

Review article

Human tandem repeat sequences in forensic DNA typing

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Abstract

It has been 20 years since the first development of DNA fingerprinting and the start of forensic DNA typing. Ever since, human tandem repeat DNA sequences have been the main targets for forensic DNA analysis. These repeat sequences are classified into minisatellites (or VNTRs) and microsatellites (or STRs). In this brief review, we discuss the historical and current forensic applications of such tandem repeats. © 2005 Elsevier Ireland Ltd. All rights reserved.

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1. ‘DNA fingerprinting’ using multi-locus probes (MLPs) and ‘DNA profiling’ using single-locus probes (SLPs)

Human tandem repeats account for about 3% of the human genome [1] and (excluding satellite DNA) are classified into two groups according to the size of the repeat unit and the overall length of the repeat array. Human minisatellites or variable number tandem repeat (VNTR) loci have repeat units from 6 bp to more than 100 bp long depending on the locus, with arrays usually kilobases in length. Human GC-rich minisatellites are preferentially found clustered in the recombination-proficient subtelomeric regions of chromosomes [2]. Some minisatellite loci show very high levels of allele length variability.

The DNA revolution in forensic investigation began in 1984 with the discovery of hypervariable minisatellite loci detectable with MLPs [3]. These minisatellites were detected by hybridization of probes to Southern blots of restriction-enzyme-digested genomic DNA, to reveal restriction fragment length polymorphisms (RFLPs). A common 10–15 bp ‘core’ GC-rich sequence shared between different minisatellite loci allowed MLPs to detect many different minisatellites simultaneously, producing multi-band (barcode-like) patterns known as ‘DNA fingerprints’.

Using only a single MLP designated 33.15, the match probability between unrelated people was estimated at $<3 \times 10^{-11}$ and two MLPs (33.15 and 33.6), which detect different sets of minisatellites, together gave a value of $<5 \times 10^{-19}$ [4]. These probabilities are so low that the only individuals having identical DNA fingerprints are monozygotic twins. MLPs have been used very successfully in paternity testing [5] and immigration cases [6]. However, several micrograms of good quality genomic DNA are required to obtain reliable DNA fingerprints. Forensic specimens are often old and yield small quantities of often degraded DNA. MLPs are therefore not generally suitable for forensic sample analysis although they were used successfully in a few early criminal investigations [7].

To circumvent these limitations, specific cloned minisatellites were used as single-locus probes (SLPs) to produce simpler ‘DNA profiles’ and were applied in criminal casework even before MLPs were commercially established as the standard method for paternity testing. Since each SLP detects only a single minisatellite, it produces two band (two allele) patterns, but still highly polymorphic due to the use of hypervariable minisatellites. Compared with MLPs, SLPs have considerable advantages for analyzing forensic specimens. The method is far more sensitive, with the limit of detection of bands at around 10 ng of genomic DNA. Mixed DNA samples such as semen in vaginal swabs can be analysed. Comparison of DNA profiles does not require side-by-side electrophoresis since allele sizes can be

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estimated and databased, which overcomes the inter-blot comparison problem in DNA fingerprinting. However, SLP allele sizing cannot be done with absolute precision due to essentially continuous allele size distributions and to the resolution limits of agarose gel electrophoresis. Two procedures for determining allele frequencies and match probabilities in the face of measurement errors are the floating-bin and the fixed-bin methods [8]. The real discriminating power of SLPs was unreasonably decreased by genetically inappropriate calculations based on the ‘ceiling principle’ or ‘interim ceiling principle’ invented by the National Research Council of the United States in 1992 [9]; these calculations were abandoned in 1996 [10].

2. Amplified fragment length polymorphisms (AMPFLPs, AFLPs)

Some minisatellite loci with relatively short (~1000 bp) alleles can be amplified by PCR to yield amplified fragment length polymorphisms (AMPFLPs, AFLPs). Before PCR-based typing of microsatellite loci eventually became established, one such minisatellite locus called *DIS80* [11,12] was extensively used by some forensic DNA laboratories. In the *DIS80* system, fragments in the range of 14–42 repeat units (16 bp per repeat) are amplified to yield alleles considerably smaller than the fragments normally analyzed in DNA fingerprinting and profiling. Although the *DIS80* locus in particular contains four common alleles with frequencies >10% in Japanese, the likelihood of discrimination between two unrelated individuals is still high (0.977 in Japanese [13]).

In contrast to RFLP analysis, *DIS80* alleles fall into discrete size classes and thus can be compared directly to a standard composite of most alleles (an allelic ladder) on the same gel. This was a significant improvement that was also employed in subsequent STR systems. In *DIS80*, the amplified DNA fragments were commonly detected using a silver stain, with the final profile usually showing two bands from which the numbers of repeat units can be easily estimated. This locus has been extensively used worldwide to analyze forensic specimens, along with other PCR-based methods that exploit single nucleotide polymorphisms (SNPs) including *HLA-DQ α* and the 5 PolyMarker loci (*LDLR*, *GYP A*, *HBGG*, *D7S8* and *GC*).

However, after the detailed evaluation of allele frequency data in the world population at *DIS80* [14] and increasing practical usage of multiplex STR systems, *DIS80* has been gradually abandoned in favour of STRs.

3. MVR-PCR

Most minisatellite loci consist of heterogeneous arrays of two or more subtly different repeat unit types (minisatellite variant repeats). All human hypervariable minisatellites

characterized to date vary not only in repeat copy number (allele length) but also in the interspersion pattern of these variant repeat units within the array. This internal variation provides a powerful approach to the study of allelic variation and processes of mutation. Interspersion patterns can be determined by minisatellite variant repeat (MVR) mapping and reveals far more variability than can be resolved by allele length analysis.

The first MVR mapping was developed at locus *DIS8* (minisatellite MS32) [15]. This minisatellite consists of a 29 bp repeat unit showing two classes of MVR which differ by a single base substitution, resulting in the presence or absence of a *HaeIII* restriction site [16]. Very high levels of variation in the interspersion patterns of two type repeats, designated a-type and t-type, within the alleles have been revealed by *HaeIII* digestion of PCR-amplified alleles. Subsequently, a technically much simpler PCR-based mapping system (MVR-PCR) was invented [17] (see also a detailed review [18]). This assay reveals the internal variation of the same sites by using an MVR primer specific to one or other type of variant repeat plus a primer at a fixed site in the DNA flanking the minisatellite. In the PCR reaction, the MVR-specific primers at low concentration will bind to just one of their complementary repeat units; thus, MVR locations will be represented as an array of sequentially sized amplified DNA fragments. Using a single allele and two different MVR primers corresponding to the two different types of repeat, MVR-PCR will generate two complementary ladders of amplified products corresponding to the length between the flanking primer and the location of one or other repeat type within the minisatellite repeat array. Progressive shortening of PCR products by internal priming of the MVR-specific primers is prevented by the use of ‘tagged’ amplification which uncouples MVR detection from subsequent amplification.

MVR-PCR products are separated by electrophoresis on an agarose gel and detected by Southern blotting and hybridization to an isotope-labeled minisatellite probe. An important point is that the reaction for each of the two MVR-specific primers is carried out in a separate tube, and they are loaded in adjacent lanes in an agarose gel. Some work has been done on labeling the variant primers with different colored fluorescent tags and amplifying both sets of MVR products in a single reaction, to facilitate comparison of the complementary MVR profiles [19,20]. MVR-PCR has revealed enormous levels of allelic variation at several human hypervariable minisatellites; MS32 (*DIS8*) [17,21–23], MS31A (*D7S21*) [24,25], MS205 (*D16S309*) [26,27], CEB1 (*D2S90*) [28], g3 (*D7S22*) [29], YNH24 (*D2S44*) [30], B6.7 [31,32] and insulin minisatellite [33].

MVR-PCR is the best approach for exploiting the potential of hypervariable minisatellite loci because of the unambiguous nature of MVR mapping and the generation of digital MVR codes suitable for computer analysis. Code generation does not require standardization of

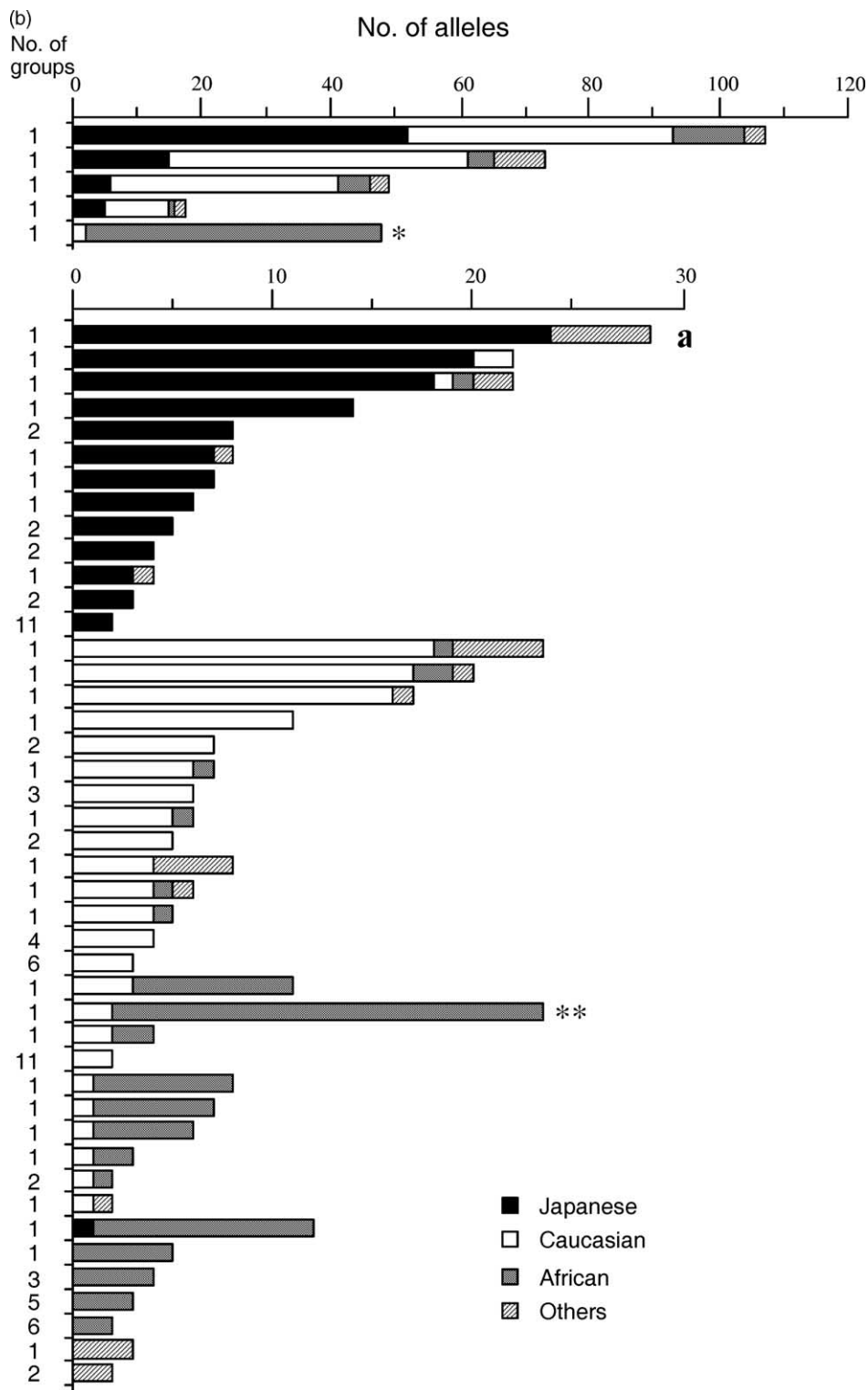


Fig. 1 (continued)

from mutation. In contrast, detailed knowledge of mutation processes coupled with MVR analysis of allele structure can help distinguish mutation from non-paternity. This was tested at MS32 using both real and simulated allele data [42]. Since MVR-PCR allows information to be recovered

from at least 40 repeat units, a mutant paternal allele will usually show extensive structural identity with the progenitor paternal allele except over the first few repeats; most germline mutation events altering repeat array structure are targeted to this region, most likely due to its proximity to

a flanking recombination hot spot that appears to drive repeat instability (reviewed in [43]). Thus, a mutant paternal allele in a child will tend to be more similar to one of the father's alleles than to most other alleles in the population. This approach is unlikely to work at extremely hypervariable minisatellite loci such as CEB1 and B6.7 given their very high rate of germline instability coupled with complex germline mutation events that can radically alter allele structure in a single mutation event [31,44].

MVR-PCR reveals enormous levels of variation, far in excess of any other typing system. At MS32, almost all alleles in several ethnic populations surveyed were different. However, different alleles can show significant similarities in repeat organization [17]. Heuristic dot-matrix algorithms have been developed to identify significant allele alignments and have shown that 74.8% of alleles mapped to date can be grouped into 98 sets of alignable alleles, indicating relatively ancient groups of related alleles present in diverse populations [45] (Fig. 1). Some small groups of alleles show a strong tendency to be population-specific, consistent with recent divergence from a common ancestral allele (Fig. 1a). In most groups, the 5' ends of the aligned MVR maps show most variability due to the existence of the flanking recombination hotspot. Therefore, MVR allele analysis at MS32 can act as a tool not only for individual identification but also for giving clues about ethnic background (Fig. 1b), [45]. MS205 is another locus which successfully gave a clear and detailed view of allelic divergence between African and non-African populations [47]. A restricted set of allele families was found in non-African populations and formed a subset of the much greater diversity seen in Africans, which supports a recent African origin for modern human diversity at this locus. Very similar findings emerged from MVR analyses of the insulin minisatellite, again

pointing to a major bottleneck in the 'Out of Africa' founding of non-African populations [48].

Finally, MVR-PCR has been developed at the Y chromosome-specific variable minisatellite *DYF155S1* (MSY1), with potential for extracting male-specific information from mixed male/female samples [49]. This marker is also useful for paternity exclusion and, if adequate population data are available and the allele is rare, also for individual identification and paternity inclusion. Forensic application of Y-chromosomal microsatellites has also become a very powerful tool, as discussed elsewhere in this volume.

It is unfortunate that MVR-PCR has been little used in forensic analysis despite the simplicity of the method and the fact that it reveals enormous levels of polymorphism and has considerable discriminating power.

4. Microsatellites

As with minisatellites, microsatellites are also tandemly repeated DNA sequences and are also known as simple sequence repeats or short tandem repeats (STRs). They consist of repeat units of 1–5 bp repeated typically 5–30 times. Most microsatellite loci can be efficiently amplified by standard PCR since the repeat regions are shorter than 100 bp. Microsatellites can show substantial polymorphism (though are far less variable than the most variable minisatellites), and are abundant throughout the human genome. Microsatellites are particularly suitable for analyzing forensic specimens containing degraded and/or limited amount of DNA. The first forensic application was microsatellite typing from skeletal remains of a murder victim [50], followed by the identification of Josef Mengele, the Auschwitz 'Angel of Death' [51]. Small PCR products can be sized with precision by polyacrylamide gel electrophoresis (PAGE) although the spurious shadow or

Table 1
Properties of STR loci used in SGM plus and FBI CODIS

Locus	SGM plus™	FBI CODIS	Chromosome	Genomic position (kb)	Repeat motif	No. alleles in Japanese ^a	PD in Japanese ^a
<i>TPOX</i>	–	+	2	1470	AATG	7	0.814
<i>D2S1338</i>	+	–	2	218,705	TTCC	14	0.971
<i>D3S1358</i>	+	+	3	45,557	TCTR	10	0.852
<i>HUMFIBRA/FGA</i>	+	+	4	155,865	CTTT	17	0.962
<i>D5S818</i>	–	+	5	123,139	AGAT	9	0.919
<i>CSF1PO</i>	–	+	5	149,436	AGAT	10	0.886
<i>D7S820</i>	–	+	7	82,751	AGAT	12	0.908
<i>D8S1179</i>	+	+	8	125,976	TCTA	9	0.952
<i>HUMTH01</i>	+	+	11	2149	AATG	7	0.876
<i>HUMVWA</i>	+	+	12	5963	AGAT	10	0.921
<i>D13S317</i>	–	+	13	81,620	AGAT	9	0.934
<i>D16S539</i>	+	+	16	84,944	AGAT	8	0.908
<i>D18S51</i>	+	+	18	59,100	AGAA	17	0.965
<i>D19S433</i>	+	–	19	35,109	AAGG	13	0.907
<i>D21S11</i>	+	+	21	19,476	TCTA	14	0.928

R = A or G. PD, the power of discrimination.

^a Italic values in no. of alleles and PD in Japanese are from [55] ($n=526$) and others from [54] ($n=1200$).

stutter bands often observed at dinucleotide repeat loci can make interpretation difficult; for this reason, current typing systems use microsatellites with repeat units 4 bp long, to reduce the incidence of stuttering. The STR approach allows very high throughput via multiplex PCR (single-tube PCR reactions that amplify multiple loci) and fluorescent detection systems have been developed to allow substantial automation of gel electrophoresis and DNA profile interpretation [52].

STR analysis is more sensitive than other methods and can recover information even at the level of a single cell. The unambiguous assignment of alleles makes the method suitable for the development of databases. In the United Kingdom, 10 autosomal STR loci plus the amelogenin sex test, typed using the 'second-generation multiplex' (SGM) Plus system, are used in forensic practice (Table 1). The SGM Plus loci generate random match probabilities of typically 10^{-11} between unrelated two individuals in the three UK racial groups (Caucasian, Afro-Caribbean, and Asian) [53]. The US FBI CODIS (Combined DNA Index System) uses 13 STRs plus amelogenin. These loci produce extremely low random match probabilities. For example, around 60% of Japanese individuals show match probabilities of 10^{-14} – 10^{-17} (estimated from [54,55]). The Japanese Police Agency introduced in 2003 a 9 STR locus system, which uses some of the CODIS loci (the AmpFISTR[®] Profiler[®] kit), for analysing forensic specimens. From allele frequencies at these loci [54], around 60% of Japanese individuals have match probabilities of 10^{-9} – 10^{-11} . This system also detects the XY-homologous amelogenin genes to reveal the sex of a sample. Recently, new multiplexes that amplify 16 loci in a single reaction, including amelogenin, have been commercially developed (AmpFLSTR[®] Identifier[®] PCR Amplification Kit, PowerPlex[®] 16 System). This system produces even lower match probabilities without losing sensitivity, and it is likely that such systems will remain standard for analysing forensic specimens and in paternity testing. Detailed information of forensic STR can be obtained at STRBase [56].

In the future, single nucleotide polymorphisms (SNPs) might provide an alternative typing platform; while large numbers of loci (~100) would need to be typed to obtain the discrimination power of current STR systems, they do offer the potential for DNA typing without electrophoresis, conceivably using miniaturised devices ('lab on a chip') that could greatly accelerate typing and offer the potential for DNA analysis at the scene of crime.

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