Novel dynamin 2 mutations in adult T-cell acute lymphoblastic leukemia

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Abstract. Genetic mutations on signaling pathways are found in patients with T-cell acute lymphoblastic leukemia (T-ALL) and act as markers of high-risk leukemia. Mutations in dynamin 2 (DNM2) have been reported in T-ALL, particularly in early T-cell precursor-ALL. In the present study, DNM2 mutations were screened by sequencing DNM2 exons obtained by polymerase chain reaction amplification and gel purification in adult T-ALL patients. A total of 4 novel DNM2 mutations were identified in adult T-ALL patients, with a mutation rate of 9.5%, and the DNM2 mutations were found to co-exist with NOTCH1 and PHD finger protein 6, and were also associated with high-risk leukemia. A high rate of silent mutation was also found in the patients, but no significant association was found between the silent mutations and patients' clinical features. The present findings suggested the DNM2 mutations may be involved in the oncogenesis of T-ALL.

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in B cells, immature T lymphocytes or lymphoid progenitors (1). T-cell acute lymphoblastic leukemia (T-ALL) accounts for ~15 and 25% of ALL in pediatric and adult patients, respectively (2). Patients with T-ALL usually have high white blood cell (WBC) counts and may present with organomegaly, particularly mediastinal enlargement and central nervous system (CNS) involvement (3). The biological knowledge of T-ALL is limited. Previously, T-ALL was classified into five subgroups (pro-T, pre-T, cortical, mature T-ALL and ETP) based on the results of fluorescent *in situ* hybridization (FISH), molecular biology and gene expression profiling (4). With exome-sequencing and whole genome sequencing, genetic mutations on genes including NOTCH1, F-box and WD repeat domain containing 7 (FBXW7), Ras, PHD finger protein 6 (PHF6) and Janus kinase 1 (JAK1) have been found to be high-risk markers in patients with T-ALL (3,5,6).

The GTPase dynamin 2 (DNM2) is essential for intracellular vesicle formation and trafficking, cytokinesis and receptor endocytosis. DNM2 contains five domains, as follows: GTPase domain; intermediate domain (MD); pleckstrin homology domain (PH); GTPase effector domain (GED); and proline-arginine-rich domain (PRD). High DNM2 expression is observed in prostate cancer and associated with cancer progression (7). DNM2 potentiates invasive migration of pancreatic tumor cells (8). Inhibition of DNM2 induced cell death in 11 cancer cell lines (9). Previously, DNM2 genetic mutations were identified in a subtype of T-ALL, termed early T-cell precursor (ETP) ALL, which accounts for up to 15% of T-ALL and is associated with a high risk of treatment failure (6,10). However, to the best of our knowledge, no studies have investigated DNM2 genetic mutations in adult ALL. The present study sequenced the exons of DNM2 genes in 42 patients with T-ALL, and the clinical features in the patients with DNM2 mutations were analyzed.

Materials and methods

Patients and samples. Bone marrow (BM) samples from 42 patients with newly diagnosed T-ALL, consisting of 31 male patients with a median age of 26 years (range, 16-62 years) and 11 female patients with a median age of 29 years (range, 19-60 years), were collected between July 2010 and December 2014 at the First Affiliated Hospital of Nanjing Medical University (Nanjing, Jiangsu, China). The diagnosis of ALL was made according to the morphological, immunophenotypical, cytogenetic and molecular criteria of the 2008 World Health Organization Diagnosis and Classification of ALL (11). All patients provided written informed consent, in accordance with the Declaration of Helsinki, prior to enrollment in the study. The present study was approved by the Institutional Review Board of Nanjing Medical University.

Mutational analysis of DNM2. Mutational analysis of DNM2 exons 2-22 was performed. Genomic DNA was isolated using a Wizard® Genomic DNA Purification kit (Promega Corporation, Madison, WI, USA) according to the manufacturer's protocol. DNA fragments spanning the aforementioned DNM2 exons were amplified by PCR using AmpliTaq Gold kit (Applied Biosystems; Thermo Fisher Scientific, Inc., Waltham, MA, USA) and exon-specific primers. The primers for PCR amplification of DNM2 exons were as follows: exon 2 forward, TGCAAGACAGAG TTGCTCCAC and reverse, TGTGTAAGTGTTCACTGA GCCG; exon 3 forward, CCAGCCTGGGTCATTACTTTC and reverse, ACACAGGCTCACCCATAGCAC; exon 4 forward, GTGGTTCAGGCAGAGTGTCAG and reverse, GACTTGGAACCAAGGATGCTG; exon 5 forward, CTG TGAGATCAGGGCTGTGAC and reverse, GGAGAAGCA ATGACTTCCAGG; exon 6 forward, TACTTGAATCTT GCCCATCCC and reverse, CTGAAACAAGTGCCAGTG AGG; exon 7 forward, ATAGTGGCACCCTGGTGTTG and reverse, GTGGACGAGTGATGAGTGGTG; exon 8 forward, GTAAACCCTGGCTTGACTTGG and reverse, CTTGAG ACCTTATTGCCTGGG; exon 9 forward, GTGTGAGCC ACTGTATCTGGC and reverse, GGACTCAGAGGTGTG GGTGAC; exon 10 forward, CAACCTTCATTCCTTGTT GGG and reverse, CTGGGAGCCTGATACCAAACC; exon 12 forward, TCTTCTGCTCTTAGCTCCCAG and reverse, TGTCAGCATGCACAGAACAGT; exon 13 forward, TCTGTTGCCTATGAGGGTGTG and AATCCCAACTCA GTCACCTCC; exon 14 forward, CTACCTGTGGCTGCT CACTTG and reverse, TAGAGAGAGCAGATGGCCTGG; exon 16 forward, GGGCTGGAGGTGTCTCTATTG and reverse, GCAGTGACTGAGTTCTGCCC; exon 17 forward, TCATATACAGCAGCGACCAGC and reverse, GTGCTC AGTGCTCAGTGAAGG; exon 18 forward, CTAGAGCCC ATTCCTCTCGG and reverse, CATGATTTCAGAGAC TCCTGGC; exon 19 forward, TAGGGCAGATGGTTTCCA GAG and reverse, CTCCTTAGCTCGTGATCCGC; exon 20 forward, CCCGCCCTGTGAGAGATG and reverse, AGG ACCCTGCAGGACACAC; exon 21 forward, CACCTCAGG TTCTGGCAGC and reverse, ACTGGGAGGAAGTGAGAC AGG; and exon 22 forward, GAGTTGATGCCTAGGTTT GGC and reverse GAGCCTGGTCCCAGCATAG. Exons in NOTCH1, FBXW7, PHF6, phosphatase and tensin homolog (PTEN), JAK1 and interleukin (IL)-7R were also amplified as previously reported (11-15).

The PCR products of the DNM2 gene exons 2-22, NOTCH1 gene exons 26-28 and 34, FBXW7 gene exons 5-12, PHF6 gene exons 2-10, PTEN gene exons 1-9, JAK1 gene exons 13, 14, 16, 18 and 19 and IL-7R exons 2-8 were purified in 2% agarose gel and cloned into the vector by The Beijing Genomics Institute (BGI; Beijing, China) and sequenced by BGI or Shanghai Bojin Medical Instrument Co., Ltd. (Shanghai, China).

Cytogenetic and molecular analyses. Conventional cytogenetic analysis was performed at the time of diagnosis, using unstimulated short-term cultures, according to the recommendations of the International System for Human Cytogenetic Nomenclature (16). For each sample, at least 20 BM metaphase cells were analyzed.

Immunophenotypical analyses were performed by flow cytometry on fresh BM samples as described previously (17,18). The following antibody conjugates were used: anti-cluster of differentiation (CD)3-fluorescein isothiocyanate (FITC; catalog no., 555339), anti-CD2-allophycocyanin (APC; catalog no., 560642), anti-CD5-phycoerythrin (PE; catalog no., 555353), anti-CD7-brilliant violet 421 (BV421; catalog no., 562635), anti-CD19-FITC (catalog no., 555412), anti-CD20-APC (catalog no., 559776), anti-CD10-BV421 (catalog no., 562902), anti-CD34-PE (catalog no., 555822) and anti-CD33-BV605 (catalog no., 740400). All the antibodies were mouse anti-human and purchased from BD Biosciences (San Jose, CA, USA) and used for cell staining according to the manufacturer's protocol. FITC, PE, BV605 and BV421-conjugated antibodies were diluted 1:5; APC-conjugated antibodies were diluted 1:20. The stained cells were analyzed on a FACScalibur flow cytometer (BD Biosciences), which was equipped with red and blue lasers. Routine machine calibration was performed daily according to the standard operating procedures of our laboratory. Fluorescence compensation calibration was run at least once a week using standard fluorescence beads (Calibrite beads; BD Biosciences). Data analysis was performed using BD CellQuest™ Pro software version 6.0 (BD Biosciences), and lymphocytes were delineated using forward scatter/side scatter dot plots. Cell-surface antigens were defined as present when the fluorescence intensity of ≥20% of cells exceeded the fluorescence of the negative control.

Statistical analysis. For qualitative parameters, overall group differences were analyzed using a χ^2 test. All statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). $P<0.05$ was considered to indicate statistical significance.

Results

Mutational analysis of DNM2. DNM2 mutations were identified in 4 out of 42 T-ALL patients, resulting in a mutation incidence of 9.5%. The 4 mutations were the point mutations c.1081C>T, c.1453T>C, c.1609G>A and c.1801C>T, which were located in exons 8, 13, 16 and 18, respectively. In the 4 mutations, 1 mutation was a nonsense mutation and 3 mutations were missense mutations. All 4 mutations led to amino acid changes (R361X, Y485H, G537S and R601W). The R361X

Table I. Co-existence of DNM2, NOTCH1 and PHF6 mutations in adult patients with T-cell acute lymphoblastic leukemia.

	DNM2		NOTCH1		PHF6	
Patient ID	Mutation	Location	Mutation	Location	Mutation	Location
Mu1#	c.1081C>T, p.R361X	exon 8	c.4732_4734delGTG, p.V1578delV, c.5094C>T, p.D1698D	exon 26 exon 27	c.820C>T, p.R274X	exon 8
Mu2#	c.1453T>C, p.Y485H	exon 13	c.5033T>C, p.L1678P c.7400C>A, p.S2467*	exon 27 exon 34	c.346C>T, p.R116X	exon 4
Mu3#	c.1609G>A, p.G537S	exon 16	c.4721T>C, p.L1574P	exon 26	c.385C>T, p.R129X	exon 5
Mu4#	c.1801C>T, p.R601W	exon 18	c.7427G>C, p.V7427L c.7171delinsTTTT, p.Q2391fs*3	exon 34		

DNM2, dynamin 2; PHF6, PHD finger protein 6.

and Y485H mutations are located within the DNM2 MD; G537S and R601W mutations are located within the DNM2 PH domain (Fig. 1).

DNM2 mutation in combination with NOTCH1 and PHF6 mutation. The present study found that in these 4 patients, DNM2 mutations co-existed with NOTCH1 mutations. In 3 of the 4 patients, the DNM2 mutation co-existed with two NOTCH1 mutations (point mutations and/or indel mutations) located in NOTCH1 exons 26, 27 and 34. In addition, 3 of the 4 patients with DNM2 mutations had PHF6 mutations located in PHF6 exons 4, 5 and 8 (Table I).

Clinical characteristics of the patients with DNM2 mutations. The clinical characteristics of the patients with DNM2 mutations are listed on Table II. No significant differences in clinical characteristics were observed between the patients with DNM2 mutations and those without mutations in terms of age (P=0.094), sex (P=1.000), T/B subtype diagnosis (P=1.000), initial WBC (P=0.453), HGB (P=0.602), platelets (P=0.950), lactate dehydrogenase (P=0.317), blasts in bone marrow (P=0.939), blasts in peripheral blood (P=0.900), immune phenotype $CD34^+$ (P=0.098), $CD10^+$ (P=0.866), $CD19^+$ (P=1.000), $CD20^+$ (P=1.000), $CD33^+$ (P=1.000), $CD2^+$ (P=0.525), $CD3^+$ (P=0.535), $CD5^+$ (P=0.777) and $CD7^+$ (P=1.000), frequency of extramedullary infiltration on liver (P=0.888), spleen (P=0.204) and lymph nodes (P=1.000), and days for complete remission (P=0.234). However, it was found that 1 patient experienced relapse, 1 patient had a high WBC count, and 2 patients had complex karyotypes and lymph node infiltration. Notably, the time taken to reach complete remission was >4 weeks in all 4 patients. These data suggest that the patients with DNM2 mutation exhibit high-risk leukemia and possess a poor prognosis.

DNM2 synonymous amino acid mutations. DNM2 synonymous amino acid mutations were identified in exon 4 (1/42 patients; 2.38%), exon 6 (1/42 patients; 2.38%), exon 22 (1/42 patients; 2.38%), and exon 20 (34/42 patients; 80.95%) in the T-ALL patients. There were two synonymous amino acid mutations, Ala713Ala and Asp720Asp, in exon 20, and the former mutation was found in 31 patients (31/42 patients; 73.81%) and the latter in 3 patients (3/42 patients; 7.14%). The coexistence of the two mutations was identified in 1 case (1/42 patients; 2.38%) (Table III). The clinical features of the patients with DNM2 synonymous amino acid mutations were also observed, but these synonymous amino acid mutations were not significantly associated with any clinical features observed (data not shown).

Discussion

The DNM2 protein is involved in a wide range of cellular functions, including phagocytosis, phagosome formation of actin and microtubule interactions, cytokinesis, cell migration and regulation of apoptosis (19). It has been reported that DNM2 gene mutation is an important factor for patients with autosomal dominant centronuclear myopathy (20) and Alzheimer's disease (21,22).

Recurrent DNM2 mutations have also been identified in patients with ETP-ALL by whole-exome sequencing (6,10,23). These mutations include: E78fs in the Ras-like GTPase domain; L3354P, R364C, K382E, T404N and E468* in the dynamin MD domain; S528fs, E544fs and K557_K558>K in the PH domain; S698L in the GTPase effector domain; and K770*, P791T, L789fs and I805fs in the C-terminus. In addition, it has been shown that certain mutations appear in patients that experience relapse with induction failure. The present study identified 4 novel DNM2 mutations in 42 adult T-ALL patients, with a mutation rate of 9.5%. These mutations also mainly appear in the dynamin central region (MD domain), PH domain and GTPase effector domains. It was also found that the patients with DNM2 mutations were more likely to demonstrate high-risk factors, such as a high WBC count, complex karyotype, lymph node infiltration and difficulty achieving complete remission. These data indicated that patients with T-ALL with DNM2 mutations have a poor outcome.

Patient Mu1# was diagnosed with a type of hypoproliferative leukemia termed ‘hypocellular leukemia’, with less tolerance to

Table II. Clinical characteristics of T-ALL patients with DNM2 mutations.

Characteristics	Mutation				No mutation, median (range)
	Mu1#	Mu2#	Mu3#	Mu4#	
Age, years	27	26	26	14	30.0 (14.0-70.0)
Gender	F	M	M	M	F/M
Diagnosis	T-ALL	T-ALL	T-ALL	T-ALL	T-ALL
DNM2 mutations	R361X	Y485H	G537S	R601W	No
WBC, $nx10^9/l$	2.9	106.7	28.9	54.4	44.2 (1.0-546.0)
HGB, g/l	117	124	92	114	115.5 (56.0-171.0)
PLT, $nx10^9/l$	85	76	46	56	58.5 (17.0-267.0)
LDH, U/l	934	731	861	588	1,144.0 (131.0-8601.0)
Blasts in bone marrow, %	56.4	95.6	90.2	72.4	76.0 (20.0-100.0)
Blasts in peripheral blood, %	6.0	68.0	88.0	89.0	64.0 (0.0-100.0)
Immune phenotype[a]					
$CD34^+$	Negative	Negative	Negative	Negative	
$CD10^+$	Negative	Negative	Positive	Negative	
$CD19^+$	Negative	Negative	Negative	Negative	
$CD20^+$	Negative	Negative	Negative	Negative	
$CD33^+$	Negative	Positive	Negative	Negative	
$CD2^+$	Negative	Positive	Negative	Positive	
$CD3^+$	Negative	Positive	Positive	Negative	
$CD5^+$	Positive	Positive	Negative	Positive	
$CD7^+$	Positive	Positive	Positive	Positive	
Extramedullary infiltration					
Liver	No	No	No	No	
Spleen	No	No	No	No	
Lymph node metastasis	No	No	No	Yes	
Karyotype	46, XX[20]	46, XY, der (1), 9p-, 14q+[3]/47, XY, t(6;11) (p10;p10), +?8,9p-[1]/46, XY[6]	46, XY[20]	46, XY, 11q +[3][inc]/46, XY[1] 2013.1.7: 47-48, XY, -1,2q-, -4,4q-, -5, +8,9p-, der (9), +11,11q-*2,12q+, 16q+, 17q-, +2mar[7cp]/46, XY[3]	
Rearrangement	TCR/TCR	TCR/TCR	TCR/TCR	TCR/TCR	
Time to complete remission, days	61	43	60	65	28 (9-169)

[a]Cell-surface antigens were defined as present when the fluorescence intensity of ≥20% of cells exceeded the fluorescence of the negative control. F, female; M, male; T-ALL, T-cell acute lymphoblastic leukemia; DNM2, dynamin 2; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; LDH, lactate dehydrogenase; CD, cluster of differentiation; TCR, T cell receptor.

chemotherapy and poor clinical outcome compared to individual's with normal/increased WBC counts. Hypocelluar leukemia is most commonly observed in cases of acute myeloid leukemia, and certain cases are secondary leukemia resulting from myelodysplastic syndrome, indicating high-risk leukemia (24,25). The mechanism of hypoproliferative leukemia is not fully understood. The present study identified that 5 immunotypes were present in patient Mu2#, but only 2-3 immunotypes were present in the other 3 patients with detected mutations. Only CD33 was observed in patient Mu2#, suggesting this immunotype may lead to a poorer outcome compared with those observed in the other 3 patients. In addition, the association of the mutations with survival of the patients requires clarification with more patients with the mutations in future.

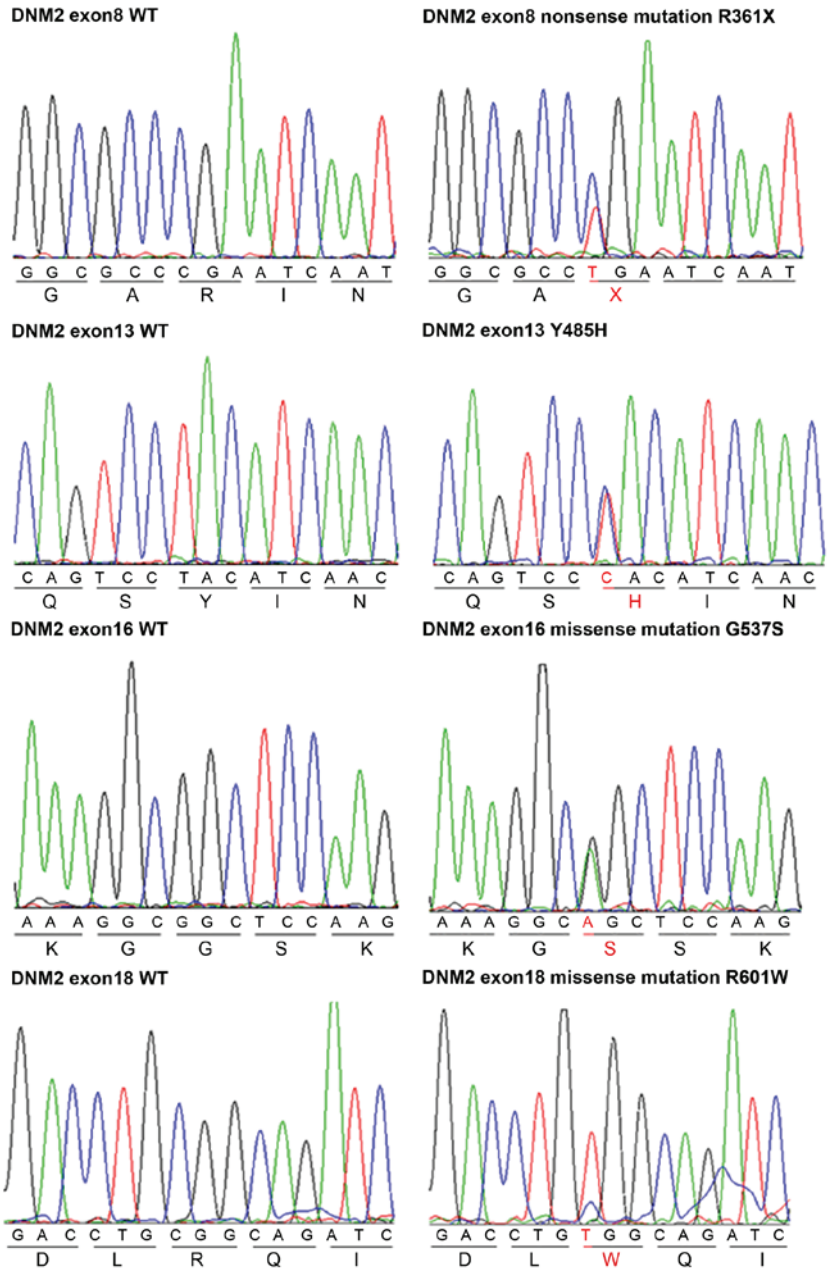

Figure 1. Representative DNA sequencing chromatograms of T-cell acute lymphoblastic leukemia genomic DNA samples showing mutations in exons of DNM2. DNM2, dynamin 2; WT, wild type.

Table III. Mutations of synonymous amino acids in exons of DNM2.

Exon	Cases, n	Mutation, nucleotide	Mutation, amino acid
4	1	c.450A>G	p.P150P
6	1	c.789G>A	p.P263P
20	31	c.2139T>C	p.A713A
20	3	c.2160C>T	p.D720D
20	1	c.2139T>C^{+} c.2160C>T	p.A713A^{+} p.D720D
22	1	c.2571G>A	p.R857R

DNM2, dynamin 2.

DNM2 can bind to membrane phospholipids through PH domains and the endogenous GED can activate GTPase activity. In addition, high DNM2 expression is associated with a poor prognosis and high rate of metastasis in patients with solid cancer. Inhibition of DNM2 induces the apoptosis of cancer cells (8-10). Therefore, the present authors hypothesize that the DNM2 mutations identified in the present study may be gain-of-function mutations. The effects of these newly-identified DNM2 mutations on the proliferation of leukemia cells in the current study may be examined in future studies.

Notably, a high rate of DNM2 synonymous amino acid mutations (also termed silent mutations) was identified in the patients. Silent mutations are the evolutionary substitution of one base for another in an exon of a gene coding for a protein, such that the produced amino acid sequence is not modified. However,

mutations do not always result in silent mutations (26-28). The point mutation may affect transcription, splicing, mRNA transport and translation, any of which may alter the phenotype, rendering the synonymous mutation non-silent (26-28).

In the present study, DNM2 expression was not observed in the patients with DNM2 silent mutations, and no significant changes in DNM2 expression were found in the patients with silent mutations compared to patients without mutations. In addition, no significant association between the DNM2 silent mutations and any clinical features was observed. These data indicated that the sites with silent mutations may only be the hot spots and the nucleotides in these sites are easily changed, but the nucleotide changes may also be quickly corrected. The clinical relevance of DNM2 silent mutations requires additional clarification. It was hypothesized in the present study that silent mutations may affect DNM2 translation in patients (26-28).

In summary, the present study identified 4 novel DNM2 mutations in T-ALL and their associations with high-risk leukemia. The current findings suggest the DNM2 mutations may be involved in the oncogenesis of T-ALL.

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