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REVIEW **Open Access**

Forensic short tandem repeat markers alteration in cancerous tissues: a scoping review

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Abstract

Background Short Tandem Repeats (STRs) are segments of DNA composed of a short sequence of nucleotides that repeat consecutively. These repeating sequences exhibit distinct lengths and nucleotide sequences among individuals, showcasing high variability and uniqueness. The STR profile remains consistent across all cells in an individual's body. Nonetheless, changes in the STR profile have been documented in cancerous tissues. This scoping review aimed to investigate the occurrence and pattern of forensic STR markers alterations in cancerous tissues. We conducted a scoping review of the English-language publications published between 2002 and 2022 in the PubMed, Science Direct, and Scopus databases and a manual search of reference lists from reviewed papers. The review was carried out in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

Results Our search resulted in a total of 1,065 articles associating forensic STR studies with cancerous tissues. A total of 18 of these studies met our inclusion criteria. The D18S51 marker was most often found to be altered when associated with cancers such as breast, colorectal, gastric, gynaecology, and lung cancers. Following with that, FGA, VWA, D19S433, and D13S317 markers could as well be seen to have allelic alteration in cancerous tissues. Four other STR markers (TPOX, D7S820, D2S1338, and Penta D) could be potentially represented as stable STR markers in cancerous tissues.

Conclusions According to our review, colorectal cancer tissue has the highest level of genomic instability compared to that of other cancer types. In summary, the genetic instability caused by faulty DNA mismatch repair processes in human carcinomas can pose challenges for forensic genotyping and DNA profile matching.

Keywords Forensic genetic, DNA typing, Cancer, Short tandem repeat, Microsatellite instability

Background

Microsatellites, also known as short tandem repeats (STRs), are segments of DNA consisting of repeat units between two and seven base pairs (bp) in length. Each STR sequence displays a unique combination of repetition frequency, repeat pattern, and sequence variation. Compared to nonrepetitive sequences, STRs undergo mutation at a much greater rate: 10 − 6 to 10 − 2 mutations per locus, per gamete, and per generation. These mutations were discovered because of replication errors, sister chromatid exchange, unequal crossing over, and gene conversion (Fan & Chu 2007). Consequently, STR regions are highly polymorphic markers with the capacity

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to individualise individuals, making them ideal for forensic applications such as human identification and DNA paternity (Dang et al. 2020). Much et al. (2014) found that tissue identification testing using STR genotyping could fix mislabelled samples, mixed-up tissues, and cross-contamination in diagnostic pathology labs. This would be especially helpful in cancer diagnosis. In some cases, malignant tissue may be the sole option for obtaining a reference sample for a forensic DNA analysis. However, several variables have been identified as potential threats to microsatellite stability in malignant tissues. These include impairments in repair processes, high rates of mutation, and chromosomal abnormalities (Vauhkonen et al. 2004). It is reported that a patient's chromosome status may undergo various changes as their condition develops (Hou et al. 2017). Some of these mutations occurred in STR markers that have been linked to the diagnosis and prognosis of diseases such as lung, breast, gastric, colorectal, oesophageal, and renal cell carcinoma (Chen et al. 2021; Qi et al. 2018; Vauhkonen et al. 2004; Zhang et al. 2018). In general, there are two types of STR alterations that affect the results of STR genotyping: loss of heterozygosity (LOH) and microsatellite instability (MSI). In the context of genetic pathology, LOH was identified by allelic loss (allelic deletion) in the tumour tissue as compared with the heterozygotic control sample. Samples were also determined to have LOH if the fluorescence signal was lower than expected in comparison to the other allele. Allelic deletions could be further classified into complete LOH (cLOH) and partial LOH (pLOH) (Margiotta et al. 2006). Meanwhile, MSI refers to an alteration in the length of the STRs resulting from the genetic or epigenetic inactivation of genes responsible for the maintenance of DNA integrity. These MSIs could be in the form of additional alleles (Aadd) or the occurrence of a new allele (Anew) instead of those found in normal tissue (Tozzo et al. 2021; Vauhkonen et al. 2004). Regardless of the tumour type or STR marker, allelic loss has remained the most frequently altered mutational type, followed by the insertion of an additional allele (Qi et al. 2018). Therefore, the presence of Aadd, Anew, and LOH could lead to STR genotype alteration, especially in cancerous tissues. Given the large number of studies that have reported LOH and MSI on various cancerous tissues (Chen et al. 2021; Qi et al. 2018; Vauhkonen et al. 2004; Zhang et al. 2018), we decided to conduct this scoping review to identify and map existing evidence describing and evaluating STR genotype alterations occurrences found on cancerous tissues. In this review, we will look at the pattern and occurrence (%) of STR alterations in five major types of cancerous tissues: breast cancer (BC), lung cancer (LC), colorectal cancer (CRC), gastric cancer (GC), and gynaecology cancer (GCC).

Main text

Study design

The six steps of a scoping review were used to guide the design of this study (Arksey & O'Malley 2005; Levac et al. 2010). The following are the steps in the six-step research process: 1) define the research question; 2) identify the relevant studies by defining the inclusion and exclusion criteria; 3) search for and select relevant literature; 4) chart the evidence; 5) collate, summarize, and report the evidence; and finally, 6) consult with relevant stakeholders to ensure that our findings are accurate. The review was carried out in compliance with the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and the Meta-Analysis extension for Scoping Reviews) according to Tricco et al. (2018).

Data source

To construct inclusion and search keywords, the literature search was driven by the review objectives and the population, concept, and content criteria. The Boolean operators 'AND' and 'OR' were used to combine search terms and free-text words. Search keywords were as follows: ("STR markers" OR "short tandem repeat markers" OR "short tandem repeat allelic alteration" OR "STR allelic alteration") AND ("cancerous tissues" OR "cancer" OR "tumour" OR "tumor"). Literature searches were conducted using electronic databases (PubMed, Science Direct, and Scopus) and by hand (searching reference lists of included papers). English-language publications published between 2002 and 2022 are eligible for consideration.

Selection criteria and data extraction

The population, concept, and content framework proposed by Peter et al. were used to define inclusion criteria (Peters et al. 2015). The inclusion criteria include a) multinational patients diagnosed with cancer (population); b) articles on the use of STR markers for cancerous tissue analysis (concept); c) studies of STR markers involving multiple types of cancer (content); d) multinational literature; and e) observational studies with or without controls. Exclusion criteria included: a) articles with fewer than ten samples; b) cancers with less than three studies; c) articles focusing solely or mainly on gene promoter sequence in cancerous tissues; d) articles assessing cancer pathways unrelated to forensic STR markers; e) irrelevant studies; f) repeated publication; g) articles with only an abstract available; and h) literature review articles. To widen the scope of the research, all publications were reviewed by two reviewers. The data was extracted from all included studies by the first reviewer using a standard data abstraction form, and it was independently checked by a second reviewer. The study's eligibility was

re-evaluated before and during data extraction. Disagreements among the reviewers were resolved by calling in other experts to weigh in.

Association between STR and cancerous tissues

In this scoping review, we summarised all the findings of eighteen studies based on the prevalence of STR alterations in different five types of cancerous tissues: BC, GCC, LC, CRC, and GC, according to each type of STR mutation. As previously discussed, MSI includes alteration types of Aadd and Anew. Since some studies have reported MSI on cancerous tissues instead of Aadd and Anew, we have included the MSI term as a separate category in this paper. We then organised the data into a visual illustration and a table to provide a clear and comprehensive overview of the findings for the readers.

Results

Search result

A total of 1065 studies were retrieved from three databases: PubMed, Science Direct, and Scopus, including articles in their reference lists (Fig. 1). Among all, 430 studies were selected for further screening for eligibility. Based on readily available full-text articles that were able to be retrieved, eighty-seven full-text articles from 430 potentially accepted studies were assessed for eligibility, and 18 were chosen to be included in the study, while the remaining 412 were deemed ineligible for a variety of reasons. Figure 1 presents the PRISMA-ScR flowchart of the study selection process and reasons for exclusion.

Characteristics of included studies

Based on the data collected, there were five types of cancer that have been studied for forensic STR analysis (Table 1). The research studies were published between 2002 and 2021 and covered a wide range of countries. The following countries (number of studies) were represented: China (7), Italy (3), Germany (2), Poland (2), United States (1), Saudi Arabia (1), Brazil (1), and Finland (1). Nearly all the studies included were quantitative in design including twelve case–control, and six cohort-type longitudinal studies. Most of the studies discussing the use of STR kits were focused on gastrointestinal (GI) cancers, with CRC and GC being the main cancers of discussion (9 and 6 studies, respectively). Meanwhile, studies on BC, GCC, and LC with total of six, three, and four studies, respectively.

Association between STR markers and cancer

In this review, we are able to relate the association between the STR markers and various types of cancerous tissues. An illustration is made to visualise the broad picture of the STR alteration that can be found in these five major cancerous studies, including BC, GCC, LC, CRC, and GC (Fig. 2). In all, 28 distinct forensic STR markers were analysed, and all could be found to be altered. To make it clearer, Tables 2 and 3 demonstrates the percentage of each STR alteration type according to the STR markers and their cancerous types. Based on Tables 2 and 3, the D18S51 marker was the most often found to be altered throughout all the cancerous tissues studied. Following with that, FGA, VWA, D19S433, and D13S317 markers could as well be seen to have allelic alteration at

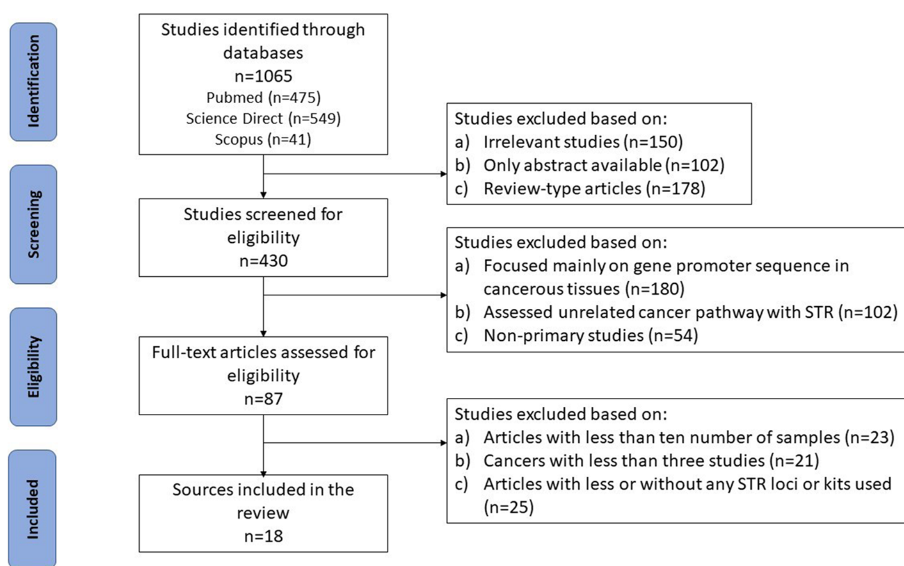

Fig. 1 The PRISMA flowchart of study selection process and the total number of studies included at four stages and their reasons for exclusions

Table 1 Studies of cancer involving STR marker(s) included in the review by cancer site, country of study, sample size (n), study design and STR marker(s)/kit(s) used

Author(s)	Year	Cancer Type	Country	Study design	n	STR marker(s)/kit(s)	No. of markers
Peloso et al. 2003	2003	Lung	Italy	Case–control	48	AmpFISTR™ Profiler Plus	9
Powierska-Czarny et al. 2003	2003	Breast	Poland	Cohort	70	D1S103, THO1, D21S11, D18S51 and FGA	5
Edelmann et al. 2004	2004	Gynecology	Germany	Case–control	27	SE33, D3S1358, D3S1768, D3S2456, D17S1537, VWA, D16S539, D2S1338, D8S1179, D21S11, D18S51, D19S433, TH01, and FGA	14
Poetsch et al. 2004	2004	Colorectal	Germany	Case–control	236	AmpFISTR™ Profiler Plus	9
Vauhkonen et al. 2004	2004	Gastric and Colorectal	Finland	Case–control	82	AmpFISTR™ Profiler and AmpFISTR™ SGM Plus	9–10
Li et al. 2009	2009	Colorectal	China	Case–control	154	AmpFISTR® Identifiler™	15
Pepiński et al. 2009	2009	Gynecology	Poland	Case–control	45	AmpFISTR® Identifiler™	15
Ananian et al. 2011	2011	Breast, Gastric, Colorectal	Italy	Case–control	122	AmpFISTR® Identifiler™, AmpFISTR® Profiler Plus™, AmpFISTR® Minifiler™, AmpFISTR® Yfiler™ PCR Amplification, Kits and Mentype® Argus X-UL PCR Amplification Kit	
dos Santos et al. 2012	2012	Breast	Brazil	Case–control	64	D2S123, TPOX, D3S1358, FGA, D7S820, TH01, D13S317, D16S539, D3S1611, D13S790, D17S796	11
Hui et al. 2014	2014	Gastric	China	Cohort	75	AmpF/STR Sinofiler™ PCR Amplification kit	15
Hou et al. 2017	2017	Breast, Gynecology	China	Case–control	6000	PowerPlex 21 system and Argus X-12 kit	12–21
Qi et al. 2018	2018	Lung	China	Cohort	300	AmpFISTR® Identifiler™	15
Wang et al. 2018	2018	Colorectal	United States	Cohort	258	Powerplex 16 HS System	16
Zhang et al. 2018	2018	Lung	China	Cohort	225	Microreader™ 21 Direct ID System kit	21
Chen et al. 2020	2019	Colorectal and Gastric	China	Case–control	500	Goldeneye®20A Forensic Identifier Kit	20
Al-Qahtani et al. 2021	2021	Colorectal	Saudi Arabia	Case–control	73	Powerplex® 16 System	16
Chen et al. 2021	2021	Breast, Lung, Colorectal and Gastric	China	Case–control	407	Goldeneye®20A Forensic Identifier Kit	20
Tozzo et al. 2021	2021	Gastric, Breast and Colorectal	Italy	Cohort	132	AmpFISTR® NGM Select™	16

all five types of cancerous tissues. Nonetheless, the least STR alteration could be seen on the D7S820, D2S1338, Amel, D22S1045, D2S441, D1S1656, Penta D, and D3S1768 markers.

Breast Cancer (BC)

BC is considered to have the lowest mutation rates, ranging from 0% to 48.60% (Fig. 2) (Ananian et al. 2011; Chen et al. 2021; dos Santos et al. 2012; Hou et al. 2017; Powierska-Czarny et al. 2003). Nineteen STR loci affected by allelic mutations were observed, with LOH occurring in all 19 markers (Tables 2 and 3). The most altered markers for LOH are D13S790, D18S51, FGA, TH01, and D21S11, with mutation rates ranging from 5.97% to 36.00% (Tables 2 and 3). Furthermore, BC tissues show low rates of pLOH alterations, ranging from 1.23% to 1.43% for markers D16S359, D21S338, D22S1045, D2S441, D3S1358, D1S1656, and SE33 (Ananian et al. 2011; Tozzo et al. 2021). Additionally, low mutation rates of MSI (1.00% to 4.00%) were observed in FGA, D18S51, and D1S103 markers (Tables 2 and 3 and Fig. 2).

Gynaecology Cancer (GCC)

GCCs have been found to exhibit higher STR mutation rates compared to BCs but lower rates than LC, CRC, and GC, with alteration rates ranging from 0% to 70.0% (Fig. 2) (Edelmann et al. 2004; Hou et al. 2017; Pepiński et al. 2009). Observations of allelic mutations revealed that 11 STR loci were affected, with LOH occurring in nine of the markers (Tables 2 and 3 and Fig. 2). Among these, the most frequently occurring LOH alterations were found in the STR markers D3S1358,

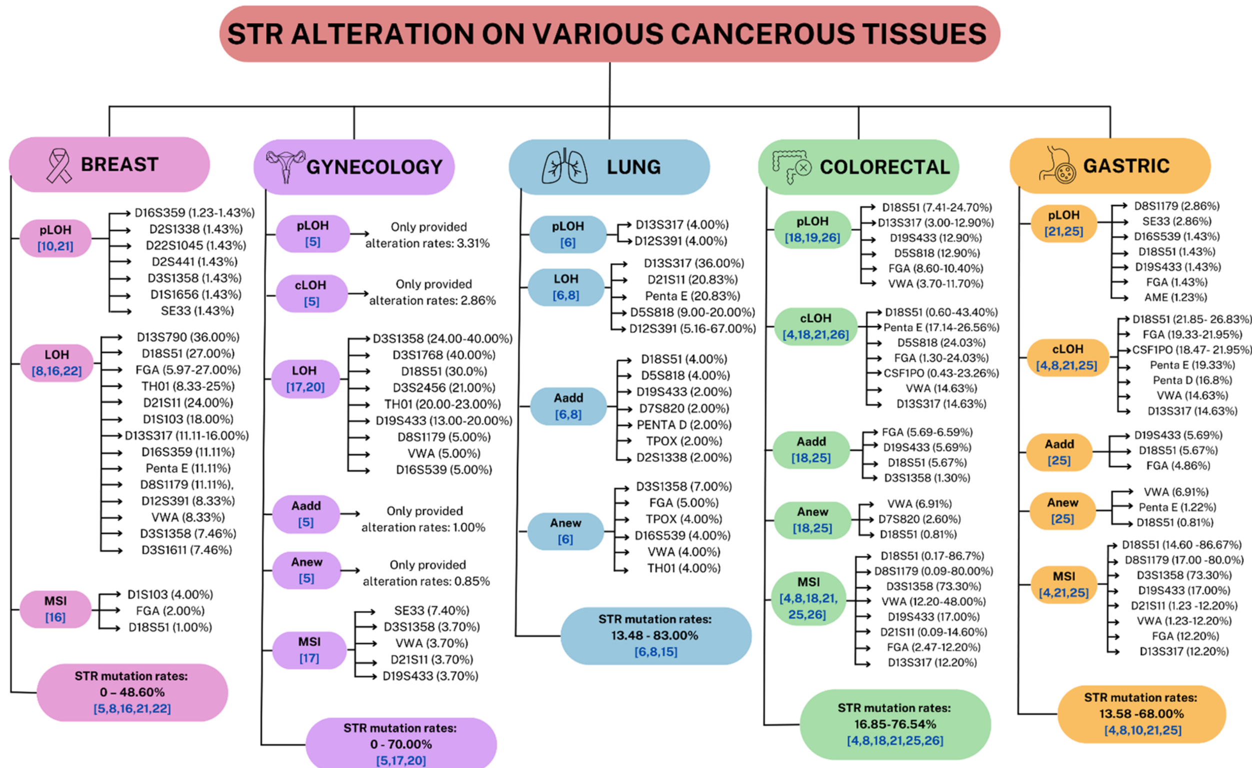

Fig. 2 Types of STR alterations and their occurrence percentage in various cancerous tissue. Abbr: LOH, loss of heterozygosity; cLOH, complete loss of heterozygosity; pLOH, partial loss of heterozygosity; MSI, microsatellite instability; Aadd, additional alleles; Anew, new alleles; [n], 4, Vauhkonen et al. (2004); 5, Hou et al. (2017); 6, Zhang et al. (2018); 8, Chen et al., (2021); 10, Tozzo et al. (2021); 15, Peloso et al. (2003); 16, Powierska-Czarny et al. (2003); 17, Edelmann et al. (2004); 18, Poetsch et al. (2004); 20, Pepiński et al. (2009); 21, Ananian et al. (2011); 22, dos Santos et al. (2012); 25, Chen et al. (2020); 26, Al-Qahtani et al., (2021)

D3S1768, D18S51, D3S2456, and TH01, with rates ranging from 20.00% to 40.00% (Tables 2 and 3) (Edelmann et al. 2004; Pepiński et al. 2009). Edelmann et al. (2004) conducted a study on MSI in GCCs and found that the SE33 marker exhibited the highest frequency of alterations, followed by D3S1358, VWA, D21S11, and D19S433, each with a 3.7% alteration rate (Tables 2 and 3). Unfortunately, in our review, we were unable to identify specific altered markers for pLOH, cLOH, Aadd, and Anew due to the limited number of studies in which only one author measured the alteration rates for these mutation types.

Lung Cancer (LC)

On LC tissues, the STR mutation rate falls within the intermediate range when compared to BC, GCC, CRC, and GC, ranging from 13.48% to 83.00% (Fig. 2) (Chen et al. 2021; Peloso et al. 2003; Zhang et al. 2018). Sixteen STR loci were observed to be altered, with LOH, including pLOH, occurring in five different STR markers (Tables 2 and 3). The most frequently altered marker for LOH in LC was found to be D12S391, ranging from 5.16% to 67.00%, followed by D13S317 (36.00%), and both of D21S11 and PENTA E with 20.83%, respectively (Tables 2 and 3) (Chen et al. 2021; Zhang et al. 2018). Additionally, pLOH was detected in both D13S317 and D12S391 markers, with low alteration rates of 4.0% for each marker (Tables 2 and 3). It was also noted that out of the nine STR markers examined (TPOX, D7S820, D2S1338, D19S433, PENTA D, D16S539, D5S818, VWA, and THO1), they showed the least alterations of MSI in LC samples, with rates ranging from 2.00 to 4.00% (Chen et al. 2021; Zhang et al. 2018).

Colorectal Cancer (CRC)

In our review, the STR mutation rate for CRC is the highest compared to the other four types of cancerous tissues, ranging from 16.85% to 76.54%, making CRC samples the most genetically unstable cancerous tissues (Fig. 2) (Ananian et al. 2011; Chen et al. 2020, 2021; Poetsch et al. 2004; Tozzo et al. 2021; Vauhkonen et al. 2004). We observed allelic mutations in 12 STR loci, with eight different markers experiencing LOH, specifically seven cLOH and six pLOH mutations (Tables 2 and 3). Notably,

Table 2 Percentage and type of STR alterations on D3S1358, VWA, FGA, TH01, TPOX, CSF1PO, D5S818, D13S317, D7S820, D8S1179, D21S11, D18S51, D16S539, D2S1338 in the cancerous tissues

STR Markers	Percentage of STR alteration rates (%)																		
	BC			GCC		LC				CRC					GC				
	pLOH	LOH	MSI	LOH	MSI	pLOH	LOH	Aadd	Anew	pLOH	cLOH	Aadd	Anew	MSI	pLOH	cLOH	Aadd	Anew	MSI
D3S1358	1.43	7.46	-	24.00–40.00	3.70	-	-	-	7.00	-	-	1.30	-	73.30	-	-	-	-	73.30
VWA	-	8.33	-	5.00	3.70	-	-	-	4.00	3.70–11.70	14.63	-	6.91	12.20–48.00	-	14.63	-	6.91	1.23–12.20
FGA	-	5.97–27.00	2.00	-	-	-	-	-	5.00	8.60–10.40	1.30–24.03	5.69–6.59	-	2.47–12.20	1.43	19.33–21.95	4.86	-	12.20
TH01	-	8.33–25.00	-	20.00–23.00	-	-	-	-	4.00	-	-	-	-	-	-	-	-	-	-
TPOX	-	-	-	-	-	-	-	2.00	4.00	-	-	-	-	-	-	-	-	-	-
CSF1PO	-	-	-	-	-	-	-	-	-	-	0.43–23.26	-	-	-	-	18.47–21.95	-	-	-
D5S818	-	-	-	-	-	-	9.00–20.00	4.00	-	12.90	24.03	-	-	-	-	-	-	-	-
D13S317	-	11.11–16.00	-	-	-	4.00	36.00	-	-	3.00–12.90	14.63	-	-	12.20	-	14.63	-	-	12.20
D7S820	-	-	-	-	-	-	-	2.00	-	-	-	-	2.60	-	-	-	-	-	-
D8S1179	-	11.11	-	5.00	-	-	-	-	-	-	-	-	-	0.09–80.00	2.86	-	-	-	17.00–80.00
D21S11	-	24.00	-	-	3.70	-	20.83	-	-	-	-	-	-	0.09–4.60	-	-	-	-	1.23–12.20
D18S51	-	27.00	1.00	30.00	-	-	-	4.00	-	7.41–24.70	0.60–43.4	5.67	0.81	0.17–86.70	1.43	21.85–26.83	5.67	0.81	14.60–86.67
D16S539	1.23–1.43	11.11	-	5.00	-	-	-	-	4.00	-	-	-	-	-	1.43	-	-	-	-
D2S1338	1.43	-	-	-	-	-	-	2.00	-	-	-	-	-	-	-	-	-	-	-

Abbr: BC Breast cancer, *LC* Lung cancer, *CRC* Colorectal cancer, *GC* Gastric cancer, *GCC* Gynecology cancer, *LOH* Loss of heterozygosity, *cLOH* Complete loss of heterozygosity, *pLOH* Partial loss of heterozygosity, *MSI* Microsatellite instability, *Aadd* Additional alleles, *Anew* New alleles,—No STR alteration

Table 3 Percentage and type of STR alterations on D19S433, D12S391, D22S1045, D2S441, D1S103, D13S790, D1S1656, SE33, PENTA E, PENTA D, Amel, D3S1768, D3S1611 and D3S2356 in the cancerous tissues

STR Markers	Percentage of STR alteration rates (%)																		
	BC			GCC		LC				CRC					GC				
	pLOH	LOH	MSI	LOH	MSI	pLOH	LOH	Aadd	Anew	pLOH	cLOH	Aadd	Anew	MSI	pLOH	cLOH	Aadd	Anew	MSI
D19S433	-	-	-	13.00–20.00	3.70	-	-	2.00	-	12.90	-	5.69	-	17.00	1.43	-	5.69	-	17.00
D12S391	-	8.33	-	-	-	4.00	5.16–67.00	-	-	-	-	-	-	-	-	-	-	-	-
D22S1045	1.43	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D2S441	1.43	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D1S103	-	18.00	4.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D13S790	-	36.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D1S1656	1.43	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SE33	1.43	-	-	-	7.40	-	-	-	-	-	-	-	-	-	2.86	-	-	-	-
PENTA E	-	11.11	-	-	-	-	20.83	-	-	-	17.14–26.56	-	-	-	-	19.33	-	1.22	-
PENTA D	-	-	-	-	-	-	-	2.00	-	-	-	-	-	-	-	16.80	-	-	-
Amel	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.23	-	-	-	-
D3S1768	-	-	-	40.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D3S1611	-	7.46	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
D3S2356	-	-	-	21.00	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Abbr: BC Breast cancer, *LC* Lung cancer, *CRC* Colorectal cancer, *GC* Gastric cancer, *GCC* Gynecology cancer, *LOH* Loss of heterozygosity, *cLOH* Complete loss of heterozygosity, *pLOH* Partial loss of heterozygosity, *MSI* Microsatellite instability, *Aadd* Additional alleles, *Anew* New alleles,—No STR alteration

VWA, FGA, CSF1PO, D5S818, D13S317, D18S51, and Penta E exhibited prominent cLOH mutations, ranging from 0.43% to 43.40% (Al-Qahtani et al. 2021; Ananian et al. 2011; Chen et al. 2021; Vauhkonen et al. 2004). The D18S51 marker was commonly altered in all types of mutations, including pLOH (7.41% to 24.70%), cLOH (0.60% to 43.40%), Aadd (5.67%), Anew (0.81%), and MSI (0.17% to 86.70%) (Tables 2 and 3) (Ananian et al. 2011; Chen et al. 2020; Li et al. 2009; Tozzo et al. 2021). Similarly, the D13S317 marker exhibited the highest rate of alteration among forensic STR markers, with pLOH (3.00% to 12.90%), cLOH (14.63%), and MSI (12.20%) (Fig. 2). We also observed that nine markers were affected by the MSI mutation, including Aadd and Anew, with prominent markers such as D3S1358, VWA, D8S1779, D18S51, and D19S433 markers. Based on Tables 2 and 3, three STR markers, such as D3S1358, D7S820, and D18S51, had low alteration rates in MSI, particularly in Aadd and Anew mutation types, ranging from 0.81% to 2.60%.

Gastric Cancer (GC)

Following CRC samples, GC samples were reported to have the second highest average STR mutation rates, ranging from 13.58% to 68.00% (Ananian et al. 2011; Chen et al. 2020, 2021; Tozzo et al. 2021; Vauhkonen et al. 2004). We found changes in 14 STR loci in GC tissues. Twelve of these markers had seven cLOH mutations and seven pLOH mutations (Tables 2 and 3). Notably, D18S51, FGA, CSF1PO, Penta E, and Penta D exhibited prominent cLOH mutations, ranging from 14.63% to 26.83% (Ananian et al. 2011; Chen et al. 2020, 2021; Vauhkonen et al. 2004). In our review, the D18S51 marker was the most frequently altered marker in GC samples across all mutation types, including pLOH (1.43%), cLOH (21.85% to 26.83%), Aadd (5.67%), Anew (0.81%), and MSI (14.60% to 86.67%) (Tables 2 and 3). Additionally, the FGA marker showed frequent alterations in pLOH (1.43%), cLOH (19.33% to 21.95%), Aadd (4.86%), and MSI (12.20%) (Tables 2 and 3). We also observed that nine markers were affected by the MSI mutation, including Aadd and Anew, with prominent markers such as D3S1358, D8S1779, D18S51, and D19S433 markers. The least altered MSI markers that could be observed were FGA, D18S51, and PENTA E markers.

Discussion

This review has revealed a significant gap in the number of studies focusing on the application of forensic STR markers in various types of cancerous tissues. Only 18 published research articles were found over a period of 20 years (2002–2022), indicating a limited research emphasis in this area. Among these studies, the majority (10 out of 18 studies) focused on investigating STR allelic changes in GI cancers, particularly in CRC and GC, while other cancer types were relatively understudied. Additionally, only four studies involved cohort subjects that were organised based on factors such as gender, age, geography, and histological characteristics.

STR alleles may not be directly associated with cancer development. However, variations in STR alleles, such as changes in the number of repeats, can occur because of genetic instability in cancer cells. For instance, Zhang et al. (2018) reported a significant correlation between STR variations in LC and the age of patients as well as the stages of the disease, suggesting potential associations between STR markers and disease progression. In another study by Qi et al. (2018), a genetic risk analysis was conducted in LC based on the theory of programmed onset. They identified D18S51-20 as a marker associated with an increased risk of developing LC. Meanwhile, regarding GC, Hui et al. (2014) found that individuals with specific sets of alleles, namely D8S1179-16 and D5S818-13, D2S1338-23, and D6S1043-11, had a significantly higher frequency of GC and an earlier average age of diagnosis. This suggests that certain STR-associated functional genes located near one another may interact, potentially increasing the risk of GC. Nevertheless, it is important to carefully consider the quality and reliability of the DNA sample and conduct additional testing and validation as needed to ensure accurate results.

Breast Cancer (BC) as the most stable cancerous tissues

Hou et al. (2017) conducted a study on BC and found that STR variation was observed in most STR markers, except for the Amel and Penta D markers. Nonetheless, the autosomal STR variation was generally low in all stages of BC differentiation (Hou et al. 2017). Recent research has shown that BC contains fewer mutations compared to colorectal cancers and gastrointestinal neoplasms, indicating the relative genetic stability of BC (Kalfoglou et al. 2006). These findings have been supported by subsequent investigations, which consistently found that the mutation rates of STRs in BCs were generally lower than those of GCCs (ranging from 0% to 48.60%) (Fig. 2) (Ananian et al. 2011; Chen et al. 2021; dos Santos et al. 2012; Powierska-Czarny et al. 2003; Tozzo et al. 2021).

Although BC samples are generally claimed to have microsatellite stability, a few loci were observed to have a variable high percentage of mutation. This discrepancy in findings may be attributed to sample heterogeneity across studies. It is possible that some studies claiming microsatellite stability focused on specific breast cancer subtypes that are generally considered to have a low frequency of MSI (Ananian et al. 2011; Hou et al. 2017;

Powierska-Czarny et al. 2003). On the other hand, studies reporting loci with high mutation rates might have focused on different subtypes or specific genomic regions that are inherently prone to instability (Chen et al. 2021; dos Santos et al. 2012; Tozzo et al. 2021).

Currently, the mechanism by which allelic mutations may promote the development of BC is not yet fully understood. Numerous studies have emphasised the complex nature of BC development, involving multiple genetic and environmental factors. While it is known that genetic mutations, including allelic mutations, contribute to BC, the specific mechanisms linking these mutations to cancer development are still under investigation. In general, STR polymorphism can impact the transcription and translation rates of specific genes and has been implicated in breast cancer-related genes. These genes include androgen receptor, oestrogen receptor, transcription factor E2F-4, cytochrome C P450, insulin-like growth factor I, breast cancer amplify gene 1, and interferon-gene (Hou et al. 2017). The variations in these genes can influence gene translation and potentially contribute to the development of BC by playing a role in the disease progression. However, further research is needed to fully understand the precise mechanisms and interactions involved in BC development.

High occurrence of STR alteration in Gynaecology Cancer (GCC)

Genomic alterations, such as LOH or MSI, can occur in multiple chromosomes, including the X-chromosome, in cases of GCC tissues. However, there is a lack of reported data specifically regarding the alterations on the X-chromosome in GCC. Studies have indicated that patients with GCC tumours are more likely to exhibit STR variants, and the extent of variation is correlated with tumour differentiation and stage (Edelmann et al. 2004; Hou et al. 2017; Pepiński et al. 2009).

In an analysis conducted by Hou et al. (2017), STR variation was investigated on both BC and GCC tissues. It was found that the detection of GCCs was more frequent in autosomal STR markers, while the detection of BCs was more likely in X-chromosome STR markers. This suggests that the genetic changes associated with GCC and BC may involve different genomic regions. Notably, LOH was observed in approximately 60% of GCC cases, including those with microsatellite instability–high (MSI-H) GCCs (Hou et al. 2017). The authors also explored STR variations within GCC subtypes, such as cervical, ovarian, vulvar, and endometrial cancers. However, the study did not delve into the specific details of STR variations at individual loci within these subtypes. Instead, the emphasis was placed on comparing the STR variations between GCC tissues and BC tissues. The study of STR variations on GCC subtypes is limited (Edelmann et al. 2004; Pepiński et al. 2009). Both articles focus on cervical carcinoma and consistently reported frequent LOH at four specific STR loci: D3S1358, TH01, D19S433, and D18S51.

Lung Cancer (LC) with intermediate STR mutation rates

LC was reported to have allelic imbalances across multiple STR markers (Peloso et al. 2003; Zhang et al. 2018; Chen et al. 2021). Two studies had categorized the LC tissues into its subtypes including adenocarcinomas, squamous cell carcinomas, and small-cell carcinomas. According to Peloso et al. (2003), small-cell carcinoma sample revealed cLOH at D5S818 and D13S317 loci. However, it is crucial to note that this particular study had a limited sample size, consisting of only one small-cell carcinoma sample. Therefore, a larger sample size is essential to validate and reinforce this observation. Meanwhile, adenocarcinomas and squamous cell carcinomas in LC displayed notable STR variations at D13S317, D21S11, Penta E, D5S818, and D12S391 loci (Peloso et al. 2003; Zhang et al. 2018).

The instability of these markers may be influenced by the presence of tumour suppressor genes located near the markers. For instance, a tumour suppressor gene such as the *Retinoblastoma 1* gene is located on chromosome 13q14.2 near the D13S317 marker, while the *Adenomatous Polyposis Coli* (*APC*) gene is located on chromosome 5q22.2 near the D5S818 marker. Several studies have reported frequent deletions or alterations in these genes in LC patients, supporting the association between these markers and the disease (Guo et al. 2014; Kim et al. 2016). However, it is important to note that the association between these STR markers and lung cancer may not be solely due to the proximity of tumour suppressor genes. The markers themselves may undergo alterations or exhibit instability in cancerous tissues, providing insights into the genomic changes associated with lung cancer. There are also contradictory findings regarding the stability of STR markers in LC tissues. Interestingly, Peloso et al. (2003) reported the absence of MSI with new alleles of varied sizes in LC tissues, suggesting that MSI may not play a prominent role in LC development. In line with this finding, Zhang et al. (2018) found that neither the D2S441 nor Penta E markers were altered in any of the 75 LC specimens analysed, indicating their relative stability in LC. These findings suggest the potential utility of D2S441 and Penta E markers as stable genetic markers for further research and clinical applications in LC. This broadens our understanding of the genetic variability in LC.

However, other research has linked the presence of MSI and LOH to tumour development. The extent of the

tumour's progression has been proven to increase with the number of STR loci that are altered (Filoglu et al. 2014; Vaderhobli et al. 2014). Additionally, a higher frequency of STR variants has been associated with older age at surgery or diagnosis in LC patients ($p < 0.05$), suggesting that genetic instability and the accumulation of STR variants may increase with age (Zhang et al. 2018).

Gastrointestinal (GI) tumours with instability STR polymorphisms

GI tumours have been extensively studied due to their well-characterized genetic aberrations, such as LOH and MSI. Vauhkonen et al. (2004) observed that two-thirds of the genetic alteration in GI tumours is associated with LOH (high LOH frequency, LOH-H), while Chen et al. (2020) found that MSI-H tumours are affected by the two-thirds of the genetic alteration studied. Interestingly, Vauhkonen et al. (Vauhkonen et al. 2004) also reported a negative correlation between the LOH-H phenotype and the MSI-H phenotype in GI tumours. The LOH-H phenotype was believed to reflect chromosomal instability in these tumours, as they exhibited a high mutation frequency in tumour samples compared to the reference germline mutation frequency. This indicated widespread STR alterations in GI tumour samples (Vauhkonen et al. 2004). Specifically, allelic loss was observed in chromosomes 18q (D18S51) and 5q (CSF1PO and D5S818), contributing to 26.32% and 16.27% allelic loss, respectively, in a cohort of 250 patients with GI (Chen et al. 2020). These findings support previous literature suggesting the involvement of these chromosomal regions in GI tumorigenesis.

In terms of mutation prevalence, GI samples exhibited mutations in 55.6% of cases, which is consistent with findings from previous studies. For instance, Vauhkonen et al. (2004) observed mutations in 68% of 41 GI cases; Pelotti et al. (2007) found mutations in 66% of 56 sporadic GI cases analysed; and Ananian et al. (2011) detected mutations in 54.6% of frozen sample cases. These findings collectively demonstrate the high genomic instability observed in GI tumours, surpassing the levels observed in BC. Specifically, in this study, the most frequently mutated STR markers in GI tumours were identified as D18S51, FGA, and SE33. These findings align with conclusions from different studies, highlighting D18S51 and FGA as two of the most mutated markers in GI tumours (Ananian et al. 2011; Pelotti et al., 2007; Tozzo et al. 2021; Vauhkonen et al. 2004). It is worth noting that the studies mentioned primarily focused on two common categories of GI tumours: CRC and GC.

Colorectal Cancer (CRC)

CRC is a significant global health concern, ranking as the fourth leading cause of death and the third most common type of cancer. It is a prevalent malignancy that originates in the GI tract. Studies have found a strong link between the development of CRC and problems with DNA mismatch repair proteins (Ananian et al. 2011; Tozzo et al. 2021). These proteins are very important for fixing replication errors caused by nucleotide mismatches. CRCs with MSI-H have unstable mono- or dinucleotide repeats, which is another sign that these tumours don't have enough mismatch repair. MSI-H CRCs are of particular interest in several studies as they provide insights into the molecular mechanisms underlying mismatch repair-related CRC development. Tables 2 and 3 presents the findings from several studies on CRC, highlighting the most frequently observed alterations in specific genetic markers. Among the included CRC studies, the D18S51 marker was commonly found to be altered, particularly in malignant tissues such as those found in BC, CRC, GC, and GCC. However, Wang et al. (2018) did not find evidence of allelic variation at the D18S51 markers but observed it at VWA and D13S31, making those two markers the most frequently unstable gene markers in their study. These findings align with previous studies that have also reported frequent alterations in VWA and additional FGA markers in CRC tissues. The high number of different alleles (ranging from 11 to 24 for VWA and 14 to 51 for FGA) likely contributes to their frequent instability in CRC.

Also, the instability of STR on CRC may be due to longer repetitive regions with complex sequence motifs, where two or more types of repeat motifs are right next to each other in the same locus. This complexity is evident in the VWA and FGA repeat motifs (i.e., TCTA[TCTG]n[TCTA]n and [TTTC]nTTTTTTCT[CTTT]nCTCC[TTCC]n, respectively). In contrast, homogenous repeat regions with low repeat number < 10, as seen in D8S1179, D5S818, D13S317 and D7S820, were found to rarely mutate in non-neoplastic tissues, supporting the low frequency of alteration observed in the study (Poetsch et al. 2004). In colon carcinomas, the deleted colon cancer (*DCC*) and *APC*, located in chromosomes 18q, and 5q, respectively, are frequently deleted through LOH, as supported by previous studies (Goel et al. 2003). The alterations observed in the D18S51 and D5S818 markers, which are near the *DCC* and *APC* genes, respectively, further highlight their involvement in CRC studies, providing evidence of genetic instability in these specific regions (Li et al. 2009; Poetsch et al. 2004; Vauhkonen et al. 2004). The proximity of these STR markers to the tumour suppressor genes that undergo changes during CRC progression may explain the increased genetic instability observed in CRC.

Several studies have also found significant differences in other markers, such as D21S11 and CSF1PO, especially between CRC tissue samples and adjacent non-cancerous

tissue samples, as well as between CRC samples and the control group (Al-Qahtani et al. 2021; Pepiński et al. 2009). These findings suggest the potential utility of these markers for distinguishing CRC cases. In a study by Tozzo et al. (2021), no significant difference was observed when comparing mutated and non-mutated markers on other tumour types such as GC and BC. However, when CRC data was included in their analysis, a significant difference was detected. These results indicate that CRC may exhibit a higher number of mutations, which can complicate the accurate interpretation of STR genotypes in this specific cancer type. Therefore, caution should be exercised when attributing STR genotypes in CRC cases due to the potential interferences caused by the increased mutation burden.

Gastric Cancer (GC)

GC samples are recognised as being the second most highly genetically unstable, with average STR mutation rates ranging from 13.58% to 68.00% (Fig. 2) (Chen et al. 2021; dos Santos et al. 2012; Much et al. 2014). These rates indicate a significant level of genetic instability within GC, comparable to that observed in CRC. Interestingly, there is a high similarity in the patterns of STR alteration between CRC and GC. STR markers such as FGA, CSF1PO, D13S317, D18S51, and Penta E exhibit prominent cLOH mutations in both CRC and GC, as shown in Tables 2 and 3. Furthermore, a similar pattern of high prevalence of MSI can also be observed at markers including D3S1358, VWA, D8S1779, D18S51, and D19S433, as depicted in Fig. 2 (Chen et al. 2020; Vauhkonen et al. 2004). These consistent patterns of STR alteration, encompassing both cLOH mutations and MSI prevalence across these markers in both CRC and GC, suggest the existence of common mechanisms contributing to genetic instability in these cancers. However, it is noteworthy that CRC exhibits a distinct STR alteration pattern at the D5S818 marker, which is not observed in GC. Conversely, a high occurrence of cLOH at the Penta D marker appears to be specific to GC. It is important to acknowledge that further specific research studies or reports addressing the mutation or alteration of these markers in CRC and GC are necessary to validate these findings. Currently, there is only one available study that provides insights into the instability of these markers in both cancers. Therefore, additional investigations are warranted to elucidate the significance of D5S818 in CRC and Penta D in GC and their potential implications for the respective diseases.

Forensic significance of STR mutations

Long-term studies have consistently demonstrated the effectiveness of STR polymorphisms in identifying tissue samples, including those derived from malignant tissues. The occurrence of loss of function in a tumour suppressor gene is responsible for regulating cell growth and division, which can lead to regions affected by LOH. The extent of LOH can vary across different tumour types. It is important to note that a reduction of one allele by more than 40–50% does not significantly impact forensic STR typing. This is particularly relevant because larger alleles may appear as very small peaks in the analysis, especially when dealing with low amounts or severely degraded DNA samples. In forensic practice, only the complete loss of one allele and the occurrence of a new allele in the tumour tissue, instead of the one detected in normal tissue, would lead to incorrect STR typing. In the determination of genetic profiles, it is crucial to thoroughly assess the effects of genetic alterations, such as LOH and MSI, on STR markers to accurately evaluate the suitability of cancerous tissues for forensic purposes. Moreover, it is worth noting that many STR markers are shared among different commercial kits, allowing for the utilisation of common markers as internal controls. Among the various cancerous tissues studied, the D18S51 marker consistently exhibits the highest frequency of alteration. This marker shows a higher percentage of pLOH and cLOH, which may be attributed to its longer size (273–341 bp) and potential DNA degradation. Our review indicates that only a few studies have demonstrated minimal alterations in certain STR markers, including CSF1PO, TPOX, D7S820, D2S1338, Amel, D22S1045, D2S441, D1S1656, Penta D, and D3S176, in malignant tissues. However, it is important to acknowledge that these findings would benefit from further replication due to the limited sample sizes employed in these studies. Therefore, larger-scale investigations will be necessary to validate these results.

Strengths, limitation and recommendation

This scoping review aimed to provide a comprehensive understanding of the association between STR markers and various types of cancerous tissues. The findings of this review have significant implications for researchers, clinicians, and other stakeholders in the field of oncology as they shed light on the prevalence and clinical significance of STR mutations in different types of cancerous tissues. While this review contributes considerably to the current body of research on the diversity of STR markers in malignant tissues, it is important to acknowledge its limitations. The small sample size and non-representativeness of participants in some studies compromise both the internal and external validity of the findings, making it challenging to generalise the results to broader populations. Furthermore, despite conducting a thorough literature search, it is possible that not all relevant studies were included in the review. Future research should try to get around these problems by using larger sample sizes and more diverse

populations. This will make sure that the clinical applications of STR markers for preventing, diagnosing, and treating cancer are more reliable and accurate. In order to enhance the comprehensiveness of future studies investigating the prevalence of STR mutations in cancer, we recommend the inclusion of blood cancer samples. Currently, there are a limited number of studies published on this specific area (Alharbi et al. 2022; Filoglu et al. 2014). Adding blood cancer samples to the research would provide a more holistic understanding of the prevalence and clinical significance of STR mutations across different cancer types. This inclusion is highly relevant in forensic investigations, particularly for DNA identification purposes, as blood is the most common evidence found at the crime scene. By addressing these limitations and expanding the scope of research, future studies can build upon the findings of this review and advance our knowledge of the role of STR markers in cancer, ultimately contributing to improved cancer management and patient care.

Conclusions

CRC samples exhibit the highest level of genomic instability, followed by LC, GC, and GCC samples. The BC samples are determined to have the lowest STR alteration rate. In addition, several STR markers have been discovered to be repetitively changed in malignant tissues. Among them, D18S51 is frequently observed to be altered, followed by FGA, VWA, D19S433, and D13S317 markers. Conversely, markers such as TPOX, D7S820, D2S1338, and Penta D are often found to be stable in cancerous tissues. In summary, the genetic instability caused by faulty DNA mismatch repair processes in human carcinomas can pose challenges for forensic genotyping and DNA profile matching. Careful consideration is required when evaluating whether cancer tissue should be used as a reference sample in certain situations.

Abbreviations

STR	Short Tandem Repeat
BC	Breast cancer
LC	Lung cancer
CRC	Colorectal cancer
GC	Gastric cancer
GCC	Gynaecology cancer
LOH	Loss of heterozygosity
cLOH	Complete loss of heterozygosity
pLOH	Partial loss of heterozygosity
MSI	Microsatellite instability
Aadd	Additional alleles
Anew	New allele
DCC	Deleted colon cancer
APC	Adenomatous Polyposis Coli

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OIS drafted the manuscript and performed data analysis; MYNH draft the manuscript; ZZ supervised the study; MNSN, MISI and MYS provided statistical expertise; HZAN designed the study. All authors read and approved the final manuscript.

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Declarations

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