)	34 (29.7)	10 (12.15)	.262

Table 2

Distribution of C3435T genotypes in case group and control group.

SNP Site	Allele (T/C)	Group	Genotype n (%) TT	CT	CC	χ^2	*P* value
rs1045642	T/C	Case Group	6 (0.111)	25 (0.463)	23 (0.426)	10.754	.005
		Control group	16 (0.267)	34 (0.567)	10 (0.167)		

SNP = single nucleotide polymorphism.

Table 3

Distribution and odds ratio estimate of different C3435T allele frequencies in case group and healthy group.

	Genotype	Case Group	Healthy Group	*P* value	OR	95%CI
	CT	25 (0.463)	34 (0.57)	.006		
rs1045642	CC	23 (0.426)	10 (0.17)	.012	3.209	[1.288–7.997]
	TT	6 (0.111)	16 (0.26)	.200	0.487	[0.162–1.464]

Table 4

Distribution of C3435T genotypes in clinical pathology of DLBCL.

Group	n	Genotype CC (n=23)	CT (n=25)	TT (n=6)	Allele C (n=48)	T (n=31)	*P* (T vs C) *OR* (95%CI)
Age							
>60 yr	18	7	10	1	17	11	.995[a]
≤60 yr	36	16	15	5	31	20	.99 (0.39,2.56)
Gender							
Male	27	11	12	4	23	16	.748[a]
Female	27	12	13	2	25	15	.86 (0.35,2.13)
Ethnicity							
Han	35	16	15	4	31	19	.767[a]
Uygur	19	7	10	2	17	12	1.15 (0.45,2.93)
Pathology							
Germinal center	17	8	12	3	20	15	.557[a]
Non-germinal center	31	15	13	3	28	16	.76 (0.31,1.89)
Stage							
I-II	24	14	7	3	21	10	1.63 (0.64, 4.21)
III-IV	30	9	18	3	27	21	.307[a]
IPI score							
0–2	34	15	15	4	30	19	.914[a]
3–5	20	8	10	2	18	12	1.05 (.42,2.67)
B symptom							
No	42	17	19	6	36	25	.559[a]
Yes	12	6	6	0	12	6	.72 (.24,2.17)
EB virus antibody							
Positive	17	6	9	2	15	11	.696[a]
Negative	37	17	16	4	33	20	.83 (.32,2.15)
Hepatitis B surface antigen							
Positive	5	2	1	2	3	3	.574[a]
Negative	49	21	24	4	45	28	.62 (.12,3.30)

Table 5

Distribution of C3435T genotypes in clinical efficacy.

		Genotype			Allele		
Efficacy	**n**	**CC (n=23)**	**CT (n=25)**	**TT (n=6)**	**C (n=48)**	**T (n=31)**	***P* (T vs C) *OR* (95%CI)**
Effective (CR+PR)	45	19	21	5	40	26	.950[a]
Ineffective (SD+PD)	9	4	4	1	8	5	.96 (.28,3.26)

PD = progressed disease, SD = stable disease.

Table 6

Distribution of C3435T Genotypes in Myelosuppression.

		Genotype			Allele		
Myelosuppression	**n**	**CC (n=23)**	**CT (n=25)**	**TT (n=6)**	**C (n=48)**	**T (n=31)**	***P* (T vs C) *OR* (95%CI)**
I-II	28	14	11	3	25	14	.479[a]
III-IV	26	9	14	3	23	17	0.74 (.32,1.71)

tion of chemotherapeutic agents in tumor cells to induce apoptosis.[19] The inconsistency of results may be related to the different grouping of efficacy in study design. In terms of study mechanism, it may be related to the linkage disequilibrium between genes, different mRNA stability induced by C3435T gene polymorphism, and substrate specificity,[8] or the different transcriptional regulation of MDR by inflammatory mediators such as cytokines, interleukins, and prostaglandins, while tumor species and type of tumor cells also determine different MDR pump types.[20]

A Mexican study[21,22] showed that children with acute lymphoblastic leukemia carrying CC genotype had a reduced risk of leukopenia, while another study showed that children with acute lymphoblastic leukemia carrying TT genotype had an increased risk of myelosuppression after chemotherapy, which was not observed in our study though. It may be related to different experimental methods.

In summary, MDR1 C3435T gene polymorphism was associated with an increased risk of DLBCL, but not associated with clinical pathology, response rate to R-CHOP regimen, and myelosuppression, which were not completely consistent with domestic and foreign studies. The specific causes and mechanisms remain to be further investigated and confirmed. It still requires further unification or standardization of experimental methods to reach a consistent conclusion.

Author contributions

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