

# A 3-way Rare Variant Ph Translocation t(7;9;22) in a patient with Chronic Myeloid Leukemia

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## ABSTRACT

Chronic Myeloid Leukemia (CML) is associated with translocation between chromosome 9 & chromosome 22, t(9;22)(q34;q11.2) and with the formation of BCR-ABL fusion gene. In few newly diagnosed CML cases, complex cytogenetics variants of the Philadelphia (Ph) chromosome can be observed with the involvement of a third chromosome other than chromosome 9 & chromosome 22. Here in, we describe a 45 yrs old male, diagnosed as CML in Chronic phase with a complex translocation involving chromosomes 7, 9 & 22. Cytogenetics investigations for confirmation of CML revealed 46,XY, t(7;9;22)(q11.2;q34;q11.2) in 100% metaphases counted. Fluorescence in-situ hybridization (FISH) showed BCR-ABL fusion signals pattern in 100% nucleated cells analyzed. A review of the literature revealed that CML patients with this translocation tend to have an aggressive course and poor outcome. Additional 3-way chromosome translocations associated with CML are also reviewed.

**Keywords:** Chronic myeloid leukemia, Philadelphia chromosome, Fluorescence *In-situ* hybridization, 3-way variant Ph translocation

## INTRODUCTION

Chronic myeloid leukemia (CML) is characterized by the reciprocal translocation of chromosomes 9 and 22, resulting in formation of the BCR-ABL fusion gene on chromosome 22, which is also known as Philadelphia chromosome.<sup>1</sup> There are 5-10% of CML cases noted to have variant Ph translocations and these findings have been reported since the past 25 years.<sup>2</sup> Although three-way novel Philadelphia (Ph) variant translocation has been uncommonly (3~8%) reported in chronic myeloid leukemia (CML).<sup>3</sup> Simple variants are cases that involved chromosome 22 with a chromosome other than 9, and complex variants are cases that involved chromosomes 9, 22 and one or more other chromosomes.<sup>4</sup> The Philadelphia chromosome originating by the rearrangement of three or more chromosomes reveals that chromosomes 9 and 22 are always involved, while the third chromosome is a different one.<sup>5</sup> However, only two cases with the

deletion of long arm of chromosome 7 associated with long arm of chromosomes 9 and 22 involvements have been reported so far. We report a case of typical CML in chronic phase with complex variant translocations involving chromosomes 7, 9 and 22.


## CASE REPORT

A 45 yrs male diagnosed as a case of CML was referred from Civil Hospital Karachi Pakistan for cytogenetic analysis. Clinical features of the patient included mild back ache since one year, massive splenomegaly and abdominal distension without any history of blood transfusion. Haematological Parameters included: Hb 9 g/dl, TLC 176.19 x10<sup>9</sup>/L, Platelets 206 x 10E<sup>9</sup>/L with differential counts: Neutrophils 50%, Lymphocytes 14%, Monocytes 02%, Eosinophils 04%, Myelocytes 18%, Metamyelocytes 09% & Blast 03%. Peripheral blood film showed leucoerythroblastic picture suggestive of Chronic Myeloid Leukemia. This was further confirmed by bone marrow aspirate and trephine biopsy showing bi-modal peak of neutrophils and myelocytes. Eosinophil and basophil precursors were also prominent.

## Cytogenetics

Cytogenetic analysis was performed on overnight, 24-hr unstimulated BM cultures and 72-hr stimulated BM

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cultures using standard procedures. The GTG (G-bands via trypsin using Giemsa) banding technique was applied to the slides, karyotypes were described according to the International System for Human Cytogenetic Nomenclature (ISCN) 2013, and 15 metaphases were analyzed and karyogram were made using Cytovision System.

### FISH Analysis

Fresh slides were used for FISH analysis using a LSI BCR/ABL dual color dual fusion translocation probe (Abbott Molecular/Vysis). A total of 100 interphase + metaphase were analyzed, using a fluorescence microscope Nikon Eclipse Ci microscope equipped with appropriate filters. Image capturing and processing were carried out using a Cytovision imaging system (Leica, Richmond, USA).

### Results

Karyotyping was performed which revealed complex variant Ph translocations in patient using G-banding analysis, and were confirmed by FISH analysis. G-banding and FISH results.

### Patient's Karyotype

Complex Translocation 46,XY,t(7;9;22)(q11.2;q34;q11.2) (15) (Figure 1).

### Hybridization Pattern

100 interphase + metaphase were analyzed all cells (100%) showed evidence of bcr/abl fusion signal pattern (Figure 2).

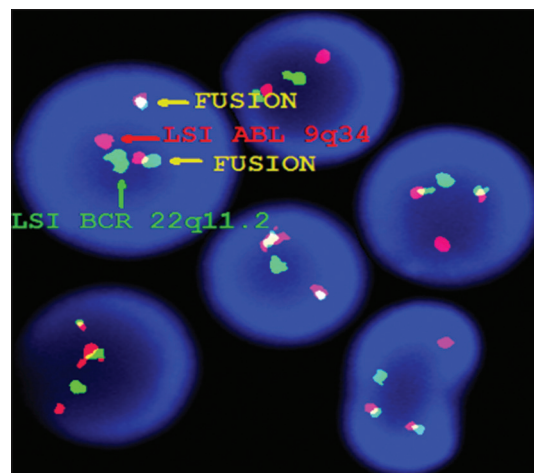


**Figure 1:** Two photographic karyograms showing Variant Ph translocation t(7;9;22) in a patient with Chronic Myeloid Leukemia

## DISCUSSION & CONCLUSION

So far only two cases of complex variant involving chromosomes' (7;9;22) rearrangement have been reported. One case had variant translocation t(7;9;22) during lymphoid blast crisis in a Philadelphia positive Chronic Myelogenous Leukemia with previous EBV Infection.<sup>6</sup> Chromosomes are known to be involved in variant rearrangements in CML (19). However, it has been suggested that the distribution of the break-points is non-random with the chromosomal bands most susceptible to breakage being: 1p36, 3p21, 5q31, 6p21, 7p22, 9q22, 10q22, 11q13, 12p13, 17p13, 17q21, 17q25, 19q13, 21q22, 22q12 and 22q13 (19). However, the fusion gene remained on chromosome 22.<sup>7</sup> Other than chromosomes 22 and 9, the variant translocations commonly involved chromosomes no 1, 19, 12, 7, and 6. The identification of these variant translocations and their co-relation with the clinical behavior may identify new prognostic markers.<sup>8</sup> Occasionally, the chromosomal changes are submicroscopic so the translocation could be masked and the BCR-ABL fusion can only be detected by more sensitive techniques such as fluorescence in situ hybridization (FISH) or molecular analysis.<sup>3</sup>

The availability of double-fusion probe by FISH provides a useful tool to investigate the mechanism of the genesis of the variant translocation.<sup>9</sup> Variant type Ph translocations have been described using cytogenetic analysis<sup>4</sup> and molecular techniques.<sup>10</sup> To the best of our knowledge, the present study is the first to observe a case of variant Ph chromosome-positive CML in CP with t(7;9;22)(q11.2;q34;q11.2).<sup>11</sup> Variant Ph translocations may be important as they are associated with prognosis and therapy for CML patients.<sup>12</sup> Variant Ph translocations in CML are associated with a comparatively unfavorable prognosis for the patient.<sup>13</sup> In conclusion, we report a unique case of a Ph chromosome-positive CML



**Figure 2:** A photographic image of Fluorescence In-situ Hybridization showing BCR/ABL dual fusion signal pattern

in the Chronic Phase with a new variant Ph translocation involving three chromosomes which has not previously been described. The patient was further advised for the detection of type of BCR/ABL1 fusion transcript by RT-PCR and initially treated with Hydrea and later enrolled into Nilotinib program.

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