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### Telomere length could be one of the risk factors for non-Hodgkin’s lymphoma. We studied the association of four functional single nucleotide polymorphisms rs2853669, rs2736100, rs7726159 and rs10069690 in the TERT gene that encodes telomerase reverse transcriptase with the risk of non-Hodgkin’s lymphoma in ethnical Russians. The case group consisted of 344 patients, including 139 patients with diffuse large B-cell lymphoma and 77 patients with small lymphocytic lymphoma/chronic lymphocytic leukemia. The control group comprised 893 individuals with no history of cancer. Genotyping was carried out by real-time PCR allelic discrimination with TaqMan probes. None of the studied polymorphisms and haplotypes showed statistically significant association with non-Hodgkin’s lymphoma and its subtypes diffuse large B-cell lymphoma and small lymphocytic lymphoma/chronic lymphocytic leukemia. Our results provide evidence that tested polymorphisms do not influence the risk of non-Hodgkin’s lymphoma in Russian population.

**Keywords:** TERT gene; polymorphism; non-Hodgkin’s lymphoma; Russian population

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### Introduction

Non-Hodgkin’s lymphomas (NHL) are the most common form of hemoblastosis. The incidence of NHL has doubled over the past two decades [1-3]. The biological mechanisms and etiology of NHL still remain elusive, and the confirmed risk factors account for only a small percentage of the total cases.

Telomere length and telomerase activity are supposed to play an important role in cancer development. Telomeres cap human chromosomes and protect their ends from degradation due to the incomplete replication and from being identified as break points by the DNA repair system, and therefore promote genomic stability and integrity [4,5]. Telomere length is maintained by the telomerase complex, which consists of a catalytic telomerase reverse transcriptase (TERT) protein, an intrinsic RNA template (TERC) and associated proteins. Telomerase is expressed in embryonic cells, germline cells, activated lymphocytes and the stem cell compartments of actively proliferating tissues [6,7]. Other cells naturally lack telomerase activity and show progressive telomere shortening with each round of DNA replication. When telomeres reach a critical length, cellular checkpoints are
 activated and arrest cell cycle. This growth-arrested state is termed replicative senescence. Cells that lose critical cell cycle checkpoint functions escape this initial growth arrest and eventually enter a second growth arrest state (cellular crisis), when the end-protective function of telomeres is lost and widespread genomic instability occurs [8,9]. This instability commonly results in apoptotic cell death [8]. Telomere erosion, replicative senescence and cellular crisis play a key role in the control of proliferative capacity of the cells, and thereby provide a tumor-suppressive mechanism [10]. Constitutively longer telomeres were hypothesized to increase the risk of cancer by extending cellular proliferative lifespan and allowing the cell to accumulate oncogenic mutations.

To date, two prospective studies have revealed the association of longer telomere length with increased risk of NHL [11,12]. It is therefore of interest to explore whether variants in telomerase genes contribute to genetic predisposition to this oncological disease. A large number of studies, including genome-wide association studies (GWAS), fine-scale mapping studies, candidate gene studies and meta-analyses revealed association of polymorphisms in the TERT gene mapped at 5p15.33 with various types of cancer, such as breast [4,13-16], lung [17-19], prostate [14,20], ovarian [14-16,21], testicular germ cell cancer [22], glioma [23], pancreas cancer, bladder cancer and central nervous system tumors [8]. This locus also reached marginal genome-wide significance in the recent GWAS of chronic lymphocytic leukemia, which is one of the subtypes of NHL [24]. The association was subsequently validated in the meta-analysis of two GWAS [25]. Several TERT polymorphisms were studied in a case-control study on NHL conducted by Lim et al. [26], but none of the revealed associations remained significant after multiple test correction. Since these studies are the only studies that examined the association between TERT polymorphisms and NHL, further research is warranted to investigate this association in different ethnic groups. Our study is the first study examining the influence of polymorphic loci in the TERT gene on the risk of NHL in Russian population. We chose four single-nucleotide polymorphisms (SNPs) for our analysis: rs2853669 in promoter region, which has been shown to alter telomerase activity and telomere length [27,29], two SNPs in intron 2 - rs2736100 and rs7726159, which are the top SNP associated with telomere length from recent GWAS [14,30,31], and rs10069690 in intron 4, which was found to be associated with chronic lymphocytic leukemia in the above-mentioned GWA studies [24, 25].

Materials and Methods

All the individuals enrolled in this study gave signed informed consent, and the study was approved by the local Ethics Committee. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Patients

The case group comprised 344 people with NHL who were inpatients of the Hematology Center of Municipal Clinical Hospital No. 2 in Novosibirsk during the period 2006-2013 (174 men, 160 women; mean age 56.5 ± 13.2, range 18-85 years). All cases were subtyped according to the World Health Organization classification of lymphoid neoplasms introduced in 2008 (Table 1). All patients were staged according to the Ann Arbor classification (1971). The control group included 370 men and 523 women with no personal or family history of cancer (mean age 57.0 ± 14.9, range 19-91 years). Control subjects were enrolled during an epidemiological study conducted by the Altai Branch of the N. N. Blokhin Cancer Research Centre of the Russian Academy of Medical Sciences in 2006-2009. All cases and controls were Russian Caucasians.

Genomic DNA was isolated from leukocytes in venous blood by proteinase K digestion followed by phenol/chloroform extraction and ethanol precipitation, and also from buccal epithelium using a standard method of DNA separation by silica adsorption. DNA samples were stored at -20°C in a freezer compartment.

### Table 1. Descriptive characteristics of NHL cases

<table>
<thead>
<tr>
<th>characteristic</th>
<th>Number and percent for each category</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHL subtype</strong></td>
<td></td>
</tr>
<tr>
<td>B-cell lymphomas</td>
<td>324 (97%)</td>
</tr>
<tr>
<td>diffuse large B-cell</td>
<td>139 (41.6%)</td>
</tr>
<tr>
<td>small lymphocytic lymphoma/chronic lymphocytic leukemia</td>
<td>77 (23.0%)</td>
</tr>
<tr>
<td>follicular</td>
<td>26 (7.8%)</td>
</tr>
<tr>
<td>mucosa-associated lymphoid tissue (MALT)</td>
<td>25 (7.5%)</td>
</tr>
<tr>
<td>nodal marginal zone</td>
<td>16 (4.8%)</td>
</tr>
<tr>
<td>mantle cell</td>
<td>16 (4.8%)</td>
</tr>
<tr>
<td>lymphoplasmocytic</td>
<td>9 (2.7%)</td>
</tr>
<tr>
<td>prolymphocytic</td>
<td>9 (2.7%)</td>
</tr>
<tr>
<td>extraosseous plasmacytoma</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>hairy-cell leukosis</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Burkitt-like</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>splenic marginal zone</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td><strong>T-cell lymphomas</strong></td>
<td>10 (3.0%)</td>
</tr>
<tr>
<td>anaplastic large cell</td>
<td>6 (1.8%)</td>
</tr>
<tr>
<td>mycosis fungoides</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Sezary syndrome</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17 (5.1%)</td>
</tr>
<tr>
<td>2</td>
<td>36 (10.8%)</td>
</tr>
<tr>
<td>3</td>
<td>36 (10.8%)</td>
</tr>
<tr>
<td>4</td>
<td>245 (73.4%)</td>
</tr>
</tbody>
</table>
Genotyping was carried out by real-time PCR allelic discrimination with TaqMan probes. PCR was performed in 20 μL reaction volumes containing 20-100 ng of genomic DNA, 65mM Tris-HCl (pH 8.9), 24mM ammonium sulfate, 3.5 mM MgCl2, 0.05% Tween 20, 0.2mM dNTP, 0.3 mM of each primer, 0.1 mM of each probe (Supplemental Table 1), and 1.0 U of Taq polymerase. PCR thermal cycling conditions were as follows: denaturation for 3 min at 96°C followed by 48 cycles of 8 s at 96°C and 40 s at 60°C. Amplification procedure was conducted using CFX96 Thermal Cycler (Bio-Rad, USA).

Statistical analysis

To evaluate the effects of the polymorphisms on cancer susceptibility, odds ratio (OR) and 95% CI were calculated by logistic regression analysis adopting co-dominant and additive models of inheritance. All data were adjusted for sex and age. The expected frequencies of genotypes in the control group were tested for accordance with Hardy-Weinberg equilibrium using exact test. Differences were considered statistically significant at \( P < 0.05 \). Statistical analyses were performed using the GenABEL statistical package for the R language (version 2.15.1, http://www.r-project.org; glm function). Haplotype frequencies and the corresponding OR and CI 95% values were calculated using the haplo.stats statistical package for the R language (version 2.15.1; haplo.score and haplo.glm functions). Linkage disequilibrium was analyzed based on \( D' \) and \( r^2 \) values calculated using the CubeX program (http://www.oege.org/software/cubex/). To estimate the statistical power of study, Genetic power calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/cc2.html) was used.

Results

The genotypes of polymorphisms rs2853669, rs2736100, rs7726159 and rs10069690 were determined in the group of NHL patients including two major subgroups - diffuse large B-cell lymphoma (139 patients) and small lymphocytic lymphoma/chronic lymphocytic leukemia (77 patients), and in the control group (Table 2). The distribution of genotypes in the control group was in accordance with Hardy-Weinberg equilibrium for all studied polymorphisms.

Association analysis revealed no statistically significant association of any of the tested SNPs with the risk of NHL, diffuse large B-cell lymphoma and small lymphocytic lymphoma/chronic lymphocytic leukemia (Table 3).

We evaluated the linkage disequilibrium between studied polymorphisms (Fig. 1) and performed a haplotype analysis (Table 4). Polymorphisms rs2736100 and rs7726159 were tightly linked with \( D' = 0.97, r^2 = 0.53 \); rs10069690 and rs2736100 were linked with \( D' = 0.87, r^2 = 0.29 \); rs10069690 and rs7726159 were linked with \( D' = 0.82, r^2 = 0.46 \); rs2853669 and rs2736100 were linked with \( D' = 0.73, r^2 = 0.21 \). Polymorphism rs2853669 was not in linkage disequilibrium with rs7726159 (\( D' = 0.19, r^2 = 0.03 \)) and rs10069690 (\( D' = 0.02, r^2 = 0.0002 \)). Two haplotypes were absent in the case and control groups, and four haplotypes were very rare, so that we were not able to perform a haplotype analysis. None of the remaining TERT gene haplotypes was significantly associated with the risk of NHL (Table 4).

Discussion

In our study, we examined the association of four functional SNPs in the TERT gene with the risk of NHL in ethnical Russians. Polymorphisms rs2853669 is a T/C transition located 190 bp upstream the TERT transcription start site. This SNP have previously been shown to interfere with Ets2 binding and reduce telomerase activity [27]. It also showed an association with decreased promoter activity of the TERT gene [28,29] and shorter mean leukocyte telomere length [28], although it was not consistent with the findings revealed by some other studies [15,16,32]. Polymorphisms rs2736100 (T/G transversion) is located in intron 2 in a putative regulatory region. This SNP have previously been shown to interfere with Ets2 binding and reduce telomerase activity [27]. It also showed an association with increased telomere length in several studies [15,33,34], including two recent GWAS [30,31]. Polymorphisms rs2736100 (T/G transversion) is located in intron 2 in a putative regulatory region. This polymorphism was associated with longer telomere length in several studies [15,33,34], including two recent GWAS [30,31]. Polymorphisms rs7726159 (C/A transversion) also locates in intron 2 about 4 kb downstream of the rs2736100 and associates with longer telomeres according to GWAS [14] and the fine-scale mapping study of Bojesen et al. [15]. Polymorphism rs10069690 (C/T transition in intron 4) showed an
<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype/allele</th>
<th>NHL</th>
<th>DLBCL</th>
<th>SLL/CLL</th>
<th>Control</th>
<th>HWE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2853669</td>
<td>T&gt;C</td>
<td>168 (52.8%)</td>
<td>62 (47.7%)</td>
<td>42 (58.3%)</td>
<td>491 (55.5%)</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>TC</td>
<td>131 (41.2%)</td>
<td>59 (45.4%)</td>
<td>23 (31.9%)</td>
<td>322 (36.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>19 (6.0%)</td>
<td>9 (6.9%)</td>
<td>7 (9.7%)</td>
<td>71 (8.0%)</td>
<td></td>
</tr>
<tr>
<td>rs2736100</td>
<td>T&gt;G</td>
<td>94 (28.9%)</td>
<td>46 (34.3%)</td>
<td>18 (23.7%)</td>
<td>237 (26.9%)</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>160 (49.2%)</td>
<td>63 (47.0%)</td>
<td>35 (46.1%)</td>
<td>444 (50.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>71 (21.8%)</td>
<td>25 (18.7%)</td>
<td>23 (30.3%)</td>
<td>199 (22.6%)</td>
<td></td>
</tr>
<tr>
<td>rs7726159</td>
<td>C&gt;A</td>
<td>140 (43.1%)</td>
<td>67 (50.0%)</td>
<td>27 (35.5%)</td>
<td>368 (42.5%)</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>CA</td>
<td>146 (44.9%)</td>
<td>52 (38.8%)</td>
<td>36 (47.4%)</td>
<td>400 (46.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>39 (12.0%)</td>
<td>15 (11.2%)</td>
<td>13 (17.1%)</td>
<td>97 (11.2%)</td>
<td></td>
</tr>
<tr>
<td>rs10069690</td>
<td>C&gt;T</td>
<td>174 (53.0%)</td>
<td>77 (57.9%)</td>
<td>37 (48.1%)</td>
<td>469 (53.2%)</td>
<td>0.55</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>131 (39.9%)</td>
<td>49 (36.8%)</td>
<td>32 (41.6%)</td>
<td>353 (40.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>23 (7.0%)</td>
<td>7 (5.3%)</td>
<td>8 (10.4%)</td>
<td>59 (6.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T</td>
<td>27 (0.0%)</td>
<td>24%</td>
<td>31%</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>

* - P-value for deviation of genotype distribution in the control group from the Hardy-Weinberg equilibrium (exact test).

**Table 3.** Association of polymorphisms in TERT gene with the risk of NHL and its major subtypes - diffuse large B-cell lymphoma (DLBCL) and small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL). OR and 95% CI were adjusted for sex and age

<table>
<thead>
<tr>
<th>SNP</th>
<th>Co-dominant model OR (95% CI)</th>
<th>P</th>
<th>Additive model OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2853669</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC vs. TT</td>
<td>1.31 (0.76-2.25), 0.33</td>
<td>1.57 (0.91-2.72), 0.11</td>
<td>1.01 (0.83-1.24), 0.89</td>
<td></td>
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<tr>
<td>TG vs. TT</td>
<td>1.06 (0.50-2.24), 0.88</td>
<td>1.52 (0.72-3.23), 0.27</td>
<td>1.15 (0.86-1.52), 0.34</td>
<td></td>
</tr>
<tr>
<td>rs2736100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG vs. TT</td>
<td>1.13 (0.78-1.62), 0.52</td>
<td>1.03 (0.74-1.43), 0.85</td>
<td>0.94 (0.78-1.13), 0.50</td>
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<tr>
<td>TG vs. TT</td>
<td>1.54 (0.91-2.61), 0.11</td>
<td>1.16 (0.70-1.90), 0.57</td>
<td>0.80 (0.61-1.04), 0.09</td>
<td></td>
</tr>
<tr>
<td>rs7726159</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA vs. CC</td>
<td>0.97 (0.64-1.48), 0.89</td>
<td>0.94 (0.62-1.43), 0.76</td>
<td>1.00 (0.82-1.21), 0.99</td>
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<tr>
<td>CA vs. CC</td>
<td>1.18 (0.64-2.17), 0.59</td>
<td>0.85 (0.46-1.59), 0.62</td>
<td>0.84 (0.64-1.12), 0.24</td>
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<tr>
<td>rs10069690</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT vs. CC</td>
<td>1.00 (0.60-1.68), 0.99</td>
<td>1.01 (0.77-1.32), 0.96</td>
<td>1.00 (0.82-1.23), 0.96</td>
<td></td>
</tr>
<tr>
<td>TG vs. TT</td>
<td>0.69 (0.30-1.57), 0.38</td>
<td>0.87 (0.59-1.29), 0.49</td>
<td>0.83 (0.63-1.16), 0.31</td>
<td></td>
</tr>
<tr>
<td>rs2853669-rs2736100-rs7726159-rs10069690</td>
<td>1.59 (0.70-3.60), 0.27</td>
<td>1.13 (0.69-1.85), 0.63</td>
<td>1.21 (0.84-1.75), 0.31</td>
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</tr>
</tbody>
</table>

**Table 4.** Association of TERT gene haplotypes with NHL. OR and 95% CI were adjusted for sex and age

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>frequency</th>
<th>OR (95% CI)</th>
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<td></td>
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<td>control</td>
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<td>TTCC</td>
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<td>0.468</td>
</tr>
<tr>
<td>TGAT</td>
<td>0.176</td>
<td>0.158</td>
</tr>
<tr>
<td>CGCC</td>
<td>0.101</td>
<td>0.099</td>
</tr>
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<td>CGAT</td>
<td>0.071</td>
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<tr>
<td>CGAC</td>
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<tr>
<td>TGAC</td>
<td>0.039</td>
<td>0.045</td>
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<td>0.034</td>
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<td>TGCC</td>
<td>0.017</td>
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<tr>
<td>TGTC</td>
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<td>0.013</td>
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<td>0.013</td>
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<tr>
<td>CGCT</td>
<td>0.003</td>
<td>0.005</td>
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<tr>
<td>TTAT</td>
<td>0.006</td>
<td>0.003</td>
</tr>
<tr>
<td>TTAC</td>
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<td>0.003</td>
</tr>
<tr>
<td>CTCT</td>
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<td>0.002</td>
</tr>
<tr>
<td>CTAT</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>CTAC</td>
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</tr>
</tbody>
</table>

* - Unable to calculate.
association with increased risk of chronic lymphocytic leukemia in recent GWAS [24,25]. Kote-Jarai et al. [20] observed a significant increase in TERT expression for the minor allele of this SNP, providing evidence for its functionality.

The distribution of genotypes in the control group of our study was in accordance with Hardy-Weinberg equilibrium for all studied SNPs (Table 2). The observed frequencies of minor alleles were similar or close to those reported in different populations of European ancestry. The frequencies of rs2853669 C, rs2736100 G, rs7726159 A and rs10069690 T alleles in the control group were 0.26, 0.48, 0.34 and 0.27, correspondingly. According to literature and HapMap data, these allele frequencies in Caucasians are as following: 0.26-0.30 for rs2853669 C [15,32,35], 0.49-0.52 for rs2736100 G [4,15,22,23], 0.33-0.35 for rs7726159 A [14,15,21], and 0.25-0.27 for rs10069690 T [4,15,24,36].

In our association analysis, we observed no statistically significant association between the studied SNPs as well as haplotypes and the risk of NHL in Russian population (Table 3, 4), so our results do not support the hypothesis of their involvement in the etiology of NHL in Russia. Nevertheless, since our study had 80% statistical power to reveal associations with OR = 1.28 - 1.31 or greater, we cannot exclude the possibility that these polymorphism could potentially have weaker effects, that could be revealed only in larger studies. Previously, the association of rs2736100 was studied by Lim et al. [26] in a multi-ethnic sample of NHL cases and controls. They found no association of this SNP with NHL, which is consistent with our results. The remaining three SNPs were not tested in previous studies, except rs10069690, which was shown to be associated with one of the NHL subtypes, chronic lymphocytic leukemia, in recent GWAS [24,25]. We performed a subgroup analysis and studied the association of SNPs with small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) and diffuse large B-cell lymphoma (DLBCL), but also observed no evidence of association. Our inability to confirm GWAS result could be explained by ethnic factors. It could also be a result of a limited size of studied groups. In the subgroup analysis, we had 80% statistical power to detect associations with minimal OR = 1.38 - 1.88 depending on SNP frequency. Therefore, we can conclude that if the tested polymorphisms still influence the risk of these NHL subtypes in Russia, their effects are weaker. In future studies, larger samples of NHL patients from different ethnic groups are warranted to further investigate the association of TERT polymorphisms with the risk of this pathology, and analyzing large samples of patients with identical NHL subtypes would be beneficial.

Conclusion. Our study is the first study examining associations of functional polymorphisms in the TERT gene with the risk of NHL in Russian population. We did not reveal any significant association of TERT genotypes and haplotypes with this oncological disease. Our results indicate that tested SNPs do not influence NHL susceptibility in Russia, or their effects are quite small.

Acknowledgments

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Conflict of interest

The authors declare that they have no Conflicting interests.

List of abbreviations


Authorship Contribution

ASS performed the research and wrote the paper; OVB, VSO, ENV provided clinical data and extracted DNA from samples; TIP, MLF supervised the research and provided clinical data.

References

5. Maser RS, DePinho RA. Connecting chromosomes, crisis, and
### Supplemental Table 1. Sequences of primers and probes

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Direction/label</th>
<th>Sequence 5′-3′</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs2853669</td>
<td>Forward</td>
<td>CCGGGTCCCCAGTCCCCTC</td>
</tr>
<tr>
<td></td>
<td>Reverse</td>
<td>CGGCTCCCCAGTGGATTCG</td>
</tr>
<tr>
<td>rs2736100</td>
<td>Forward</td>
<td>CTAATGAGGCACTCTTGACAC</td>
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<td></td>
<td>Reverse</td>
<td>AGAAGACAGACGGGAACA</td>
</tr>
<tr>
<td>rs7726159</td>
<td>Forward</td>
<td>GCTTGTTGATTGTTTCCATCTA</td>
</tr>
<tr>
<td></td>
<td>Reverse</td>
<td>AAGTCTCTGACTGCCGTGA</td>
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