The Sibship Index can't discriminates Half-Sibs from Full-Sibs; a new algorithm, including maternal genotype, can do it.

Giuseppe Cardillo, PhD.

Viale Colli Aminei, 461 – lotto 29
80131
Napoli
Italy

Tel: +393883947558

Email: giuseppe.cardillo.75@gmail.com

Highlights

- Usually used Sibship Index (SI) greatly overestimates likelihood ratios;
- Rising up the number of investigated STR, all Half-Sibs are declared Full-Sibs;
- The only way to avoid this overestimate is to use a Sibship Index Corrected by the common parent genotype, that usually is the mother (SICMG); all likelihood ratio formulas can be reconducted to five scenarios;
- For both SI and SICMG there is a better cut-off than 1 to discriminate Half-Sibs: this cut-off is computed for all commercial available forensic STR kit.

Abstract and Introduction

Sibship DNA testing is conducted in order to determine if two subjects share one or both biological parents: Full-sibs have both parents in common, whereas Half-sibs have one parent in common, either the mother or the father. When an alleged father is not available for a paternity test, sibship testing is one way to determine family relationships. Results of a sibship test have also been accepted as proof in Social Security benefit and other inheritance claims. To analyze the possibility that the siblings share two common parents versus only one common parent, the ratio of the full sibship index versus half sibship index is computed: a sibship index less than 1, provides genetic evidence which does not favor a full-sibling relationship. In this paper we will demonstrate that the actually used Sibship Index is unable to distinguish Full-sibs from Half-Sibs and the only way to distinguish them is to use a new Index including the genotype of the Mother, that, usually, is the known common parent.

Methods

The likelihood ratio

The probability of sibship after the DNA fingerprint determination is computed using the Bayes' theorem. To apply the theorem, it is needed to compute, for each analyzed locus, the likelihood ratio: this is the ratio of two maximum probabilities that can be assumed seeing the evidences, under two alternatives hypothesis. In our case, the likelihood ratio is the probability to observe the subjects' genotypes under the

hypothesis they are Full-Sibs over the probability to observe the same genotypes under the hypothesis they are Half-Sibs. Since the loci are independent from each other, the single likelihood ratios can be multiplied together to obtain the cumulative likelihood ratio. The loci used in DNA fingerprint are in Hardy-Weinberg Equilibrium (HWE) and this law will be used to compute the likelihood ratios. Under HWE hypothesis:

- the probability to observe a homozygous locus for the allele A, that has frequency p in the population, will be p^2;
- the probability to observe a heterozygous locus for the alleles A and B, that have, respectively, frequency p and q in the population, will be $2pq$;
- the sum of all possible genotypes probabilities is 1.

Derivation of Sibship Index (SI) for Full-sibs versus Half-sibs

The Sibship Index under the two alternatives hypothesis of Full-sibs and Half-sibs was derived as described elsewhere [1]. Briefly, it can be resumed as follows. For each locus, let δ_{ij} and δ_{kl} be the Kronecker's deltas of the sibs' alleles:

$$\delta_{ij}=\begin{cases}1, i=j\\ 0, i\neq j\end{cases}$$

The Kronecker's delta will be 1 if the locus is homozygous and 0 if the locus is heterozygous. Sibs can share 0, 1 or 2 alleles and so, all possible SI can be resumed using the set theory notation:

$$SI=\begin{cases}\frac{1}{2}, if\ S1\cap S2=\varnothing\\ \frac{1+p+q+2pq}{p+q+4pq}, else\ if\ S1\cap S2=\{A,B\}, \delta_{ij}=0, \delta_{kl}=0\\ \frac{1}{2}+\left[1+\frac{1}{(2-\delta_{ij})(2-\delta_{kl})p}\right], otherwise\end{cases}$$

where p and q are the alleles frequencies in the population. Table 1 summarizes all possible Sibship Index.

Derivation of Sibship Index Corrected by Maternal Genotype (SICMG)

There are five possible states for SICMG. In the first one, there are two conditions to verify:

1. maternal and paternal origin of both Sibs alleles can be clearly identifiable because Mother shares only one allele with each of them;
2. Sibs share the paternal allele.

An example of this state is Mother=AB; SIB1=AC and SIB2=BC. To compute the numerator of the SICMG, we assume that Sibs are Full-Sibs. The common Father could be homozygous (p^2) and there is 100% of probability he gave the same allele to both Sibs; on the other hand, the Father could be heterozygous (*2pq*) and there is 50% of probability that he gave the allele A to one sib and 50% that he gave the same allele to the other. Using compound and total probability laws:

$$N_1 = 1 \cdot 1 \cdot p^2 + \frac{1}{2} \cdot \frac{1}{2} \cdot 2\,px$$

Under the Hardy-Weinberg Equilibrium hypothesis, the sum of all alleles frequencies is equal to 1, so:

$$x = 1 - p \therefore N_1 = p^2 + \frac{1}{2} p(1-p) = p^2 + \frac{1}{2} p - \frac{1}{2} p^2 = \frac{1}{2} p^2 + \frac{1}{2} p = \frac{p(p+1)}{2}$$

To compute the denominator, we have to hypothesize two different Fathers and each of them could be homozygous or heterozygous, generating four possible combinations of these situations:

$$D_1 = \left[p^2 + \frac{1}{2} p(1-p)\right] \cdot \left[p^2 + \frac{1}{2} p(1-p)\right] = \left[\frac{p(p+1)}{2}\right]^2$$

$$SICMG = \frac{N_1}{D_1} = \frac{\frac{p(p+1)}{2}}{\left[\frac{p(p+1)}{2}\right]^2} = \frac{4[p(p+1)]}{2[p(p+1)]^2} = \frac{2}{p(p+1)}$$

In the second possible state:

1. Again none of the Sibs shares the same heterozygous Mother's genotype;
2. Sibs do not share the paternal allele.

An example of this state is Mother=AB; SIB1=AC and SIB2=BD. Under the hypothesis that Sibs have the same Father, he can only be heterozygous:

$$N_2 = \frac{1}{2} \cdot \frac{1}{2} \cdot 2\,pq = \frac{pq}{2}$$

Under the hypothesis of two different Fathers, if one is homozygous or heterozygous for one allele, the other is homozygous or heterozygous for the other allele:

$$D_2=2\cdot\left[p^2+\frac{1}{2}\cdot 2\cdot p(1-p)\right]\cdot\left[q^2+\frac{1}{2}\cdot 2\cdot q(1-q)\right]=2\cdot\left[p^2+p-p^2\right]\cdot\left[q^2+q-q^2\right]=2pq$$

$$SICMG=\frac{N_2}{D_2}=\frac{pq}{2\cdot 2\cdot pq}=\frac{1}{4}$$

In the third possible state:

1. The Mother is heterozygous and one of the Sibs is heterozygous with the same genotype of the Mother;
2. The other Sib is homozygous.

An example of this state is Mother=AB; SIB1=AB and SIB2=AA. In this case, for the first Sib it is impossible to establish which allele was inherited from the Mother. If the Sibs inherited different maternal alleles, they share the same paternal allele; on the contrary, if they share the same maternal allele, they inherited different paternal alleles.

$$N_3=N_1+N_2=\frac{1}{2}p(p+1)+\frac{1}{2}pq=\frac{p(p+q+1)}{2}=\frac{p}{4}\cdot 2(p+q+1)$$

$$D_3=D_1+D_2=\left[\frac{p(p+1)}{2}\right]^2+2pq=\frac{p}{4}\cdot\left[p(p+1)^2+8q\right]$$

$$SICMG=\frac{N_3}{D_3}=\frac{2(p+q+1)}{p(p+1)^2+8q}$$

In the fourth possible state:

1. The Mother is heterozygous, one of the Sibs is heterozygous with the same genotype of the Mother;
2. The other Sib is heterozygous and shares only one allele with the first Sib.

An example of this state is Mother=AB; SIB1=AB and SIB2=BC.

This state is equal to the second one, even if the derivation is slightly different.

$$N_4=\frac{1}{2}\cdot\frac{1}{2}\cdot 2pq+\frac{1}{2}\cdot\frac{1}{2}\cdot 2pr=\frac{p(q+r)}{2}$$

$$D_4=2pq+2pr=2p(q+r)$$

$$SICMG=\frac{N_4}{D_4}=\frac{p(q+r)}{2\cdot 2\cdot p(q+r)}=\frac{1}{4}$$

Finally, in the fifth possible state, Mother and Sibs share the same heterozygous genotype: Mother=AB; SIB1=AB and SIB2=AB.

$$N_5=\frac{p(p+1)}{2}+\frac{q(q+1)}{2}+2\cdot\frac{pq}{2}=\frac{2\cdot(p+q)(p+q+1)}{4}$$

$$D_5=\left[\frac{p(p+1)}{2}\right]^2+\left[\frac{q(q+1)}{2}\right]^2+2\cdot(2pq)=\frac{1}{4}\cdot\left\{[p(p+1)]^2+[q(q+1)]^2+16pq\right\}$$

$$SICMG=\frac{N_5}{D_5}=\frac{2(p+q)(p+q+1)}{[p(p+1)]^2+[q(q+1)]^2+16pq}$$

Table 1 summarizes all possible SICMG.

Algorithm for the simulation of population

To simulate a population, we wrote an algorithm using MatLab R2017a (MathWorks Inc. Natick, MA, USA). We used 50 loci: one half of them are routinely used in commercial kits (CSF1PO, D1S1656, D2S441, D2S1338, D3S1358, D5S818, D6S1043, D7S820, D8S1179, D10S1248, D12S391, D13S317, D16S539, D18S51, D19S433, D21S11, D22S1045, FGA, PENTA D, PENTA E, SE33, TH01, TPOX and vWA); the other is not (D1GATA113, D1S1677, D2S1776, D3S3053, D3S4529, D4S2364, D4S2408, D5S2500, D6S474, D6S1017, D6S1043, D9S1122, D10S1435, D11S4463, D12ATA63, D14S1434, D17S974, D17S1301, D18S853, D20S482, F13A1, F13B, FES, LPL, PENTA B, PENTA C). The Italian allelic frequencies of these loci were retrieved from http://www.allstr.de/allstr/home.seam; for D6S1043, Penta B and Penta C we used the Caucasian frequencies reported by Phillips et al [2]. The input of the algorithm is a column vector of described alleles frequencies for a given locus. In a population it can happen that, for a given locus, some previously described alleles are absent: when this occurs, alleles with null frequency are erased. Matrix multiplication of the column vector by itself transposed generates a square matrix where on the main diagonal there are the squared allelic frequencies (p^2 homozygotes) and in the other cells there are products of two allelic frequencies (the matrix is symmetric with respect to the main diagonal). For example:

$$freq=\begin{bmatrix}0.25\\0.35\\0.40\end{bmatrix};G=\begin{bmatrix}0.25\\0.35\\0.40\end{bmatrix}\begin{bmatrix}0.25 & 0.35 & 0.40\end{bmatrix}=\begin{bmatrix}0.0625 & 0.0875 & 0.1000\\0.0875 & 0.1225 & 0.1400\\0.1000 & 0.1400 & 0.1600\end{bmatrix}$$

Performing a scalar multiplication for another square matrix that have the same size of the first one, all ones on the main diagonal, all zeros above the main diagonal and all two below the main diagonal, we obtain a matrix where on the main diagonal there are again the p^2 homozygotes, below the main diagonal there are the $2pq$ heterozygotes and above the main diagonal all values are zero.

$$G_{triangular}=\begin{bmatrix}0.0625 & 0.0875 & 0.1000\\ 0.0875 & 0.1225 & 0.1400\\ 0.1000 & 0.1400 & 0.1600\end{bmatrix}\cdot\begin{bmatrix}1 & 0 & 0\\ 2 & 1 & 0\\ 2 & 2 & 1\end{bmatrix}=\begin{bmatrix}0.0625 & 0 & 0\\ 0.1750 & 0.1225 & 0\\ 0.2000 & 0.2800 & 0.1600\end{bmatrix}$$

The sum of all matrix elements is 1, as consequence of the Hardy-Weinberg law.

$$\sum G_{triangular}=[0.0625+0.1750+0.2000+0.1225+0.2500+0.1600]=1$$

The matrix shows the fraction of the population that has a specific genotype: for example, 6.25% of the population is homozygous for the allele 1 and 17.50% is heterozygous for the alleles 1 and 2. Performing a scalar multiplication for 10 million we obtain a good representation of rare genotypes too:

$$Pop=\begin{bmatrix}625000 & 0 & 0\\ 1750000 & 1225000 & 0\\ 2000000 & 2800000 & 1600000\end{bmatrix}$$

Now, it is possible to construct the genotypes matrix with 10 million rows and 2 columns that represents the genotypes of the population: using this example there are 625000 rows [1 1]; 1750000 rows [1 2] and so on.

The genotypes matrix is randomly shuffled using the Fisher-Yates-Sattolo algorithm and divided in two halves: the first one will be the Mother's genotypes and the other the Father's genotypes. We can use these two matrix to generate Full-Sibs pairs.

The mechanism by which the Mother and the Father transmit one or the other of their alleles is like tossing a coin. This process can be simulated using a 5 million rows and 2 columns random matrix chosen from a binomial distribution with parameters p=0.5 and n=1: the first column indicates if from the Mother is inherited the first or the second allele; the second column indicates if from the Father is inherited the first or the second allele. The binomial matrix is reinitialized to generate the second Sib.

To generate Half-Sibs, the Father's matrix is shuffled again using the Fisher-Yates-Sattolo algorithm and third binomial 5 million rows and 2 columns random matrix is generated. Resuming, there are 5 million pairs of Full-Sibs and 10 million pairs of Half-Sibs. Finally, the algorithm computes the SI and SICMG for each pair of Full-Sibs and Half-Sibs and then stores the results on to the hard disk.

Determination of single locus and cumulative accuracy of SI and SICMG

SI and SICMG are formulated so that a value greater than 1 suggests that we are observing a Full-Sibs pair and a value lower than 1 suggests that we are observing a Half-Sibs pair. For each locus, we computed how many Full-Sibs had a SI or SICMG greater than 1 and how many Half-Sibs had a SI or SICMG lower than 1. For each locus were determined: Sensitivity, Specificity and Youden's J Index (JI).The cumulative Index is computed by multiplying together the Indices of single loci. The distributions of SI and SICMG at each locus are not Gaussian but the logarithms of their cumulative distributions are Gaussian, so it is possible to easily compute the crossing points between Full-Sibs and Half-Sibs cumulative distributions obtained from SI and SICMG. In fact, each Gaussian distribution has an equation:

$$Y \sim N(\mu,\sigma)=\frac{1}{\sigma\sqrt{2\pi}}e^{\frac{-(x-\mu)^2}{2\sigma^2}}$$

where μ is the mean and σ is the standard deviation. Equating two distribution equations and placing $\tau=1/\sigma^2$, the crossing points will be found by solving the second degree equation:

$$(\tau_2-\tau_1)x^2-2(\tau_2\mu_2-\tau_1\mu_1)x+\left(\tau_2\mu_2{}^2-\tau_1\mu_1{}^2-\ln\frac{\tau_2}{\tau_1}\right)=0$$

Of course, there are two roots that solve this equation; for our purpose, we used the crossing point (CP) between means. This CP is used to find the Equivalent Error Rate Point (ERRP), that is the point where misclassification rates for both Half-Sibs and Full-Sibs are equal (Sensitivity=Specificity). To find ERRP we used Bisection Method using CP as guessing starting point to find the zero of the function:

$$f(x)=1-cdf(x,\mu_{HS},\sigma_{HS})-cdf(x,\mu_{FS},\sigma_{FS})$$

where the Cumulative Density Function (cdf) for a Gaussian distribution is:

$$cdf(x,\mu,\sigma)=\frac{1}{2}\left[1+erf\left(\frac{x-\mu}{\sigma\sqrt{2}}\right)\right]$$

and the Error Function (erf) is:

$$erf(x)=\frac{1}{\sqrt{\pi}}\int_{-x}^{x} e^{-t^2}dt=\frac{2}{\sqrt{\pi}}\int_{0}^{x} e^{-t^2}dt$$

Again, the performances of cumulative SI and SICMG were computed using as threshold 1 or the ERRP.

Results and Discussion

Tables 2 and 3 summarize, respectively, SI and SICMG performances computed for each locus and cumulatively. STRs are sorted to maximize the Youden's J index (JI). A randomization t-test [3] using a Monte Carlo naïve method, performed on the arrays of JI showed a statistically significative difference between methods (p-value=0). Moreover, when SI algorithm is used, increasing the number of considered loci, JI dramatically decreases (Table 2); on the contrary, when SICMG algorithm is used JI increases (Table 3). It is interesting to highlight that, when SICMG algorithm is used, the JI increases, reaches a maximum and then decreases (Table 3). In the sibship analysis, usually, a likelihood ratio greater than 1 indicates a Full-Sibs kinship and a likelihood ratio lower than 1 indicates a Half-Sibs kinship. As shown in Table 2, when all loci are used to compute SI, all couples have a likelihood ratio grater than 1 and so the SI is completely useless to discriminate Half-Sibs from Full-Sibs. The phenomenon is clearly highlighted in Figure 1: when unusual STRs are added and SI algorithm is used, both Full-Sibs and Half-Sibs distributions means move to the right and about 35% of the areas overlaps; on the contrary, when SICMG algorithm is used, Full-Sibs distribution mean moves to the right, the Half-Sibs distribution mean moves to the left and the areas overlap is about 3%, ten fold lower than SI overlap.

To improve the results, the EERP must be taken in account and Table 4 shows the performances of commercial kits.

When SI algorithm is used and cutoff=1 is chosen as threshold, practically all Half-Sibs couples are declared as Full-Sibs; using cutoff=10^{EERP}, 25% of couples are mis-classified.

When SICMG algorithm is used and cutoff=1 is chosen as threshold, less than 1% of Half-Sibs are declared Full-Sibs and about 12% of Full-Sibs are declared Half-Sibs; on the contrary, using cutoff=10^{EERP}, about 3% of couples are misclassified; eight fold lower respect to SI algorithm. We defined "Core" the set of all 24 STRs showed in Table 4. Tables 5 and 6 show the performances obtained adding unusual STRs to the "Core" using SI and SICMG, respectively, and EERP as cutoff. Again, it is possible to observe the same phenomenon showed in Table 3: the Youden's Index increases, reaches a maximum and then decreases.

Table 5 shows that using SI algorithm and adding 18 STRs to the Core set the misclassified couples decrease from about 21% to 17% ; the addition of other 8 STRs only succeeds in worsening the performances.

Similarly, Table 6 shows that using SICMG algorithm the maximum Youden's Index is reached adding a set of 14 STRs but there is a gain of less than 1% in performances.

Anyway, there is a set of 8 STRs that are useless in both cases (D1GATA113, D2S1776, D4S2364, D9S1122, F13A1, F13B, FES and PENTA C).

In conclusion, it is impossible to discriminate Full-Sibs from Half-Sibs using usually SI index and cut-off; it is possible to greatly improve the performances taking into account the Maternal genotype and the Equivalent Error Rate Point, taking in mind that also in this condition 1-2% of couples will be misclassified.

Bibliography

[1] Wing Kam Fung and Yue-Qing Hu. Statistical DNA Forensics: Theory, Methods and Computations. John Wiley & Sons, Ltd. 2008. Pages 43 and 80.

[2] Phillips C, Kind S, Fernandez-Formoso L, et al. Global population variability in Promega PowerPlex CS7, D6S1043, and Penta B STRs. Int J Legal Med 2013;127(5):901-6.

[3] Rndttest: An alternative to Student t-test assessing difference in means. 2008. http://www.mathworks.com/matlabcentral/fileexchange/20928.

Table 1: All possible combinations among Mother and Probands and corresponding Sibship Index and Sibship Index Corrected by Maternal Genotype. In Sibship Index, p and q are the frequencies of shared alleles; in the Sibship Index Corrected by Maternal Genotype, p is the frequency of the Paternal shared allele; if Mother and almost one the Sibs are AB then both alleles frequencies are considered.

Mother		Sib 1		Sib 2		Sibship Index	Sibship Index Corrected by Maternal Genotype
A	A	A	A	A	A	1/2*(1+1/p)	2/(p*(p+1))
				A	B	1/2*(1+1/(2*p))	1/4
		A	B	A	A	1/2*(1+1/(2*p))	1/4
				A	B	(1+p+q+2*p*q)/(p+q+4*p*q)	2/(p*(p+1))
				A	C	1/2*(1+1/(4*p))	1/4
A	B	A	A	A	A	1/2*(1+1/p)	2/(p*(p+1))
				A	B	1/2*(1+1/(2*p))	(2*(p+q+1))/(8*q+p*(p+1)^2)
				A	C	1/2*(1+1/(2*p))	1/4
				BB or BC		1/2	1/4
		A	B	AA or BB		1/2*(1+1/(2*p))	(2*(p+q+1))/(8*q+p*(p+1)^2)
				A	B	(1+p+q+2*p*q)/(p+q+4*p*q)	(2*(p+q)*(p+q+1))/((p*(p+1))^2+(q*(q+1))^2+16*p*q)
				AC or BC		1/2*(1+1/(4*p))	1/4
		A	C	A	A	1/2*(1+1/(2*p))	1/4
				AB or AD		1/2*(1+1/(4*p))	1/4
				A	C	(1+p+q+2*p*q)/(p+q+4*p*q)	2/(p*(p+1))
				BB or BD		1/2	1/4
				B	C	1/2*(1+1/(4*p))	2/(p*(p+1))

Table 2: Performance of the Sibship Index (SI) for each locus and cumulatively computed.

STR	Single Performance					Cumulative Performance				
	True Full Sibs	True Half Sibs	Sensitivity	Specificity	Youden's J	True Full Sibs	True Half Sibs	Sensitivity	Specificity	Youden's J
SE33	4044968	3814526	0.8090	0.3815	0.1904	4044968	3814526	0.8089936	0.3814526	0.1904462
D20S1082	4707210	1035698	0.9414	0.1036	0.0450	4664248	1738711	0.9328496	0.1738711	0.1067207
PENTA B	4162954	3281881	0.8326	0.3282	0.1608	4830025	1308168	0.9660050	0.1308168	0.0968218
D2S1776	4548016	1865150	0.9096	0.1865	0.0961	4914174	722285	0.9828348	0.0722285	0.0550633
D6S1043	4306988	2739176	0.8614	0.2739	0.1353	4944090	658876	0.9888180	0.0658876	0.0547056
D1S1656	4182848	3268384	0.8366	0.3268	0.1634	4975373	448821	0.9950746	0.0448821	0.0399567
PENTA E	4202795	3191654	0.8406	0.3192	0.1597	4990690	277549	0.9981380	0.0277549	0.0258929
D12S391	4199930	3205346	0.8400	0.3205	0.1605	4994827	234616	0.9989654	0.0234616	0.0224270
D18S51	4232062	3073122	0.8464	0.3073	0.1537	4997673	160498	0.9995346	0.0160498	0.0155844
D6S474	4487803	2000718	0.8976	0.2001	0.0976	4998902	108517	0.9997804	0.0108517	0.0106321
D2S1338	4268848	2924997	0.8538	0.2925	0.1463	4999458	82341	0.9998916	0.0082341	0.0081257
D21S11	4272751	2908211	0.8546	0.2908	0.1454	4999755	54341	0.9999510	0.0054341	0.0053851
D12ATA63	4401833	2300417	0.8804	0.2300	0.1104	4999862	40165	0.9999724	0.0040165	0.0039889
FGA	4308332	2767285	0.8617	0.2767	0.1384	4999927	28186	0.9999854	0.0028186	0.0028040
D4S2408	4498190	1939247	0.8996	0.1939	0.0936	4999976	19179	0.9999952	0.0019179	0.0019131
FES	4612651	1534922	0.9225	0.1535	0.0760	4999978	16441	0.9999956	0.0016441	0.0016397
D3S4529	4512856	1984773	0.9026	0.1985	0.1010	4999987	11327	0.9999974	0.0011327	0.0011301
PENTA D	4365869	2535771	0.8732	0.2536	0.1268	4999993	8061	0.9999986	0.0008061	0.0008047
D3S3053	4575271	1728556	0.9151	0.1729	0.0879	4999995	5485	0.9999990	0.0005485	0.0005475
D5S2500	4591030	1677812	0.9182	0.1678	0.0860	4999998	3792	0.9999996	0.0003792	0.0003788
D7S820	4415563	2341539	0.8831	0.2342	0.1173	4999999	2621	0.9999998	0.0002621	0.0002619
LPL	4572258	1745319	0.9145	0.1745	0.0890	5000000	1804	1.0000000	0.0001804	0.0001804
F13A1	4534413	1745724	0.9069	0.1746	0.0815	5000000	1398	1.0000000	0.0001398	0.0001398
D4S2364	4801799	565081	0.9604	0.0565	0.0169	5000000	948	1.0000000	0.0000948	0.0000948
vWA	4448049	2203011	0.8896	0.2203	0.1099	5000000	675	1.0000000	0.0000675	0.0000675
D16S539	4468826	2128730	0.8938	0.2129	0.1066	5000000	455	1.0000000	0.0000455	0.0000455
D1S1677	4597707	1685875	0.9195	0.1686	0.0881	5000000	322	1.0000000	0.0000322	0.0000322
PENTA C	4554888	1657573	0.9110	0.1658	0.0767	5000000	248	1.0000000	0.0000248	0.0000248
F13B	4685895	1209365	0.9372	0.1209	0.0581	5000000	181	1.0000000	0.0000181	0.0000181
D8S1179	4387267	2452261	0.8775	0.2452	0.1227	5000000	143	1.0000000	0.0000143	0.0000143
TH01	4477222	2093723	0.8954	0.2094	0.1048	5000000	98	1.0000000	0.0000098	0.0000098
D20S482	4621374	1587853	0.9243	0.1588	0.0831	5000000	67	1.0000000	0.0000067	0.0000067
D14S1434	4634337	1458663	0.9269	0.1459	0.0727	5000000	45	1.0000000	0.0000045	0.0000045

D11S4463	4519073	1891739	0.9038	0.1892	0.0930	5000000	33	1.0000000	0.0000033	0.0000033
D19S433	4445223	2220715	0.8890	0.2221	0.1111	5000000	23	1.0000000	0.0000023	0.0000023
D18S853	4607547	1441253	0.9215	0.1441	0.0656	5000000	15	1.0000000	0.0000015	0.0000015
D1GATA113	4822360	743924	0.9645	0.0744	0.0389	5000000	11	1.0000000	0.0000011	0.0000011
D6S1017	4639276	1284896	0.9279	0.1285	0.0563	5000000	10	1.0000000	0.0000010	0.0000010
D3S1358	4497007	2011157	0.8994	0.2011	0.1005	5000000	6	1.0000000	0.0000006	0.0000006
CSF1PO	4602749	1589921	0.9205	0.1590	0.0795	5000000	5	1.0000000	0.0000005	0.0000005
D10S1435	4570178	1492333	0.9140	0.1492	0.0633	5000000	4	1.0000000	0.0000004	0.0000004
D17S974	4663007	1357872	0.9326	0.1358	0.0684	5000000	2	1.0000000	0.0000002	0.0000002
D5S818	4596296	1614679	0.9193	0.1615	0.0807	5000000	1	1.0000000	0.0000001	0.0000001
D9S1122	4662707	1083447	0.9325	0.1083	0.0409	5000000	1	1.0000000	0.0000001	0.0000001
D2S441	4541342	1834184	0.9083	0.1834	0.0917	5000000	0	1.0000000	0.0000000	0.0000000
D10S1248	4538174	1850079	0.9076	0.1850	0.0926	5000000	0	1.0000000	0.0000000	0.0000000
D13S317	4477849	2090859	0.8956	0.2091	0.1047	5000000	0	1.0000000	0.0000000	0.0000000
D17S1301	4682333	1294711	0.9365	0.1295	0.0659	5000000	0	1.0000000	0.0000000	0.0000000
D22S1045	4629687	1480791	0.9259	0.1481	0.0740	5000000	0	1.0000000	0.0000000	0.0000000
TPOX	4691085	1232995	0.9382	0.1233	0.0615	5000000	0	1.0000000	0.0000000	0.0000000

Table 3: Performance of the Sibship Index Corrected by Maternal Genotype (SICMG) for each locus and cumulatively computed.

STR	Single Performance					Cumulative Performance				
	True Full Sibs	True Half Sibs	Sensitivity	Specificity	Youden's J	True Full Sibs	True Half Sibs	Sensitivity	Specificity	Youden's J
SE33	2591958	9318668	0.5184	0.9319	0.4503	2591958	9318668	0.5183916	0.9318668	0.4502584
D1S1656	2652355	8933171	0.5305	0.8933	0.4238	3712974	8535908	0.7425948	0.8535908	0.5961856
D12S391	2663306	8882135	0.5327	0.8882	0.4209	3730809	8770834	0.7461618	0.8770834	0.6232452
PENTA E	2665605	8867483	0.5331	0.8867	0.4199	3713086	9456691	0.7426172	0.9456691	0.6882863
D18S51	2680617	8777175	0.5361	0.8777	0.4138	4052961	9340945	0.8105922	0.9340945	0.7446867
PENTA B	2739600	8468239	0.5479	0.8468	0.3947	4071341	9514549	0.8142682	0.9514549	0.7657231
D21S11	2705720	8626140	0.5411	0.8626	0.4038	4162829	9641678	0.8325658	0.9641678	0.7967336
D2S1338	2702576	8646281	0.5405	0.8646	0.4051	4280818	9651741	0.8561636	0.9651741	0.8213377
D6S1043	2838203	8119458	0.5676	0.8119	0.3796	4326337	9727393	0.8652674	0.9727393	0.8380067
FGA	2719592	8516592	0.5439	0.8517	0.3956	4379815	9777702	0.8759630	0.9777702	0.8537332
PENTA D	2758541	8301877	0.5517	0.8302	0.3819	4422081	9808087	0.8844162	0.9808087	0.8652249
D8S1179	2777374	8210247	0.5555	0.8210	0.3765	4448568	9850096	0.8897136	0.9850096	0.8747232
D19S433	2830801	7938249	0.5662	0.7938	0.3600	4481349	9871149	0.8962698	0.9871149	0.8833847
D12ATA63	2948278	7282833	0.5897	0.7283	0.3179	4514045	9880568	0.9028090	0.9880568	0.8908658
D7S820	2795659	8104051	0.5591	0.8104	0.3695	4537756	9899704	0.9075512	0.9899704	0.8975216
D3S4529	2941294	7487810	0.5883	0.7488	0.3370	4563995	9906242	0.9127990	0.9906242	0.9034232
D6S474	3021899	7110574	0.6044	0.7111	0.3154	4589089	9910202	0.9178178	0.9910202	0.9088380
vWA	2822565	7944315	0.5645	0.7944	0.3589	4606657	9924019	0.9213314	0.9924019	0.9137333
D4S2408	3000494	7138532	0.6001	0.7139	0.3140	4626495	9927698	0.9252990	0.9927698	0.9180688
D16S539	2845411	7848506	0.5691	0.7849	0.3539	4641622	9938740	0.9283244	0.9938740	0.9221984
D13S317	2852159	7802579	0.5704	0.7803	0.3507	4655335	9948290	0.9310670	0.9948290	0.9258960
D3S3053	3159246	6559247	0.6318	0.6559	0.2878	4670354	9950273	0.9340708	0.9950273	0.9290981
D2S441	2923072	7457641	0.5846	0.7458	0.3304	4681215	9957676	0.9362430	0.9957676	0.9320106
TH01	2843199	7837043	0.5686	0.7837	0.3523	4691802	9964150	0.9383604	0.9964150	0.9347754
D3S1358	2862199	7735336	0.5724	0.7735	0.3460	4701286	9968979	0.9402572	0.9968979	0.9371551
D5S2500	3134986	6700703	0.6270	0.6701	0.2971	4712176	9970293	0.9424352	0.9970293	0.9394645
D11S4463	2985294	6928844	0.5971	0.6929	0.2899	4722928	9971284	0.9445856	0.9971284	0.9417140
D10S1248	2910053	7519876	0.5820	0.7520	0.3340	4730143	9975497	0.9460286	0.9975497	0.9435783
LPL	3044556	6908648	0.6089	0.6909	0.2998	4738126	9976650	0.9476252	0.9976650	0.9452902
D14S1434	3279335	5934420	0.6559	0.5934	0.2493	4745040	9976763	0.9490080	0.9976763	0.9466843

D5S818	2775334	7466223	0.5551	0.7466	0.3017	4750327	9979865	0.9500654	0.9979865	0.9480519
D18S853	2652423	7522221	0.5305	0.7522	0.2827	4756342	9980916	0.9512684	0.9980916	0.9493600
D22S1045	2539991	7712817	0.5080	0.7713	0.2793	4760439	9983358	0.9520878	0.9983358	0.9504236
D1S1677	3043564	6836021	0.6087	0.6836	0.2923	4765268	9984465	0.9530536	0.9984465	0.9515001
CSF1PO	2981845	7131608	0.5964	0.7132	0.3095	4768968	9986499	0.9537936	0.9986499	0.9524435
D20S482	3164263	6369768	0.6329	0.6370	0.2698	4772546	9987060	0.9545092	0.9987060	0.9532152
TPOX	2946662	6797909	0.5893	0.6798	0.2691	4775382	9988608	0.9550764	0.9988608	0.9539372
D10S1435	2698804	7285156	0.5398	0.7285	0.2683	4777904	9989130	0.9555808	0.9989130	0.9544938
D20S1082	2663714	7280251	0.5327	0.7280	0.2608	4779053	9989576	0.9558106	0.9989576	0.9547682
D17S974	2545028	7388159	0.5090	0.7388	0.2478	4779525	9990089	0.9559050	0.9990089	0.9549139
D6S1017	2917211	6803358	0.5834	0.6803	0.2638	4780490	9990718	0.9560980	0.9990718	0.9551698
D17S1301	2379392	7610555	0.4759	0.7611	0.2369	4780656	9991175	0.9561312	0.9991175	0.9552487
PENTA C	3045620	6624301	0.6091	0.6624	0.2716	4781237	9991031	0.9562474	0.9991031	0.9553505
D2S1776	3162890	6537791	0.6326	0.6538	0.2864	4778311	9990991	0.9556622	0.9990991	0.9547613
D9S1122	2999529	5902130	0.5999	0.5902	0.1901	4775210	9990974	0.9550420	0.9990974	0.9541394
D1GATA113	3581165	4157776	0.7162	0.4158	0.1320	4771850	9991185	0.9543700	0.9991185	0.9534885
F13A1	3105796	6253732	0.6212	0.6254	0.2465	4769291	9990387	0.9538582	0.9990387	0.9528969
FES	3195207	6340255	0.6390	0.6340	0.2731	4765215	9990034	0.9530430	0.9990034	0.9520464
F13B	3299071	5448406	0.6598	0.5448	0.2047	4758536	9989157	0.9517072	0.9989157	0.9506229
D4S2364	3053343	5296001	0.6107	0.5296	0.1403	4740958	9987558	0.9481916	0.9987558	0.9469474

Table 4: Performances of different commercial available test in Full-Sibs versus Half-Sibs discrimination using Sibship Index corrected by maternal genotype. 1 = the STR is present in the kit; 0 = the STR is absent in the kit.

STR	LIFE Technologies - AmpFLSTR				Promega – Powerplex					CORE
	Identifiler	NGM	NGM Select	GlobalFiler	16	18D	17ESX	21	Fusion	
CSF1PO	1	0	0	1	1	1	0	1	1	1
D1S1656	0	1	1	1	0	0	1	1	1	1
D2S441	0	1	1	1	0	1	1	0	1	1
D2S1338	1	1	1	1	0	0	1	1	1	1
D3S1358	1	1	1	1	1	1	1	1	1	1
D5S818	1	0	0	1	1	1	0	1	1	1
D6S1043	0	0	0	0	0	0	0	1	0	1
D7S820	1	0	0	1	1	1	0	1	1	1
D8S1179	1	1	1	1	1	1	1	1	1	1
D10S1248	0	1	1	1	0	0	1	0	1	1
D12S391	0	1	1	1	0	0	1	1	1	1
D13S317	1	0	0	1	1	1	0	1	1	1
D16S539	1	1	1	1	1	1	1	1	1	1
D18S51	1	1	1	1	1	1	1	1	1	1
D19S433	1	1	1	1	0	1	1	1	1	1
D21S11	1	1	1	1	1	1	1	1	1	1
D22S1045	0	1	1	1	0	0	1	0	1	1
FGA	1	1	1	1	1	1	1	1	1	1
PENTA D	0	0	0	0	1	1	0	1	1	1
PENTA E	0	0	0	0	1	1	0	1	1	1
SE33	0	0	1	1	0	0	1	0	0	1
TH01	1	1	1	1	1	1	1	1	1	1
TPOX	1	0	0	1	1	1	0	1	1	1
vWA	1	1	1	1	1	1	1	1	1	1
SIBSHIP INDEX										
Half Sibs μ	5.1607	5.1954	5.5896	7.2936	5.1615	5.8591	5.5896	6.8599	7.5995	8.2835
Half Sibs σ	1.4984	1.5798	1.6853	1.8474	1.5123	1.6044	1.6853	1.8115	1.862	1.9949
Full Sibs μ	6.7984	7.038	7.6848	9.7815	6.8367	7.7302	7.6848	9.3273	10.1427	11.2317
Full Sibs σ	1.274	1.3473	1.4439	1.5818	1.2844	1.3655	1.4439	1.5467	1.5876	1.711

Overlap	0.55	0.53	0.5	0.47	0.55	0.53	0.5	0.46	0.46	0.42
Sensitivity at cut off =1	0.99999995	0.99999991	0.99999995	1	0.99999995	0.999999993	0.99999995	1	1	1
Specificity at cut off =1	0.00028644	0.00050351	0.00045565	0.00003940	0.0003212	0.00013017	0.00045565	0.00007628	0.00002240	0.00001646
Crossing point	5.8602	6.0088	6.5408	8.4536	5.8814	6.4841	6.5408	8.0134	8.789	9.6944
Equal Error Rate point	6.0458	6.1899	6.718	8.6339	6.0673	6.8699	6.718	8.1909	8.9723	9.8706
Sensitivity=Specificity	0.72263656	0.73549397	0.74842939	0.7659258	0.7254111	0.73566106	0.74842939	0.76875289	0.766952062	0.78685027
SIBSHIP INDEX CORRECTED BY MATERNAL GENOTYPE										
Half Sibs μ	-5.2462	-5.4644	-5.9402	-7.5101	-5.2855	-5.9602	-5.9402	-7.2219	-7.8282	-8.6338
Half Sibs σ	2.1202	2.1091	2.1633	2.4855	2.119	2.2549	2.1633	2.4496	2.5554	2.6697
Full Sibs μ	3.2970	3.6862	4.1663	4.9699	3.3539	3.7727	4.1663	4.9717	5.0939	5.9344
Full Sibs σ	3.2202	3.3309	3.5084	3.9057	3.23339	3.4424	3.5084	3.8448	3.9641	4.2201
Overlap	0.1067	0.09	0.07	0.05	0.10	0.09	0.07	0.05	0.05	0.03
Sensitivity at cut off =1	0.84705376	0.86578283	0.88249009	0.89839977	0.85015523	0.86344659	0.8824009	0.90201327	0.90060878	0.92017107
Specificity at cut off =1	0.99332706	0.99521291	0.99698222	0.99874282	0.99369068	0.99589433	0.99698222	0.99840176	0.99890594	0.99938967
Crossing point	-1.5259	-1.572	-1.7285	-2.3097	-1.5357	-1.7756	-1.7285	-2.1328	-2.4231	-2.6387
Equal Error Rate point	-1.8544	-1.9167	-2.0853	-2.6567	-1.8656	-2.1081	-2.0853	-2.4765	-2.7632	-2.9888
Sensitivity=Specificity	0.94517378	0.953725	0.96261791	0.97457297	0.94673241	0.95621262	0.96261791	0.97364083	0.97626578	0.98276229

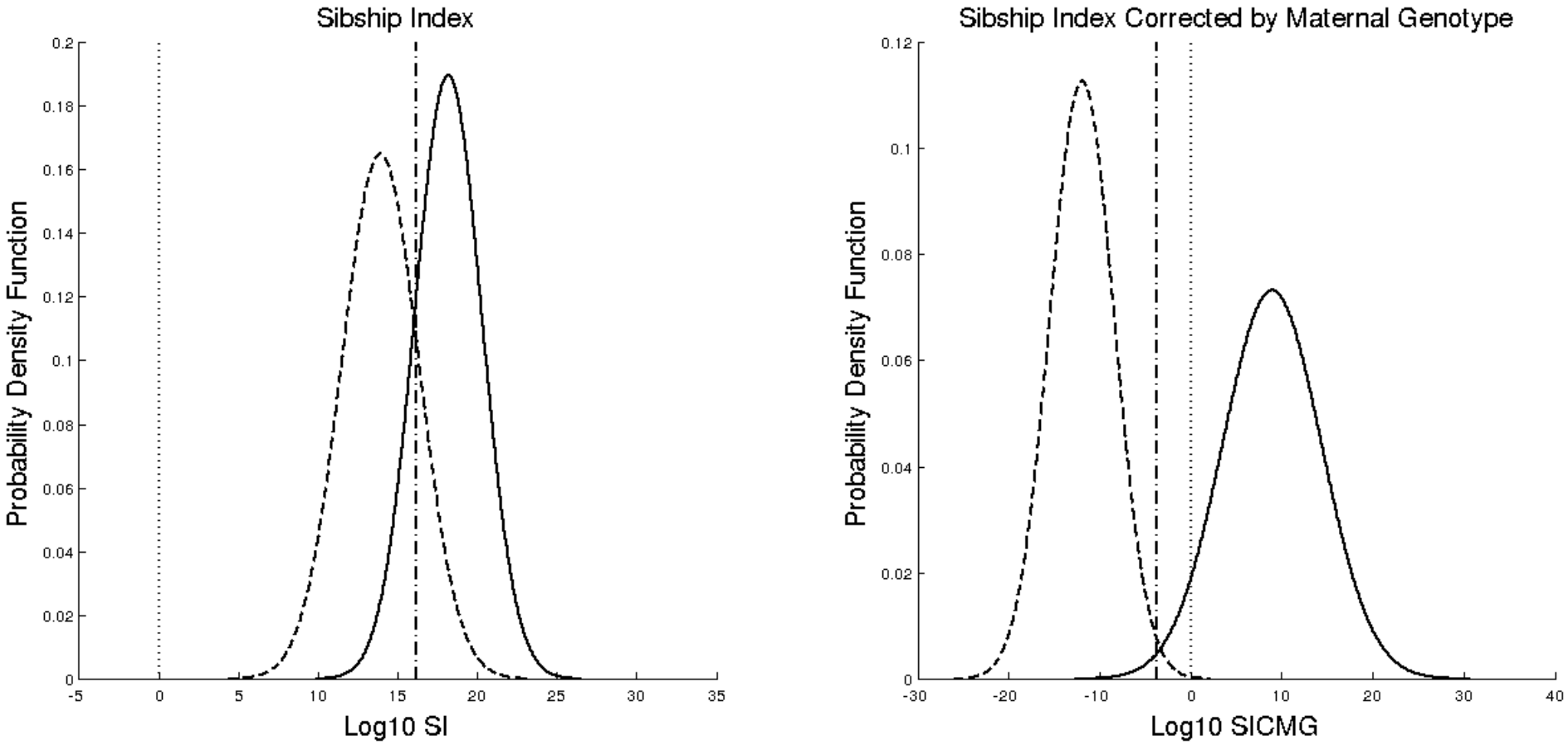
Table 5: Performances of SI algorithm adding STRs to the Core of commercial used STR. In gray background STRs that worsen the performances.

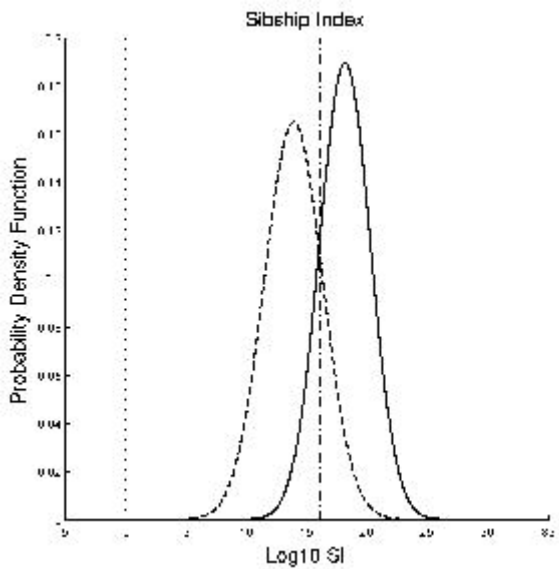
STR	Half-Sibs log-normal distribution		Full-Sibs log-normal distribution		Overlap	Crossing Point	EERP	Sensitivity =	Youden's
	μ	σ	μ	σ				Specificity	Index
Core	8.2835	1.9949	11.2317	1.7110	0.42415	9.69443	9.87058	0.78685	0.57370
PENTA B	8.6256	2.0535	11.7572	1.7666	0.41042	10.13607	10.30896	0.79382	0.58765
D12ATA63	8.9282	2.0835	12.1687	1.7942	0.40146	10.49823	10.66930	0.79834	0.59668
D3S4529	9.2246	2.1089	12.5514	1.8143	0.39464	10.84117	11.01292	0.80177	0.60355
D6S474	9.5083	2.1318	12.9164	1.8331	0.38820	11.16894	11.34072	0.80499	0.60997
D4S2408	9.7974	2.1540	13.2814	1.8522	0.38273	11.49905	11.67067	0.80776	0.61552
D3S3053	10.0914	2.1756	13.6481	1.8714	0.37775	11.83224	12.00346	0.81026	0.62052
D5S2500	10.3809	2.1964	14.0095	1.8928	0.37324	12.16067	12.32991	0.81256	0.62512
D1S1677	10.6939	2.2200	14.3967	1.9155	0.36900	12.51335	12.68167	0.81470	0.62941
LPL	11.0042	2.2420	14.7770	1.9355	0.36488	12.86106	13.02904	0.81677	0.63354
D11S4463	11.3332	2.2679	15.1785	1.9587	0.36138	13.22824	13.39646	0.81853	0.63706
D18S853	11.6592	2.2886	15.5633	1.9765	0.35847	13.58529	13.75412	0.81999	0.63999
D17S1301	11.9614	2.3047	15.9157	1.9914	0.35583	13.91420	14.08273	0.82133	0.64266
D6S1017	12.2914	2.3220	16.2984	2.0091	0.35339	14.27216	14.43963	0.82257	0.64513
D17S974	12.5994	2.3405	16.6597	2.0273	0.35114	14.60821	14.77512	0.82371	0.64741
D20S482	12.9259	2.3624	17.0445	2.0483	0.34901	14.96521	15.13182	0.82479	0.64958
D14S1434	13.2434	2.3797	17.4111	2.0666	0.34723	15.30844	15.47394	0.82571	0.65142
D20S1082	13.5716	2.3960	17.7826	2.0812	0.34559	15.65926	15.82515	0.82653	0.65306
D10S1435	13.9084	2.4168	18.1724	2.1017	0.34403	16.02353	16.18906	0.82733	0.65466
D9S1122	14.2401	2.4319	18.5327	2.1187	0.34424	16.36949	16.53410	0.82724	0.65448
D1GATA113	14.5632	2.4494	18.8871	2.1379	0.34464	16.70811	16.87202	0.82705	0.65410
FES	14.8540	2.4851	19.2406	2.1727	0.34511	17.02991	17.19448	0.82685	0.65370
PENTA C	15.1979	2.5217	19.6391	2.2021	0.34591	17.40016	17.56870	0.82643	0.65287
D4S2364	15.5258	2.5350	19.9728	2.2127	0.34769	17.72964	17.90022	0.82553	0.65107
D2S1776	15.8497	2.5867	20.3734	2.2620	0.34958	18.09039	18.26297	0.82458	0.64917
F13B	16.1747	2.6200	20.7323	2.2866	0.35168	18.43036	18.60833	0.82352	0.64705
F13A1	16.5438	2.6742	21.1465	2.3292	0.35631	18.81792	19.00379	0.82119	0.64237

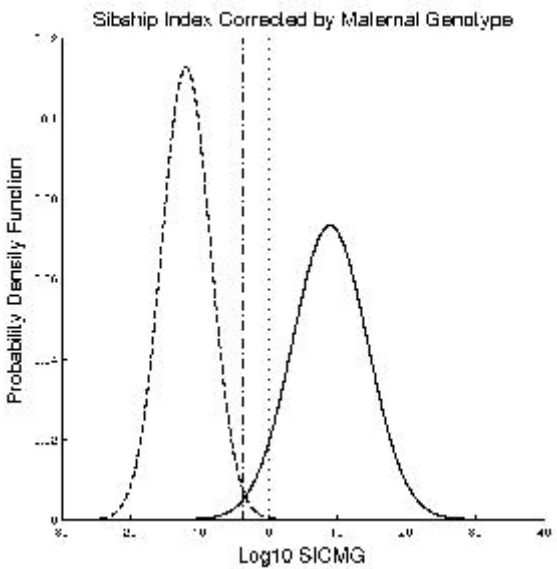
Table 6: Performances of SICMG algorithm adding STRs to the Core of commercial used STR. In gray background STRs that worsen the performances.

STR	Half-Sibs log-normal distribution		Full-Sibs log-normal distribution		Overlap	Crossing Point	EERP	Sensitivity = Specificity	Youden's Index
	μ	σ	μ	σ					
Core	-8.63382	2.66970	5.93436	4.22007	0.03346	-2.63872	-2.98884	0.98276	0.96552
PENTA B	-8.98588	2.73767	6.33319	4.33707	0.02947	-2.70521	-3.05795	0.98482	0.96964
D3S4529	-9.25513	2.80666	6.56340	4.41171	0.02761	-2.75415	-3.10454	0.98579	0.97158
D12ATA63	-9.50583	2.87232	6.82591	4.49660	0.02593	-2.78895	-3.13991	0.98666	0.97333
D6S474	-9.73645	2.94031	7.05192	4.56349	0.02459	-2.81000	-3.15805	0.98737	0.97473
D4S2408	-9.96409	3.00690	7.27074	4.63490	0.02349	-2.83574	-3.18252	0.98794	0.97589
D3S3053	-10.17551	3.06818	7.46990	4.70201	0.02256	-2.86190	-3.20795	0.98842	0.97685
D1S1677	-10.41300	3.12716	7.65294	4.78294	0.02182	-2.92199	-3.27085	0.98881	0.97762
D5S2500	-10.62720	3.18824	7.85699	4.86312	0.02116	-2.95644	-3.30769	0.98916	0.97831
LPL	-10.85851	3.24965	8.04397	4.94870	0.02061	-3.01105	-3.36598	0.98943	0.97887
D18S853	-11.10353	3.31058	8.25836	5.05859	0.02018	-3.08086	-3.44458	0.98965	0.97930
D11S4463	-11.32485	3.37127	8.45350	5.16076	0.01993	-3.13832	-3.50982	0.98978	0.97956
D14S1434	-11.47140	3.42685	8.62081	5.23409	0.01985	-3.14652	-3.52157	0.98983	0.97965
D17S1301	-11.70035	3.48255	8.74772	5.32452	0.01975	-3.23276	-3.61464	0.98988	0.97976
D10S1435	-11.93507	3.54060	8.92945	5.44430	0.01972	-3.31896	-3.71317	0.98989	0.97978
D20S482	-12.13808	3.59362	9.09007	5.55031	0.01974	-3.39032	-3.79528	0.98987	0.97974
D6S1017	-12.36467	3.64506	9.26853	5.68700	0.01989	-3.49240	-3.91484	0.98978	0.97956
D17S974	-12.59803	3.69990	9.42227	5.81783	0.02011	-3.59955	-4.03791	0.98966	0.97931
D20S1082	-12.82459	3.75369	9.63063	5.97487	0.02037	-3.70069	-4.16041	0.98951	0.97901
PENTA C	-13.01983	3.82160	9.81769	6.10379	0.02075	-3.75313	-4.22663	0.98930	0.97860
D1GATA113	-13.16160	3.86447	9.85071	6.18960	0.02141	-3.83176	-4.31639	0.98896	0.97791
D2S1776	-13.35897	3.93019	10.05920	6.36338	0.02218	-3.90860	-4.41767	0.98855	0.97710
D9S1122	-13.49278	3.98075	10.18114	6.49265	0.02302	-3.96667	-4.49475	0.98810	0.97620
FES	-13.68187	4.06507	10.36922	6.65619	0.02405	-4.01433	-4.56267	0.98756	0.97512
F13A1	-13.82957	4.15018	10.55270	6.80187	0.02513	-4.02488	-4.59013	0.98700	0.97400
F13B	-13.96140	4.23215	10.66837	6.91240	0.02620	-4.03237	-4.60822	0.98645	0.97290
D4S2364	-14.04029	4.33046	10.75044	7.11483	0.02928	-4.05110	-4.66043	0.98485	0.96969

Figure 1: Distributions of logarithms of cumulative Sibship Index and Sibship Index Corrected by Maternal Genotype. Solid line = Full Sibs; dashed line = Half Sibs; dotted line = Cumulative Likelihood Ratio cut off set at 1; dash dot line = Cumulative Likelihood Ratio cut off set as Equivalent Error Rate Point.




Sibship Index
Probability Density Function
Log10 SI


Sibship Index Corrected by Maternal Genotype
Probability Density Function
Log10 SICMG