EZH2 Mutations in Follicular Lymphoma from Different Ethnic Groups and Associated Gene Expression Alterations

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Abstract

Purpose: Gain-of-function mutations of enhancer of Zeste homolog 2 (EZH2) occur frequently in diffuse large B-cell lymphomas and in follicular lymphomas. However, the frequency of EZH2 mutation in Chinese follicular lymphomas and the potential targets affected by this mutation are unknown.

Experimental Design: We determined EZH2 codon 641 mutations in Chinese follicular lymphomas (n = 124) and compared them with Western follicular lymphomas (n = 70) using a sensitive pyrosequencing assay. Gene expression profiling (GEP) was performed to determine differential gene expression between the mutated versus unmutated subgroups, and selected genes were validated using immunohistochemistry.

Results: Our results showed similar frequencies of EZH2 mutation in Chinese and Western follicular lymphoma cohorts (16.9% vs. 18.6%, $\chi^2$ test, $P = 0.773$), including all five reported mutation variants. We observed significant association of EZH2 mutation with low morphologic grade follicular lymphomas (grade 1–2, 23.6% vs. grade 3, 7.7%, $\chi^2$ test, $P = 0.02$). EZH2 mutations also showed significant association with BCL2 rearrangement in the Chinese cohort (26.8% vs. 8.8%, $\chi^2$ test, $P = 0.008$) and combined cohorts (26.3% vs. 9.1%, $\chi^2$ test, $P = 0.002$). GEP analysis identified several genes, including TCF4, FOXP1, TCL1A, BIK, and RASSF6P, with significantly lower mRNA expression ($P < 0.01$) in mutated cases, and the potential target TCL1A showed consistent results at the protein level.

Conclusion: Similar prevalence of EZH2 mutation in two ethnic groups suggests shared pathogenetic mechanisms. The much lower frequency of EZH2 mutation in cases without BCL2 translocation suggests a different pattern of evolution of this subtype of follicular lymphoma. GEP studies showed a set of differentially expressed genes and suggested that EZH2 mutation may help to lock the tumor cells at the germinal center stage of differentiation.

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Introduction

Follicular lymphoma is a common germinal center B-cell (GCB)-derived non-Hodgkin lymphoma (NHL) exhibiting a spectrum of morphologies, immunophenotypes, and genetic aberrations. It is the second most common type of NHL representing about 30% of NHL in Western countries (1, 2); however, the incidence of follicular lymphoma is lower in Asian countries (3, 4). A recent study of 98 Chinese follicular lymphoma cases revealed a lower frequency of BCL2 rearrangement in Chinese follicular lymphoma (58.5%) than in Western follicular lymphoma (80%–90%; ref. 5). The BCL2 rearrangement results in constitutive expression of the antiapoptotic BCL2 protein, which plays an important role in tumorigenesis of follicular lymphoma; however, BCL2 rearrangement alone is not sufficient for malignant transformation of B cells. Multiple genetic abnormalities, including mutation of enhancer of Zeste homolog 2 (2 EZH2), have recently been reported in follicular lymphoma (6–9). The EZH2 gene encodes a histone methyltransferase that constitutes the catalytic component of the polycomb repressive complex 2 (PRC2) and is involved in repressing gene expression through methylation of histone H3 on lysine 27 (H3K27). EZH2 codon 641 mutation, the most common mutation hotspot, is a gain-of-function mutation leading to enhanced trimethylation of histone H3K27 and plays an important role in the tumorigenesis of GCB-type diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (6–11). Interestingly, highly selective EZH2 inhibitors have now been developed which is a potential therapeutic strategy for lymphomas with EZH2 activating mutations (12). However, it is unclear whether Chinese follicular lymphoma utilizes similar pathogenetic pathways as their Western counterpart and the frequency of
Translational Relevance
Follicular lymphoma is an indolent, but incurable subtype of non-Hodgkin lymphoma. These tumors harbor t(14;18) translocation in at least 90% of patients. Recently, activating enhancer of Zeste homolog 2 (EZH2) mutations have been found in a significant number of patients with follicular lymphoma. However, the reported incidence has been quite variable and has come almost exclusively in Western countries. We have developed a sensitive pyrosequencing assay for all mutation variants affecting codon 641. Our study has shown that Chinese and Western patients with follicular lymphoma exhibit EZH2 Y641 mutation at similar frequencies, and the mutation is far more frequently associated with the BCL2 rearranged group in both populations. We have also demonstrated by gene expression profiling that follicular lymphoma cases with this mutation showed a set of significantly downregulated genes in EZH2-mutant cases. The gene signature provided some insight on the mechanisms of action of abnormally enhanced EZH2 function. EZH2 mutations may play a similar role in lymphomagenesis in different ethnic groups and can serve as a biomarker for potential EZH2 targeted therapy.

EZH2 mutation in Chinese follicular lymphoma is not known. The aim of the present study is to identify the frequency of EZH2 gene codon 641 mutation in Chinese follicular lymphoma and the association with the status of BCL2 expression and rearrangement. We also analyzed the gene expression profiling (GEP) data of follicular lymphomas with and without EZH2 gene mutation to identify unique associations with EZH2 mutation in follicular lymphoma.

Materials and Methods
Patient materials
One hundred twenty-four Chinese follicular lymphomas diagnosed between January 1999 and May 2010 were obtained from Hong Kong and provinces of Shandong, Tianjing, and Shaan Xi, China, among which 109 cases had BCL2 rearrangement data detected by interphase FISH. We also included 70 Western follicular lymphomas with BCL2 rearrangement data by FISH from the University of Nebraska Medical Center (UNMC; Omaha, NE) for comparison. As follicular lymphoma with or without t(14;18) may evolve through different molecular pathways, our initial hypothesis is that EZH2 mutation may be present at different frequencies in follicular lymphoma with different t(14;18) status. We enriched both cohorts with a substantial number of follicular lymphoma cases with no BCL2 rearrangement (from previous cytogenetic and FISH studies) to test the hypothesis as such cases are uncommon particularly in Western follicular lymphoma. The cases were reviewed by expert hematopathologists (J.K.C. Chan, W.C. Chan, and B. Meng) and re-reviewed by W.C. Chan and S. Guo, and classified on the basis of the World Health Organization criteria. These cases showed at least 30% to 40% of the sectional areas consisting of malignant follicles on hematoxylin and eosin (H&E) examination. This study was approved by the Institutional Review Boards of the respective institutions.

Construction of tissue microarray and immunohistochemistry
Representative areas of follicular lymphoma tissue blocks were selected to prepare the tissue microarray (TMA) by examination of the corresponding H&E-stained slides. To ensure accurate representation, three areas of each tumor were selected for core preparation. Each target area on the selected blocks was punched to obtain a 1-mm diameter tissue core to be placed consecutively on the recipient master blocks. TMAs containing representative tumor sections from 124 Chinese and 70 Western follicular lymphomas were used for this retrospective analysis. Sections from the TMAs were stained with anti-human BCL2 (clone 124), CD20 (clone L26), BCL6 (clone PG-B6), (Dako Corp), and CD10 (clone 56C6), CD21 (clone EP3093), CD3 (clone SP7), (Abcam), and anti-TCL1A antibody (clone 1–21, Santa Cruz Biotechnology Inc.). Of note, 5 μm thick tissue sections were deparaffinized with xylene, washed with ethanol, and blocked with methanol with 3% hydrogen peroxide. Sections were incubated with the above antibodies using Bond polymer refine detection kit and bond IHC Stainer (Leica Microsystems Inc.). For TCL1A staining, GCB cells and Naive B cells in the mantle zone of reactive tonsil were used as positive controls. The percentage of positive tumor cells and the staining intensity were graded from 0 to 3, and the two scores were added to form a final score to divide the cases from negative to strong TCL1A expression as described in Supplementary Table S1A.

FISH
Full sections and/or TMAs of 124 Chinese follicular lymphomas and 70 Western follicular lymphomas were assessed for the presence of BCL2 rearrangement on 4 μm formalin-fixed, paraffin-embbedded (FFPE) sections using the Vysis LSI BCL2 dual color break-apart rearrangement probe (Abbott Molecular). Cases were scored as BCL2 rearranged on the basis of detecting unambiguous probe separation above the set threshold.

DNA extraction, PCR, and pyrosequencing
Five to 10 μm thick tissue sections of representative FFPE tissue blocks were prepared. Genomic DNA was extracted using a Qiagen DNA FFPE Tissue Kit. Genomic DNA encompassing EZH2 codon 641 was PCR amplified using forward primer 5’-GGCTGGGGATTTTTATCAA-3’ and biotinylated reverse primer 5’-GTATCAGTGCTTACCTCCTCCA-3’. The PCR products were sequenced on a Qiagen Pyromark Q24 instrument using a forward sequencing primer 5’-GAAAAATGAAATTAGATCG-3’. Genomic
DNA of cell line SU-DHL-6, harboring an **EZH2** codon Y641N mutation, and normal tonsil lacking *EZH2* mutation, was mixed with SU-DHL-6 DNA constituting 5%, 10%, 20%, 30%, 50%, and 70% of the total DNA, respectively. The mixture was used as template to determine the sensitivity of pyrosequencing to detect the mutant. The sensitivity of the assay was determined to be at 5% of the genomic DNA of the cell line SU-DHL-6. According to the principle of pyrosequencing, the light emission in the process of sequencing is proportional to the quantity of deoxynucleotide triphosphate (dNTP) incorporated into the template. dNTPs were dispensed in a novel order of G, A, A, T, C, G, A, T, C, based on the sequence of wild-type **EZH2** codon 641 and five mutation variants. With this order of addition, at least one addition results in nucleotide incorporation for the mutant but not the wild-type allele, allowing all five mutations to be identified and detected with maximal sensitivity (Table 1). All detected mutations were validated by repeating the assay.

### GEP data analysis

The GEP data from 68 cases of UNMC follicular lymphoma were analyzed to find genes differentially expressed between follicular lymphomas with or without **BCL2** rearrangement. We used HG-U133 plus 2 arrays (Affymetrix Inc.) for our analysis, and the methods for isolation and processing of RNA and acquisition of GEP raw data have been described previously (13). The raw data were uploaded in BRB-Array Tools (version 3.7.0) for normalization, and the analysis was supervised by the **EZH2** gene mutation status. Genes were selected at a significance of \( P < 0.01 \) and >1.5-fold difference in expression levels between the two groups. To enhance the identification of differential gene expression in follicular lymphoma tumor cells, only follicular lymphoma cases with a high B-cell content [enriched B-cell signature of >2-fold above the mean of the B-cell signature (pan B-cell markers) in the entire follicular lymphoma dataset] were chosen for analysis (Data available in the GEO database: GSE 55267.)

### Statistical analysis

Statistical significance of differences in **EZH2** mutation frequency between lymphoma groups with or without **BCL2** rearrangement and expression was assessed by \( \chi^2 \) test. Statistical significance was defined as \( P < 0.05 \).

### Results

**Patient characteristics**

One hundred and twenty-four Chinese follicular lymphoma patients were included in this study. The median age of these patients was 59.5 years (range, 26–89 years), and included 64 (51.6%) males and 60 (48.4%) females. These cases were enriched in **BCL2** translocation negative cases so that only 56 harbored a **BCL2** rearrangement and 68 lacked a **BCL2** rearrangement. Among the 70 Western follicular lymphomas, the median age was 60 (range, 35–88 years), and there were 33 (47.1%) male and 37 (52.9%) female patients. This cohort was also enriched in **BCL2** wild-type cases, 39 harbored a **BCL2** rearrangement and 31 lacked a **BCL2** rearrangement. There were no significant differences in clinical features between Chinese and Western follicular lymphomas. On histologic morphologic assessment, 72 of 124 (58%) in Chinese cohort and 39 of 70 cases (55.7%) in the Western cohort were of grade 1–2.

**Frequencies of **EZH2** codon 641 mutations**

We observed **EZH2** codon 641 mutations in 16.9% (21 of 124) Chinese follicular lymphoma and 18.6% (13 of 70) Western follicular lymphomas using pyrosequencing and the results are summarized in Table 2. No significant differences in clinical features between Chinese and Western follicular lymphomas. On histologic morphologic assessment, 72 of 124 (58%) in Chinese cohort and 39 of 70 cases (55.7%) in the Western cohort were of grade 1–2.

### Table 1. **EZH2** codon 641 mutation variants by adding dNTPs in the designated order (G,A,A,T,C,G,A,T,C) during pyrosequencing

<table>
<thead>
<tr>
<th>Amino acid change</th>
<th>Nucleotide change</th>
<th>Signal strength by nucleotide</th>
</tr>
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<tbody>
<tr>
<td>Y641I</td>
<td>TAC</td>
<td>W-AATACT</td>
</tr>
<tr>
<td>Y641F</td>
<td>TAC&gt;TTC</td>
<td>W-AATACT</td>
</tr>
<tr>
<td>Y641S</td>
<td>TAC&gt;TCC</td>
<td>M-AAAACTerequisites</td>
</tr>
<tr>
<td>Y641C</td>
<td>TAC&gt;TGC</td>
<td>M-AATCTerequisites</td>
</tr>
<tr>
<td>Y641N</td>
<td>TAC&gt;AAC</td>
<td>M-AATGCT prerequisites</td>
</tr>
<tr>
<td>Y641H</td>
<td>TAC&gt;CAC</td>
<td>M-AAACT prerequisites</td>
</tr>
</tbody>
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Abbreviations: W, wild-type; M, mutant; Y, tyrosine.
wild-type EZH2 codon 641 and five mutant variants are shown in Fig. 1. The five mutation variants resulted in the amino acid change from tyrosine (Y) 641 to phenylalanine (F), serine (S), cysteine (C), asparagine (N), and histidine (H) as shown in Table 1. These five variants were detected in Chinese follicular lymphoma with frequencies similar to those of Western follicular lymphoma. Y641F was the most common mutation, accounting for 38% of mutants, with decreasing frequencies from Y641S (24%), Y641H (14%), Y641C (14%) to Y641N (10%).
Association between EZH2 mutation and morphologic follicular lymphoma grades

The EZH2 mutation frequency was related to the morphologic follicular lymphoma grades, with higher frequency in low morphologic grade follicular lymphomas in both Chinese (grade 1–2, 23.6% vs. grade 3, 7.7%, χ² test, P = 0.02) and Western population (grade 1–2, 25.6% vs. grade 3, 9.7%, χ² test, P = 0.09; Table 2). The distribution of EZH2 mutation in different morphologic grades of Western follicular lymphoma was similar to that of Chinese follicular lymphoma. The percentage of EZH2 mutation in grade 1 (7/33; 21.2%) and grade 2 (10/39; 25.6%) follicular lymphoma was quite similar in Chinese and Western cases (23.5% vs. 22.8%; P = 0.155; Fig. 2). EZH2 mutation was also significantly associated with the BCL2 protein expression in Chinese (22.4% vs. 8.3%, χ² test, P = 0.042) and the combined follicular lymphoma cohorts (22.8% vs. 7.5%, χ² test, P = 0.007, respectively). The percentage of EZH2 mutation was enriched in BCL2 protein-positive cases in Western cohort; however, it did not reach statistical significance (23.5% vs. 5.3%, χ² test, P = 0.155; Fig. 2).

Differential gene expression analysis

Our analysis focused on follicular lymphoma cases with high B-cell contents to facilitate the detection of changes related to the tumor cells. A set of genes was significantly downregulated in mutated cases. Among these downregulated genes, a number of them, such as TCF4, FOXP1, TCL1A, BIK, and RASSF6P were also marked repressed compared with normal centroblasts (Fig. 3). There was also a set of genes such as PTPN22, which was upregulated in mutant cases probably as secondary changes. We also compared our signature with the specific gene signature derived previously using an EZH2-specific inhibitor (GSK126) on GCB cell lines with EZH2 mutation (12). Notably, this signature was significantly (P < 0.02) downregulated in cases with EZH2 mutation compared with wild-type cases (Fig. 3).

Downregulation of TCL1A in EZH2-mutated follicular lymphomas

One of the target genes that were reported to be upregulated upon treatment of EZH2-mutant cell lines by a specific inhibitor of EZH2-mutant protein (GSK126) is TCL1A (12).
Consistent with this observation, we observed that this gene was downregulated in follicular lymphoma cases carrying EZH2 Y641 mutation compared with our wild-type. There have been reports suggesting variable expression of TCL1A in follicular lymphoma. We evaluated TCL1A expression at the protein level and observed that B cells in the mantle zone of reactive tonsil showed strong expression of TCL1A, whereas GCB cells showed moderate expression in both cytoplasm and nucleus. Of the follicular lymphoma cases without EZH2 Y641 mutation, the majority of the follicular lymphoma cases (67.2%, 39 of 58) showed strong homogenous expression of TCL1A, whereas 10.3% (6 of 58) were moderate, and 22.4% (13 of 58) were either weak or negative. Interestingly, none of the follicular lymphoma cases with EZH2 Y641 mutation showed strong expression; it was generally variable from moderate (6 cases) to weak (1 case), or negative (3 cases) in 10 mutant cases. The results are summarized in Supplementary Table S1B, and representative images are shown in Fig. 4.

Discussion

EZH2 is the catalytic subunit of the PRC2 and is involved in repressing gene expression through methylation of lysine 27 of histone H3. The EZH2 codon 641 mutation is a gain-of-function mutation leading to enhanced trimethylation of histone H3K27 (6). EZH2-mediated epigenetic silencing in GCB cells contributes to proliferation and lymphomagenesis (14).

The frequency of EZH2 mutations varied from 7.2% to 22% (Supplementary Table S2) in prior studies (7, 9–10); the variation is probably due to the different assay methods used. Pyrosequencing was used in the present study because it is more sensitive than conventional Sanger sequencing and is widely used clinically to detect point mutations in FFPE tissues. The assay was able to detect 5% of the mutant genomic DNA of the cell line SU-DHL-6, which harbors an EZH2 codon Y641N mutation. Assays with lower sensitivity may miss the mutation in cases with low tumor content, which are not uncommon in follicular lymphomas. We detected a similar frequency of EZH2 codon 641 mutations in Chinese follicular lymphoma [21 of 124 (16.9%)] and in Western follicular lymphoma [13 of 70 (18.6%)]. All of the five reported mutations, Y641F, Y641S, Y641C, Y641H, and Y641N, were detected in Chinese follicular lymphoma with frequencies similar to those previously reported in Western follicular lymphoma (7, 9–11). Y641F was the most common mutation, accounting for 38% of mutants. It has been reported that all of the five mutant proteins confer a gain-of-function phenotype and that Y641N is the most potent at generating H3K27me3, whereas Y641H is the least potent (8).

The BCL2 rearrangement is a genetic hallmark of follicular lymphomas, but a small percentage of follicular lymphoma cases lack this rearrangement; the latter are much more frequent in the Chinese population (5). It is possible that cases with or without BCL2 rearrangement may have different pathogenetic mechanisms that may be reflected in different profiles of genetic mutations. A recent study in Western patients indeed found a marked difference in EZH2 mutation frequency between the two subgroups (7). We investigated the association of EZH2 mutation and the status of BCL2 rearrangement in follicular lymphoma, including a substantial number of cases with no BCL2
rearrangement. The frequency of EZH2 mutation was significantly associated with BCL2 rearrangement in Chinese follicular lymphoma, but did not reach statistical significance in Western follicular lymphoma, probably due to the small number of cases. However, overall (combining both cohorts) EZH2 mutation was significantly associated with BCL2 rearrangement. The frequency of EZH2 codon 641 mutation in Chinese follicular lymphoma with BCL2 rearrangement was very close to that reported in a previously study (28%), using a sensitive detection technique (7). The mutation frequency in Chinese follicular lymphoma lacking BCL2 rearrangement was low and comparable with similar patients in Western countries but far higher than reported previously (7). As EZH2 codon 641 mutation was first identified in a grade 1 follicular lymphoma lacking BCL2 rearrangement (9), the reported lack of EZH2 mutation in cases negative for BCL2 rearrangement (7) is probably spurious and due to the low number of cases investigated. The low frequency of EZH2 mutation in follicular lymphomas without BCL2 rearrangement and in grade 3 follicular lymphoma suggests the preferential use of different pathways to promote the malignant transformation of GCB lymphocytes to follicular lymphoma.

Although it has been demonstrated that the EZH2 codon 641 mutation enhances trimethylation of histone H3K27, the genomic targets that are affected by the mutation and thus promote lymphomagenesis have not been identified. Our GEP data analysis revealed a set of differentially expressed genes; among them TCF4, FOXP1, RASSF6, TCL1A, and BIK were downregulated, compared with both wild-type follicular lymphoma and normal centroblast. Both TCF4 and FOXP1 were consistently upregulated in
ABC-DLBCl compared with GBC-DLBCl (15). This observation suggests that one of the functions of EZH2 mutation may be locking the cells at the GCB cell stage of differentiation by downregulating the expression of crucial genes for further differentiation. TCL1A is also of particularly interest; it was initially identified as an oncogene in T-cell prolymphocytic leukemias, but may also be expressed in B-cell lymphomas, including follicular lymphoma (16). TCL1A serves as a coactivator of the AKT/mTOR pathway and has also been reported as an inhibitor of de novo DNA methylation in B-cell chronic lymphocytic leukemia (17), so downregulation of TCL1A may have diverse effects, including epigenetic alterations. We further confirmed the frequent expression of TCL1A protein in follicular lymphomas. It was revealed that follicular lymphomas displayed striking variability in the intensity of TCL1A staining and there is a correlation with EZH2 Y641 mutation. Thirty-nine cases showing strong positivity for TCL1A harbored no EZH2 Y641 mutation, whereas the expression of TCL1A in the mutant cases varied from moderate to weak, or negative, and none showed strong positivity. The immunohistochemical results are in keeping with the GEP analysis and may explain the reported variability of TCL1A expression in follicular lymphoma. Interestingly, it was also noted that the expression of TCL1A increased in DLBCL cell lines harboring EZH2 mutation when treated with the EZH2-specific inhibitor GSK126 (12). This observation is consistent with our finding and suggests that TCL1A is likely targeted by EZH2 mutation in follicular lymphoma. We also observed that specific gene signature generated by EZH2-mutant inhibitor (GSK126; ref. 12) showed expected correlation in mutant follicular lymphoma cases, suggesting that such inhibitors may provide a rational and viable therapeutic approach for these patients. Downregulation of BIK (Bcl2-interacting killer), a proapoptotic gene, is also of interest as 40% of cases of multiple myeloma were reported to have a methylated BIK CpG island (18). Another downregulated gene is RASSF6, a Ras-association family (RASSF) member that has been shown to be frequently epigenetically inactivated by promoter CpG island hypermethylation in childhood leukemias (19).

Among the upregulated genes, PTPN22 is intriguing. The expression of PTPN22 in follicular lymphomas with EZH2 mutation is significantly higher than in normal B cells (naive B cells, centrocytes, and centroblasts) and in follicular lymphomas without EZH2 mutation. PTPN22 is considered to be one of the principal negative regulators of antigen receptor signaling in normal B and T lymphocytes, but it can also positively regulate the kinase AKT, providing a powerful survival signal. B-cell receptor signaling in follicular lymphoma may need to be finely tuned to avoid further differentiation, and simultaneous activating the AKT pathway may optimize cell survival, perhaps compensating for the effects of TCL1 downregulation on the AKT/mTOR pathway (20).

In conclusion, EZH2 codon 641 mutations occur at similar frequency in Western and Chinese follicular lymphoma and more often associated with low-grade cases. The mutations are far more frequent in the BCL2 rearranged group. This mutation, probably plays a similar role in the pathogenesis of follicular lymphomas in both Chinese and Western patients and may serve as a marker for potential EZH2 targeted therapy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Analysis and interpretation of data (e.g., statistical analysis): S. Guo, J.K.C. Chan, J. Iqbal, K. Fu, R. Wang, W. Zhang, T.C. Greiner
Writing, review, and/or revision of the manuscript: S. Guo, J.K.C. Chan, J. Iqbal, T. McKeithan, K. Fu, T.C. Greiner, W.C. Chan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B. Meng, Y. Pan, D. Luo, W.C. Chan

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