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Effect of Reference Database on Frequency Estimates of Polymerase Chain Reaction (PCR)-Based DNA Profiles*

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ABSTRACT: A variety of general, regional, ancestral and ethnic databases is available for the polymerase chain reaction (PCR)-based loci LDLR, GYPA, HBGG, D7S8, Gc, DQA1, and D1S80. Generally, we observed greater differences in frequency estimations of DNA profiles between racial groups than between ethnic or geographic subgroups. Analysis revealed few forensically significant differences within ethnic subgroups, particularly within general United States groups, and multi-locus frequency estimates typically differ by less than a factor of ten. Using a database different from the one to which a target profile belongs tends to overestimate rarity. Implementation of the general correction of homozygote frequencies for a population substructure, advised by the 1996 National Research Council report, *The Evaluation of Forensic DNA Evidence,* has a minimal effect on profile frequencies. Even when it is known that both the suspect and all possible perpetrators must belong to the same isolated population, the special correction for inbreeding, which was proposed by the 1996 National Research Council report for this special case, has a relatively modest effect, typically a factor of two or less for 1% inbreeding. The effect becomes more substantial (exceeding a factor of ten) for inbreeding of 3% or more in multi-locus profiles rarer than about one in a million.

KEYWORDS: forensic science, polymerase chain reaction, DQA1, LDLR, GYPA, HBGG, D758 EC, population databases, frequency estimation, population genetics

When the results of DNA identity testing fail to exclude a defendant as a possible contributor of biological evidence, the trier of fact is aided by an estimate of the statistical significance of the match. The chance of obtaining a match from another, randomly chosen, individual is derived by multiplicatively combining the frequencies of the alleles constituting the DNA profile. Allele frequencies are estimated from reference databases consisting of profiles of unrelated individuals (1).

Forensic scientists, the courts, and defendants share the concern that such estimates not substantially underestimate the frequency of occurrence of DNA profiles and therefore place undue bias against a defendant. When objections to the aptness of estimates have been posited, they have usually been on the grounds that the reference databases were not representative, and that subgroup databases would yield substantially different estimates of the rarity of a profile. For restriction fragment length polymorphism (RFLP) loci, ethnic or geographic subdivision within the major population groups has been shown to have little effect on forensic estimates of the likelihood of profile occurrence. This conclusion derives from the conservatism of defining alleles by fixed bins (2–4), availability of an extensive collection of databases (5–7), empirical frequency estimation of profiles in major groups and subgroups to which they do not belong (6–9), and evaluation of the minor contribution of inbreeding (8,10).

DNA typing based on the polymerase chain reaction (PCR) offers advantages of increased sensitivity of detection and the ability to type DNA that has degraded beyond the point of utility of the RFLP method. Further, allelic data that are more discrete can be obtained for PCR-based loci than is possible with variable number of tandem repeats (VNTRs) typed by RFLP analysis. Although loci with fewer and better-defined alleles are easier to size accurately, they are less polymorphic, and the question of the consequences of misassignment to a population subgroup, or to a major group, should be revisited.

Based on extensive published data, the 1996 National Research Council (NRC) report on DNA testing (8) opined and recommended that for RFLP systems, profile frequency estimates in a database of adequate size are correct within a factor of about ten in either direction (using the product rule and $2p$ for single-band phenotypes, where p is allele frequency). This rule of thumb compensates for uncertainties arising from genetic or mathematical assumptions, from inadequate database size, or that a particular person belongs to a subgroup with frequencies differing from those of the population average. For PCR-based loci, the 1996 NRC report (8) suggested compensating the homozygote genotype frequency for substructure effects by a parameter θ, analogous to the inbreeding coefficient (equation numbering is that of the report)

$$P_{ii} = p_i^2 + p_i(1 - p_i)\theta_{ii} \qquad (4.4a)$$

If substructure is a significant factor, heterozygote genotype frequencies will generally be overestimated, therefore a corresponding correction is not used. The report suggested a value of 0.01 for θ, or possibly 0.03 if limited data are available. Budowle (11) showed that values of θ for African Americans, Asians, and U.S. Caucasians for the PCR-based loci HLA-DQA1 (12), LDLR (13), GYPA (14), HBGG (15), D7S8 (16), and Gc (17) are on average well below 0.01. Thus, a θ value of 0.01 is generally a conservative upper bound.

In the unusual situation where it is known that all possible persons contributing to the evidentiary sample as well as the suspect belong to the same subgroup, the NRC report (8) proffers formulas

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which further augment the frequency estimates, after Balding and Nichols (18,19) (equation numbering is that of the report)

Homozygotes:

$$P(A_iA_i/A_iA_i) = \frac{[2\theta + (1-\theta)p_i][3\theta + (1-\theta)p_i]}{(1+\theta)(1+2\theta)} \quad (4.10a)$$

Heterozygotes:

$$P(A_iA_j/A_iA_j) = \frac{2[\theta + (1-\theta)p_i][\theta + (1-\theta)p_j]}{(1+\theta)(1+2\theta)} \quad (4.10b)$$

In this paper, we explore the consequences on profile frequency estimates of group or subgroup misassignment and the forensic significance of using various reference databases for several PCR-based loci whose alleles differ by variation in their nucleotide sequence: HLA-DQA1, LDLR, GYPA, HBGG, D7S8, and Gc. The latter five loci compose the AmpliType PM® DNA Test System (Perkin-Elmer Corporation, Norwalk, CT) (20). We also include the PCR-based locus D1S80, a VNTR whose amplicons are separated by electrophoresis based on size (21,22).

Materials and Methods

Sources of Data

Databases used in this study originate from a variety of sources. General U.S. groups are represented by the databases designated FBI African-Americans, FBI Caucasians, FBI Southeast (SE) Hispanics, and FBI Southwest (SW) Hispanics. These databases show no departures from Hardy-Weinberg expectations and scant evidence for inter-locus associations (22,23). Additional general, regional, and ethnic reference databases or samples (the latter subsequently analyzed in our laboratory and designated ''by FBI'' below) derive from published sources and our research collaborators: Alabama African-American and Caucasian (G. S. Rogers, Alabama Department of Forensic Sciences, Birmingham); Australian Aborigine (J. Kuhl, Darwin, Northern Territory); Chilean (H. Jorquera, Servicio Medico Legal, Ministerio de Justicia); Detroit Hispanic (M. Scarpetta, Detroit Police Department); Dubai, U.A.E. Arab (24); French Antilles (C. Doutremepuich, Université Bordeaux, France; by FBI); Haitian (R. Wenk, Baltimore Red Cross; by FBI); Hungarian (25); Illinois Caucasian (E. Benzinger, Illinois State Police Crime Lab, Springfield); Israeli (N. Gallili, Israeli Police; by FBI); Japanese (R. Reynolds, Roche Molecular Systems, Alameda CA); Korean (26); Mexican (A. L. Vasquez, Dirección General de Servicios Periciales, Mexico City); Navajo, Pueblo and Sioux (27); Nevada African-American (R. Romero, Washoe County Sheriff's Office, Reno); North Slope Borough (NSB) Alaskan (28); Northern and Southern Croatian (29); Palestine Arab (30); Roche Hispanic (R. Reynolds, Roche Molecular Systems, Alameda CA); Spanish Basque (31); Swiss (32); and Vietnamese (J. Hartmann, Orange County Sheriff's-Coroner Department, Santa Ana, CA; by FBI). All target profiles used in this study derive from unrelated individuals and consist of seven PCR loci: D1S80, DQA1, and AmpliType PM® system (5 loci).

Calculation of Target Profile Frequencies

We wrote a computer program (''PCRFreq'') which calculates frequencies for every profile in a database chosen by the user, termed ''target'' profiles. A ''reference'' database, in which the frequency of each target profile is to be calculated, is also selected. The reference database may consist either of a list of individual profiles or a table of allele frequencies. If the target and reference databases are the same, each target record is temporarily removed from the reference database during the calculation of that particular target profile frequency. Doing so avoids an artifactual increase in multiple locus profile frequency that is problematic in small databases (33). Although analytical approaches based on locus heterozygosity or sample size or both can be used to derive minimum allele frequencies to compensate for sparse sampling (34), in this study a minimum value of 0.01 was used. Individual locus frequencies were evaluated as p^2 for homozygotes (that is, uncorrected for substructure) and $2pq$ for heterozygotes (where p and q are allele frequencies), which were in turn multiplied together to produce multi-locus profile frequencies. Additional comparisons examined the effect of inbreeding on profile frequency estimations. For this purpose, corrections for presumed inbreeding of 1% and 3% ($\theta = 0.01$ and 0.03) were imposed on homozygote genotypes using either Eq 4.4*a* or on all genotypes using formulas 4.10*a* and 4.10*b* given in the first section.

Assessing Forensic Significance of Reference Database Choice

Logarithmic scatter plots, where the inverse frequency (probability of occurrence) evaluated for each target profile in its source database of the remaining target profiles (ordinate) is plotted against that in a different reference database (abscissa), provide one way of exploring the consequences of using a different database. Points close to the diagonal show negligible difference between databases. Points above and below the diagonal reveal instances where the estimate is rarer in the source database or in the different database, respectively (Fig. 1).

A difference exceeding a factor of ten between multiple locus probability estimates, particularly when the probability is more common than one in 10^5 or one in 10^6, has been deemed forensically significant in previous studies (6–8). Scrutinizing the times these conditions are met in different comparisons, and whether it is the similar or different database that produces the lower frequency estimate, is therefore informative.

Results and Discussion

As with RFLP markers (6–9), profile frequencies estimated from a geographic or ethnic subgroup database are usually within a factor of ten of those derived from the associated general U.S. group, indeed without an inbreeding correction (Fig. 1). Thus, differences are generally negligible between: (1) SE Hispanics and other general Hispanic groups from Detroit and Roche (Fig. 1), general Caucasians, or Caucasians from Alabama (data not shown); (2) SW Hispanics and samplings from Detroit, Chile or Mexico (Fig. 1), or another general Hispanic group (''Roche'' data not shown); (3) general African-Americans and samplings from Nevada, Haiti, and French Antilles (Fig. 1) or Alabama (data not shown); (4) general Caucasian-Americans and subgroups from Illinois, Northern Croatia, Hungary (Fig. 1) or from Alabama, Basque Spain, Israel, Southern Croatia or Switzerland (data not shown). Furthermore, in the very small percentage of target profiles for which the profile frequency differences in an associated general group exceed a factor of ten, they are usually rarer in the different database or occur in estimates less than one in 10^5 or one in 10^6. Examples illustrated in Fig. 1 include the comparisons: SW Hispanics versus Mexico (two profiles out of 96 below the lower ''$10\times$'' line); SW Hispanics versus SE Hispanics (six out of 96 below); Chinese versus Korean (out of 105, two below and one above the upper

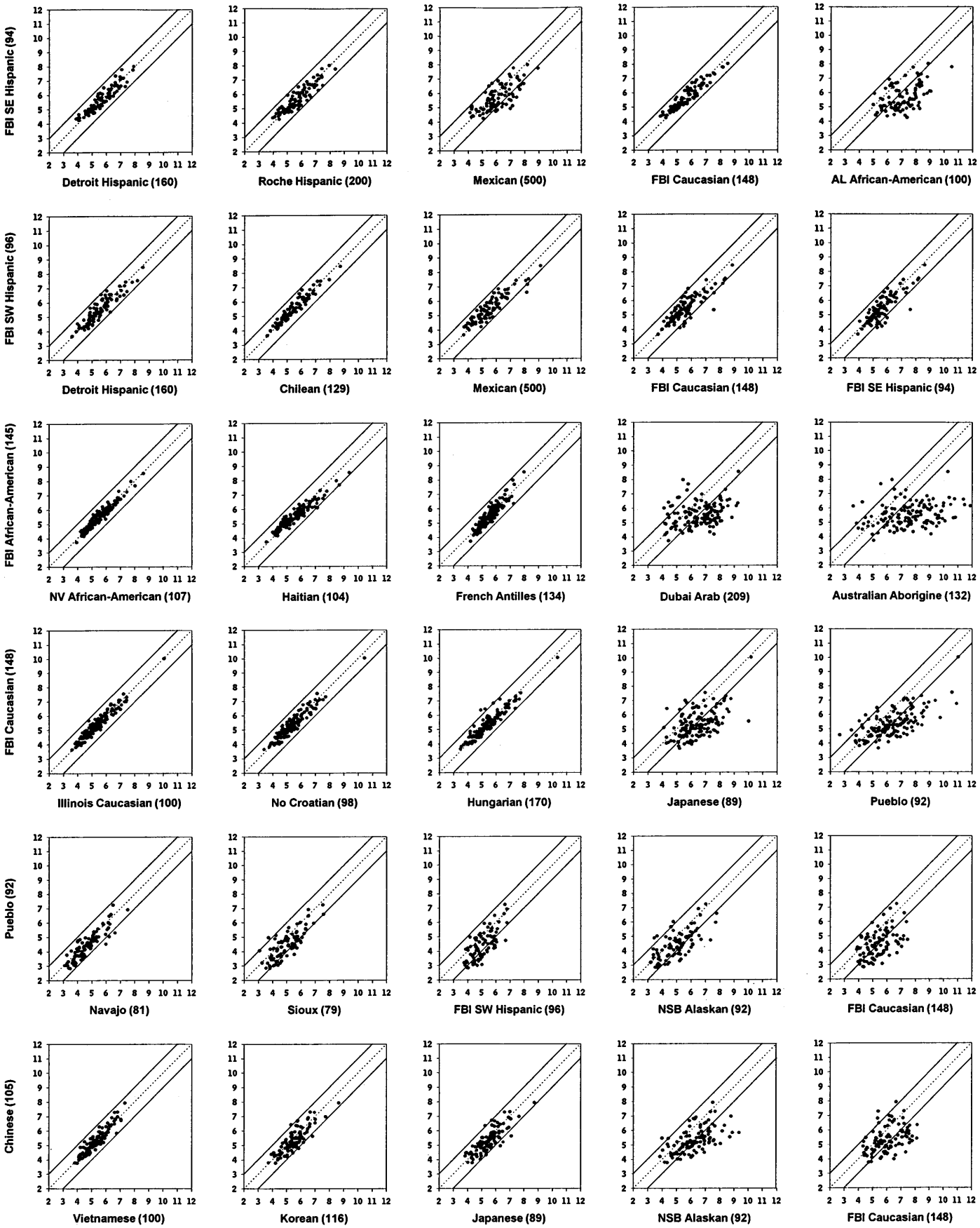

FIG. 1—*Logarithms of multi-locus frequency evaluations for target profiles estimated within their own group (ordinate) and within another group (abscissa). All target databases consist of complete profiles at the seven PCR-based loci LDLR, GYPA, HBGG, D7S8, Gc, DQA1, and D1S80. Numbers of unrelated individuals in each database are in parentheses. Solid diagonals bracket a factor of ten above and below the dotted line of identity.*

TABLE 1—*A Caucasian profile much rarer among Caucasians.*

	LDLR	GYPA	HBGG	D7S8	GC	DQA1	D1S80	Composite Frequency
	AB	AB	CC	AB	BC	1.1,3	22,34	
FBI Caucasian	0.5	0.5	5×10^{-5}	0.5	0.2	0.05	8×10^{-4}	10^{-10}
FBI African-American	0.4	0.5	9×10^{-2}	0.5	0.3	0.02	2×10^{-2}	10^{-6}

10× line, with a 13.5 ratio); Chinese versus Japanese (out of 105, four below and one above, with a ratio of 12.6); Pueblo versus Navajo (three out of 92 below).

Although the two databases are not greatly divergent, the estimation of general Caucasian profiles in the Hungarian database is illustrative in that it discloses three exceptions out of 148 to the foregoing observation that frequency estimates tend to be similar, if not more conservative, in the same group compared with a different group. For these three profiles, estimates are more conservative in the Hungarian database by factors of 10.5, 16.0, and 27.6. The profiles producing the latter two ratios are both homozygous for the 1.3 allele at locus DQA1. The frequency of the DQA1, 1.3 allele in our sampling of 190 Hungarians is higher compared with other Caucasian databases, for example, 0.131 compared with 0.041 in the FBI Caucasians. The frequency of the 1.3 homozygous genotype at this locus alone then contributes a factor of 10.2 to the observed difference. DQA1 allele frequencies are particularly variable both within and across groups. An exemplary range of DQA1, 1.3 allele frequency measurements includes: Pueblos, 0.016; Dubai Arabs, 0.055; Northern Croatians, 0.057; Swiss, 0.095; Koreans, 0.116; Palestinian Arabs, 0.165; Australian Aborigines, 0.280. These exceptions illustrate that the calculations can be inaccurate at some candidate loci (particularly DQA1) for a person who belongs to a particular group in which the frequencies differ from the general group (8). However, differences in allele frequencies among subgroups cancel on average over multiple loci (35,36).

Deviations between profile frequencies estimated in another major group exceed those derived from the group to which the profile belongs, in accord with previous conclusions drawn from data on RFLP systems (1,4–8,33,35,36). Progressive divergence in frequency estimates is shown by comparisons of Chinese to FBI Caucasians and to North Slope Alaskans; of SE Hispanics to Alabama African-Americans; of FBI Caucasians to Japanese; of FBI African-Americans to Dubai Arabs. The greatest divergences illustrated are the estimations of FBI Caucasians in the Pueblo group and of FBI African-Americans in a group of Australian Aborigines.

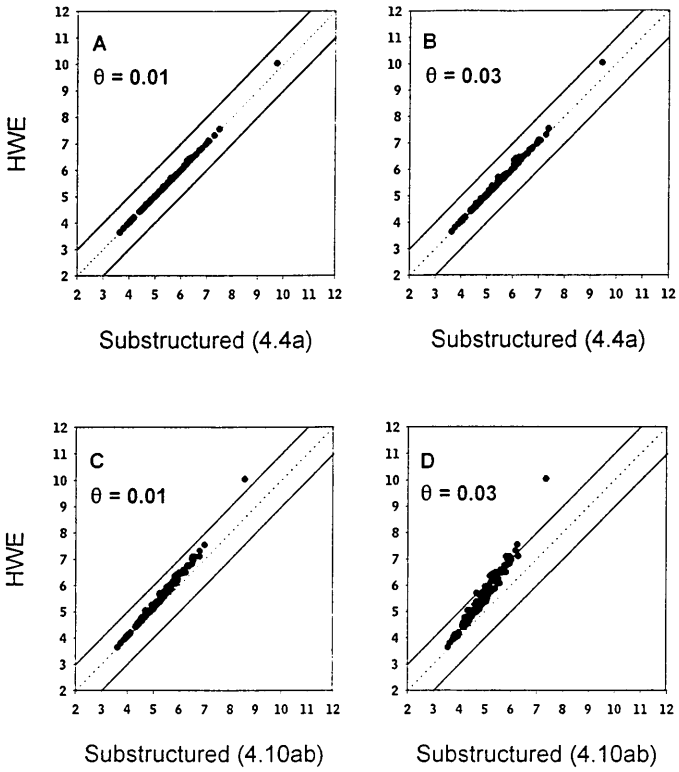

FIG. 2—*Effect of correction to multi-locus frequency estimates based on Hardy-Weinberg expectations (HWE) for presumed extents of substructure in the FBI Caucasian population (*N = *148). Calculations performed using Eq 4.4*a *in the text and inbreeding coefficients of* θ = *0.01 (A) and* θ = *0.03 (B) and for the case where suspect and perpetrator are assumed to belong to the same subgroup (Eqs 4.10a and 4.10b), also with inbreeding coefficients of* θ = *0.01 (C) and* θ = *0.03 (D). (Note that empirical estimates of substructure in this population are in the range of 0.0015 to 0.0034) (11).*

However, the range of frequencies estimated for FBI Caucasian target profiles in a Pueblo reference database is much wider than when Pueblo profiles are estimated in the FBI Caucasian database (Fig. 1). Since the Pueblo group is less polymorphic than the FBI Caucasians, certain alleles occurring among Caucasians will be exceedingly rare or absent entirely among Pueblos; thus the scattergram extends very far to the right, to about one in 10^{11}. On the other hand, all the alleles occurring in the Pueblo group are well represented in the more polymorphic Caucasians, so that no estimate is rarer than one in 10^{8}. In either case, however, frequency estimates still tend to be higher (more common) in the group to which the profiles belong.

Occasionally a profile may be rarer in the target group to which it belongs than in another group (although the possibility of misassignment to a group, either of the person being typed or during the generation of a population database, cannot be excluded). The FBI Caucasian database provides such an example: a profile with a frequency of approximately one in 10^{10}, visible in Fig. 1, in comparison to other Caucasians, Japanese and Pueblos. Yet that profile is more common in the FBI African-American database by four orders of magnitude, attributable mainly to the far greater prevalence of the CC genotype at the HBGG locus and of allele 34 at the D1S80 locus (Table 1).

Figure 2 illustrates that for the FBI Caucasian population, implementation of the simple correction to homozygote frequencies for population substructure advised by the 1996 NRC report (Eq 4.4*a*),

has a barely noticeable effect on profile frequencies, even for presumed extensive inbreeding of 3% (the empirically estimated extent of inbreeding in this population is 0.0015 to 0.0034 over all loci) (11). The special correction for inbreeding (Eqs 4.10*a* and 4.10*b*), recommended by the 1996 NRC report for use only when there is evidence that all possible perpetrators could only come from a single isolated population (8), has a somewhat greater effect. In that case, the correction is typically a factor of two or less for 1% inbreeding, becoming significant (exceeding a factor of ten) only for inbreeding of 3% or more and in multi-locus profiles rarer than about one in a million.

Conclusions

Conclusions drawn from frequency estimations of the PCR-based markers LDLR, GYPA, HBGG, D7S8, Gc, DQA1, and D1S80 parallel those previously articulated for RFLP systems (4,6–9,36). A variety of databases is available. Generally, we observed greater differences between racial groups than between associated groups. Analysis revealed few forensically significant differences between ethnic subgroups and their related general U.S. groups, and estimated multi-locus frequencies typically differ by less than a factor of ten. In general, using a database different from the one to which a target profile belongs tends to overestimate rarity. Of the PCR loci examined, DQA1 allele frequencies are often particularly variable both within and across groups (although differences in allele frequencies among subgroups tend to cancel out on average over multiple loci). Implementation of the simple correction to homozygote frequencies for population substructure advised by the 1996 NRC report (8) has a barely noticeable effect on multi-locus profile frequencies. Even when it is known that both the suspect and all possible perpetrators must belong to the same isolated population, the correction for inbreeding which was proposed by the 1996 NRC report for this special case has a relatively modest effect, typically a factor of two or less for 1% inbreeding. The effect becomes more pronounced (exceeding a factor of ten) only for inbreeding of 3% or more in multi-locus profiles rarer than about one in a million.

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