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Repetitive Deoxyribonucleic Acid (DNA) and Human Genome Variation—A Concise Review Relevant to Forensic Biology

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ABSTRACT: The various classes of human repetitive deoxyribonucleic acid (DNA) are described, with particular emphasis being given to their variation in the human genome. The significance of this information to forensic science is discussed.

KEYWORDS: pathology and biology, deoxyribonucleic acid (DNA), genomes, forensic biology, human repetitive deoxyribonucleic acid (DNA)

There has been a vast amount of work published recently in the field of human molecular genetics and human genome variation in repetitive deoxyribonucleic acid (DNA) sequences. Much of this work will have an impact on the future of forensic science investigations in cases involving human tissues, especially blood, hair, and semen. Although the recent editorial by Sensabaugh [*1*] examined aspects of recombinant DNA in forensic biology, he did not draw much attention to the one class of DNA likely to be of particular use in this area, namely repetitive DNA. Recent discoveries concerning human genome variation serve to emphasize this point. It is obviously important that forensic scientists begin to familiarize themselves with this complex field. To this end the literature concerning repetitive DNA is reviewed, providing a concise commentary on the topic. The various classes of repetitive DNA and their properties are described and discussed in the context of variation in the human genome.

Content of the Human Genome

The human genome contains in total approximately 6×10^9 nucleotides per diploid genome, these nucleotides being distributed unequally between 23 pairs of chromosomes [*2*]. Each chromosome consists of 2 long, linear polynucleotides, DNA, the polymers being hydrogen bonded via specific nucleotide pairing and coiled as a double helix. This helix is

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structurally stabilized by nuclear proteins called histones, the complex of DNA and histones being referred to as chromatin. Chromatin may be condensed to varying degrees of compactness, and in its most compact form is visualized microscopically as chromosomes at the metaphase stage of each cell cycle.

The genome of higher eucaryotes, including humans, may be divided into different classes based very broadly on *known* functional properties (Fig. 1). The so-called "coding regions" contain DNA sequences (genes) which determine primarily the amino acid sequences of the proteins for which they code, and also the degree of expression of the gene in any tissue at any time. Most genes are present as a single DNA copy, located specifically in the genome. A few important genes, such as the histone and ribosomal RNA genes, are present in multiple copies, and some closely related genes are in clustered complexes, for example, globin and actin.

"Noncoding" DNA generally contains DNA sequences for which no function has yet been established or possibly for which no function exists (Fig. 1). Such sequences may either be as a single copy (acting as "spacer DNA" between the coding regions of the genome) or exist in multiple copies, thus being called *repetitive* DNA [*3-9*].

Some 20 to 30% of the human genome is comprised of repetitive sequences [*10*], these having no clearly ascribed functional attributes. Most are not transcribed and the few that are, are not translated [*3-7*]. Their function is still a matter of investigation. It has been postulated that they may be functionless but able to propagate and spread themselves through the genome for no apparent purpose or benefit to the genome itself. Hence their description as "selfish" DNA [*11*].

Generally the "coding" and "noncoding" regions of DNA collate with two different classes of chromatin. Much of the former is associated with a less condensed form of chromatin capable of transcription (euchromatin), while much of the latter (particularly highly repeated DNA at chromosome centromeres) is associated with condensed and transcriptionally inactive DNA (heterochromatin).

Human Variation in Coding and Noncoding Sequences

The ability of *single* copy genes to make *multiple* copies of identical proteins (or protein isomers from gene alleles) has underpinned the successes thus far of forensic biology. This amplification of what originally is a DNA base sequence variation has allowed the analysis

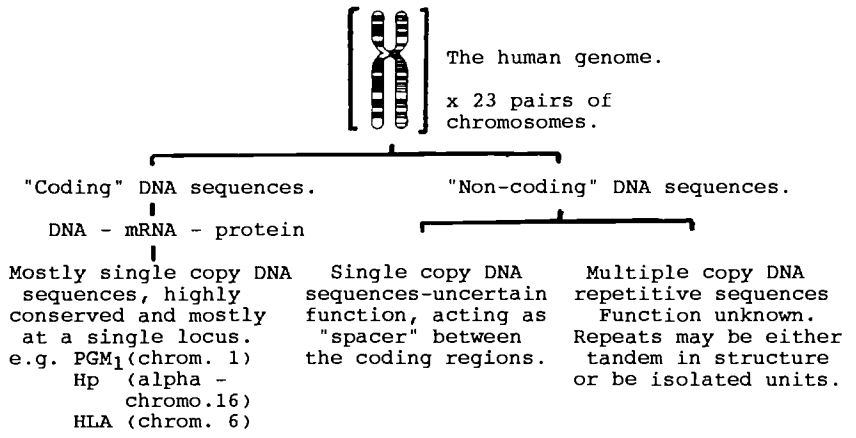


FIG. 1—*Schematic representation of the human genome and its division by function into "coding regions" and "noncoding" regions.*

for antigen, isoenzyme, and protein polymorphisms of minute amounts of biological fluids. By definition, this variation arises from coding regions of DNA (see examples in Fig. 1). The major limitations to successful assay have been the level of, and tissue specificity of, gene expression (or in the case of erythrocytes the residue of such expression). the stability of such products in the environment external to their host, and lastly the limited interindividual variation.

Very broadly speaking, DNA sequences that confer a functional purpose or product upon an organism will be under selective pressure to be conserved (an average sized protein of 400 amino acids changes an amino acid about once every 200 thousand years [*12*]). Repetitive DNA appears not to be under the same rigid functional constraints. The evidence for this apparent lack of conservation pressure is first the finding that repetitive sequences have spread and diversified throughout the genome. Second, they are now known to be very rich sources of interindividual genetic variation [*13*], generally showing greater diversity than unique DNA sequences [*14,15*]. Thus, their immense significance to forensic science.

A further practical advantage of repetitive DNA is that sequences which may exist in multiple copies per haploid genome might be detected from smaller quantities of DNA than sequences which exist in only single copy. Given the limitations of DNA recoverable from typical forensic science samples [*1*], the quantity of target sequence per haploid genome is thus significant.

Demonstration of Human Genomic Variation

Variation between human genomes at the DNA level may be demonstrated by enzyme restriction of DNA, electrophoresis, and "Southern Blotting" [*16,17*]. This is generally referred to as restriction fragment length polymorphism (RFLP). The reliable demonstration of this phenomenon is primarily dependant upon: first, the precision by which a particular restriction enzyme (reviewed [*18,19*]) cuts the DNA at a defined sequence (such sequences are normally between four and six base pairs long); and second, the precision with which a probe length of DNA (generally radioisotopically labelled) hybridizes with complimentary sequences in the population of fragment lengths created by the restriction enzyme.

Hybridization, the process of hydrogen bonding between the bases of the probe and target sequences, may be conducted at different levels of stringency. This term refers to the ionic and temperature conditions at which base pairing is effected. Generally, the lower the ionic concentration and the higher the temperature the more precise is the base pairing (high stringency), while higher ionic concentration and lower temperatures generally tolerate greater numbers of mismatched base pairs in the hybridized species (low stringency). Thus the probe DNA sequence and the stringency of hybridization/washing primarily determine which restriction fragments are highlighted from the smear of fragment lengths separated by electrophoresis.

RFLPs generally occur for one of two reasons. Either they occur because of mutation in the base sequences associated with the cutting recognition sequence of the enzyme (point mutational polymorphism), or they occur by way of an alteration in the DNA sequence length between the restriction sites (insertion/deletion polymorphism). There are no established criteria by which any one restriction enzyme may be predicted as useful in detecting RFLPs. An exception to this are enzymes such as TaqI and MspI which cleave at the mutable CpG dinucleotide [*20*].

RFLPs occur in both single-copy coding and noncoding DNA [*21–25*], and in all classes of repetitive DNA. As explained above, little mutation is expected in DNA coding sequences, the chance of interindividual heterozygosity in single copy DNA sequences being about 0.004 [*15*]. That variation which is present is generally some point mutational change. Thus RFLPs in such sequences are invariably simple and mostly diamorphic (restriction site either present or absent). Repetitive sequences in the human genome are by contrast now known to

be highly polymorphic. Explanation of the classification and the variation in such sequences follows.

Repetitive DNA—Discovery and Classification

Repetitive DNA is generally confined to higher eucaryotes. Some 20 to 40% of mammalian genomes consist of either highly repeated (more than 10^5 copies per haploid genome) or moderately repeated (about 10^3 to 10^5 copies per haploid genome) sequences [*3-7,26*]. By contrast, lower eucaryotes and procaryotes have smaller genomes, consisting of mostly low or single copy number coding sequences only [*5*].

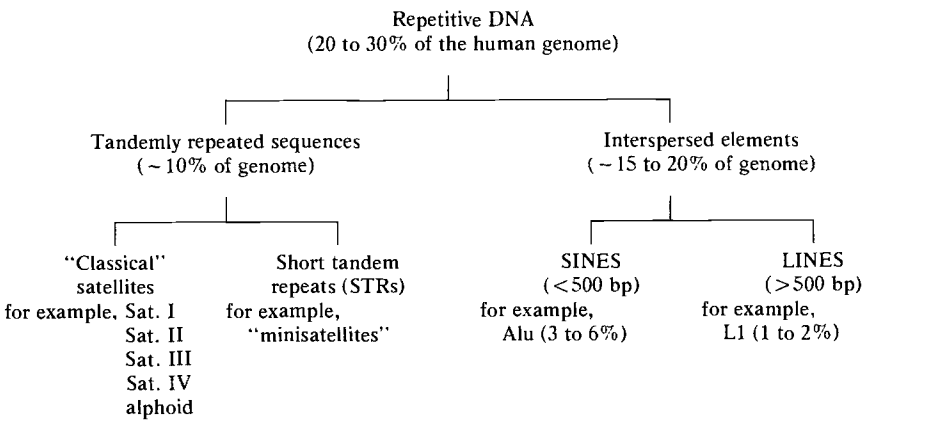
The existance of repeated sequences in higher eucaryotes was generally established by one of three methods [*3*]: a fraction of the genome reannealed very rapidly after denaturation (this being multiple copy number sequences, whereas single copy sequences reannealed much slower); secondly, centrifugation of genomic DNA in cesium chloride (CsCl) gradients (this method separated fractions of DNA that were of different buoyancy to the main band DNA and these so-called "satellites" were found to be highly repeated sequences); and thirdly, restriction of whole genomic DNA by some enzymes (for example, Hae III), separation of the fragments by electrophoresis in agarose gels, and staining with ethidium bromide (this showed the presence of distinct banding resulting from repeated sequences upon a background smear of DNA fragments).

A system of *nomenclature* and *classification* of *repetitive* DNA has evolved, this being largely based on the structural organization and reiteration frequency of each species [*3-7*]. There are two broad classes, namely (1) the tandemly repetitive sequences and (2) the interspersed repetitive sequences (Table 1). These two classes will be discussed.

Tandem Repetitive Sequences

Such sequences comprise some 5 to 10% of mammalian genomes and are characterized by the head-to-tail tandem repetition of lengths of DNA of generally some common sequence.

TABLE 1—*Classification of repetitive DNA in human genomes.*



There are four *classical* classes of tandem repeat sequences in the human genome: Satellite I (0.2 to 0.5%), Satellite II (1 to 2%), Satellite III (1 to 3%), and Satellite IV (0.5 to 2%) (Table 1), totalling about 5% of the genome [*3*]. These classes are representative of the DNA "satellite" bands separated by CsCl centrifugation of whole genomic DNA. As a consequence, the term "satellite" has become generally adopted to describe *all* tandemly repeated sequences (whether separable by centrifugation or not). This has lead further to the description of short tandem repeats (STRs) as "minisatellites" [*27*] and recently longer tandem repeats as "midisatellites" [*28*].

A further classical repetitive DNA is the alphoid class (Table 1). This was originally found in abundance in higher primates, but is also present in human genomes (1 to 2%) [*29–31*]. A large proportion of human satellite DNA (particularly alphoid and Satellite I) is located at centromeres of chromosomes (centromeric repetitive DNA) [*26*].

The simplest tandem structure and base sequences for each of the major classical human satellite DNAs are known [*32–35*]. The lengths of the simplest repeating unit in each class is generally constant, but sequence divergence within these units is possible, thus generating a "family" of sequences within each class. The repeat units may be as small as 5 base pairs (bp) (for example, Satellite III and Satellite II being structurally related), but more typically are 170 to 250 bp in length [*26*]. Often these can be demonstrated as "ladders" of DNA lengths on electrophoretic separations (Fig. 2), the "rungs" being multiples of the basic repeat unit either as a result of the loss of the appropriate restriction site at the junction of individual units [*32*] or as a result of incomplete digestion [*32,36*].

The lengths of tandem repeat sequences revealed experimentally depends entirely upon the restriction enzyme used. For example, the long arm of the Y chromosome contains about 5000 copies of a 3.4 kilobase (kb) tandem repeat (for example, Hae III digestion—Fig. 2) accounting for as much as 40% of the whole chromosome [*37*]. Many of these 3.4-kb repeats

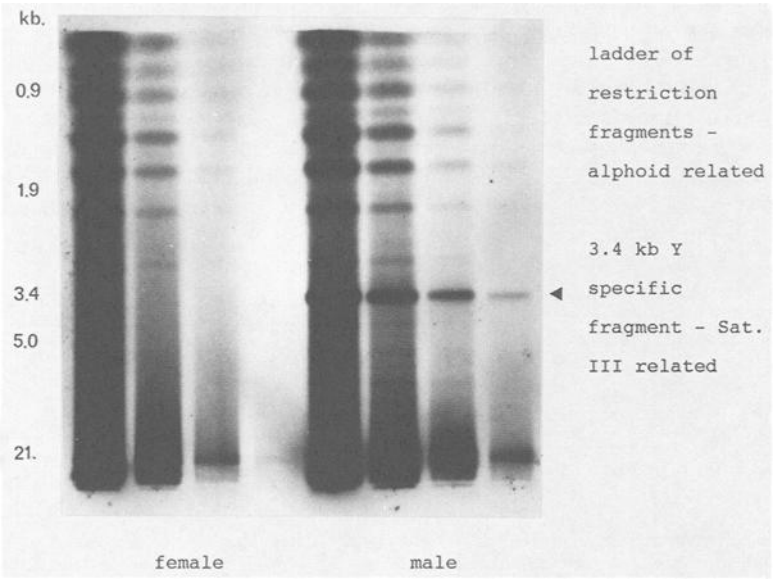


FIG. 2—*Demonstration of a "ladder" of restriction fragments (using an alphoid sequence related probe) and a Y chromosome specific fragment (using a Satellite III sequence related probe). The DNA samples were decreasing concentrations of Hae III digested female and male DNA. (The results are from biotinylated probes hybridized simultaneously to the same membrane—unpublished observations).*

contain short tandem repeats constructed as pentameric (5-bp) units of a moderately divergent base sequence [*38*].

Thus each "classical" satellite generally consists of a diverged "family" of sequences, with particular restriction fragment lengths arising from specific chromosomes and the sequences of individual family members (in any one class) being chromosome specific (or nearly specific) in origin, for example, alphoid [*30,31,39-41*] and Satellite III [*42*]. This might have functional significance. For example, centromeric repetitive DNA may assist in chromosome recognition at meiotic divisions [*43*]. Generally, however, the evolution and function of these "classical" satellites is still the subject of research [*8,44,45*].

Besides the "classical" satellites in human genomes, there are other tandemly repeated sequences (Table 1). Some of these have been found to exist as a small single block of a tandemly repeated DNA sequence, at unique genomic loci and within noncoding DNA regions. Such blocks (often containing a common "core" portion to their sequences) may be dispersed at multiple genomic loci. The single most important property of these tandem repeats, first described in 1980 [*46*], was their genomic variability.

Polymorphism in Tandemly Repeated DNA

All polymorphisms associated with tandemly repeated DNA arise from restriction enzymes creating DNA fragment lengths that contain *variable numbers* of the repeated species. There are, in general, two contrasting causes by which this occurs (Figs. 3*a* and 3*b*). The distinction between these mechanisms is vital. In one case, the enzyme cuts the DNA *externally* to the block of tandem repeats (Fig. 3*a*), and in the other, the DNA is cut *within* the lengths of tandemly repeating units (Fig. 3*b*). Note—Figs. 3*a* and 3*b* are schematic only and are not drawn to a common or defined scale.

The consequence of this is that in the first mechanism any enzyme that cuts the DNA in regions flanking (but not within) the tandem repeat will reveal any variation that may exist in the number of repeats, and hence the fragment size. The second mechanism is enzyme specific, polymorphism being generally a result of an enzyme that cuts (or fails to cut) infrequently into the higher order repeat units of each tandem array. Examples illustrating these mechanisms will be discussed in separate sections. Before doing so, however, comment regarding nomenclature is helpful.

Polymorphisms arising by the first mechanism have been referred to as "minisatellites" [*27*], hypervariable regions (HVRs) [*47*], variable number of tandem repeats (VNTRs) [*48*],

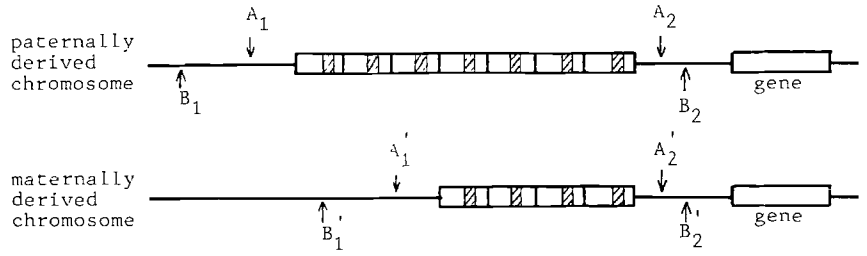


FIG. 3*a*—*Schematic representation of a "minisatellite" polymorphism at a single genomic locus. (Many "minisatellites" have been found near or within genes—often because the gene and its surroundings were being studied. Probing with a sequence containing both the "core" [hatched] and other site specific sequences [the blocked but nonhatched regions in the tandem repeats and solid lines immediately external to this] will generally show two restriction fragment lengths from a single locus: either* $A_1 - A_2$ *and* $A'_1 - A'_2$ *fragments using enzyme A or* $B_1 - B_2$ *and* $B'_1 - B'_2$ *using enzyme B. Use of a "polycore" probe* [47] *[being tandem repeats of the hatched region only] may give complex patterns arising from more than one locus* [27].)

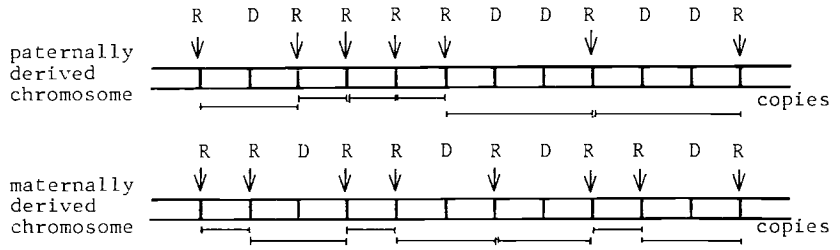


FIG. 3*b*—*Schematic representation of a polymorphism in a long tandemly repeating satellite. (The target sequence of the probe may be formed by all or part of the sequence in each repeat unit. Restriction sites may exist* [R] *or be deleted* [D]*, giving rise to fragments of variable lengths. Some of these may be duplicated during evolution, giving multiple copies of the same length. Highly complex fragment patterns can arise from multiple loci of the same sequence* [97].*)*

and variable length polymorphisms (VLPs). Polymorphisms arising by the second mechanism have also been referred to as VNTRs [*25*]. As long as the reader remains conscious of the presumptive cause for each polymorphism, there appears to be no strong reason to prefer one name to another.

"Minisatellite" Polymorphism

The polymorphism in all such examples is an insertion/deletion mutational event, thereby lengthening or shortening the overall fragment length. The length of repeat units inserted or deleted is typically between 64 and 10 bp long [*49*]. Tandem arrays of such units may exist at either a unique or a number of dispersed genomic sites. Most of the presently known examples are listed in Table 2*a* and *b* [*50–85*]. The supplementary references are given for extended information regarding each example.

The cause of a loss or gain in the number of repeat units at any genomic site may be either (1) integral numbers of unit slippage at replication or (2) unequal recombination between the tandemly repeated sequences or both [*47*]. This recombination may indeed be directed by a particular GC rich "core sequence" which (with some sequence diversity) has been found to be embedded in many of the GC rich "minisatellites" (Table 2*a*). This core is represented as the hatched regions within the repeats drawn in Fig. 3*a*. Jeffrey's conclusion is that such core sequences, 11 to 16 bp in length in his examples, either promote the initial duplication of DNA immediately adjacent to it or assist in changing the number of repeat units so created by unequal recombination or faulty replication or both [*47*].

Supportive evidence is that the "core" sequence bears some sequence homology to the so-called "Chi" (crossover hotspot instigator) sequence believed to be active in procaryotes (reviewed [*86,87*]). The "Chi" sequence is postulated to be a target for a protein assisted recombination event between homologous DNA sequences, perhaps initiating alteration in the number of repeats and providing the interindividual variation. The "Chi" sequence has also been noted as showing homology to the X gene region of the hepatitis B virus [*48*], a sequence potentially recombinogenic as it is believed to be responsible for viral integration into human genomes.

The practical consequence of these details is as follows. If a "polycore" probe (exemplified by Jeffrey's probes 33.15 and 33.6 [*27*]) is hybridized under moderate stringency to suitably restricted DNA, the multiple loci (between 40 to 60) of this "core" sequence are revealed as complex patterns of restriction fragments (genetic "fingerprints"). This method of individualization has been applied to forensic science samples [*72–74*].

If the probe, however, contains tandem repeats of both the "core" sequence and also flanking DNA specific to particular loci (represented by the nonhatched but blocked regions

TABLE 2—*STR (short tandem repeat) polymorphisms in the human genome—"minisatellites."*

2*a*			
Source of Probe—"GC" Rich Sequences	Variation in RFs "Alleles" (Enzyme)	Ref	Supp.
5′ to insulin gene:	21 (Sac I)	*50*	*51–54*
3′ to H Ras 1 Onco gene:	18 (Taq I)	*55*	*56–59*
"D14S1" regions:	>40 (Taq I)	*55*	*58–61*
Intron zeta 1 globin gene:	4 (Hinf I)	*62*	*63*
Intragenic globin genes:	3 (Pvu II)	*62*	*64–66*
3′ to alpha globin gene[a]:	>20 (Pvu II)	*64*	*49,66,67*
"Fragment g"[b]:	>77 (Hinf I)	*68*	
Intron myoglobin gene[c]:	many (Hinf 1)	*27*	*47,69–76*
Protein III gene M13 phage[c]:	many (Hae III)	*77*	*78,79*
Clones hybridizing with synthetic oligomers:			
for example, MLJ 14	>20 (Rsa I)	*48*	*28,80,81*
for example, YNH 24	>20 (Msp I)	*48*	
Intron apolipoprotein C-II gene[c]:	many (EcoR I)	*82*	
2*b*			
Source of Probe— "AT" Rich Sequences			
3′ apolipoprotein B gene:	>3 (Msp I)	*83*	
3′ type II collagen gene:	3 (EcoR I)	*84*	
Pseudo-autosomal X\Y chromosome:			
for example, DXYS15[a]	>8 (Taq I)	*85*	

[a]Probe to multiple loci at reduced stringency of hybridization.
[b]Probe for single locus related to Ref *27*.
[c]Probe to multiple loci in human genomes.

of each repeat and the solid lines external to these—Fig. 3*a*), then under high stringency conditions such a probe will generally detect only two (heterozygous) fragments from a single genomic locus. Probes of this sort have also been used in the analysis of forensic science samples [*58,59*]. If a "mixture" of single-locus probes is used simultaneously, a combined fragment pattern arises [*88*], while some single locus probes used at lower stringency conditions may reveal weaker hybridization from other loci (see examples in Table 2*a*).

There are estimated to be at least 1500 "minisatellites" in the human genome [*47*]. These include both GC and AT rich "cores" in the sequence repeats, suggesting that there may be different classes of sequences which may serve as primers to "minisatellite" formation (for example, Jarman et al. [*49*] consider their GC rich "core" to be distinct from that of Jeffreys et al. [*27*]). The AT rich "minisatellites" show no sequence homology with the "Chi" sequence, and other explanations for "minisatellite" formation and propagation are proposed [*89*].

Table 2 gives an indication of the reported variability detected at each "minisatellite" loci. Extensive population frequency data and evidence of ethic variation exist for the variable length polymorphisms associated with the 3′ region of the HRAS-1 onco-gene and the "D14S1" region [55]. Other loci are yet to be as well characterized.

Some "minisatellite" core sequences show remarkable conservation throughout nature [*75,76*], the most interesting example thus far being a "minisatellite" found in the protein III gene of the "wild"-Type M 13 phage (a bacterial virus) used to locate VNTRs in human, bovine, equine, murine, and canine genomes [*77–79*].

Polymorphism in Long Tandem Repeats

Relatively complex human polymorphisms exist in sequences of long tandem repeats (LTRs); known examples have been listed in Table 3 [*90–107*], including those found in the "classical" satellites, alphoid, and Satellite III. The distinction between such examples and those of the "minisatellites" is that polymorphism appears to be the result of either point mutational or more complex insertion/deletion/crossover events within the long tandem repeats (Fig. *3b*). They are most likely to be detected using restriction enzymes which cut infrequently (or as a result of a site deletion fail to cut) into the higher order repeat units of each tandem array [*90*].

Generally, the polymorphisms in the LTR examples are seen experimentally as variable fragment lengths within more complex patterns, some or most of the fragments being constant between different individuals (for example, alphoid [*90, 92, 93*], Bkm [*99*], and Sau 3a [*104, 105*]. There is also some quantitative (copy number) variation between individuals.

In the case of Satellite III, the probe used to establish the polymorphism has dual properties of hybridizing with a 3.4-kb Y specific repeat as well as hybridizing with a complex series of restriction fragments upon Taq 1 digestion of human genomes [*97*]. The polymorphism may be the result of a specific base mutation in the small pentameric repeat typical of Satellite III [*32*].

Polymorphisms of the alphoid, Satellite III, or Bkm type (which contain multiple numbers of particular restriction fragment lengths—see Fig. *3b*) might be expected to be detected in smaller quantities of DNA than "minisatellite" polymorphisms (the fragments for which occur in only single copy per haploid genome, at either one or multiply dispersed loci). However, the "minisatellite" polymorphisms may be more discriminating between individuals (see Tables 2 and 3).

Probes for LTRs (or indeed for interspersed repeats) that show no human polymorphisms will have an important role in forensic science analyses. Such probes will not only assist estimation as to the quantity of DNA under examination, and importantly the efficiency of its restriction, but will also demonstrate the extent of its degradation. The resultant invariant fragment patterns will be necessary as controls to probes producing polymorphic patterns [*98*]. An advantage of DNA methodology is that this control information can be obtained by stripping and reprobing membranes with different probes.

Interspersed Repetitive Sequences

The second major class of repetitive DNA, comprising as much as 20% of the human genome, is composed of interspersed repetitive sequences [*2–4, 6, 7*] (Table 1). These *single* units are scattered individually throughout the genome. They have been classified into two class sizes: short interspersed elements (SINES, less than 500 bp) and long interspersed elements (LINES, more than 500 bp) [*3, 4, 6, 7*].

TABLE 3—*LTR (long tandem repeat) polymorphisms in the human genome.*

Source of Probe for Polymorphism	Variation in RFs "Alleles" (Enzyme)	Ref	Supp.
Alphoid—chromosome X	4 (Hind III)	*90*	*91*
—chromosome 17	3 (EcoR I)	*90*	
—chromosome 11	4 (Xba I)	*92*	
—chromosome 6 predominantly	5 (Taq I)	*93*	*94–96*
Satellite III	>15 (Taq I)	*97*	*98*
Bkm	>15 (Mbo I)	*99*	*100–103*
Sau3a	>6 (EcoR I)	*104*	*105–107*

The most abundant SINES in the human genome are the Alu repeats. These SINES amount to about 3 to 6% of the human genome or about 3×10^5 copies per haploid genome. On average they are spaced every 8 kb of the human genome [*3,4*], though there is evidence for their clustering [*108*]. The Alu element (about 300 bp) is strongly sequence conserved and is bounded by short direct repeats. SINES of moderate homology to Alu are found in higher primates and rodents [*3*].

The most abundant LINES in human genomes are the L1 (Kpn) element. These elements are very variable in length, ranging from 7 kb down to about 500 bp, truncation occurring from the 5′ end of the L1 element towards the 3′ end [*4,6,7*]. The sequences occur about 1 to 4×10^4 times, constituting 1 to 2% of the human genome [*4*]. Homologous L1 sequences are found in other mammals, particularly rodents [*3*].

The mechanism by which SINES and LINES are dispersed in multiple copies throughout the genome is not completely understood. However, both appear to be examples of *mobile* genetic elements (transposons). As a consequence of their origins (Alu likely being derived from a small RNA gene [*109*] and Kpn perhaps from retroviral DNA [*7*]), both have the ability to be transcribed (into RNA). The copied sequence may then be integrated (as DNA) into *another* genomic site, in a manner analogous to integration of retroviruses into eucaryotic genomes (termed retrotransposition [*5,6*]).

The structural distinction made between tandem and interspersed repetitive sequences in Table 1 should not be regarded as rigid, but rather extremes (see for example Ref *89*). The Sau 3a family of repeats (closely related to the alphoid family) consists of five tandem subunits (about 170 bp each), thus producing a "LINE-like" element (about 850 bp long) [*104*]. This can either exist independently or as tandem arrays of the 850-bp unit. Significantly, a small fraction of the 850-bp unit in the human genome is extrachromosomal, suggesting it to have properties of a mobile genetic element [*105*]. The Sau 3a family of repeats shows moderate variable length polymorphism in human genomes (Table 3).

Polymorphism in Interspersed Repeats

Interspersed repeats have thus far not disclosed the same degree of RFLPs as that associated with tandem repeats. One example is noteworthy. This is the L2(H) (Kpn 0.6 kb) human polymorphism [*110*], which perhaps is a result of unspecified sections of the human genome containing clusters (but not tandem repeats) of a particular Kpn core sequence. The arrangements of such sequences show both constant fragments as well as qualitative and quantitative variation of other fragments in the human genome.

Sex Chromosomes—Identity and Polymorphism

The unusual structure of human sperm chromatin [*111-114*], compared with somatic tissue [*115*] (in particular the almost complete replacement of histones with small proteins called protamines), allows somatic DNA, for example, vaginal material, to be separated from sperm DNA by differential digestion [*59,73*]. Such a step would be unnecessary if, in forensic science examination of sexual assaults, analysis was confined to Y chromosome specific sequences and polymorphisms. A number of different repetitive sequences and restriction fragments have been advocated as a means for absolute identification of the Y chromosome, and hence sexing, of the genome [*37,116,117*]. Further, a number of complex polymorphisms have been identified as Y chromosome specific [*118-120*]. However, an analytical approach based on examination of the Y chromosome only may be limited in forensic science applications since only half the available sperm would be anticipated to carry this chromosome, and the chromosome itself forms only a minor fraction of the total genome [*116*].

The X chromosome may also be uniquely identified [*121, 122*] and has unique RFLPs [*90*]. Further complex human polymorphisms have been associated with the pseudoautosomal region of the X and Y chromosomes [*123*] (distal portions of their short arms [*124*]) including the existence of two complex minisatellites in this region [*85*].

Repetitive DNA in Forensic Science Examinations

As noted in the text above, some repetitive sequences, of both the tandem and interspersed type, have already found forensic science application in the sexing and identification of human tissues [*125–127*] and in associating body fluid stains with their human source [*58, 59, 73, 74*]. No doubt other examples will follow. It is critical that forensic scientists be aware of the vast amount of information in the field of human molecular genetics and human genomic variation in repetitive sequences. They can then establish at a practical level which systems most readily meet the performance criteria expounded by Sensabaugh [*1*].

As a cautionary note, the very mechanisms that give repetitive DNA its advantage could also be a disadvantage. Variations caused by point mutation or recombination or other mechanisms will continue to arise, particularly in germ cells. While this may not cause any detectable problems in the analysis of somatic tissues, it is a potential problem which disputed paternity testing. For example, Jeffreys et al. [*27*] have reported one instance of recombination at a "minisatellite" locus, thereby providing a restriction fragment length not present in either parent. Slightly modified RFLP patterns in different tissues from one individual occasionally occur [*47*]. This is presumably caused by restriction enzymes being influenced by the methylation state of the DNA [*128*].

Though repetitive DNA appears to have an assured future in forensic science examinations, note that it has a keen competitor. In vitro amplification of short DNA sequences by the so-called "chain-polymerase reaction" [*129, 130*] promises sensitivity [*130, 131*], automation, and, when targeted to the highly polymorphic HLA complex [*129, 132, 133*], exceptional discrimination between human genomes. Either way, it is a time of revolution in forensic biology.

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