Kumar *et al.*
Egyptian Journal of Medical Human Genetics (2023) 24:56
https://doi.org/10.1186/s43042-023-00435-9

Egyptian Journal of Medical Human Genetics

RESEARCH

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Higher incidence of co-expression of BCR-ABL fusion transcripts in an Eastern Indian population

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Abstract

Background Chronic myeloid leukaemia (CML) is a haematopoietic stem cell disorder, caused by a balanced reciprocal translocation (t(9;22) (q34;q11)) that leads to the formation of BCR (Breakpoint Cluster Region)-ABL (Abelson) fusion transcripts known as Philadelphia (Ph) chromosome. The prevalence of BCR-ABL fusion transcripts in Indian CML population is poorly understood, and few studies have been reported from India. The aim of the present study was to determine the frequencies as well as prognostic effects of the three fusion transcripts, i.e. b2a2, b3a2 and e1a2 in an Indian population.

Methods RNA was isolated from total 123 samples, 27 bone marrow (BM) samples and 96 peripheral blood (PB) samples, of CML patient followed by cDNA synthesis. Real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) was performed using TaqMan® assay (ABI, CA, USA) to monitor BCR-ABL transcript.

Results Ph' chromosome was observed in 103 patients whereas it was not detected in 20 cases. qRT-PCR revealed that the b3a2 fusion transcripts were the most common transcript in CML patients (63.41%) while b2a2 fusion transcript was present in 16.26% cases. Co-expression of b3a2 + b2a2 fusion transcript was observed in 0.81% cases whereas co-expression of b3a2 + e1a2 fusion transcript was found in 1.63% cases. There was no correlation observed between b3a2 fusion transcript and platelet count. The fusion transcript b2a2 was observed in relatively younger patients compared to b3a2 fusion transcript. Although this correlation was not statistically significant.

Conclusion The co-expression of BCR-ABL fusion transcripts was higher (63.41% aggregate of b3a2) in the present population in contrast with other populations reported. This finding was consistent with the frequency data reported from Sudan.

Keywords CML, Fusion transcripts, Translocation, qRT-PCR, Co-expression, Philadelphia chromosome

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Background

Chronic myeloid leukaemia (CML) is a haematopoietic stem cell disorder characterized by splenomegaly, leucocytosis with myelocyte neutrophil predominance, low neutrophil alkaline phosphatase (NAP) score and hypercellular BM with granulocytic/megakaryotic hyperplasia [1]. CML is a myeloproliferative neoplasm with an incidence of 1–2 cases per 100,000 adults and approximately 15% of newly diagnosed cases of leukaemia in adults. CML is caused due to the formation of Philadelphia chromosome characterized by a balanced reciprocal translocation, t(9;22)(q34;q11) involving BCR (Breakpoint Cluster Region) gene on chromosome 22 and ABL (Abelson) gene on chromosome 9 in the haematopoietic stem cells [2–4]. This balanced reciprocal translocation results in the formation of the BCR-ABL oncogene, which is translated into a protein with constitutive tyrosine kinase activity, possibly the most effectively therapeutically targeted oncoprotein [5]. The exact causal factor of this translocation is not understood well but few studies reported ionizing radiations and exposure of benzene as important risk factors. An interesting study revealed that the higher incidence of CML was observed in population, survived atomic bomb attack [6].

The ABL gene is translocated within BCR gene results into the formation of chimeric gene (BCR/ABL) on chromosome 22 [7] which is translated into a protein with constitutive tyrosine kinase activity [5]. The translocation results into the formation of three categories of transcripts; the M-BCR (b2a2, b3a2, b2a3 and b3a2), m-BCR (e1a2) and μ-BCR (e19a2) [8, 9]. All of these fusion transcripts show enhanced tyrosine kinase activity [10–13]. In general, b3a2, b2a2 and e1a2 are the most frequent whereas others are rare in the reported populations [14]. In some cases, co-expression of b2a2 and b3a2 occurs due to alternate splicing was also observed [15]. The significance prognostic of the BCR-ABL transcripts has been reported from patients treated with interferon. The first-line treatment of CML patient is approved by the US Food and Drug Administration for tyrosine kinase inhibitors (TKIs) such as imatinib, nilotinib, dasatinib and bosutinib for CML in chronic phase (CML-CP) [16]. Response has been reported in patients carrying the e14a2 (b3a2) transcript as compared with the e13a2 (b2a2) transcripts after treatment with standard-dose imatinib [17].

The prevalence of the BCR-ABL fusion transcripts in CML cases was not well explored in India. A study reported the incidence of CML in India is 0.8–2.2 out of 100,000 male populations and 0.6–1.6 out of 100,000 female populations [18]. There are five reports available on the frequency of the BCR-ABL fusion transcripts from India (Mumbai, Kolkata, Delhi and Chandigarh) [1, 19–22]. The main aim of the present study was to determine the frequency of different BCR-ABL fusion transcripts in an Eastern Uttar Pradesh cohort of India and their correlation with the disease prognosis.

Methods

The institutional ethical approval was taken from ethical committee (Ref. No.: I.Sc./ECM-XII/2021–22) Institute of Science, Banaras Hindu University, and written informed consent was obtained from the patient/participant for publication. Detail clinical history and blood sample were collected from each patient after receiving written informed consent for the study.

For the current study, 123 CML cases (80 males and 43 females) were registered from the out-patient and in-patient department of the Sir Sundar Lal Hospital of the Institute of Medical Sciences, Banaras Hindu University. The patient's median age at the time of diagnosis was 40 years. All registered patients were under treatment and were administered with one or the other tyrosine kinase inhibitor. About 0.5–4 ml of BM blood was collected from each of the patient. About 0.3 ml of it was used for whole blood culture, 200 μl was used for RNA isolation and rest was used for DNA isolation. Cytogenetic analysis was also performed for all the patients. For cytogenetics analysis, whole blood culture was performed in RPMI 1640 culture medium containing 10% foetal bovine serum. Metaphases were arrested with colchicine treatment and harvested after incubation of 72 h at 37 °C. Under a microscope (Carl Zeiss Microscopy GmbH, Göttingen, Germany), chromosome G-banding was performed, and metaphases with 450 G-band resolution were observed, and karyotyping was performed using Ikaros karyotyping system—Metasystems software (Carl Zeiss Microscopy GmbH, Göttingen, Germany).

The RNA was isolated using Tri Reagent BD (Sigma-Aldrich®). The integrity of RNA was checked on 1.5% agarose gel. After isolation of RNA, DNase-I treatment was done using DNase-I treatment Kit (Applied Biosystems), and the concentration of RNA was checked using spectrophotometer. The cDNA was synthesized using cDNA synthesis Kit (Applied Biosystems). The integrity of cDNA was also checked by expression of beta-actin gene using specific primers [23]. The presence of b2a2, b3a2 and e1a2 fusion transcripts was confirmed in each sample by qRT-PCR using TaqMAN Gene expression Assay (Applied Biosystems).

Microscopy, karyotyping and cytogenetic analysis

A total of 45 metaphase plates were captured under the microscope, and karyotyping was done with 450 G-banding resolution (Fig. 3) using automated

karyotyping workstation having Metasystem's software (Ikaros®, Carl Zeiss® Microscopy GmbH, Göttingen, Germany). Chromosomes were analysed following guidelines provided by the International System for Human Cytogenetic Nomenclature.

Results and discussion

Karyotype revealed the presence of Philadelphia chromosome in 103 CML cases whereas 20 cases have no chromosomal abnormality. qRT-PCR identified the presence of various types of BCR-ABL fusion transcript in CML cases (Table 1). The observed frequency of fusion transcripts b3a2 transcript was 63.41% and of b2a2 was 16.26%. The frequency of co-expressing b3a2 + e1a2 fusion transcript was in 1.63%, while co-expression of b3a2 + b2a2 fusion transcript was detected in 0.81% of the patients. Surprisingly, in 3.25% cases, none of these fusion transcripts were detected possibly due to having the rarest fusion transcripts (Fig. 1).

The fusion transcript b3a2 was most prevalent in the present population followed by fusion transcript b2a2. This finding was consistent with other reported population although b2a2 fusion transcript was frequently reported in children (Fig. 2) [1, 19–22]. Interestingly, the present study observed that the co-expression of fusion transcript e1a2 + b3a2 (1.63%) was higher than other previously reported Indian as well as other population except Sudan [24]. The frequency of fusion transcript b3a2 + b2a2 and b3a2 + e1a2 was strikingly lower in observed population than other reported population. There are very few studies which reported the co-expression of M-BCR and μ-BCR. One such study carried out in Sudan population reported very high frequency (20.2%) of such co-expressions in CML cases.

The present study also explored to establish a correlate of fusion transcript with platelet count as many previous suggested that patient with b3a2 fusion transcript has higher platelet count [3, 4, 25–31]. No such correlation was observed in the present study which might be due to low sample size, or this population is different from others.

Table 1 Type of BCR-ABL1 fusion transcript along with other clinical features of the patients

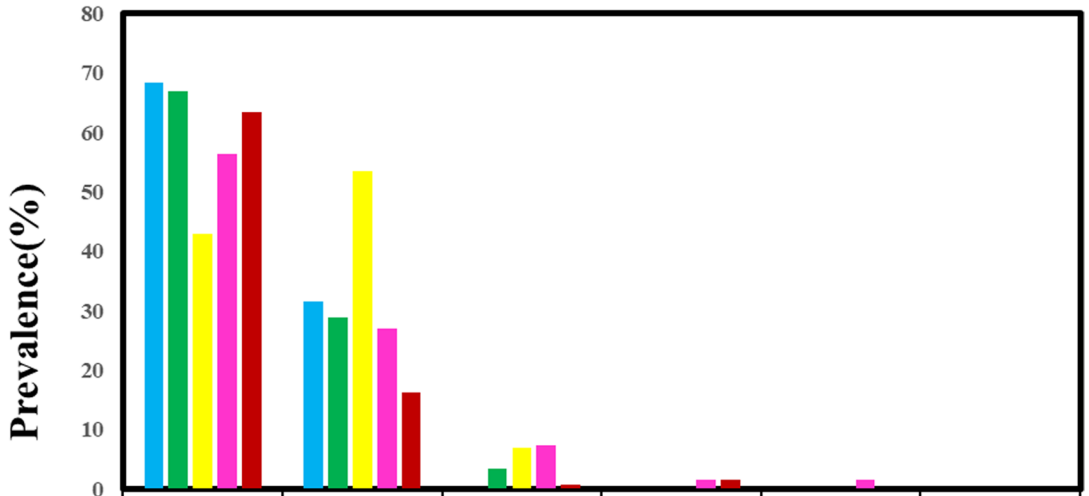
Patients no.	Sex	Age	Transcript	Ph chromosome	Platelet (lakhs/mm^3)	Haemoglobin
1	Male	31	b3a2	+	6.8	4.00 g/μL
2	Male	50	b3a2	+	9.15	9.40 g/μL
3	Male	34	b3a2	+	1.72	9.90 g/μL
4	Female	35	b3a2	+	1.44	9.70 g/μL
5	Female	27	b2a2	+	1.72	10.50 g/μL
6	Male	22	b2a2	+	3.31	11.10 g/μL
7	Male	60	b3a2	+	5.77	9.70 g/μL
8	Male	68	b3a2	+	5.4	10.10 g/μL
9	Female	53	b2a2	+	1.07	11.30 g/μL
10	Male	70	X	–	1.8	4.80 g/μL
11	Male	33	b3a2	+	1.28	10.90 g/μL
12	Male	67	b3a2	+	7.5	6.30 g/μL
13	Male	46	b3a2	+	2.43	7.80 g/μL
14	Male	31	b2a2	+	1.05	11.10 g/μL
15	Female	24	b3a2	+	6.37	8.60 g/μL
16	Female	28	b3a2	+	1.28	11.80 g/μL
17	Male	32	b3a2	+	9.6	8.50 g/μL
18	Male	70	X	–	2.97	12.50 g/μL
19	Male	31	b3a2	+	6.8	8.00 g/μL
20	Male	27	b3a2	+	9.3	10.50 g/μL
21	Female	35	b3a2	+	5.3	5.50 g/μL
22	Male	39	X	+	2.32	11.90 g/μL
23	Female	50	b2a2	+	1.77	10.50 g/μL
24	Female	45	b3a2	+	3.6	9.80 g/μL
25	Male	50	X	–	1.22	12.00 g/μL

Table 1 (continued)

Patients no.	Sex	Age	Transcript	Ph chromosome	Platelet (lakhs/mm^3)	Haemoglobin
26	Female	26	b3a2	+	1.13	10.50 g/µL
27	Male	60	b3a2	+	5.66	8.30 g/µL
28	Female	35	b3a2	+	5.3	5.50 g/µL
29	Male	35	b3a2	+	1.51	7.10 g/µL
30	Female	33	b3a2	+	1.44	11.00 g/µL
31	Female	51	b3a2	+	3.52	11.80 g/µL
32	Male	34	b2a2	+	1.54	12.80 g/µL
33	Male	62	b3a2	+	1.48	12.10 g/µL
34	Male	35	b3a2	+	4.92	11.80 g/µL
35	Male	30	X	–	4.86	13.10 g/µL
36	Male	40	b2a2	+	4.71	15.40 g/µL
37	Male	40	X	+	4.23	13.30 g/µL
38	Male	22	b3a2	+	1.5	10.1 g/µL
39	Male	48	b3a2	+	6.47	13.4 g/µL
40	Male	32	b3a2	+	4.9	9.5 g/µL
41	Male	31	b3a2	+	3.5	8.99 g/µL
42	Female	26	b2a2	+	4.16	8 g/µL
43	Male	24	b3a2	+	2.96	11.7 g/µL
44	Female	42	b3a2	+	6.7	9.3 g/µL
45	Female	27	b3a2 + b2a2	+	1.9	11.6 g/µL
46	Male	35	b3a2 + e1a2	–	4.3	11.5 g/µL
47	Male	30	b3a2	+	6	7.8 g/µL
48	Male	28	b2a2	+	5.6	10.5 g/µL
49	Female	55	b3a2	+	4.5	11.2 g/µL
50	Male	64	b3a2	+	4.6	9.8 g/µL
51	Male	49	Other	–	1.63	12.6 g/µL
52	Male	55	b2a2	+	7.66	11.2 g/µL
53	Female	30	b3a2	–	6.95	6.8 g/µ
54	Male	38	b3a2	+	8.5	8.2 g/µL
55	Male	40	b2a2	+	5.6	7.9 g/µL
56	Female	50	b3a2	+	5.44	8.7 g/µL
57	Male	30	b2a2	+	8	10.9 g/µL
58	Male	42	Other	+	6	9.9 g/µL
59	Female	30	b3a2	–	3.55	8.6 g/µL
60	Male	39	Other	+	4.45	10.6 g/µL
61	Female	36	b3a2	+	8.37	9.8 g/µL
62	Male	35	b3a2	+	6.43	10.2 g/µL
63	Female	35	Other	+	3.48	7.9 g/µL
64	Female	28	b3a2 + e1a2	+	5.21	8.8 g/µL
65	M	50	b3a2	+	6.4	4.80 g/µL
66	M	58	X	–	8.15	10.90 g/µL
67	M	14	b3a2	+	1.57	6.30 g/µL
68	M	48	b3a2	+	1.24	7.80 g/µL
69	M	22	b2a2	+	1.82	11.10 g/µL
70	M	40	b3a2	+	3.51	8.60 g/µL
71	M	29	b3a2	+	4.56	11.80 g/µL
72	F	52	X	–	4.9	8.50 g/µL
73	F	34	b2a2	+	1.7	12.50 g/µL
74	M	42	b3a2	+	1.25	8.00 g/µL

Table 1 (continued)

Patients no.	Sex	Age	Transcript	Ph chromosome	Platelet (lakhs/mm^3)	Haemoglobin
75	M	58	b3a2	+	1.83	10.50 g/µL
76	F	62	b3a2	+	6.7	5.50 g/µL
77	F	56	X	–	2.48	11.90 g/µL
78	M	35	b2a2	+	2.05	10.50 g/µL
79	M	37	X	–	6.76	12.80 g/µL
80	M	42	X	–	2.28	12.10 g/µL
81	M	45	b3a2	+	9.3	11.80 g/µL
82	M	44	b3a2	+	2.49	13.10 g/µL
83	M	43	b2a2	+	5.9	15.40 g/µL
84	F	26	b2a2	+	9.1	13.30 g/µL
85	M	56	b3a2	+	6.49	10.1 g/µL
86	M	58	b3a2	+	4.3	13.4 g/µL
87	F	24	b3a2	+	4.7	9 g/µL
88	M	20	b2a2	+	4.13	10.9 g/µL
89	F	38	X	–	2.65	8 g/µL
90	M	38	b3a2	+	6.2	12.7 g/µL
91	M	40	b3a2	+	1.06	9.3 g/µL
92	M	48	b3a2	+	4.61	11.6 g/µL
93	F	20	b3a2	+	6	11.2 g/µL
94	F	50	b3a2	+	5.9	7.8 g/µL
95	F	31	b3a2	+	4.4	10.5 g/µL
96	F	33	b3a2	+	4.6	9.60 g/µL
97	F	19	b3a2	+	1.63	10.70 g/µL
98	M	65	X	–	6.62	10.50 g/µL
99	M	48	b3a2	+	6.54	11.10 g/µL
100	M	32	b3a2	+	5.96	9.50 g/µL
101	M	55	X	–	6.42	8.10 g/µL
102	F	33	b3a2	+	5.46	12.6 g/µL
103	F	45	X	–	6.23	9.90 g/µL
104	M	56	b3a2	+	1.22	9.70 g/µL
105	F	40	b3a2	+	1.21	10.50 g/µL
106	M	36	b3a2	+	5.78	11.20 g/µL
107	M	63	b3a2	+	4.92	9.70 g/µL
108	M	35	b3a2	+	1.49	10.90 g/µL
109	F	71	X	–	1.41	8.58 g/µL
110	M	20	b2a2	+	3.02	10.20 g/µL
111	M	35	b3a2	+	1.6	9.86 g/µL
112	F	27	b3a2	+	1.82	8.98 g/µL
113	M	40	b3a2	+	5.02	10.24 g/µL
114	F	62	b3a2	+	4.86	11.23 g/µL
115	M	30	b3a2	+	4.62	11.45 g/µL
116	M	72	b3a2	+	2.34	9.90 g/µL
117	M	52	X	–	2.75	8.70 g/µL
118	F	27	b3a2	+	7.3	11.50 g/µL
119	M	42	b3a2	+	1.64	12.10 g/µL
120	F	40	b2a2	+	1.84	9.30 g/µL
121	M	20	b3a2	+	5.45	7.10 g/µL
122	F	28	X	–	4.46	10.54 g/µL
123	M	76	b3a2	+	3.22	12.34 g/µL



	b3a2	b2a2	b3a2+b2a2	e1a2+b3a2	e19a2	e1a2
Mumbai	68.31	31.68	0	0	0	0
Chandigarh	66.87	28.84	3.36	0	0	0
Delhi	43	53.5	7	0	0	0
Kolkatta	56.5	27	7.3	1.64	1.64	0
Uttar Pradesh	63.41	16.26	0.81	1.63	0	0

Fig. 1 Comparison of the frequency of BCR-ABL fusion transcripts in the present and other studies of India

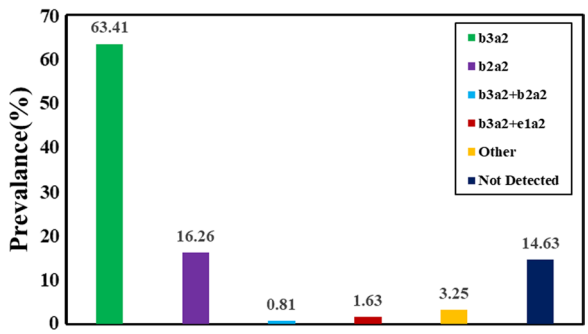


Fig. 2 Prevalence of different BCR-ABL fusion transcripts observed in the present study (Uttar Pradesh)

Age and sex biasedness were also taken in account and observed a higher incidence of CML in males compared to females in this population which is inconsistent with the previous studies [6]. The fusion transcript b2a2 was observed frequently in younger patient as contrast to fusion transcript b3a2 but these data were statistically not significant (Fig. 3).

Frequency of BCR-ABL1 fusion transcripts studies in different countries worldwide

Depending upon the location of the breakage, a CML patient may have anyone the various fusion transcripts or may have co-expressions of two or more fusion transcripts. Various studies have been conducted worldwide to study the prevalence of fusion transcripts in CML patients. This is focuses mainly on the prevalence of fusion transcripts in various populations worldwide and their prognostic significance. Data of 50 studies which have been conducted worldwide are described in Table 2, and this table gives the percentage of the prevalence of different fusion transcripts in different countries.

In the present analysis on 51 studies from 23 countries, we see that there is a high variability in the frequency of different BCR-ABL transcripts in different populations. In general, b3a2 is the most common transcript worldwide followed by b2a2. But in a few reports on the studies conducted in Sudan [2], the UK [30], Germany [26], Mexico [28, 39] Ecuador [40] and the USA [42, 43], b2a2 transcript was most prevalent. In one of the studies from Sudan, co-expression of e1a2 + b2a2 is the most prevalent [38]. A study from India showed that among children, b2a2 transcript is most prevalent [22] whereas study on children in France showed that b3a2 transcript is the most prevalent one [37]. Rest of the variants b3a2 + b2a2, e1a2 + b2a2, e1a2, e19a2, e1a2 + b3a2 and e1a2 are either not found or in very low frequency except in a

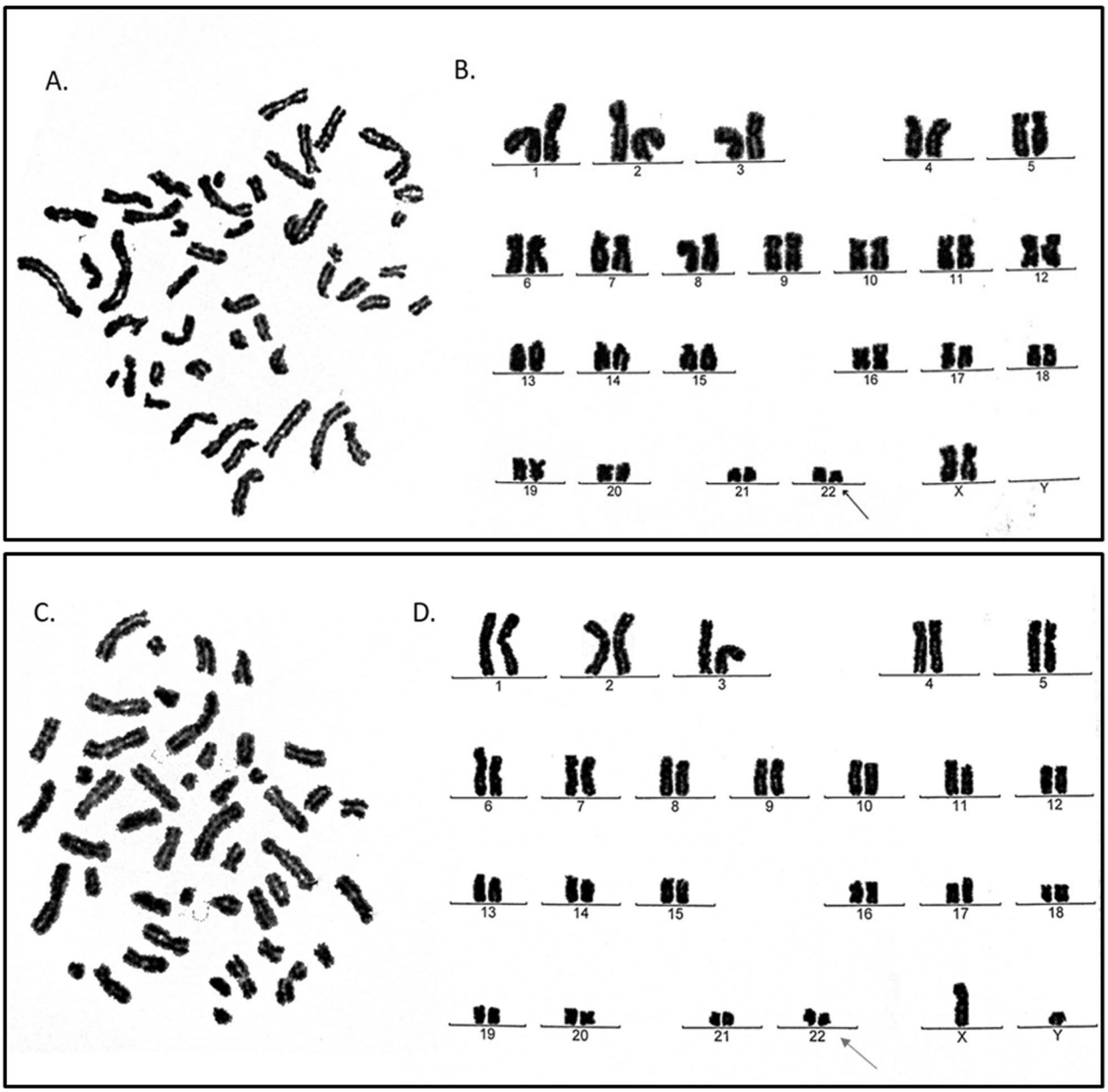


Fig. 3 **A**, **C** Metaphase shown in human chromosome. **B**, **D** Karyogram of a Philadelphia chromosome human female and male karyotype

Sudanian population and, therefore, are not being tested in many populations. These variations in frequency of transcript could be a chance due to low sample size in many studies or could be due to some factor(s) acting on it. One major factor could be some SNP(s) acting as genetic modifiers. Apart from fusion transcripts reported from various studies in Table 2, there are certain rare, unusual fusion transcripts such as e6a2, e8a2 and e15a2 also found along with common fusion transcripts [22].

Conclusion

The present study reports the frequency of BCR-ABL fusion transcript in CML cases in Eastern Uttar Pradesh population showing higher level of co-expression of the BCR-ABL fusion transcripts (63.41% aggregate of b3a2). This is the first observation of greater co-expression of BCR-ABL fusion transcript in the present Eastern Indian population. There was no correlation observed between patient with b3a2 transcript and higher platelet count which is contrary to previously reported studies.

Table 2 Prevalence of BCR-ABL1 fusion transcripts in worldwide (data in percentage)

Country	Sample size	b3a2	b2a2	b3a2 + b2a2	e1a2 + b2a2	e1a2	e19a2	e1a2 + b3a2	e1a2 + b2a2 + b3a2	References
UK	546	50.76	43.23	5.75	nr	nr	nr	nr	nr	[16, 30]
Italy	312	59.72	39.59	0.54	nr	nr	nr	nr	nr	[32, 33]
Bulgaria	98	54	44	1	nr	nr	nr	nr	nr	[34]
Germany	232	44.31	37.43	17.66	nr	0.58	nr	nr	nr	[26]
Serbia	136	74.07	25.15	0.740	nr	nr	nr	nr	nr	[35]
Poland	61	62.30	29.50	8.20	nr	nr	nr	nr	nr	[36]
France	16	62.5	37.5	nr	nr	nr	nr	nr	nr	[37]
Austria	108	69.2	29.8	nr	nr	nr	nr	nr	nr	[38]
Sudan	158	23.7	36.38	3.66	15.14	nr	nr	10.09	8.71	[38]
Tunisia	94	61	39	nr	nr	nr	nr	nr	nr	[36]
Mexico	656	40.82	51.50	7.57	nr	nr	nr	nr	nr	[39]
Ecuador	40	5.4	94.6	nr	nr	nr	nr	nr	nr	[40]
Brazil	73	61.46	34.64	3.89	nr	nr	nr	nr	nr	[41]
USA	1093	42.38	47.84	5.8	nr	nr	nr	nr	nr	[42, 43]
Korea	634	67.8	32.05	0.64	nr	nr	nr	nr	nr	[44]
Japan	218	70.61	26.18	2.63	nr	nr	0.4	nr	nr	[45]
Malaysia	37	37	0	nr	nr	nr	nr	nr	nr	[46]
China	573	67.28	32.72	nr	nr	nr	nr	nr	nr	[47, 48]
Iran	75	62	20	5	nr	nr	nr	nr	nr	[49]
Thailand	91	63.63	36.36	nr	nr	nr	nr	nr	nr	[50]
Russia	27	66.66	33.33	nr	nr	nr	nr	nr	nr	[51]
Australia	105	43	34	23	nr	nr	nr	nr	nr	[52]
India (Kolkata)	122	56.5	27	7.3	nr	1.639	1.639	nr	nr	[53]
India (Kolkata)	80	56.25	41.25	nr	nr	nr	nr	nr	nr	[53]
India (Mumbai)	202	68.31	31.68	nr	nr	nr	nr	nr	nr	[54]
India (Chandigarh)	208	66.87	28.84	3.36	nr	nr	nr	nr	nr	[55]
India (Delhi)	87	54	39	7	nr	nr	nr	nr	nr	[21]
India (Delhi)	47	32	68	nr	nr	nr	nr	nr	nr	[56]

nr not reported

Abbreviations

CML	Chronic myeloid leukaemia
BCR	Breakpoint cluster region
ABL	Abelson
Ph	Philadelphia
qRT-PCR	Quantitative reverse transcription polymerase chain reaction
NAP	Neutrophil alkaline phosphatase
BM	Bone marrow

Acknowledgements
We acknowledge the patients for their participation in the study and the Interdisciplinary School of Life Sciences (ISLS), Institute of Science, Banaras Hindu University, for providing the real-time PCR facility. I also acknowledge the Dr. Lal path laboratory for BCR-ABL transcript identification through RT-PCR. Ajeet Kumar is also grateful to UGC, New Delhi, India, for funding through the UGC NET SRF. I also acknowlwdge the IoE Banaras Hindu University for financial support.

Author contributions
AK: Development of the idea, carried out experiments, analyzed the data, and writing this manuscript. VM, CBS, RP: Sample collection, Contributed to data analysis and manuscript writing. SS: Contributed to data analysis and manuscript writing. MR, NK: Assisted in data analysis and manuscript writing. VT, VG: Provided support in manuscript writing. AA: Supervised the study, and analyzed and reviewed the study. All authors approved the final version of the manuscript.

Funding
None.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The institutional ethical approval was taken from the ethical committee (Ref. No.: I.Sc./ECM-XII/2021–22) Institute of Science, Banaras Hindu University.

Consent for publication
The written informed consent was obtained from the patient/participant for publication.

Competing interests
The authors declare that they have no competing interests.

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Received: 19 April 2023 Accepted: 4 September 2023
Published online: 05 October 2023

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