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TYRO3 Truncation Resulting From a t(10;15)(p11;q15) Chromosomal Translocation in Pediatric Acute Myeloid Leukemia

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Abstract. *Background/Aim: Novel acquired chromosome aberrations in cancer may provide insights into pathogenetic mechanisms, be of diagnostic and/or prognostic significance and pave the way for new modes of therapeutic intervention. Here, we report a novel chromosome translocation and its molecular genetic consequences in a pediatric acute myeloid leukemia (AML) case. Materials and Methods: Cytogenetic, RNA sequencing, and molecular analyses were performed on the bone marrow cells of a child with AML. Results: The patient entered complete hematologic remission after treatment according to the NOPHO-AML 2004 protocol. A novel t(10;15)(p11;q15) translocation was found in leukemic cells at diagnosis resulting in a fusion of exon 13 of TYRO3 with a sequence from 10p11. The transcript codes for a putative TYRO3 protein lacking the tyrosine kinase domain. Conclusion: The t(10;15)(p11;q15) translocation in neoplastic bone marrow cells results in truncated TYRO3. Because the role of the truncated TYRO3 cannot be predicted functional studies are required.*

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by clonal expansion of abnormal myeloid precursors and accounts for 15% of all pediatric leukemias (1, 2). For the classification of AML, integration of morphology, immunophenotype, cytogenetic analysis, and molecular genetics are required (3-8).

Because chromosome abnormalities acquired by the leukemic cells have been shown to be remarkable diagnostic and prognostic parameters (9-11), the cytogenetic examination of bone marrow cells is now an indispensable component of the clinical management of patients with hematological malignancies, including AML. Sometimes, cytogenetic information is decisive in the choice of optimal treatment for AML-patients as illustrated by the finding at diagnosis of the chromosomal translocation t(15;17)(q24;q11), the hallmark of acute promyelocytic leukemia (APL), which is treated and monitored differently from other AML subtypes (12-14).

The detection of acquired chromosomal abnormalities in leukemic cells, in particular translocations and inversions, has helped identify breakpoint genes that, when rearranged or otherwise deregulated, launch or contribute to the leukemogenic process (15). Numerous pathogenetic or genetic subgroups have thus been identified (15). Nevertheless, new recurrent or unique chromosome aberrations (mainly balanced translocations) corresponding to smaller cytogenetic subgroups continue to be reported in AML and myelodysplasia (MDS) (16-19). The subsequent description of additional cases carrying the same genetic abnormality is far from uncommon. This establishes the acquired aberration in question as a recurrent change, and may help determine its prognostic significance, as well as offers the opportunity to probe further the mechanisms of leukemogenesis in patients with these rare abnormalities. By way of example, the t(7;21)(p22;q22), which generates the *RUNX1-USP42* fusion gene, was originally found in a 7-year-old boy with minimally differentiated AML (AML-M0) (20). Today,

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t(7;21)(p22;q22)/*RUNX1-USP42* is acknowledged as a rare but non-random genomic aberration of myeloid malignancies, where it frequently occurs together with del(5q) (20-25).

We report here a t(10;15)(p11;q15) chromosomal translocation in a case of pediatric AML. The translocation caused fusion of the *TYRO3* gene with a non-genic sequence from 10p11 leading to the generation of a putative truncated TYRO3 protein.

Materials and Methods

Ethics statement. The study was approved by the regional ethics committee (Regional komité for medisinsk forskningsetikk Sør-Øst, Norge, 2010/1389/REK sør-øst A). Written informed consent was obtained. The Ethics Committee's approval included a review of the consent procedure. All patient information has been de-identified.

Case history. A seven years eight months old boy presented with fatigue developed over several weeks and a weight loss of 1.5 kg. Physical examination revealed hepatosplenomegaly and enlarged cervical, axillary, and inguinal lymph nodes. Tests showed a white blood cell count of 127×10^9/l, a platelet count of 70×10^9/l, and a hemoglobin value of 11.2 g/dl.

A bone marrow investigation revealed 60% myeloblasts and an overall morphological picture corresponding to myelomonocytic leukemia or AML-M4. Immunophenotyping confirmed the diagnosis of AML-M4 with myelomonocytic cells representing 93%. Chromosome analysis (see also below) of G-banded bone marrow preparations revealed a t(10;15)(p11;q15) chromosomal translocation. There were no signs of extramedullary leukemia (CNS involvement, myelosarcomas).

The boy was treated according to the NOPHO-AML 2004 protocol (26) (NOPHO=Nordic Society of Paediatric Haematology and Oncology) with six chemotherapy courses: AIET (cytarabine-idarubicin-etoposide-thioguanin), AM (cytarabine-mitoxantrone), HA1M (high dose cytarabine 1 g-mitoxantrone), HA2E (cytarabine 2 g-etoposide), HA3 (cytarabine 3 g), and HA2E (cytarabine 2 g-etoposide). After completion of the courses, the patient was randomized to the non-GO arm (no additional therapy with gentuzumab-otogamizin). Treatment was uneventful except for expected side effects such as mucositis and repeated infections due to severe cytopenia.

The patient has been healthy and relapse-free for ten years after cessation of treatment. There have not been any signs of late effects at regular follow-ups.

G-banding and karyotyping. Bone marrow cells were cytogenetically investigated as part of our diagnostic routine by standard methods (27). Chromosome preparations were made from metaphase cells of a 24-h culture, G-banded using Leishman's stain and karyotyped according to the International System for Human Cytogenomic Nomenclature (ISCN, 2016) guidelines (28).

Molecular genetic analyses. Total RNA was extracted from bone marrow at the time of diagnosis using miRNeasy (Qiagen, Hilden, Germany) and QIAcube (Qiagen). The RNA quality was evaluated using 2100 Bioanalyzer (Agilent, Santa Clara, CA, USA) according to the manufacturer's instructions. Three μg of total RNA were sent for high-throughput paired-end RNA-sequencing at the Norwegian Sequencing Centre, Ullevål Hospital, Oslo, Norway. Detailed information about these analyses has been given elsewhere (29). A total of 104 million reads were obtained. FASTQC software was used for quality control of the raw sequence data. TopHat-Fusion software was used for the detection of fusion transcripts (30, 31).

One μg of total RNA was reverse-transcribed in a 20 μl reaction volume using iScript Advanced cDNA synthesis Kit for Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) according to the manufacturer's instructions (Bio-Rad, Hercules, CA, USA). For the detection of the *TYRO3* fusion transcript, the primer combination TYRO3-1730F1 (5'-GGGCATCAGCGATGAACTAAAGGA-3') and 10p11R1 (5'-CGAATCCCACCACCAGCATCAC-3') was used. PCR amplification was performed on a C-1000 Thermal cycler (Bio-Rad) with an initial denaturation at 94˚C for 30 s followed by 35 cycles at 98˚C for 7 s, 68˚C for 2 min, and a final extension at 68˚C for 5 min. Three μl of the PCR product were stained with GelRed (Biotium, Hayward, CA, USA), analyzed by electrophoresis through 1.0% agarose gel, and photographed. The remaining PCR products were purified using the QIAquick PCR Purification Kit (Qiagen) and sequenced at Eurofins GATC Biotech (Cologne, Germany). The basic local alignment search tool (BLAST) software was used for computer analysis of sequence data (32). The BLAST alignment tool and the human genome browser at UCSC were also used to map the sequences on the Human GRCh37/hg19 assembly (33).

Results

G-Banding analysis of bone marrow cells at diagnosis yielded the karyotype 46,XY, t(10;15)(p11;q15)[8]/46,XY[2] (Figure 1A). Using the TopHat-Fusion on the raw sequencing data a fusion was found between exon 13 of the *TYRO3* gene from 15q15 (nucleotide 1896 on the sequence with the accession number NM_006293.4) and a non-genic sequence mapping to 10p11: GAAGCAAGAGGATGGCTCCTTTGTGAAAGTG GCTGTGAAGATGCTGAAAG/ATGAAACATGAGCAAAA ACAGGGAAATGGAGACCTGGAAAAGAGAGGGCA. RT-PCR with the specific primer combination TYRO3-1730F1/10p11R1 confirmed the presence of the *TYRO3*-fusion transcript (Figure 1B).

Discussion

We present a case of pediatric AML-M4 in which the leukemic cells had a novel t(10;15)(p11;q15) chromosome translocation as the sole cytogenetic abnormality. The molecular analysis of the translocation showed that it resulted in rearrangement of the *TYRO3* gene from 15q15.

TYRO3, together with the genes encoding the AXL receptor tyrosine kinase (*AXL* on 19q13.2) and the MER proto-oncogene tyrosine kinase (*MERTK* on 2q13), constitute the TAM family of receptor tyrosine kinases (RTK) (34-36). Like all RTK, TYRO3, AXL, and MER are transmembrane proteins that transduce signals from the extracellular environment to the cytoplasm and nucleus, regulating a wide range of normal cellular processes that include cell survival, growth, differentiation, adhesion, and motility (34).

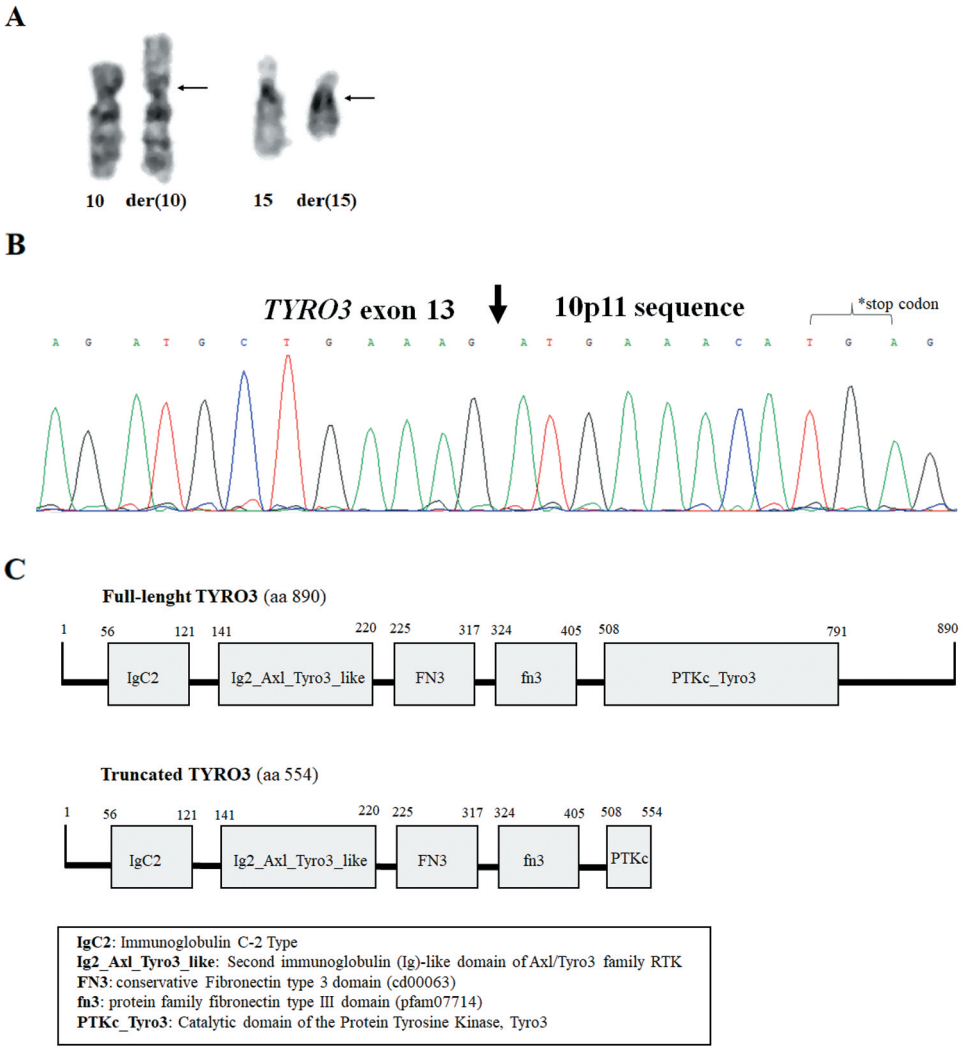

Figure 1. *Genetic analyses of the pediatric acute myeloid leukemia. A) Partial karyotype showing (10;15)(p11;q15) chromosomal translocation; B) Partial sequence chromatogram of the amplified cDNA fragment showing the fusion point of the TYRO3 (exon 13) and a short sequence mapping on chromosome 10p11. C) Illustration of the full-length and truncated TYRO3 protein. All domains and amino acids numbers are shown.*

Overexpression of TAM family kinases occurs in many human cancers, including leukemia, glioma, colorectal carcinoma, breast cancer, gastrointestinal stromal tumor, hepatocellular carcinoma, melanoma, pancreatic adenocarcinoma, and prostate cancer (35, 37-39). Compared to *MERTK* and *AXL*, less is known about *TYRO3* (40), although *TYRO3* mutations have been reported in human malignancies (40, 41). Missense mutations within the kinase domain have been reported in colon cancer, lung cancer, melanoma, brain cancer, and AML (34). Premature stop codon mutations have been described in melanoma and lung cancer (40, 42, 43). Because functional studies have not been performed, the significance of these mutations is currently unknown (40). Furthermore, elevated expression of *TYRO3* has been found in several cancers, including leukemic cells (40).

The present study is the first to demonstrate rearrangement and disruption of *TYRO3* in a hematologic malignancy stemming from the chromosomal translocation t(10;15)(p11;q15). Molecular analysis of the translocation showed fusion of *TYRO3* with a non-genic sequence from 10p11, resulting in an abrogated *TYRO3* and a 554 aa putative TYRO3 truncated protein (Figure 1C). This protein would contain the extracellular domain with the two immunoglobulin domains, the two fibronectin type III domains, and the transmembrane domain. It will lack the catalytic domain of the protein tyrosine kinase TYRO3, the autophosphorylation sites, and the carboxyl-terminal part, which is required for maintaining TYRO3 stability (44, 45). The precise

role of TYRO3 truncated protein in the development of leukemia cannot be predicted without functional studies. However, an anomaly in signal transduction can be assumed. Alternatively, loss of a functional *TYRO3* allele may contribute to leukemogenesis.

Chromosomal translocations are common in cancer and typically generate transforming oncogenes by fusing genes or by inducing overexpression of one or more genes near the breakpoints (15). However, translocations resulting in gene truncations have also been reported (46-51). These typically replace or delete long 3'-untranslated genomic regions that contain regulatory sequences such as miRNA- and AU-rich sequences. Alternatively, they may generate a premature stop codon in the open reading frames, thus acting as nonsense mutations and leading to the expression of C-terminal-truncated forms of the proteins (52-59).

Truncated RUNX1 proteins have been found to function as inhibitors of the normal RUNX1 protein, increase proliferation, and disrupt the cells' differentiation program (52-54). In a recent study, truncated RUNX1 protein has also been found to induce expression of the granulocyte colony-stimulating factor (G-CSF) receptor on 32D myeloid leukemia cells (59). Truncated forms of ETV6 have been shown to have a dominant-negative effect on normal ETV6 function and disrupt both primitive and definitive hematopoiesis in the zebrafish model (60).

In the Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer (61), 89 cases of AML are listed with breakpoints in the chromosome band 15q15 where *TYRO3* maps. Eight of them were myelomonocytic AMLs, the same type of AML as the one in the present case. It is possible that *TYRO3* could have been pathogenetically involved in these leukemias.

Conflicts of Interest

The Authors declare that no potential conflicts of interest exist in relation to this study.

Authors' Contributions

MB performed molecular genetic experiments, evaluated the data, and drafted the manuscript. BZ made clinical evaluations and treated the patient. AT made the immunophenotypic investigation. SH evaluated the data and assisted with the writing of the manuscript. FM made cytogenetic examination and evaluated the data. IP designed and supervised the experiments, performed bioinformatics analysis, molecular genetic experiments, evaluated the data, and drafted the manuscript. All Authors read and approved the final manuscript.

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