

Case Report

# A Rare t (8;9;22)(p21;q34;q11.2) Three Way Philadelphia Variant in Chronic Myeloid Leukemia

#### Pankaj Gadhia\*and Salil Vaniawala

S. N. Gene Laboratory and Research Centre, President Plaza-A, Near RTO Circle, Ring Road, Surat-395001, India

\*Corresponding author: Pankaj Gadhia, Molecular Cytogenetic Unit, S. N. Gene Lab and Research Centre, President Plaza-A, Near RTO Circle, Ring Road, Surat, India, Tel: 098251 63395; E-mail: pankajkgadhia@gmail.com

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#### Abstract

**Background:** Chronic myeloid leukemia (CML) is characterized by Philadelphia (Ph) chromosome. The Ph detected by karyotyping in 90% CML but 5-10% may have variant translocation where another chromosome addition to chromosome # 9 and 22. The aim of present report is to describe a rare three-way translocation with rarely describe 8p21 breakpoint.

**Case report:** Retrospective cytogenetic database between March 2104 and February, 2015 was searched for CML cases along with variant translocation. Out of 732 confirmed CML, one male patient with 22 year age showed a variant translocation as 46,XY,t(8;9;22) (p21;q34;q11.2).

**Conclusion:** A rare three-way translocation of chromosome 8, 9 and 22 was detected with cytogenetic and Dual Fluorescence In Situ Hybridization technique (D-FISH) as novel breakpoint at 8p21 which was earlier reported by Abe et al., (1989) before 26 years.

**Keywords:** Chronic myeloid leukemia; Three way translocation; Breakpoint; Karyotype

### Introduction

Chronic myeloid leukemia (CML) is characterized by the Philadelphia chromosome (Ph) resulting from a balanced translocation between 9 and 22 t(9;22)(q34;q11.2). Due to this rearrangement, the break-point cluster region (BCR) gene at position 22q11.2 is juxtaposed to the C-Abelson (ABL1) gene at 9q34 resulting in the BCR-ABL1 fusion gene, encoding active tyrosine kinase. The identification of Ph chromosome is important for diagnosis and treatment purpose [1].

There are 5-10% of CML cases noted to have variant Ph translocations and these findings have been reported since past 20-25 years [2,3]. Simple variants are cases that involved chromosome 22 with a chromosome other than 9, and a Complex Variant Translocations (CVTS) chromosome other than 22 or 9 have been reported to act as third chromosome [4,5].

The mechanisms of the generation of the variant translocations are not fully understood; some authors have suggested 2 different mechanisms: a 1-step mechanism in which chromosome breakage occurs simultaneously on 3 or 4 different chromosomes in 3 way or 4way translocation, respectively, and a 2-step mechanism involving 2 sequential translocation in which a standard t(9;22) translocation is followed by a second translocation (Figure 1a and 1b) involving addition chromosomes [6,7].



Figure 1A: Metaphase plate.

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Figure 1B: G-banded karyotype with 46,XY,t(8; 9;22)(p21;q34;q11.2)

# **Case Report**

A-22 year young man presented with abdominal complaints. Initial CBC counts were: white blood cells (WBC)  $130 \times 10^9$ /L, platelets count 410 × 10<sup>9</sup>/L, haemoglobin 10.5 g/dL. Differential counts were: lymphocytes 12%, monocytes 2%. The patient was initially treated with Imatinib (400 mg/day). The patient had splenomegaly and bone marrow was hyper cellular with marked granulocytic hyperplasia. Increased number of megakaryocytes diagnosed him as CML.

# Cytogenetic and FISH

A total of 732 patients between March, 2014 and February, 2015 were diagnosed cytogenetically as CML with typical t(9;22). While screening database of 732 cases, we found only one (0.14%) rare translocation as t(8;9;22)(p21;q34;q11.2). The' written informed consent' was obtained from each person and the Institutional ethical committee clearance was obtained for publication as case presentation. The conventional cytogenetic analysis was performed on unstimulated bone marrow followed by GTG banding and karyotype was described according to ISCN [8]. Fluorescence In Situ Hybridization (FISH) performed on BM interphase cells (Figure 2) using break point cluster /Abelson tyrosine kinase fusion gene (BCR/ABL1) dual color fusion kit (Vysis, Germany) [9].



**Figure 2:** FISH Interphase Cell Showing 1 Fusion, 1 Green and 1 Orange confirming Ph positive variant chromosome (two step mechanism).

## Discussion

Although complex translocations (CT) have often reported in CML, there is contradictory evidence for clinical significance of prognosis in published reports. Gorusu et al., have suggested that mechanism by which these CT arise could influence prognosis [6]. Some authors attributed the adverse outcome associated with these CT to deletion at either ABL1 or BCR locus [10].

In the present study we screened 732 cases of which one case was found with three way translocation involving chromosome 8 and breakpoint p21 t(8;9;22)(p21;q34;q11.2).

The breakpoint p21 was a rare breakpoint when it was referred to Mitelman database (http://www.cgap.nci.nih.gov/chromosomes/ Mitelman [5]. There was only one case reported in database with p21 of Abe et al., way back in 1989 [11] with t(8;9;22)(p21;q34;q11.2). We report second case with p21 breakpoint on chromosome 8. The complex abnormalities in CML remain intriguing because of wide range of chromosomal involvement with no clinical effect [12]. It is established that additional chromosomal abnormalities are encountered throughout the course of disease; however, clinically it is believed that additional chromosomal anomalies serve as predictor of diagnostic for blast crises. The breakpoints of variants Ph translocation in CML patients may be important as they are associated with carcinogenesis [13]. The monitorization of chromosomes and localization of precise breakpoints involved in CT will improve our understanding of the genetic mechanisms play role in malignancy. We trust that present results will contribute to the scientific community's knowledge of CML cytogenetic in general and variant translocations in particular.

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