

## Brief report

Recurrent *TET2* mutations in peripheral T-cell lymphomas correlate with T<sub>FH</sub>-like features and adverse clinical parameters

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**Inactivating mutations of the *Ten-Eleven Translocation 2 (TET2)* gene were first identified in myeloid malignancies and more recently in peripheral T-cell lymphomas (PTCLs). In the present study, we investigated the presence of *TET2* coding sequence mutations and their clinical relevance in a large cohort of 190 PTCL patients. *TET2* mutations were identified in 40 of 86 (47%) cases of angioimmunoblastic**

**T-cell lymphoma (AITL) and in 22 of 58 (38%) cases of peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), but were absent in all other PTCL entities, with the exception of 2 of 10 cases of enteropathy-associated T-cell lymphoma. Among PTCL-NOS, a heterogeneous group of lymphoma-comprising cases likely to derive from Th follicular (T<sub>FH</sub>) cells similarly to AITL, *TET2* mutations were more frequent when PTCL-**

**NOS expressed T<sub>FH</sub> markers and/or had features reminiscent of AITL (58% vs 24%, *P* = .01). In the AITL and PTCL-NOS subgroups, *TET2* mutations were associated with advanced-stage disease, thrombocytopenia, high International Prognostic Index scores, and a shorter progression-free survival. (*Blood*. 2012;120(7):1466-1469)**

## Introduction

Inactivating mutations of the *Ten-Eleven Translocation 2 (TET2)* gene were first identified in myeloid malignancies.<sup>1,2</sup> *TET2* encodes a 2 oxoglutarate/Fe<sup>2+</sup>-dependent oxygenase that catalyses the oxidation of 5-methylcytosine to 5-hydroxymethylcytosine,<sup>3-5</sup> and its inactivation in mice results in expansion of the hematopoietic progenitor cells and in pleiotropic abnormalities affecting both myeloid and lymphoid lineages.<sup>6-8</sup> Recently, *TET2* mutations have been reported in human lymphomas with a higher frequency in T cell- than B cell-derived neoplasms (12% vs 2%).<sup>7,9</sup> Among peripheral T-cell lymphomas (PTCLs), the mutations identified were almost exclusively in the angioimmunoblastic T-cell lymphoma (AITL) and PTCL, not otherwise specified (PTCL-NOS) subtypes, the 2 most common PTCL entities in Western countries.<sup>10</sup> These mutations were demonstrated in tumor cells, with evidence that they may be acquired either in early CD34<sup>+</sup> progenitors or at later steps of lymphoid development.<sup>7</sup>

In the present study, we extended the analysis of *TET2* mutations to a larger, independent series of PTCL samples to correlate mutational status with pathologic features and clinical outcome.

## Methods

## Patients and tumor samples

A series of 190 PTCL patients with frozen lymphoma samples available at diagnosis were selected within the framework of a multicentric T-cell lymphoma consortium (Tenomic). The study was approved by the local ethic committee (CPP Ile de France IX 08-009). Clinical data were collected retrospectively. All cases were reviewed and a consensus diagnosis was made at a multihead microscope by 3 hematopathologists according to the criteria of the 2008 World Health Organization classification.<sup>11</sup>

Within PTCL-NOS, a group without typical morphology of AITL but expressing Th follicular (T<sub>FH</sub>) cell markers (ie, PD1, BCL6, and/or CXCL13) and/or having some other features reminiscent of AITL (ie, the presence of 2 of the following criteria: CD20<sup>+</sup> large B cells, EBV-encoded small RNAs (EBER)<sup>+</sup> cells, CD21 and/or CD23 follicular dendritic cell expansion, or CD10 expression), was designated "T<sub>FH</sub>-like" PTCL-NOS.

*TET2* genotyping

DNA was extracted from several frozen tissue sections with morphologic control using QIAamp DNA mini Kit (QIAGEN) and an aliquot amplified by linear amplification. Analysis of the coding sequences of *TET2* was

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**Table 1. TET2 mutations in the different PTCL entities**

| PTCL entity           | TET2 mutation |    | %  |
|-----------------------|---------------|----|----|
|                       | n             | n  |    |
| AITL                  | 86            | 40 | 47 |
| <b>PTCL NOS*</b>      | 58            | 22 | 38 |
| T <sub>FH</sub> -like | 24            | 14 | 58 |
| Others                | 34            | 8  | 24 |
| ALCL                  | 18            | 0  | 0  |
| EATL*                 | 10            | 2  | 20 |
| Extranodal NK/T       | 12            | 0  | 0  |
| HSTL                  | 6             | 0  | 0  |
| Total                 | 190           | 64 | 34 |

ALCL indicates anaplastic large-cell lymphoma; HSTL, hepatosplenic T-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; and extranodal NK/T, extranodal NK/T-cell lymphoma, nasal-type.

\*TET2 mutations were found in 3 extranodal tissue samples (1 skin, 1 spleen, and 1 liver) diagnosed as PTCL-NOS and in 2 intestinal tissue samples diagnosed as EATL.

performed by direct sequencing of the PCR fragments and candidate mutations were confirmed by sequencing, an independent PCR product was amplified from native genomic DNA as described previously.<sup>7</sup> Frameshift, nonsense mutations, mutations in splice site, and missense mutations (only those affecting the evolutionary conserved regions of the protein) were considered. Single nucleotide polymorphisms either published previously or recorded in the National Center for Biotechnology Information Single Nucleotide Polymorphism database were excluded.

### Statistical analysis

Continuous and dichotomic variables were compared with the Wilcoxon sum-rank test or Cochran Armitage and  $\chi^2$  or Fisher exact tests. Overall and progression-free survival (PFS) were estimated using the Kaplan-Meier method and compared with the log-rank test. All tests were 2-sided and  $P < .05$  was considered significant.

## Results and discussion

TET2 mutations were found in 64 of 190 samples at diagnosis (34%). The frequency of TET2 mutations was extremely variable according to the diagnosis category. TET2 mutations were present in 40 of 86 (47%) cases of AITL, in 22 of 58 (38%) cases of PTCL-NOS, and in 2 of 10 (20%) cases of enteropathy-associated T-cell lymphoma. In contrast, no mutation was observed in any of the 18 anaplastic large-cell lymphomas (12 ALK-positive and 6 ALK-negative), the 12 extranodal NK/T lymphomas, nasal-type, or the 6 hepatosplenic T-cell lymphomas tested (Table 1).

Interestingly, and in accordance with previous results,<sup>7</sup> the highest frequency of mutations was found in AITL, which is thought to derive from T<sub>FH</sub> cells normally present in germinal centers.<sup>12-14</sup> Within the large group of PTCL-NOS, it is also now recognized that a subset has “T<sub>FH</sub>-like” features in the form of a molecular profile bearing imprints of the T<sub>FH</sub> cell signature, the expression of T<sub>FH</sub>-associated molecules,<sup>15-17</sup> and/or overlapping pathologic features.<sup>16</sup> Therefore, we questioned whether TET2 mutations were correlated with T<sub>FH</sub>-like features in PTCL-NOS. Among the 58 PTCL-NOS in our series, 24 were classified as “T<sub>FH</sub>-like” PTCL-NOS. TET2 mutations were present in 14 of 24 (58%) of the T<sub>FH</sub>-like PTCL subgroup compared with 8 of 34 (22%) of those lacking AITL features and T<sub>FH</sub>-markers. Therefore, TET2 mutations in PTCL appear to be correlated with T<sub>FH</sub> derivation (ie, they occur at a higher frequency in AITL and T<sub>FH</sub>-like PTCL-NOS), than in non-T<sub>FH</sub>-like PTCL-NOS and other PTCL entities (49% vs 12.5%,  $P < .0001$ ).

Among the 64 PTCL patients with TET2 mutations, 37 had single mutations and 27 had 2 or more mutations. TET2 mutations were mainly insertions/deletions generating frameshift and nonsense mutations similar to those found in myeloid malignancies (supplemental Table 1, available on the Blood Web site; see the Supplemental Materials link at the top of the online article). Eighteen of 19 missense mutations were predicted as probably damaging by the Polyphen-2 software (<http://genetics.bwh.harvard.edu/pph2/>) and one as possibly damaging. For 3 mutated patients with available biopsy at relapse, an identical pattern of TET2 mutations was found in paired samples (supplemental Figure 1), suggesting that TET2 mutations are associated with the main driving clone.

When focusing on AITL and PTCL-NOS patients ( $n = 144$ ), 62 patients had TET2 mutations and 82 were TET2 wild-type. Clinical factors associated with TET2 mutated status (Table 2 and supplemental Figure 2) were advanced-stage disease ( $P = .02$ ), increased number of involved extranodal sites ( $P = .017$ ), presence of B symptoms ( $P = .02$ ), thrombocytopenia ( $P = .04$ ), high International Prognosis Index ( $P = .028$ ) and Prognosis Model for PTCL-NOS<sup>18</sup> ( $P = .025$ ) scores, indicating that TET2 mutations are associated with adverse clinical parameters at presentation. Despite incomplete clinical data and heterogeneous therapies in this multicentric retrospective cohort, anthracycline-based chemotherapy was the most common regimen in both the mutated and nonmutated groups (73% and 70%, respectively). TET2-mutated patients with AITL or PTCL-NOS appeared to have a shorter PFS ( $P = .04$ ) than TET2 wild-type patients, but no significant difference in overall survival was observed ( $P = .1$ ; supplemental Figure 2). The association among TET2 mutations, poor prognosis clinical parameters, and outcome was even stronger when focusing on the group of patients with AITL and T<sub>FH</sub>-like PTCL-NOS. In this group, TET2 mutations were associated with a shorter PFS ( $P = .022$ ) and a trend to a shorter overall survival ( $P = .058$ ; supplemental Table 2 and supplemental Figure 3).

We recently reported recurrent IDH2 mutations in AITL.<sup>19</sup> These mutations alter IDH enzymatic function and may result in the functional inactivation of TET protein activity.<sup>20</sup> In acute myeloid leukemia, IDH and TET2 mutations are reported to be mutually exclusive.<sup>20</sup> Of the 31 AITL samples in the present study also analyzed for IDH2 mutations,<sup>19</sup> 6 had both IDH2 and TET2 mutations, 2 were IDH2 mutated/TET2 wild-type, and 10 were TET2 mutated/IDH2 wild-type, indicating that both mutations can accumulate in AITL. Ultimately, both IDH2 and TET2 mutations, which are recurrent in AITL and in T<sub>FH</sub>-derived PTCL, may deregulate the control of chromatin structure. This situation may be reminiscent of that observed in B-cell lymphomas, in which mutations of several genes involving epigenetic changes and chromatin remodeling, such as CREBBP, EP300,<sup>21</sup> EZH2,<sup>22</sup> MLL2, or MEF2B,<sup>23</sup> have been described recently.

In addition to similarities in their ontogeny, AITLs and a subset of T<sub>FH</sub>-like PTCLs share common oncogenic alterations, including TET2 abnormalities, further supporting their close relationship. The strong association among TET2 mutations, AITL, and T<sub>FH</sub>-like PTCL may provide molecular rationale to merge together AITL and PTCL-NOS-expressing T<sub>FH</sub> markers, as has been suggested previously,<sup>15-16</sup> and to refine the spectrum of AITL. Overall, the identification of frequent TET2 mutations in AITL and other T<sub>FH</sub>-related PTCLs extends the importance of epigenetic alterations in lymphomagenesis. The results of the present study suggest that in these diseases, in which conventional chemotherapies are ineffective<sup>24</sup> in most patients, the use of new agents such as demethylating agents should be considered.

**Table 2. Clinical data according to *TET2* status in AITL and PTCL-NOS patients**

| n   | <i>TET2</i> mutation |     | <i>TET2</i> wild-type |     | P       |
|---|----------------------|-----|-----------------------|-----|---------|
|   | 62                   |     | 82                    |     |         |
| <b>Sex</b>  |                      |     |                       |     |         |
| Male  | 38                   | 61% | 43                    | 52% | .18*    |
| Female  | 24                   | 39% | 39                    | 48% |         |
| Median age, y   | 67                   |     | 65                    |     | .3†     |
| <b>Stage</b>  |                      |     |                       |     |         |
| 1   | 0                    | 0%  | 4                     | 5%  | .028‡   |
| 2   | 0                    | 0%  | 3                     | 4%  |         |
| 3   | 11                   | 21% | 17                    | 23% |         |
| 4   | 42                   | 79% | 49                    | 67% |         |
| Median no. of extranodal localizations                    | 2                    |     | 1                     |     | .056†   |
| <b>Lactate dehydrogenase</b>                              |                      |     |                       |     |         |
| Elevated  | 41                   | 76% | 46                    | 65% | .24*    |
| Normal  | 13                   | 24% | 25                    | 35% |         |
| <b>Hemoglobin</b>   |                      |     |                       |     |         |
| ≥ 10 g/dL   | 35                   | 74% | 33                    | 60% | .14*    |
| < 10 g/dL   | 12                   | 26% | 22                    | 40% |         |
| <b>Platelet count</b>                                     |                      |     |                       |     |         |
| ≥ 150 000/mm <sup>3</sup>                                 | 34                   | 72% | 48                    | 89% | .04*    |
| < 150 000/mm <sup>3</sup>                                 | 13                   | 28% | 6                     | 11% |         |
| <b>Direct Coombs test</b>                                 |                      |     |                       |     |         |
| Positive  | 14                   | 52% | 13                    | 43% | .6*     |
| Negative  | 13                   | 48% | 17                    | 57% |         |
| <b>Hypergammaglobulinemia</b>                             |                      |     |                       |     |         |
| Yes   | 11                   | 32% | 12                    | 33% | > .999* |
| No  | 23                   | 68% | 24                    | 67% |         |
| <b>B symptoms</b>   |                      |     |                       |     |         |
| Yes   | 40                   | 78% | 38                    | 58% | .028*   |
| No  | 11                   | 22% | 27                    | 42% |         |
| <b>Performance status</b>                                 |                      |     |                       |     |         |
| 0-1   | 22                   | 44% | 41                    | 62% | .06*    |
| 2-4   | 28                   | 56% | 25                    | 38% |         |
| <b>International Prognosis Index score</b>                |                      |     |                       |     |         |
| 0   | 0                    | 0%  | 4                     | 6%  | .0062†  |
| 1   | 2                    | 4%  | 4                     | 6%  |         |
| 2   | 8                    | 16% | 11                    | 16% |         |
| 3   | 10                   | 20% | 22                    | 33% |         |
| 4   | 19                   | 37% | 23                    | 34% |         |
| 5   | 12                   | 24% | 3                     | 4%  |         |
| <b>Prognosis Model for PTCL<sup>18</sup></b>              |                      |     |                       |     |         |
| 0   | 2                    | 5%  | 4                     | 9%  | .0045†  |
| 1   | 3                    | 7%  | 11                    | 24% |         |
| 2   | 9                    | 21% | 13                    | 29% |         |
| 3   | 18                   | 43% | 13                    | 29% |         |
| 4   | 10                   | 24% | 4                     | 9%  |         |
| <b>Treatment</b>  |                      |     |                       |     |         |
| Anthracycline-based regimen                               | 37                   | 69% | 40                    | 58% | .5*     |
| Anthracycline-based regimen and frontline transplantation | 2                    | 4%  | 8                     | 12% |         |
| Other combination of chemotherapy                         | 7                    | 13% | 8                     | 12% |         |
| Single-agent chemotherapy                                 | 5                    | 9%  | 7                     | 10% |         |
| Palliative treatment                                      | 3                    | 6%  | 6                     | 9%  |         |
| 5-y overall survival                                      | 28%                  |     | 31%                   |     | .11§    |
| 5-y PFS   | 10%                  |     | 21%                   |     | .047§   |

\*Fisher exact test.

†Wilcoxon sum-rank test.

‡Cochran Armitage test.

§Log-rank test.

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## Authorship

Contribution: O.B., C.B., and P.G. designed the research; F.L., P.G., L.d.L., and M.P. analyzed and interpreted the results; L.C., T.M.,

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