

Chromosome Translocation t(14;21)(q11;q22) Activates Both *OLIG1* and *OLIG2* in Pediatric T-cell Lymphoblastic Malignancies and May Signify Adverse Prognosis

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Abstract. *Background/Aim:* The chromosome translocation t(14;21)(q11;q22) was reported in four pediatric T-cell lymphoblastic leukemias and was shown to activate the *OLIG2* gene. *Materials and Methods:* A pediatric T-cell lymphoblastic lymphoma was investigated using G-banding chromosome analysis, fluorescence in situ hybridization (FISH), and immunocytochemistry. *Results:* The malignant cells carried a t(14;21)(q11;q22) aberration. The translocation moves the enhancer elements of *TRA/TRD* from band 14q11 to 21q22, a few thousands kbp downstream of *OLIG1* and *OLIG2*, resulting in the production of both *OLIG1* and *OLIG2* proteins. *Conclusion:* The translocation t(14;21)(q11;q22) occurs in some pediatric T-cell lymphoblastic malignancies. Activation of both *OLIG1* and *OLIG2* by t(14;21)(q11;q22) in T-lymphoblasts and the ensuing deregulation of thousands of genes could explain the highly malignant disease and resistance to treatment that has characterized this small group of patients.

T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphomas (T-LBL) are malignant diseases in which early T-cell precursors proliferate and replace the

normal hematopoietic cells. Although there is a difference between them with regards to gene expression profiles (1-3), the two diseases are considered to be aspects of the same malignancy and distinguished only by the degree of blast cell infiltration in the bone marrow (4-6). Bone marrow blast cell infiltration higher than 25% defines T-ALL whereas less than 25% infiltration defines T-LBL (2, 4, 5). Thus, in T-LBL, the abnormal lymphocytes are found in the lymph nodes or thymus whereas in T-ALL, the abnormal lymphocytes are seen mainly in the blood and bone marrow.

T-ALL and T-LBL patients carry in their malignant cells acquired genetic changes that contribute to increased proliferation, prolonged survival, and/or impaired differentiation of lymphoid hematopoietic progenitors (7-11). Many of the changes are in the form of non-random numerical or structural chromosome aberrations that can be detected microscopically and often carry prognostic significance (8).

We herein present a T-cell lymphoblastic lymphoma with the chromosome aberration t(14;21)(q11;q22), review the relevant literature, and conclude that the translocation probably carries an adverse prognosis.

Materials and Methods

Ethics statement. The study was approved by the regional ethics committee (Regional komité for medisinsk forskningsetikk Sør-Øst, Norway, <http://helseforskning.etikkom.no>).

Case report and immunocytochemical studies. A 13-year-old boy was admitted with vena cava superior syndrome, night sweats, and pain below the right costal margin. Diagnostic work-up showed a large mediastinal tumor, pleural fluid that almost filled the whole right lung, and metastases in both kidneys as well as in the skin. T-

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lymphoblasts were found in the pleural fluid, bone marrow, and spinal fluid (Figure 1A-D). Cytogenetic analysis revealed a translocation t(14;21) in T-cells from a mediastinal tumor biopsy and from the pleural fluid. The final diagnosis was T-cell non-Hodgkin's lymphoma. Because of the genetic findings (see below), immunocytochemistry was performed using OLIG1 and OLIG2 antibodies (Figure 1E and F). The OLIG1 antibody was a mouse monoclonal antibody (OLIG1 Monoclonal antibody 257219) purchased from Thermo Fisher Scientific (Waltham, Massachusetts, United States; Catalogue number MA5-23954) and applied at 1:400 dilution. For visualization, the Dako EnVision Flex + System (K8012; Dako, Glostrup, Denmark) was used as previously described (12). The OLIG2 antibody was a polyclonal goat antibody purchased from R&D Systems (Catalog number AF2418) and applied at 1:50 dilution. The Roche Ventana BenchMark ULTRA instrument was used. The section was pretreated with Cell Conditioning Solution (CC1) and detected using the OptiView DAB system.

The patient started on the EURO-LB-02 lymphoma protocol (13) but developed a large sinus venous thrombosis. Evaluation after 2 weeks of treatment showed some reduction of disease load, but after 4 weeks the tumor had again increased in size. Treatment was then switched to the NOPHO ALL 2008 high-risk protocol with intensive block treatment (14). No response after the first block (cyclophosphamide/etoposide) was seen, but there was good response after the second block (high dose methotrexate/high dose cytarabin). Before onset of the third block, however, the tumor again increased in volume. The patient received Nelarabin for five days with no effect on tumor and, during the following week, the blast count increased rapidly in the blood. The patient died peacefully in his sleep 4 months after diagnosis.

G-banding analysis. Cells from bone marrow, lymph node, and pleural effusion were cultured and harvested using standard techniques (15, 16). Chromosome preparations were G-banded with Leishman stain and examined (Figure 2). The karyotype was written according to The International System for Human Cytogenomic Nomenclature (ISCN) 2016 guidelines (17).

Fluorescence in situ hybridization (FISH). FISH analyses were performed on metaphase spreads and interphase nuclei using a commercial break apart probe (CytoCell) for the T cell receptor alpha/delta locus on chromosome band 14q11 (*TRA/TRD*) and a home-made break apart probe for chromosome band 21q22 (Figures 3 and 4). The BAC probes were purchased from the BACPAC Resource Center located at the Children's Hospital Oakland Research Institute (Oakland, CA) (<https://bacpacresources.org/>). Selection of BAC probes was based on the published (18) genomic breakpoint on der(21) (see below).

The BAC clones used were RP11-79D9 (proximal part of the probe, containing both the *OLIG1* and *OLIG2* genes, Position: chr21:32910480-33075022, GRCh38/hg38 assembly) and RP11-996D17 (distal part of the probe, Position: chr21:33281951-33446033). DNA was extracted whereupon the RP11-79D9 and RP1-995D17 probes were labelled with Fluorescein-12-dCTP (PerkinElmer, Boston, MA, USA) and Texas Red-5-dCTP (PerkinElmer) in order to obtain green and red signals, respectively, using the Abbott's nick translation kit (Des Plaines, IL, USA), and hybridized according to Abbott Molecular recommendations (<http://www.abbottmolecular.com/home.html>). Chromosome preparations were counterstained with 0.2 µg/ml DAPI and overlaid with a 24 x

50 mm² coverslip. Fluorescent signals were captured and analyzed using the CytoVision system (Leica Biosystems, Newcastle, UK).

Sequence analysis. The BLAT alignment tool and the human genome browser at UCSC (19, 20) were used to map on the Human GRCh38/hg38 assembly the previously published (18) nucleotide sequence resulting from the t(14;21)(q11;q22).

Results

Cytogenetics. G-banding analysis of bone marrow cells yielded a normal karyotype (46,XY), whereas the analysis of lymph node cells showed 46,XY,t(14;21)(q11;q22)[3], and pleura effusion cells had the karyotype 46,XY,t(14;21)(q11;q22)[17]/46,XY,idem,del(6)(q13q23)[3] (Figure 2).

FISH. FISH with the *TRA/TRD* break apart probe showed that the *TRA/TRD* locus (14q11) had been rearranged and that the distal part of the probe had moved to the 21q22 band (green signal in Figure 3B and C). FISH with the 21q22 break apart probe showed that the distal part of the probe with BAC RP11-996D17 (red signal in Figure 4B and C) had moved to 14q11 whereas the proximal part with BAC RP11-79D9 and containing both the *OLIG1* and *OLIG2* genes, hybridized to the der(21)(q22) (green signal in Figure 4B and C).

Immunocytochemistry. Immunostaining experiments with OLIG1 and OLIG2 antibodies showed that both proteins were produced in the T-cells (Figure 1E and F).

Sequence analysis. The sequence of the genomic breakpoint on der(21) reported by Wang *et al.* (18) was: AGGTGTTTCAGT GCCTTGCGCGCGTGGCTGTGCG-GGGATAGCAACTA TAAACTGACATTTGG. Using the BLAT alignment tool, we mapped this sequence on the Human GRCh38/hg38 assembly and found that the breakpoint occurred at position Chr21:33110158 (AGGTGTTTCAGTGCCTTGCGCGCGTGG CTGTGCG: position chr21:33,110,127-33,110,158 and GGGA TAGCAACTATAAACTGACATTTGG position chr14:22,483,012-22,483,040). Our mapping of the above-mentioned sequence showed that the 3'-end of *TRA/TRD*, including the gene's enhancer, was placed distal to both the *OLIG1* and *OLIG2* genes which are transcribed from centromere to telomere. The genetic distance from the breakpoint to *OLIG1* is 40 kbp, the genetic distance from the breakpoint to *OLIG2* is 82 kbp, and hence the distance between *OLIG1* and *OLIG2* is 42 kbp.

Discussion

Including the present case, the cytogenetic aberration t(14;21)(q11;q22) has now been reported in five patients (18, 21-23). The four previously described patients had ALL whereas the present case was a T-LBL. Four of the patients

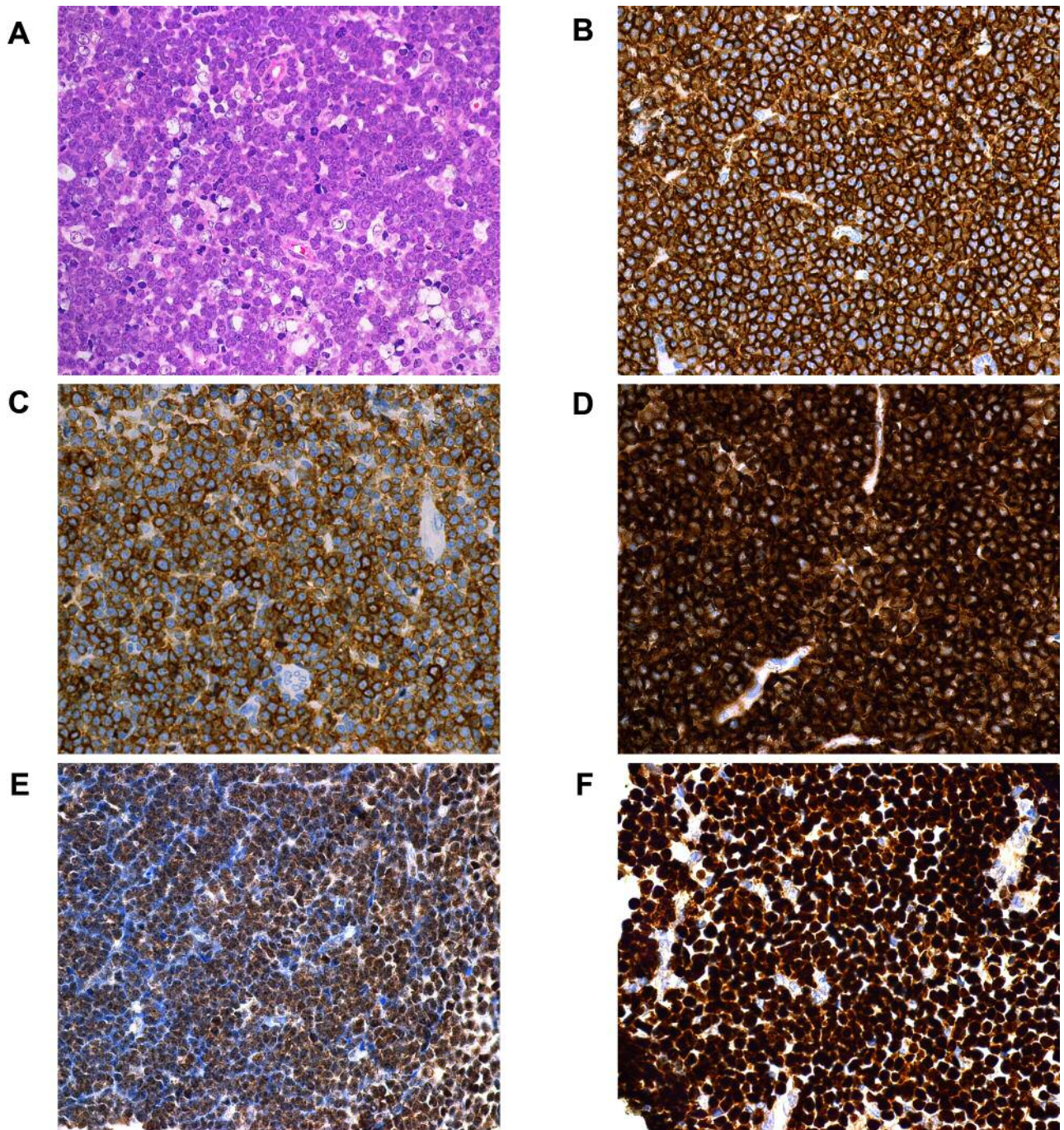


Figure 1. Microscopic examination of the T-cell lymphoblastic lymphoma. A: H&E stained image, magnification: $\times 60$. B: Immunocytochemical staining with anti-CD3, magnification: $\times 60$. C: Immunocytochemical staining with anti-CD1a, magnification: $\times 60$. D: Immunocytochemical staining with anti-CD10, magnification: $\times 60$. E: Immunocytochemical staining with anti-OLIG1, magnification $\times 60$. F: Immunocytochemical staining with anti-OLIG2, magnification: $\times 60$.

were children aged 7, 8, 13, and 13 years whereas the fifth was a 50-week-old infant (Table I). Four patients died of their disease (including our case) whilst one was reported as being in relapse. Thus, although information is limited, the

chromosome translocation t(14;21)(q11;q22) seems to occur in children with T-cell lymphoblastic malignancies, mostly in boys (male-to-female ratio is 4:1 so far), and may signify an adverse prognosis.

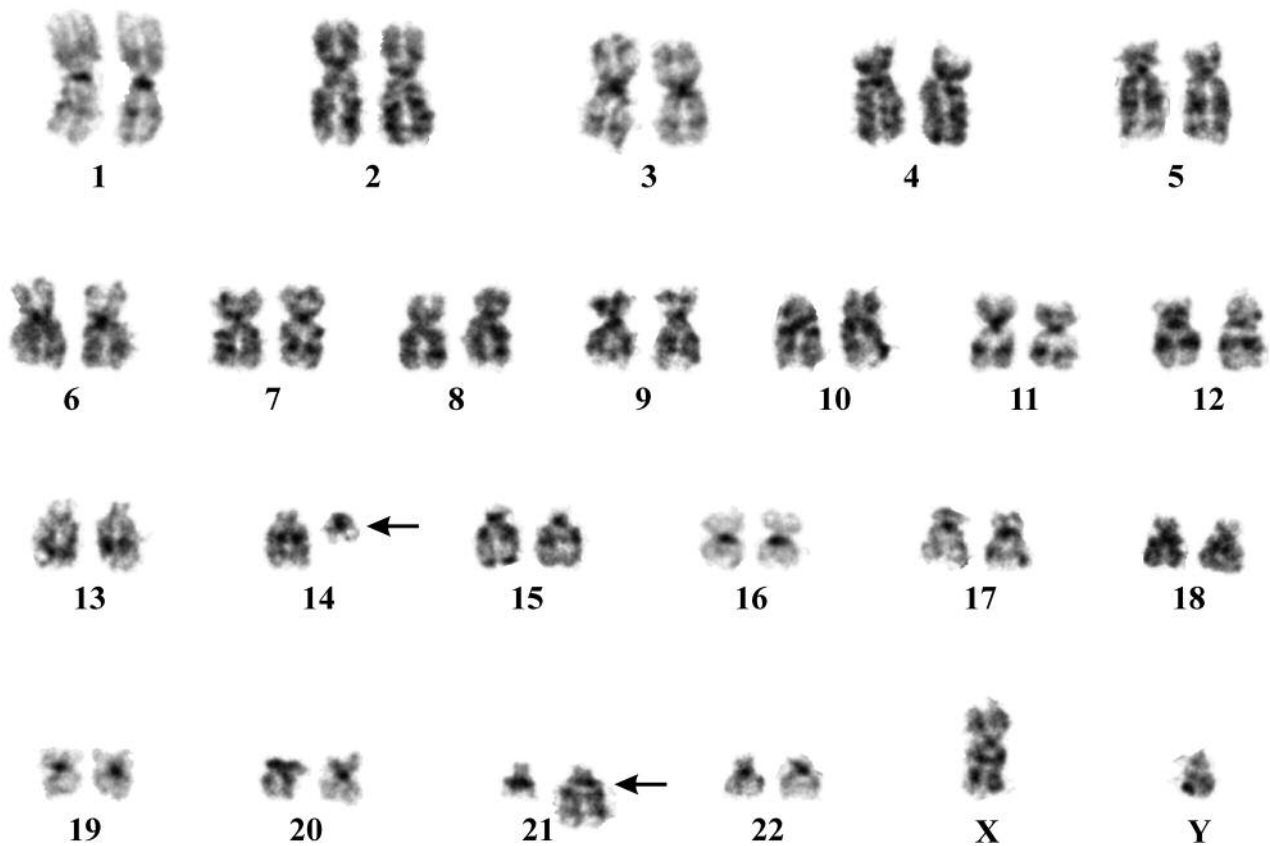


Figure 2. G-banding analysis of cells from a lymph node showing the 46,XY,t(14;21)(q11;q22) chromosome translocation. Breakpoint positions are indicated by arrows.

In the first report of t(14;21)(q11;q22), cloning of the translocation breakpoint showed rearrangement of *TRA/TRD* in 14q11, identified *OLIG2* in 21q22 (it was originally named *BHLHB1*), and showed that the latter gene was activated by the translocation (18). In the present study, we mapped the sequence of the genomic breakpoint on der(21) reported by Wang *et al.* (18) and found that the 3'-end of *TRA/TRD*, including the enhancer, was placed distal to both the *OLIG1* and *OLIG2* genes. We therefore estimated that, although only the *OLIG2* gene was discovered and studied by Wang *et al.* (18), the result of t(14;21)(q11;q22) in their case probably was activation of both *OLIG1* and *OLIG2*. FISH investigation of our case with a 21q22 break apart probe (Figure 4) indicated that the breakpoint was in the same region as that reported by Wang *et al.* (18). Furthermore, immunostaining experiments showed that both OLIG1 and OLIG2 proteins were produced by the T-cells (Figure 1E and F). Thus, the main molecular consequence of t(14;21)(q11;q22) is the relocation of enhancer elements of *TRA/TRD* from band 14q11 to 21q22, a few thousand kbp downstream of the *OLIG1* gene, resulting in activation of both the *OLIG1* and *OLIG2* genes leading to the

production of OLIG1 and OLIG2 proteins (Figure 1E and F).

The proteins OLIG1, OLIG2, and OLIG3 form the OLIG sub-family of transcription factors within the larger family of basic helix-loop-helix (bHLH) transcription factors (24). The *OLIG1* and *OLIG2* genes are expressed exclusively within the central nervous system where they play an important role in the development of motor neurons, oligodendrocytes, and a subset of astrocytes and ependymal cells (25-28). *OLIG3* maps on chromosome band 6q23 and, at least in mice, plays a role in the development of class A and B neurons of the dorsal horn of the spinal cord (29). Expression profiling in mice models has shown that OLIG1 and OLIG2 regulate thousands of genes (24): 2,570 were up-regulated whereas 2,654 genes were down-regulated specifically in *Olig2*^{-/-} mice, 2265 genes were up-regulated and 2,096 genes were down-regulated specifically in *Olig1*^{-/-} mice, and there were also 1,383 commonly upregulated genes and 1491 commonly downregulated genes found in both *Olig2*^{-/-} and *Olig1*^{-/-} mice (24).

The *OLIG2* gene has been shown to be involved in the development of brain cancers and can be used as a molecular

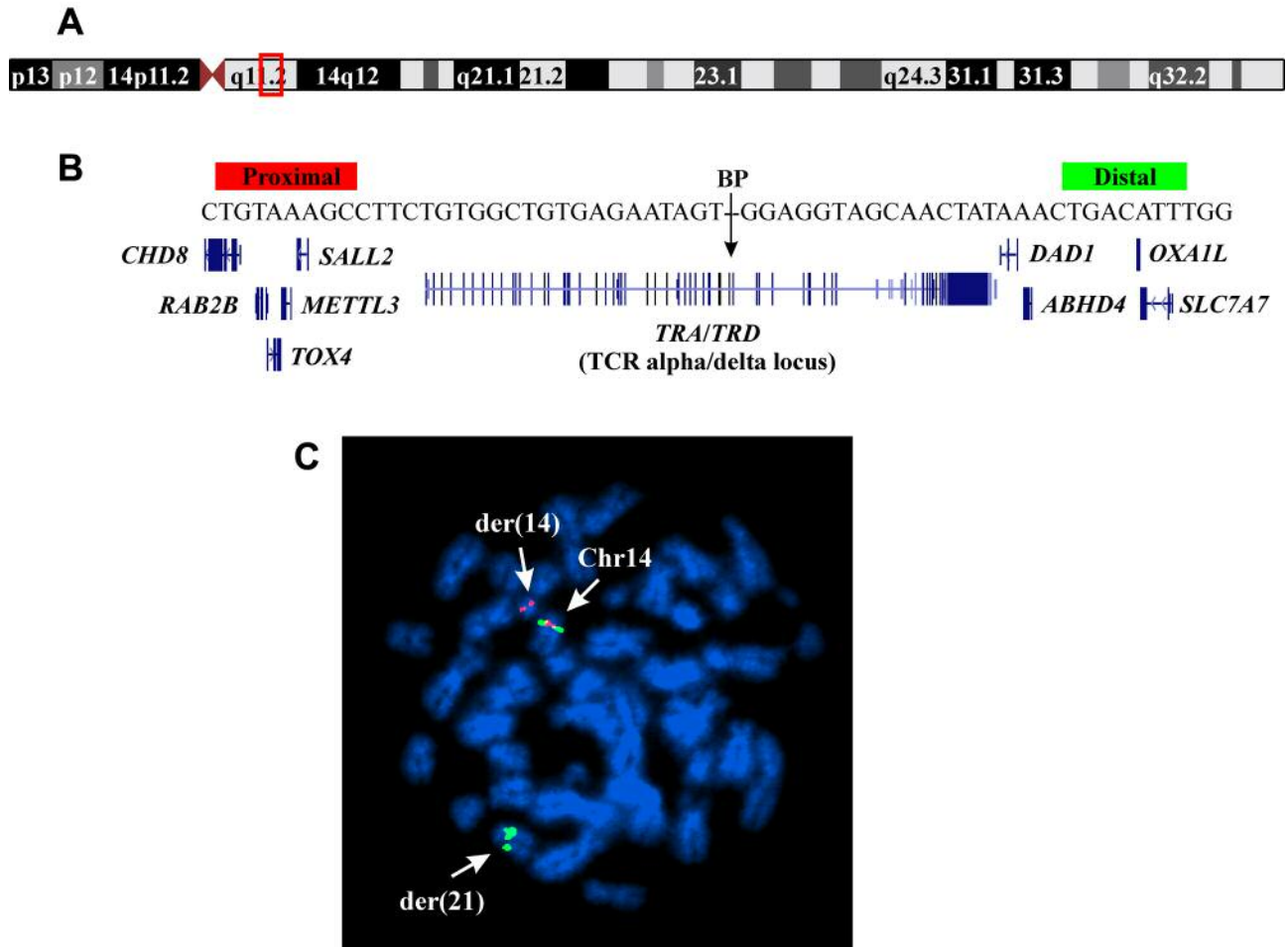


Figure 3. *FISH* analysis of cells from a lymph node using a commercial TCR alpha/delta locus (TRA/TRD) break apart probe. A: Ideogram of chromosome 14 showing the mapping of TRA/TRD on chromosome band 14q11.2 (red box). B: Diagram showing the proximal (red) and distal (green) parts of the TRA/TRD break apart probe. Additional genes in this region are also shown. Arrow indicates the genomic breakpoint (BP) reported by Wang *et al.* (18). The reported sequence around the BP is also given. C: Metaphase spread showing splitting of the TRA/TRD probe. The distal part (green label) of the probe hybridized to der(21) whereas the proximal part (red label) hybridized to der(14). Both distal and proximal parts hybridized to normal chromosome 14.

Table I. The published lymphoblastic malignancies carrying the chromosome translocation t(14;21)(q11;q22).

Gender/Age (years)	Reported karyotype	Diagnosis	Clinical output	Reference
F/7	46,XX,del(6)(q21),t(14;21)(q11;q22)	T-ALL	Died after 4 months of therapy	18
M/<1	46,Y,t(X;4)(p21;q31),t(14;21)(q11;q22)	ALL	Died 62 months after relapse	21
M/8	46,XY,t(14;21)(q11;q21)[29]/46,XY[1]	T-ALL	Relapse	22
M/13	46,XY,t(14;21)(q11;q21)[22]/46,XY[12]	T-ALL	Died after 18 months of therapy	23
M/13	46,XY,t(14;21)(q11;q22)[17]/46,XY,idem,del(6)(q13q23)[3]	T-LBL	Died 4 months after diagnosis	Present case

marker for diffuse gliomas (30-32). Expression of *OLIG2* was also reported in leukemia cell lines as well as breast cancer, melanoma, and non-small cell lung carcinoma cell lines (33). In the same study, the authors concluded that expression of

OLIG2 in thymocytes was only weakly oncogenic and required collaborative events such as overexpression of *LMO1*, *NOTCH1* or other cell proliferation signals in order to induce a highly penetrant leukemia (33). Recently, *OLIG2* was

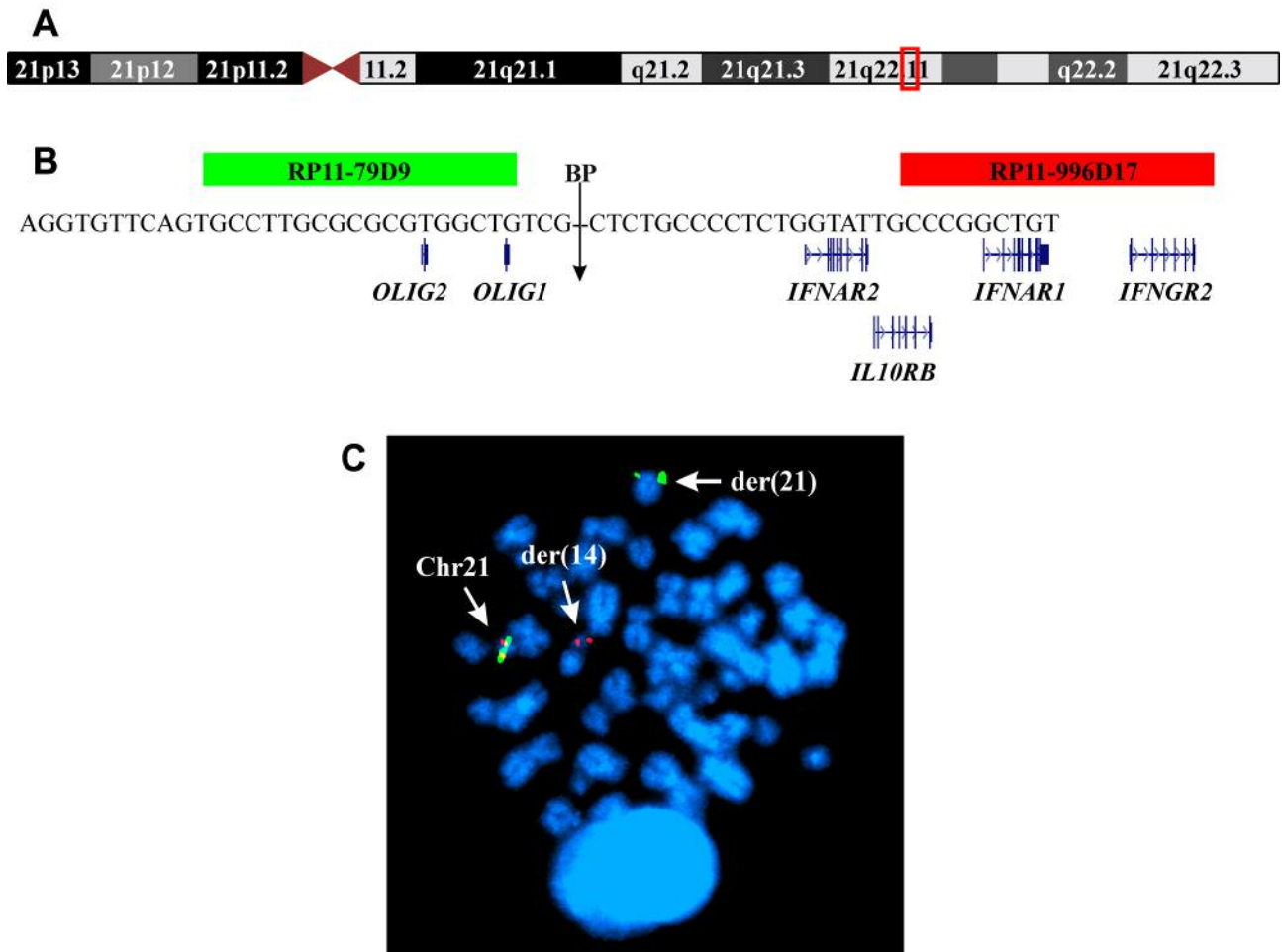


Figure 4. FISH analysis of cells from a lymph node using an *OLIG2/OLIG1* break apart probe which was made from commercially available BACs. A: Ideogram of chromosome 21 showing the mapping of *OLIG2/OLIG1* on chromosome band 21q22.1 (red box). B: Diagram showing the proximal (BAC RP11-79D9, green) and the distal (BAC RP11-996D17, red) parts of the *OLIG2/OLIG1* break apart probe. Additional genes in this region are also shown. Arrow indicates the genomic breakpoint (BP) reported by Wang et al (18). The reported sequence around the BP is also given. C: Metaphase spread showing splitting of *OLIG2/OLIG1* probe. The distal part (red label) of the probe hybridized to der(14) whereas the proximal part (green label) hybridized to der(21). Both distal and proximal parts hybridized to normal chromosome 21.

found to be epigenetically regulated via DNA methylation in acute myeloid leukemia and expressed in two patients carrying the translocation t(15;17)/*PML-RARA* (34). Furthermore, stable overexpression of *OLIG2* in non-expressing cell lines Kasumi-1 (a leukemic cell line with a t(8;21)(q22;q22) translocation resulting in the *RUNX1-RUNX1T1* fusion gene) and U-937 (a histiocytic lymphoma cell line with a t(10;11)(p14;q23) translocation resulting in the *CALM-AF10* fusion gene), using a lentiviral vector system, led to moderate growth inhibition after 4 days and resulted in signs of differentiation in U-937 cells (34). The authors concluded that *OLIG2* may exert anti-proliferative activity in leukemia cell lines. The two studies mentioned above indicate that the

expression of *OLIG2* is not sufficient for the development of malignancy; additional genetic/expression events may be required.

We conclude that activation of both *OLIG1* and *OLIG2* is of the essence in T-cell acute lymphoblastic leukemia/lymphoma brought about by the translocation t(14;21)(q11;q22). Deregulation of a plethora of genes by the proteins OLIG1 and OLIG2 may be the key to the highly malignant disease profile characteristic of these lymphoid malignancies.

Conflicts of Interest

The Authors declare that they have no potential conflicts of interest.

Authors' Contributions

IP conceived the study, designed the experiments, evaluated the data, and drafted the manuscript. LG performed cytogenetic analysis and evaluated the FISH data. IMRJ made clinical evaluations and treated the patient. KA performed cytogenetic and FISH experiments and evaluated the data. AH performed immunocytochemistry examinations. KB performed pathological examination and evaluated immunocytochemical staining. SH assisted with experimental design and writing of the manuscript. All authors read and approved of the final manuscript.

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