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Scientific standards for studies in forensic genetics

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Abstract

Forensic molecular genetics has evolved from a rapidly developing field with changing technologies into a highly recognized and generally accepted forensic science, leading to the establishment of national DNA databases with DNA profiles from suspects and convicted offenders. DNA evidence has taken a central role by carrying a significant weight for convictions, as well as by excluding innocent suspects early on in a criminal investigation. Due to this impact on the criminal justice system, guidelines for research in forensic genetics have been introduced already since many years. The most important issues regarding the selection and definition of typing systems both for paternity testing and for forensic identification, the criteria for technical and biostatistical validation, as well as the use of mitochondrial DNA analysis are summarized and discussed.

Keywords: PCR; Forensic DNA typing; Short tandem repeat (STR); mtDNA; Population genetics; Quality assurance

1. Introduction

Modern DNA-based forensic genetics comprise a number of important applications. Examples are the investigation of biological stains to obtain evidence for the presence of an alleged perpetrator at the crime scene by comparing the genetic profiles from crime scene samples of human origin to those of potential stain donors, the identification of unknown corpses in the context both of natural death and of crime or mass disaster, as well as the investigation of family relationships.

In the last 20 years, forensic molecular genetics has evolved from a rapidly developing field with changing technologies into a highly recognized and generally accepted forensic science, leading to the establishment of national DNA databases with DNA profiles from suspects and convicted offenders [1–4]. The methodology has become quite reliable and the analytical equipment has reached a high level of automation. The genetic typing systems are standardized based on generally accepted recommendations from scientific bodies such as the National Research Council (NRC) of the Academy of Sciences of the United States, and the International Society for Forensic Genetics (ISFG). At a very early stage, the ISFG has recognized the potential significance of DNA-based typing methods for the entire field of criminal investigation and paternity testing, and has addressed relevant topics initially regarding the introduction of hybridization-based single and multi-locus minisatellite probes [5,6], and very soon as well on PCR-based typing systems [7,8].

DNA evidence has taken a central role by carrying a significant weight for convictions in the court of justice, as well as by excluding innocent suspects early on in a criminal investigation. A typical and highly publicized crime case involving the rape and murder of two girls clearly demonstrated this capacity, and was the first example for carrying out a mass screening among a defined subgroup of the male population to identify the true perpetrator [9,10]. In contrast to other fields of applied research where quality problems leading to genotyping errors are being discussed only recently [11], the consequences of error in the forensic field carry a heavy burden on all scientific studies, as these may end up as a basis for a ruling on the admissibility, or for analysing and interpreting evidence in a crime case. In this regard, the guidelines developed for forensic genetics may serve as a model system for establishing and assessing the quality of research also for other fields of molecular genotyping studies [12]. To provide an overview about the standards for applied research in forensic genetics, typical areas relevant for scientific studies will be subsequently addressed.

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2. Paternity testing

Genetic studies on family relationships are pivotal to any application of DNA markers as they serve to establish and validate new typing technologies and genetic systems. Typically, family trios with confirmed genetic relationship using a reference method and from a homogeneous population are selected for study. The results of such validation studies are relevant both for paternity testing and for forensic identification.

2.1. Definition of systems and alleles

Following the initial ISFG guidelines [5,6], a new genetic typing system is defined by "a segment of unique DNA sequence" occupying a specific chromosomal position, and by the "unique identification of complementary primer sequences". Furthermore, the alleles of a system are defined by "DNA fragments of variable length agreeing with a formal genetic model". This model should be Mendelian inheritance which is applicable for all DNA typing systems, notwithstanding the possible occurrence of "silent" alleles [13] which can be formally handled following the example of classical blood group markers such as the ABO system. Furthermore, chromosomal linkage data to other systems should be known to consider the possible relevance of haplotype information.

2.2. Standardization requirements

Appropriate size markers with discrete sizes flanking and spanning the entire range to be analyzed are necessary for determining the length of allelic DNA fragments. For the currently used PCR-based short tandem repeat (STR) systems, allelic ladders comprising a complete range of the commonly observed allelic fragments have to be included in each analysis [7,8]. Specific guidelines have been established regarding the nomenclature of STR alleles [14,15]. They are based on the agreement that only denaturing gel systems shall be used for electrophoretic separation of DNA fragments. Thus, only the molecular weight of a fragment (i.e. the size in basepairs) is relevant but not a variation within the DNA sequence, which would become visible using a non-denaturing gel system due to sequence-based secondary structures within the variant alleles [16]. Allele designations are based on the number of variable repeats. These are derived from the coding DNA sequence information in the human genome database, e.g. the GenBank, or, if missing, based on the first original description in the literature. In some cases, this has led to confusion in particular for X- und Y-chromosomal STR systems which had to be resolved by exchange of samples [17,18]. Specific issues regarding Y-STRs have also been addressed by the DNA Commission [19,20]. A useful tool in this context are reference DNA samples such as generally available cell lines with known genotypes, as these can be used to standardize typing systems and allelelic ladders for population studies [21]. This is particularly relevant since it is recommended to include a known human control DNA sample in each experiment. An additional approach is the provision of reference DNA samples available from public institutions such as the National Institute of Standards and Technology (NIST) offering traceable standard reference materials for PCR typing [22].

2.3. System validation studies

To establish the relevant genetic parameters such as Mendelian inheritance, mutation rates and allele frequencies, at least 500 meioses should be studied using a standardized approach [7,8]. It can be expected that mutation rates for autosomal STRs are in the range of 0.1–0.5%, and that paternal mutations exceed maternal mutations [23]. For the Y-chromosomal systems, similar mutation rates have been obtained [24]. By counting the parental genotypes from family trios, allele frequencies can be established provided that the families have been randomly selected from a representative and homogeneous population (see also below). Under these conditions, observed and expected genotype frequencies based on the assumption of Hardy–Weinberg equilibrium (HWE) have to be compared using adequate statistical tests [25]. In any case, it is recommended to apply an exact test [26] rather than the less accurate chi-square test which may be misleading when rare alleles are found in a population sample. It has to be kept in mind, however, that a deviation from HWE may be more indicative for a technical problem in the typing procedure rather than for a non-representative population sample. If a significant excess of homozygous genotypes is observed, a critical assessment of allele detection procedures and electrophoretic conditions should be made, as these may have been a cause for a loss of DNA fragments outside the detection range, or due to poor electrophoretic resolution.

If multiple systems are validated such as multiplex STR kits, the results from the population studies have to be corrected for multiple testing, and the independence of loci has to be demonstrated, e.g. using a modification of the exact test [27,28]. Although slight deviations will occasionally be observed for individual loci, this is normally not critical, as the chromosomal locations of the tested systems are known and not closely linked. Another typical source for such deviations are small population sample sizes of less than 500 individuals. Testing at least 500 meioses implies that 250 family trios have to be tested comprising 250 unrelated male and female individuals with a total number of 1000 alleles. From the scientific literature it becomes evident that not all published studies fulfill this requirement, mostly for practical reasons of obtaining a sufficient number of validated family trios. Therefore, data from such studies may have to be treated with caution. It should also be noted that it is highly desirable to have access to the original genotype data (or haplotype data, respectively, in the case of Y-chromosomal markers) in addition to the normally published allele frequencies. Nowadays, using online publication resources, such data can easily be made available as supplementary data for downloading from the journal's website.

3. Forensic identity testing

The criteria described above also apply for research on typing systems designed for identity testing. However, there are further issues to be considered due to the nature of the application. Identity testing involves a direct comparison of somatic cell samples (e.g. from a blood stain) with a reference samples from a suspect (e.g. a buccal swab). Furthermore, biological stains are not found in a defined environment such as a laboratory, so that other sources of human or nun-human DNA may be intermixed with an evidence sample. Finally, the statistical interpretation has to consider different circumstances related to the population-of-origin of an alleged or unknown perpetrator.

3.1. System validation for identity testing

The direct comparison of somatic cells requires that the genetic loci exhibit a sufficient somatic stability. Under normal conditions in a healthy individual, this is not critical. There may be instances where microsatellites are prone to spontaneous mutations, e.g. if cells become malignant and proliferate to tumor tissue leading to genetic instabilities as well as loss of heterozygosity [29]. This is particularly relevant if clinical specimen are used as reference samples. A critical aspect is a potential crossreaction of hybridization probes or primers with non-human DNA samples. There is clear evidence that most PCR primers designed for human identity typing will crossreact with primate DNA [30]. This scenario is normally not problematic in casework samples, in contrast, it may actually be quite helpful for research to resolve nomenclature issues [31]. Generally, it has to be ascertained that DNA from other mammals does not mimick alleles of a human STR profile.

Furthermore, performance testing of typing systems under evaluation must include extensive sensitivity and reproducibility studies using both intact high molecular weight as well as degraded human DNA [32–34]. If DNA samples are tested in the dilution range below 200 pg, PCR amplification will lead to stochastic effects such as allelic drop out and drop in. This effect is further influenced by the size of the target sequence to be amplified as well by degradation of template DNA [34,35] due to environmental exposure (heat, light, humidity, bacterial and fungal growth).

3.2. Population genetics

The inherent problems of appropriately defining and validating ‘‘populations’’ or ‘‘ethnic groups’’ for forensic identification are obvious. If the genotype of a suspect matches the DNA profile of the evidence, there is still the possibility that this match has occurred by chance (the ‘‘random man not excluded’’), or that the true perpetrator does not come from the same population as the suspect. Match probabilities or likelihood ratios are based on assumptions about the ethnic origin of the suspect or an unknown perpetrator. Therefore, such populations have to be defined in a socio-anthropological context to be able to carry out research studies on allele frequency distributions. These difficulties were brought to light by the vigorous discussions about the definition of ethnic groups and the speculations about the existence of subgroups within populations. It was postulated that genotype frequencies could be more distinct between ethnic subgroups of the same major population than between the other major populations [36,37]. The debate has stimulated world-wide collaborative efforts to collect more population data on the currently used typing systems, and has led to recommendations by the NRC which are now widely accepted [38,39]. The assumption that such subgroups may invalidate samples population data has been dismissed, and a correction factor Θ (theta) [39] or F_{st} [40] has been introduced for population data where the existence of subgroups (or inbreeding) cannot be excluded. Nevertheless this does not relieve any scientist from the burden of carefully planning and selecting samples for population genetic validation studies [41].

4. Laboratory requirements and quality assurance

The demand for rigorous quality control for all laboratories handling routine casework resulted from the obvious lack of standards and failures to present conclusive evidence in the early days of forensic DNA analysis [42,43], and has been a major element in all recommendations from scientific bodies [7,39]. The internal organisation of a forensic research laboratory has to fulfill the same criteria as a laboratory for routine casework. Due to the high sensitivity of PCR-based typing systems, contamination prevention is the most important requirement. This includes the introduction of dedicated work areas and complete physical separation of pre- and post-PCR processes. Ideally, three separate work areas with dedicated equipment should be available for DNA extraction, PCR setup, and handling and analysis of amplified PCR products. All analyses should include a positive control from a known DNA sample [21], as well as a negative extraction control without DNA, and a PCR reagent contamination control with water instead of DNA. Furthermore, traceability of samples and reagents by proper internal documentation helps to identify sources of contamination or failure.

In addition to internal quality assurance, the participation in external proficiency testing exercises is the second major element to obtain the necessary competence both for carrying out research as well as for routine casework. There are numerous proficiency trial schemes for DNA laboratories both for paternity analysis [44,45] as well as for forensic identity testing [46,47]. In addition to offering a certificate about the competence of the participating laboratory to obtain correct typing results, such exercises also provide insights into potential sources of errors, both of human and technical origin. These may help to educate the participants and offer support to develop strategies for avoiding these errors in their future work. For routine casework laboratories, only rigorous quality assurance as well as accreditation according to internationally accepted standards will become a prerequisite for accepting casework samples [48,49]. However, accreditation cannot be extended to research laboratories. It would be too

restrictive, as it prevents the development and testing of new strategies and innovative protocols.

5. Considerations on mitochondrial DNA research

Sequence analysis of the mitochondrial DNA-loop hypervariable regions is the focal point of an ongoing discussion about quality control in forensic genetics. In forensic applications, analysis of mtDNA is suitable to obtain results even from hair shafts and aged compact bones [50,51]. Furthermore, it provides anthropological information about the maternal lineage of mtDNA haplogroups [52]. The effort to validate mtDNA sequence analysis has produced recommendations about their use and guidelines for their interpretation in the forensic context [53,54]. In recent years, databases of mitochondrial DNA sequences have been compiled for an assessment of the distribution and frequencies of mtDNA HV-I and HV-II sequences. A major setback occurred when it was discovered mostly by phylogenetic comparisons that numerous publications and database collections contain erroneous data [55,56]. These errors mainly originated from mishandling of data, and by misreading DNA sequences due to a lack of understanding of possible artefacts caused by the sequencing enzymes and reagents [57]. It has led to a situation where it appears almost impossible to generate fully validated results without the help of experts and expert systems specialized for cross-checking all data. Nevertheless, a set of rules has been proposed recently which may help to avoid most of these pitfalls [58]. These include the following elements: (a) correct sample labelling and handling, preferably using bar-coded samples and robotic equipment (if large numbers of samples have to be sequenced), (b) proper contamination prevention and control [53], (c) overlapping DNA sequencing of both strands [59], (d) optimizing sequencing chemistry to reduce background noise leading to erroneous intepretations, (e) automatic software-assisted basecalling including quality values, which must be accompanied by a thorough visual inspection of sequence traces, and, finally, (f) either automated generation of data tables from confirmed sequence traces, or two independent manual tabulations from two persons which can be compared. A final check is performed by phylogenetic analysis [57]. It is obvious that it will take time building meaningful forensic population databases but there is not alternative to this approach [60].

6. Conclusions

As the field of forensic genetics is an applied science in the best sense with an extremely important impact on the society by providing reliable evidence both for exonerating the innocent and for convicting the perpetrator, quality standards for research cannot be separated from the application of its results in casework. At present, a robust system for forensic DNA typing has been established due to the successful collaborative efforts of the international scientific community, and new typing systems such as the analysis of single nucleotide polymorphisms are under evaluation [61]. These new technologies and systems need to be developed according to the same scientific standards established for the currently used systems. In addition, forensic geneticists should be aware about the ethical and legal consequences of their research on the society and the criminal justice system [62–64]. New technologies will only be accepted by the society if the scientists can demonstrate that their research is based on sound and reliable principles. Therefore, it is important to demonstrate that such standards exist and are generally accepted.

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