# VARIETY OF TP53 GENE MUTATIONS IN RUSSIAN B-CELL LYMPHOMA PATIENTS

Biderman BV, Severina NA., Koroleva DA, Gabeeva NG, Belyaeva AV, Tatarnikova SA, Babaeva FE, Nesterova ES, Mangasarova YaK, Margolin OV, Kravchenko SK, Obukhova TN., Julhakyan Hunan, Zvonkov EE, Sudarikov AB.
National Medical Research Center for Hematology

## Background

The TP53 gene plays a key role in cell cycle control, DNA repair, initiation of apoptosis, and other critical cellular processes. Mutations of this gene are found in almost all types of malignant neoplasms and the vast majority of cases are associated with poor prognosis. Among hematological malignancies, TP53 gene lesions are most actively studied in CLL, while for other lymphomas fewer data are available so far.

## Aims

To study the frequency, variation, and allelic load of TP53 mutations in Russian patients with B-cell lymphomas.

## Materials & Methods

The study included 145 DNA samples from patients with B-cell lymphomas admitted to the National Research Center for Hematology (Moscow, Russia) in 2020-2021: 53 patients with DLBCL (29F, 24M, age 25-87 years, median 54 years), 47 patients with MCL (17F, 30M, age 42-73 years, median 59 years) and 45 patients with FL (28F, 17M, age 30-72 years, median 49 years), 16 of them with transformation to DLBCL. Mutations in the TP53 gene (exons 4-10) in most samples were detected using NGS according to Pavlova et al., or Sanger sequencing (7 patients). The clinical significance of the detected variants was assessed using the Seshat online tool based on the UMD TP53 database.

| Diagnosis | Variant | VAF, % | Significance | Diagnosis | Variant | VAF, % | Significance | Diagnosis | Variant | VAF, % | Significance |
|---|---|---|---|---|---|---|---|---|---|---|---|
| DLBCL | p.A76V | 16 | VUS | DLBCL | p.A307T | 34 | VUS | MCL | p.C277X | 84 | LP |
| DLBCL | p.T125P | 17 | LP | DLBCL | p.P316L | 10 | VUS | MCL | p.E286K | 49 | LP |
| DLBCL | p.A138V | >45* | LP | DLBCL | p.R337C | 20 | LP | MCL | p.E287G | 5 | VUS |
| DLBCL | p.V173L | 59 | P | DLBCL | c.729_730ins | 32 | VUS | MCL | p.R290H | 4 | VUS |
| DLBCL | p.C176S | >15* | LP | DLBCL | c.783-4G>A | 6 | VUS | MCL | p.H296Y | 3 | VUS |
| DLBCL | p.I195T | 73 | LP | DLBCL | c.559+2T>A | 7,5 | LP | MCL | c.560-2A>G | >15 | LP |
| DLBCL | p.V216L | >15* | LP | MCL | p.T125R | 80 | LP | FL | p.W53X | 95 | LP |
| DLBCL | p.N247N | 5,5 | VUS | MCL | p.T126C | >15* | LP | FL | p.E62Kfs*61 | 65 | VUS |
| DLBCL | p.R249M# | 44 | V | MCL | p.V173M | 14 | P | FL | p.R175H# | 15 | P |
| DLBCL | p.G262D | 9 | VUS | MCL | p.V173G | 52 | P | FL | p.C238Y | 8 | P |
| DLBCL | p.G266E | 53 | LP | MCL | p.H214R | 49 | LP | FL | p.R248Q# | 32 | P |
| DLBCL | p.G266R | 27 | LP | MCL | p.S215R | 74 | LP | FL | p.R249M# | 4 | P |
| DLBCL | p.R267W | 3 | LP | MCL | p.R248W# | >15* | P | FL | p.S269G | 9 | VUS |
| DLBCL | p.C277F | 80 | LP | MCL | p.R248Q# | >15* | P | FL | p.R273H# | 17 | P |
| DLBCL | p.R282W# | 63,5 | V | MCL | p.R248W# | >15* | P | FL | p.K321E | 5 | VUS |
| DLBCL | p.E286K | 36 | LP | MCL | p.R248W# | 26 | P | FL | p.Q331Q | 56 | LP |
| DLBCL | p.E287E | 2,5 | VUS | MCL | p.L252P | 67 | LP | FL | p.R342X | 20 | LP |
| DLBCL | p.R306X | 7 | LP | MCL | p.I255N | 70 | LP | FL | c.920-1G>A | 7 | LP |
| | | | | MCL | p.E271K | 45,6 | LP | | | | |

Table 1. TP53 gene mutations in patients with B-cell lymphomas. # - hot spot mutations; * - Sanger detected mutations (VAF is unreliable); "P" - pathogenic, "LP" - likely pathogenic, VUS - variant of uncertain significance.

## Results

TP53 gene mutations were detected in 24 DLBCL patients (45.4%). Missense mutations (N=21) were found in the "hot spots" p.R249M and p.R282W (2 cases), in one position p.G266 (2 cases), 2 splicing site mutations, and 1 insertion. Also, 16 variants were identified as (probably) pathogenic, 13 of which had a mutation load (VAF) greater than 15%. Of the 8 mutations of unclear significance, 4 had a VAF<10%. Del17p was simultaneously detected in 7 patients with TP53 mutations (out of 11 examined). In the MCL patients mutations were found in 19 cases (40%). 18 of them are missense mutations (4 in the “hot spot” p.R248 and 2 in position p.V173) and 1 splicing mutation. 16 variants were identified as

## Results

(probably) pathogenic and had a VAF>14%. All 3 variants of unclear significance were minor. Chromosome 17 abnormalities were found in 7 MCL patients with TP53 mutations out of 11 studied. In the FL patients, TP53 mutations were detected in 12 cases (26.7%). Out of 8 missense mutations, 4 were in hotspots p.R175H, p.R248Q, p.R249M, p.R273H. Also in this group, 2 nonsense mutations, 1 splicing mutation, and 1 deletion were observed. Of the 9 variants recognized as (probably) pathogenic, only 1 was minor, as were 2 variants of unclear significance. Only 1 patient out of 6 examined had del17p. All results are presented in Table 1.

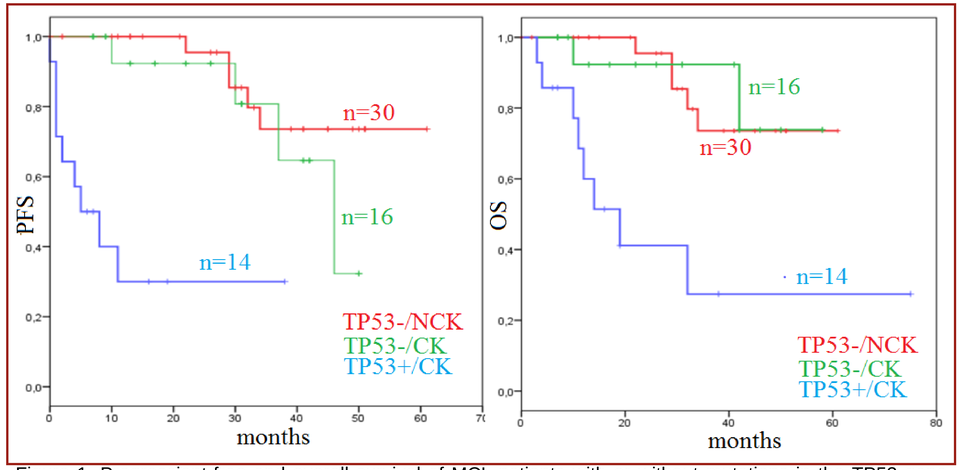



Figure 1. Progressiont-free and overall survival of MCL patients with or without mutations in the TP53 gene and chromosomal abnormalities. (NCK – normal karyotype, CK – complex karyotype, TP53- - no mutations in TP53 gene, TP53+ - mutation in TP53 gene

## Conclusion

The frequency of mutations in the TP53 gene in patients with B-cell lymphomas in our sample is significantly higher than according to the literature data. One can explain this bias by patient selection. A significant portion of DLBCL and FL patients admitted to our center in the state of progression or relapse. Most MCL cases were primary, however, MCL patients with advanced stages of the disease are more often admitted to the our center. At the same time, the occurrence of “hot spots” mutations in MCL and FL is also higher than expected.

The analysis of TP53 gene mutations is extremely important in lymphomas. According to preliminary data from MCL-2016 clinical trial (Russia), allo HSCT and CAR-T therapy are the only treatment options for MCL patients with TP53 gene mutations. Further studies concerning the type of mutations, their allelic load, and their combination with 17th chromosome lesions in association with disease course are on the way.