

Mutation analysis of the tyrosine phosphatase PTPN2 in Hodgkin's lymphoma and T-cell non-Hodgkin's lymphoma

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ABSTRACT

We recently reported deletion of the protein tyrosine phosphatase gene *PTPN2* in T-cell acute lymphoblastic leukemia. Functional analyses confirmed that *PTPN2* acts as classical tumor suppressor repressing the proliferation of T cells, in part through inhibition of JAK/STAT signaling. We investigated the expression of *PTPN2* in leukemia as well as lymphoma cell lines. We identified bi-allelic inactivation of *PTPN2* in the Hodgkin's lymphoma cell line SUP-HD1 which was associated with activation of the JAK/STAT pathway. Subsequent sequence analysis of Hodgkin's lymphoma and T-cell non-Hodgkin's lymphoma identified bi-allelic inactivation of *PTPN2* in 2 out of 39 cases of peripheral T-cell lymphoma not otherwise specified, but not in Hodgkin's lymphoma. These results, together

with our own data on T-cell acute lymphoblastic leukemia, demonstrate that *PTPN2* is a tumor suppressor gene in T-cell malignancies.

Key words: mutation, phosphatase, T-cell NHL, tumor suppressor.

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Introduction

Protein tyrosine phosphatases are important enzymes that control the activity of multiple signaling pathways downstream of cytokine receptors and tyrosine kinases. In agreement with this pivotal function, mutations in tyrosine phosphatases have been associated with the development of cancer. In hematologic malignancies, activating mutations in *PTPN11* have been associated with a set of myeloid malignancies next to precursor B-cell acute lymphoblastic leukemia, while so far inactivation of *PTPN2* has only been identified in T-cell acute lymphoblastic leukemia (T-ALL).¹⁻³

PTPN2 (also known as TC-PTP) is a classical protein tyrosine phosphatase that is highly expressed in the hematopoietic system.^{4,5} In line with its ubiquitous expression pattern, homozygous deletion of *Ptpn2* from the mouse system is fatal and mice succumb rapidly after birth (3-5 weeks). Knockout mice display multiple phenotypic changes including severe defects in the blood system.⁶ Its pivotal role in hematopoiesis and the inflammatory phenotype of *PTPN2* knockout mice together with the identification of cancer associated kinases and transcription factors as direct substrates of *PTPN2*, have pointed to a potential role of *PTPN2* in tumorigenesis and the development of immune diseases.^{7,8}

We have previously identified focal deletions of the *PTPN2* gene (chromosome 18p11) in 6% of T-ALL cases. Functional analysis confirmed *PTPN2* to be a classical tumor suppressor gene repressing proliferation of T cells. Downregulation of *PTPN2* expression provided a proliferation advantage to the leukemic cells due to increased sensitivity to cytokine stimulation and increased activation of the JAK/STAT pathway. In addition, loss of *PTPN2* also had a direct effect on the activation of oncogenic kinases such as NUP214-ABL1, LCK, and mutant JAK1.³

In the current study, we screened a set of lymphoma cell lines for mutations or deletion of *PTPN2* and we sequenced *PTPN2* in Hodgkin's lymphoma (HL) and T-cell non-Hodgkin's lymphoma (T-NHL) samples.

Design and Methods

Patients' samples and cell lines

After obtaining informed consent according to the guidelines of the local ethical committees, a series of 50 Hodgkin's lymphomas (HL) and 69 T-cell non-Hodgkin's lymphomas (T-NHL) were collected from the archives of the Department of Pathology of the University Hospital Leuven and the University of Würzburg. A review of the diagnosis of HL and T-NHL was based on morphology, immunophe-

The online version of this article has a Supplementary Appendix.

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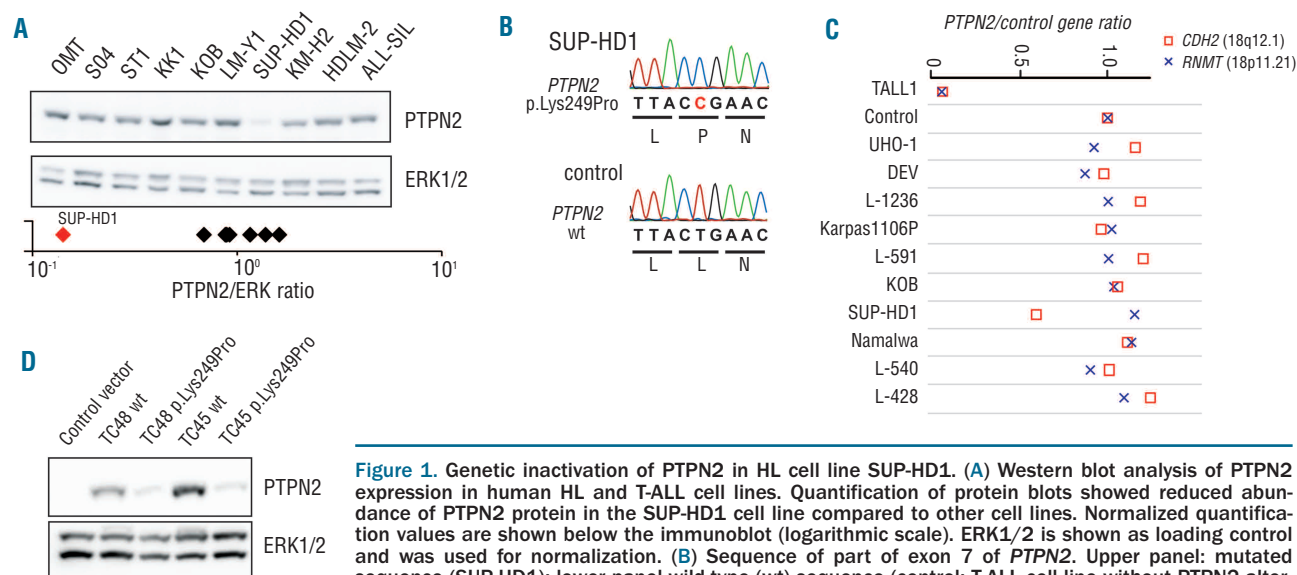


Figure 1. Genetic inactivation of PTPN2 in HL cell line SUP-HD1. (A) Western blot analysis of PTPN2 expression in human HL and T-ALL cell lines. Quantification of protein blots showed reduced abundance of PTPN2 protein in the SUP-HD1 cell line compared to other cell lines. Normalized quantification values are shown below the immunoblot (logarithmic scale). ERK1/2 is shown as loading control and was used for normalization. (B) Sequence of part of exon 7 of PTPN2. Upper panel: mutated sequence (SUP-HD1); lower panel wild-type (wt) sequence (control; T-ALL cell line without PTPN2 alteration). Hemizygous missense mutation resulted in the amino acid substitution p.Lys249Pro. (C) Quantitative PCR analysis of the PTPN2 copy number status in human cell lines (KOB (ATL), Namalwa (Burkitt's lymphoma), Karpas1106P (B-cell lymphoma), all others (HL)) depicted monoallelic loss of PTPN2 in SUP-HD1 cells. Analysis of publically available genomics data of the SUP-HD1 cell line (GSE22208) showed heterozygous loss of a 3.5 Mb region on chromosome 18 including the PTPN2 gene (del(18p)(p11.21p11.21).¹⁴ Primer sets for CDH2 (□, 18q12.1) and RNMT (×, 18p11.21) were used as control genes and all values were normalized to a control. A genomic DNA sample from an individual (TALL1) harboring a homozygous deletion of PTPN2 was included as positive control and has been previously described.³ (D) Western blot analysis of whole cell lysates prepared from Ba/F3 cells stably expressing either human wild-type (wt) or mutated variants (p.Lys249Pro) of indicated PTPN2 isoforms (TC45 and TC48). PTPN2 protein levels were detected with human specific antibody allowing the discrimination between endogenous murine and reconstituted human PTPN2. Ba/F3 cells transfected with the empty vector were used as negative control. Blots were stripped and re-probed with ERK1/2 to ensure equal loading.

notyping and molecular genetic and T-cell gene rearrangement studies, according to the World Health Organization criteria.⁹ Human cell lines were purchased from DSMZ (Braunschweig, Germany) and detailed information can be found at <http://www.dsmz.de>. All cells were cultured under standard conditions as previously described.¹⁰

Sequence analysis of PTPN2

Sequence reactions were performed on genomic DNA. All exons of PTPN2 (with exception of the GC-rich exon 1) were amplified in separate reactions with either specific Sanger sequencing primers (conventional sequence analysis) or amplicon fusion primers (454 deep sequence analysis). Next to the template specific sequence, fusion primers contained a directional titanium primer at the 5'-prime end followed by a multiplex identifier for barcode sample identification. Samples from 8 different patients were mixed and processed for 454 deep sequencing. The 454 sequence readings were analyzed using CLC Genomics Workbench software and were mapped to the human reference sequence (NCBI Build 36.1) using BWA. Variants were called with SAMTools (with a SNP-quality threshold of 20).^{11,12} For conventional sequence analysis of PTPN2 in T-NHL patients and cell lines, PCR amplicons were sent directly for sequencing to the VIB Genetics Service Facility (Antwerp, Belgium). The Mutation Nomenclature guidelines from the Human Genome Variation Society (HGVS) were followed to describe mutations at the cDNA and protein levels.

Transfection, virus production and retroviral transduction

In this study, 293T cells were used for virus production and

transfection experiments to evaluate the activity of identified PTPN2 variants. Twenty-four hours after seed out, cells were transfected using Turbofect™ *in vitro* Transfection Reagent (Fermentas). For virus production, one µg of plasmid DNA was mixed with 1 µg of retroviral envelope vector. Transfection mixture was refreshed 24 h post transfection and harvested another 24 h later. Cells were transduced as previously described.¹⁰ All re-expression experiments were performed using the bicistronic, retroviral vector pRetroX-PTuner (Clontech). Protein expression was induced for 24 h (Shield1 concentration: 500nM) before samples were lysed for protein analysis.³

Results and Discussion

Genetic and functional characterization of PTPN2 in leukemia and lymphoma cell lines

Based on our study of PTPN2 deletions in T-ALL, we sought evidence for the involvement of PTPN2 in the pathogenesis of other hematologic malignancies. We screened a panel of cell lines including T-ALL, adult T-cell leukemia/lymphoma (ATL) and Hodgkin's lymphoma (HL) cell lines for variations in PTPN2 at the protein and DNA level. Among the studied cell lines, the SUP-HD1 Hodgkin's lymphoma cell line displayed very low PTPN2 protein levels (Figure 1A). Subsequent genetic analysis confirmed that the SUP-HD1 cell line harbored biallelic inactivation of PTPN2. We identified deletion of one PTPN2 allele and a missense mutation in exon 7 of the other allele, resulting in a p.Lys249Pro substitution, in the

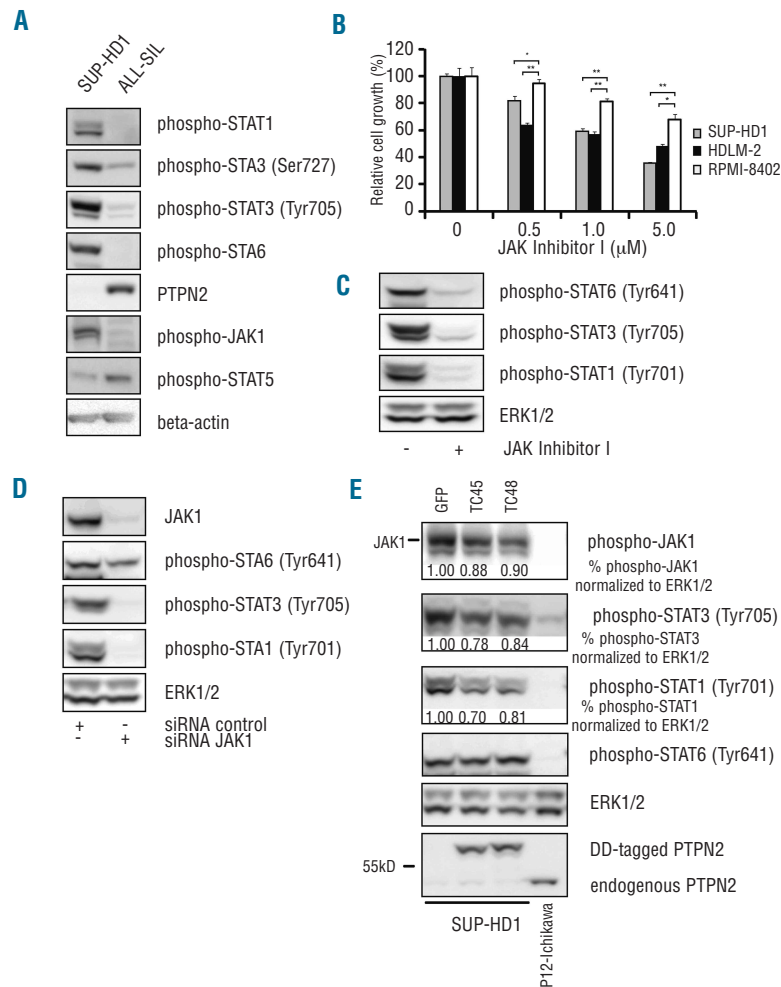


Figure 2. SUP-HD1 cells show constitutive activation of the JAK/STAT pathway. **(A)** Identification of constitutively activated JAK/STAT proteins in SUP-HD1 by Western blot analysis of WCL. T-ALL cell line ALL-SIL is known to harbor no genetic abnormality of the *PTPN2* gene locus and is shown as control.³ **(B)** SUP-HD1 and HDLM-2 cells showed sensitivity to JAK inhibitor I. HDLM-2 cells feature a deletion and mutation in the *SOCS1* gene and *JAK2* amplification causing sensitivity to JAK/STAT inhibition,^{14,17} whereas RPMI-8402 cells display no activated JAK/STAT pathway and were used as negative control. Y axis represents cell growth relative to respective DMSO treated control recorded 72 h after treatment initiation and bars show average \pm s.e.m. n=3; * $P < 0.05$, ** $P < 0.005$. **(C)** Western blot analysis of SUP-HD1 cells upon exposure to JAK inhibitor I (1 μ M) demonstrated dephosphorylation of JAK1 downstream targets STAT1, STAT3 and STAT6. ERK1/2 is shown as loading control. **(D)** Downregulation of JAK1 protein levels using human JAK1 targeting short interfering RNA (siRNA JAK1) resulted in a profound effect on the activation status of STAT family members STAT1 and STAT3 and a slightly minor effect on STAT6 phosphorylation. Equal amount of total protein was assured by detection of ERK1/2. **(E)** Re-expression of inducible forms of PTPN2 (DD-tagged) resulted in decreased JAK1 phosphorylation, and inhibition of STAT1 and STAT3 activation. GFP fused to the destabilizing domain was used as negative control. Normalized quantification values of phosphorylation levels calculated as relative change compared to GFP-transduced control cells are shown below respective blots. T-ALL cell line P12-Ichikawa was included as control with normal PTPN2 protein expression level. Loading control: ERK1/2.

SUP-HD1 cell line (Figure 1B and C). The mutation (Lysine to Proline) occurs in an α -helical region, a substitution known to break the helix. We tested whether the proline mutation indeed caused instability of the PTPN2 protein in both isoforms TC45 and TC48, known to have a different subcellular localization.^{4,13} Both isoforms, wild-type or those containing the p.Lys249Pro mutation, were cloned and stably expressed in the murine pro-B cell line Ba/F3. Our data confirmed that the mutant proteins were expressed at low levels, whereas expression of wild-type isoforms showed comparable levels to endogenous expression observed in other cell lines (Figure 1A and D).

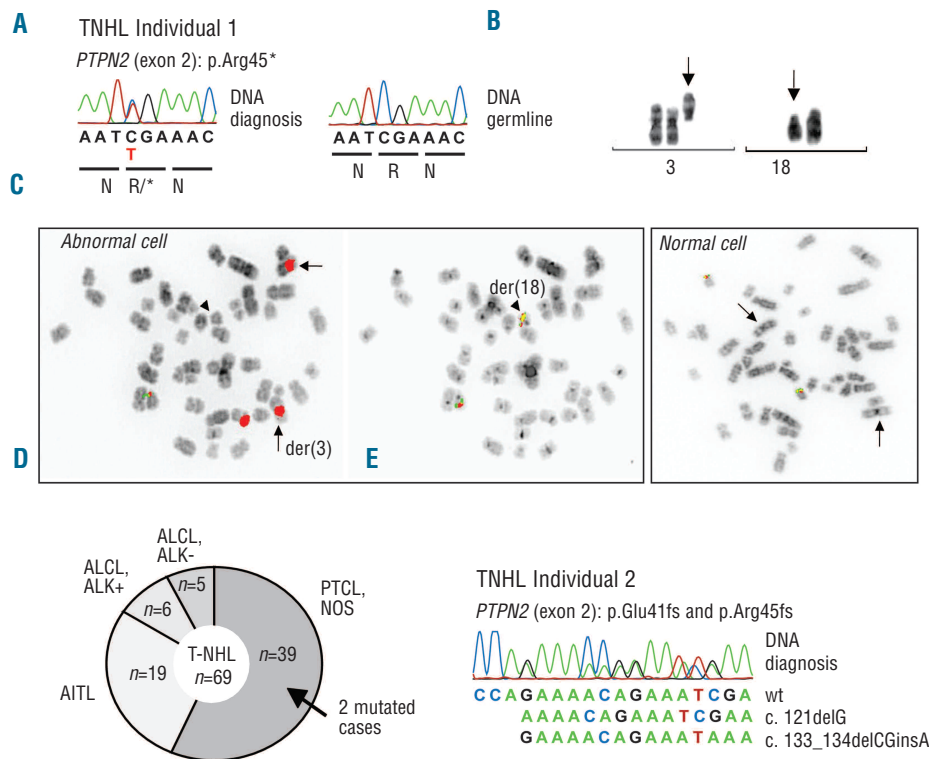
From the other cell lines, HDLM-2 and KM-H2 showed loss of one chromosome 18 (where *PTPN2* is located),¹⁴ but did not have reduced PTPN2 protein expression (Figure 1A). The cell line L-540, a HL cell line derived from a patient with HL of the nodular sclerosis subtype and assigned to the T-cell lineage,¹⁵ showed a heterozygous variation in exon 6 of *PTPN2* (p.Val234Ile). We could not, however, detect decreased phosphatase activity of the PTPN2 p.Val234Ile variant (*Online Supplementary Figure S1*), and this variation was recently identified as a polymorphism present in the normal population (www.ensembl.org). Taken together, these data illustrate that PTPN2 was inactivated in the SUP-HD1 cell line, but not in other lymphoma cell lines.

PTPN2 is a negative regulator of JAK/STAT signaling. In

agreement with low PTPN2 expression in SUP-HD1 cells, these cells showed constitutive phosphorylation of JAK1 and several members of the STAT family (Figure 2A). Treatment of SUP-HD1 cells with a JAK kinase inhibitor resulted in a clear dephosphorylation of all STATs, and a dose dependent inhibition of the proliferation of the SUP-HD1 cells (Figures 2B and C), confirming that SUP-HD1 cells are largely dependent on JAK/STAT signaling for their proliferation. Similarly, siRNA mediated knockdown of JAK1 expression reduced STAT activation (Figure 2D).

To evaluate whether PTPN2 indeed modulates JAK/STAT signaling in SUP-HD1, we re-expressed the PTPN2 isoforms using an inducible retroviral vector system.³ Re-expression of the TC45 or TC48 isoform of PTPN2 diminished JAK1 activation as observed by a slight reduction in JAK1 phosphorylation itself and a more clear effect on the downstream targets STAT1 and STAT3 (Figure 2E). No effect was observed on STAT6 phosphorylation. These data demonstrate that PTPN2 modulates JAK/STAT signaling in the cells, but also suggest that additional signaling proteins upstream of the JAK/STAT pathway are activated that are not negatively regulated by PTPN2. Indeed, JAK2 is known to be over-expressed in SUP-HD1 cells due to high-level 9p24 amplification, but JAK2 is not a direct substrate of PTPN2.¹⁴

In conclusion, we demonstrate that SUP-HD1 cells harbor bi-allelic inactivation of PTPN2, which causes activa-



FISH was performed with gene locus specific dual-color FOSMID probes for *PTPN2*,³ with centromeric satellite DNA probes for chromosome 3 (CEP3) and with *BCL2* Dual-Color break apart probes for *BCL2/18q21* (RP11-215A20, SpectrumGreen; RP11-95C15, SpectrumOrange). (D) Schematic overview of the T-NHL cohort (n=69) analyzed in this study. Both subjects harboring mutations of *PTPN2* belong to the PTCL, NOS subgroup. PTCL: peripheral T-cell lymphoma; NOS: not otherwise specified; AILT: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large-cell lymphoma; ALK+: ALK-positive; ALK-: ALK-negative. (E) Sequence of part of exon 2 of *PTPN2* (T-NHL individual 2). Double peaks resulted from the presence of two mutations on the different alleles (confirmed by cloning of PCR products and subsequent sequence analysis). The wild-type coding sequence is shown below the electropherogram.

tion of JAK1 and several STAT proteins, required for proliferation of the SUP-HD1 cells. Our data also suggest that additional genetic lesions present in SUP-HD1 cells cooperate with loss of *PTPN2* to activate the JAK/STAT signaling pathways.¹⁴

Sequence analysis of *PTPN2* in HL and T-NHL

STAT activation has been described in HL and partially attributed to the presence of JAK2 amplification and mutations in SOCS genes.^{16,17} Since *PTPN2* represents a phosphatase for both JAKs and STATs, and since *PTPN2* was found to be mutated in HL cell line, we investigated whether mutation of *PTPN2* could be responsible for the deregulation of the JAK/STAT signaling cascade in HL.^{8,18} We selected a cohort of HL samples (10 nodular lymphocyte-predominant HL, 27 nodular sclerosis cHL, 6 mixed-cellularity cHL, 5 lymphocyte-rich cHL, and 2 lymphocyte-depleted cHL) for a comprehensive sequence analysis of the coding region of *PTPN2* using the 454 amplicon deep sequencing technology (Roche 454 GS-FLX). This technology was chosen because HL samples usually carry only a very low percentage of clonal Hodgkin's and Reed Sternberg cells; typically less than 1%. Even though in this way we achieved sufficient coverage of all exons to be able to detect mutations in such a low percentage of cells (Online Supplementary Table S1), we identified only a single missense mutation located in exon 2 of *PTPN2* (c.89A>G). The percentage of readings carrying the muta-

tion was in the expected range: 54 of 3,659 readings, corresponding to 3% of diploid cells carrying a heterozygous mutation. Readings carrying the mutation were equally present in both forward and reverse readings. The base pair alteration A>G replaced a histidine at position 30 by an arginine (p.His30Arg). Even though substituted amino acids are very different, no functional consequence was found in our *in vitro* assays. Transient expressed His30Arg mutant (239T cells) effectively dephosphorylated a co-transfected constitutively active JAK1 mutant (p.Ala634Asp), suggesting that this variation in *PTPN2* is unlikely to be an inactivating mutation (Online Supplementary Figure S1).

Surprisingly, we also identified a nonsense mutation in approximately 50% of the cells in one of the HL samples. This sample carried two cytogenetically unrelated abnormal clones of distinct disease origins, T-NHL (peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)) and classical HL (mixed-cellularity cHL). Genetic characterization of this case identified complete inactivation of the *PTPN2* gene in the T-cell lymphoma clone. The 454 sequence analysis showed a nonsense mutation located in exon 2 (c.133G>A, p.Arg45*) of *PTPN2* in about 50% of the cells, which was subsequently confirmed by Sanger sequencing (Figure 3A). Moreover, fluorescence *in situ* hybridization (FISH) analysis showed loss of the second copy due to deletion of the short arm of chromosome 18 (18p) in the T-NHL clone (Figure 3B and C). These data

document a bi-allelic inactivation of *PTPN2* in the T-NHL clone in this patient.

To determine whether *PTPN2* inactivation is a recurrent event in T-NHL, we sequenced *PTPN2* in lymph node biopsies obtained from 69 T-NHL (Figure 3D and *Online Supplementary Table S2*). In one additional sample obtained from a patient with PTCL, NOS was identified with bi-allelic inactivation of *PTPN2*. This lymphoma was characterized by the presence of two frameshift truncating mutations in exon 2 (p.Glu41fs and p.Arg45fs, Figure 3E) resulting in bi-allelic inactivation of *PTPN2*. Another T-NHL sample had a missense mutation in one allele of *PTPN2* (c.1111A>G, p.Arg371Gly in exon 9 of *PTPN2*), but functional assays showed normal phosphatase activity of the *PTPN2* Arg371Gly protein (*Online Supplementary Figure S4*). Based on this, we conclude that the p.Arg371Gly variation is either a passenger mutation or a rare polymorphism. No other variations were identified, but several samples had low tumor cell content, making detection of the mutations more difficult with Sanger

sequencing (*Online Supplementary Table S2*). In total, 2 of 69 T-NHL had *PTPN2* mutations, with both cases belonging to the PTCL, NOS subgroup (2 of 39 (5%) PTCL, NOS cases) (Figure 3D).

In conclusion, we have previously identified *PTPN2* as a tumor suppressor gene in T-ALL, where *PTPN2* is deleted in 6% of cases.³ In this study, we identified inactivation of *PTPN2* by nonsense mutations in 5% of PTCL/NOS cases. These data further demonstrate the tumor suppressor activity of *PTPN2* in T-cell malignancies.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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