Co-existence of PHF6 and NOTCH1 mutations in adult T-cell acute lymphoblastic leukemia

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Abstract. T-cell acute lymphoblastic leukemia (T-ALL) results from the collaboration of multiple genetic abnormalities in the transformation of T-cell progenitors. Plant homeodomain finger protein 6 (PHF6) has recently been established as a key tumor suppressor, which is mutated in T-ALL; however, the clinical significance of PHF6 mutations has not been fully determined in adult T-ALL. In the present study, amplification of the PHF6 exons was performed, followed by DNA sequencing to identify the genomic mutations and examine the expression of PHF6 in adult patients with T-ALL. The correlation between PHF6 mutations and clinical features was also analyzed using a χ² test, and between PHF6 mutations and survival curve using the Kaplan-Meier methods. PHF6 mutations were detected in 27.1% of the Chinese adults with T-ALL (16/59), 10 of which were found to be novel mutations. A significantly lower expression level of PHF6 was observed in T-ALL patients with PHF6 mutations compared with those without mutations. Of the observed mutations in PHF6, 6/16 were frame-shift mutations, indicating a PHF6 dysfunction in those patients. Of note, PHF6 mutations were found to be significantly associated with older age, lower hemoglobin levels, higher frequency of CD13 positivity and higher incidence of splenomegaly or lymphadenopathy. Furthermore, PHF6 mutations were found to be significantly correlated with Notch homolog 1, translocation-associated (Drosophila) (NOTCH1) mutations. The patients with T-ALL with co-existence of the two mutations had a significantly shorter event-free survival and a poor prognosis. The present results indicated that PHF6 is inactivated in adult T-ALL, due to its low expression and mutations. The present data indicated the synergistic effect of PHF6 and NOTCH1 mutations, as well as their co-existence, on the oncogenesis of adult T-ALL, and their potential as a prognostic marker for the disease.

Introduction

T-cell acute lymphoblastic leukemia (T-ALL) comprises an aggressive malignancy, in which multiple genetic abnormalities collaborate in the transformation of T-cell progenitors. Abundant genetic alterations in T-ALL have been identified by whole-genome sequencing and DNA copy number analysis of candidate genes, including deletions and/or sequence mutations of the cyclin-dependent kinase inhibitor 2A/B, lymphoid enhancer binding factor 1, Notch homolog 1, translocation-associated (Drosophila) (NOTCH1), F-box and WD repeat domain containing 7 (FBXW7), phosphatase and tensin homolog (PTEN), neuroblastoma RAS viral oncogene homolog, Wilms tumor 1, plant homeodomain finger protein 6 (PHF6), interleukin 7 receptor and runt related transcription factor 1 genes (1-4).

PHF6 encodes a PHD factor containing four nuclear localization signals and two PHD zinc finger domains, and has a proposed role in the control of gene expression (5). Inactivating mutations of the PHF6 gene were originally found to be associated with a form of syndromic X-linked mental retardation, Börjeson-Forssman-Lehmann syndrome (6). In addition, PHF6 has been identified as a novel key tumor suppressor gene in T-ALL. PHF6 mutations were detected...
in adult and pediatric patients with T-ALL, as well as also in adults with acute myeloid leukemia (7,8); however, the association between PHF6 mutations and clinical outcome in these patients has not been fully determined.

**NOTCH1** mutations have been shown to play an important role in the pathogenesis of T-ALL (9); however, the clinical significance of the co-existence of **NOTCH1** and PHF6 mutations (PHF6<sup>mut</sup>NOTCH1<sup>mut</sup>) has not been sufficiently explored. The present study demonstrated the characteristics of PHF6 mutations in adult Chinese patients with T-ALL, with 10/16 of the detected mutations being reported for the first time. In addition, the correlation between PHF6<sup>mut</sup>NOTCH1<sup>mut</sup> co-existence in T-ALL and event-free survival (EFS) was explored and found to be significant in this cohort of adult T-ALL patients.

**Materials and methods**

**Patients and samples.** Bone marrow (BM) samples were collected from 79 adult patients (age, 14–62 years) with ALL (57 males and 22 females; 59 T-ALL and 20 B-ALL samples) at the First Affiliated Hospital of Nanjing Medical University (Nanjing, China) between May 2008 and 2014. The diagnosis of ALL was made based on the molecular, immunophenotypic, morphologic and cytogenetic criteria established by the World Health Organization Diagnosis and Classification of ALL (2008) (10). Informed consent was obtained from all individuals prior to their participation to the study, in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of Nanjing Medical University.

**Mutation analysis of PHF6, NOTCH1, FBXW7, PTEN and Janus kinase 1 (JAK1).** Mutation analysis was performed for PHF6 exons 2-10. Genomic DNA was isolated with a QIAamp DNA Blood Mini kit (Qiagen Inc., Valencia, CA, USA) following the manufacturer's instructions. DNA fragments spanning the above PHF6 exons were amplified by polymerase chain reaction (PCR) using AmpliTaq Gold (Applied Biosystems, Thermo Fisher Scientific, Inc., Waltham, MA, USA) and exon-specific primers (5). DNA sequencing was performed on the purified PCR products. In addition, exon 26/N-terminal region of the heterodimerization domain (HD-N), exon 27/C-terminal region of the heterodimerization domain (HD-C), exon 28 and exon 34/proline-glutamic acid-serine-threonine (PEST) domain of NOTCH1 were amplified for mutation screening, as previously described (9). Exons in FBXW7, PTEN and JAK1 were also screened as previously reported (11,12).

**Cytogenetic and molecular analysis.** Conventional cytogenetic analysis was performed using unstimulated short-term cultures at the time of diagnosis, according to the International System for Human Cytogenetic Nomenclature recommendations (13). For each sample, ≥20 BM metaphase cells were analyzed.

Immunophenotypic analysis was performed by flow cytometry on fresh BM samples. The cell-surface antigen was considered positive when fluorescence intensity of ≥20% of cells exceeded the fluorescence of negative control.

**Statistical analysis.** Patients were divided into high or low PHF6 expression groups [the median (0.0020925) was used as cut-off value based on SPSS 17.0]. For quantitative parameters, the overall differences between the cohorts were evaluated using the Mann-Whitney U-test. For qualitative parameters, the overall group differences were analyzed using the χ² test. Survival analysis was calculated using the Kaplan-Meier method. Experimental data are presented as the mean ± standard error. Determinations of statistical significance were performed using a Student t-test for comparisons of two groups or using analysis of variance (ANOVA) for comparing multiple groups. Statistical analysis was performed using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). P<0.05 was considered to indicate a statistically significant difference.

**Results**

**PHF6 mutations in adult T-ALL.** PHF6 mutations were detected in 27.1% of the Chinese adults with T-ALL (16/59). The identified mutations located in exons 2 and 4-10. The most common locations for mutations were in exon 9 and exon 8, in which the mutation rate reached 25.0 and 18.8%, respectively. The majority of the mutations detected were nonsense mutations (7/16, 43.8%), followed by insertion (4/16, 25.0%) and missense mutations (3/16, 18.75%), a deletion (1/16, 6.3%), and insertion/deletion mutations (1/16, 6.3%) (Fig. 1 and Table I). No PHF6 mutations were identified in the 20 DNA samples from patients with B-ALL (data not shown), suggesting that PHF6 mutations in lymphoid tumors could be restricted to T-ALL. Of note, 10/16 (62.5%) PHF6 mutations identified in the present study were novel mutations (Table I). In addition, 6/16 (37.5%) mutations were frame-shift mutations, which may result in the deletion of the gene.

**PHF6 expression and its association with mutations.** PHF6 mRNA expression was detected in 46 patients whose cDNA samples were available. The PHF6 expression was divided into high and low expression groups (G1-2 vs. G3-4). A significant correlation was observed between low PHF6 expression levels and high frequency of splenomegaly and lymphadenopathy in adult T-ALL (73.9% (17/23) vs. 37.5% (9/24) (P=0.012) and 69.6 (16/23) vs. 29.2% (7/24) (P=0.006), respectively) (Fig. 2), suggesting that low PHF6 expression levels may be associated with the markers of leukemic cell proliferation, which involved extramedullary infiltration in T-ALL. Furthermore, it was observed that PHF6 expression was significantly lower in patients with T-ALL with PHF6 mutations, as compared with those with PHF6 wild-type (WT) (0.00423 vs. 0.06464; P=0.035) (Fig. 3), which further indicated PHF6 mutations could result in loss of function mutations.

**Cooperative genetic lesions of PHF6 mutations in adult T-ALL.** The mutations in NOTCH1, FBXW7, PTEN and JAK1 were also screened in this cohort of patients with T-ALL. It was found that the frequency of PHF6<sup>mut</sup>NOTCH1<sup>mut</sup> co-existence was significantly higher in patients with PHF6 mutations than in those with PHF6 WT (75.0 vs. 44.2; P=0.035), suggesting an association between PHF6 and NOTCH1 mutations in this cohort (Table II). No significant associations were observed between PHF6 and FBXW7, PTEN or JAK1 mutations (Table II).

The domains involving PHF6<sup>mut</sup>NOTCH1<sup>mut</sup> co-existence were further analyzed. The most commonly mutated domains...
in NOTCH1 co-existing with PHF6 mutations in same patient were the HD-N domain (6/12, 50.0%), followed by HD-C (2/12, 16.7%), PEST (2/12, 16.7%), HD-C + PEST (1/12, 8.3%) and HD-N + HD-C 1/12 (8.3%) (Table III). These data indicated that the HD domain (particularly the HD-N) of NOTCH1 may contribute to the synergistic oncogenic effect of the two genes.

### Table I. Plant homeodomain finger protein 6 mutations in adult T‑cell acute lymphoblastic leukemia.

| Patient ID | Mutation (nucleotide) | Exon | Type of mutation | Mutation (amino acid) | Previously reported |
|------------|-----------------------|------|------------------|------------------------|-------------------|
| PHF6mu 1#  | c.631A>T              | 7    | Nonsense         | p.K211X                | N                 |
| PHF6mu 2#  | c.479_480insA         | 6    | Frame-shift      | p.K161fs               | N                 |
| PHF6mu 3#  | c.820C>T              | 8    | Nonsense         | p.R274X                | Y                 |
| PHF6mu 4#  | c.93_94insG+94_95insCTA | 2   | Frame-shift      | p.L322fs               | N                 |
| PHF6mu 5#  | c.517A>T              | 6    | Nonsense         | p.K173X                | N                 |
| PHF6mu 6#  | c.821G>A              | 8    | Missense         | p.R274Q                | Y                 |
| PHF6mu 7#  | c.731_732delTG         | 8   | Frame-shift      | p.L244fs               | N                 |
| PHF6mu 8#  | c.955C>T              | 9    | Nonsense         | p.R319X                | Y                 |
| PHF6mu 9#  | c.385C>T              | 5    | Nonsense         | p.R129X                | Y                 |
| PHF6mu 10# | c.346C>T              | 4    | Nonsense         | p.R116X                | Y                 |
| PHF6mu 11# | c.134delG+insCC        | 2   | Frame-shift      | p.C45fs                | N                 |
| PHF6mu 12# | c.586_587insA         | 7    | Frame-shift      | p.R196 K               | N                 |
| PHF6mu 13# | c.971T>C              | 10   | Missense         | p.L324P                | N                 |
| PHF6mu 14# | c.957_958insGT        | 9    | Frame-shift      | p.G320fs               | N                 |
| PHF6mu 15# | c.903C>A              | 9    | Nonsense         | p.Y301X                | Y                 |
| PHF6mu 16# | c.905A>C              | 9    | Missense         | p.H302P                | N                 |

N, no; Y, yes.

Figure 1. Representative DNA sequencing chromatograms of T‑cell acute lymphoblastic leukemia genomic DNA samples showing mutations in exons 2, 4, 6 and 10 of PHF6. PHF6, plant homeodomain finger protein 6; WT, wild‑type.
Correlation of PHF6 mutations with clinical features. The association between PHF6 mutations and clinical characteristics was analyzed in the patients with T-ALL. No gender differences were observed in the incidence of PHF6 mutations in this cohort of adult Chinese patients with T-ALL.
Table III. Correlation of PHF6 mutations with NOTCH1 mutations in adult T-cell acute lymphoblastic leukemia.

| Patient ID | PHF6 mutations | NOTCH1 mutations |
|------------|----------------|------------------|
|            | Nucleotide     | Exon | Amino acid | Nucleotide | Exon | Amino acid | Domain |
| PHF6mu 1#  | c.631A>T       | 7    | p.K211X    | c.7355C>A  | 34   | p.A2452E   | PEST    |
| PHF6mu 2#  | c.479_480insA  | 6    | p.K161fs   | c.4732_4734delGTG | 26 | p.V1578delV | HD-N    |
| PHF6mu 4#  | c.93_94insG+94_95insCTA | 2 | p.L32fs | c.5126T>C  | 27   | p.L1709P   | HD-C    |
| PHF6mu 6#  | c.821G>A       | 8    | p.R274Q    | c.4815_4817delinsAGC | 26 | p.F1606AGGD | HD-N    |
| PHF6mu 7#  | c.821G>A       | 8    | p.R274Q    | c.7541_7542insG    | 26 | p.E2515fs’1 | HD-N    |
| PHF6mu 8#  | c.955C>T       | 9    | p.R319X    | c.4799T>A  | 26   | p.L1600Q   | HD-N    |
| PHF6mu 9#  | c.385C>T       | 5    | p.R129X    | c.4721T>C  | 26   | p.L1574P   | HD-N    |
| PHF6mu 10# | c.346C>T       | 4    | p.R116X    | c.5033T>C  | 27   | p.L1678P   | HD-C    |
| PHF6mu 13# | c.971T>C       | 10   | p.L324P    | c.4845_4846insCCT | 26 | p.A1705V   | HD-C    |
| PHF6mu 14# | c.957_958insGT | 9    | p.G320fs   | c.7368_7369insTA | 34 | p.L2457fs’21 | PEST    |
| PHF6mu 15# | c.903C>A       | 9    | p.Y301X    | c.4776_4777insGAA | 26 | p.F1592LNPTLP | HD-N    |
| PHF6mu 16# | c.905A>C       | 9    | p.H302P    | c.5033T>C  | 27   | p.L1678P   | HD-C    |

PHF6, plant homeodomain finger protein 6; NOTCH1, Notch homolog 1, translocation-associated (Drosophila); PEST, exon 28 and exon 34/proline-glutamic acid-serine-threonine; HD-N, heterodimerization domain; HD-C, C-terminal region of the HD-N.

Figure 4. Effect of PHF6mut on EFS and OS. (A-B) Comparison of (A) EFS and (B) OS between patients with PHF6mut and PHF6WT mutations; (C-D) comparison of (C) EFS and (D) OS between patients with NOTCH1mut and NOTCH1WT; (E and F) comparison of (E) EFS and (F) OS between patients with PHF6mut NOTCH1mut and non-PHF6mut NOTCH1mut. EFS, event-free survival; OS, overall survival; PHF6, plant homeodomain finger protein 6; NOTCH1, Notch homolog 1, translocation-associated (Drosophila); mut, mutation; WT, wild-type.
It was found that the PHF6 mutations were significantly associated with older age, lower hemoglobin levels, higher frequency of CD13 positivity, and higher incidence of splenomegaly or lymphadenopathy, compared with PHF6 WT patients (Table II).

Since an association was found between PHF6 and NOTCH1, PHF6<sup>mut</sup>NOTCH1<sup>mut</sup> co-existence was further analyzed in relation to the clinical features of the cohort. It was found that the patients with PHF6<sup>mut</sup>NOTCH1<sup>mut</sup> co-existence had lower hemoglobin levels, along with a higher incidence of splenomegaly or lymphadenopathy, compared with patients without such co-existence (Table III).

In addition, the survival status of this population was analyzed. The EFS and overall survival (OS) in patients with PHF6 mutations vs. PHF6 WT were 2.5 vs. 11.5 months (P=0.057) and 13.0 vs. 18.0 months (P=0.246), respectively (Fig. 4A and B), while those in patients with NOTCH1 mutations vs. NOTCH1 WT were 6.0 vs. 14.0 months (P=0.100) and 13.0 vs. 21.0 months (P=0.122), respectively (Fig. 4C and D). These results indicated that there were no significant differences in the EFS and OS between patients with PHF6 or NOTCH1 mutations and patients with PHF6 WT or NOTCH1 WT; however, it was found that patients with PHF6<sup>mut</sup>NOTCH1<sup>mut</sup> co-existence had a significantly shorter EFS compared with that of patients without such co-existence (2.0 vs. 12.0 months, respectively; P=0.027). No differences in the OS were observed between patients with PHF6<sup>mut</sup>NOTCH1<sup>mut</sup> co-existence and those without (7.0 vs. 18.0 months, respectively; P=0.494) (Fig. 4E and F). The patients with PHF6<sup>mut</sup>NOTCH1<sup>mut</sup> co-existence also exhibited a higher rate of splenomegaly and lymphadenopathy compared with those without this co-existence (Table IV).

### Discussion

To the best of our knowledge, this study is the second report of PHF6 mutations in an Asian adult population with T-ALL. Of note, a higher incidence of PHF6 mutations was observed in Asian adults with T-ALL in the present study (27.1%), compared with the previous one (18.6%) (8). A different study showed that the frequency of PHF6 mutations in pediatric patients with T-ALL in the USA was 16% (5), which was lower than the frequency found in the present study (27.1%). This variance was possibly attributable to differences in age, area and race of the observed populations.

PHF6 has been reported to be a novel tumor suppressor in T-ALL (5). Of note, out of the 16 PHF6 mutations identified in
this cohort of adult patients with T-ALL, 10 were novel mutations. Consistent with other reports (5,7,9), no PHF6 mutations were detected in B-ALL samples, suggesting that PHF6 inactivating mutations are restricted to lymphoid tumors of the T-cell lineage.

It has been reported that PHF6 is an X-linked gene, and that PHF6 mutations were almost exclusively found in T-ALL samples from male subjects (5); however, no significant differences were observed in PHF6 mutations in relation to gender in this cohort of Chinese adults with T-ALL, which is consistent with another study conducted on a Chinese population (8,9), which suggests that ethnic factors may contribute to gender differences in the risk of PHF6 mutations, and this requires further investigation in larger cohorts.

In the present study, it was observed that patients with T-ALL exhibited significantly lower PHF6 expression, and that low PHF6 expression in T-ALL is associated with leukemic cell proliferation. In addition, 6 of the 16 mutations were found to induce a frame-shift, which may result in the deletion of the PHF6 protein and its eventual dysfunction. These data indicated that PHF6 inactivation in T-ALL is a result of genetic abnormalities and/or low PHF6 expression.

No associations were observed between PHF6 and NOTCH1 mutations in either pediatric (n=65) or adult (n=34) cohorts with T-ALL in the previous study (5). However, the significant correlation found between PHF6 and NOTCH1 mutations in the present study is consistent with another study on Chinese patients with T-ALL (8). PHF6 serves a potential role in transcriptional regulation, but its effects on genomics are not fully understood. Both PHF6 and NOTCH1 mutations have a high incidence in T-ALL. Whether PHF6 inactivating mutations could induce the genomic alterations of other genes in T-ALL, such as NOTCH1, requires further research.

In order to further explore the effect of PHF6 mutations on clinical outcomes, the OS and EFS of patients with T-ALL were analyzed. Despite the fact that no significant differences were identified in the OS and EFS of patients with PHF6 mutations compared with those with PHF6 WT, a significantly shorter EFS was observed in patients with PHF6mutNOTCH1mut co-existence. This result further indicated the synergistic effects of PHF6 and NOTCH1 mutations on the oncogenesis of T-ALL; therefore, PHF6mutNOTCH1mut co-existence could serve as a prognostic marker for the disease and should be integrated into future prognostic models of adult T-ALL.

In conclusion, a high incidence of PHF6 mutations was observed in Chinese adults with T-ALL. The low expression of PHF6 was found to be associated with the markers of leukemic cell proliferation. A PHF6mutNOTCH1mut co-existence was observed and shown to be correlated with a shorter EFS in patients with T-ALL. The present results indicated a synergistic effect of PHF6 and NOTCH1 mutations on the oncogenesis of adult T-ALL, suggesting that their co-existence could serve as a prognostic marker for the disease.

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References

1. Graux C, Cools J, Michaux L, Vandenberghhe P and Hage‑meijer A: Cytogenetics and molecular genetics of T-cell acute lymphoblastic leukemia: From thymocyte to lymphoblast. Leukemia 20: 1496‑1510, 2006.
2. Mullighan CG and Downing JR: Genome‑wide profiling of genetic alterations in acute lymphoblastic leukemia: Recent insights and future directions. Leukemia 23: 1209‑1218, 2009.
3. Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne‑Turner D, Easton J, Chen X, Wang J, Rusch M, et al: The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature 481: 157‑163, 2012.
4. Della Gatta G, Palomero T, Perez‑Garcia A, Ambesi‑Impolda A, Bansal M, Carpenter ZW, De Keersmaecker K, Sole X, Xu L, Paietta E, et al: Reverse engineering of TLX oncogenic transcriptional networks identifies RUNX1 as tumor suppressor in T‑ALL. Nat Med 18: 436‑440, 2012.
5. Van Vlierberghe P, Palomero T, Khabbazian H, Van der Meulen J, Castillo M, Van Roy N, De Moerloose B, Philippé J, Gonzalez‑Garcia S, Toribio ML, et al: PHF6 mutations in T-cell acute lymphoblastic leukemia. Nat Genet 42: 338‑342, 2010.
6. Lower KM, Turner G, Kerr BA, Mathews KD, Shaw MA, Gedeon AK, Schelley S, Hoyme HE, White SM, Delatycki MB, et al: Mutations in PHF6 are associated with Börjeson‑Forsmann‑Lehmann syndrome. Nat Genet 32: 661‑665, 2002.
7. Van Vlierberghe P, Patel J, Abdel‑Wahab O, Lobry C, Hedvat CV, Baibin M, Nicolas C, Payer AR, Fernandez HF, Tallman MS, et al: PHF6 mutations in adult acute myeloid leukemia. Leukemia 25: 130‑134, 2011.
8. Wang Q, Qiu H, Jiang H, Wu L, Dong S, Pan J, Wang W, Ping N, Xia J, Sun A, Qiu HR and Ge Z: Mutations of PHF6 are associated with mutations of NOTCH1, JAK1 and rearrangement of SET‑NUP214 in T‑cell acute lymphoblastic leukemia. Haematologica 96: 1808‑1814, 2011.
9. Lin ZK, Zhang R, Ge Z, Liu J, Guo X, Qiao C, Wu YJ, Qiu HR, Zhang JF and Li JY: Characteristics of NOTCH1 mutation in adult T‑cell acute lymphoblastic leukemia. Zhongguo Shi Yan Xue Ye Xue Za Zhi 21: 1403‑1408, 2013 (In Chinese).
10. Swerdlow, SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J and Vardiman JW (eds): WHO Classification of T‑cell acute lymphoblastic leukemia. West Sussex, John Wiley & Sons, 2008.
11. Liu JY, Li M, Song C, Dovat S, Li M, Xu JY, Guo X, Zhang R, Ge Z, Liu J, Guo X, Qiao C, Wu YJ, Qiu HR, Zhang JF and Li JY: Characteristics of NOTCH1 mutation in adult T‑cell acute lymphoblastic leukemia. Zhongguo Shi Yan Xue Ye Xue Za Zhi 23: 612‑618, 2015 (In Chinese).
12. Shaffer LG, Slovak ML and Campbell LJ (eds). An International System for Human Cytogenetic Nomenclature. Recommendations of the International Standing Committee on Human Cytogenetic Nomenclature. S Karger AG, Basel, Switzerland, 2009.