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Original Article

STR profiling in a cohort of Saudi patients with acute leukemia

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الملخص

أهداف البحث: هدفت هذه الدراسة إلى تحديد ما إذا كانت التكرارات القصيرة الترادفية الجسدية المستخدمة في التعرف الجنائي تختلف في عينات الدم المصابة بسرطان الدم مقارنة بنظيراتها من عينات اللعاب.

طريقة البحث: تم جمع الدم واللعاب من 27 مريضا تم تشخيصهم بسرطان الدم الحاد في مدينة الرياض بالمملكة العربية السعودية. تم استخراج الحمض النووي وتم تضخيم 15 موضعا من التكرارات القصيرة الترادفية الجسدية.

النتائج: أظهر حوالي 59.3٪ من مرضى سرطان الدم طفرات في مواضع التكرارات القصيرة الترادفية الجسدية. حدث فقدان التماثل الزيجوتي في 40.7٪ من المرضى في (دي19اس433) و (دي16اس539) و (في دبليو ايه) و (دي13اس317) و (تي اتش 01) و (اف جي ايه) و (دي2اس1338). تم الكشف عن عدم استقرار الميكروساتالايت في 22.2٪ منهم في (تي ببي اوه اكس) و (في دبليو ايه) و (دي19اس433) و (دي16اس539) و (دي18اس51). كان (دي19اس433) و (دي16اس539) أكثر المواقع تأثرا حيث أظهرت تغيرات وراثية بنسبة 18.52٪ تليها (في دبليو ايه) (11.11٪) ، بينما كانت (دي2اس1338) و (تي ببي اوه اكس) و (دي18اس51) أقل المواقع تأثرا حيث أظهرت نسبة طفرة بلغت 3.7٪. وأظهرت (دي13اس317) و (تي اتش 01) و (اف جي ايه) طفرة وراثية معتدلة (7.41٪). لم تظهر (سي اس اف 1 ببي اوه) و (دي21 اس11) و (دي3اس1358) و (دي5اس818) و (دي7اس820) و (دي8اس1179) والأميلوجينين تغيرات وراثية في جميع العينات. كان التباين الوراثي العام بين عينات اللعاب والدم مختلفا بشكل كبير .

الاستنتاجات: توضح النتائج التي تم الحصول عليها إمكانية استخدام تكرارات قصيرة مترادفة جسمية تستخدم في الطب الشرعي لتشخيص ومراقبة مرضى اللوكيميا. هناك حاجة إلى دراسة أخرى تطبق تقنية التسلسل الجيني للجيل التالي للتحقق من صحة هذه النتائج واستكشاف التطبيقات السريرية لتكرارات قصيرة مترادفة جسمية تستخدم في الطب الشرعي كأدوات تشخيصية لسرطان الدم.

الكلمات المفتاحية: سرطان الدم؛ تحديد النمط الجيني لتكرارات قصيرة مترادفة جسمية؛ الطفرة الجينية؛ التشخيص الجزيئي؛ السكان السعوديون.

Abstract

Objective: This study was aimed at characterizing whether the autosomal short tandem repeats (STRs) used in forensic identification might differ between leukemic blood samples and saliva samples.

Methods: Blood and saliva samples were collected from 27 patients diagnosed with acute leukemia in Riyadh City, KSA. DNA was extracted, and 15 STR loci were amplified.

Results: Approximately 59.3% of patients with leukemia exhibited mutations at the STR loci. Loss of heterozygosity (LOH) occurred in 40.7% of the patients at D19S433, D16S539, vWA, D13S317, TH01, FGA, and D2S1338. Microsatellite instability (MSI) was detected in 22.2% of patients at TPOX, vWA, D19S433, D16S539, and D18S51. D19S433 and D16S539 were the most affected loci, exhibiting an alteration percentage of 18.52%, followed by vWA (11.11%); in contrast, D2S1338, D18S51, and TPOX were the least affected loci, showing a mutation percentage of 3.7%. D13S317, TH01, and FGA showed moderate genetic mutation (7.41%). CSF1PO, D21S11, D3S1358, D5S818, D7S820, D8S1179, and amelogenin did not show genetic changes in all samp

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saliva and blood samples significantly differed ($P < 0.001$).

Conclusion: Our results demonstrate the potential application of forensically used STR loci in diagnosis and monitoring of patients with leukemia. Further study applying next generation sequencing technology is necessary to validate these findings and explore the clinical applications of forensically used STRs as diagnostic tools for leukemia.

Keywords: Genetic mutation; Leukemia; Molecular diagnosis; Saudi population; STR genotyping

Introduction

Short tandem repeats (STRs), nuclear DNA with repeats of 2−6 base pairs, make up approximately 3% of the human genome.[1] STRs have been used in multiple identity typing methods worldwide, because of their high discriminatory power in human identification, paternity testing, and missing person identification, as well as their use in diagnosing genetically induced diseases.[2]

Two types of genetic mutations have been found to occur in these human genome microsatellite markers. The first type is microsatellite instability (MSI), describing when one or more new alleles appear in the genotype.[3−5] The second is loss of heterozygosity (LOH), which indicates allelic loss in many cases of cancerous tumors, on the basis of loss of an allele at heterozygous loci[3] through either complete deletion or a decrease in the peak height to ≥50% relative fluorescence units. Several studies have used LOH and MSI to examine STR loci for forensic purposes.[2,3,6,7] In some situations, these loci may contribute to controlling gene expression, thereby affecting phenotype; however, they are suitable for the working circumstances in forensic settings.[8] Microsatellite markers may show instability in various cancerous tissues, owing to defects in DNA repair pathways and the accumulation of alterations in these markers.

STRs have been used to detect and monitor various types of cancers.[9,10] They have been found to indicate instability in lung cancer,[11] papillary thyroid disease,[12] esophageal cancer,[13] breast cancer,[14,15] colorectal cancer,[16] and 21 cancer types[17] including the abovementioned types and leukemia. Active leukemia is clinically defined by an elevated percentage of blasts in the bone marrow. For acute myeloid leukemia (AML), a diagnosis is established when at least 20% of the cells in the bone marrow are classified as blasts.[18] Untreated leukemia is newly diagnosed on the basis of low numbers of normal red blood cells, white blood cells, and platelets. Alternatively, this condition is characterized by more than 25% of cells in the bone marrow being immature white blast cells with symptoms of acute lymphocytic leukemia (ALL).[19] Leukemia affects the examination of forensic autosomal STR markers.[2,21−23]

Few studies have been conducted on STR markers to recognize allelic variations in Saudi subpopulations contributing to the genetic diversity of forensic STR markers. The overall prevalence of leukemia in the Saudi population has been estimated to be 7.6% in males and 4.4% in females.[20] Studies on genetic information in patients with leukemia in KSA are limited.[2] The unique genetic and environmental nature of the Arabian Peninsula might be a potential factor influencing the prevalence and characteristics of leukemia in KSA; thus, the disease is considered a major health concern.

This study was aimed at characterizing the STR loci frequently used in forensic investigations in randomly selected Saudi patients with leukemia, to examine the potential application of STR markers in the molecular diagnosis of leukemia. The study might contribute valuable insights not only for leukemia diagnosis and monitoring, but also for the interpretation of forensic DNA evidence in individuals with leukemia in Saudi populations and potentially in other populations with similar genetic backgrounds.

Materials and Methods

Sample collection

Blood and saliva samples were collected from 27 Saudi participants (n = 54) diagnosed with leukemia at the oncology ward of King Fahad Medical City, Riyadh, KSA. Signed informed consent was obtained from the patients at the time of sample donation. Demographic data and clinical information were collected, including age, sex, and type of leukemia. Chronic diseases were also determined through review of the patients' medical records. Samples were kept confidential, and DNA was used only for this study, in accordance with to the policy of King Fahad Medical City and the ethical committee of Naif Arab University for Security Sciences. Approximately 3 mL blood was collected at the clinic through cephalic venipuncture with a syringe and transferred to EDTA tubes. Saliva was collected from inside the oral cavity with a sterilized cotton swab and stored at −45 °C until use.

DNA extraction

DNA was extracted from blood and saliva with a QIAamp® DNA Mini and Blood Mini kit (Qiagen, USA) according to the manufacturer's instructions. A Quantifiler® Duo DNA Quantification Kit was used to quantify the DNA (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. The optimum amount of DNA for the Identifiler™ Kit was 100 pg in a maximum input volume of 10 μL for 28 PCR cycles.

PCR amplification

Fifteen autosomal STR loci (D8S1179, D21S11, D7S820, CSF1PO, D3S1358, TH01, D13S317, D16S539, D2S1338, D19S433, vWA, TPOX, D18S51, D5S818, and FGA) in addition to the sex specific genetic locus (Amelogenin) were amplified with an AmpFLSTR™ Identifiler™ PCR Amplification Kit (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. A total volume of 25 μL reaction mixture was prepared, containing 5 μL amplification grade water, 5 μL master mix, and 5 μL primers. The mixture was pulse vortexed for 5–10 s. Subsequently, 15 μL DNA template at a concentration of 0.25–0.5 ng/μL for each sample was added to the respective well containing the PCR amplification mixture. The positive 9947A control DNA with at a concentration of 0.5 ng/μL was added to the reaction well containing PCR amplification mixture. PCR mixture with only TE buffer without DNA template was added to a reaction well containing the PCR amplification mixture, as a negative control. PCR amplification was performed on a Veriti-Pro™ Thermal Cycler (Thermo Fisher Scientific, Waltham, MA, USA). After denaturation at 95 °C for 11 min, 28 amplification cycles were performed, comprising 94 °C denaturation for 1 min, 59 °C annealing for 1 min, and 72 °C extension for 1 min. The amplification was completed with a final extension at 60 °C for 60 min, and reactions were held at 4 °C until use for STR genotyping.

Genotyping

STR genotyping was performed through capillary electrophoresis with a default injection time of 30 s and a run time of 6000 s. Approximately 8.3 μL Hi-Di™ Formamid and 0.4 μL internal size standard (GeneScan™-500 LIZ™) was added to 1 μL PCR product. The mixture was incubated at 95 °C for 3 min for denaturation, then placed at a temperature of 4 °C for 3 min and transferred onto a plate until injection into a Genetic Analyzer (Applied Biosystems 3130).

The sample files (run files) from Data Collection Software were transferred to Gene Mapper ID Software ID-X1.4 (Thermo Fisher Scientific, Waltham, MA, USA) for analysis and reading of alleles at specific loci, after the separation process had been completed. Identification of each sample was automatically performed by detection of allele peaks and matching against the internal genetic ladder included in the Identifiler® Plus reagents. The analytical and stochastic thresholds were adjusted to 50 and 175 relative fluorescence units, respectively.

Statistical analysis

The allele frequencies of the 15 autosomal loci, and the forensic parameters power of discrimination (PD), polymorphic information content (PIC), random matching probability (RMP); expected heterozygosity (H_{exp}), observed heterozygosity (H_o), and probability of exclusion (PE), were calculated in STRAF 2.1.5.[24] To evaluate genetic variability between saliva and blood samples, we tested the estimated forensic parameters of six loci (D19S433, D16S539, vWA, FGA, D13S317, and TH01) exhibiting high and moderate mutation with Student's t-test, with a threshold of $P < 0.05$. The genetic variability for all data was also compared between saliva and blood samples, with a threshold of $P < 0.01$.

A chi-square test of independence was conducted to examine the association of alleles 15, 11, and 9 of the loci D3S1358, D13S317, and TH01 associated with leukemia. The allele frequencies were compared between patients with leukemia in this study and the controls from a prior study by Alharbi et al.[2]

Results

Demographic and clinical characterization

Table 1 shows the distribution of characteristics of patients with leukemia who participated in this study. The participants' ages ranged from 8 to 63 years. Most participants (40.8%) were older than 40 years, their age was 34.70 ± 17.55 (mean ± SD) years, and 55.6% were males. A total of 63% of patients had AML, whereas 37% had ALL. Approximately 26% of the patients had a family history of leukemia, and 37% had a family history of other cancers. Moreover, 63% of cases were active disease, whereas 37% were untreated. B-cell leukemia accounted for 37% of cases, and was followed by M2 (22.2%), M1 (18.5%), M3 (11.1%), M5 (7.4%), and M0 (3.7%). No patients received chemotherapy or radiotherapy, and 85.2% had infections. The most common infections were blood circulation infections (56.5%), pulmonary infections (21.7%), urinary tract infections (8.7%), other infections (8.7%), and gastrointestinal infections (4.4%). The main causes of infection were bacteria (60.9%), viruses (21.6%), unknown (8.7%), fungi (4.4%), and parasites (4.4%). Regarding the aberration or affected chromosomes, most cases were not otherwise specified (40.7%), whereas the remainder had normal karyotype (18.5%), 19q and t16 (14.8% each), 12p (7.4%), and t (1–22) (3.7%). Leukemia severity was determined according to the type of leukemia, chromosomal aberrations, and the number of loci acquiring genetic mutations (Table 2).

DNA genotyping

The DNA concentration in blood samples averaged 32.42 ± 21.23 ng/μL, and ranged between 7.33 and 84.89 ng/μL. The DNA concentration in saliva samples averaged 55.73 ± 51.92 ng/μL, and ranged between 2.00 ng/μL and 211.49 ng/μL.

The complete profiles of the 15 autosomal STR loci and the sex specific locus amelogenin were obtained for the 54 leukemic blood and saliva samples. Alleles at each locus studied are shown in Table 3. The potential alleles at the studied loci included 8 alleles at each of D8S1179 and D21S1; 7 alleles at each of D13S317, D16S539, and vWA;

Table 1: Demographic information for patients diagnosed with leukemia in this study.

Variables	Category	Frequency	Percentage
	<18 years	5	18.5%
Age	18–28 years	6	22.2%
	29–40 years	5	18.5%
	>40 years	11	40.8%
Sex	Male	15	55.6%
	Female	12	44.4%
Leukemia type	Acute myeloid leukemia (AML)	17	63.0%
	Acute lymphocytic leukemia (ALL)	10	37.0%
Leukemia stage	Active disease	17	63.0%
	Untreated	10	37.0%
Leukemia subtypes	M0	1	3.7
	M1	5	18.5
	M2	6	22.2
	M3	3	11.1
	M5	2	7.4
	B-cell	10	37.0
	NOS	11	40.7
Chromosomal aberration	t(1–22)	1	3.7
	Normal karyotype	5	18.5
	12p	2	7.4
	19q	4	14.8
	t16	4	14.8
Family history with leukemia	Yes	7	25.6%
	No	20	74.4%
Family history with cancer	Yes	10	37.0%
	No	17	63.0%
Receiving chemotherapy	Yes	0	0.0%
	No	27	100%
Receiving radiation therapy	Yes	0	0.0%
	No	27	100%
Infection	Yes	23	85.2%
	No	4	14.8%
Type of infection	Blood circulation infection	13	56.5
	Urinary tract infection	2	8.7
	Gastrointestinal infection	1	4.4
	Pulmonary infection	5	21.7
	Other[a]	2	8.7
Laboratory results for infections	Bacteria	14	60.9
	Viruses	5	21.6
	Fungi	1	4.4
	Parasites	1	4.4
	Unknown	2	8.7

NOS = not otherwise specified.
[a] Other includes perianal skin infection and skin infection.

Table 2: Blood samples of patients diagnosed with leukemia, and severity according to type and subtype, number of mutated loci, and chromosomal aberrations.

Blood samples	Number of loci mutated	Leukemia type (subtype)	Chromosomal aberrations
B2	2	AML (M5)	t1-t22
B3	2	ALL (B cell)	Normal
B5	2	ALL (B cell)	12p
B10	2	AML (M3)	t16
B16	2	AML (M3)	12p
B22	2	AML (M3)	t16
B8	1	ALL (B cell)	19q
B9	1	AML (M2)	NOS
B13	1	ALL (B cell)	19q
B14	1	ALL (B cell)	19q
B17	1	AML (M5)	NOS
B20	1	ALL (B cell)	19q
B25	1	AML (M2)	t16

NOS = not otherwise specified.

Table 3: Allocated alleles in the 15 loci, as recorded in the 27 leukemia cases studied.

Locus	No. of allocated alleles	Identified alleles/loci
D8S1179	8	10, 11, 12, 13, 14, 15, 16, 17
D21S11	8	27, 28, 29, 30, 31.2, 32.2, 33.2, 35
D7S820	5	8, 9, 10, 11, 12
CSF1PO	6	8, 9, 10, 11, 12, 13
D3S1358	6	14, 15, 16, 17, 18, 19
TH01	6	6, 7, 8, 9, 9.3, 10
D13S317	7	8, 9, 10, 11, 12, 13, 14
D16S539	7	8, 9, 10, 11, 12, 13, 15
D2S1338	11	16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26
D19S433	10	12, 12.2, 13, 13.2, 14, 14.2, 15, 15.2, 16, 17
VWA	7	14, 15, 16, 17, 18, 19, 20
TPOX	5	8, 9, 10, 11, 12
D18S51	10	11, 12, 13, 14, 15, 16, 17, 18, 19, 20
D5S818	13	8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
FGA	13	18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30

6 alleles at each of CSF1PO, D3S1358, and TH01; 5 alleles at each of D7S820 and TPOX; 0 alleles at each of D19S433 and D18S51; 13 alleles at D5S818 and FGA; and 11 alleles at D2S1338.

Figure 1 illustrates representative electropherograms of both LOH and MSI in the studied cases. Table 4 shows the amplified loci and their alleles from 27 saliva samples and 27 leukemic blood samples donated by 27 people. Genetic mutations were detected in 16 of the 27 leukemic blood samples (59.3%). LOH was observed in 11 samples (40.7%), at 7 of 15 STR loci, including D19S433, D16S539, vWA, D13S317, TH01, FGA, and D2S1338, representing 46.7% of the total loci. MSI was detected in 6 of the 27 samples (22.2%), including at D19S433, D16S539, vWA, TPOX, and D18S51, representing 31.3%

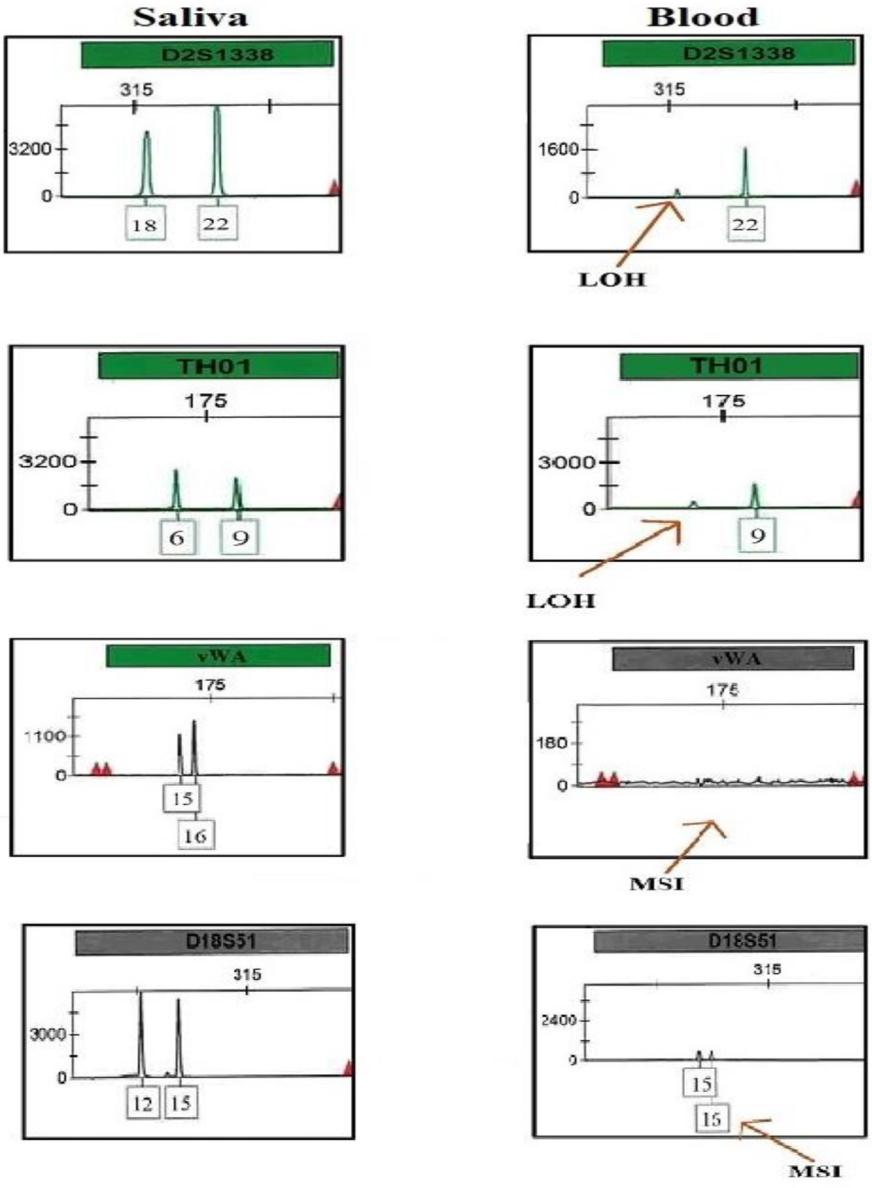

Figure 1: Representative electropherograms of LOH and MSI at selected alleles.

of the 15 studied loci. Only one sample (3.7%) was affected by both LOH at D16S539 and MSI at vWA.

Table 5 summarizes the types and frequencies of genetic mutations observed at the 15 STR loci analyzed in 27 leukemia cases. Among the 432 STR loci studied, 22 (5.10%) mutations were found, and the mutation frequencies were 0.032 for LOH and 0.018 for MSI. Most loci remained unaffected: 94.90% showed no genetic mutation. Fourteen mutations were found to have LOH (3.25%), whereas eight had MSI (1.85%). Allelic alteration was observed at nine loci: D19S433, D16S539, vWA, D13S317, TH01, FGA, TPOX, D18S51, and D2S1338. Among these, the most affected loci were D19S433 and D16S539, which exhibited alteration percentages of 18.52% (five people each), followed by vWA (11.11%). D2S1338, D18S51, and TPOX, the least affected loci, showed an alteration percentage of 3.70% (Figure 2). The loci D13S317, TH01, and FGA showed moderate genetic mutation (7.41%). Six loci (CSF1PO, D21S11, D3S1358, D5S818, D7S820, and D8S1179) did not show any allelic changes in all samples, and amelogenin was normal in all cases. Significant differences in the forensic parameters of highly and moderately mutated loci were observed between saliva and blood samples (PIC, $P \leq 0.05$; Ho, $P < 0.001$;

Table 4: Genetic traits of STR loci of blood and oral swab samples. S and B indicate swab and blood samples, respectively. Loci in gray indicate LOH, whereas those in red indicate MSI.

Samples	STR loci														
	D8S1179	D21S11	D7S820	CSF1PO	D3S1358	TH01	D13S317	D16S539	D2S1338	D19S433	VWA	TPOX	D18S51	Amelogenin	D5S818	FGA
S1	13,15	28,30	8,9	10,10	15,17	6,9	11,12	12,15	20,20	12,15	18,18	8,10	16,16	X,X	13,13	24,25
B1	13,15	28,30	8,9	10,10	15,17	6,9	11,12	12,15	20,20	12,15	18,18	8,10	16,16	X,X	13,13	24,25
S2	11,12	29,30	11,12	10,11	15,17	7,9	8,11	8,11	17,20	12,13	16,19	8,8	11,11	X,X	10,12	24,25
B2	11,12	29,30	11,12	10,11	15,17	7,9	8,11	11,11	17,20	12,13	18,19	8,8	11,11	X,X	10,12	24,25
S3	12,14	29,32.2	10,12	10,11	14,15	6,9	11,14	11,11	16,21	15,15	17,18	8,8	12,13	X,X	11,11	20,24
B3	12,14	29,32.2	10,12	10,11	14,15	9,9	11,14	11,11	16,21	15,15	17,18	8,8	12,13	X,X	11,11	24,24
S4	12,15	29,30	8,9	11,11	15,18	7,9	11,13	9,9	22,23	14,15.2	14,17	9,11	19,19	X,X	12,13	21,30
B4	12,15	29,30	8,9	11,11	15,18	7,9	11,13	9,9	22,23	14,15.2	14,17	9,11	19,19	X,X	12,13	21,30
S5	11,13	30,30	10,11	12,12	15,17	7, 7	8,11	11,11	17,23	12,13	17,18	8,8	14,16	X,Y	10,12	23,24
B5	11,13	30,30	10,11	12,12	15,17	7, 7	11,11	11,11	17,23	12,13	17,17	8,8	14,16	X,Y	10,12	23,24
S6	15,16	29,29	9,9	10,11	15,17	6,9	10,11	12,12	19,19	13,15	15,17	8,10	12,13	X,Y	11,13	18,22
B6	15,16	29,29	9,9	10,11	15,17	6,9	10,11	12,12	19,19	13,15	15,17	8,10	12,13	X,Y	11,13	18,22
S7	11,13	30,31.2	8,12	12,12	14,15	8,9	11,12	9,11	23,23	15,16	15,18	8,9	12,12	X,Y	12,12	19,21
B7	11,13	30,31.2	8,12	12,12	14,15	8,9	11,12	9,11	23,23	15,16	15,18	8,9	12,12	X,Y	12,12	19,21
S8	11,14	30,32.2	8,12	11,12	15,16	7,9	11,14	11,12	17,23	12,14	17,18	8,8	12,13	X,X	10,13	22,24
B8	11,14	30,32.2	8,12	11,12	15,16	7,9	11,14	11,12	17,23	14,14	17,18	8,8	12,13	X,X	10,13	22,24
S9	11,11	28,29	8,10	11,12	15,18	6,6	11,12	11,11	18,22	13,16	16,18	8,11	13,17	X,Y	10,11	20,24
B9	11,11	28,29	8,10	11,12	15,18	6,6	11,12	11,11	22,22	13,16	16,18	8,11	13,17	X,Y	10,11	20,24
S10	15,17	30,34.2	10,10	10,11	15,18	7,9.3	11,12	9,13	20,24	13,14	17,18	8,9	14,15	X,X	11,11	19,29
B10	15,17	30,34.2	10,10	10,11	15,18	7,7	11,12	9,9	20,24	13,14	17,18	8,9	14,15	X,X	11,11	19,29
S11	13,15	30,32.2	10,11	10,11	15,17	9,9.3	11,11	8,12	25,25	15,16	15,16	8,11	13,15	X,Y	11,12	22,22
B11	13,15	30,32.2	10,11	10,11	15,17	9,9.3	11,11	8,12	25,25	15,16	15,16	8,11	13,15	X,Y	11,12	22,22
S12	11,16	32.2,32.2	11,12	10,11	15,17	9,9	11,14	11,11	16,17	12,15.2	17,17	8,9	12,20	X,Y	13,13	19,24
B12	11,16	32.2,32.2	11,12	10,11	15,17	9,9	11,14	11,11	16,17	12,15.2	17,17	8,9	12,20	X,Y	13,13	19,24
S13	10,11	29,30	9,11	10,12	15,16	8,9	11,12	12,13	19,24	14.2,15.2	17,18	8,10	13,17	X,Y	9,12	20,27
B13	10,11	29,30	9,11	10,12	15,16	8,9	11,12	12,13	19,24	14.2,14.2	17,18	8,10	13,17	X,Y	9,12	20,27
S14	15,16	32.2,32.2	10,11	11,12	15,18	6,9	11,11	9,12	18,18	14.2,17	17,18	11,12	14,15	X,X	11,12	22,24
B14	15,16	32.2,32.2	10,11	11,12	15,18	6,9	11,11	9,12	18,18	16,17	17,18	11,12	14,15	X,X	11,12	22,24
S15	13,14	29,29	9,11	9,11	15,17	6,9.3	9,11	12,13	19,24	13,16	16,17	8,8	12,15	X,Y	11,12	20,22
B15	13,14	29,29	9,11	9,11	15,17	6,9.3	9,11	12,12	19,24	13,16	16,17	8,8	12,15	X,Y	11,12	20,22
S16	10,10	28,32.2	9,11	10,12	15,16	7,9	11,11	11,12	19,26	12.2,14	15,16	8,12	13,16	X,X	11,11	23,25
B16	10,10	28,32.2	9,11	10,12	15,16	7,9	11,11	12,13	19,26	12.2,14	-	8,12	13,16	X,X	11,11	23,25
S17	14,15	29,30	12,12	10,12	15,17	6,9	11,13	11,12	20,20	13,15.2	16,18	8,10	16,18	X,X	10,12	19,21
B17	14,15	29,30	12,12	10,12	15,17	6,9	11,11	11,12	20,20	13,15.2	16,18	8,10	16,18	X,X	10,12	19,21
S18	12,15	29,33.2	10,12	10,11	14,15	6,9	11,12	11,11	19,20	14,14	17,18	9,12	15,17	X,Y	8,13	20,24
B18	12,15	29,33.2	10,12	10,11	14,15	6,9	11,12	11,11	19,20	14,14	17,18	9,12	15,17	X,Y	8,13	20,24
S19	13,14	32.2,35	11,11	10,12	15,17	6,9	8,11	8,11	19,21	13.2,13.2	15,17	8,8	16,21	X,X	12,13	25
B19	13,14	32.2,35	11,11	10,12	15,17	6,9	8,11	8,11	19,21	13.2,13.2	15,17	8,8	16,21	X,X	12,13	25
S20	14,15	29,32.2	8,11	11,12	14,15	6,9	11,12	10,12	17,20	12,15.2	17,18	8,9	16,17	X,Y	9,10	23,24
B20	14,15	29,32.2	8,11	11,12	14,15	6,9	11,12	10,12	17,20	12,13	17,18	8,9	16,17	X,Y	9,10	23,24
S21	12,13	27,30	9,10	12,12	15,16	6,7	11,14	8,11	16,19	13,16	17,18	8,8	16,20	X,X	12,13	21,22
B21	12,13	27,30	9,10	12,12	15,16	6,7	11,14	8,11	16,19	13,16	17,18	8,8	16,20	X,X	12,13	21,22
S22	13,17	29,32.2	10,10	11,12	15,15	9,9	11,12	9,12	17,23	15,16.2	17,20	8,11	15,16	X,Y	10,10	18,20
B22	13,17	29,32.2	10,10	11,12	15,15	9,9	11,12	11,12	17,23	15,16.2	17,20	9,11	15,16	X,Y	10,10	18,20
S23	12,16	30,33.2	9,10	9,12	15,15	9,9.3	11,11	11,12	19,20	15.2,16	17,18	8,11	15,16	X,X	9,10	19,19
B23	12,16	30,33.2	9,10	9,12	15,15	9,9.3	11,11	11,12	19,20	15.2,16	17,18	8,11	15,16	X,X	9,10	19,19
S24	12,15	30,30	8,9	11,11	15,19	7,9	11,13	9,9	22,23	14,15.2	14,17	9,11	19,19	X,X	12,13	21,30
B24	12,15	30,30	8,9	11,11	15,19	7,9	11,13	9,9	22.23	14,15.2	14,17	9,11	19,19	X,X	12,13	21,21
S25	13,15	29,32.2	8,10	11,12	15,16	9,9.3	8,11	11,13	21,23	14,16	16,18	8,8	12,15	X,X	12,12	22,24
B25	13,15	29,32.2	8,10	11,12	15,16	9,9.3	8,11	11,13	21,23	14,14	16,18	8,8	12,15	X,X	12,12	22,24
S26	14,14	28,30	10,12	8,11	14,15	7,7	11,11	9,11	17,20	13,15.2	16,18	8,11	12,16	X,X	11,12	26,29
B26	14,14	28,30	10,12	8,11	14,15	7,7	11,11	9,11	17,20	13,15.2	16,18	8,11	12,16	X,X	11,12	26,29
S27	12,15	29,30	10,10	12,13	15,17	9,10	9,11	8,9	17,25	14.2,17.2	17,18	10,11	12,15	X,Y	9,13	22,24
B27	12,15	29,30	10,10	12,13	15,17	9,10	9,11	8,9	17,25	14.2,17.2	17,18	10,11	15,16	X,Y	9,13	22,24

Table 5: Comparison of STR loci of blood samples from patients diagnosed with leukemia versus reference buccal swab samples.

Mutation type	Frequency of incidence	Locus	RFU	Allelic alteration		Case number	Sex
				Saliva	Blood		
LOH	0.032	D16S539	32.4	8,11	11,11	2	Female
		TH01	35.1	6,9	9,9	3	Female
		FGA	37.3	20,24	24,24	3	Female
		D13S317	47.9	8,11	11,11	5	Male
		VWA	29.6	17,18	17,17	5	Male
		D19S433	49	12,14	14,14	8	Female
		D2S1338	17.5	18,22	22,22	9	Male
		TH01	12.8	7,9.3	7,7	10	Female
		D16S539	33.4	9,13	9,9	10	Female
		D19S433	44.2	14.2,15.2	14.2,14.2	13	Male
		D16S539	36.8	12,13	12,12	15	Male
		D13S317	22.1	11,13	11,11	17	Female
		FGA	41.7	21,30	21,21	24	Female
		D19S433	46.6	14,16	14,14	25	Female
MSI	0.018	VWA	–	16,19	18,19	2	Female
		VWA	–	15,16	–	16	Female
		D19S433	–	14.2,17	16,17	14	Female
		D16S539	–	11,12	12,13	16	Female
		D19S433	–	12,15.2	12,13	20	Male
		D16S539	–	9,12	11,12	22	Male
		TPOX	–	8,11	9,11	22	Male
		D18S51	–	12,15	15,16	27	Male

RFU: relative fluorescence units.

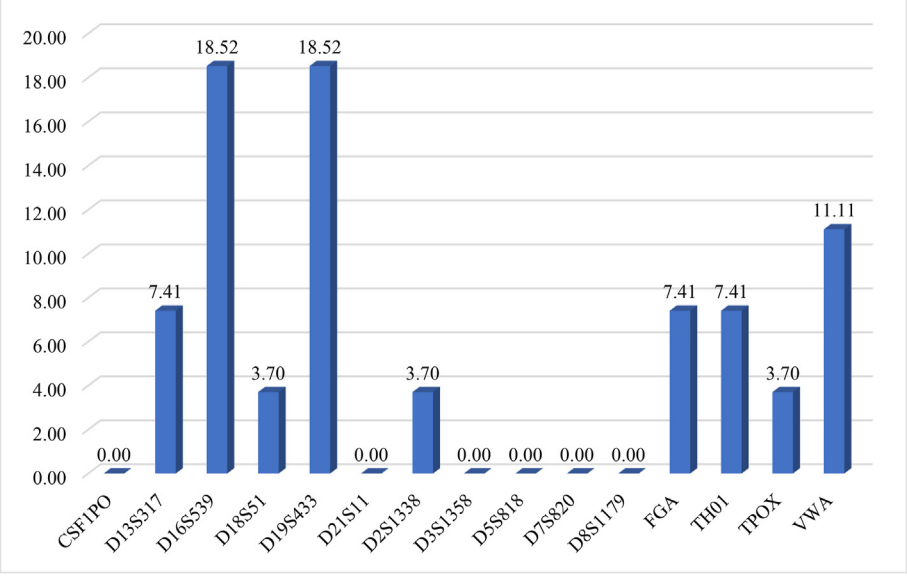

Figure 2: Percentage distribution of detected STR loci with mutations.

Table 6: Mean and standard deviation for the forensic parameters calculated from allele frequencies for the highly and moderately mutated loci (D19S433, D16S539, vWA, D13S317, FGA, and TH01) in blood samples versus control saliva samples. GD: genetic diversity (total heterozygosity); PIC: polymorphic information content; RMP: random matching probability; PD: power of discrimination; Ho: observed heterozygosity; PE: probability of exclusion.

Samples	PD	PIC	PM	H_{exp}	Ho	PE
Saliva	0.87 ± 0.05	0.74 ± 0.08	0.13 ± 0.06	0.77 ± 0.08	0.84 ± 0.07	0.68 ± 0.12
Blood	0.87 ± 0.05	0.71 ± 0.09	0.13 ± 0.05	0.76 ± 0.09	0.76 ± 0.07	0.54 ± 0.12
P-value	0.47	0.02[a]	0.77	0.018[a]	0.0004***	0.0002***

[a] Significant at $P < 0.05$, ** significant at $P < 0.01$, *** significant at $P < 0.001$.

Table 7: Differential association between genotypes and leukemia, compared between patients with leukemia in this study (N = 27) and controls in Alharbi et al.[2] (N = 15).

Locus	Allele	Percentage of leukemia cases (this study)	Percentage of controls (Alharbi et al.)[2]	Chi-square test of significance
D3S1358	15	27/42 (64.3)	8/42 (33.3)	$\chi^2 = 11.59$, df = 1, N = 42; P-value = 0.0006; $\phi^2 = 0.28$
D13S317	11	27/42 (64.3)	8/42 (33.3)	$\chi^2 = 11.59$, df = 1, N = 42; P-value = 0.0006; $\phi^2 = 0.28$
TH01	9	21/42 (50)	5/42 (11.9)	$\chi^2 = 6.30$, df = 1, N = 42; P-value = 0.01; $\phi^2 = 0.19$

Confidence interval was 99% for alleles 15 and 11, and 95% for allele 9.

PE, $P < 0.001$) (Table 6). The overall genetic variability between saliva and blood samples was also significant at $P < 0.001$.

Discussion

The present study revealed significant genetic alterations at forensic STR loci among Saudi patients with leukemia. Approximately 59.3% of the studied patients exhibited genetic alterations. LOH of 40.7% was observed across the markers D19S433, D16S539, vWA, D13S317, TH01, FGA, and D2S1338. Among the changes, MSI was detected at D19S433, D16S539, vWA, TPOX, and D18S51 in 22.2% of patients. The loci D19S433 and D16S539 showed the highest frequency of genetic changes, whereas D2S1338, D18S51, and TPOX were the least affected loci. These findings highlight the potential utility of STR loci analysis in diagnosing and monitoring patients with leukemia, thus offering a new method for genetic profiling in leukemia research and clinical management.[23]

Associations between forensic STR markers and diseases have been studied, and several investigations support their application in identifying cancer-related alleles. In a study by Wei et al.,[25] the highest levels of serum norepinephrine were found in patients with the TH01-9 allele, whereas patients with the TH01-7 allele had the lowest levels. Ceccardi et al.[26] have examined the STR profiles commonly used in forensic identification across a diverse array of human tumor tissues. The samples studied included 48 gastrointestinal cancers, 13 urogenital cancers, and 7 oral cancers. The vWA, FGA, and D18S51 loci were the most frequently altered loci. That study has contributed valuable insights into the stability of genetic markers in cancerous tissues, which might potentially affect the field of forensic science and the understanding of genetic changes in tumor development. Stomach and intestinal carcinomas have been found to exhibit alteration at D18S51, vWA, and FGA.[27] Many studies have reported associations of D16S539, D19S433, vWA, and TH01 polymorphisms with several diseases.[2,17,28] Al-Harthi[17] has examined autosomal STR profiling in Saudi women diagnosed with breast cancer and found mutations in 54.84% of cases; moreover, the STR loci D16S539, D22S1045, TH01, and TPOX were found to be highly susceptible to MSI and LOH. Despite its small sample size, the current study yielded findings consistent with those reported by Qi et al.,[29] in which CODIS loci were used for screening lung and liver cancer predisposition. The authors found a statistically significant difference between the alleles associated with lung cancer (D18S51-20) and liver cancer (D21S11−30.2 and D6S1043-18). These results demonstrated the predictive power of using CODIS loci to assess cancer susceptibility. A considerably high frequency of two pairs of alleles, D8S1179-16 and D5S818-13, and D2S1338-23 and D6S1043-11, has been reported in young people diagnosed with stomach cancer.[28]

The frequency of STR alterations differs according to the type of cancerous tissue. The highest alteration rates have been reported in esophageal cancer, followed by colorectal, hepatocellular, gastric, lung, renal cell, breast, and pancreatic cancers.[9] Moreover, that study demonstrated that all eight tumor types showed alterations (LOH and MSI) at the STR loci used for forensic applications, including the STR loci examined in the present study. Leukemia has been detected and diagnosed on the basis of more 9.3 and 9 alleles at the locus TH01 than observed in healthy controls.[2] The authors of that study have provided evidence of an association between TH01 alleles and leukemia. Although MSI was associated with AML and ALL in the present study, Walker et al.[30] have reported that patients with AML do not exhibit MSI. This genetic instability is often detected in patients with chronic myeloid leukemia (CML) and found in some STR loci frequently used in forensic human identification (D17S261 and D3S643).[31] To our knowledge, studies published to date have indicated the presence of LOH and MSI in patients diagnosed with CML[2,21,32,33] at only some CODIS STR loci usually used for forensic purposes. However, the present study is not the first to find STR mutations in patients diagnosed with AML and ALL. Faderl et al.[34] have reported that LOH at some STR markers located on chromosome 5 is associated with AAL (loci other than those included in CODIS, e.g., D52818). Among patients exposed to hematopoietic stem cell transplantation, Pereira et al.[35] have found LOS at D21S11 and CSF1PO, and length mutations at other STR loci, in patients diagnosed with AML. Patients with prognostically adverse AML have been diagnosed with LOS in chromosome 13 at several markers other than the CODIS D13S317 locus.[36] Some aspects of LOH have been found at STR loci in chromosomes 1, 3, 5, 10, and 12 in patients with ALL.[37,38] Zuho et al.[39] have revealed deletions in some STR loci in chromosomes 9 and 17 in novel childhood ALL cell lines.

The current study analyzed 16 STR loci previously targeted by Alharbi et al.[2] Both studies focused on randomly selected Saudi patients and showed similar allelic ranges of the potential alleles identified. Allele 15 at locus D3S1358 (100%), allele 11 at locus D13S317 (100%), and allele 9 at locus TH01 (77.8%) are frequently detected in saliva and

blood samples. The distribution of both alleles was compared between the leukemic cases studied herein and the controls in the study by Alharbi et al.[2] Allele 15 at locus D3S1358 and allele 11 at locus D13S317 were found in all 27 cases in this study and in 8 of 15 control cases reported by Alharbi et al.[2] Allele 9 at the locus TH01 was found in 21 leukemic cases in this study and 5 controls in Alharbi et al.[2] The proportions of alleles 15 (D3S1358), 11 (D13S317), and 9 (TH01) were significantly higher in patients with leukemia than controls (Table 7). Among patients with leukemia, 64.3% had alleles 15 and 11, and 50% had allele 9; among controls, 19% had alleles 15 and 11, and 11.9% had allele 9. These findings indicated a strongly significant association between leukemia and these alleles ($\chi^2 = 11.59$, $P = 0.0006$; $\chi^2 = 6.30$, $P = 0.01$). The significant difference observed in the distribution of these alleles between the leukemia and control cases suggested a possible contribution to the risk leukemia development. The square ϕ coefficient showed moderate correlations ($\phi^2 = 0.28$ and 0.19, respectively), thus indicating that patients with leukemia were more likely to have the three alleles than controls. The presence of these alleles might be associated with elevated risk of developing leukemia. However, further exploration is necessary to understand the potential mechanisms underlying the relationship between these alleles and leukemia.

The small sample size in this study is a potential limitation that might have introduced errors in result estimation and hindered the ability to detect statistically significant differences between cases. Additionally, the unbalanced distribution of characteristics among samples might have prevented important differences from being observed. To address this limitation, a similar study with a larger sample size is recommended, particularly including the newly identified acute leukemia mutations. This approach would enhance the accuracy of the results, decrease error risks, and increase statistical power for discrimination. Challenges in sample collection, such as patient health status or refusal to participate, might further have limited this study's representativeness and introduced bias by leading to the exclusion of certain disease categories. To mitigate these challenges, establishing sample banks at medical centers with informed consent procedures would facilitate access to larger, more diverse patient samples, thus enhancing the study's ability to represent broader population groups.

The observed high proportion of leukemia cases with a family history in this study, despite its limited sample size, is a notable finding that warrants further investigation. This observation aligns with those from recent studies reporting elevated incidence of leukemia in KSA.[20,40,41] Although data on familial leukemia rates in the region remain scarce, the elevated family history rates observed herein might indicate genetic predisposition, shared environmental exposures, or a combination of factors unique to the Saudi population. To elucidate the molecular mechanisms underlying different leukemia subtypes, and to validate our findings, future research should expand the study to include both acute (AML and ALL) and CML cases, with larger sample sizes and comprehensive genomic analyses. Such an approach might provide valuable insights into the etiology of leukemia in this population and potentially inform targeted prevention and treatment strategies.

Conclusion

In conclusion, genetic mutations were found in 59.3% of patients with leukemia herein. The STR loci included in the study showed varying susceptibility to genetic mutations. Both LOH and MSI were observed at three sites (D19S433, D16S539, and vWA), whereas LOH was recorded at four sites (D13S317, TH01, FGA, and D2S1338), and MSI was found in only TPOX. The associations of allele 15 at D3S1358, allele 11 at D13S317, and allele 9 at TH01 might be considered potential genetic elements for leukemia diagnosis. Further research is required to confirm and explore the clinical applications of forensically applied STRs as a diagnostic tool for leukemia.

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Conflict of interest

The authors have no conflicts of interest to declare.

Ethical approval

This study was initially approved by the Institutional Review Board (IRB) of King Fahad Medical City, Riyadh, KSA (reference: H-01-R-012 IRB), and the experimental procedure was performed in accordance with their relevant guidelines and regulations.

Authors' contributions

Conceptualization, H.A., M.N.A., and S.A.A.; methodology, H.A.; software, H.A. and S.A.A.; formal analysis, H.A. and S.A.A.; investigation, H.A., M.N.A., S.A.B., S.A.A., and A.N.; data curation, H.A., M.N.A., S.A.B., and A.N.; writing—original draft preparation, H.A. and M.N.A.; writing—review and editing, S.A.A. and M.N.A.; visualization, M.N.A., S.A.B., and A.N.; supervision, M.N.A., S.A.A., S.A.B., and A.N. All authors have read and agreed to the published version of the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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