ENCODED EVIDENCE: DNA IN FORENSIC ANALYSIS

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Abstract | Sherlock Holmes said "it has long been an axiom of mine that the little things are infinitely the most important", but never imagined that such a little thing, the DNA molecule, could become perhaps the most powerful single tool in the multifaceted fight against crime. Twenty years after the development of DNA fingerprinting, forensic DNA analysis is key to the conviction or exoneration of suspects and the identification of victims of crimes, accidents and disasters, driving the development of innovative methods in molecular genetics, statistics and the use of massive intelligence databases.

DNA FINGERPRINTING
Generation of a pattern of bands, by Southern blotting and hybridization with a multilocus probe, which is highly individual-specific.

FORENSIC GENETICS
The application of genetics for the resolution of legal cases.

PATERNITY TESTING
Determining whether or not a particular man is the father of a child, using genetic analysis. This generally uses similar autosomal markers to individual identification work.

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doi:10.1038/nrg1455

Forensic science (known in some countries as legal medicine) is a specialism that aims to help judges and juries solve legal issues, not only in criminal law but also in civil cases. The field has great breadth, crossing the boundaries between biology, chemistry, physics and mathematics, and including disciplines as varied as botany and ballistics, and the analysis of fingerprints, ear-prints, recorded sound and handwriting. Over the past 20 years, however, one particular biological tool has revolutionized forensic investigations — the analysis of DNA. As all living things contain DNA, and all DNA exhibits variability both among and within species, any biological material associated with a legal case carries in it information about its source.

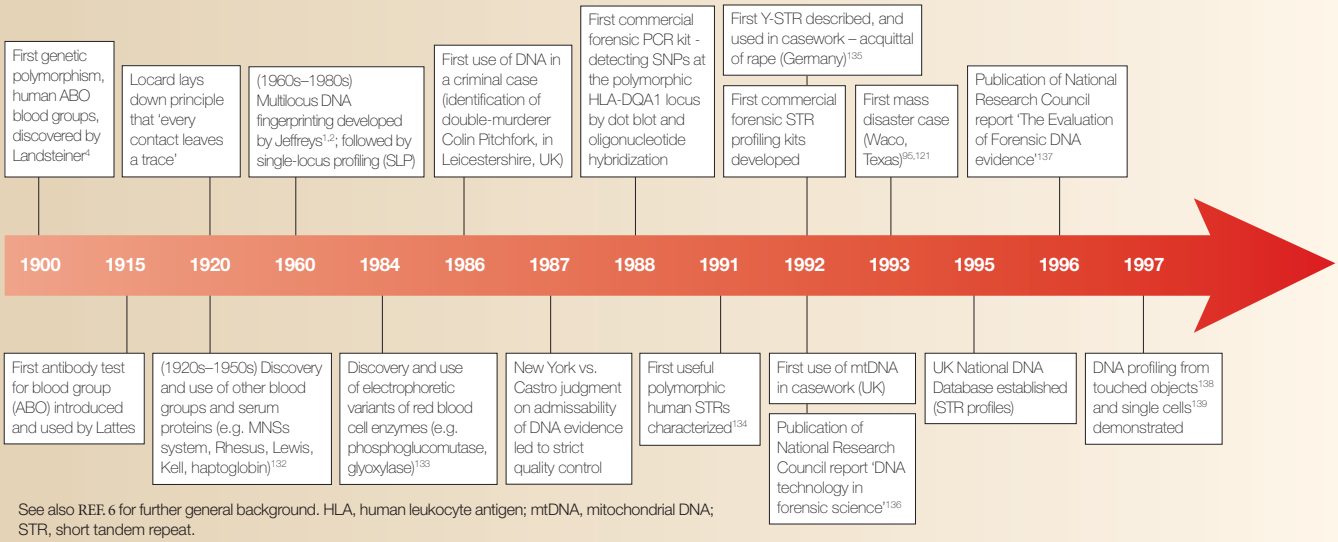
In this review, with the twentieth anniversary approaching of the development of DNA FINGERPRINTING[1,2] — the first molecular genetic forensic technique — we take this opportunity to present an overview of the field. DNA analysis has evolved to become an indispensable and routine part of modern forensic casework, employing extremely sensitive PCR-based techniques to analyse biological material. Suspects can be linked to crime scenes, or one crime scene to another, using DNA evidence from as little as the saliva on a cigarette butt, skin cells on a steering wheel or pet hairs on clothing. Large DNA databases can be rapidly interrogated for matches to DNA profiles found at the scene of a crime, or even partial matches to close relatives of a perpetrator. Undetected 'cold' cases involving sexual assault can be solved decades after investigations were begun by analysing degraded DNA from stored swabs or microscope slides. Victims of mass disasters such as air crashes, where physical identification might be impossible, can be identified unambiguously in days. However, as powerful as DNA analysis is, it is far from being the *sine qua non* of forensic casework. DNA evidence must always be considered within the framework of other evidence of many types, and the role of the forensic geneticist is not to make presumptions of guilt or innocence, but to provide unbiased information to judge and jury.

We concentrate here on the analysis of human DNA, including a discussion of recent massive forensic cases following wars and disasters. However, we also describe applications of non-human DNA analysis, in particular the use of animal and plant DNA-typing and the field of 'microbial forensics', which has expanded as a response to the threat of bioterrorism. Finally, we ask what the future holds for FORENSIC GENETICS, including a consideration of new technological developments and ethical issues arising from expanding DNA databases. PATERNITY TESTING (reviewed in REF. 3) forms part of the field of forensic genetics and is of great importance in civil and immigration cases, but owing to space restrictions we cannot discuss it here.

The evolution of forensic genetics

The aim of the forensic geneticist is one of attribution — to identify with as much certainty as possible the origin of a biological sample. The amount of variation that is currently accessible in DNA is extremely informative

Timeline | **Developments in forensic genetics**



See also REF. 6 for further general background. HLA, human leukocyte antigen; mtDNA, mitochondrial DNA; STR, short tandem repeat.

and the degree of certainty can be correspondingly high. However, it was not always this straightforward.

Early markers. The evolution of forensic genetics has been driven by the analysis of human genetic variation, beginning more than a century ago with Karl Landsteiner's discovery[4] of the human ABO blood group polymorphisms and his early realization that this variation was applicable to solving crimes. The TIMELINE summarizes the important developments that have occurred since that time. It is noteworthy that even a simple genetic system such as ABO can be used to show conclusively that a sample did *not* come from a specific person —to prove an 'exclusion'. However, showing that the sample actually *did* come from another specific person is more difficult and depends on the degree of variation revealed by the typing system. Until the 1980s, serological and protein electrophoretic methods were used to access diversity in blood groups and polymorphic proteins, but the main drawback of these markers was that they tended to rapidly degrade or were compromised by bacterial enzymes. In addition, they showed relatively low variability and informativeness; when eight systems were used together to analyse a bloodstain, the probability of two unrelated people sharing a combination (the MATCH PROBABILITY, *Pm*) was ~0.01–0.001, but for other body fluids, such as semen, not all markers were present and so the match probability was greater. Also, contamination of body fluid from one person by that from another (a 'mixed stain'), such as in rape cases, was difficult to resolve because the vaginal cellular component tended to mask the contribution from the sperm.

DNA fingerprinting. The DNA revolution began in 1984 with the discovery, by Alec Jeffreys in Leicester, UK, of hypervariable loci known as MINISATELLITES[1]. These were detected by hybridization of probes to Southern blots of restriction-enzyme-digested genomic DNA. Shared 'core sequences' between different minisatellite loci allowed probes to detect many independent minisatellites simultaneously, yielding the hypervariable multi-band patterns known as DNA fingerprints[2,5]. Using only a single probe, the match probability was estimated to be $<3 \times 10^{-11}$ and two probes together gave a value of $<5 \times 10^{-19}$ (REF. 2) — so low that the only individuals sharing DNA fingerprints are monozygotic twins. At the same time, a method known as DIFFERENTIAL LYSIS was developed[5] that selectively enriched the sperm concentration in vaginal fluid/semen mixtures, thereby avoiding the problem of the victim's DNA (which is in great excess) masking the rapist's. This is the only protocol to have remained unchanged throughout the past 20 years.

Single-locus probes. Although use of DNA fingerprinting persisted for some years in paternity testing, criminal casework soon concentrated on the use of specific cloned minisatellites — 'single-locus probes' (SLPs) — that each revealed only a single, highly polymorphic, restriction fragment length polymorphism, therefore simplifying interpretation. Typically, four SLPs were used successively to probe a Southern blot, yielding eight hypervariable fragments per individual.

It was with SLPs that the first DNA-based criminal investigation was carried out; this case, culminating in the conviction of Colin Pitchfork for a double rape and homicide in Leicestershire in 1986, encapsulated many of the defining characteristics and virtues of DNA analysis. First, the two killings, spaced three years apart, were shown to have been committed by the same individual, because SLP profiles (and DNA fingerprints) from the crime scenes matched. Second, a suspect who had confessed was excluded because his SLP profile and that found on the victims did not match, demonstrating the power of DNA to exonerate innocent people. Third, the first ever 'mass screen' was organized by the Forensic Science Service, in which all 500 local men not

MATCH PROBABILITY
The chance of two unrelated people sharing a DNA profile.

MINISATELLITES
Loci made up of a number (~10–1,000) of tandemly repeated sequences, each typically 10–100 bp in length. Usually GC-rich and often hypervariable.

DIFFERENTIAL LYSIS
A method to enrich for sperm DNA in a mixture of sperm and epithelial cells by preferentially lysing the latter using detergent and protease, so that sperm nuclei can be recovered by centrifugation.

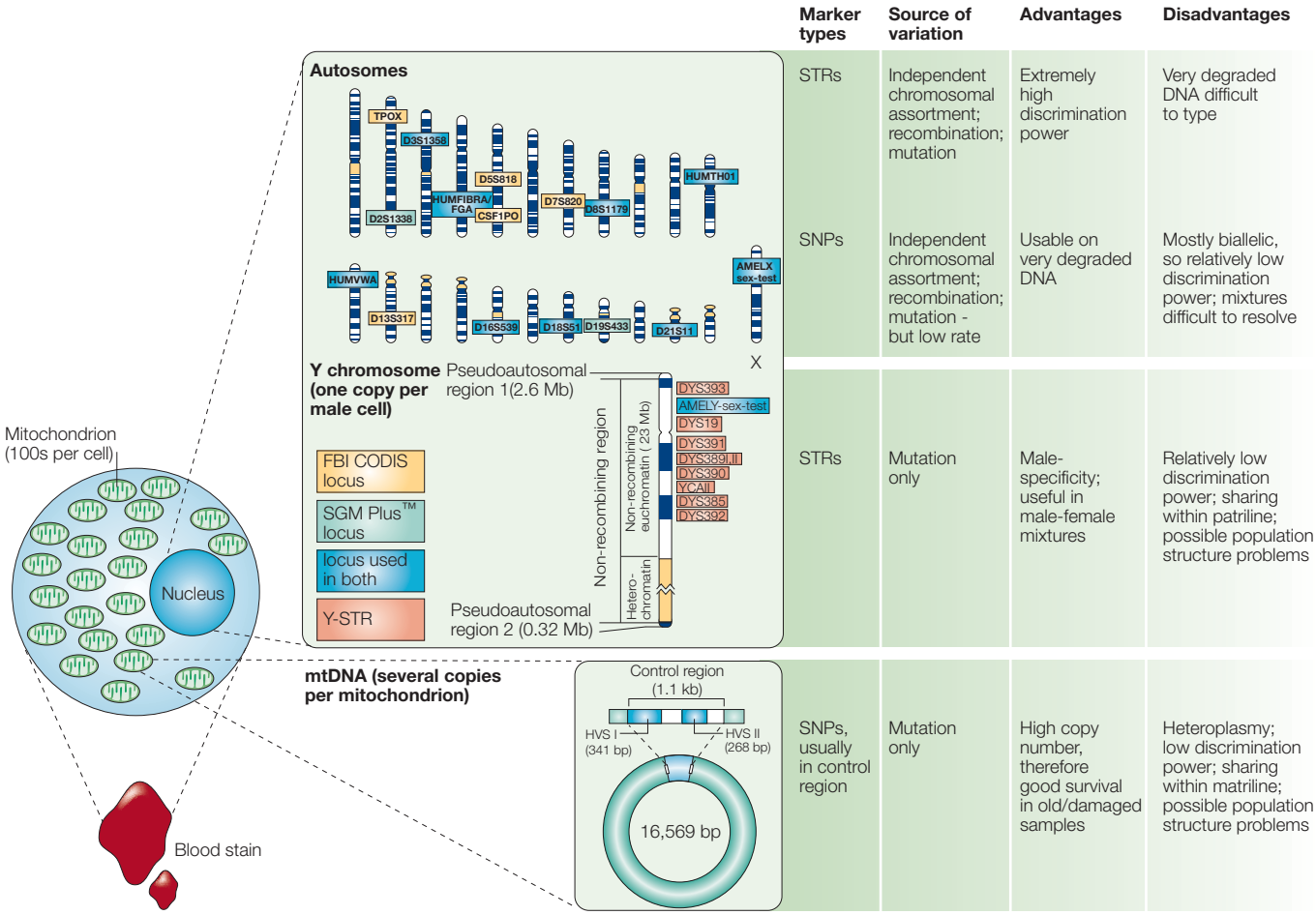


Figure 1 | **Sources of human genetic variation used in forensic analysis.** Further details of the properties of different loci can be found in the text. Heteroplasmy describes the presence of two or more different mitochondrial DNA sequences in the same cell, or individual. FBI CODIS, US Federal Bureau of Investigation Combined DNA Index System; HVS, hypervariable site; Mb, megabase; mtDNA, mitochondrial DNA; SGM, second generation multiplex; STR, short tandem repeat.

eliminated by a preliminary test for conventional protein markers were recruited for DNA testing. Pitchfork showed prescience in realizing the power of DNA analysis: he attempted to evade the screen, but his evasion was detected, and when his profile was shown to match those from the crime scenes, he pleaded guilty to the killings.

Methods in forensic genetics must surmount several hurdles before being applied to casework. First, techniques must be adapted to work on samples that are not pristine and are often limited in quantity. Second, extensive validation is required to demonstrate robustness, to pass the test of admissibility in court[6] (admissibility criteria and legislation differ between countries and even among states in the United States). Finally, quality management systems must be implemented once processes are introduced into casework: external accreditation of forensic laboratories to internationally recognized standards (such as ISO17025) is a prerequisite. Because of these constraints, adoption of new technical developments can sometimes be slow. For example, SLP technology was still widely in use long after methods based on the polymerase chain reaction (PCR) were developed in 1988.

PCR-based methods. DNA amplification by PCR provided an enormous increase in sensitivity, allowing minute amounts of degraded DNA to be analysed, and now forms the basis of all forensic DNA typing. Early PCR-based systems targeted a small number of SNPs in the HLA-DQA1 GENE[7]. Although these systems were useful when the SLP technology failed, discriminating power was low and mixtures were difficult to interpret. Consequently, there was a period when both PCR and SLP tests were done in parallel. It was the discovery of SHORT TANDEM REPEATS (STRs), discussed in the next section, together with the introduction of automated sequencing technology, that led to the current powerful systems for individual identification. Subsequently, the use of STRs supplanted both the early PCR and SLP tests worldwide once their advantages of high discriminating power, sensitivity and ability to resolve simple mixtures were realized. In addition, the time needed to carry out an analysis was greatly reduced. Reduction of costs resulting from partial automation paved the way for the creation of national STR DNA databases.

ISO17025
A global standard, established by the International Organization for Standardization, for the technical competence of calibration and testing laboratories (see Online links box).

HLA-DQA1 GENE
A polymorphic gene within the MHC class II region on chromosome 6, encoding a human leukocyte antigen cell-surface protein.

SHORT TANDEM REPEAT
A DNA sequence containing a variable number (typically ≤50) of tandemly repeated short (2–6 bp) sequences, such as $(GATA)_n$; forensic STRs are usually tetranucleotide repeats, which show little PCR stutter.

Table 1 | **International coordinating bodies in forensic genetics**

Organization/subgroup	Purpose	Web site
International Society of Forensic Genetics (ISFG) • DNA Commission • European DNA Profiling (EDNAP) group • Paternity Testing Workshops	International organization promoting scientific knowledge in forensic genetics • Makes recommendations for use of DNA markers • Harmonization of European DNA technologies	http://www.isfg.org/ http://www.rechtsmedizin.uni-mainz.de/Remedneu/ednap/ednap.htm
European Network of Forensic Science Institutes (ENFSI)	Mainly represents government institutions; coordinates efforts to develop European DNA databases	www.enfsi.org/
American Academy of Forensic Sciences (AAFS)	Academic body for north American forensic scientists	http://www.aafs.org/
Federal Bureau of Investigation (FBI) • Scientific Working Group DNA Analysis Methods (SWGDAM)	Responsible for setting standards, training and development of the national DNA database	http://www.fbi.gov/publications.htm
National Institute of Science and Technology (NIST) • STRBase	Supports the forensic community by organizing collaborative proficiency exercises • Database giving characteristics of forensically useful short tandem repeats (STRs) and SNPs	http://www.nist.gov/ http://www.cstl.nist.gov/biotech/strbase/index.htm

Current methods in human identification

Human forensic casework is now done using commercially developed autosomal STR multiplexes (single-tube PCR reactions that amplify multiple loci); other sources of genetic variation that find more specialized uses are autosomal SNPs, and markers on the Y chromosome and mitochondrial DNA (mtDNA) (FIG. 1). Differences in practice between jurisdictions are considerable owing to historical, social and legal circumstances. Detailing these is beyond the scope of this article, so we take a predominantly UK perspective here. However, despite these differences, the rapid development and universal acceptance of new DNA-based technology in forensic genetics is mostly owing to active collaboration between international groups that are coordinated under various academic and government-sponsored institutions (TABLE 1). Recommendations on standard practice, quality issues and collaborative activities are made at a global level.

Autosomal STR profiling. The first widely used multiplex (the 'quadruplex'[8]) consisted of four SIMPLE STRS. However, because it had a high match probability of ~1 in 10,000, the first criminal cases involving autosomal STR profiling were reported in conjunction with SLP profiling. Subsequent addition of two highly variable COMPLEX STRS decreased the match probability to ~1 in

Box 1 | **Evaluating the weight of DNA evidence**

The evidential weight of a match between crime stain profile and suspect is quantified by the match probability (*Pm*); the chance of two unrelated people sharing a profile. For independently inherited loci, *Pm* is calculated by multiplying the individual allele frequencies in the profile in question (the 'product rule'): the greater the number of loci, and the greater the heterozygosity of each locus, the lower the value of *Pm*. However, there are a number of situations in which *Pm* can be substantially increased:

• if the profile is partial because of degradation, reducing the number of informative loci;

• if a suspect and a perpetrator share many alleles by descent (for example, are brothers);

• if a suspect and a perpetrator originate from the same subpopulation.

POPULATION STRUCTURE can cause frequencies of alleles (and hence profiles) to vary between subpopulations — an issue that caused great controversy in the application of SLP profiling[90]. The debate was resolved by applying guidelines to ensure match probabilities quoted in court were conservative (that is, favourable to the defendant). Similar conservatism is now applied to STR profiles[91].

Despite the high discriminating power of very low *Pm* values, interpretation in the courtroom has not been without controversy[92], and this is because of the way that DNA evidence is sometimes presented. A wellknown example is the 'prosecutor's fallacy', or 'fallacy of the transposed conditional': suppose a crime is committed in London (population ~7 million) and a crime-scene profile is obtained that has a *Pm* of 10^{-6}. The prosecutor, finding that a defendant matches the profile, might say: 'The odds are a million to one in favour of the defendant being guilty.' But, given the population size, ~7 people in the city are expected to match the profile, so it can then be argued that the odds are actually 7 to 1 in favour of innocence; however, this 'defence fallacy' unrealistically assumes that each of the 7 people has equal probability of guilt, which is untrue as DNA evidence is not used in isolation. This problem of logic can be avoided by an approach based on a likelihood ratio, using conditional probabilities based on prosecution and defence scenarios: the job of the court, based on an evaluation of both DNA and non-DNA evidence, is to decide the ultimate issue of guilt or innocence, given *all* of the evidence. Under complex scenarios with many different variables, 'Bayesian networks'[93,94] — intuitive graphical means to display hypotheses regarding the probabilistic relationships between variables — are a powerful aid to understanding, although they are not intended to supplant the role of the jury.

POPULATION STRUCTURE
The absence of random mating within a population, leading to allele frequency differences among subpopulations.

SIMPLE STRS
Short tandem repeat loci composed of uninterrupted runs of a single repeat type.

COMPLEX STRS
Short tandem repeat loci containing more than one run of repeats that can be of one or more repeat type.

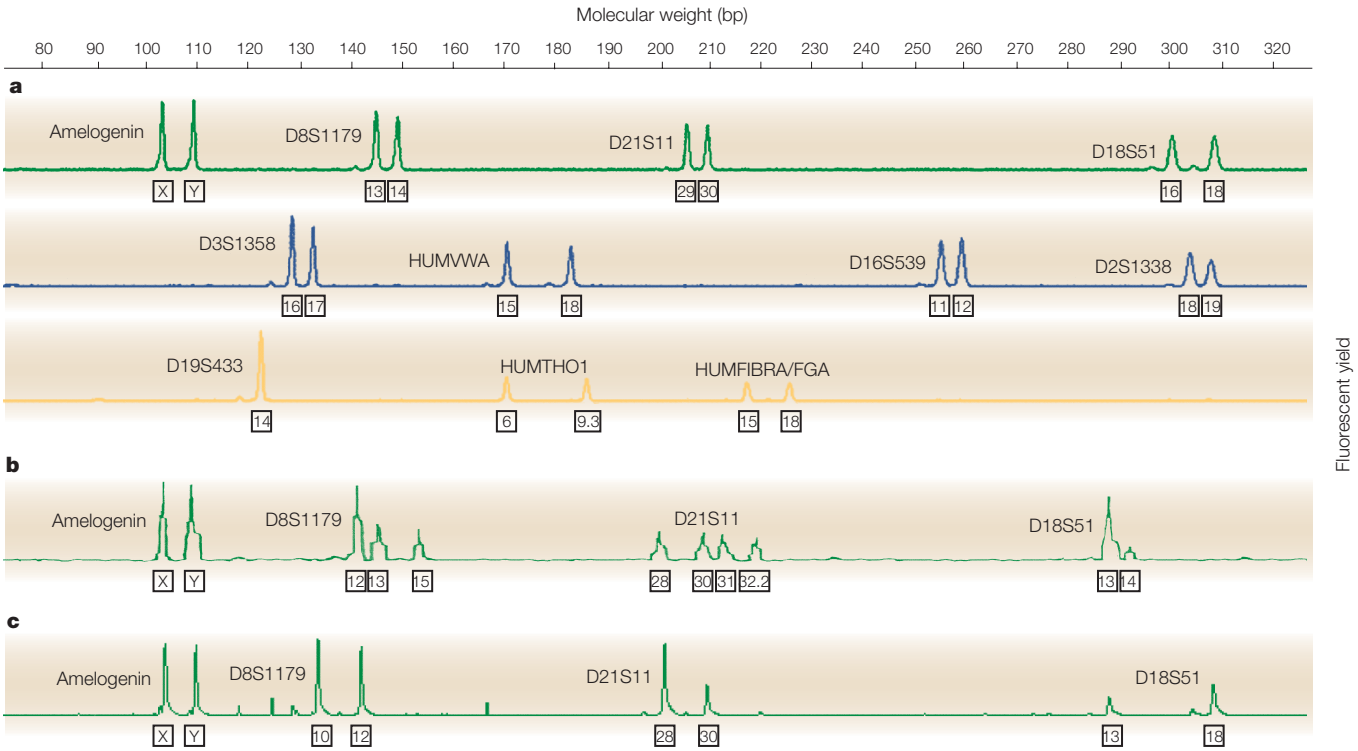


Figure 2 | **Electropherograms illustrating autosomal STR profiles. a** | An electropherogram of the second-generation multiplex 'SGM Plus' profile from a male, including X- and Y-specific amelogenin products of 106 and 112 bp, respectively. Most short tandem repeats (STRs) are heterozygous and the alleles are evenly balanced. Numbers beneath STR peaks indicate allele sizes in repeat units. The STR profile is displayed in the green, blue and yellow channels of a four-colour fluorescent system, with the red channel being used for a size marker (not shown). **b** | A typical mixture from two individuals (green channel only shown). Mixtures can only be identified if the alleles of the minor component are above the background 'noise' in an electropherogram (in practice a ratio of ~1:10) and can usually be resolved by inspection[95]. In this example, the contributions are in even proportions — for example, D21S11 shows four alleles where the peaks are approximately equal in height, whereas D18S51 shows two peaks in a 3:1 ratio. The X- and Y-specific amelogenin peaks are of approximately equal height, indicating that this is a mixture from two males. More complex mixtures might require interpretative methods based on likelihood ratios[96,97], calculations based on peak area[98] and consideration of PCR stutter[99], and have led to the development of computer programs to deduce potential underlying genotypes[100,101]. **c** | A profile (green channel only shown) obtained by 'low copy number' (LCN) testing[102], a method used in the United Kingdom when little DNA (typically <100 pg or <17 diploid genomes) is available. The method uses an increased number of PCR cycles (for example, 34, rather than the usual 28), and leads to marked heterozygote imbalance at some loci (here, D21S11 and D18S51) because of stochastic variation in amplification. Extreme imbalance is drop-out (failure to amplify) of an allele (not shown). Drop-out is a stochastic effect of the limited number of template molecules, and therefore no two amplifications of the same extract will behave the in the same way. The LCN protocol requires duplicate PCR of an extract and only those alleles that are observed in both PCRs are reported. (See also BOX 2.)

50 million. This 'second-generation multiplex' (SGM) also included a PCR assay targeted at the XY-homologous amelogenin genes[9], thereby revealing the sex of a sample donor. It became clear that STRs were more sensitive than other methods and allowed unambiguous assignment of alleles, making the method suitable for the development of databases. In 2000, an additional four loci were added to the multiplex, which was renamed SGM Plus[10], thereby reducing the match probability to less than 10^{-13}. The above account tracks developments in the United Kingdom; events elsewhere unfolded differently, and globally there are now a number of different systems that nonetheless have many loci in common. The US FBI CODIS (Combined DNA Index System) contains 13 STRs plus the amelogenin sex test (FIG. 1), with a match probability lower than that of the UK system. Typically, two separate multiplexes are used in the United States[11], but to improve efficiency, new multiplexes that amplify 16 loci in a single reaction (including amelogenin) have also been introduced[12]. In Germany, eight loci are used, including the *ACTBP2* locus[13]. International collaborations have recommended core loci to facilitate international data exchange — for example, a set of seven for common use in Europe[14]. Detailed information on most forensic STR markers can be found at STRBase (see Online links box) and in REF. 15, which also describes the technology of STR typing.

The match probabilities obtained with STR multiplexes are so low that their reciprocals vastly exceed the entire human population. However, although DNA profiling is often referred to as 'individual identification' and assessments can be made whether or not a DNA profile is unique in an unsampled population[16], it would

ALLELIC LADDER
An accurate marker used to identify alleles at a particular STR, generated by PCR amplification of a series of sequenced alleles from that STR.

ELECTROPHEROGRAM
The graphical output of electrophoresis devices in STR and sequencing analysis, showing fluorescence intensity as a function of molecular weight; peak at a particular wavelength (colour) corresponds to a specifically labelled molecule of a particular size.

HETEROZYGOTE BALANCE
The proportion of the two alleles of a heterozygote, expressed as the area of the smaller peak divided by the area of the larger peak in an electropherogram.

be a rare case in which everyone on the planet could be considered as the pool of potential contributors for a crime-scene sample[17]. Reporting of DNA evidence in court takes a conservative approach to the low match probabilities and commonly uses likelihood-based methods to take account of the factors applying to a particular case (BOX 1).

Multiplexes are analysed and typed using automated sequencing equipment. These are typically multi-channel capillary electrophoresis systems that are used to detect fluorescently labelled PCR products (FIG. 2a) and are combined with robotics and laboratory information management systems, including bar-coding of samples to reduce operator errors. This automation reduces cost and increases throughput. Interpretation (defining the alleles in a profile) is more difficult to automate. However, there has been progress in converting traditional subjective expert opinion into programmable (heuristic) rules for computer programs (known as 'expert systems'[18]), generally intended to complement, rather than replace, the human expert. These take into account fragment size (accurately measured with respect to internal standard markers and to an ALLELIC LADDER[19] used to identify alleles), ELECTROPHEROGRAM peak height and area and an assessment of HETEROZYGOTE BALANCE, and include automated checks to interpret artefacts such as PCR STUTTER[20]. DNA quality from 'reference samples' (taken from individuals to create databases — see next section) is predictably good and makes automation of typing and interpretation relatively straightforward. In the UK Forensic Science Service, if two expert systems working on different principles agree on a profile it is accepted, but there are regular challenges with 'blind' controls. For casework samples, preliminary assessment is vital to determine the best method of processing; but automation is more difficult because DNA quality and quantity are variable and DNA mixtures are often encountered, complicating interpretation. Anomalous profiles can also arise for biological reasons (such as mutation) and if methods are used that are sensitive enough to detect single DNA molecules ('low copy number'), then laboratory-based contamination of single or multiple alleles is a strong possibility and interpretation strategies are needed to deal with this. These situations are discussed in BOX 2.

STR-based forensic DNA analysis has achieved worldwide public and professional acceptance as a reliable means of individual identification and has had a major impact on criminal justice systems. The increase in sensitivity of DNA methods has allowed the reopening and solving of 'cold' cases and has also led to the exoneration of prisoners (some of whom were awaiting execution) convicted through miscarriages of justice. Most of these cases have been in the United States (see the Innocence Project web site in the Online links box), where post-conviction testing attracts federal funding, although one case in the United Kingdom has been described[21].

DNA databases of autosomal STR profiles. As well as matching a crime-scene profile to that from an apprehended suspect, a match ('hit') can be made to a DNA database of offender profiles (an 'intelligence database'), allowing a new suspect to be investigated. The advances in automation described above have allowed the establishment of such databases, which are now in use or under development in many countries. Criteria for including a profile in a database vary among countries (TABLE 2). The largest example, the UK National DNA Database[22,23], contains (at July 25th 2004) ~2.5 million reference profiles (mostly from buccal scrapes) and ~200,000 crime-scene profiles. Since 1995, there have been more than 550,000 matches between reference profiles and crime-scenes, and more than 30,000 matches between crime scenes. A new method of using the database, 'familial searching', has recently been introduced. In 2003, a lorry driver was killed in Surrey, UK, by a brick thrown through his windscreen. A DNA profile was obtained from the brick, but had no match in the database. A geographically restricted search of the database was carried out for potential close relatives of the perpetrator, under the assumption that close

Box 2 | Dealing with anomalous autosomal STR profiles

As shown in FIGURE 2, several factors can complicate the interpretation of DNA profiles. These include mixed samples and the availability of only small amounts of DNA, which (in the UK) is analysed by 'low-copy number' (LCN) methods and can lead to allele drop-out. LCN analysis also increases the probability of contamination (additional 'foreign' alleles in the profile), despite stringent precautions to prevent it.

Contamination can be gross and lead to full additional profiles, where typically the negative control will be affected; these can be searched against forensic staff elimination databases and stored in a separate database to allow detection and monitoring of problems such as contamination of plasticware during manufacture[103,104]. Alternatively, contamination can contribute an extra one or two alleles per DNA profile (allele DROP-IN[102,104]), where the negative control is usually unaffected. The probabilities of a match, of drop-out and of contamination (based on computer simulation analysis of negative control data[104]) can be readily incorporated into the calculation of the likelihood ratio (LR) when the significance of the DNA evidence is being assessed[102]; calculations are complex but are aided by a computer program (LoComatioN)[105] that can also combine the results of several profiles into a single LR. Here, we no longer think of a DNA profile either matching or not matching a suspect, because the twin effects of drop-in and drop-out will alter the suspect's apparent profile so that it does not match the crime scene sample, without indicating an exclusion; rather, the probability of the evidence is lowered.

Anomalous profiles can arise from causes other than mixtures but can readily be resolved by careful analysis:

- Mutations in the PCR primer target region can cause allele drop-out or heterozygote imbalance[106,107].
- An STR can be duplicated and segregated in a normal Mendelian fashion or a somatic STR mutation occurring early in development can lead to a three-peak profile for the STR, which might vary between tissues; examples are on STRBase (see Online links and REF. 108).
- The STR D21S11 can reveal three alleles in trisomy 21 cases (reviewed in REF. 109).
- Discordant results in the amelogenin sex test can be observed in rare individuals, including cases of sex-reversal (XX males and XY females) and males[110–112] carrying deletions that remove *AMELY*.
- A true mixed profile can also originate from a single individual. Analysis of DNA from people who had undergone successful bone marrow transplants ≥5 years previously[113], showed a mixed profile in buccal and fingernail samples; in blood, the recipient's own profile had been completely replaced by that of the donor, whereas in hair, the recipient's profile remained unmixed.

Table 2 | **Characteristics of some national DNA databases**

Country (Year established)	Reference profile size	Crime-scene sample size	Suspect to scene hits	Scene to scene hits	Entry criteria for suspects	Entry criteria for convicted offenders	Removal criteria
UK (1995)	2.5 million	200,000	550,000	30,000	Any recordable offence*	Entered as suspect	Never removed, including suspects
USA (1994)	1.52 million	67,000	Figure unavailable	Figure unavailable	No suspects entered, but under revision	Depends on state law	Depends on state law
Germany (1998)	286,840	54,570	13,700	5,500	Offence leading to >1 yr in prison	After court decision	After acquittal or 5–10 years after conviction, if prognosis is good
Austria (1997)	64,740	11,460	3,200	1,350	Any recordable offence*	Entered as suspect	Only after acquittal
New Zealand (1996)	44,000	8,000	4,000	2,500	No suspects entered	A relevant offence (including ≥7 yr in prison)	Never removed, unless conviction quashed
Switzerland (2000)	42,530	7,240	4,840	5,540	Any recordable offence*	Entered as suspect	After acquittal or 5–30 years after conviction
France (2001)	14,490	1,080	50	70	No suspects entered	Sexual assault and serious crime	40 years after conviction
Finland (1999)	8,170	5,450	2,080	780	Offence leading to >1 yr in prison	Entered as suspect	Only after acquittal
Slovenia (1998)	4,820	2,360	370	80	Any recordable offence*	Entered as suspect	Depends on severity of crime
Netherlands (1997)	4,260	13,700	2,520	4,260	No suspects entered‡	Offence leading to >4 yr in prison	20–30 years after conviction
Sweden (2000)	3,980	9,860	2,500	4,750	No suspects entered	Offence leading to >2 yr in prison	10 years after release from prison

*That leads to a term of imprisonment. ‡Except when the suspect's DNA is tested for the case. Adapted from REF. 140, with additional information from Peter Schneider and Jill Vintiner (personal communications). See also BOX 3.

relatives are more likely to share alleles than unrelated people (50% for brothers). This highlighted 150 candidates, leading to the identification of a suspect whose profile matched that on the brick. He was convicted of manslaughter[24].

Legal differences between countries make such speculative searches impossible in some jurisdictions and can also complicate the international exchange of data when crime is itself becoming increasingly international. However, although large databases with permissive entry criteria can be powerful, they also raise ethical questions (BOX 3).

Autosomal SNP typing. Compared to STRs, SNPs have much lower heterozygosities (a per-SNP maximum of 0.5) and so ~50 SNPs are required to approach the low match probability of an STR profile[25] (see BOX 1). In addition, mixtures are especially difficult to resolve for

Box 3 | **DNA databases: ethical issues**

DNA databases are seen by some as without fault[114], but they have not been without their critics[115,116]. Any criminal whose profile is in a database risks detection in further criminal activity — the probability of identifying a suspect when a crime-scene profile is checked against the UK database is >40%[23]. Culprits are apprehended more quickly and criminals might be deterred from future offending, but it is unclear whether overall crime rates are reduced. The UK database is projected to reach 5 million samples[22], which is ~10% of the population and >30% of 10–50-year-old men (those most likely to offend[30]). This enormous size is a result of the relatively liberal criteria for database entry: most samples are taken (with or without consent) from individuals arrested for offences that could lead to a prison sentence, whereas in some other jurisdictions only more serious offences are considered and a specific degree of connection (decided by a court) between the suspect and the offence is necessary before DNA can be sampled (TABLE 2). One justification given for the United Kingdom practice is that minor criminals might also be perpetrators of more serious crimes — one example is the arrest and subsequent conviction, in 2001, of a man for a murder committed in 1968, triggered by a match between crime-scene DNA evidence and a sample taken from the culprit in connection with a motoring offence[114]. Recent legislative changes allow retention of profiles from exonerated suspects and from individuals profiled during mass screens (albeit with consent).

The use of any database involves a balance between the rights of the individual and the interests of the state; this differs from country to country, and some believe it is tipped too far towards the state in systems like that of the UK[117]. However, the discoverer of DNA fingerprinting, Alec Jeffreys[118], has argued for the UK database to be extended to the entire population, under the auspices of an independent authority, arguing that the current database is discriminatory because some groups in the population are probably overrepresented among suspects. James Watson[119] has called for a global database to fight crime and terrorism — an enormously costly and complex endeavour, raising serious issues in ethics and law[117].

Retention of samples for possible retesting with future technologies (as is done in the UK) is also considered controversial by some, who argue that it could reveal private genetic information.

PCR STUTTER
A PCR artefact in which, as well as a band of the expected size, an additional band is seen which is typically one repeat unit smaller, resulting from slippage synthesis errors by the PCR polymerase

DROP-IN
Addition of (typically) one or two alleles to a DNA profile, owing to contamination.

Box 4 | **The challenge of large human identification cases**

DNA analysis has a key role in the identification of victims of accidents, disasters and wars, therefore aiding emotional closure for bereaved relatives. Reference material often comes from these relatives[3] — for example, an approach used early on in the identification of the skeletal remains of murder victim Karen Price compared STR alleles with her presumptive parents[120].

An early example of a mass identification case followed the Waco disaster[95,121] in 1993, in which more than 70 occupants of a heavily fortified compound in Waco, Texas, perished in a fire following a siege by US law enforcement agencies. About 40 bodies were unidentifiable by conventional means and, of these, 26 could be identified by quadruplex STR profiling. Reference samples came from living or dead (but positively identified) relatives. For instance, given the alleles present in parents, the possible genotypes of children could be sought among profiles of victims (taking account of the possibility of STR mutations between the generations), and the weight of identification evidence considered on a likelihood basis (BOX 1).

Air crashes, such as the August 1996 Spitzbergen disaster[122] or the September 1998 Swissair flight 111 air crash[123], present problems because of the level of damage to bodies from fragmentation and burning. However, given an accurate list of passenger and crew, the site can be considered a 'closed scene', where there are no unknown victims; families are often among the dead, so allele sharing is expected. Reference profiles can be obtained from personal effects of victims such as clothing or toothbrushes[123], and samples provided by relatives, leading to complete identification.

Without doubt the largest mass identification cases are those arising from wars and genocides, such as that in the former Yugoslavia, where >30,000 people went missing; in Bosnia-Herzegovina alone >10,000 bodies required identification (reviewed in REF. 124). On a comparable scale, and with unique challenges, has been the effort to identify the remains of the estimated 2,819 people who died in the World Trade Center terrorist attacks of September 11th, 2001 (reviewed in REF. 125). Physical identification was impossible for most victims and mixed profiles were common[126]. Technical developments during the identification process have included:

- new computer programs to deal with large and complex kinship calculations, involving reference samples from ~6,000 relatives and ~5,000 personal effects[127,128];
- novel DNA extraction procedures[129];
- redesigned STR multiplexes ('miniSTRs', based on shorter DNA amplicons[27]) and autosomal SNP multiplexes to allow analysis of severely degraded DNA[125].

Despite these efforts, the remains of ~1,000 people might never be identified[125].

binary markers, although this limitation might be overcome by targeting rare tri-allelic SNPs[26].

The practical advantage of SNP typing is that DNA template size can in principle be only as large as a pair of specific primers; ~50 bp. This is considerably smaller than the ~300 bp needed for successful STR profiling (although special STR multiplexes have been developed that use particularly small amplicons[27]) and makes SNPs of interest for the analysis of severely degraded material. The technical challenges of the World Trade Center disaster (see BOX 4) have led to the application of forensic SNP typing. The European Network of Forensic Science Institutes (ENFSI) and the US FBI Scientific Working Group on DNA Analysis Methods (SWGDAM) (TABLE 1) working groups are assessing potentially useful multiplexes and will make recommendations for global standardization[28], although it is hard to imagine that SNP profiling will replace STR-based systems.

Y-chromosomal analysis. Autosomal STR profiles owe their variability to three processes: independent chromosomal reassortment, recombination and mutation. On the Y chromosome, mutation alone functions to diversify STR HAPLOTYPES. These haplotypes are therefore less diverse than autosomal profiles (genotypes) containing an equivalent number of markers, leading to relatively high average-match probabilities of ~0.003 for 11 Y-STRs[29]. However, Y chromosomes have one crucial forensically useful property: they are confined to males. As most serious offences are committed by men[30], we expect to find their Y chromosomes at crime scenes; in male–female body-fluid mixtures where conventional methods fail to resolve autosomal profiles, Y-STR typing can give specific information about the male component. Although differential lysis often allows autosomal profiling of a rapist, the vasectomized or naturally azoospermic rapist leaves no sperm; in such cases[31], Y-specific profiling is effective, even in the presence of a 4,000-fold excess of female DNA[32]. In multiple rape it might be possible to gain information about the number of assailants.

There are 219 known useful STRs on the Y chromosome[33], but a set of 9 or 11 loci is commonly typed in casework, and there is a large collaborative quality-controlled online population database of more than 24,000 9-locus profiles from 200 populations[29,34]. Clearly, the product rule (see BOX 1) for independently segregating autosomal STRs cannot be applied to markers on the non-recombining Y chromosome and haplotype frequencies are instead often determined simply by counting or by more sophisticated BAYESIAN methods[35]. Excluding STR mutation, all patrilineal relatives (brothers, father, sons, paternal uncles and so on) of a suspect will share his Y haplotype and this needs to be considered when assessing the strength of the evidence[36]. Furthermore, the potential association of surnames inherited through the paternal line[37] with Y haplotypes has led to suggestions that surname prediction from haplotype might be possible. However, the complexity of the relationship[38] probably precludes this approach as an absolute determinant, although it might be powerful if used in the context of a Bayesian method

HAPLOTYPE
The combination of allelic states of a set of polymorphic markers lying on the same DNA molecule, such as the Y chromosome or mtDNA

BAYESIAN
Statistical method, based on Bayes' theorem, that allows inferences to be drawn from both the data themselves and any prior information.

of analysis. On a larger scale, the Y chromosome shows particularly strong population structure[39] and the availability of local population databases is essential. These difficulties can complicate the evaluation of match significance, but exclusion of a suspect remains straightforward. The use of Y-chromosome analysis will increase, particularly in rape casework, aided by the availability of standardized commercial Y-STR[40] and Y-SNP kits (reviewed in REF. 41).

Mitochondrial DNA. mtDNA shares many of the theoretical disadvantages of the Y chromosome: it is non-recombining, so markers (almost all SNPs, but including length variation in a run of C nucleotides) do not segregate independently, thereby reducing diversity; it is uniparentally inherited (through the mother), so all members of a matriline share a haplotype; and it shows marked population structure[42]. Furthermore, there is the complication of heteroplasmy.

The advantage of mtDNA lies in its copy number, which is between ~200 and 1,700 per cell (reviewed in REF. 43); this means that it has a greater probability of survival than nuclear DNA does. Forensic applications[43,44] include analysis of samples that are old or severely damaged, or low in DNA (such as hair shafts), and include historical criminal cases (see BOX 5). The normal practice is to sequence two segments of the CONTROL REGION that are particularly polymorphic, known as hypervariable segments I and II (HVSI, HVSII). SNPs outside the hypervariable segments will increase the power of mtDNA typing[45,46].

Rather than considering the average-match probability (which is high[47], at ~0.005–0.025), match significance is usually evaluated by the 'counting method' — how many times a specific sequence has been observed in a population database[48,49], with a correction for sampling error. There has been criticism of the quality of some forensic datasets, on the basis of highly improbable sequences that are detectable by phylogenetic analysis[50].

Heteroplasmy can lead to different sequences being found between hairs or tissues in a single individual, and even along the length of a single hair shaft[51]. Mutation, which distinguishes heteroplasmic types, is particularly common at some sites ('hot spots'), but this can be built into the interpretation using a likelihood ratio approach[52]. Shared heteroplasmy between two samples can actually increase the strength of evidence, as was the case in confirming the matrilineal relationship between the putative Tsar Nicholas II and his brother Georgij Romanov[53] (BOX 5).

Putting face and place to a DNA profile

When a profile from a crime scene does not find a 'hit' in an intelligence database, any information that can be deduced from the DNA about the donor is useful. A basic piece of information, sex, has already been mentioned, but two other areas, population of origin and phenotypic features, have also been investigated and used to aid criminal investigations.

Deducing population of origin. Most (~85%; REFS 54,55) genetic variation is found within human populations. Nonetheless, individuals from different populations are, on average, slightly more different from each other than are individuals from the same population, and this allows sets of markers to be used to predict population of origin (reviewed in REF. 56). Similar methods might be applicable to the analysis of a crime-scene sample.

Forensic STR profiles are very variable among individuals and so show low inter-population variance (F_{ST}). They are therefore not ideal for predicting population of origin. The ability of SGM Plus profiles to classify individuals into one of five police-defined 'ethnic groups' has been assessed[57], and showed, for example, that 67% of profiles known to be from

Box 5 | Forensic DNA analysis of historical samples — the case of the Russian royal family

The first DNA-based historical criminal investigation was carried out in 1994 when bones purported to be those of the Russian royal family (the Romanovs), executed by a Bolshevik firing squad in 1918, were analysed using a combination of mitochondrial DNA (mtDNA) sequencing, sex typing, STR analysis and PCR cloning[130].

The samples were more than 70 years old, yet yielded autosomal STR profiles consistent with the presence of a family group and mtDNA sequences matching reference sequences from living matrilineal relatives: the sequence obtained from Prince Philip, Duke of Edinburgh, matched those of the putative Tsarina and her children, whereas those from the Duke of Fife and Princess Xenia Cherememeteff-Sfiri matched that of the putative Tsar Nicholas II, except for one discrepant base. After PCR cloning, the putative Tsar's mtDNA was shown to comprise two different molecules (one of which matched the living reference samples) and was concluded to be an example of heteroplasmy, thought at the time to be rare; this led to speculation about the reliability of the results. However, when an independent analysis was carried out on the remains of the Tsar's brother, Georgij Romanov, by the Armed Forces DNA Identification Laboratory in Rockville, Maryland[53], it was discovered that he shared a heteroplasmy at the same position in the mtDNA molecule; this effectively dispelled any lingering doubts. After a consideration of all of the DNA and non-DNA (anthropological) evidence, the Russian authorities pronounced the remains to be those of the Romanovs.

The remains of one of the Tsar's daughters, Anastasia, were absent from the grave, and controversy surrounded the claim that she escaped execution and survived, under the identity of Anna Anderson. STR analysis[131] of 20-year-old paraffin wax embedded samples from Anderson was inconsistent with her being a daughter of the Tsar and Tsarina. However, the mtDNA sequences matched those of Carl Maucher, a putative maternal relative of a woman named Franzisca Schankowska. The mtDNA results were confirmed by an independent group from Penn State University, who concurrently analysed hair shafts purported to have come from Anna Anderson[131].

CONTROL REGION
Part of mitochondrial DNA that is non-coding and therefore more able to accumulate variation than the rest of the molecule.

African-Caribbeans were classified correctly, whereas the remainder were wrongly assigned to other ethnic groups. Despite the misclassification, prediction is useful if it reduces the number of suspect investigations carried out before the actual perpetrator is reached. Policemen are not anthropologists and one problem with interpreting these studies is the over-simplified way in which populations are defined. The haploid Y chromosome and mtDNA show strong geographic differentiation because their small EFFECTIVE POPULATION SIZE (one quarter of that of any autosome) leads to enhanced GENETIC DRIFT. Mating practices might also contribute to inter-population differences. These markers therefore contain information on population of origin, but, owing to ADMIXTURE, can give misleading results.

Markers with greater power have emerged from studies of admixed populations for epidemiological purposes or for mapping disease genes by LINKAGE DISEQUILIBRIUM. Autosomal binary or STR loci have been identified that show large allele frequency differences (30–50%) between parental population groups[58,59]. Multilocus genotypes based on such ANCESTRY INFORMATIVE MARKERS (AIMS) can be analysed using model-based clustering algorithms, yielding individual proportions of ancestry from a number of populations. Although forensic evaluation has not yet been carried out, tests using 175 AIMs are already available commercially for forensic applications[60]; their use will probably increase, although it might be limited in admixed populations.

Phenotypic information. A strong prediction of population of origin might indicate some aspects of phenotype, such as skin colour. However, direct genetic tests would be more useful. Many human phenotypes (for example, stature, facial features and pigmentation) have a strong genetic component.

The only relevant trait that has undergone serious investigation is pigmentation. However, although there are many human genes that when mutated are known to cause abnormal pigmentation such as albinism[61], only a minority appear to influence 'normal' variation. The best studied is the melanocortin 1 receptor (*MC1R*) gene, the gene product of which lies in the cell membrane of the MELANOCYTE. Binding of α-melanocyte stimulating factor to the receptor leads to production of black/brown pigments, whereas in the absence of a signal through *MC1R*, red/yellow pigments predominate. The *MC1R* gene has more than 30 known variant alleles involving amino-acid substitutions, three of which are associated with red hair, fair skin and freckling[62,63]. Population studies[64] show that homozygosity or compound heterozygosity for such a variant gives a >90% probability of having red hair. This test is therefore useful as an investigative tool in populations such as that of the United Kingdom where red hair is found at an appreciable frequency.

Other candidate pigmentation genes have been investigated, but with less success. Linkage analysis has identified a locus on chromosome 15 that influences eye colour[65], for which the *P* gene, the product of which is involved in melanin production, is a candidate[66]. Two amino-acid substitutions in the gene are associated with blue or grey eyes[66]. A broader association study including SNPs in several candidate genes[67] has identified 61 SNPs that explain 15% of the variation in eye colour in a sample, but probably do not provide useful predictive testing. Work on these and other phenotypes will probably increase in the future. However, the complexity of these quantitative traits, coupled with variability introduced by environmental and nutritional differences, means that even if the genes influencing them were identified there is no guarantee that simple deterministic tests would emerge.

Non-human species in forensic genetics

Forensic analysis of animal DNA has been used both when animal material (usually pet hairs) is found at crime scenes, and in investigations of the illegal trade in endangered species. The best-known example of the former was the matching, using 10 feline-specific dinucleotide STRs, of cat hairs on a bloodstained leather jacket with a pet cat, known as Snowball, who lived with the suspect in a murder case[68]. More recently, a commercial kit containing 11 tetranucleotide STRs has been produced for the individual identification of cats. Work on canine identification is mostly based on STRs developed for parentage testing[69], but also includes mtDNA profiling[70]. In a recent case, the conviction of a man for the murder of a seven-year-old girl in California was supported by mtDNA analysis of dog hairs that matched a pet belonging to the victim.

In the endangered species field, species-specific methods target the gene that encodes cytochrome b of mtDNA[71,72]; examples include tests for tiger-bone DNA in traditional Chinese medicines (all of which proved to be cow or pig[73]), and also for rhinoceros horn[74].

As with animal material, plant material can be associated with a crime scene and provide vital evidence. When morphology is uninformative, DNA could, in principle, offer species identification or a link to a specific place. However, in the analysis of plant DNA there is no easy equivalent of the widely studied animal mtDNA sequences (although regions of the chloroplast genome and the nuclear ribosomal RNA loci seem promising) and STRs in most species are poorly characterized. PCR-based fingerprinting methods such as RANDOM AMPLIFIED POLYMORPHIC DNA (RAPD) can allow identification of plant strains and have been used in the analysis of mosses in a murder case[75], and in civil disputes over the identity of commercially valuable cultivars of strawberry[76] and chilli[77]. A species-specific PCR assay is available for *Cannabis sativa*[78] and the isolation of a hexanucleotide STR from the same species provided a marker with some potential to identify the source of cannabis samples[79].

Microorganisms can be sources of evidence in situations such as foodstuff contamination and medical negligence cases involving infections, such as HIV transmission[80]. However, in October 2001, at least five people died in the United States from inhalation anthrax after

EFFECTIVE POPULATION SIZE
The size of an idealized population that has the same properties with respect to genetic drift as does the actual population in question.

GENETIC DRIFT
The stochastic fluctuation of allele frequencies in a population owing to chance variations in the contribution of each individual to the next generation.

ADMIXTURE
The formation of a hybrid population through the mixing of two ancestral populations.

LINKAGE DISEQUILIBRIUM MAPPING
Analysing single nucleotide polymorphism alleles in population-based studies to identify loci that are associated with a particular disease or phenotype.

ANCESTRY INFORMATIVE MARKERS
Markers showing marked allele frequency differences between ancestral populations, useful for determining the probable ancestry of an individual.

MELANOCYTE
The specialized cell type, lying at the boundary between the dermis and epidermis, in which the pigment melanin is synthesized.

RANDOM AMPLIFIED POLYMORPHIC DNA
Polymorphic markers generated by using short (8–12 bases long) primers to amplify random fragments of DNA.

MULTIPLE DISPLACEMENT AMPLIFICATION
A method for whole-genome amplification using a highly processive polymerase from bacteriophage ϕ29 and random primers to synthesize long molecules from the template.

DROP-OUT
Absence of one or more alleles in a DNA profile, owing to stochastic failure of PCR amplification when the number of template molecules is small.

handling mail deliberately contaminated with spores of *Bacillus anthracis* and it is the threat of acts of bioterrorism like this, as well as potential attacks on crops and animals, that has led to a surge in interest in the field of forensic microbiology, renamed 'microbial forensics'[81]. Its aim is to develop methods to show that a micro-organism has come from a particular source and DNA analysis will probably have a major role. There are formidable problems in the wide range of possible species that could be encountered, the limited sequence diversity between strains and sub-strains and the lack of universally applicable cross-species methods to detect variation. Microbiologists, epidemiologists and forensic scientists have met to define problems and make recommendations, many of which will be expensive to implement. Although the extent of the bioterrorism threat is unclear, the 2001 attacks showed the major impact that even small-scale incidents can have; also, developments in this area will probably have useful spin-offs in tracing natural disease outbreaks.

Future developments

Forensic genetics will continue to take advantage of technical developments in DNA analysis. A 'sci-fi' vision of a hand-held device (the 'lab on a chip') that would allow rapid DNA profiling at the crime scene is close to realization, with developments in microfabrication of capillary electrophoretic arrays[82]; single integrated platforms that extract, amplify and sequence DNA have already been developed[83], but it will be some time before such devices are validated for forensic use. Methods of whole-genome amplification (in particular, MULTIPLE DISPLACEMENT AMPLIFICATION[84]) have potential forensic value when the amount of template DNA is extremely small. However, allele DROP-OUT and imbalance has been observed with less than 50 picograms of input DNA[85], and further work is needed to determine whether there are any advantages over conventional low copy number typing methods.

One of the most difficult problems facing the forensic biologist is the identification of body fluids. Molecular biological approaches to the identification of blood, semen and saliva stains using analysis of specific mRNAs (which are surprisingly stable) have been described[86] and will probably increase in use and importance.

As our understanding of the genetic basis of disease and differences in the response to drugs increases, it will be increasingly applied to determining the cause of death — 'forensic molecular pathology'. Work has already been done[87,88] on molecular diagnosis of the genetic cardiac arrhythmia long QT syndrome, which can cause sudden unexplained death leaving no trace at autopsy, and also on the post mortem determination of functional copy number of a gene (*CYP2D6*) encoding a drug metabolizing enzyme[89], variation in which can lead to adverse drug effects, including death.

The most important and controversial developments, however, probably lie in the area of DNA databases (BOX 3) and debates on database issues seem set to continue well into the second two decades of forensic DNA analysis.

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Acknowledgements

We thank Alec Jeffreys, Chris Tyler-Smith and four anonymous reviewers for helpful comments on the manuscript. We apologize to colleagues whose work we were unable to cite owing to space restrictions. M.A.J. is supported by a Wellcome Trust Senior Fellowship in Basic Biomedical Science.

Competing interests statement

The authors declare no competing financial interests.

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