

# Single nucleotide polymorphisms of microRNA processing genes and outcome of non-Hodgkin's lymphoma

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**Objective:** microRNA (miRNA)-related single nucleotide polymorphisms (miR-SNPs) in miRNA-processing machinery genes can affect cancer risk, treatment efficacy, and patients' prognosis by mediating the expression of targeted genes. Five miR-SNPs in miRNA processing machinery genes, including *XPO5* (rs11077), *RAN* (rs14035), *TNRC6B* (rs9623117), *GEMIN3* (rs197412), and *GEMIN4* (rs2740348), in 168 non-Hodgkin's lymphoma (NHL) patients were evaluated for their association with the cancer risk and outcomes associated with NHL.

**Materials and methods:** miR-SNPs were genotyped using polymerase chain reaction–ligase detection reaction. The survival curves were calculated using the Kaplan–Meier method, and comparisons between the curves were made using the log-rank test. Multivariate survival analysis was performed using a Cox proportional hazards model.

**Results:** Among the five SNPs, only rs197412 located in the coding region of the *GEMIN3* gene was identified; it was independently associated with overall survival in NHL patients, as determined by multivariate analysis (relative risk: 1.649; 95% confidence interval: 1.110–2.449;  $P=0.013$ ). The prognostic value of this miR-SNP in patient outcomes was also observed in the diffuse large B-cell lymphoma and T-cell lymphoma NHL subtypes.

**Conclusion:** Our results suggested that the specific genetic variants observed in the miRNA machinery genes may affect NHL survival.

**Keywords:** miR-SNP, rs197412, *GEMIN3*, NHL, survival

## Introduction

Human non-Hodgkin's lymphoma (NHL) is the fifth most common cause of cancer worldwide, with diffuse large B-cell lymphoma (DLBCL), T-cell lymphoma (TCL), and follicular lymphoma (FL) as the most common NHL subtypes.<sup>1</sup> Quite a few patients do not achieve complete remission after conventional chemotherapy for this potentially curable disease.<sup>2</sup> Clinical factors such as age, stage, number of nodal or extranodal sites, performance status, B symptoms, and certain biochemical measurements have been identified as predictors of NHL outcomes, and these predictive factors were combined as the International Prognostic Index for the prognostic prediction of DLBCL and TCL, and they were subsequently combined as the follicular IPI for FL.<sup>1,3–5</sup> A number of NHL outcome associated biomarkers have been identified and are associated with NHL outcomes, but few are applied in routine clinical examination.<sup>6</sup>

microRNAs (miRNAs) are RNA molecules with lengths of ~22 nucleotides, and they act as posttranscriptional regulators of mRNA expression. They are also responsible for regulating the expression of at least 30% of protein-coding genes.<sup>7–9</sup> miRNA is implicated in a broad range of biological processes, such as embryonic development, cellular differentiation, proliferation, apoptosis, cancer development,

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and insulin secretion.<sup>7,8</sup> In the miRNA processing, long primary transcripts of miRNAs are processed in the nucleus by the RNase III *Drosha*, which is transported to the cytoplasm by the nuclear transport factor exportin-5 (*XPO5*) and Ran-GTPase (*RAN*). In the cytoplasm, RNase III *Dicer* and transactivation-responsive RNA-binding protein mediate pre-miRNAs processing to release a 21-bp double-stranded (ds)RNA; the RNA-induced silencing complex, including *GEMIN3*, *GEMIN4*, and trinucleotide repeat containing 6B (*TNRC6B*), will select one strand as the mature miRNA, and they will guide the mature miRNAs to their target mRNA sites.<sup>8,10–14</sup> miRNA-related single nucleotide polymorphisms (miR-SNPs) – defined as single nucleotide polymorphisms (SNPs) in the miRNA genes, at the miRNA binding site, or in the miRNA processing machinery – can modulate miRNA and targeted genes expression so as to affect cancer risk, treatment efficacy, and patients' prognosis.<sup>14–17</sup>

In the present study, we performed a genotype analysis of five miR-SNPs from the miRNA processing machinery genes, including *XPO5* (rs11077), *RAN* (rs14035), *TNRC6B* (rs9623117), *GEMIN3* (rs197412), and *GEMIN4* (rs2740348), which showed an association with cancer risk in a previous study<sup>14</sup> conducted with 168 NHL patients who received treatment at our hospital. We subsequently evaluated the impact of these miR-SNPs on NHL survival.

## Materials and methods

### Tissue specimens and DNA extraction

Blood samples were collected from 168 NHL patients at the Fourth Hospital of Hebei University who underwent

chemotherapy treatment at the Department of Hematology between 2000 and 2007. An NHL diagnosis was made according to the World Health Organization Classification of Tumors.<sup>18</sup> Blood was also collected from healthy controls. Genomic DNA was extracted immediately with a Wizard Genomic DNA extraction kit (Promega Corporation, Fitchburg, WI, USA). All procedures were supervised and approved by the hospital's Human Tissue Research Committee.

### Genotyping of miR-SNPs

The miR-SNP of the miRNA processing genes including *XPO5* (rs11077), *RAN* (rs14035), *TNRC6B* (rs9623117), *GEMIN3* (rs197412), and *GEMIN4* (rs2740348) were genotyped using the ligase detection reaction method, using forward and reverse primers to amplify the DNA fragments that flank the miR-SNPs based on the National Center for Biotechnology Information (NCBI) SNP database (<http://www.ncbi.nlm.nih.gov/snp/>). Polymerase chain reaction was performed using a polymerase chain reaction Master Mix Kit according to the manufacturer's instructions (Promega Corporation). The ligation was performed using the different probes matched to the miR-SNPs, and the ligated products were separated using the ABI PRISM Genetic Analyzer 3730XL (Thermo Fisher Scientific, Waltham, MA, USA). Polymorphisms were confirmed based on the difference in the length of the ligated products. All primer and probe sequences are listed in Table 1.

### Statistical analysis

The  $\chi^2$  test was used to analyze dichotomous values, such as the presence or absence of an individual SNP in NHL patients

**Table 1** Five miR-SNPs examined in NHL patients

Genes	rs (NCBI)	Primers	Probes
<i>XPO5</i>	rs11077 (A/C)	F GAATCTGGTCACCTGATGGGA R GTGCCTGAGTGGACCTTGAG	S1 GTACCTCCAAGGACCAGGGCTGGGA S2 TTTGTACCTCCAAGGACCAGGGCTGGGC S3 AGTCTTTAGTGCTAACATCCCCTTT
<i>RAN</i>	rs14035 (C/T)	F GCACCTGCTCAAAATCTGTGA R TAACAGCAAGAATCCCAACC	S1 TTTTAGTAATCATGTTTTAATGTAGAACC S2 TTTTTTTAGTAATCATGTTTTAATGTAGAACC S3 TCAAACAGGATGGAACATCAGTGGATTT
<i>GEMIN4</i>	rs2740348 (G/C)	F TTGCCTCTGAGAAGAAGTGG R GACTCAGGGATGGCTCTGTG	S1 TTTTTTTGGGAGTAACAGGGCCCTCTCCGAC S2 TTTTTTTTTTTGGGAGTAACAGGGCCCTCTCCGAG S3 AGCCAGACTTGGTGTGAGGCTGCTTTTTTT
<i>TNRC6B</i>	rs9623117 (C/T)	F TTTCTGTCTCCTCCTATCCAT R CATTAGTTTAGCCCAACAAGGT	S1 TCTCCCTGTTACTCTTAAGTAGTGC S2 TTTTCTCCCTGTTACTCTTAAGTAGTGT S3 CTCCTTTCCCCATCCCACTCTC
<i>GEMIN3</i>	rs197412 (T/C)	F TAGAGAAACCTGTGGAAATCA R GAAGAGGTTCTTGAGCTGTAA	S1 TTTTATGGTTTTGTGAGAAATAAAGTTAC S2 TTTTTTTATGGTTTTGTGAGAAATAAAGTTAT S3 TGAACAGAGAGTCCCTGTGTTGGCATT

**Notes:** F, represents forward primer for PCR; R, represents reverse primer for PCR; S1 and S2, represent probes matched to different alleles of the SNP, S3 represents probes downstream of the SNP.

**Abbreviations:** miR-SNP, miRNA-related single nucleotide polymorphisms; NHL, non-Hodgkin's lymphoma; NCBI, National Center of Biotechnology Information; *XPO5*, nuclear transport factor exportin-5PCR; *TNRC6B*, trinucleotide repeat containing 6B; PCR, polymerase chain reaction; SNP, single nucleotide polymorphism.

and healthy controls. Pearson's correlation coefficient was used to determine the relationship between clinical characteristics and SNPs. Survival curves were calculated using the Kaplan–Meier method, and comparisons between the curves were made using the log-rank test. Multivariate survival analysis was performed using a Cox proportional hazards model. All of the statistical analyses were performed using the SPSS 18.0 software package (SPSS Inc., Chicago, IL, USA). A  $P$ -value  $<0.05$  was considered statistically significant.

## Results

A total of 177 patients enrolled in this study were reviewed every 3 months for 5 years. Nine patients were lost during follow-up: one in the first year, three in the second year, two in the third year, and three in the fourth year. The remaining 168 patients, including 47 DLBCL, 65 TCL, and seven FL patients, were assessed by univariate and multivariate analyses. At first, the relationship between the data collected during the 5-year follow-up and patients' clinical characteristics

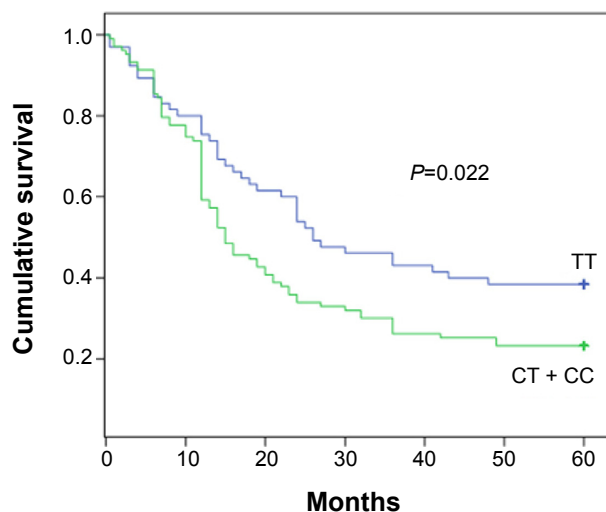
was analyzed by log-rank test. The clinical characteristics, including Ann Arbor stage, lactic dehydrogenase (LDH) levels, bone marrow invasion, and the presence of B symptoms, displayed a potential association with the 5-year survival rate. After adjusting the Cox-hazard model using the multivariate analysis findings, Ann Arbor stage, LDH levels, and the presence of B symptoms were identified as the independent predictors for NHL survival (Table 2).

We performed a genotype analysis of these five miR-SNPs of the miRNA processing machinery genes, including *XPO5* (rs11077), *RAN* (rs14035), *TNRC6B* (rs9623117), *GEMIN3* (rs197412), and *GEMIN4* (rs2740348) in 168 NHL patients and 80 healthy controls. No statistically significant association ( $P>0.05$ ) was detected (data not shown) in terms of cancer risk in this case–control study. We subsequently evaluated the association of these genes with overall survival using the Kaplan–Meier methods. Among the five SNPs analyzed, only rs197412 of the *GEMIN3* genes had a prognostic impact on overall survival, as determined by the log-rank test analysis

**Table 2** Univariate and multivariate analysis of clinical factors associated with NHL survival

Factors	Number of cases	5-year survival rate (%)	Univariate analysis	Multivariate analysis		
			P-value	RR	95% CI	P-value
Age (years)			0.898	1.084	0.706–1.663	0.712
≤60	125	28.8				
>60	43	30.2				
Sex			0.736	1.271	0.849–1.904	0.245
Male	104	30.8				
Female	64	26.6				
Ann Arbor stage			0.000	1.721	1.063–2.786	0.027
I/II	52	46.2				
III/IV	116	21.6				
LDH			0.000	0.509	0.334–0.776	0.002
Abnormal	61	11.5				
Normal	107	39.3				
Bone marrow invasion			0.008	1.301	0.834–2.029	0.246
Normal	112	33.9				
Abnormal	56	19.6				
B symptoms			0.000	0.646	0.420–0.992	0.046
Yes	103	21.4				
No	65	41.5				
Tumor size			0.114	0.956	0.620–1.474	0.839
>5 cm	39	20.5				
≤5 cm	129	31.8				
rs197412			0.022	1.649	1.110–2.449	0.013
TT	65	38.5				
CT + CC	103	23.3				
Subtypes			0.137	0.856	0.724–1.012	0.069
DLBCL	47	25.5				
TCL	65	24.6				
FL	7	71.4				
Others	49	32.7				

**Abbreviations:** NHL, non-Hodgkin's lymphoma; LDH, lactic dehydrogenase; DLBCL, diffuse large B-cell lymphoma; TCL, T-cell lymphoma; FL, follicular lymphoma; CI, confidence interval; RR, relative risk.



**Figure 1** Genotype of rs197412 and its association with total NHL survival.  
**Abbreviation:** NHL, non-Hodgkin's lymphoma.

among NHL patients. The 5-year survival rate of CC + CT and TT were 23.3% and 38.5%, respectively (Table 2). The patients with the CT + CC genotype showed a shorter overall survival when compared with that of the TT types (Table 2 and Figure 1). Moreover, the rs197412 SNP was also identified as an independent predictor of NHL outcomes (relative risk:

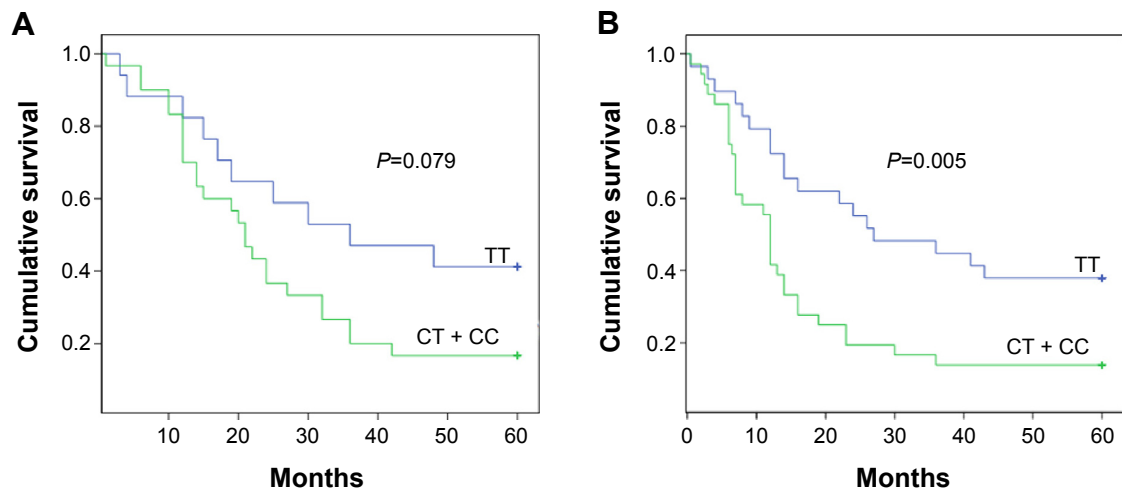
1.649; 95% confidence interval [CI]: 1.110–2.449;  $P=0.013$ ) by multivariate analysis with the Cox-hazard model. The correlation analyses of the clinical characteristics and their association with SNPs using Pearson's correlation are listed in Table 2; it was determined that no correlations exist.

The predictive power of rs197412 was assessed in the NHL subtypes by univariate and multivariate analyses. For DLBCL, the 5-year survival rate was 16.7% in the patients with the CC + CT genotype and 41.2% in those with the TT genotype. The patients with the CC + CT genotype displayed a shorter overall survival, as indicated by the log-rank test; this result was marginally statistically significant ( $P=0.079$ ; Table 3 and Figure 2A). After adjusting for Ann Arbor stage, IPI score, LDH levels, and the presence of B symptoms using multivariate analysis, the rs197412 was identified as an independent predictor of DLBCL outcomes; this result was also marginally statistically significant (relative risk: 2.276; 95% CI: 0.982–5.273;  $P=0.055$ ). For the TCL, the predictive power for survival of this miR-SNP was also validated by univariate ( $P=0.005$ ) and multivariate analysis (relative risk: 3.106; 95% CI: 1.539–6.267;  $P=0.002$ ); this result was statistically significant (Table 4 and Figure 2B).

**Table 3** Univariate and multivariate analysis of clinical factors associated with DLBCL survival

Factors	Number of cases	5-year survival rate (%)	Univariate analysis	Multivariate analysis		
			P-value	RR	95% CI	P-value
Age			0.140	1.716	0.721–4.087	0.222
≤60	27	29.6				
>60	20	20.0				
Sex			0.577	1.332	0.534–3.325	0.539
Male	29	24.1				
Female	18	27.8				
Ann Arbor stage			0.066	1.106	0.376–3.254	0.855
I/II	21	33.3				
III/IV	26	19.2				
LDH			0.037	0.759	0.207–2.782	0.678
Abnormal	8	12.5				
Normal	39	28.2				
Bone marrow invasion			0.691	0.953	0.210–4.328	0.950
Normal	41	26.8				
Abnormal	6	16.7				
B symptoms			0.000	0.304	0.115–0.807	0.017
Yes	25	12.0				
No	22	40.9				
Tumor size			0.583	0.733	0.299–1.795	0.497
>5 cm	12	25.0				
≤5 cm	35	25.7				
rs197412			0.079	2.276	0.982–5.273	0.055
TT	17	41.2				
CT + CC	30	16.7				
IPI			0.088	0.987	0.464–2.100	0.973
0–1	17	29.4				
2	20	30.0				
3–5	10	10.0				

**Abbreviations:** DLBCL, diffuse large B-cell lymphoma; CI, confidence interval; LDH, lactic dehydrogenase; IPI, International Prognostic Index; RR, relative risk.



**Figure 2** Genotype of rs197412 in subtypes of NHL patients.

**Notes:** (A) Borderline level survival difference for CC + CT and TT genotype of rs197412 in DLBCL patients. (B) Significant survival difference for CC + CT and TT genotype of rs197412 in TCL patients.

**Abbreviations:** NHL, non-Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; TCL, T-cell lymphoma.

## Discussion

In the present study, we reported, for the first time, that miR-SNPs have predictive power on the overall survival of NHL patients. The miR-SNP of rs197412 in the miRNA-processing machinery genes of *GEMIN3* are involved in

the prognosis of NHL outcomes. Only a marginal level of significance was observed for the association between miR-SNPs and survival among DLBCL patients, which should be further validated using a larger sample size and in laboratory-based studies.

**Table 4** Univariate and multivariate analysis of clinical factors associated with TCL survival

Factors	Number of cases	5-year survival rate (%)	Univariate analysis	Multivariate analysis		
			P-value	RR	95% CI	P-value
Age			0.755	1.348	0.447–4.065	0.596
≤60	58	24.1				
>60	7	28.6				
Sex			0.229	1.129	0.646–2.452	0.499
Male	43	27.9				
Female	22	18.2				
Stage			0.016	1.655	0.694–3.945	0.256
I/II	18	44.4				
III/IV	47	17.0				
LDH			0.004	1.128	0.501–2.540	0.771
Abnormal	32	12.5				
Normal	33	36.4				
Bone marrow invasion			0.034	1.154	0.557–2.387	0.700
Normal	44	29.5				
Abnormal	21	14.3				
B symptoms			0.057	0.578	0.252–1.325	0.195
Yes	49	18.4				
No	16	43.8				
Tumor size			0.546	1.429	0.664–3.077	0.362
>5 cm	13	15.4				
≤5 cm	52	26.9				
rs197412			0.005	3.106	1.539–6.267	0.002
TT	29	37.9				
CC/CT	36	13.9				
IPI			0.000	2.164	1.129–4.146	0.020
0–1	20	55				
2	31	16.1				
3–5	14	0				

**Abbreviations:** TCL, T-cell lymphoma; CI, confidence interval; LDH, lactic dehydrogenase; IPI, International Prognostic Index; RR, relative risk.

*GEMIN3* is reportedly implicated in the etiology of spinal muscular atrophy, as it is a core component of the motor neuron complex.<sup>19</sup> In addition, this protein has been identified in the miRNA ribonucleoprotein particle, which is involved in the processing of miRNA precursors through their interaction with the key components of the RNA-induced silencing complex.<sup>19–21</sup> For miR-SNP rs197412 located in exon 11 of the *GEMIN3* gene, the T to C transition resulted in Ile and Thr substitution at the 636 amino acid position of the *GEMIN3* protein. This miR-SNP was found to be associated with cancer risk and outcomes in renal cell carcinoma.<sup>21,22</sup> The underlying mechanism behind how this SNP modifies NHL survival remains unclear; it might affect mRNA stability, which is associated with the altered expression of *GEMIN3*. The altered *GEMIN3* expression may affect the miRNAs as a whole, leading to overall suppression of the miRNA expression profiles, and thus mediating NHL survival. In addition, *GEMIN3* can form a complex with *p53* and *EBNA3C* to block the DNA binding affinity of *p53*. In this way, it blocks *p53*-mediated apoptosis. The C-terminal domain (amino acid 546–825) of *GEMIN3* binds to *p53* and is responsible for the interaction between *GEMIN3* and *p53*.<sup>23</sup> The amino acid substitution of this miR-SNP, which is located in the C-terminal of *GEMIN3*, might alter its binding affinity to *p53* and mediate the apoptosis of NHL cells.

Although miR-SNP studies on the miRNA processing machinery genes are in their early stages, our results are encouraging as they indicate that miR-SNPs have an effect on cancer survival. However, the results from this study require validation in other populations and in laboratory-based functional studies. miRNAs have been emphasized as a key factor in patients' susceptibility to therapeutic response in many complex diseases, including cancer.<sup>24</sup> In conclusion, an miR-SNP in the code region of *GEMIN3* was found to be an independent prognostic marker for NHL survival.

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## Disclosure

The authors declare that they have no competing interests.

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