Whole-genome Sequencing of Angioimmunoblastic T-Cell Lymphoma Combined With Plasma Cell Leukemia: A Case Report and Review of the Literature

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Research Article

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Abstract

Purpose Angioimmunoblastic T-cell lymphoma (AITL) is a distinct subtype of peripheral T-cell lymphomas, sometimes involves proliferation of plasma cells. Currently, only 7 cases of AITL with monoclonal plasmacytosis have been reported. However, the molecular mechanisms underlying the interaction between monoclonal plasma cells and T cells have not been identified. We describe a rare case of AITL with plasma cell leukemia (PCL) in this report.

Methods The patient was a 67-year-old female diagnosed with AITL and PCL. CD138 positive plasma cells and CD138-negative mixed bone marrow populations of this patient were collected for whole-genome sequencing (WGS). A review of the literature on AITL cases with monoclonal plasma cells is presented.

Results WGS showed that the two cell populatoins shared 282 non-synonymous single nucleotide variants (SNVs) and excess of G to A and C to T transitions. We identified 14 potential driver genes in this patient. Functional enriched analysis of mutant genes confirmed several significantly enriched pathways, including VEGF signaling. The patient was treated with one cycle of PD (combined Bortezomib and Dexamethasone) and Chidamide. However, the patient developed severe pneumonia and pancytopenia, refused to receive further treatment, and died one week after discharge.

Conclusion Being aware of the coexistence of PCL and AITL is important for accurate diagnosis and appropriate treatment. In addition, our results suggested the involvement of a group of genes and pathways in AITL with coexisting PCL, providing valuable information for further exploration of the underlying molecular mechanisms.

Introduction

Angioimmunoblastic T-cell lymphoma (AITL), a common subtype of peripheral peripheral T-cell lymphomas (PTCL), accounts for about 19% of PTCL [1]. AITL mainly occurs in elderly patients and is associated with generalized lymphadenopathy, hepatomegaly or splenomegaly, eosinophilia, skin rash, and fever [2]. Immunophenotypically, AITL is of the classic form of T-follicular helper (T_{FH}) cells [3]. Interestingly, polyclonal plasma cells and large B immunoblasts were found in lymph nodes and overexpression of B cell genes was shown by gene expression profiling studies [4]. Therefore, patients with AITL often present with B cell hyperactivity signs, such as polyclonal hypergammaglobulinemia, Coombs-positive hemolytic anemia, and other B-cell associated hematological abnormalities. Moreover, cases of AITL with coexisting clonal B cell disorders, mostly large B-cell lymphoma and small B-cell proliferation, had been reported [5; 6]. Cases of AITL with coexisting plasmacytoma or myeloma, and rarely, with coexisting plasma cell leukemia (PCL), have also been reported [7; 8; 9]. However, the mechanisms underlying the interaction between monoclonal plasma cells and T cells have not been identified.

To date, only one case of AITL with coexisting PCL has been reported. Here we reported another case of AITL with coexisting PCL. We performed whole-genome sequencing (WGS) of both CD138 positive and CD138 negative bone marrow cells to understand the molecular alterations.

Case Presentation

A 67-year-old female presented with 3-week history of progressive fatigue, weakness, diarrhea, and fever. She had the medical history of rheumatoid arthritis, hypertension, and diabetes.

After admitted to the hospital, laboratory studies revealed the following: hemoglobin, 69 g/L; leukocytes, 4.2×10^9/L; platelets, 44×10^9/L; fibrinogen 1.6 g/L (normal range, 2-4 g/L); albumin, 26.5 g/L (normal range, 40-55 g/L); globulin, 70.8 g/L (normal range, 20-40 g/L); direct bilirubin 58 μmol/L (normal range, 0-8 μmol/L); indirect bilirubin 28 μmol/L (normal range, 3-14 μmol/L); lactate dehydrogenase, 357 IU/L (normal range, 120-250 IU/L); β2-microglobulin, 17.90 mg/L (normal range, 1.05-2.50 mg/L); C-reactive protein, 34.6 mg/L (normal range, < 8 mg/L). Coombs direct antiglobulin test was positive. Serum protein electrophoresis revealed a monoclonal protein spike (Fig. 1A). The monoclonal protein was identified as IgG lambda by serum protein immunofixation (Fig. 1B). Peripheral blood smears showed circulating enlarged immature plasma cells (20% of total white blood cells) (Fig. 1C). Other laboratory studies included negative test for anti-nuclear antibody and elevated concentration

of serum IL-6 14.6 pg/ml (normal range, 0.1-2.9 pg/ml). Epstein-Barr virus (EBV) concentration detected by quantitative polymerase chain reaction was 1.04×10^5.

Marrow aspirate smears demonstrated an increase in the number of plasma cells (55.0% among all nucleated cells). The plasma cells had foamy basophilic cytoplasm and open chromatin. Flow cytometric analysis of the patient's BM showed a predominant CD45dim cell population which expressed CD19, CD38, and CD138, and did not express CD56, CD117, CD20, or CD22, and were lambda chain restricted (lambda to kappa ratio was 6) (Fig. 1D). Based on these findings, the diagnosis of plasma cell leukemia was rendered. A BM trephine biopsy revealed diffuse CD138 positive clonal plasma cells. Notably, there were infiltrating atypical lymphoid cells that were CD3 positive (Fig. E-G). Karyotypic analysis of the BM cell culture showed 46, XX in all metaphase cells analyzed (n=20). Fluorescent in situ hybridization (FISH) analysis did not show abnormality in IGH, 1q21, D13S319, P53, and RB.

Positron emission tomography (PET) computed tomography scan revealed high uptake of extensive lymphadenopathy in the chest, abdomen as well as pelvis. In addition, mild uptake of liver, spleen, and BM were seen (Fig. 2A).

A left cervical lymph node was biopsied. Unexpectedly, the structure of the lymph node was effaced and there was a diffuse infiltration of small to medium-sized atypical lymphoid cells admixed with scattered plasma cells. These lymphoid cells had clear cytoplasm, distinct cell membranes and atypical nuclears. Immunohistochemical stains demonstrated a high proliferation rate of the atypical lymphoid cells (Ki-67 index was 70%). These cells were positive for CD2, CD3, CD4, CD7, CD10 and PD-1, partially positive for CD5. They were negative for CD8, CD20, CD21, Bcl-2, PAX-5, ALK, or CyclinD1. Some cells were positive for CXCL13, Bcl-6, and EBV by in situ hybridization (EBER). The plasmacytic cells expressed CD138, CD79a, MUM1 and lambda but not kappa light chain (Fig. 2C-H). TCR gene rearrangements detected by capillary electrophoresis showed (Fig. 2B). These findings led to the diagnosis of AITL with coexisting plasma cell infiltrate for the lymph node.

There was no evidence of osteolytic lesions. Previous plasma disorders were excluded based on the patient's medical history and clinical laboratory. Finally, the patient was diagnosed with PCL with coexisting AITL.

To further understand the molecular characteristics of the disease, WGS of CD138 purified plasma cells and CD138 negative mixed bone marrow populations (mixed BM) was performed separately by Illumina technology. Clean FASTQ sequence reads were first mapped to human genome 19 (UCSC) using Burrows-Wheeler Alignment Tool (BWA), and then local realignment was performed using the Genome Analysis Tool Kit (GATK). 464 and 540 coding non-synonymous single nucleotide variants (SNVs) for PCL and mixed BM, respectively, were obtained, 282 of which were shown in both samples (Fig. 3A). Excess of C > T and G > A nucleotide transitions were shown (Fig. 3B). Using MutSigCV, we identified 14 potential driver genes in this patient (Table 1). Functional enriched analysis of muted genes confirmed several significantly enriched pathways, including VEGF signaling.

Table 1
Significantly affected genes in both PCL and Mixed BM

PSMB4	TPO	TTC31	FLNB	CEP63	RANBP3L	PCDHA3
C5orf46	CENPQ	MLIP	TPD52L3	PTCH1	OR1L6	LYZL1

The patient was treated with one cycle of combined PD (Bortezomib 1.3 mg/m^2 and Dexamethasone 20 mg/day at days 1 and 2) and Chidamide 20 mg biweekly. However, the patient developed severe pneumonia and pancytopenia, refused to receive further treatment, and discharged subsequently. She died one week after discharge.

Conclusions And Discussion

The case we presented here is an elderly female patient with generalized lymphadenopathy and a positive Coomb's test. A diagnosis of AITL, which was consistent with the clinical findings, was made by lymph node biopsy and bone marrow studies, including immunophenotyping and analysis of TCR gene rearrangement. Meanwhile, the patient was also found to have IgG-

type M-protein, extensive bone marrow clonal plasma cells, more than 20% abnormal plasma cells in peripheral blood as well as elevated LDH and β2-microglobulin serum levels. These findings indicated the coexistence of PCL.

The 2016 World Health Organization classification of lymphoid neoplasms defined AITL as one of the nodal T-cell lymphomas with T_{FH} cell origin [10]. T_{FH} cells are the effector T-cell subset, essential for antibody responses in a germinal center by promoting B cell differentiation to either plasma cells or memory B cells [11]. Abnormal differentiation or clonal expansion of T_{FH} cells could lead to autoimmune disease, even development of AITL.

It has been observed that AITLs were concomitant with polytypic plasmacytosis in patients with sepsis, autoimmune conditions, human immunodeficiency virus infections, and organ transplantation. Ahsanuddin et al. reported 3 cases of AITL with an exuberant population of plasma cells and plasmacytoid lymphocytes presented in the peripheral blood [12]. Further tests proved these plasma cells were polyclonal, indicating that the plasmacytosis was a reactive process. Another study compared 3 AITL cases with prominent polyclonal plasmacytosis with 12 AITL cases without plasmacytosis [4] and found that the 3 patients with AITL and plasmacytosis had worse performance status compared with AITL without plasmacytosis. However, other parameters, including B symptoms, serum levels of lactate dehydrogenase, C-reactive protein and soluble interleukin-2 receptor, showed no significant differences between the two groups. Furthermore, another case was reported that circulating reactive plasma cells mimicked plasma cell leukemia after chemotherapy in patient with a peripheral T-cell lymphoma [13].

Although most of the proliferating plasma cells in AITL were reported to be polyclonal [14], there were rarely monoclonal cases. We searched and compiled the reported 7 cases of AITL with monoclonal plasma cells [7; 8; 9; 15; 16; 18], as presented in Table 2.

Table 2
Cases of AITL with clonal plasma cells

Sex/Age(year)	Pattern of plasma cell proliferation	Site of plasma cell proliferation	Interval (mo)	Light chain restriction	EBER	Treatment	Follow-up (mo)	Reference
M/61	Clonal	lympho node	96	NA	positive	NA	AWD (24)	Zettl et al. 2002
F/70	Clonal	lympho node	N	lamda	Negative	R-CHOP	AWD (39)	Balague et al. 2007
M/56	Clonal	lympho node	N	lamda	Negative	NA	NA	Balague et al. 2007
F/60	Clonal	lympho node	N	kappa	Negative	E-CHOP	NA	Huppmann et al. 2013
F/80	Multiple myeloma	bone marrow	N	IgA lambda	Positive	modified COP	deceased (6)	Xu et al. 2015
M/73	Plasma cell leukemia	bone marrow	N	IgM kappa	Negative	CHOP	NA	Jang et al.2015
M/87	Clonal	lympho node	N	NA	Negative	NA	deceased (after diagnosis)	Okuyama 2017

Among the 7 AITL cases 6 cases had concurrent clonal plasmacytosis and 1 case developed a secondary plasmacytosis 96 months after diagnosis of AITL. 5 cases presented with monoclonal plasma cells in lymph nodes and 2 cases were diagnosed with multiple myeloma (MM) and PCL, respectively. The plasma cell population commonly exhibited CD79a positive and lacked CD20 expression. Five cases showed immunoglobulin light chains restriction. Surprisingly, only 2 cases were positive for EBER in clonal plasma cells, which was distinct from usual observation that B-cell proliferations in AITL are EBV-positive.

In the current case, the patient suffered from two infrequent malignancies, AITL and PCL. Clonal T cells and plasma cells were present in both lymph node and bone marrow. PCL is the most aggressive clonal plasma cell dyscrasia [17]. Approximately, 60-70% of PCL are primary (pPCL) and 30-40% are secondary (sPCP) [19]. Compared to MM, pPCL has distinct clinical and laboratory features. The median age of patients with pPCL is about 10 years earlier than patients with MM or sPCL. PCL exhibits a higher tumor burden with enlargement of organs, hypercalcemia, anemia, and thrombocytopenia. However, osteolytic lesions are less common in pPCL [20].

The mechanisms of AITL concomitant with plasma disorders are probably multifactorial. It was hypothesized that EBV activation played an important role [21]. As EBV infects B cells, the infected B cells can present EBV protein to T cells and upregulate CD28 ligand which promote the high expression of CXCL13 in T_{FH} cells. Then, T_{FH} cells in turn stimulate B cells enrichment and form a loop of immune stimulation [22]. However, some cases like our case are EBV-negative. Various high expression of cytokines, such as interleukin-6 (IL-6), IL-5, IL-10, and tumoral necrosis factor may promote the growth of plasma cells in an EBV-independent way [4; 7; 16].

To explore the potential mechanism, we analyzed the gene expression profile of CD138 purified plasma cells and CD138-negative mixed bone marrow populations by performing WGS. We found 458 and 540 SNVs in PCL and Mixed BM samples, respectively, with 282 of the SNVs shared in both samples. Furthermore, we observed excess of C > T and G > A transitions in somatic mutations, which has been reported in MM. We also identified 14 genes that might have played a driver role in this patient. Interestingly, several pathways, especially the VEGF signaling pathway, were identified by functional enriched analysis to be enriched in the mutant genes.

Overall, our results suggested the involvement of a group of genes and pathways in AITL with coexisting PCL, which may help us understand the underlying molecular mechanisms. As plasma cell expansion can partially overshadow the coexisting T-cell neoplasm, thoughtful diagnostic investigations are required when a wide array of clinical symptoms are present that are often seen in patients with lymphoma.

Abbreviations

AITL: Angioimmunoblastic T-cell lymphoma; EBV: Epstein-Barr virus; EBER: EBV by in situ hybridization; MM: multiple myeloma PCL: plasma cell leukemia; FISH: Fluorescent in situ hybridization; PET: Positron emission tomography; SNVs: single nucleotide variants; WGS: whole-genome sequencing

Declarations

Authors' contributions

YY structured and wrote the manuscript. ZEF collected the clinical sample. HJS and CZ structured and reviewed the manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials

Data sharing not applicable to this article as all the data are already listed in this paper.

Ethics approval and consent to participate

Our study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University, and informed consent was obtained from this patient.

Consent for publication

Written consent for publication was obtained from the patients relative.

Competing interests

The authors declare that they have no competing interests.

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Figures

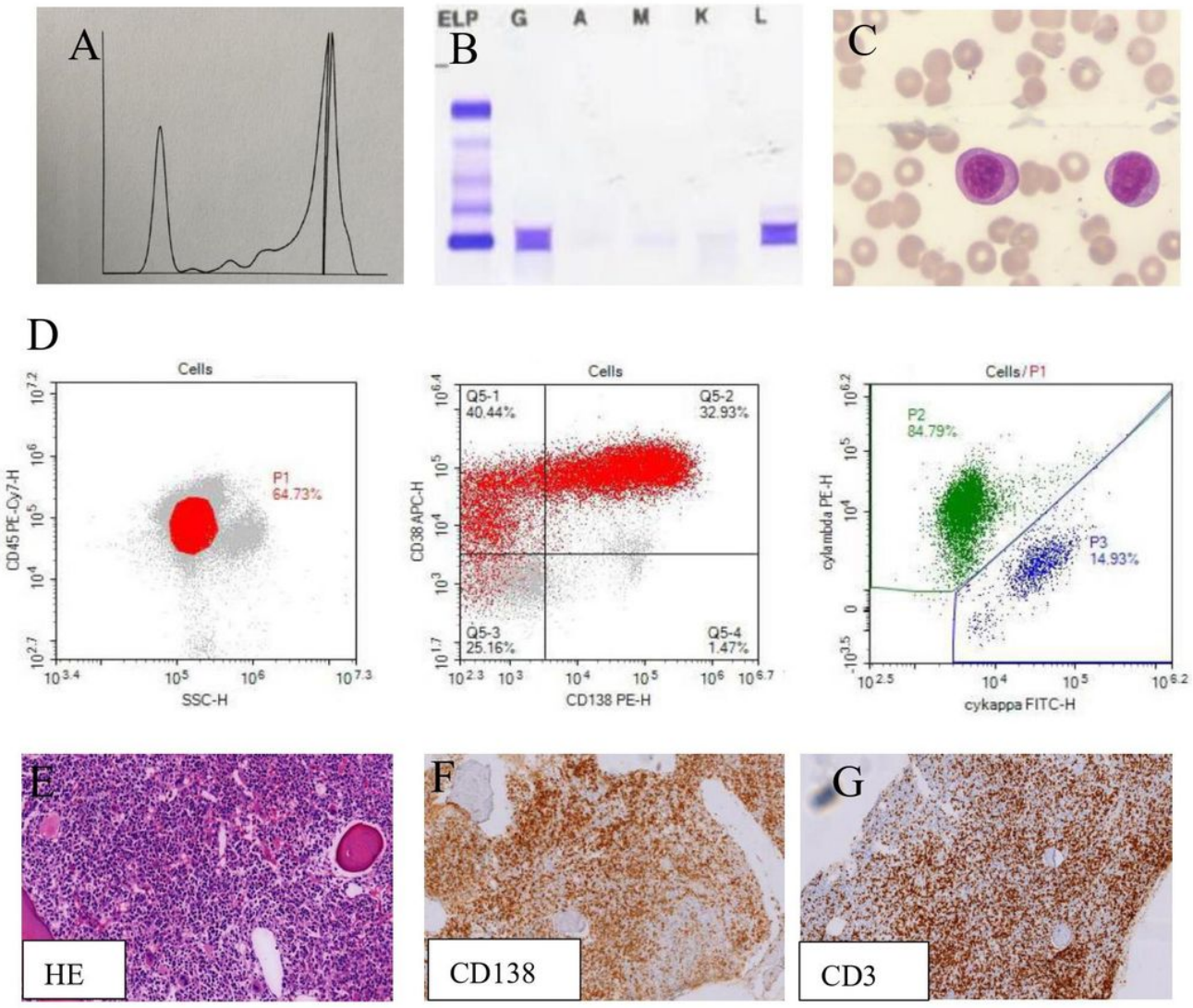

Figure 1

Plasma cell leukemia

A. Serum protein electrophoresis showing a monoclonal protein spike.

B. The monoclonal protein was identified as IgG lambda by immunofixation electrophoresis.

C. Peripheral blood smears showing proliferation of immature plasma cells (×1000).

D. Bone marrow flow cytometry indicating aberrant plasma cells expressing CD38, CD138, and restricted lambda light chain.

E. Hematoxylin and eosin staining of bone marrow biopsy showing hypercellular bone marrow (× 200).

F. Plasma cells expressed CD138 (×200).

G. The infiltrating atypical lymphoid cells were positive for CD3 (×200).

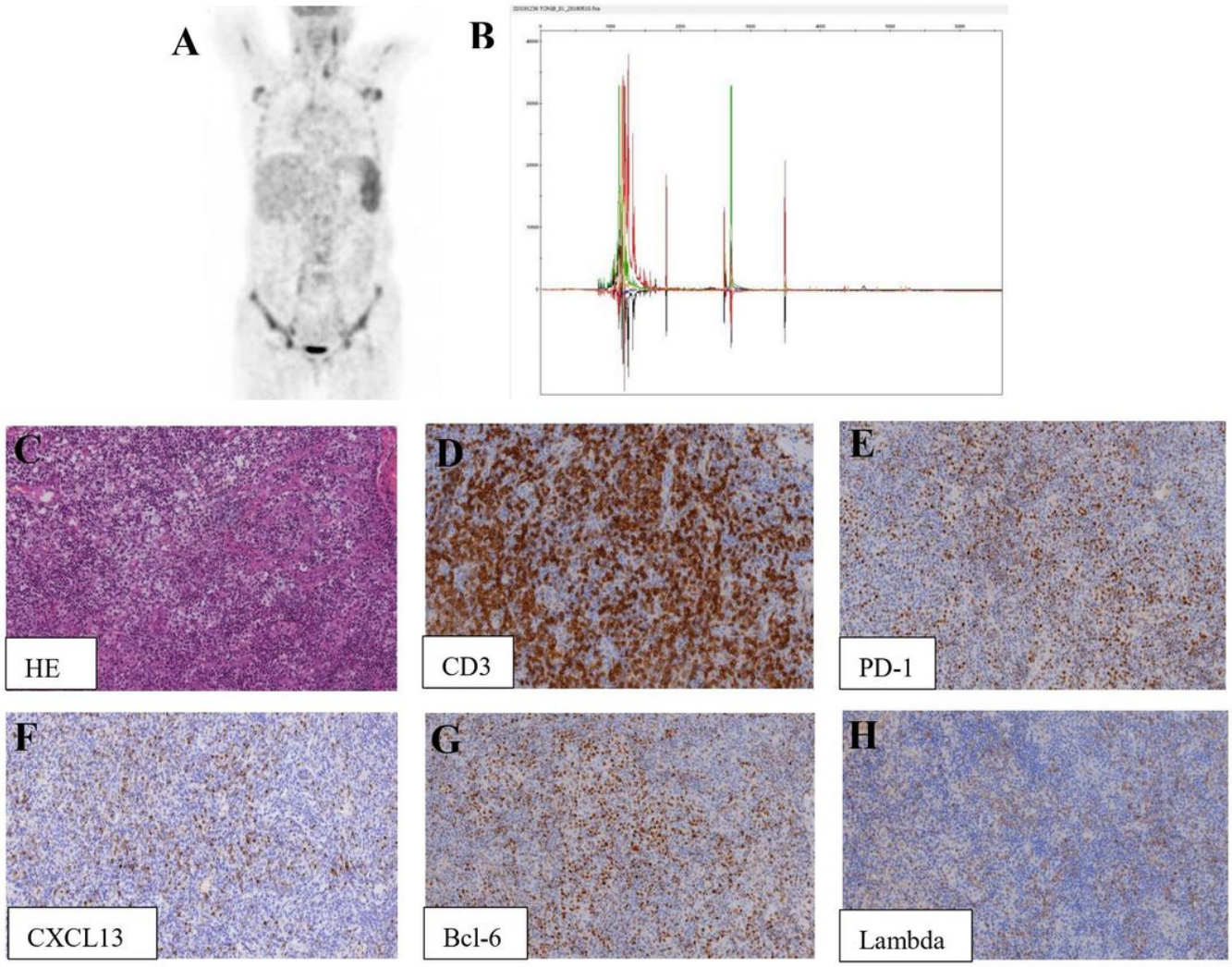

Figure 2

Angioimmunoblastic T-cell lymphoma

A. PET image showing high uptake of extensive lymphadenopathy as well as hepatomegaly and splenomegaly.

B. Capillary electrophoresis showing TCR gene rearrangement.

C. Hematoxylin and eosin staining of lymph node (× 200).

Immunophenotyping of the lymph node revealed strong expression of CD3 (D)、PD-1 (E) and scattered expression of CXCL13 (F), Bcl-6 (G) and Lambda (H)

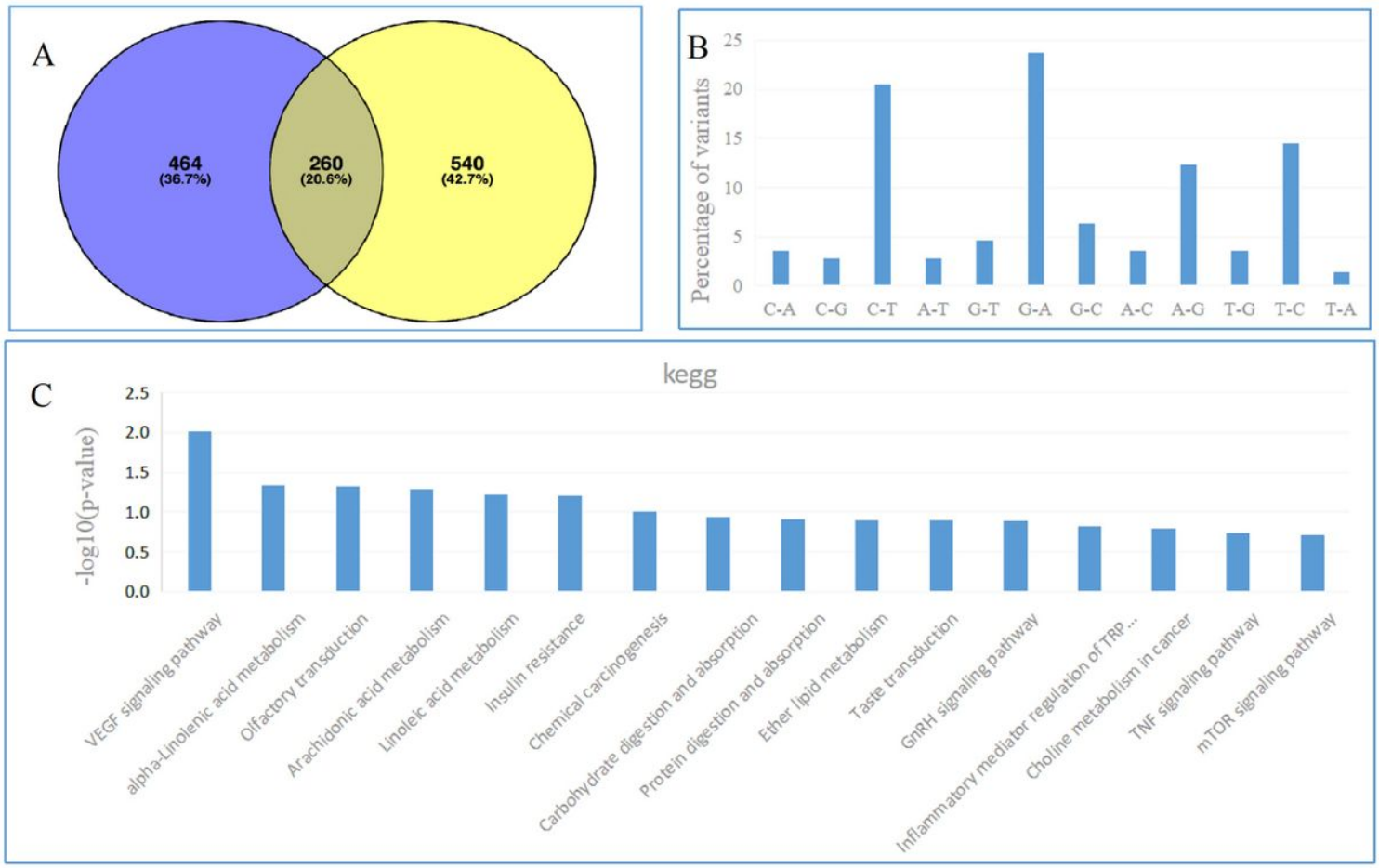

Figure 3

Whole-genome Sequencing

A. Coding single nucleotide variants (SNVs) by nucleotide change.

B. SNVs in PCL and Mixed BM.

C. Pathways identified by functional enriched analysis of muted genes in both PCL and Mixed BM.