

# Patterns of chromosome abnormalities in a sample of Colombian patients with chronic myeloid leukemia

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## Abstract

Chronic Myeloid Leukemia (CML) is characterized by the presence of the Philadelphia (Ph) chromosome, resulting from a translocation between chromosomes 9 and 22 that gives rise to the *BCR-ABL1* fusion gene. The Ph chromosome is present in 95 % of CML cases. In 5 %-10 % of these cases Ph variants occur and, approximately 5 % of these cases present with additional chromosomal abnormalities (ACAs). In this work we describe the prevalence of chromosome abnormalities in a sample of Colombian CML patients. A descriptive cross-sectional study was conducted, analyzing cytogenetic and molecular data from 142 CML patients. Data were collected between 2016 and 2019 at the laboratory of Biogenética Diagnóstica S.A.S. Among the 142 patients were analyzed, 56 % were male, and the average age was 45 years. The Ph chromosome was observed in 81 % of the cases. Three-way chromosome variants involving chromosomes 3, 7, and 8 were detected. The most frequent additional chromosomal aberration was +der(22)t(9;22). Atypical patterns associated with poor prognosis were found, via FISH analyses, in 88.2 % of the patients. The *BCR-ABL1* fusion gene was detected in 100 % of the 18 patients subjected RT-PCR tests. This retrospective study reveals intriguing findings regarding chromosomal abnormalities in Colombian patients with CML, including rare three-way chromosome variants and atypical FISH patterns associated with a poor prognosis. Further investigation is warranted to explore the clinical implications, prognosis, and survival outcomes associated with these cytogenetic findings in CML patients.

**Keywords:** leukemia; neoplasm; chromosome aberrations; Philadelphia chromosome; trisomy; fluorescence *in situ* hybridization; reverse transcriptase polymerase chain reaction.

## 1. Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm of pluripotent stem cells, leading to an overproduction of cells from one or more myeloid lines [1]. CML mainly affects adults [2], aged 30 to 70 years [3, 4]. The global incidence of this condition is 1 to 2 cases per 100,000 people per year and represents 15 % of all adult leukemias [5].

CML is characterized by the presence of the Philadelphia (Ph) chromosome, formed by the reciprocal translocation (t) between chromosomes 9 and 22, described as t(9;22)(q34;q11.2) [6]. On the altered chromosome 22, a *BCR-ABL1* fusion gene is formed, observed in 95 % of CML patients, 25 % of acute lymphoblastic leukemia (ALL) cases, and less than 5 % of acute myeloid leukemia (AML) cases. Thus, this gene fusion appears to exert a leading pathogenetic role. However, in 5-10 % of CML cases, the t(9;22)(q34;q11.2) features chromosomal rearrangements involving three or more autosomal chromosomes, giving rise to complex variants of the Ph

chromosome. Some authors have suggested that these variants can arise through two mechanisms: the first, whereby three chromosomes simultaneously break, and the second, in which another chromosome attaches to a standard t(9;22) as a product of a clonal evolution. This second scenario is related to a poor prognosis [7, 8]. Similarly, additional chromosomal alterations (ACAs) occur in approximately 5 % of CML cases. The most frequent ACAs in CML are +8, +19, -Y, and the isochromosome (i) of chromosome 17's long arm, [i(17)(q10)] [9]. Current evidence indicates that the genetic instability triggered by the presence of the Ph chromosome and the resulting oncogenic fusion causes the continuous acquisition of ACAs and mutations, which lead to the progression of the disease to an accelerated phase (AP) and the blast crisis (BC) of the disease [10, 11].

The banding technique (karyotype) is the commonly used method to identify the presence of t(9;22) and related chromosomal abnormalities (ACAs or Ph variants) at the time of diagnosis [12]. However, this technique is not sensitive enough to detect subtle changes or the Ph chromosome itself, so fluorescent *in situ* hybridization (FISH), using a dual color fusion probe, can confirm the presence of a masked or cryptic t(9;22) and detect typical or atypical signal patterns [13, 14]. Atypical patterns usually consist of a derivative chromosome 9, deletions, gain of an additional Ph chromosome, three or more pathway Ph variants, and other abnormalities [14]. Notwithstanding, the prognostic impact of *BCR-ABL1* signal patterns identified by FISH in Ph+ CML patients remains a subject of debate within the scientific community.

Currently, the *BCR-ABL1* fusion gene and its molecular response (MR) are monitored via the reverse transcription polymerase chain reaction (RT-PCR) since this technique can detect small copy numbers of the oncogene *BCR-ABL1* [15]. In 2005, the international scale (IS) was proposed to normalize the quantitative results of *BCR-ABL1*'s expression rate. Based on the IRIS trial, the cut-off values for monitoring *BCR-ABL1* transcripts comprise: 100 % of transcripts correspond to IS basal levels; values  $\geq 10$  % indicate a null molecular response (MR, *i.e.*, remission);  $\leq 10$ -1 %, a minimum MR;  $\leq 1$ -0.1 %, lower MR;  $\leq 0.1$ -0.01 %, higher RM; and  $\leq 0.01$  as undetectable [15, 16, 17].

The present retrospective study aimed at describing the prevalence of chromosome abnormalities reported in a sample of Colombian patients with CML. To this end, cytogenetic and molecular analyses performed at the Biogenética Diagnóstica laboratory between 2016 and 2019 were analyzed. All detected Ph chromosome variants, ACAs, typical and atypical FISH patterns, and RT-PCR-detected *BCR-ABL1* gene fusions were described since these analyses are currently employed to direct the diagnosis and follow-up of the patients with CML.

## 2. Materials and methods

A retrospective descriptive cross-sectional study was performed to analyze the patterns of chromosome abnormalities reported in a sample of Colombian patients with CML. The results of 142 patients, referred to the Biogenética Diagnóstica S.A.S. laboratory between 2016 and 2019, were analyzed and reported. G-Banding karyotypes, FISH and/or RT-PCR data were retrieved from the Athenea database at the laboratory, using the following search criteria: patients with confirmed diagnosis of CML, any age and sex, tests performed at the time of diagnosis, patients referred to karyotype, FISH and/or RT-PCR studies, and non-failed analysis. For cytogenetics studies, a nomenclature readjustment of the reports prior to 2020 was also carried out in accordance with the standards of the current International System for Human Cytogenomic Nomenclature (2020) (ISCN 2020).

## 2.1. Statistical analysis

Categorical variables were described as the frequency and percentage of subjects in each category. Continuous variables were summarized as a mean  $\pm$  standard deviation (SD) or median (range) according to data distribution. All statistical analyses were performed with the IBM SPSS 25.0 statistical software (IBM, Armonk, NY, USA).

## 3. Results

Cytogenetic and molecular studies were performed in 142 patients with confirmed diagnostic of CML at the Biogenética Diagnóstica S.A.S. laboratory, from 2016 to 2019. Men accounted for 56 % (80/142) of the patients and 44 % 62/142 were women (**Table 1**). Average patient age was 45 ( $\pm 17$ ) years, being 44 ( $\pm 17$ ) years in men and 47 ( $\pm 16$ ) years in women.

**Table 1.** Description of patients analyzed and results obtained by cytogenetic and molecular techniques.

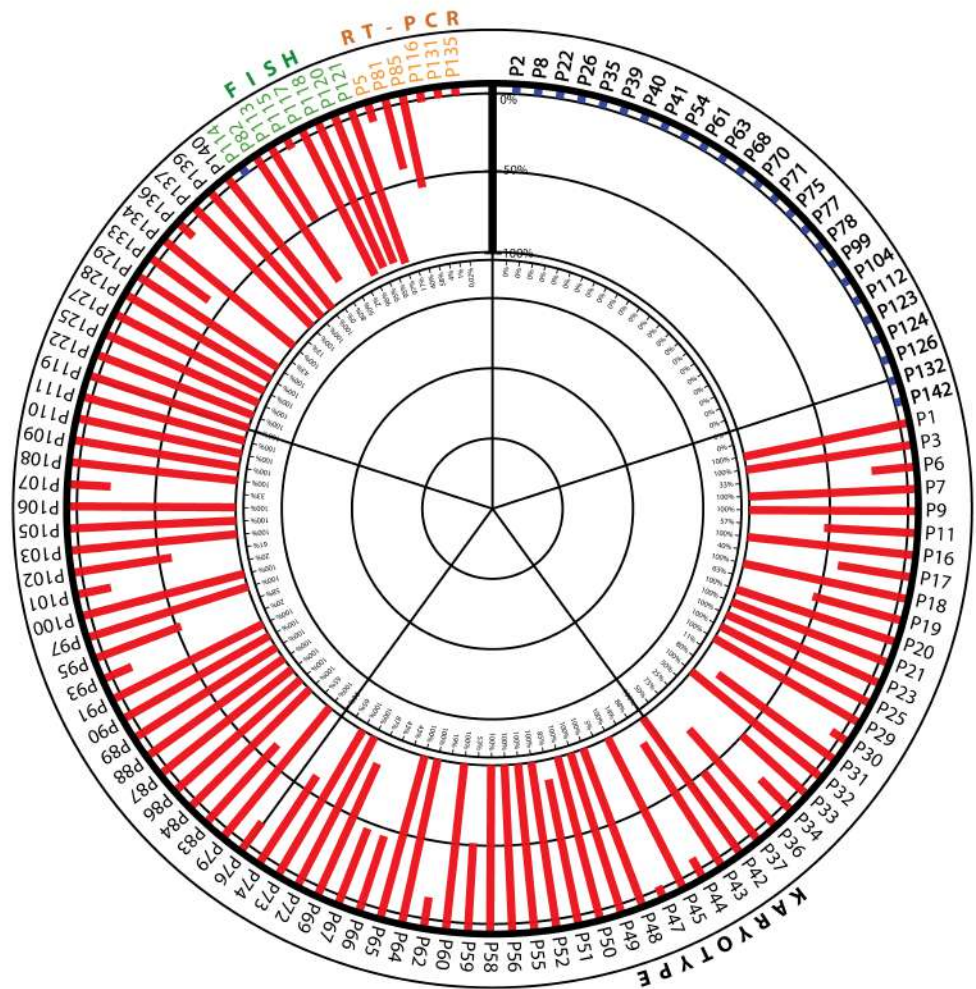
Parameter	All	Normal	Altered
n	142 (100 %)	27 (19 %)	115 (81 %)
Male	80 (56 %)	17 (12 %)	63 (44 %)
Female	62 (44 %)	10 (7 %)	52 (37 %)
Age (Standard deviation)			
Whole cohort	45 ( $\pm 17$ )	46 ( $\pm 15$ )	45 ( $\pm 17$ )
Male	44 ( $\pm 17$ )	44 ( $\pm 15$ )	44 ( $\pm 18$ )
Female	47 ( $\pm 16$ )	50 ( $\pm 15$ )	46 ( $\pm 16$ )
Test +			
Karyotype	128 (78.53 %)	31 (24.22 %)	97 (75.78 %)
FISH	17 (10.43 %)	2 (11.76 %)	15 (88.24 %)
RT-PCR	18 (11.04 %)	0 (0 %)	18 (100 %)
Total	163 (100 %)	33 (20.25 %)	130(79.75 %)

+ In 21 cases, more than one analysis was performed on the same sample.

A total of 163 analyzes were performed on 142 patients with CML. The studies comprised 128 karyotypes, 17 FISH, and 18 RT-PCR. Of these analyses, 33/142 (20.3 %) revealed a normal cytogenetic result (Table 1), and 130 showed an altered result, corresponding to 81 % (115/142) of the patients analyzed. **Figure 1** shows the distribution of normal and altered results for each of the tests performed.

For a total of 121 patients a single analysis was performed; 107 thereof consisted of G banding karyotyping. The median number of cells analyzed was 9 (range 2-25), with an average of 81 % (range 5 % to 100 %) of Philadelphia chromosome (Ph) positive clones. Regarding FISH studies, the number of cells analyzed was 200 in all cases, revealing an average of 96 % (range 2-100 %) of clones with the presence of the *BCR-ABL1* fusion. RT-PCR analyses showed that positive cases had a median *BCR-ABL1* ratio of 17 % (range 0.02 % – 58 %; Fig. S1).

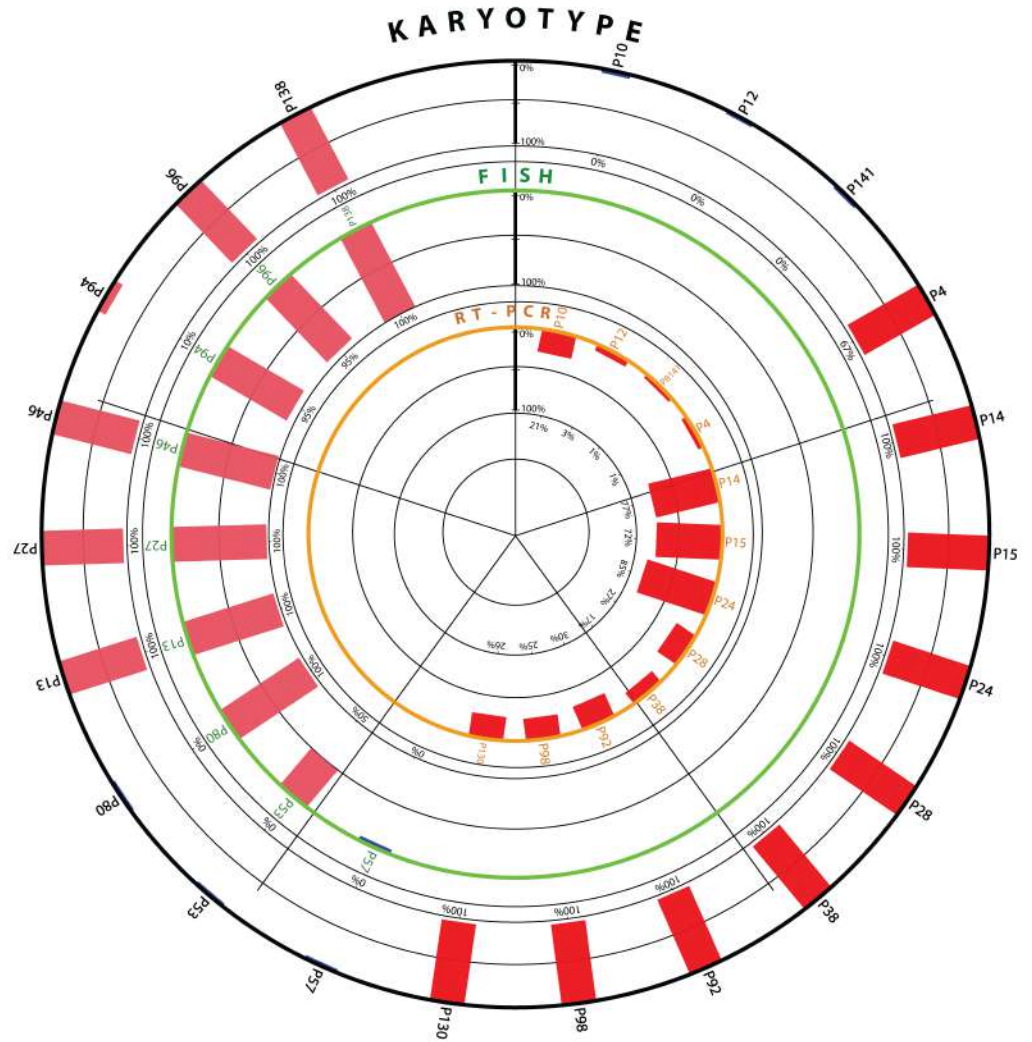
Twenty-one patients were subjected to more than one test, namely G banding karyotype and FISH ( $n = 9$ ) or G banding karyotype and RT-PCR ( $n = 12$ ). Only 6 of 9 (66.7 %) patients who underwent G banding karyotype and FISH, showed an altered result with both techniques, two (22.3 %) only by FISH, and one (11.1 %) had a normal result by two methods. Furthermore,



**Figure 1.** Percentage of altered or normal cells in patients with CML to whom only one test was performed ( $n = 121$ ). The bars show the percentage of normal (blue) or altered cells (red).

nine patients out the 12 (75 %) who were done G banding karyotype and RT-PCR test, showed abnormal results with both tests, and 3/12 (25 %) patients showed altered results by RT-PCR technique only (**Figure 2**).

The cytogenetic findings in each karyotype are indicated in the Supplementary Tables S1 and S3. Of the 97 altered karyotypes, 83 (87.3 %) showed the classical translocation 9;22, and 3 (3.1 %) carried variants of the Ph chromosome involving the chromosomes 3, 7, and 8 (**Figure 3A-C**). The variants  $t(3;9;22)$ ,  $t(7;9;22)$  and  $t(8;9;22)$  were observed in two female patients and in one male patient, respectively (Table S1).

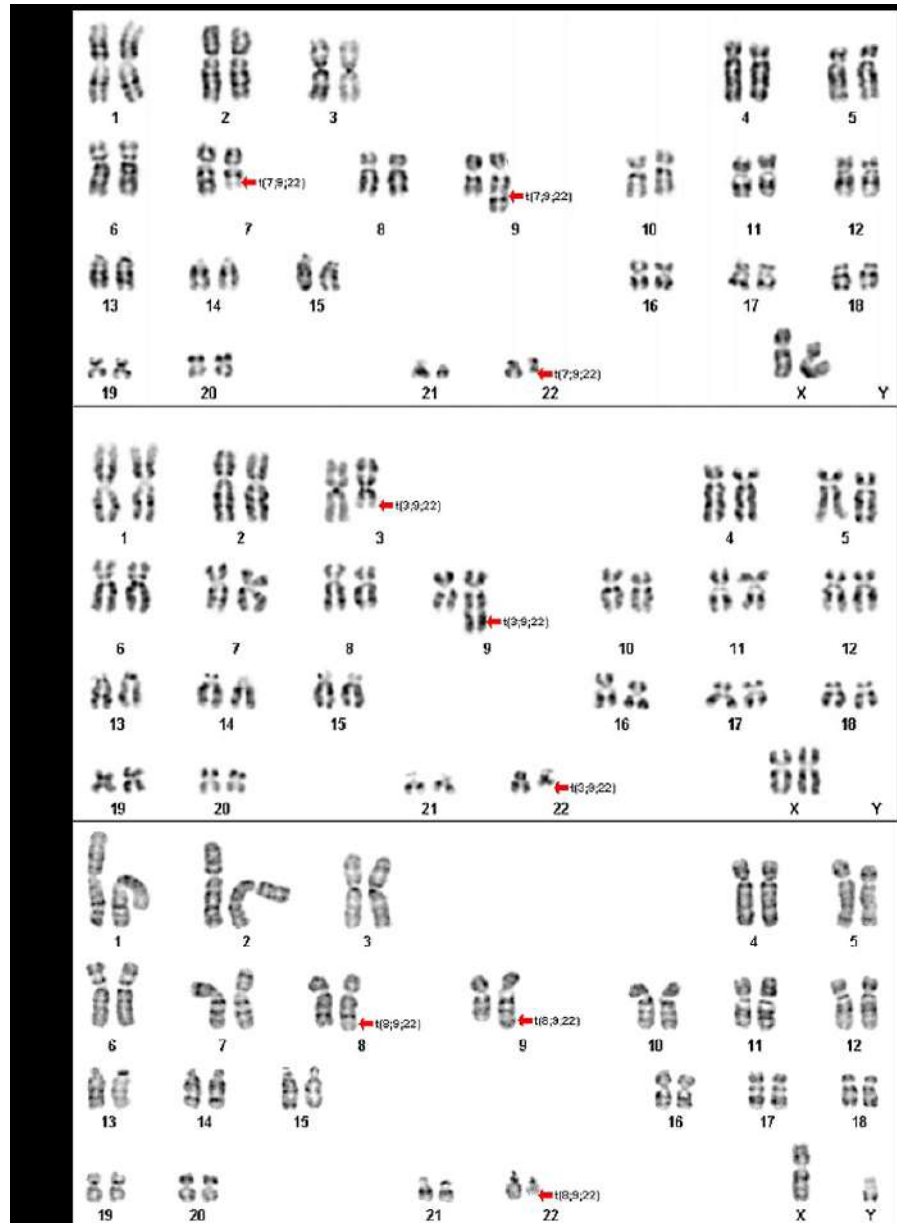


**Figure 2.** Percentage of altered cells in 21 cases who underwent more than one study from the same sample. The red bars show the percentage of altered cells.

We highlight that 9.3 % (9/97) of the patients with altered karyotype harbored ACAs to t(9;22), identified on average in 86 % (range 53 % - 100 %) of the cells analyzed. The most common ACAs involved structural abnormalities (58.3 %), involving translocations as the most frequent alterations (2/12, 16.7 %) and the most observed numerical abnormalities were trisomies, observed in 41.6 %, (4/12, 33.3 %) of the cases (Table S2).

The chromosomes most frequently involved in numerical alterations were: 8, 12, 19, and Y, whereas chromosomes 3, 17, and 21 were more frequently involved in structural chromosomal alterations.

The gain of the derivative chromosome 22 [+der(22)t(9;22)] was the main ACA observed (3/14, 21.4 %), followed by the loss of Y chromosome, trisomy of chromosome 12 (+12), trisomy of chromosome 19 (+19), trisomy of chromosome 21 (+21), deletion of the long arm of chromosome 3 [del(3)(q27)], additional material of unknown origin (add) on the long arm of chromosome

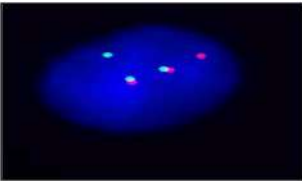
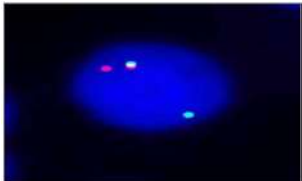
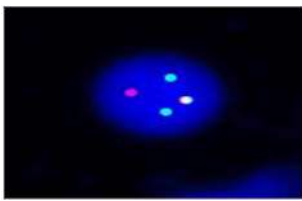
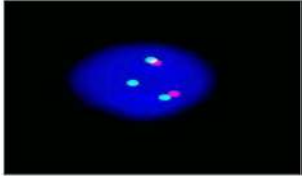


**Figure 3.** Karyotypes of the Philadelphia chromosome variants in CML patients, obtained by G banding technique. A. 46,XX,t(7;9;22)(q22;q34;q11;q11.2)[4]; B. 46,XX,t(3;9;22)(q21;q34;q11.2)[10]/46,XX[5]; C. 46,XY,t(8;9;22)(q24;q34;q11.2)[9].

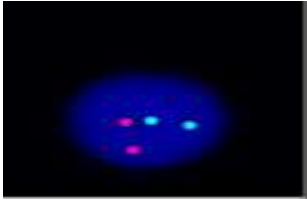
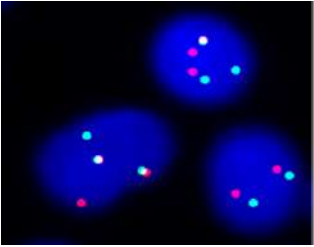
21 [add(21)(q22)], isochromosome (i) of the long arm of chromosome 17 [i(17)(q10)], chromosome insertion (ins) of the long arm of chromosome 22 into the long arm of chromosome 17 [ins(17;22)(q21;q11.2q13)], a balanced translocation between the long arms of chromosomes 3 and 15 [t(3;15)(q23;q24), t(10;11)(p15;p10)], and trisomy of chromosome 8 (+8), observed each in a single patient (S2). The numerical alteration +8 was observed in a patient who also revealed more than one clone with several alterations; this case was considered as a complex cytogenetic alteration (patient ID: P53) (Table S3).

Regarding FISH analyses, a total of 13 patients were analyzed with the ON BCR/ABL t(9;22) Fusion CytoCell Aquarius probe, and four patients were analyzed with the ON BCR/ABL t(9;22) Fusion Kreatech Diagnostics probe. FISH analyses revealed altered results in 88.24 % (15/17) of the investigated patients. The typical normal pattern (two red signals and two green signals - 2R2G) was identified in 11.7 % (2/17) of the patients, indicating a negative result for t(9;22). On the other hand, the typical positive fusion pattern (2 fusion signals, one red signal, and one green signal - 2F1R1G) was identified in 52.9 % (9) of the patients, representing the typical positive result for t(9;22). Additionally, other atypical FISH patterns were observed, such as 1F1R1G (two patients), 1F1R2G (two patients), and 2F1G (one patient). Noteworthy, one patient presented three clones with different FISH patterns, including 2F1R1G, 1F2R2G, and 2R2G (**Table 2**).

**Table 2.** FISH patterns identified in patients with CML.

Image	Pattern	n	Result	Nomenclature
	2F1R1G	9	Typical positive pattern	nuc ish(ABL,BCR)x3(ABL con BCRx2)[200]
	1F1R1G	2	Atypical positive pattern	nuc ish(ABL,BCR)x2(ABL con BCRx1)[200]
	1F1R2G	2	Atypical positive pattern	nuc ish(ABLx2)(BCRx3)(ABL con BCRx1)[190/200]
	2F1G	1	Atypical positive pattern	nuc ish(ABLx2,BCRx3)(ABL con BCRx2)[160/200]

**Table 2.** FISH patterns identified in patients with CML.

Image	Pattern	n	Result	Nomenclature
	2R2G	2	Typical normal pattern	nuc ish(ABL,BCR)x2[200]
	2F1R1G 1F2R2G 2R2G	1	Typical positive pattern Atypical positive pattern Typical normal pattern	nuc ish(ABL,BCR)x3 (ABL con BCR)x1 /nuc ish(ABL,BCR)x3, (ABL con BCRx2)/nuc ish(ABL,BCR)x2

\***F**: Yellow signal for the fusion *BCR-ABL1*, **R**: Red signal for *ABL* gen (Chromosome 9), **G**: Green signal for *BCR* gen (chromosome 22).

Lastly, the RT-PCR test performed on 18 patients with CML showed a median value of 23 % (range 0.02 % - 85 %) for the *BCR-ABL1* ratio, identified in all patients (100 %), of which two presented minimum values of 1 % and 3 % respectively, which could explain the normal karyotype result.

#### 4. Discussion

This study allowed us to identify the type and frequency of chromosomal alterations in a Colombian patient sample with CML. Such alterations included Ph chromosome variants, ACAs, typical and atypical FISH patterns, and the ratio of *BCR-ABL1* gene fusion by RT-PCR.

In this study, the patients had an average age of 45 years, similar to the age ranges reported in previous studies (39-65 years) [2, 18, 19, 20, 21, 22]. As expected, more of the patients were male, agreeing with previous studies [22, 23, 24].

In our group of patients, the Ph chromosome was observed in 81 % of the cases, contrary to that reported by other studies where this chromosome (Ph) was reported in 90% - 95 % of the cases [25, 26, 27].



#### 4.1. Philadelphia chromosome variants

Any chromosome can be the third one involved in variant rearrangements in CML [28]. However, authors have suggested that the distribution of breakpoints is not random and seems to have a higher incidence in the bands of different chromosomes, such as 1p36, 3p21, 5q31, 6p21, 9q22, 10q22, 11q13, 12p13, 17p13, 17q21, 17q25, 19q13, 21q22, 22q12, and 22q13 [29].

We identified variable Ph translocations in three patients (3.1 %), similar to those reported in previous studies, observing such variants with frequencies ranging between 2 % and 10 % of the patients with CML [29, 30, 31].

In addition, we observed rearrangements involving chromosomes 3, 7, and 8 in comparable frequencies. Even though any chromosome can be involved in the variant of Philadelphia, the t(3;9;22) is the most frequently observed in CML cases [32, 33]. Structural abnormalities involving the long arm of chromosome 3, e.g., t(3;9;22)(q21;q34;q11.2), have been associated with poor prognosis and decreased survival [6]. The 3q21 chromosome region harbors tumor suppressor genes *H37*, *Luca15*, *RBM5*, and *RASSF1A*, and tumor susceptibility genes like the *hMLH1* [8]. Regarding the complex variant of Philadelphia t(7;9;22)(q22;q34;q11.2), Robledo et al. [34] reported that the *CUX1* tumor suppressor gene, located in 7q22, its involvement in regulation, morphogenesis, differentiation, and cell cycle progression, representing a risk factor in CML.

The three-way translocation involving chromosome 8 and the cutoff point q24, t(8;9;22)(q24; q34; q11.2), reported in studies across the globe [18, 35], has an established clinical effect in patients with CML. Thus, the prognostic significance of this chromosome alteration remains controversial. However, several studies have reported that the prognosis of patients with variant translocations is similar to those with classic Ph translocation [22, 31, 36].

Among the Ph+ cases addressed in our study, 83 patients (87.3 %) carried the Ph chromosome as the sole cytogenetic abnormality, and the remaining nine patients (9.3 %) presented ACAs and three (3.1 %) variants of Ph (Table 1). These results are consistent with those previously reported [37]. The share of cases of Ph chromosome variants found in our study agrees with the results obtained in previous studies in which Ph chromosome variants were found in 2-10 % of patients with CML [38].

#### 4.2. Additional chromosomal abnormalities ACAs

We detected low frequencies of ACAs (9.3 %), comparable to those observed in previous reports, in which ACAs appeared in 5 % [2, 3, 39] and 7 % [18] of the cases.

Although in our study, trisomies were the most commonly identified type of ACAs (Table S1), we found that +der(22)t(9;22)(q34;q11) was the most frequent chromosomal alteration (3 patients, 21.4 %), differing from studies that report chromosome 8 trisomy, as the most common anomaly, followed by trisomy 19 and i(17)(q10) [22, 37, 40, 41]. However, the +der(22)t(9;22) anomaly is a globally reported main route one with a frequency higher than 5 % [22, 42]. In this regard, this chromosome alteration should be regarded as a red flag, requiring special attention [40] since patients with “main route” ACAs have a lower survival rate compared to those without ACAs [18].

Additional alterations appeared with equal frequencies (1 patient each) in our study: +8, +19, -Y, and i(17)(q10) and were classified within the most common ACAs and principal route [2]. According to a recent ACA prognostic risk classification system proposed by Wang et al. [43], trisomy 8 and Y were classified as ACAs with good prognosis, whereas i(17)(q10), another ACA, has a poor prognosis [40].

Regarding numerical chromosome alterations, we observed trisomy 8 in negative Ph<sup>-</sup> clones. This is a frequent alteration present in 34 % to 68 % of the CML patients [44]. Trisomy 8 was reported in a similar percentage of analyzed metaphases (100 % and 58 %) in previous studies [44, 45]. Although the clinical impact of these Ph<sup>-</sup> clones remains unclear, some authors have associated them with disease progression [44]. It is, therefore, relevant to carry out more studies that allow us to establish the clinical implications of Ph clones.

In addition, we identified the presence of trisomy 21 in one patient. This chromosome harbors the *AML1* gene, with mutations associated with resistance to treatment in patients with CML and +21 [46, 47]. Chromosome 3 is involved in two types of structural rearrangements affecting the chromosome region 3q27. The involvement of this region in structural rearrangements in CML has not been reported in the literature, making this a further target of investigation since the 3q26 region is very frequently involved in CML patients [29]. The remaining rearrangements identified in CML patients, included +12, add(21)(q22), ins(17;22)(q21;q11.2q13), and t(10;11)(p15;p10) are classified as minor route due to their low frequency and have been reported in some studies [48-50].

In summary, in our study, minor route anomalies were more prevalent than main route ones and chiefly included structural alterations and balanced translocations. These results are consistent with those previously reported in patients with CML [18].

### 4.3. FISH patterns in CML

The FISH tests performed at the time of diagnosis usually follow the suspicion of a masked or cryptic Ph chromosome. Alternatively, this analysis is done when chromosomal preparations have a low mitotic index, demonstrating FISH utility in cytogenetic smears of bone marrow to determine the presence or absence of the *BCR-ABL1* rearrangement [15].

The typical normal 2R2G pattern appeared in 11.7 % (n=2) of the patients analyzed by FISH (n=17). The typical 2F1R1G hybridization pattern, indicative of the t(9;22) translocation in CML, was observed in 52.9 % (9/17) of the patients analyzed, slightly lower than that obtained in numerous studies that report an incidence of 71 % to 88 % of typical hybridization patterns. Likewise, our results differ from Hernandez et al. [51], who observed a 94 % (n=17) typical pattern in 18 Cuban patients.

Among the atypical patterns identified in the patients analyzed by FISH, the pattern 1F1R1G was the most frequent, agreeing with previous reports [52]. This atypical pattern marks the presence of a derivative chromosome 9 deletion, associated with poor prognosis [53] and resistance to therapy [54-57].

The atypical pattern 1F1R2G appeared in 2 of the 17 (11.76 %) patients analyzed by FISH. This FISH pattern has been associated with an *ABL1* deletion and has been reported in several studies with CML patients bearing large adjacent deletions at the *ABL1* cutoff point [53, 56, 58, 59]. Furthermore, according to previous reports, this FISH pattern leads to the loss of one or more

tumor suppressor genes, influencing the progression of the disease [53]. However, the time at which this deletion of 5'*ABL1* occurs in der(9) and its prognostic implications on CML patients remain to be elucidated.

On the other hand, the atypical pattern 2F1G, corresponding to derivative chromosomes 9 and 2 and a normal chromosome 22, respectively, is associated with the 9q deletion of the non-rearranged chromosome 9 (Table 2) [14]. This FISH pattern is uncommon in the literature, and there is still much to study about the prognostic implications of its presence in CML patients.

In our study, patient P53 revealed a unique FISH pattern in three clones each. This patient, in addition to harboring the normal pattern (2R2G) and the typical positive pattern for Ph (2F1R1G), presented, in one of its clones, the atypical pattern 1F2R2G, which could correspond to a Ph variant with three or four pathways [12]. In this regard, The *BCR / ABL* gene fusion on chromosomes other than 22q constitutes a rare form of Ph translocations [52]. However, to clarify the prognostic impact of this result in our study, it is necessary to perform complementary cytogenomics and molecular tests to establish the origin and possible repercussions of the above alteration in the progression of the disease. Unfortunately, the employed banding technique revealed a normal karyotype (46, XY), thus supporting the claim that atypical FISH results should not be interpreted in isolation but should be considered with information gathered from banding cytogenetics, and, if necessary, with new molecular and cytogenomic studies [52].

#### 4.4. RT-PCR in CML

The transcription of the *BCR-ABL1* complex is central in the diagnosis, evaluation, and molecular monitoring of CML [61, 62]. Currently, the RT-PCR method is regarded as one of the most sensitive ones, detecting low numbers of *BCR-ABL1* transcripts [63]. This method determines the breakdown point of the *BCR-ABL1* and evaluates minimal residual disease in cases where other methods (G banding technique or FISH) cannot determine the presence of the *BCR-ABL1* oncogene.

The *BCR-ABL1* fusion gene was detected by RT-PCR in 100 % (18/18) of the CML patients analyzed in this study. Similar results have been described in the literature [5, 64, 65]. RT-PCR studies are central to detecting the *BCR-ABL1* oncogene at the time of diagnosis [66].

The patients analyzed showed a median expression of the *BCR-ABL1* fusion of 23 % (0.02 % to 85 %). Considering the international scale molecular response criteria (IS) proposed by Hughes [16], we find that of the 18 patients analyzed by RT-PCR, 12 were in a state of null remission (MRI), with a range of expression of *BCR-ABL1* of 17 % to 85 %, while six patients were in minor remission (RM Minor), with a *BCR-ABL1* expression range of 0.02 % to 4 %. To date, *BCR-ABL1* studies report the frequency of transcripts analyzed in patients with CML [41, 63, 64]; however, in the present study, such information was unavailable.

## 5. Conclusions

This study allowed us to determine the prevalence of patterns of chromosome abnormalities in a sample of Colombian patients with CML. In this study the Ph Chromosome was found in 81 % of the patients. Karyotype studies showed that 3.1 % of the patients had three-way Ph chromosome variant translocations that involved chromosomes 3, 7, and 8 at a time. ACAs were identified in 9.3 % of the cases. The most common ACA of major route was +der(22)t(9;22). FISH analyses revealed that 10.6 % of patients bore abnormal FISH patterns, of which the 13.3

% harbored atypical patterns associated with poor prognostic. All patients subject to RT-PCR analyses, harbored the *BCR-ABL1* fusion gene. Future studies are suggested to correlate these findings with clinical, prognosis and survival data of patients with CML.

## 6. Acknowledgements

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## 7. Ethics approval

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Review Committee of Universidad Pedagógica y Tecnológica de Colombia (Reference number: VIE, date July 02 2020).

## 8. Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

**Author contributions:** MFC, DSP and MRL conceived and designed the research. MALP, MFC, MRL, DSP and KC designed the methodology. All authors contributed to the research. MALP and MFC analyzed data, MALP, DSP and MFC performed data curation. MALP wrote the original draft of the manuscript. MFC and MRL reviewed and edited the writing of the manuscript. All authors viewed the manuscript. MFC and MRL carried out the supervision. MFC and MRL acquired the financing. All authors have read and approved the published version of the manuscript.

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### Patrones de anomalías cromosómicas en una muestra de pacientes colombianos con leucemia mieloide crónica

**Resumen:** La leucemia mieloide crónica (LMC) se caracteriza por la presencia del cromosoma Filadelfia (Ph), que resulta de una translocación entre los cromosomas 9 y 22 y da origen al gen de fusión BCR-ABL1. El cromosoma Ph se detecta en el 95 % de los casos de LMC. En un 5-10 % de los casos, se presentan variantes de Ph y aproximadamente el 5 % de los casos presentan anomalías cromosómicas adicionales (ACAs). Este artículo tuvo como objetivo describir la prevalencia de patrones de anomalías cromosómicas en una muestra de pacientes colombianos con LMC. Se realizó un estudio descriptivo de corte transversal, analizando datos citogenéticos y moleculares de 142 pacientes con LMC. Los datos se recopilieron entre 2016 y 2019 en el laboratorio de Biogenética Diagnóstica S.A.S. De los 142 pacientes analizados, el 56 % eran hombres y la edad promedio era de 45 años. El cromosoma Ph se observó en el 81 % de los casos. Se detectaron variantes cromosómicas de tres vías que involucraban los cromosomas 3, 7 y 8. La aberración cromosómica adicional más frecuente fue +der(22)t(9;22). Se encontraron patrones atípicos asociados con un mal pronóstico en el 88.2 % de los pacientes mediante análisis de FISH. El gen de fusión BCR-ABL1 se detectó en el 100 % de los pacientes mediante RT-PCR. Este estudio presenta hallazgos intrigantes sobre anomalías cromosómicas en pacientes colombianos con LMC, incluyendo raras variantes cromosómicas de tres vías y patrones de FISH atípicos asociados con un mal pronóstico. Se requiere una investigación adicional para explorar las implicaciones clínicas, el pronóstico y los resultados de supervivencia asociados con estos hallazgos citogenéticos en pacientes con LMC.

**Palabras Clave:** leucemia; neoplasma; aberraciones cromosómicas; cromosoma Filadelfia; trisomía; hibridación in situ por fluorescencia; reacción en cadena de polimerasa por transcriptasa inversa.

### **Padrões de anomalias cromossômicas em uma amostra de pacientes colombianos com leucemia mieloide crônica**

**Resumo:** A leucemia mieloide crônica (LMC) é caracterizada pela presença do cromossomo Filadélfia (Ph), resultante de uma translocação entre os cromossomos 9 e 22 que dá origem ao gene de fusão BCR-ABL1. O cromossomo Ph é detectado em 95 % dos casos de LMC. Em 5-10 % dos casos, ocorrem variantes de Ph e aproximadamente 5 % dos casos apresentam anomalias cromossômicas adicionais (ACAs). Este artigo teve como objetivo descrever a prevalência de padrões de anomalias cromossômicas em uma amostra de pacientes colombianos com LMC. Foi realizado um estudo descritivo de corte transversal, analisando dados citogenéticos e moleculares de 142 pacientes com LMC. Os dados foram coletados entre 2016 e 2019 no laboratório da Biogenética Diagnóstica S.A.S. Dos 142 pacientes analisados, 56 % eram homens e a idade média era de 45 anos. O cromossomo Ph foi observado em 81 % dos casos. Variantes cromossômicas de três vias envolvendo os cromossomos 3, 7 e 8 foram detectadas. A aberração cromossômica adicional mais frequente foi +der(22)t(9;22). Foram encontrados padrões atípicos associados a um mau prognóstico em 88,2 % dos pacientes por meio de análise de FISH. O gene de fusão BCR-ABL1 foi detectado em 100 % dos pacientes por meio de RT-PCR. Este estudo apresenta achados intrigantes sobre anomalias cromossômicas em pacientes colombianos com LMC, incluindo raras variantes cromossômicas de três vias e padrões de FISH atípicos associados a um mau prognóstico. Pesquisas adicionais são necessárias para explorar as implicações clínicas, prognóstico e resultados de sobrevivência associados a esses achados citogenéticos em pacientes com LMC.

**Palavras-chave:** leucemia; neoplasma; aberrações cromossômicas; cromossomo Filadélfia; trissomia; hibridização in situ por fluorescência; reação em cadeia de polimerase por transcriptase reversa.

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