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CPI Distribution and Cutoff Values for Duo Kinship Testing

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Abstract

DNA-based tests commonly use 13 STR (short tandem repeat) loci in human identification and paternity testing – the Combined DNA Index System or CODIS. Its average degree of accuracy of paternity identification is greater than 0.9999 under the circumstance of a mother, a child and a putative father. However, the possibility of false inclusions increases under circumstances such as [1] only two members of a family group are available – a duo case during determination of paternity or [2] identification of human remains while only one living relative is present.

In Taiwan, the National Unidentified Human Remains Database uses the CODIS 13 STR for the identification of family members. Two or more reference samples in the DNA database have been found to share one allele at all loci tested. Then the Combined Paternity Index (CPI) is used to determine and provide an estimate of kinship in such cases. Combining 499,500 sets of DNA data for the 13 STR CODIS loci, totally 431 (0.086%) cases are false inclusions where all 13 loci shared at least one allele. Simulated partial DNA profiles (not all 13 loci yielded results) were created to mimic the mutation and degradation process. All 431 real duo cases were analyzed to evaluate sensitivity and specificity. This report provided four kinship-matching situations with CPI cutoff values when the number of allele-sharing loci exceeded 11. CPI values greater or lesser than the suggested cutoff point will provide a greater degree of confidence in determining whether two samples are derived from first-degree relatives.

Key Words: forensic science, short tandem repeat (STRs), paternity, false inclusion duo, sensitivity, specificity

Introduction

The Combined DNA Index System (CODIS), originally established by the FBI in 1998, is composed of 13 autosomal short tandem repeat (STR) loci in addition to a sexual (gender) identity test (6). These loci have become the standard examination for human identification and paternity testing in many countries throughout the world. The 13 STR loci used within the CODIS have an average power of paternity exclusion greater than 0.9999 for most populations based upon mother, child and father combinations, a paternity trio case (2, 9). A duo paternity case is defined as the availability of only two sets of genetic relatives, such as one parent and one offspring. Such duo cases occur in paternity testings, *e.g.* either when the mother is unavailable to provide a sample, or in cases of identification of human remains by linking its DNA to a living relative only. In such

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duo cases, if allele sharing is found in all of the 13 loci, the probability of parentage, known as the Combined Paternity Index (CPI), is calculated. Even if high CPI values were obtained, there would still be a chance that two unrelated people might share one allele at all 13 CODIS loci resulting in a false inclusion (1, 3). In Taiwan, the CODIS 13 STRs used during determination of kinship (first-degree) match the National Unidentified Human Remains Database. There have been instances where a DNA profile matched an unrelated individual along with a known member of the family on this reference database. False inclusions such as this have been found in previous studies (4, 5, 8, 10). If fewer than 13 CODIS loci are used, then the chances of a false inclusion will increase. Fewer loci are generated if less than the optimal amount of DNA is present, such as in degraded samples. Such a situation occurs commonly in the isolation of DNA from human skeletal remains.

At any single locus the Paternity Index (PI) can be calculated between two samples that share at least one allele. The PI for each locus tested can be multiplied to generate the combined paternity index (CPI), thus increasing the odds in favor of the person being a parent of a child compared to other unrelated individuals. The probability of paternity can be determined from the CPI by a standard method[1]. For many laboratories, a minimal CPI value is used; increased values indicate a high degree of confidence that the samples tested are genetically linked as first degree relatives and not that of a false inclusion.

In a recent study conducted by 34 laboratories for the American Association of Blood Banks (AABB), the minimum CPI value that was required for determining a Mother not Tested (MNT) case, which is the same as a duo case, varied from "Whatever is obtained" (2 of the 34) to 10,000 (1 of the 34). In 23 laboratories, the minimal CPI value was 100[2]. The choice of an appropriate minimal CPI value will affect the sensitivity (the-rate of false negatives) and specificity (the-rate of false positives) of the DNA test. There is an inverse relationship between these two measures: When cutoffs were set, their capabilities can be adjusted, but capability to improve one was increased, the capability of the other would decrease (7). We report on a study to determine a CPI value that can be used in duo paternity cases that will minimize the occurrence of a false inclusion and yet not exclude real first degree relatives.

Materials and Methods

From January 2003 to December 2005, 431 real paternity cases provided by the Science and Technical Research Center for the Investigation Bureau of the Ministry of Justice, Taiwan were analyzed. The CPI use of the CODIS 13 STR from real paternity duo cases was determined by a standard formula (please see footnote 2 in page 3).

To simulate degraded DNA, either one or two loci from the 13 loci were erased randomly to create 12 loci and 11 loci matches, respectively. To simulate mutational events duo pairs matching, all 13 loci were used and a non-match was created at one locus. This resulted in a match at 12 loci and 1 mutation at the 13th loci (or 12mut/13). CPI values were modified by incorporating the rate of mutation into the probability of paternity calculation (please see footnote 1 in page 3).

One thousand members of the Chinese population in Taiwan were randomly selected and processed by Microsoft Excel Macros using the Visual Basic program. Every member of the population was paired with every other member, *e.g.* (1,000 × 999)/2 equaling 499,500 pairs. CPI values were obtained for pairs where at least one allele was shared at all 13 loci. CPI values were obtained from mimicked degraded samples with 12 allele sharing out of 12 loci and 11 alleles shared from 11 loci. CPI values were also obtained from mimicked 12mut/13 cases. When processing pairing by computer, no substructure of the population was considered.

The rate of false negatives which is equal to the percentage of real paternity cases would be excluded for any given cutoff point. The rate of false positives equaled the percentage of co-incidental matches above any given cutoff point. The sensitivity of the test is based upon 1 - the % of false negatives. The specificity of the test is based upon 1 - the % of false positives.

The optimum CPI cutoff point was obtained by choosing the maximum of square root of sensitivity^2 + specificity^2 (11).

Results

The Smallest and Largest CPI Values Found

Using the CODIS 13 STR loci for paternity test, real paternity duo cases with very low CPI values (20.81) and coincidental kinship-matched pair with very high CPI values (47,042.98) were observed in this study (Table 1).

Number of Duos and Coincidental Pairs that Meet the Different CPI Requirements

A total of 431 coincidental matches were observed

[1] AABB, Guidance for standards for relationship testing laboratories, MD, USA, American association of blood banks, 2006, pp 139.
[2] AABB, 2002 Parentage testing annual report. MD, USA, American association of blood banks,°@2002. [Available at http://www.aabb.org /Documents/ Accreditation/ Parentage_Testing_Accreditation_Program/ptannrpt02.pdf. (Accessed March 2007).

Table 1. The smallest and largest CPI values resulted from real duo paternity cases and coincidental matched duos under CODIS 13 STRs systems

Real Paternity Duo						
Locus	Child	Father	PI	Child	Father	PI
STR D3S1358	16,18	16,16	1.63	15,17	15,15	1.40
STR vWA	16,18	18,19	1.36	19,19	14,19	5.29
STR FGA	22,23	19,22	1.39	24,24	19,24	2.78
STR TH01	9,9	6,9	1.09	7,9	7,9	1.43
STR TPOX	8,11	8,9	0.43	8,8	8,8	1.73
STR CSF1PO	10,13	10,12	0.95	12,12	10,12	1.50
STR D5S818	10,12	11,12	1.13	10,11	10,10	2.62
STR D13S317	8,12	8,13	0.89	10,12	11,12	1.65
STR D7S820	11,12	12,12	2.18	9,13	8,13	7.25
STR D8S1179	11,15	11,12	2.43	13,14	14,14	2.58
STR D21S11	29,33.2	29,31	0.93	29,33	30,33	50.00
STR D18S51	13,16	13,14	1.60	15,19	15,19	8.05
STR D16S539	9,11	9,11	1.89	10,11	10,10	3.95
		Least CPI= 20.81			Largest CPI= 9,756,809.81	
Coincidental Match (False Positive might be established)						
Locus	Ind. a	Ind. b	PI	Ind. c	Ind. d	PI
STR D3S1358	15,17	15,16	0.70	16,16	16,16	3.27
STR vWA	14,18	18,18	2.71	16,18	16,16	3.16
STR FGA	22,23	20,22	1.39	20,23	23,23	2.29
STR TH01	7,9	9,9	1.09	7,8	8,9	3.94
STR TPOX	8,12	8,9	0.43	8,11	8,8	0.86
STR CSF1PO	11,12	10,12	0.75	9,10	10,12	0.95
STR D5S818	7,11	10,11	0.75	13,13	10,13	3.70
STR D13S317	11,11	11,12	2.03	11,11	10,11	2.03
STR D7S820	11,12	11,13	0.70	10,10	10,12	3.14
STR D8S1179	10,13	13,14	1.19	12,13	13,13	2.39
STR D21S11	30,31.2	30,32	0.95	31,33.2	31,32	2.23
STR D18S51	15,16	14,15	1.30	15,15	13,15	2.59
STR D16S539	11,12	9,11	1.02	9,11	9,11	1.89
		Least CPI= 1.49			Largest CPI= 47,042.98	

PI: Paternity Index was calculated as formulae suggested by AABB (please see footnote 2 in page 3)
CPI: Combined Paternity Index, the product of multiplication of all paternity indices.
Ind. a, b, c, d: Individuals from one thousand random sample population.

with at least one matching allele at all 13 loci for the 499,500 computer-generated pairs of the random population. When only 12 loci were used, such as in the degraded samples, there were 4,286 coincidental matches out of the 499,500 pairs observed, while 6,555 pairs was found when 11 alleles were shared from 11 loci (Table 2).

Sensitivity and Specificity of CPI Frequency Ratio Distribution

In Table 3, the sensitivity and specificity of the DNA test were illustrated. As the CPI cutoff values increased, there was a subsequent decrease in sensitivity and increase in specificity. In 13/13 scenario, as the increment of CPI cutoff varied from 10 to 10,000, the sensitivity varied from 100% to 47.332%; the specificity from 99.921% to 99.999%. The effect was sharper in 12mut/13, 12/12 and 11/11 scenario. If 100 was chosen as the minimum CPI requirement, the sensitivity varied from 19.258% for 12mut/13, 91.647% for 11/11, 96.752% for 12/12 to 98.144% for 13/13.

Evaluation of CPI Cutoff for Different Kinship Matching Situations

By increasing the CPI cutoff values in increments of 1 starting from 0 to 16,384, the optimum CPI value

Table 2. Number of real duos and coincidental matched pairs that meet the minimum CPI requirement

Minimum CPI requirement	Real duo 13/13	Coin. M. 13/13	Real duo 12mut/13	Coin. M. 12mut/13	Real duo12/12	Coin. M.12/12	Real duo 11/11	Coin. M. 11/11
Whatever is obtained	0	431	0	4,286	0	4,286	0	6,555
10	0	393	208	152	0	3,784	0	5,714
100	8	244	348	11	14	1,979	36	2,879
101	8	243	348	11	14	1,971	36	2,863
150	11	201	366	8	30	1,582	46	2,259
200	17	176	375	4	37	1,340	55	1,876
300	29	142	389		50	1,043	71	1,415
500	43	109	402	1 75	716	102	951	
1,000	80	54	415	0	113	413	149	534
1,001	80	54	415	0	114	413	150	534
10,000	227	7	429	0	272	28	319	39

Minimum CPI requirement: The minimum CPI requirement used in different laboratories in USA (please see footnote 1 in page 3)
Real duo 13/13: Real paternity duos with all 13 allele-sharing loci.
Coin. M. 13/13: Coincidental matched pairs with all 13 allele-sharing-loci out of 13.
Real duo 12mut/13: Real paternity duos with one locus in CODIS 13 was randomly excluded to mimic one-locus-mismatch situation and CPI mutation corrected.
Coin. M. 12mut/13: Coincidental matched pairs with only 12 allele-sharing-loci out of 13, and the CPI of the non-matched loci were mutation corrected.
Real duo 12/12: Real paternity duos with one locus in CODIS 13 was randomly erased to mimic one-locus-degraded situation, CPIs were calculated without mutation correction.
Coin. M.12/12: Coincidental matched pairs with only 12 allele-sharing-loci out of 13, CPIs were calculated without mutation correction.
Real duo 11/11: Real paternity duos with two loci in CODIS 13 was randomly erased to mimic two-locus-degraded situation, CPIs were calculated without correction.
Coin. M.11/11: Coincidental matched pairs with only 11 allele-sharing-loci out of 13.

Table 3. Sensitivity and specificity of CPI frequency ratio distribution of two sets of data; one from a computer based study and one from known sets of paternity duos

Minimum CPI requirement	13/13			12mut/13			12/12			11/11		
	sensitivity	specificity	sqrt (x)	sensitivity	specificity	sqrt (x)	sensitivity	specificity	sqrt (x)	sensitivity	specificity	sqrt (x)
Whatever is obtained	100.000%	99.914%	1.41361	100.000%	99.142%	1.40816	100.000%	99.142%	1.40816	100.000%	98.688%	1.40497
10	100.000%	99.921%	1.41366	51.740%	99.970%	1.12566	100.000%	99.242%	1.40886	100.000%	98.856%	1.40615
100	98.144%	99.951%	1.40080	19.258%	99.998%	1.01836	96.752%	99.604%	1.38859	91.647%	99.424%	1.35219
101	98.144%	99.951%	1.40080	19.258%	99.998%	1.01836	96.752%	99.605%	1.38860	91.647%	99.427%	1.35222
150	97.448%	99.960%	1.39600	15.081%	99.998%	1.01129	93.039%	99.683%	1.36356	89.327%	99.548%	1.33750
200	96.056%	99.965%	1.38635	12.993%	99.999%	1.00840	91.415%	99.732%	1.35289	87.239%	99.624%	1.32422
300	93.271%	99.972%	1.36726	9.745%	99.999%	1.00473	88.399%	99.791%	1.33314	83.527%	99.717%	1.30078
500	90.023%	99.978%	1.34535	6.729%	100.000%	1.00226	82.599%	99.857%	1.29592	76.334%	99.810%	1.25654
1,000	81.439%	99.989%	1.28958	3.712%	100.000%	1.00069	73.782%	99.917%	1.24206	65.429%	99.893%	1.19413
1,001	81.439%	99.989%	1.28958	3.712%	100.000%	1.00069	73.550%	99.917%	1.24069	65.197%	99.893%	1.19286
10,000	47.332%	99.999%	1.10635	0.464%	100.000%	1.00001	36.891%	99.994%	1.06582	25.986%	99.992%	1.03313

13/13: There were 13 allele-sharing loci between a pair.
12mut/13: There were 12 out of 13 allele-sharing loci between a pair, the CPI for the mismatched loci were mutation-corrected.
12/12: There were 12 out of 13 allele-sharing loci between a pair.
11/11: There were 11 out of 13 allele-sharing loci between a pair.
Calculation of sensitivity and specificity was based on the ratio of pair numbers in table 2 and their CPI value.
sqrt(x) : sqrt (sensitivity 2+ specificity 2).

Table 4. Evaluation of CPI cutoff for different matching situation.

	12mut/13			13/13			12/12			11/11		
CPI	sensitivity	specificity	sqrt (x)	sensitivity	specificity	sqrt (x)	sensitivity	specificity	sqrt (x)	sensitivity	specificity	sqrt x)
0	100.000%	99.142%	1.408159	100.000%	99.914%	1.413604	100.000%	99.142%	1.408159	100.000%	98.688%	1.404965
0.25	94.664%	99.562%	1.373816	100.000%	99.914%	1.413604	100.000%	99.142%	1.408161	100.000%	98.688%	1.404968
0.5	89.559%	99.686%	1.340084	100.000%	99.914%	1.413604	100.000%	99.143%	1.408166	100.000%	98.689%	1.40497
1	83.991%	99.798%	1.304383	100.000%	99.914%	1.413604	100.000%	99.146%	1.408189	100.000%	98.694%	1.405008
2	76.102%	99.873%	1.255637	100.000%	99.915%	1.413609	100.000%	99.154%	1.408247	100.000%	98.710%	1.405121
5	64.269%	99.944%	1.188246	100.000%	99.917%	1.413628	100.000%	99.189%	1.408493	100.000%	98.768%	1.405530
10	51.740%	99.970%	1.125653	100.000%	99.921%	1.413657	100.000%	99.242%	1.408867	100.000%	98.856%	1.406148
11	50.116%	99.974%	1.118321	100.000%	99.922%	1.413663	100.000%	99.251%	1.408930	100.000%	98.871%	1.406252
12	49.652%	99.976%	1.116265	100.000%	99.923%	1.413669	100.000%	99.258%	1.408978	100.000%	98.885%	1.406351
13	48.260%	99.978%	1.110166	100.000%	99.923%	1.413670	100.000%	99.268%	1.409045	100.000%	98.899%	1.406453
14	47.564%	99.981%	1.107180	100.000%	99.924%	1.413674	100.000%	99.277%	1.409112	99.768%	98.912%	1.404889
15	46.404%	99.982%	1.102257	100.000%	99.926%	1.413688	100.000%	99.285%	1.409170	99.768%	98.924%	1.404977
16	45.708%	99.983%	1.099354	100.000%	99.926%	1.413688	100.000%	99.293%	1.409227	99.768%	98.939%	1.405082
17	44.548%	99.985%	1.094596	100.000%	99.927%	1.413696	100.000%	99.302%	1.409286	99.768%	98.952%	1.405175
18	44.084%	99.985%	1.092723	100.000%	99.927%	1.413698	100.000%	99.308%	1.409327	99.768%	98.965%	1.405263
19	43.387%	99.987%	1.089945	100.000%	99.927%	1.413700	99.768%	99.314%	1.407728	99.768%	98.976%	1.405345
20	41.299%	99.987%	1.081809	100.000%	99.928%	1.413703	99.768%	99.321%	1.407772	99.768%	98.986%	1.405416
25	35.731%	99.989%	1.061818	99.768%	99.930%	1.412079	99.768%	99.352%	1.407996	99.072%	99.036%	1.400833
30	33.411%	99.991%	1.054256	99.768%	99.932%	1.412091	99.768%	99.386%	1.408237	98.840%	99.086%	1.399546
40	29.466%	99.994%	1.042452	99.768%	99.936%	1.412118	99.304%	99.437%	1.405311	96.984%	99.163%	1.387054
50	25.986%	99.996%	1.033177	99.768%	99.939%	1.412140	98.840%	99.481%	1.402348	95.824%	99.231%	1.379457
100	19.258%	99.998%	1.018352	98.144%	99.951%	1.400801	96.752%	99.604%	1.388590	91.647%	99.424%	1.352194
128	16.473%	99.998%	1.013458	97.680%	99.957%	1.397593	94.432%	99.655%	1.372895	90.487%	99.502%	1.344938
256	12.065%	99.999%	1.007246	94.896%	99.969%	1.378369	90.023%	99.770%	1.343809	84.687%	99.683%	1.307996
512	6.729%	100.000%	1.002259	89.791%	99.979%	1.343807	82.367%	99.858%	1.294448	75.870%	99.814%	1.253755
1,024	3.712%	100.000%	1.000689	81.206%	99.989%	1.288114	73.086%	99.919%	1.237954	64.501%	99.895%	1.189090
2,048	2.552%	100.000%	1.000326	74.942%	99.994%	1.249607	62.645%	99.956%	1.179640	52.204%	99.944%	1.127565
4,096	1.856%	100.000%	1.000172	64.269%	99.997%	1.188690	51.276%	99.980%	1.123624	40.603%	99.975%	1.079058
8,192	0.464%	100.000%	1.000011	52.204%	99.998%	1.128049	39.675%	99.990%	1.075736	28.538%	99.987%	1.039803
16,384	0.000%	100.000%	1.000000	39.443%	100.000%	1.074974	29.234%	99.997%	1.041828	19.026%	99.996%	1.017896

sqrt(x) : sqrt(sensitivity 2+ specificity 2). The sensitivity and specificity percentage for the CPIs between the CPI categories were omitted.

was obtained empirically by choosing the maximum of the square root of (sensitivity^2 + specificity^2), when there is one allele shared at all 13 loci, and under the circumstances of degraded DNA and/or a single mutation (Table 4). The optimized cutoffs for 12mut/ 13 matches, 13/13 matches, degraded DNA with 12/12 matches, further degraded DNA with only 11/11 matches were "whatever is obtained", 20, 18, and 13, respectively.

Discussion

In many relationship (identity) testing laboratories, a minimum CPI value requirement or cutoff point is used, above which there is a high degree of confidence that the samples tested are genetically linked as first degree relatives and that a false inclusion will be prevented. Real paternity duo cases with very low CPI values and coincidental kinship-matched pair with very high CPI values were observed. Therefore, false exclusions could happen by setting too high of cutoffs, and false inclusion could happen if setting too low of cutoffs. Simply applying a fixed requirement of minimum CPI for different matching situation may not be a good method.

The ability of the DNA test to correctly classify events into two categories (inclusions and exclusions) is assessed by sensitivity and specificity (7). The sensitivity and specificity of the CODIS 13 STRs system for paternity duo testing was determined for real cases and computer generated pairs from populations under different scenarios. As the CPI cutoff values increased, there was a resultant decrease in the chance of a false inclusion (sensitivity) and increase in the false exclusion (specificity). The effect was more significant when fewer loci were available, *e.g.* in the degraded sample situation. For many laboratories, a cutoff point of a minimum CPI value of 100 was used (23 in 34 laboratories in the AABB survey (please see footnote 2 in page 3) and recognized as generally accepted minimum standard for an inclusion of paternity (3) in the 13/13 scenario, with a sensitivity of 98.144% and specificity of 99.951%. As the specificity was not 100%, 0.05% of the cases were false inclusions. At a CPI of 100 the sensitivity was only 98.14%, resulting in 1.86% of real duo paternity being classified as exclusions. For example, a high CPI such as 10,000 would result in 52.668% (1-47.332%) of real duo paternity cases being reported as an exclusion. The optimized CPI value, being a balance between sensitivity and specificity, should be suggested.

From AABB data (please see footnote 2 in page 3) most of the DNA laboratories (19 of 29 laboratories) used "whatever is obtained" as CPI requirement for family reconstruction cases. Applying this criterion to these data, the sensitivity became 100% for 13/13 matches, 12/12 matches and 11/11 matches, and the specificity was 99.914%, 99.142% and 98.688% for each scenario respectively. If the cutoff of CPI = 0 were increased to CPI = 20 for 13/13 scenario, then the specificity could be increased to 99.928% and sensitivity maintained 100%, for the other two match situations, similar effects were found.

Clear differences in the sensitivity of the test when using a CPI cutoff value of 100 were observed for 13 allele shared (98.144%) compared to a single mutation (12mut/13) (19.258%). A single mutation, which is a routine observation for paternity testing laboratories (3), would result in approximately 80% of paternity case being reported as exclusions, if the cutoff were not adjusted.

By using the optimal cutoff selection method proposed by zou *et al.* (11), the optimum CPI values were obtained empirically for different scenarios. They may serve as the minimum CPI requirements.

In conclusion, a different CPI value should be applied for duo cases when there is full allele sharing at all 13 loci compared to a case where there is a possible mutation in one of the loci. For a paternity duo test and a family reconstruction test, the cutoff could be set at a CPI value of 20 if only one allele were shared at all 13 loci. If the sample were degraded and only 12 loci were available then the cutoff CPI value should be 18, and a CPI value of 13 for 11 loci. If a mutation had been suspected in a duo case, more STR tests should be added to confirm the mutation, and then DNA test results and non-DNA finding should be combined to determine the paternity. Applying CPI = 0 as the cutoff directly is not suitable although in table 4 CPI = 0 was listed as the candidate. For no optimum CPI minimum value can be set for paternity duo tests that will never result in false inclusions or false exclusions, although the application of these suggested CPI cutoffs will maximize the paternity screening. The ideal method to resolve duo cases with greater confidence would be to add more autosomal STR loci to increase the CPI value (the specificity will be higher), and if possible to use mitochondrial DNA analysis or STR loci on sex chromosome for further confirmation.

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